

ADVANCES IN
Physical Organic Chemistry
VOLUME 27

Advances in Physical Organic Chemistry

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Advances in Physical Organic Chemistry

Volume 27

Edited by

D. BETHELL

The Robert Robinson Laboratories
Department of Chemistry
University of Liverpool
P.O. Box 147
Liverpool L69 3BX



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Preface

This series of volumes, established by Victor Gold in 1963, aims to bring before a wide readership among the chemical community substantial, authoritative and considered reviews of areas of chemistry in which quantitative methods are used in the study of the structures of organic compounds and their relation to physical and chemical properties.

Physical organic chemistry is to be viewed as a particular approach to scientific enquiry rather than a further intellectual specialization. Thus organic compounds are taken to include organometallic compounds, and relevant aspects of physical, theoretical, inorganic and biological chemistry are incorporated in reviews where appropriate. Contributors are encouraged to provide sufficient introductory material to permit non-specialists to appreciate fully current problems and the most recent advances.

Within the broad definition of physical organic chemistry adopted in this series, the subject of organic reactivity is one of central importance. In this volume, three contributions are concerned with the derivation of detailed information about transition-state structure and bonding from reactivity data by application of linear free energy correlations, particularly those associated with the names Brønsted and Hammett. It is hoped that the juxtaposition of these closely related but distinctive approaches will provide readers with a useful guide to available methodology. Complementary ways of studying transition-state structure should feature in a forthcoming volume. In the fourth contribution to Volume 27, the continuing question of the factors governing the partitioning of electrophiles between mixed nucleophilic solvents is addressed in the light of new results arising from the resurgent interest in quantitative aspects of nucleophilic substitution at saturated carbon.

The Editor would welcome feedback from readers. This might merely take the form of criticism. It might also contain suggestions of developing areas of chemistry that merit a forward-looking exposition or of the need for a new appraisal of better established topics that have escaped the notice of the Editor and his distinguished Advisory Board.

D. BETHELL

Contributors to Volume 27

Claude F. Bernasconi Department of Chemistry, University of California at Santa Cruz, Santa Cruz, California 95064, USA

Ikchoon Lee Department of Chemistry, Inha University, Incheon 160, South Korea

Zvi Rappoport Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

Rachel Ta-Shma Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

Andrew Williams The University Chemical Laboratory, University of Kent, Canterbury, Kent CT2 7NH, UK

Effective Charge and Transition-state Structure in Solution

ANDREW WILLIAMS

*The University Chemical Laboratory, University of Kent, Canterbury, Kent
CT2 7NH, UK*

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1 Introduction

OBJECTIVES

For many years chemists have understood that the effects of polar substituents on rates and equilibria are caused by changes in charge at the reaction centre. The manifestation of these effects in terms of slopes of linear free energy relationships has always seemed false, and recent years have seen the development of the effective charge parameter ε , which may be derived simply from Brønsted or Hammett slopes. Discussion of the electronic structure of the states of the reaction path is logically better suited to a charge idiom.

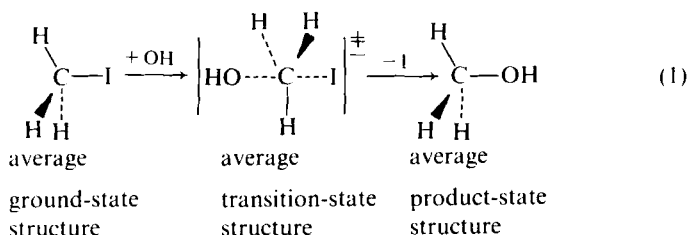
This review, while not comprehensive, aims to cover most aspects of the concept of effective charge in its application to reactions in solution. A case is not being pressed for the application of charge derived from polar effects as the *only* quantity whereby information is obtained about bonding; rather it is recognized that polar substituent effects on rates and equilibria in solution are far more easily and reliably obtained than are other data, and they constitute one of our most powerful mechanistic tools for studies of reactions in solution.

ASSEMBLIES OF MOLECULES

Chemists still discuss chemical structure in terms of the “Kekulé” model where a molecule is regarded as consisting of a number of atoms disposed in fixed positions in space. Mechanisms are often discussed in terms of change from one Kekulé representation to another, as if atoms in an assembly of reactant molecules have exactly the same disposition relative to each other and these remain constant with time. Of course, individual molecules move relative to one another. The application of this model undoubtedly puts a restriction on our understanding of mechanism and acts as propaganda for a simplistic view of mechanism. An assembly of molecules does not behave as if each constituent were identical at a given instant, and reference to the results of X-ray crystallographic studies indicates that there is an uncertainty

that arises from thermal vibration (Ladd and Palmer, 1977) in the disposition of each atom in a molecule relative to its neighbours even in crystalline solids.

The Kekulé model has many advantages, despite its shortcomings. The method of representing a reaction path as if it were for a single molecule presents the problem that the intervening structures in even the simplest mechanism, for example the hydrolysis of methyl iodide (1), do not



correspond to real molecular entities; these structures have no existence comparable to that of a compound and they do not survive even for a time of about kT/h (the period of a half-vibration, 10^{-13} s) (Kreevoy and Truhlar, 1986). Normal instrumental methods for determining structure are not applicable to transition states, which require observation times of less than 10^{-13} s. An individual particle with a Kekulé structure at an energy maximum on the reaction path takes a longer time to equilibrate into another structure than it takes to decay to product or reactant. The transition-state concept was invoked to deal with this problem, and it turned out that the transition state could be treated as if it were an assembly of molecules (at an energy maximum) in equilibrium with the assembly of real molecules in ground and product states (Ross and Mazur, 1961). The Kekulé representation of the transition state involves full bonds, which are not significantly changed on reaction, and partial bonds for the bonding changes. Thus in (1) the C—H bond-length and bond-angle changes are only second-order effects compared with the bonding changes between carbon and the entering and leaving atoms.

It is important to reiterate these ideas, which indeed form part of the basic physical chemistry in undergraduate classes (Maskill, 1985), because the measurements we shall be considering are made on *assemblies* of molecules and of the intervening “structures” in the reaction pathway. Thus the representations of reactions normally made in mechanistic discussions are not directly related to the experiments, and it is important to remember this.

MOLECULAR ORIGINS OF POLAR SUBSTITUENT EFFECTS

There are substantial changes in electrical charge on atoms in reacting bonds during a reaction. Development of charge implies that there is an energy change, so that any effect to neutralize charge will be relayed into an energy difference, resulting in a faster or slower rate (Hine, 1960). Thus substituents that withdraw electrons and hence "spread" charge will tend to make reactions go faster if there is a negative charge increase at the reacting bond from ground to transition state; this assumes that the polar substituent is located close enough on the molecule for the effect to be transmitted to the reaction site.

QUANTITATIVE MEASURES OF POLAR EFFECTS

Polar substituent effects have been measured by a number of similar approaches [for example Hammett plots, Brønsted-type plots,¹ Taft plots and Charton plots, to name the most used (Williams, 1984a)]. None of these methods is intrinsically superior to the other, as each is based on the same principle. The criterion of use is that the standard reaction should resemble as closely as possible the reaction in hand so that there is not too great an extrapolation from known to unknown. Inspection of (2) indicates that, for



example, a Brønsted-type plot of the logarithm of the rate constant for reaction of phenolate ions with methyl iodide against the $\text{p}K_{\text{a}}$ -value of the phenol is more appropriate than a Hammett plot, where the parameter is the unrelated ionization of a benzoic acid. The approach employed in a particular case is largely a matter of convenience given the above criterion, but it turns out that the Brønsted-type plot is generally more useful than is the Hammett family of plots.

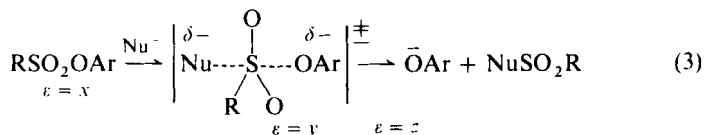
ELECTRONIC CHARGE AND MECHANISM

Given the above assumptions, the polar substituent effect reveals information about change in charge or dipole moment at the reacting bond

¹ Strictly the Brønsted plot refers only to proton-transfer reactions, but there is an increasing use of the $\text{p}K_{\text{a}}$ of the conjugate acid of a nucleophile for reactions of nucleophiles with species, and we shall refer to this type of plot as "Brønsted-type".

(Hine, 1960). If a particular atom is being considered then the polar substituent effect refers to change in charge on the atom from ground through transition to product state. The change in charge on a particular atom is probably the most fundamental result of a reaction; any method for studying charge change is therefore a very important method for demonstrating mechanism, and the polar substituent effect is one of the major tools for chemists interested in mechanism.

Charge change can be related to the extent of change in bonding in a transition state by suitable calibration. The best polar effect for calibration is that measuring the change in charge from *ground* to *product* states for the bonding change in question, and this reaction is termed the "calibrating" equilibrium. In (3) the charges on ground and product states are x and z



respectively for the oxygen atom. The difference $z - x$ represents the charge change in a full bond fission. The difference $z - y$, where y is the charge on the oxygen in the transition state, is the charge change from transition state to product state, and thus the "bonding" in the transition state can be defined as $(z - y)/(z - x)$ of the total change. Trying to relate charge change, derived from polar effects on states, with Pauling-type bond order is not very useful. It is simplest to *define* bond order in the context of charge, and we shall defer to a little later the meaning of bond order under these conditions.

Other experimental approaches to bond order depend on energy measurements where means of regulating the energies other than by effects on charge are employed. Invariably these methods are experimentally much more demanding than polar substituent effect studies. They include steric effects (Taft's δ), pressure effects (ΔV), isotope effects (vibration), temperature effects (entropy) and stereochemistry. The stereochemical method, although not usually regarded as an energy method, involves comparisons of product ratios which thus reflect differing energies of particular reaction paths as affected by molecular chirality. In order for these various approaches to be applied quantitatively, some calibration process is required so that energy changes to the transition state from ground state can be compared with that for a bonding change between two known states; a recent study with heavy atom secondary isotope effects underlines the requirement of the proper calibration process (Hengge and Cleland, 1990).

DOES THE POLAR EFFECT MEASURE CHANGE IN BOND ORDER?

It is perfectly true to say that in solution chemistry no experimental method gives the bond order of an isolated bond in ground, transition or product states. The transition state is an assembly of unstable structures, each with an average lifetime less than that of a vibration. It might be considered that, since the molecule does not exist in the transition state for more than 10^{-13} s, there will be no time for the solvent to redistribute and thus one should not be able to assume that the solvating groups are in equilibrium in ground and transition state. Since the solvent is part of the state, solvation must behave as if it were in equilibrium in transition and ground and product states (Kreevoy and Truhlar, 1986). In other words, the transition state refers to the *whole* system and not just to the isolated molecule undergoing reaction.

It is important to emphasize that the index of bonding refers to *states* and not to Kekulé *bonds*. There is an unfortunate neglect of solvent in discussing reaction mechanisms of solution reactions (or reactions in the liquid phase), which are documented as if they were carried out in the gas phase.² Confusion arises as to the applicability of polar substituent effects in estimating bonding. Polar substituent effects estimate charge or dipole-moment change that is the result of both bonding *and* solvation changes. It is also more correct (this applies to all methods) to discuss states rather than bonds, and the shorthand approach to graphics neglects this. Kinetic isotope effects are dependent on the solvent (Keller and Yankwich, 1973, 1974; Williams and Taylor, 1973, 1974; Burton *et al.*, 1977), and it is probable that strong solvation of the isotopically substituted atom will make a substantial contribution. In practice, however, only the effects of the first solvation shell need be considered. The stereochemistry of a reaction also is dependent on the solvent, as is manifest from Cram's classic text (Cram, 1965).

2 Effective charge

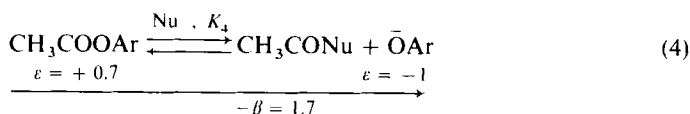
EQUILIBRIA

Change in effective charge Δe on an atom in a reaction centre is formally defined as a quantity obtained by comparison of the polar effect on the free

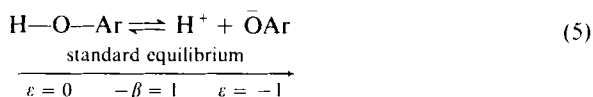
² Descriptions of mechanism in *this* article are couched in a language devised for structural studies (naturally) and can therefore be misleading if the assumptions are forgotten. For convenience, and following precedent, solvent is often omitted from descriptions of state in this text; moreover the term "bonding change" is invariably used to mean the summation of change in bonding (in its literal sense) and solvation.

energies of rate or equilibrium processes with that on a standard ionization equilibrium (Jencks, 1971; McGowan, 1948, 1960; Williams, 1984b; Thea and Williams, 1986). Thus the value of Brønsted's β is an effective charge change where the standard ionization equilibrium has a defined change in effective charge of unity. The absolute effective charge may be obtained from $\Delta\epsilon$ by defining its value for one of the states in the standard equilibrium.

Let us consider the simple reaction (4) of a nucleophile with aryl acetates.



The equilibrium constant for this reaction of hydroxide ion may be plotted as a Brønsted plot against $\text{p}K_a$ for the appropriate phenol (Fig. 1). The slope of the linear Brønsted-type plot is -1.7 (Ba-Saif *et al.*, 1987); qualitatively this indicates that there is a larger charge change on the aryl oxygen than in the ionization of the phenol (5). The substituent "sees" charge change that



can be defined in terms of that occurring on the oxygen atom in the ionization of the phenol. Thus, if the charges on the oxygen in the phenolate ion and phenol are defined as -1 and 0 respectively, the charge change on the corresponding oxygen in the ester reaction is -1.7 . Simple arithmetic shows that there must be $+0.7$ units of "effective" charge on the oxygen in the ester in the ground state. The charge derived in this way is designated "effective" charge because it is measured against a *defined* standard charge change. The real electronic charges on the oxygen in (5) are certainly not integral because of solvation and of charge removal from the oxygen by its neighbouring atoms. Linearity of the Brønsted line indicates that to a first approximation the charge on the oxygen is not altered by the substituent, at least over the ranges of $\text{p}K_a$ normally studied. The location of effective charge depends entirely on the standard equilibrium employed and the definition of effective charge therein. The ionization of any acidic species formally places charge change on the atom undergoing proton removal (Williams, 1984b). The polar effect measures charge change at the reaction centre, which will derive mainly from solvation and bonding differences between the measured states.

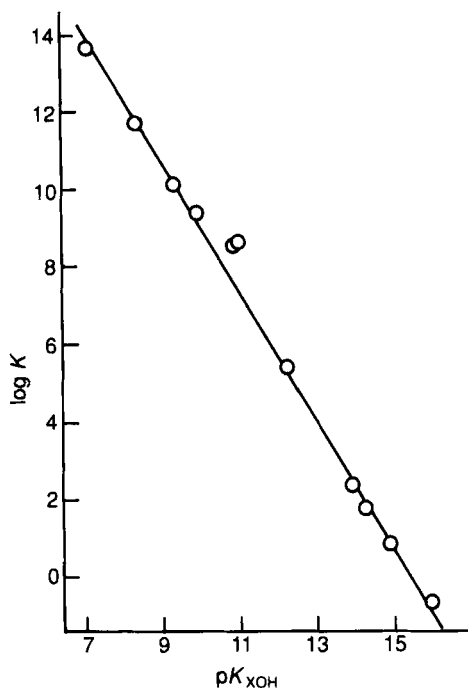


Fig. 1 Brønsted dependence of equilibrium constants for reaction of acetate esters with hydroxide ion in aqueous solution. Data from Gerstein and Jencks (1964); the product state is oxyanion and acetic acid and the hydroxy species range from phenols to alcohols.

Little work has been done to correlate effective charges with charge determined by other physical methods because there is little in the way of comparable data. The most obvious comparison is with electronic charge distributions obtained by quantum mechanical calculations (see, for example, Pople and Beveridge, 1970; Dewar, 1969); these calculations refer to isolated molecules and there are as yet no reliable calculations for states, in particular in solution, where molecules will be interacting with each other. The most obvious methods for charge measurement, namely ^{13}C nmr and esr spectroscopy, are only for ground or product states, and the data refer to the solvated species; the field awaits comparative work.

MEASUREMENT OF EFFECTIVE CHARGE IN EQUILIBRIA

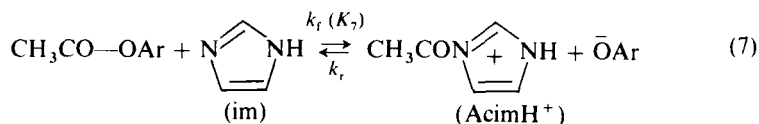
The kinetic approach offers the best approach for measuring effective charge. Explicit measurements of equilibrium constants over ranges of

substituents are very sparse for reactions for the simple reason that they are often difficult to obtain, whereas there are very sensitive methods for measuring the small concentrations of hydrogen ion necessary to estimate ionization constants of acids.

The *kinetic* method of measuring substituent effects on equilibrium derives from the fact that the equilibrium constant $K_{eq} = k_1/k_{-1}$ for (6) leads to the



equation $\beta_{eq} = \beta_1 - \beta_{-1}$ (or $\rho_{eq} = \rho_1 - \rho_{-1}$). It is not usually a simple procedure to measure both forward and reverse rate constants under the same conditions, and the first measurements of this kind for reaction (7) of



aryl acetates with imidazole (Gerstein and Jencks, 1964) employed excess imidazole over ester in the forward reaction to shift the equilibrium well to the right. Since the acetylimidazole is in its neutral form at the pH of the investigation, its pK_a and that of the phenol are used to compute the rate constant for the return reaction, which is measured in competition with the hydrolysis. It is an experimental convenience that, since we desire to obtain β_{eq} (change in K_{eq} with K_a^{ArOH}), we do not need to obtain K_{eq} explicitly; as shown in (8) and (9), the substituent effect on the return rate constant k_r is independent of the ionization constant of the acetylimidazolium ion K_a , which need not therefore be known:

$$\text{Return rate} = k_r [\text{AcimH}^+] [\text{ArO}^-] \quad (8)$$

$$= k_r \frac{[\text{Acim}][\text{H}^+][\text{ArO}^-]}{K_a + [\text{H}^+]} \quad (9)$$

Owing to problems of the position of the equilibrium, the forward and reverse rate constants are often measured with reagents where no overlap occurs in the ranges of substituent covered in the Brønsted-type plot (or whichever free energy relationship is in use); this could be due to requirements of conditions for the reaction to be forced to completion. In order to compute β_{eq} under identical conditions, it is necessary to have confidence that the free energy relationships are linear over the extrapolated range (Fig. 2).

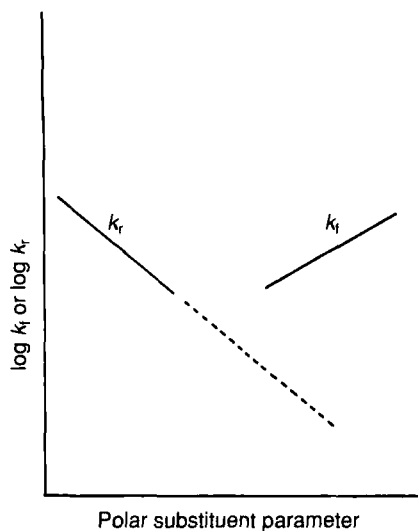
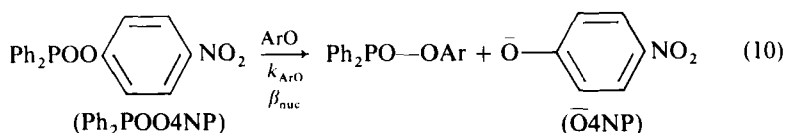
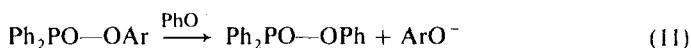


Fig. 2 Free energy relationships for forward (k_f) and reverse (k_r) rate constants in the reaction. In order to obtain β_{eq} from β_r and β_f as described in the text, it is necessary that the plots may be extrapolated with confidence to the overlap regions.

It is essential to demonstrate that the same rate-limiting step is being observed for forward and reverse measurements of the substituent effects (such as β). In the reaction of a series of nucleophiles with a substrate having a particular leaving group, the forward effect (β_{nuc}) is easily determined, as for example in (10). The return reaction of the leaving group with the aryl



esters of diphenylphosphinic acid (Bourne *et al.*, 1988) is not a convenient reaction to measure because 4-nitrophenolate anion is too weak a nucleophile to compete with interfering reactions such as hydrolysis. The value of the Brønsted exponent β_{lg} for the return reaction, where now the *leaving group* varies and the nucleophile (leaving group for the forward reaction) is constant, may, however, be computed from β_{lg} obtained from reaction of a number of similar nucleophiles, such as for example phenolate ion with reactive esters (11). In the present example the values of β_{lg} are plotted as a

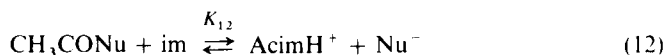


function of the nucleophilic pK_a , and the value is observed to obey the equation $\beta_g = (0.072 \pm 0.008) pK_{nuc} - (1.31 \pm 0.07)$ (Bourne *et al.*, 1988). The leaving groups in the reaction are generally more reactive than those used in the forward process, so that it is necessary to be sure that linearity holds over a wide range of nucleophiles and leaving groups. The extrapolation to give the β -value needed in the case in hand is only very small; the range of pK_a -values is from 7.66 to 9.99 and the extrapolation is to 7.14, the pK_a for 4-nitrophenol.

Even greater care is needed to obtain β_{eq} (or ρ_{eq}) by direct equilibrium measurement than in the kinetic method because the values of the equilibrium constants could change over a relatively wide range unless the polar effect parameters are close to zero. Thus accurate determination of the substituent effect would require a very sensitive technique capable of analysing over several orders of magnitude. Such an analytical tool is available for the measurement of ionization equilibrium constants in the form of the glass electrode. Although they have not been tried extensively in this problem, ion-selective electrodes might be used with great effect for measuring equilibrium constants over ranges of decades of concentration of species other than the proton such as the fluoride ion.

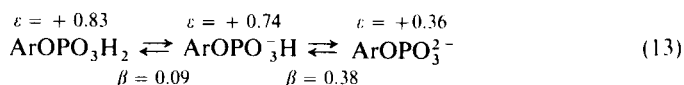
POLAR SUBSTITUENT EFFECTS ON EQUILIBRIA (FOR EXAMPLE β_{eq}) BY CALCULATION

Equations (4) and (12) indicate that β_{eq} (or any other polar effect parameter) is independent of the non-variant nucleophile. Combination of (4) and (12)



gives (7) and thus $K_4 = K_7/K_{12}$. The values of $d \log K_4 / dpK_a^{ArOH} = d \log K_7 / dpK_a^{ArOH} = \beta_{eq}$ (because K_{12} is invariant under change of the substituent in ArO^-). Such a result is manifest by intuition because the substituent variation will have no effect on the energies of Nu^- and CH_3CONu in the states in (4), although the individual equilibrium constants will vary.

The value of β_{eq} may be converted to effective charge since one of the variant species (in this case ArO^-) is that in the monostandard equilibrium (5). The ionization constants of the neutral and monoanion species of aryl-phosphoric acids (13) have β -values that may be used to estimate change in



effective charge from the known value of that for the dianion (Bourne and Williams, 1984a).

A grid of knowledge of effective charges on atoms adjacent to acyl groups may be built up independently of the structure of the nucleophile, and this is illustrated in Fig. 3.

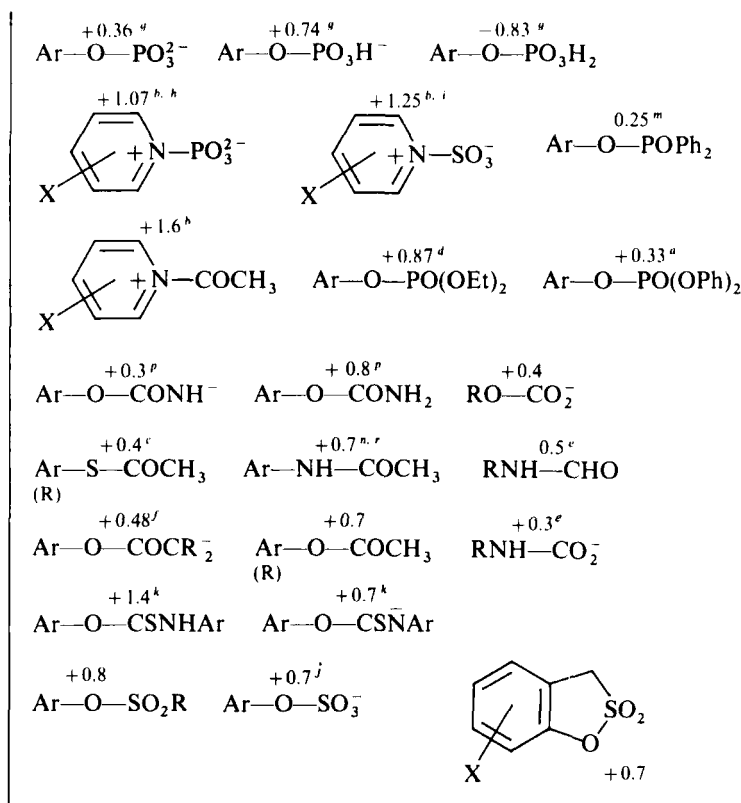
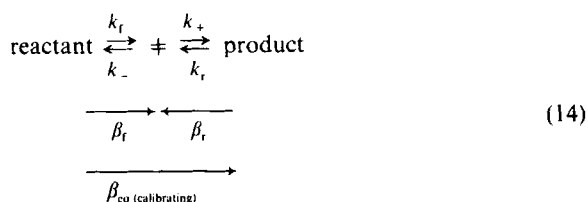


Fig. 3 Collection of effective charge data for atoms adjacent to acyl functions. Where there is no reference, the effective charges are from Deacon *et al.* (1978). Except where stated the standard equilibrium is the ionization of ArOH or ROH . Notes: ^a Ba-Saif *et al.* (1990); ^b relative to the ionization of pyridinium ions; ^c relative to the ionization of thiols (Hupe and Jencks, 1977); ^d Ba-Saif and Williams (1988); ^e relative to the ionization of ammonium ions; ^f Alborz and Douglas (1982); ^g Bourne and Williams (1984a); ^h Bourne and Williams (1984b), Skoog and Jencks (1984); ⁱ Hopkins *et al.* (1985); ^j Hopkins *et al.* (1983); ^k Hill *et al.* (1982); ^m Bourne *et al.* (1988); ⁿ relative to anilinium ions (Fersht and Requena, 1971); ^p Al Rawi and Williams (1977); ^r Jencks *et al.* (1971).

Values of β_{eq} (or ρ_{eq}) may be calculated from the data of Fig. 3 for a variety of nucleophiles. For example, the acyl function from aliphatic carboxylic acids should have a similar effect to that of the acetyl group and induce similar effective charge. The electropositivity of the group is relative to that of the hydrogen group employed in the standard equilibrium, where hydrogen is defined as inducing zero charge on the nucleophilic atom. The relative values of the induced effective charges as shown in Fig. 3 correspond approximately to those expected from, for example, Hammett σ -values for the groups. Increasing the formal negative charge on the phosphoryl group (13) will reduce the positive charge induced by it on the aryl oxygen as observed (Bourne and Williams, 1984a). The acetyl group has a Hammett σ_p -value of 0.47 compared with zero for hydrogen, consistent with its inducing more positive charge on attached nucleophilic atoms. An interesting example is that the $ArNHCS-$ group induces 1.4 units of positive charge on neighbouring oxygen possibly due to the $C=S$ bond possessing a mainly dipolar character $[C^+—S^-]$ (Hill *et al.*, 1982).

MEASUREMENT OF EFFECTIVE CHARGE IN TRANSITION STATES

It should be possible to measure effective charges for transition states essentially in the same way as has been described for *molecules* or *states*. Consider (14), where the "rate constants" for breakdown of the "species"



forward (k_+) and backward (k_-) are essentially invariant and are related to the period of a bond vibration. Thus the "equilibrium constants" for formation of the transition state (k_1/k_+) and for its breakdown (k_-/k_{-1}) will vary only according to changes in k_1 and k_{-1} ; the polar effect on the individual rate constants will therefore measure charge changes from ground or product states to the transition state.

MAPS OF EFFECTIVE CHARGE

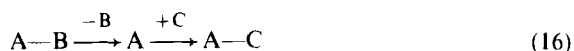
If the substituent effects for all the transformations are known, a map of the effective charges (14) may be built up where the effective charge on the

reacting atom may be assigned for each state. In the general example given, the charge on the transition state is β_1 and that on the product is β_{eq} , assuming there is zero charge on the atom in the reactant state. Unit charge change is of course defined by a standard ionization equilibrium related to that of (14).

3 Concerted mechanisms

ENFORCED CONCERTED MECHANISMS

A reaction with a concerted mechanism has no intermediate (Williams, 1989; Dewar, 1984); all bond changes occur simultaneously in the single step. Let us consider stepwise mechanisms involving intermediates $C-A-B$ or A as in (15) and (16); in the limit when the intermediate has no barrier to



decomposition, it would not be a true compound. The intermediate would not be in equilibrium with reactant and the mechanism under these conditions would be concerted since there could only be one transition state; this mechanism is special and is called an "enforced concerted" mechanism. The transition-state structure would correspond to that for the formation of the putative intermediate that approximates the structure represented by the top left or bottom right corners of the reaction map (Fig. 4).

This reaction map requires a little explanation since there are several types of similar representations, which are commonly called Jencks-More O'Ferrall diagrams (Jencks, 1972; More O'Ferrall, 1970; Williams, 1984a; Luthra *et al.*, 1988), that employ bond distances as coordinates. The use of these bond-distance coordinates is purely as a convenience in most qualitative discussions. Since Leffler-type parameters (see later) are advanced as measures of bond fission or formation (Williams, 1984b), they are ideal as *experimental* coordinates, but it must always be borne in mind that they will refer to *states* or *assemblies* including solvation and not to individual molecules (as is often the fancied representation).

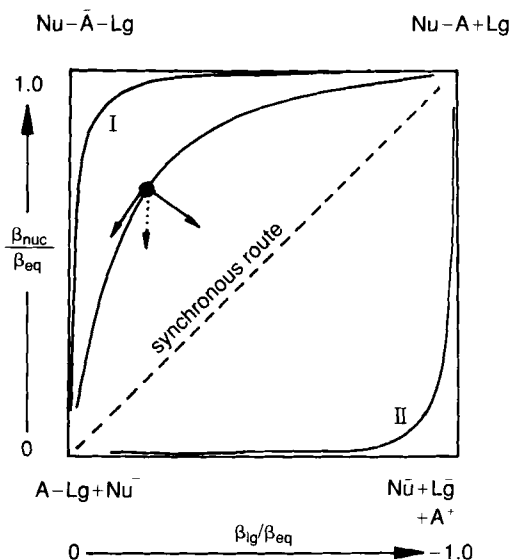
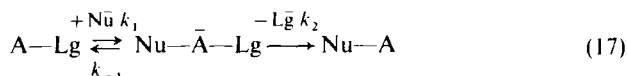


Fig. 4 Reaction map for a general substitution reaction. The coordinates of this map are empirical and do not strictly correspond to bond distances, as is often assumed for similar maps (see text).

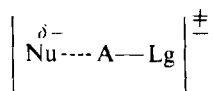
DEMONSTRATION OF CONCERTEDNESS

An observation that a transition state has "partial" entering- and leaving-group bonding is not evidence for a concerted mechanism. The question of concertedness is about the *number* of transition states along a reaction path rather than about the structure of a transition state; in order to demonstrate that a reaction has a concerted mechanism, it is necessary to use a tool that *counts* the number of transition states. The demonstration of two intersecting linear plots for a Brønsted or Hammett dependence indicates two slopes, which refer to electronic charge on *two* transition states; such evidence disproves a concerted mechanism by counting two transition states. A linear free energy relationship measures a single transition state, but more information is needed to prove that the observed transition state is not succeeded or preceded by others.

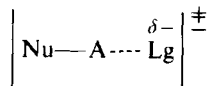
If it can be predicted that a change in rate-limiting step for a putative stepwise mechanism (17) will occur with a given range of substituents then



the absence of a break at the predicted point in the linear free energy relationship is evidence for a single-step mechanism. This methodology has recently been applied independently by two laboratories (for leading references see Jencks, 1988; Williams, 1989); it depends on the notion that when Lg^- and Nu^- are members of a group of nucleophiles of similar structure (such as pyridines or phenolate ions), the rate constants k_{-1} and k_2 obey the same linear free energy relationship and the change in rate-limiting step will occur when the $\text{p}K_{\text{a}}$ of leaving group and nucleophile are the same. Provided the range of nucleophile $\text{p}K_{\text{a}}$'s is well above and below that of a given leaving group, a linear plot is diagnostic of a single-step mechanism. The observation of a linear plot indicates that the charges on the nucleophilic atoms in both of the transition states of the putative stepwise mechanism (17) are identical. In very simple terms the charge on the nucleophile must be different in the two transition states [1] and [2] for the two step process, and this should be revealed in different slopes when each step is rate-limiting.



[1]



[2]

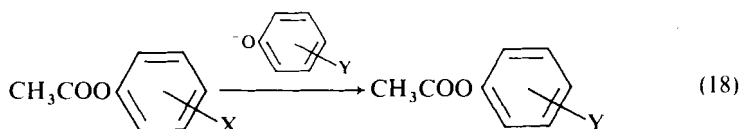
4 General considerations for the application of effective charge

THE LEFFLER PARAMETER

Comparison of charge change from ground to transition state with that for the overall (calibrating) equilibrium was first proposed by Leffler (1953; see also Leffler and Grunwald, 1963) as a measure of bond order in the transition state. A hypothetical, single-step reaction was considered where one bond only undergoes a major bonding change, and Leffler's parameter α is defined by the equation $\alpha = \text{d log } k / \text{d log } K$ (Williams, 1984b; Leffler, 1953; Leffler and Grunwald, 1963), where k and K are rate and equilibrium constants for a series of structurally related reactants. The reader should note that the symbol α is also used in Brønsted terminology (see, for example, Maskill, 1985). Real reactions usually involve at least two major

bonding changes, and considerable confusion has ensued from the erroneous application of the simple model based on the misconception that reactions could be considered merely by investigating one bonding change. In order to delineate a reaction, *all* the major bonding changes must be studied. It is of little use to try and determine whether a transition state is "advanced" or "late" on the basis of measurements at one bond alone; these terms apply to the state of bond formation or fission because the various methods of probing transition-state structure usually refer to bonding and not to *overall* structure. Recent work (Williams, 1984b; Hill *et al.*, 1982; Lewis and Kukes, 1979) has looked at the bonding changes from substituent effects on *both* bonding atoms in a bond undergoing fission (or formation) for a number of reactions. Similar values of the Leffler parameter were obtained for both effects, in agreement with Leffler's original hypothesis.

A frequent misuse in attempts to measure the extent of bonding in the transition state is the application of Brønsted or Hammett parameters without recourse to calibration. Such Brønsted or Hammett parameters are only very poor indicators of charge change. Effective charge on the oxygen of the forming bond in reactions (18) of phenolate ions with aryl acetates is

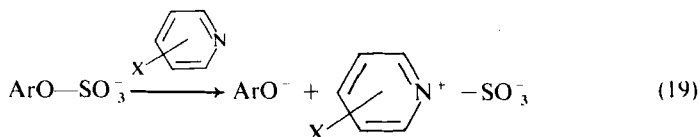


monitored by the polar effect of change in substituent Y and that on the leaving oxygen by the effect of the substituent X. The extent of "bond" formation will be given by $\beta_{\text{nuc}}/\beta_{\text{eq}} = a_{\text{formation}}$ and the extent of bond fission by $a_{\text{fission}} = \beta_{\text{lg}}/\beta_{\text{eq}}$.

BALANCE

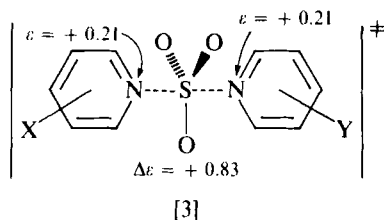
The relative extent of individual bond changes in a transition state is called the balance; in a reaction involving two major bond changes such as bond fission and bond formation, the transition state could involve a range of balance from that where formation is largely complete and fission incomplete (I in Fig. 4) to that where formation is incomplete and fission is complete (II in Fig. 4). It is useful to reserve the term "synchronous" (Jencks, 1988) to denote a mechanism where formation and fission occur to the same extent in a concerted mechanism. A formal definition of balance involves the parameter τ , developed by Kreevoy for identity reactions (see

later). We should use the ratio $a_{\text{formation}}/a_{\text{fission}}$ as a formal indicator of balance for reactions such as (19) that do not involve identical bond



formation and fission processes (Hopkins *et al.*, 1983); the uncalibrated effective charges may not be used directly to measure balance. In this case it is essential to employ Leffler α -values determined for each bonding change. Displacement reactions where entering and leaving groups have the same overall structure (for example all phenolate ions or all pyridines) are particularly useful for studies of balance because β_{eq} is the same for bond formation *and* fission; values of Leffler's α may then be compared by use of the ratios of the kinetic β -values.

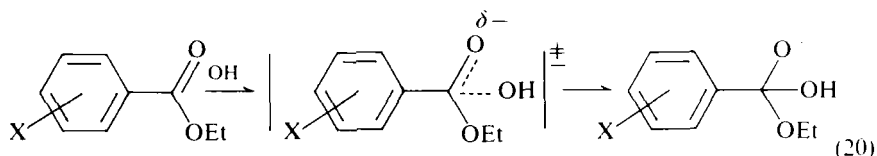
If the mechanism were not synchronous, the balance of the effective charge would reside on the transition state at a position other than at entering or leaving atoms. In the example shown in [3] (Hopkins *et al.*, 1985), the transfer of the sulphuryl group has a very low α for formation of the N—S bond and a very high α for fission of the leaving N—S bond. The value of the effective charge on the attacking nucleophile in [3] is equal to



β_{nuc} (+0.21), and by symmetry this must be the effective charge on the leaving atom. The overall change in charge on nucleophile or leaving group is equal to β_{eq} (1.25—see Fig. 3). Thus the *change* in charge on the leaving group is $1.25 - 0.21$ (=1.04); the change in charge on the nucleophile is +0.21, and therefore an increase in positive charge of 0.83 is required on the SO_3 group to keep the system neutral. This indicates that an imbalance of effective charge of 0.83 resides on the SO_3 group of atoms in the transition state.

APPLICATION OF "RAW" SELECTIVITY DATA

Since the first observations that rates and equilibria could be correlated with the ionization of benzoic acids (Hammett and Pfluger, 1933; Hammett, 1937; Burkhardt *et al.*, 1936), the "Hammett" ρ -value has been used extensively to indicate electronic requirements of the transition state. Similarly the β -value has been employed in this way. Allowing for kinetic ambiguities the qualitative knowledge of charge change can be derived simply from the rate law. Thus in the reaction of hydroxide ion with ethyl benzoates (20)

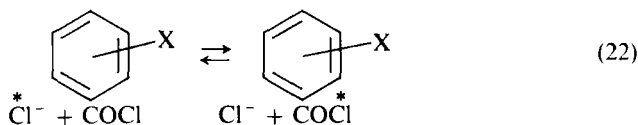
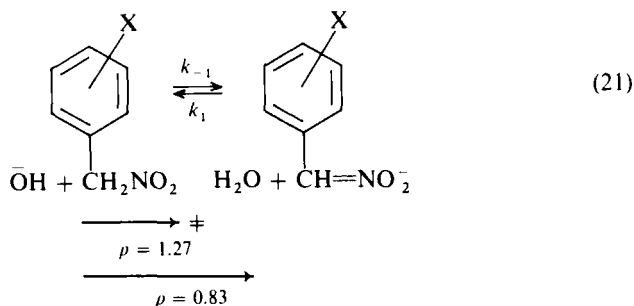


knowledge of the ρ -value (+2.5) is not required to indicate that negative charge builds up on the ester. The next important parameter—how much charge is developed—is not available from a simple consideration of ρ . It is true to say that experience tells us that a ρ -value of +2.5 results from a "large" build up of negative charge; this experience is the result of measurements of ρ -values where the transition state structure is known from other methods.

The parameters ρ , ρ^* , β and the like tend to have particular ranges of values for individual reactions and can be used in a qualitative manner. For example, nucleophilic attack of hydroxide ion on aryl esters has a ρ -value in the region of +1.1, whereas the reaction involving an elimination-addition mechanism (reaction of hydroxide ion with aryl acetoacetates) has a much higher ρ -value in the region of +3. Simple inspection of the meaning of σ (the ionization constant for benzoic acids) indicates that it represents the fission of the O—H bond coupled with a shift of charge due to delocalization on to two oxygen atoms. It is difficult to envisage a direct relationship of this standard equilibrium with many reactions, even of carboxylic acid derivatives; the Brønsted-type relationship is relatively direct even when different atoms are involved in standard and calibrating equilibria. Unless there is a fairly large body of comparable ρ -values, the "raw" ρ -value is comparatively useless as an indicator of transition-state structure.

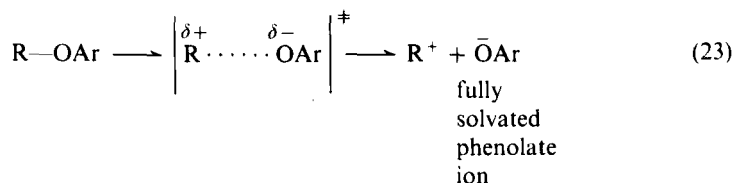
ANOMALIES

In some cases, (21) and (22), Leffler's α can take values much greater than unity, which would normally be expected as a maximum (Bordwell and

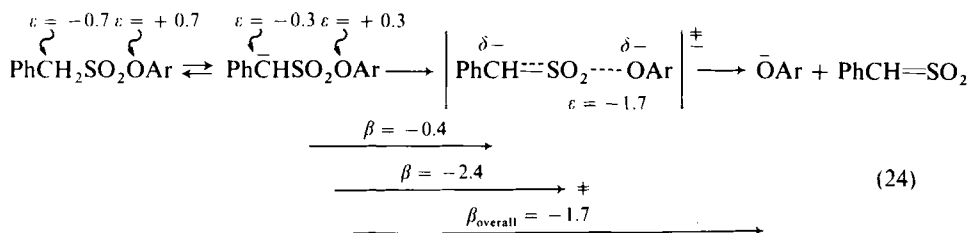


Boyle, 1971, 1972; Bordwell *et al.*, 1969; Pross, 1983, 1984). In both the above reactions, the kinetic polar effect (i.e. for the forward reaction) is *greater* than the value of the polar effect on the calibrating equilibrium, so that Leffler's ρ is greater than unity. In the latter case (Pross) the value of ρ is infinity! These simple exceptions to the Leffler approach are now realized to be cases where the anomalous behaviour provides *more* information about the mechanism rather than discrediting the polar effect approach. The "anomalies" arise because the substituent "sees" more than one bond change. In the Bordwell example the carbon is more negative in the transition state than in the product state because the charge is not delocalized on to the oxygen of the nitro group at that stage. Pross's example involves a product state identical with the ground state, so that the polar effect on the equilibrium is naturally zero.

Anomalous effects should also arise even if one of the major electronic changes were not a bonding change but were a solvation or hybridization change. A condition could hold where solvation of an atom does not keep in step with the bonding change. A β_{ts} more negative than β_{eq} might occur owing to the weaker solvation in the transition state than in the product state (23). There is some evidence that this phenomenon occurs in the



alkaline hydrolysis of aryl esters of phenylmethanesulphonic acid (24) (Thea *et al.*, 1979). The oxygen is considered to be less solvated in the transition state than in the product, thus leading to a less dispersed charge, which will be more susceptible to substituents than is the more solvated ion (Jencks *et al.*, 1982).



Much of the difficulty experienced with Brønsted anomalies is due to the desire to fit data to crude bonding models of molecules (as written on paper). If the substituent is placed so that it sees only one bonding change, the various β - or ρ -values when calibrated against equilibrium β - or ρ -values yield a figure that represents effective charge. This value is strictly anchored in its definition. It must be remembered that this is a comparison by *state*; we are not providing data on single bonds (as normally represented) but for assemblies of molecules in their solvent.

VARIATION OF TRANSITION-STATE STRUCTURE

Considerable interesting discussion has proceeded and much confusion has been suffered over the past three decades concerning the variation of transition-state structure and free energy correlations. It was felt that substituent variation ought to change the structure of the transition state, and yet in many cases the polar free energy relationships are *linear* over a wide range of reactivity. Moreover, the inverse connection between reactivity and selectivity often does not appear to hold. Considerations leading to the understanding of the problem are often referred to conveniently as the "Bema Hapothle" (Jencks, 1985) to honour a selection of the main protagonists (Bell, Marcus, Hammond, Polanyi, Thornton and Leffler).

The reaction map illustrated in Fig. 4 can be used to explain the effects of energy variation on the electronic structure of transition states in a simple and straightforward manner. The surface of the map may be distorted by changing the energies of the corners; the transition-state location will move to accommodate this change. Suppose the leaving group Lg were varied to

decrease its energy (i.e. the leaving group were to become less basic), then the transition state would be shifted *along* the reaction coordinate towards the reactant's corner and also *perpendicular* to the reaction coordinate towards the bottom right corner. The resultant movement of the transition state (dotted arrow in Fig. 4) would be downward and the bond fission as measured by the abscissa (β_{lg}) need not change significantly owing to compensation of the two movements. The value of β_{lg} could therefore be constant although the electronic structure of the transition state varies; the extent of bond formation in the transition state changes with leaving-group basicity in this scheme. The cross-correlation whereby a substituent affecting one bond changes the nature of the other bond in the transition state of a "two"-bond reaction is diagnosed by the effect of variation of the nucleophile on the substituent effect on the leaving group. A measure of these changes is most conveniently the pK of the nucleophile or leaving group when $d\beta_{nuc}/dpK_{lg} = d\beta_{lg}/dpK_{nuc}$ (Jencks and Jencks, 1977); these equalities have been tested experimentally (Ba-Saif *et al.*, 1989b) for acetyl group transfer reactions. The quantity $d\beta_{nuc}/dpK_{nuc}$ is necessarily very small by virtue of the considerations above, and to this author's knowledge this value has never been measured to an accuracy very much greater than its error and *linear* free energy relationships are observed even over very large ranges of reactivity in some cases (Kemp and Casey, 1973). Ikchoon Lee³ and his coworkers (see, for example, Lee, 1990; Lee *et al.*, 1989a,b) and Jencks (1985; Jencks and Jencks, 1977) have made extensive use of the variation of cross-correlation coefficients in studies of group-transfer reactions where polar effects of substituents attached to entering, leaving and central atoms are deployed.

The substituent effect is thus not a passive observer of charge in "bonding", and the variation in substituent does change the bonding to a greater or lesser extent. The problem is a classical philosophical tenet in that the "observer" must be part of the system in which the "observed" exists since otherwise it could not observe. Methods that do not perturb the chemistry of the system significantly such as isotope effects, stereochemistry or pressure studies have the advantage here.

SOLVENT EFFECTS

Ingold (1969) showed how solvent effects could be employed to glean information about transition-state structure. That solvent influences polar substituent effects is well known; the effective charge is a direct result of

³ See accompanying article in this volume (p. 57).

bonding and solvation, and the problem is to differentiate these. Proton transfer is the only reaction that has been studied extensively in solvents other than water, and even with this reaction there has been little work done on the transition state. Most work compares selectivity in one solvent with that in another, and in order to compare effective charge in different solvents it is necessary to know selectivity for change *between* solvents.

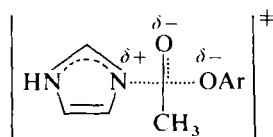
Little systematic work has been reported on the effect of solvent on polar substituent effects, but Stahl and Jencks (1986) have indicated that hydrogen bonding has a small substituent effect (phenolate ion with substituted ammonium ions), and thus small reaction selectivities might indeed include a large component due to solvation. Many anomalies in the interpretation of polar substituent effects may be explained by the different extents of development of bonding and solvation as the reaction proceeds. Bell and Sorensen (1976) and Arora *et al.* (1979) indicate that nucleophilic addition of oxyanions to substituted benzaldehydes involves little solvent reorganization in the transition state for addition compared with that in the product state. Such an imbalance in solvent reorganization and bond change has been noted, for example, in the fission of imidoesters (Gilbert and Jencks, 1979), reaction of arylmethanesulphonate esters (see later, Thea *et al.*, 1979; Davy *et al.*, 1977) and reaction of anions with acetophenones and benzyl halides (Young and Jencks, 1979).

5 Applications

CARBONYL GROUP TRANSFER

Concerted mechanisms

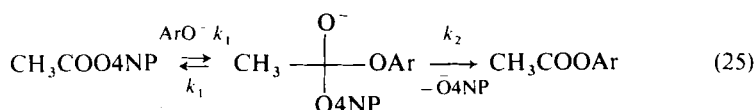
The concept of effective charge was first applied to carbonyl group transfer reactions since these were the first for which β_{eq} was measured. The reaction (7) of imidazole with aryl acetates involves significant bonding change in N—C and ArO—C bonds (Gerstein and Jencks, 1964). Substituent effects on the aryloxy leaving group will measure only the charge change in the ArO—C bond [4], so that, in order to understand the transition-state



[4]

structure fully, we need to have information from the effect of polar substituents on the imidazole function as well; these are not available for this reaction.

When the entering and leaving nucleophiles are of similar type in a concerted reaction, much more information can be obtained from a *single* linear free energy plot. The effect of varying the substituent on aryloxy anion attack on 4-nitrophenyl acetate (18) is illustrated in Fig. 5. There is no observable change in slope over a very wide range of pK_a , indicating that the effective charge on the oxygen of the forming bond is constant. The stepwise mechanism (25) can be excluded since it can be predicted that a break in the



Brønsted line should occur when the pK_a of the attacking nucleophile is equal to that of the leaving group. At this pK_a the observed transition-state changes from k_1 at high pK_a to that of k_2 at low pK_a . The constant slope indicates a single transition-state structure over the whole range of pK_a .

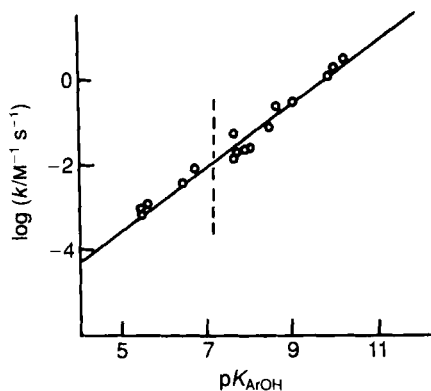
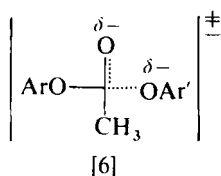
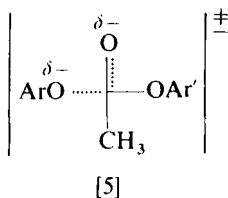


Fig. 5 Reaction of substituted phenolate anions with 4-nitrophenyl acetate in aqueous solution. Data from Ba-Saif *et al.* (1987). Dashed line indicates the predicted breakpoint for a stepwise mechanism.

It is useful to consider errors in detecting a “break”. Clearly the pK_a -values of the experimental data are required to span the pK_a of the leaving group by a significant amount to detect curvature. The theoretical equation governing the data for the stepwise process (25) is given by (26), and the data

$$\frac{k_{\text{nuc}}}{k_0} = \frac{10^{\beta_1 \Delta pK}}{1 + 10^{\Delta pK} 10^{\Delta \beta}} \quad (26)$$

may be fitted to this equation by a grid-search program. The parameter $\Delta\beta = \beta_{-1} - \beta_2$ is essentially the difference in effective charge on the attacking oxygen in the two transition states for the putative stepwise mechanism; the subscripts on the β -values correspond to those of the individual rate constants in (25). The value of $\Delta\beta$ for the reaction in hand has an upper limit governed by the error in its measurement, which in this case is 0.1. This upper limit means that the charge difference between nucleophilic oxygen in the two transition states [5] and [6] is less than 0.1 for the putative stepwise



process. Data from similar experiments on the reaction of substituted pyridines with *N*-acylisoquinolinium ion indicates that this reaction is concerted too (Fig. 6).

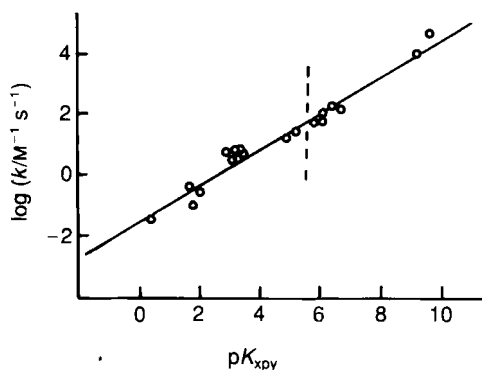


Fig. 6 Reaction of substituted pyridines with *N*-methoxycarbonylisoquinolinium ion in aqueous solution. Data from Chrystiuk and Williams (1987). Dashed line indicates the breakpoint predicted for the stepwise process.

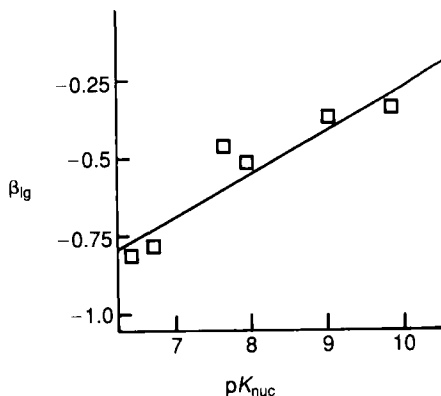


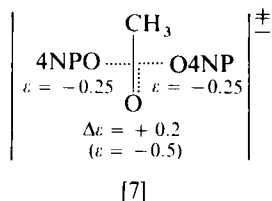
Fig. 7 Dependence of β_{lg} on pK_{nuc} for the reaction of phenolate ions with aryl acetates. Data from Ba-Saif *et al.* (1989b).

Variation of β_{lg} with the pK_a of the nucleophile for attack of phenolate ion on substituted phenyl acetates (Ba-Saif *et al.*, 1989b) is illustrated in Fig. 7; it indicates that the total transition-state structure is not constant and that the invariance in the slope of a single Brønsted plot presumably arises from a cancellation of effects on the bonding being observed as indicated in Fig. 4 and the corresponding text. The observation of a change in β_{lg} with pK_{nuc} indicates that the transition state cannot be on an edge of the reaction map (for example Fig. 4); this is further good evidence for a concerted process because the transition states for the stepwise process would lie on the edges of the diagram and would thus obey Hammond's postulate.

Identity reactions

Identity reactions, where a nucleophile expels an identical leaving group, have been proposed as useful mechanistic tools (Lewis and Kukes, 1979; Lewis and Hu, 1984; Kreevoy and Lee, 1984). If a reaction such as the acyl group transfer discussed above is concerted then the position of the transition state for an identity reaction (Fig. 8) *must* lie on the tightness diagonal [sometimes referred to as the "disparity mode" (Grunwald, 1985)]. In the case of acetyl group transfer between aryloxy anions, the transition states are illustrated by Fig. 8; reaction of 4-nitrophenyl acetate with phenolate ions has a Brønsted slope of 0.75, which must hold when the nucleophile is 4-nitrophenolate ion, whose pK_a is spanned by those of the data. The effective charges on nucleophile and leaving group must be identical in the symmetrical transition state, and are defined on the *same* standard and calibrating equilibria. We are on safe ground in saying that there is an

equivalent charge change on the other part of the transition state (presumably on the carbonyl carbon and oxygen) to balance this to unity [7]. The



effective charge on entering and leaving oxygens of this symmetrical transition state may be determined as described for [3]. The effective charge on the CH_3CO group of atoms in the reactant state is -0.7 to balance the $+0.7$ units on the ether oxygen (Fig. 3); thus a change in effective charge of $+0.2$ means that there are -0.5 units of effective charge on the acetyl group in the transition state. Moreover, the change in β_{lg} as a function of the $\text{p}K_{\text{nuc}}$ in this system means that the position of the transition state of the identity reaction in the reaction map moves along the tightness diagonal towards the acylium ion corner as the nucleophile becomes less basic. This is because the state containing the acylium ion is stabilized by weakly basic anions.

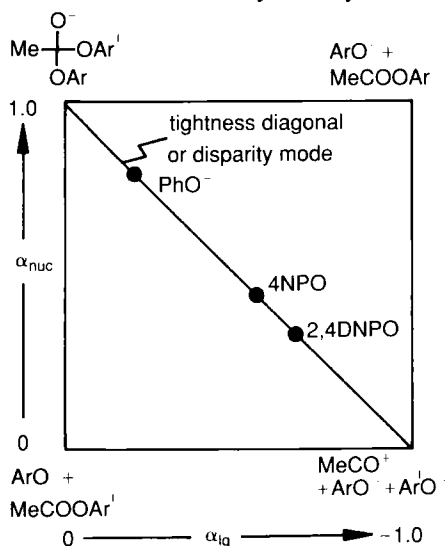
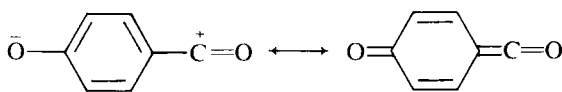
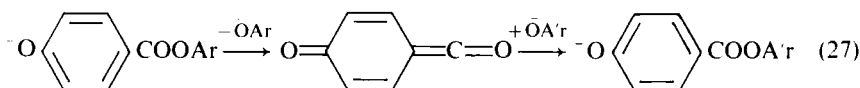


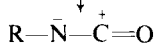
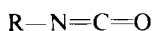
Fig. 8 Variation of transition-state structure for identity reactions of aryloxy ions with aryl acetates. The value of a_{lg} takes a negative sign because it is for bond fission; the simple equation $a_{\text{nuc}} = 1 - a_{\text{lg}}$ enables either leaving group or nucleophile variation to place the transition state of the identity reaction on the diagonal. See text for the meaning of a . The point for phenoxide is obtained from a_{lg} , and the other points are from a_{nuc} . Data from Ba-Saif *et al.* (1987, 1989b) and Waring and Williams (1990).

Leffler's a will give the position of the symmetrical transition state (on the tightness diagonal) if the sides of the reaction map are defined as $\beta_{\text{nuc}}/\beta_{\text{eq}}$ and $\beta_{\text{lg}}/\beta_{\text{eq}}$ ($a_{\text{formation}}$ and a_{fission} respectively). Kreevoy and Lee (1984) defined the tightness parameter τ as a measure of the overall bonding in the transition state of a concerted symmetrical reaction where only bond formation and fission are considered. If the term δ is defined as $d \log k_{\text{ii}}/d \log K_{\text{i}}$ then $\tau = \delta + 1$. The rate constant k_{ii} is for the identity reaction (see above) and K_{i} is the equilibrium constant for the reaction with a standard leaving group and a varying nucleophile. Simple transposition indicates that $\delta = (d \log k_{\text{ii}}/dpK_{\text{a}}) \times dpK_{\text{a}}/d \log K_{\text{i}} = \beta_{\text{ii}}/\beta_{\text{eq}}$. The parameter pK_{a} is for the ionization of the standard acid such as substituted phenol. It is well known that $\beta_{\text{eq}} = \beta_{\text{nuc}} - \beta_{\text{lg}}$ (see, for example, Thea and Williams, 1986) and that $\beta_{\text{ii}} = \beta_{\text{nuc}} + \beta_{\text{lg}}$ (Lewis and Hu, 1984); simple algebra leads to the equalities $\tau = 2a$ and $\delta = 2a - 1$, where $a = \beta_{\text{nuc}}/\beta_{\text{eq}}$ is the Leffler parameter.

Weak nucleophiles such as 2,4-dinitrophenolate ion, which are sufficiently reactive to study kinetics, are not stable enough to force the transition state of acetyl group transfer to move down the tightness diagonal to become "acylium-like." Stabilization of the putative acylium ion itself should help to move the position of the transition state into the bottom right corner of Fig. 8. Aryl benzoates with a 4-oxyanion substituent react exclusively through the *p*-oxoketene intermediate because of the stability of the acylium ion (27) caused by interactions from the 4-oxo group [8] (Thea *et al.*, 1985,



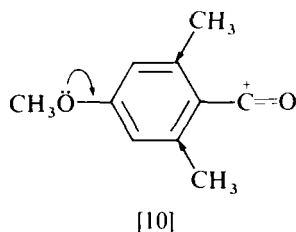
[8]



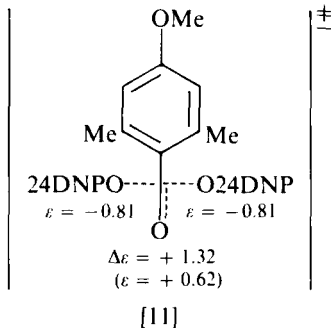
[9]

1982; Cevasco *et al.*, 1985). Aryl carbamate anions react through the isocyanate intermediate [9] for similar reasons (Williams, 1972, 1973; Williams and Douglas, 1975). In effect, the stabilization of the above acylium

ions has gone too far. The aryl esters of the simple acid 4-methoxy-2,6-dimethylbenzoic acid should give an acylium ion [10] stabilized by inductive



and resonance effects but not, as in the above examples, strongly stabilized by a direct anionic interaction. The reaction of aryloxy anions with 2,4-dinitrophenyl 4-methoxy-2,6-dimethylbenzoate has a Brønsted slope of 0.19, which would place the transition state of the symmetrical reaction 5% of the way along the tightness diagonal from the acylium ion state (Waring and Williams, 1990). The effective charge distribution in the transition state is as shown in [11], and this illustrates the power and simplicity of studying symmetrical reactions.



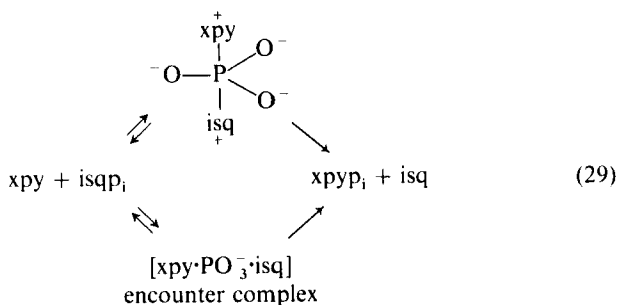
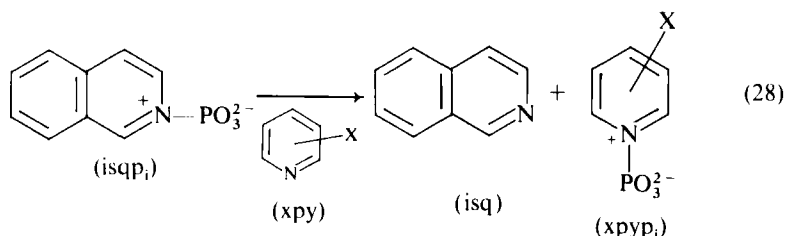
TRANSFER OF PHOSPHORUS ACYL (PHOSPHYL) GROUPS

General

Transfer reactions involving the phosphorus acyl group have been studied intensively over the past 30 or so years because of their central position in biological systems and in chemistry. Readers could refer to a recent clear review containing much more general information than is warranted here (Thatcher and Kluger, 1989).

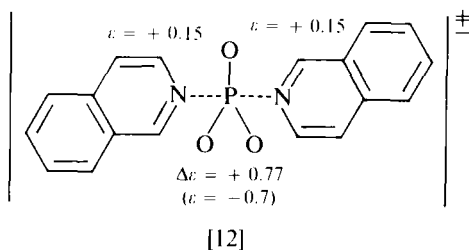
Phosphoryl group ($-PO_3^{2-}$)

Considerable effort has shown that there is no evidence for the existence of the metaphosphate ion as an intermediate in transfer reactions of the phosphoryl group in aqueous solution (Herschlag and Jencks, 1986, 1989). The situation could be different in solvents less polar than water (Freeman *et al.*, 1987; Friedman *et al.*, 1988; Cullis and Nicholls, 1987; Cullis and Rous, 1985), and metaphosphate species have certainly been observed in the gas phase (Westheimer, 1981; Harvan *et al.*, 1979; Keesee and Castleman, 1989; Henchman *et al.*, 1985). The attack of pyridines on phosphopyridines has been studied by two groups (Bourne and Williams, 1984b; Skoog and Jencks, 1984) and the linearity of the Brønsted plot for reaction (28) with isoquinoline phosphate over a range of pK_a -values well above and below that of isoquinoline indicates that neither of the two mechanisms (29)



involving intermediates is operating. A third stepwise mechanism involving free PO_3^- is excluded by the rate law and the dissociative mechanism proposed (29) involves a preassociation ternary complex, which acts as the intermediate. The simplest explanation of the linear Brønsted plot is that there is a concerted mechanism, and application of the “identity” approach indicates that the transition state of the symmetrical reaction is very close to

the structure of the bottom right corner of the reaction map (Fig. 4), with an effective charge distribution of +0.15 units on pyridine nitrogen and a depletion of +0.77 units on the phosphoryl oxygens respectively [12].



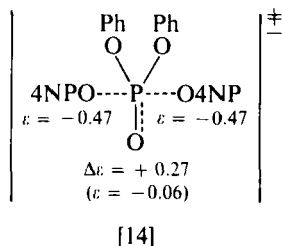
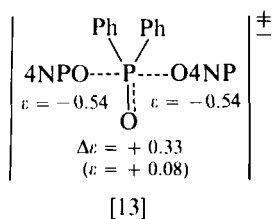
The stereochemistry of the phospho-transfer reaction should be fairly straightforward, unlike that of transfer of the carbonyl group, and should remain trigonal bipyramidal all the way along the tightness diagonal.

Attack of amines on phosphopyridines exhibits *negative* Brønsted selectivity, consistent with dominant solvation effect in this reaction (Jencks *et al.*, 1986).

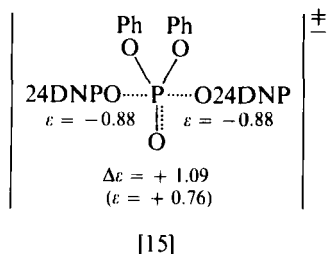
Transfer of the neutral phosphoryl group

Arguments have raged over the past two decades about concertedness in phosphoryl group transfer. The ability to synthesize stable pentaphosphoranes seemed at one stage to sway evidence in favour of the stepwise process, and many reactions have been discussed in terms of pentacoordinate intermediates (Hall and Inch, 1980). The observations that concerted mechanisms with open transition states exist for phosphodianion group transfer in water (Skoog and Jencks, 1984; Bourne and Williams, 1984b) forced the reconsideration of the possibility of concerted processes for other phosphyl group transfer reactions.

A linear Brønsted dependence has been observed for attack of phenolate ions on 4-nitrophenyl diphenylphosphinate (10) over a pK_a -range of the phenolate species where a change in rate-limiting step should manifest itself if the reaction were stepwise. The mechanism should thus be concerted, and the imbalance of charge in the transition state for the identity reaction of the 4-nitrophenyl ester (Leffler's $\alpha_{\text{formation}}$ is less than 0.5) indicates that there is some phosphylum ion character [13] in the Ph_2PO group of atoms. Similar results have been obtained for the reaction of substituted phenolate ions with 4-nitrophenyl diphenylphosphate in aqueous solution, and in the case of the symmetrical reaction the effective charge map is as shown by [14].



Studies of the attack of phenolate ions on both carbonyl (Ba-Saif *et al.*, 1989b) and phosphyl (Bourne *et al.*, 1988; Ba-Saif *et al.*, 1990) centres have indicated that β_{nuc} varies according to the $\text{p}K_{\text{a}}$ of the leaving group and that β_{lg} varies with the $\text{p}K_{\text{a}}$ of the nucleophile. In the case of diphenyl phosphates, Fig. 4 illustrates how β_{nuc} could be constant for a single leaving group although the overall structure of the transition state varies. Decreasing the basicity of the leaving group and nucleophile should therefore force the concerted transition state for diphenylphosphoryl group transfer towards the phosphorylium ion corner ($\{\text{A}^+ + \text{L}^- + \text{Nu}^-\}$). Recent work from this laboratory (Waring and Williams, 1989) has shown that the identity reaction of 2,4-dinitrophenolate ion with 2,4-dinitrophenyl diphenylphosphate has a transition state that lies on the tightness diagonal very close to the bottom right corner [15]. The value of β_{nuc} for attack of phenolate ions on the ester is



0.12, and this combined with β_{eq} of 1.33 gives a Leffler parameter of 0.09. Such an “open” transition state is compared with the corresponding phosphoryl dianion transfer, where stabilization is obtained by the effect of the internal oxygen nucleophiles. For all reactions where β is very small we must

consider that solvation plays a large role in its value because this is close to the β -values usually obtained for hydrogen bonding (Stahl and Jencks, 1986).

Values of identity rate constants can be obtained from the Brønsted plots; if these are plotted against the pK_a of the nucleophile, a non-linear plot is obtained (Fig. 9). Such plots are a useful way of demonstrating that the transition-state structure does alter with that of the nucleophile. A transition state with full bond formation and no fission will have $\delta = \beta_{ii}/\beta_{eq} = +1$ because the nucleophile will *lose* one calibrated unit of *negative* charge. A transition state with no bond formation and complete bond fission ("exploded") will have $\delta = -1$ because the leaving group *gains* one calibrated unit of *negative* charge from ground to transition state. The transition state where the calibrated effective charges on entering and leaving groups are balanced has $\beta_{ii} = 0$ (Kreevoy and Lee, 1984).

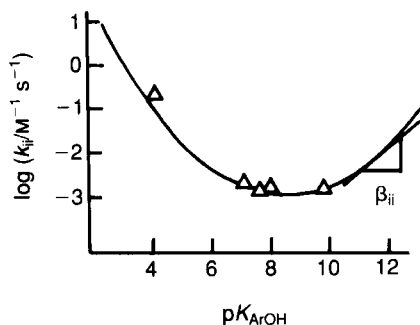
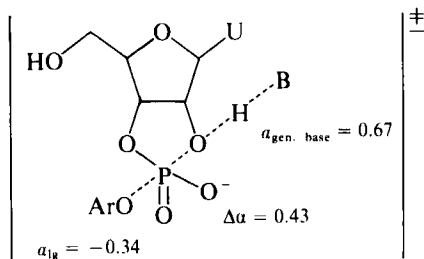


Fig. 9 Dependence of the identity rate constant on the pK_a of entering and leaving phenol for reaction of substituted phenolate ions with substituted phenyl diphenyl-phosphates in aqueous solution. The line is theoretical, obtained from the variation of β_{ii} with pK_a of the nucleophile. The slope β_{ii} is illustrated at a given pK . Data from Ba-Saif *et al.* (1990) and Waring and Williams (1989).

TRANSFER OF THE PHOSPHODIESTER MONOANION

Phosphodiester are of the greatest biological significance; they are extremely important in genetic processing since they are constituents of DNA and RNA coding material and they pervade most areas of biological activity. Transfer reactions of phosphyl groups at this level of oxidation, ionization and substitution are thus important in the formation and breakdown of these important materials. Since transfer of phosphyl groups in neutral and dianionic forms is known to be concerted in aqueous solution,

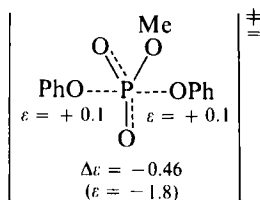
we propose that a similar mechanism holds for diester monoanion reactions. A detailed effective charge map has been elucidated for the cyclization of a uridine-3'-phosphate [16] (Davis *et al.*, 1988a) on the basis of this assumption. The map is obtained from the Brønsted β -values for variation of the



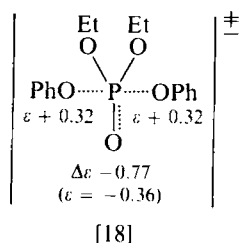
[16]

pK_a of the base **B** in reaction with the 4-nitrophenyl ester and for variation of the aryl leaving group for imidazole acting as base; the imbalance of changes in effective charge has little meaning in this case because the two bonding changes are not similar and must therefore be calibrated by different equilibria. This problem of comparison can be overcome by using the normalized effective charge change denoted by the Leffler α . Imbalance of the Leffler α -values of 0.43 indicates a build up of negative charge on the central $-\text{PO}_3^-$ group of atoms resulting from bond formation being more advanced than bond fission; the data do not distinguish where most of this charge resides (it could reside on the attacking oxygen, on the phosphoryl oxygens or it could be delocalized).

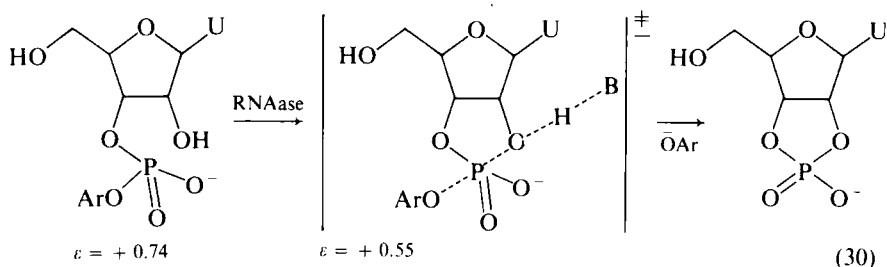
Rates of intermolecular nucleophilic displacement have been measured for the symmetrical reactions of phenoxide ions with substituted phenyl methyl phosphates (Ba-Saif *et al.*, 1989a); the analogous reaction with the neutral ester (aryl diethylphosphate) was also studied. The electronic structures of the transition states on the tightness diagonal for the identity displacement reactions of parent phenolate ion with the anionic and neutral phenyl esters involve a significant component from the pentacoordinate structure ($\alpha = 0.37$ and 0.28 respectively for [17] and [18]).



[17]



Study of the phosphodiester reaction as catalysed by ribonuclease appears to indicate a reduction in the charge change on the leaving oxygen in the transition state at the active site (Davis *et al.*, 1988b). The effective charge map is illustrated in (30) and the explanation of the smaller change in effective charge compared with that in model reactions [17] and [18] is that electrophilic interactions occur either at the phosphoryl oxygens or directly at the developing negative charge on the leaving oxygen atom.



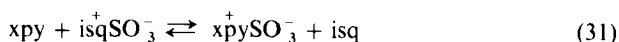
TRANSFER OF SULPHUR ACYL (SULPHYLY) GROUPS

General

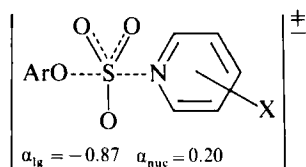
The reader is directed to an excellent general review of this subject given by Kice (1980).

The sulphuryl group ($-\text{SO}_2$)

The electronic structure of the sulphuryl group is analogous to that of the phosphoryl group, and it readily undergoes similar reactions. Transfer between pyridine nucleophiles has been studied, and the Brønsted dependence is linear for attack of substituted pyridines on isoquinoline sulphate (31) for $\text{p}K_a$ -values of the pyridines well above and below that of isoquino-



line (Hopkins *et al.*, 1985). Rate constants are slightly lower than those for the corresponding phosphoryl group transfer reaction. The electronic structure of the transition state [3] indicates considerable charge release from the $-\text{SO}_3^-$ group for the identity transfer between isoquinolines. The value of α is 0.21/1.25, consistent with a transition state very close to the bottom right corner of the reaction map (Fig. 4). Transfer of the sulphuryl group between phenolate ions and pyridines [19] is assumed reasonably to involve a concerted process (Hopkins *et al.*, 1983). The effective charge for each bond is calibrated by a different reaction type, and the balance must therefore be considered by use of the Leffler α approach. Bond formation between O and S has a Leffler α of 0.13 and bond fission has $\alpha = 0.80$; thus there is an imbalance of 0.67 [19] to be met by the negative charge on the sulphuryl

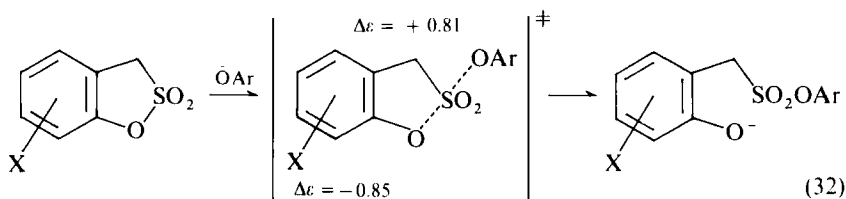


[19]

group. The situation can be illustrated by a reaction map (such as that in Fig. 4) where the transition state will be slightly off the tightness diagonal.

Transfer of the sulphonyl group

Reaction of aryloxide ions with the sultone in (32) has been measured in



both directions (Deacon *et al.*, 1978); values of β were determined for variation in substituents on the attacking group and the leaving group. The β -values for the calibrating bond changes for formation and fission were found to be the same within experimental error. The value of β_{nuc} for aryloxide ion attack was measured for the 4-nitrophenyl ester, and β_{lg} for variation of the substituent in the sultone was for attack by unsubstituted phenolate ion. The position of the transition state on the tightness diagonal for a putative concerted mechanism is $\alpha = 0.45$ for the 4-nitrophenolate

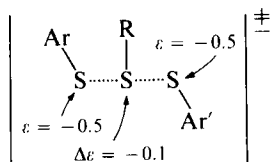
group entering and leaving, and 0.5 for the phenolate ion group entering and leaving. Thus the putative concerted process would be almost synchronous for nucleophiles and leaving groups with pK_a 7–10.

Evidence for concerted sulphonyl group transfer comes from studies on the reaction of oxyanions with 4-nitrophenyl 4-nitrobenzenesulphonate, where the Brønsted dependence of rate constant on the pK_a of the attacking oxyanion is linear over the range where a stepwise process predicts a break (D'Rozario *et al.*, 1984).

Reactions of sulphonate esters that possess α -carbon atoms bearing a proton often involve mechanisms with sulphene intermediates (Kice, 1980). In the case of substituted aryl phenylmethanesulphonate esters, the hydrolysis in alkali possesses a very high β_{lg} (–2.4), and trapping experiments indicate the participation of a sulphene (24). The effect of substituents on the ionization of the “ α -proton” is 0.4, which means that there are about 0.3 units of positive effective charge on the leaving oxygen in the ground-state carbanion (Davy *et al.*, 1977; Thea *et al.*, 1979). The oxygen of the leaving group is thus more “negative” than it is in the final product phenolate ion. This anomalous situation can only arise if the solvation change is not in synchrony with the bond-fission reaction. It is possible that, if the solvation change lags behind bond fission, the phenolate ion could form in a microscopic medium with less solvating power than that in the product state. Thus in the present example there is an excess negative charge of 0.7 on the phenolate oxygen in the transition state.

Sulphenyl group transfer

Attack of arylthiophenolate ions on aryl disulphides in aqueous solution has been studied carefully, and the absence of a break in the Brønsted line at the predicted value of the pK_a of the nucleophile indicates a concerted process. The effective charge map is shown in [20], and the relatively small

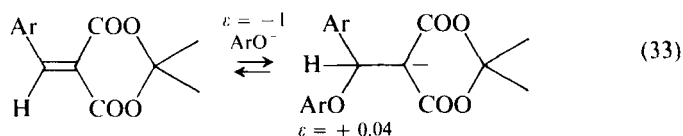


[20]

imbalance of charge on the central sulphur indicates an almost synchronous mechanism (Hupe and Wu, 1980; Frater *et al.*, 1979; Wilson *et al.*, 1977). The overall change in charge on the attacking arylthiolate sulphur atom compared with that for equilibrium is +0.9 (Fig. 10), indicating that the sulphenyl group closely resembles an alkyl group and hydrogen in its ability to induce charge on a neighbouring acceptor nucleophile.

TRANSFER OF ALKYL GROUPS BETWEEN NUCLEOPHILES

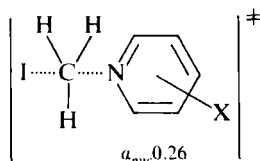
Nucleophilic aliphatic substitution and ether or acetal hydrolysis play important roles in biochemistry and chemistry. While there are many examples where substituent effects have been measured for attack of nucleophilic oxygen at carbon, most were not calibrated by the substituent effects on the corresponding equilibria. The measurement of β_{eq} appears to be much more difficult for these reactions than for the acyl group transfer reactions previously discussed. Bernasconi and Leonarduzzi (1982) were able to determine the equilibrium and rate constants for the reaction of aryloxide ions with the benzylidene derivation of Meldrum's acid (33). The value of β_{eq}



(1.04) indicates that there are +0.04 units of positive effective charge on the ether oxygen in the product. Protonation of the carbanion (33) should increase the positive charge on the oxygen; we do not possess the experimental polar effect of substituents in the aryl function on the protonation of the carbanion, but this may be estimated to be 0.16 from the β -value for the ionization of phenol and an attenuation factor of 0.4 per atom. The transfer of a neutral alkyl function between phenolate ions should thus have a β_{eq} of *ca* 1.2, and the alkyl group is thus slightly more electropositive than is the hydrogen.

Fig. 10 collects data on effective charges for transfer between nucleophiles of various groups related to the alkyl function.

It is important to note that β_{eq} -values are solvent-dependent, and if they are to be used in calibrating kinetic β -values then it is necessary to use data for similar solvents. For example, it is unlikely that methyl has a different electropositivity from that of a general alkyl group, and the difference observed is undoubtedly due to the change in solvent. Transfer of methyl between pyridines in acetonitrile solvent has been studied by Arnett and Reich (1980); it is unlikely that the effective charge of +1.47 [21] can be used



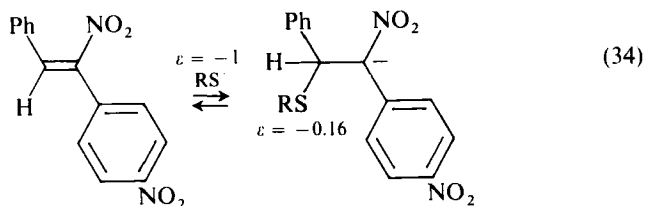
[21]

Group transferred	Acceptor	Product
CH ₃ —	$\bar{\text{S}}\text{Ar}$	$\text{CH}_3\text{—S—Ar}$ (+ 0.3) ^a
CH ₃ —		$\text{CH}_3\text{—N} \langle \text{pyridine ring} \rangle \text{X}$ (+ 1.47) ^c
CH ₃ —	$\bar{\text{Se}}\text{Ar}$	$\text{CH}_3\text{—Se—Ar}$ (+ 0.3) ^a
R—	$\bar{\text{S}}\text{Ar}$	R—S—Ar (− 0.16) ^g
R—	$\bar{\text{O}}\text{Ar}$	R—O—Ar (+ 0.2 and + 0.04) ^d
R—	NHR_2	R—NHR_2 (+ 0.86 → + 1) ^h
Ar ₃ C—	NH_2R	$\text{Ar}_3\text{C—NH}_2\text{R}$ (+ 0.59) ^c
RS—	$\bar{\text{S}}\text{AR}$	RS—SAr (− 0.1) ^f

Fig. 10 Effective charges on acceptor atoms for a range of groups transferred between basic donors and acceptors. Notes: ^a data from Lewis *et al.* (1987) for 90°C in sulpholane solvent; the effective charge is measured against the ionization of phenols in water at 25°C standard; ^b from two-point Brønsted plots for piperidine and morpholine with a number of R-groups at 20°C for 50% Me₂SO/water and water solvents (Bernasconi and Panda, 1987; Bernasconi and Killion, 1989; Bernasconi and Renfrow, 1987); ^c for acetonitrile solvent at 25°C against the standard ionization of pyridinium ions in water (Arnett and Reich, 1980); ^d data from Bernasconi and Leonarduzzi (1982); the value of the effective charge on the aryl ether oxygen of the first formed carbanion is +0.04, and is +0.2 for the neutral ether, assuming a reasonable value for the protonation step; ^e the Ar₃C group is the malachite green cation; data from Dixon and Bruice (1971); ^f data from Hupe and Wu (1980), Frater *et al.* (1979) and Wilson *et al.* (1977); ^g data from Bernasconi and Killion (1988) for addition to α-nitrostilbene in 50% Me₂SO/water at 20°C; the value −0.16 refers to formation of the carbanion PhCH(SR)—C(NO₂)Ph; the value of zero is estimated for the neutral species; ^h data from Lewis and Kukes (1979) for 95% EtOH/water at 150°C using the ionization of ArSH in the same solvent at 25°C as standard.

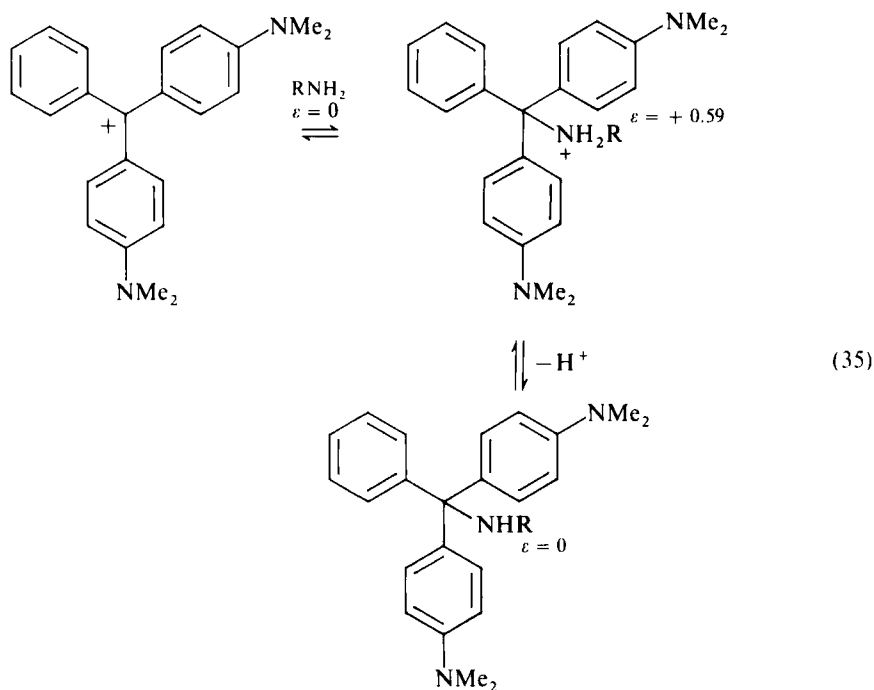
for alkyl group transfer in other solvents. Nevertheless the internal calibration gives a Leffler α -value indicating that the transition state for bond formation in nucleophilic attack is some 0.26 of the way between ground and product states for acetonitrile solvent.

The value of β_{eq} for addition of thiolate ions to nitrostilbene (34) is 0.84

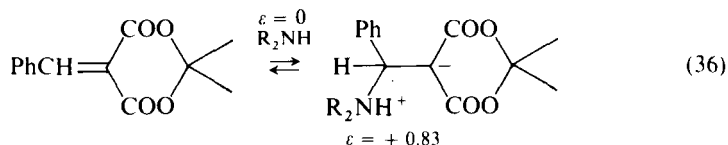


(Bernasconi and Killion, 1988). Combined with a calculated β of 0.16 for protonation of the carbanion, the data give an overall β_{eq} for formation of the neutral thioether of 1.0. This value is for 50% dimethyl sulphoxide/water and compares well with the value (1.13) for addition of thiolate ions to an acrylonitrile derivative (Fishbein and Jencks, 1988).

Transfer of an alkyl group between amines has been investigated (Dixon and Bruce, 1971; Bernasconi and Panda, 1987); interpretation of the data indicates that for the triphenylmethyl species (35) β_{nuc} is 0.52 and thus bond



formation is almost complete in the transition state for attack of RNH_2 on malachite green. The value of 0.59 for β_{eq} would indicate considerable neutralization of charge in the protonated adduct compared with that in the standard equilibrium involving protonation of RNH_2 . Bernasconi showed that for addition of amines to an olefin (36) the formation of the carbanion



has a β_{eq} of 0.83; assuming a value for β of 0.16 for the protonation, an overall β_{eq} of about 1.0 may be calculated for the formation of the cationic species (36). Addition reactions to the olefins studied by Bernasconi's group give considerable scope for imbalance since the pair of electrons from the nucleophile can be readily delocalized. Bernasconi's laboratory (Bernasconi, 1987) has indeed shown that this is the case, and imbalance is the subject of a related review in this volume (p. 119).

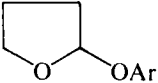
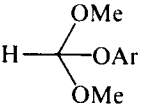
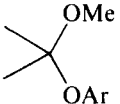
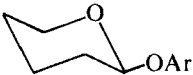
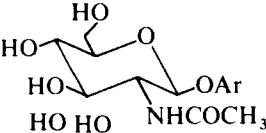
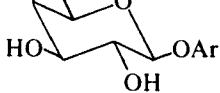
ACETAL, KETAL AND ORTHOESTER HYDROLYSES

As yet there have been no useful estimates of β_{eq} for the transfer reactions of these species. It is possible that β_{eq} will be more positive than that for transfer of simple alkyl groups because of the extra oxygens attached to the central carbon in these special ethers; Fig. 11 collects some data for the hydrolysis of aryl ketals, acetals and orthoesters. Assuming a value of *ca* 1.2 for β_{eq} for the transfer of a general alkyl group, the neutral hydrolysis of most of these ethers has a Leffler α -value that indicates considerable fission of the $\text{ArO}-\text{C}$ bond in the transition state. It is likely that some of these reactions could involve bond fission advanced over solvation in the transition state. These data are in agreement with the evidence from isotope-effect studies that the transition state has substantial carbonium ion character (Cordes and Bull, 1974; Bennet and Sinnott, 1986; Craze *et al.*, 1978; do Amaral *et al.*, 1979; Ferraz and Cordes, 1979). It should be noted, however, that the data refer only to the bond undergoing fission; the state of bond formation is *not* monitored by the substituent effects shown in Fig. 11.

SUBSTITUENTS INTERACTING WITH TWO BOND CHANGES

When a polar substituent is linked with an atom that is involved in both bond formation and fission, it is very difficult to disentangle the effects of

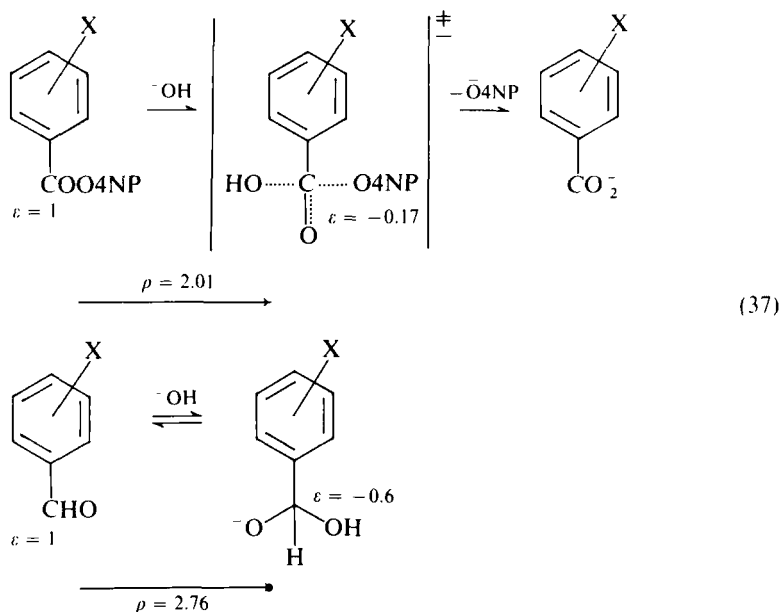
both interactions. The polar substituent effect can of course provide a measure of the change in charge at that atom, and this will give useful data concerning charge balance in the mechanism.

Ether	β_{lg}	α_{lg}
	-1.08 ^a	-0.9
	-1.21 ^b	-1.01
	-1.42 ^c	-1.18
	-1.18, ^d -1.12 ^e	-0.98, -0.93
	-1.02 ^f	-0.85
	-0.39 ^g	-0.33

(k_{cat}/K_m)

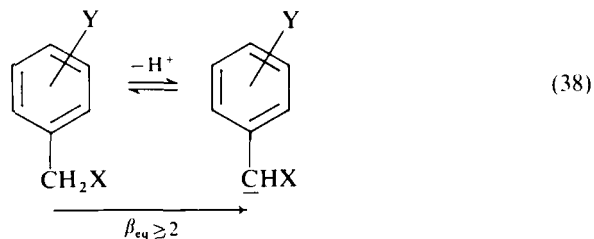
Fig. 11 Values of β_{lg} for neutral hydrolysis of aryl acetals, ketals and orthoesters in aqueous solution. Values of α_{lg} are calculated on the basis of $\beta_{eq} = 1.2$. Notes: ^a Lonnberg and Pohjola (1976); ^b Lahti (1987); ^c Lahti and Kovero (1988); ^d Craze and Kirby (1978); ^e Dyferman and Lindberg (1950); ^f Dunn and Bruice (1973); ^g Burton and Sinnott (1983).

Consider the example of attack of hydroxide ion on substituted 4-nitrophenyl benzoates (37). Since studies on similar reactions indicate the reaction to be concerted, the charge estimated at the central carbon atom will give us a good idea of the balance in the mechanism. The reaction cannot be synchronous owing to its asymmetrical nature. This is confirmed by the observation of a positive ρ -value (+2.01) consistent with a build up of negative charge. The value of ρ (Kirsch *et al.*, 1968) may be calibrated by



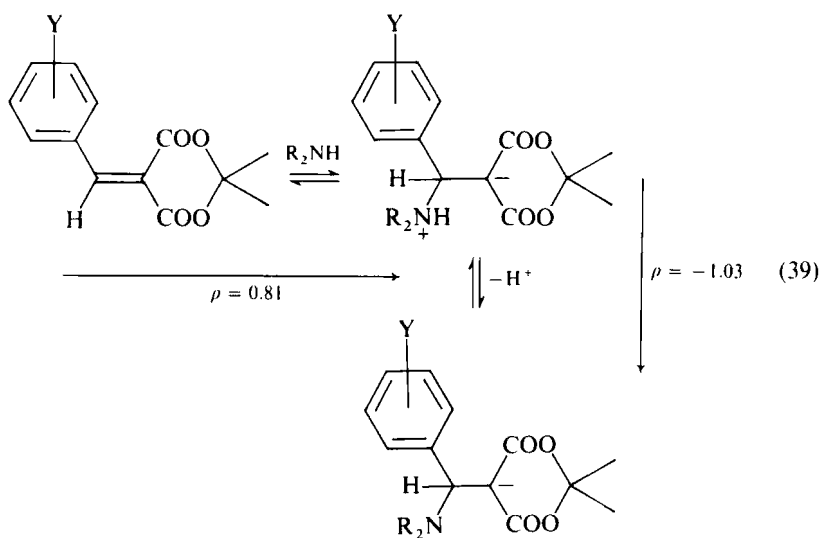
that (2.76) for the simple addition of hydroxide ion to substituted benzaldehydes (Bover and Zuman, 1973), which indicates that the transition state will lie close to the tetrahedral intermediate structure. The lower value of ρ compared with ρ_{eq} is ambiguous since it could arise from (a) smaller bond formation between nucleophile and carbon, (b) enhanced bond fission between leaving group and carbon, or (c) a combination of both effects. The effective charges, based on the standard for hydration of substituted benzaldehydes (see Fig. 13) and assuming effective charge on the ester carbon is +1, are given in (37).

The quantitative analysis of the substituent effect on the ionization of nitroalkanes (21) requires a suitable *calibrating* equilibrium, which could reasonably be the ionization of a carbon acid (38). The calibrating equilibrium must be chosen with care because charge needs to be localized as much as possible on the central carbon (38); even if one is reasonably sure that this

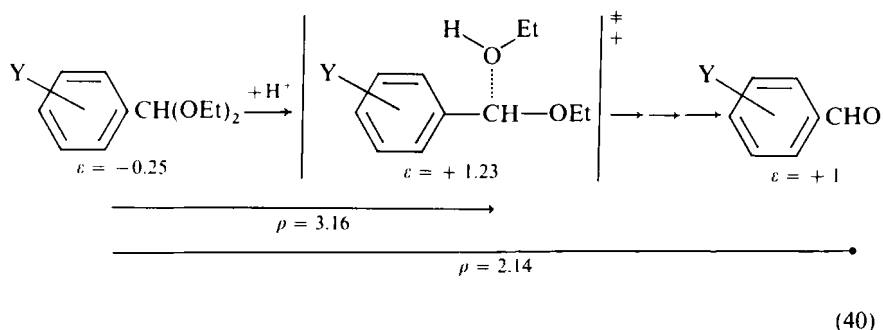


is so, the charge calibration must still resort to defining (38) as involving unit charge change on the carbon.

The overall equilibrium constant for semicarbazone formation has $\rho_{\text{eq}} = 1.81$, which, when compared with the effect on the standard equilibrium, gives an effective charge of -0.06 on the central carbon atom in the neutral carbinolamine (Fig. 12). The standard equilibrium (Fig. 13) is defined as having unit positive charge on the carbonyl carbon atom and zero charge on the carbon in the hydrated form. Fig. 13 collects data on effective charges for a selection of bond-saturation equilibria. Although there is no formal integral change in charge on the carbon, there is undoubtedly a change in dipole moment, and in any case we have already explained why there is no integral charge even with ionization reactions where there is a *formal* integral change. Bernasconi and Killion (1989) have reported work on attack of amine on olefins (39) where the substituent affects both the forming bond and rehybridization.



Substituent effects on the acid-catalysed hydrolysis of acetals, ketals and orthoacids have been extensively measured where the substituent could interact with breaking and forming bonds. Fig. 14 collects some data for the rate parameters of a number of such reactions. The quantitative interpretation of the kinetic ρ -values is complicated by the possibility of imbalance. Allowing for variation in solvent for the data in Fig. 14, the calibration equilibrium for acetal hydrolysis (40) has a ρ_{eq} -value (-2.14) less negative



(Davies *et al.*, 1975) than the kinetic ρ for acid-catalysed hydrolysis, -3.16 (Jensen *et al.*, 1979). This indicates that the central carbon atom in the controlling transition state is more positive than that in the aldehyde product; thus there is more C—O bond fission compared with bond formation to the attacking water. The extent to which a carbenium ion is formed is not available from the substituent effect data, but there is good evidence that an A1 mechanism occurs (Cordes and Bull, 1974; Fife, 1972; Satchell and Satchell, 1990).

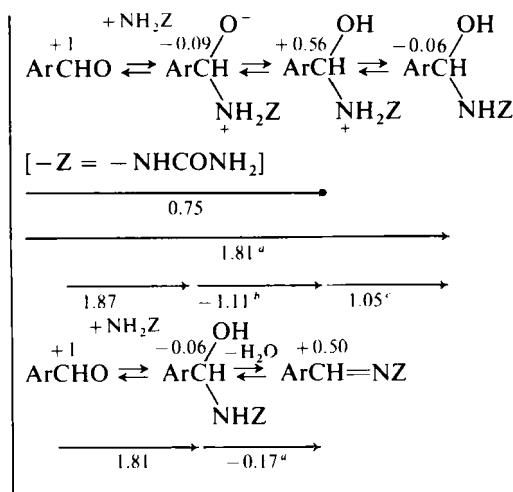
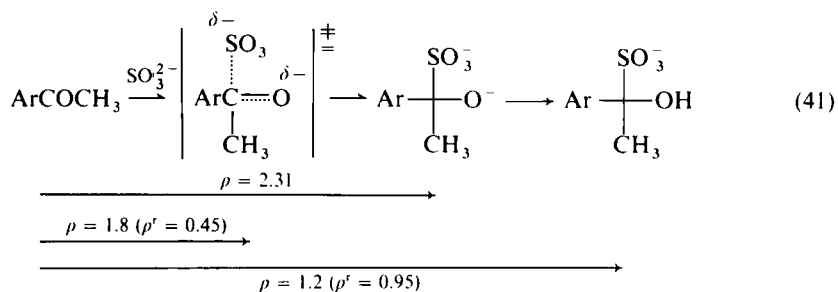


Fig. 12 Reaction of semicarbazide with benzaldehydes in aqueous solution. The effective charge (numbers adjacent to the carbons) is calculated as if it were for the central carbon. The dehydration reaction is not dissected into its component steps. Notes: ^a Anderson and Jencks (1960), Wolfenden and Jencks (1961); ^b estimated ρ -value for benzyl alcohol ionization; ^c Blackwell *et al.* (1964). Values of ρ are adjacent to the large arrows.

Equilibrium		ρ
$\overset{1}{\text{ArCHO}} + \text{H}_2\text{O} \rightleftharpoons \overset{0}{\text{ArCH(OH)}_2}$		1.71 ^a
$\overset{1}{\text{ArCHO}} + \text{OH}^- \rightleftharpoons \overset{-0.6}{\text{ArCH(OH)O}^-}$		2.76 ^f
$\overset{1^b}{\text{ArCOCH}_3} + \text{HSO}_3^- \rightleftharpoons \overset{+0.3}{\text{ArCCH}_3(\text{SO}_3^-)\text{OH}}$		1.2 ^d
$\overset{1}{\text{RCHO}} + \text{HSR}' \rightleftharpoons \overset{+0.02}{\text{RCH(OH)SR}'}$		*1.65 ^c
$\overset{1}{\text{RCHO}} + ^-\text{SR}' \rightleftharpoons \overset{-0.77}{\text{RCH(SR')O}^-}$		*2.97 ^c
$\overset{1}{\text{RCHO}} + \text{H}_2\text{O} \rightleftharpoons \overset{0}{\text{RCH(OH)}_2}$		*1.68 ^{c, e}
$\overset{1}{\text{ArCHO}} + \text{CH}_3\text{OH} \rightleftharpoons \overset{-0.25}{\text{ArCH(OCH}_3)}$		2.14 ^g
$\overset{\text{Ar}}{\underset{\text{CH}_3}{\text{C}}} \overset{+1.86}{\text{=OCH}_3} + \text{CH}_3\text{OH} \rightleftharpoons \overset{-0.25^i}{\text{ArCCH}_3(\text{OCH}_3)_2}$		3.6 ^h

Fig. 13 Polar effects for some bond saturation equilibria. The defined and measured effective charges are appended to the central carbons of the structures and the ρ^* -values are Taft parameters (Williams, 1984a). Notes: ^a McClelland and Coe (1983); ^b charge on the carbonyl carbon is defined as +1; ^c Kanchuger and Byers (1979); Burke and Fahey (1983); ^d Young and Jencks (1979); ^e Greenzaid *et al.* (1967); ^f Bover and Zuman (1973) [a lower negative charge (−0.3) is predicted from the data of Greenzaid (1973)]; ^g Davies *et al.* (1975); ^h Young and Jencks (1977); ⁱ it is assumed that the charge on the carbon of the ketal adduct is the same as that of the acetal adduct; ^j these are the standard equilibria.

The study of substituent effects interacting with both bond formation and breaking is directly pertinent to balance, and a further example is the reaction (41) of sulphite ion with acetophenones (Young and Jencks, 1977). The value of the kinetic ρ (1.8) indicates that there is a greater build up of charge on the central atom than in the monoanionic product, where the ρ_{eq} -value is 1.2. However, the initially formed product is the dianion, which protonates to give the monoanion. The ρ_{eq} for formation of dianion is estimated to be 2.31 by use of the ρ -value estimated for the ionization of the monoanion.



Ether	Hammett ρ
	-3.35 ^a
	-4.0 (H ⁺) ^b -2.0 (CH ₃ CO ₂ H) ^b
ArC(OMe) ₃	-2.02 ^c
	-2.25 ^d
	-2.9 ^e
	2.29 ^f
	-3.35 ^g , -3.16 ^h

Fig. 14 Proton-catalysed hydrolysis of acetals, ketals and orthoesters where the substituent acts on both bond formation and fission. Notes: ^a Fife and Jao (1965); ^b Anderson and Fife (1971); ^c Kwart and Price (1960); ^d Loudon *et al.* (1974); ^e Vitullo *et al.* (1974); ^f Loudon and Berke (1974); ^g Kreevoy and Taft (1955); ^h Jensen *et al.* (1979).

APPLICATION OF EFFECTIVE CHARGE TO COMPLEXATION-PREFACED CATALYSIS

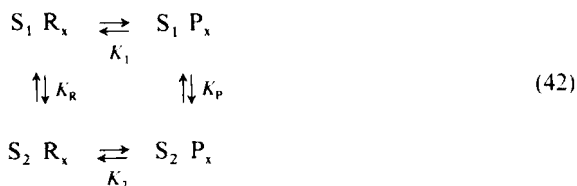
There are many contemporary strands of research in catalysis that involve complexation prior to covalent-bond fission and formation. These include enzyme and micellar catalysis and catalysis by synthetic or semisynthetic supramolecules (Page and Williams, 1987). Knowledge of the development of charge on a substrate atom during catalysis is very important for understanding; its interpretation depends on the charge change in suitable calibration equilibria for the complexation process and also for the process occurring in the complex. These calibrating values are not generally available, but very early studies of the acylation of hydrolytic enzymes by substrates indicated that negative charge development on the leaving group atom is not as pronounced as in simple model reactions in aqueous solvent (see Table 1). This result implies that the active site constituents are in some way neutralizing charge development at the acyl function. The phenomenon appears to be relatively general and applies to the hydrolysis of carboxyl acyl functions as well as of phosphyl acyl derivatives. The origin of the electrophilic neutralization could be interaction through the carbonyl oxygen ($P=O$ in the case of phosphoryl group transfer) or through stabilization of the leaving anionic group.

Table 1 Values of β_{lg} for enzymes catalysing acyl group transfer.

Enzyme	β_{lg}^a	β_{lg}^b	β_{eq}	References
Alkaline phosphatase	-0.19	-1.23	-1.35	Williams and Naylor (1971), Williams <i>et al.</i> (1973), Hall and Williams (1986)
Ribonuclease-A	-0.19	-0.59	-1.74	Davis <i>et al.</i> (1988b)
Chymotrypsin	-0.20	-0.90	-1.7	Williams (1970) ^c
Trypsin	-0.45	-0.90	-1.7	Hawkins and Williams (1976)
Papain	-0.21	-0.90	-1.7	Williams <i>et al.</i> (1972) ^d
Subtilisin	-0.16	-0.90	-1.7	Williams and Woolford (1972) ^e
Bromelain	-0.31	-0.90	-1.7	Hawkins and Williams (1976)

^a The values are for the parameter k_{cat}/K_m , the second-order rate constant for acylation of free enzyme by free substrate. ^b Value for model attack. In the case of the alkaline phosphatase the model is hydrolysis of the phosphodianion; in the case of ribonuclease it is base-catalysed ring formation; for the other hydrolases it is imidazolyl-catalysed hydrolysis of aryl acetates (Bender and Nakamura, 1962). ^c The value is taken for aryl hippurates from this reference; similar values have been obtained by Williams and Salvadori (1971) and Williams and Bender (1971). ^d The value is for aryl mesylglycinate esters; it is -0.35 for aryl hippurates. ^e The value is for aryl hippurates.

In order to calibrate the polar substituent effect on a reaction in a complex or a microscopic phase, it is necessary to know the polar substituent effect on the equilibrium constant within the medium of the reaction (42). This presents a problem that has been addressed, albeit at a tentative stage, for catalysis by micelles.



Let us consider a reaction ($R_x \rightarrow P_x$) with a substituent variation x occurring in media S_1 and S_2 . We take the meaning of "medium" as being completely general so that if S_2 is bulk solvent then S_1 can be complexing agent, an immiscible phase or even the pseudophase of a micelle or vesicle. Comparison of the effective charge on the transition state for a reaction with the change in charge for the equilibrium in a standard solvent is useful; it is better to compare the polar effect on rate constant with that on the equilibrium in the medium in question. Knowledge of the substituent effect on K_1 and K_2 will almost certainly include substituent effects on the partition coefficients K_R and K_P ; indeed it is possible that these coefficients could be used generally to compute K_1 from K_2 if the latter is the equilibrium in the bulk solvent.

Substituent interactions with the solvent are assumed to cancel between reactant and product in bulk solvents provided the substituent is reasonably well removed from the reaction centre. For partitioning between solvents or media, this assumption cannot be made because the medium surrounding the substituent differs between the two "phases". Nevertheless, the substituent will still interact with charge at the remote centre (such as the reaction site) in both "states", and this is recognized in Hansch's (1969) treatment.

Micellar catalysis has recently been studied by the use of effective charge. The catalytic action of CTAB (cetyltrimethylammonium bromide) on phenolysis of aryl laurate esters and hydrolysis of aryl laurate esters possesses β_{nuc} - and β_{lg} -values that, when calibrated by the appropriate β_{eq} -values, indicate a different electronic structure for the transition state of the reactions from that in the bulk solvent (Al-Awadi and Williams, 1990). Although it is recognized that the enhanced reactivity caused by CTAB is due to the bringing together of the reactants, the fact that the reaction occurs in a different medium from the bulk solvent implies that the transition-state structure should be different.

So far as we are aware, there has been little work on polar substituent effects on complexation catalysis. The apparent complete absence of a linear Hammett dependence for the reaction of aryl acetates with β -cyclodextrin indicates that over-riding non-polar forces are involved (Van Etten *et al.*, 1967). Hansch (1978) quantitated the binding effect of cyclophanes in complexation-prefaced catalysis of ester hydrolysis by an attached imidazole. It is important in studies of complexation catalysis that non-polar interactions are allowed for so that the polar effect and hence charge change may be unambiguously determined.

Acknowledgements

Thanks are extended to colleagues both here and abroad for their help in providing data and encouragement. I am especially grateful to Bill Jencks for his leadership in this field and for introducing me to the effective charge approach.

Summary of terms employed in this review that are not in general chemical use

- 1 *Acyl group*: refers to a general acid group A— derived from the acid A—OH (see Williams, 1989)
 - phosphyl*: a general phosphorus acyl group
 - sulphyl*: a general sulphur acid group
 - carbonyl*: refers to the carboxylic acid acyl group
- 2 *Bema Hapothle*: see p. 21
- 3 *Bond order*: the summation of classical bond order and solvation—this term is employed because experimental methods in solution do not distinguish these components
- 4 *Brønsted-type plots and parameters*: these are extensively used in contemporary studies, even in reactions where there is no formal proton transfer
 - β_{lg} , β_{nuc} : Brønsted slopes where leaving group and nucleophile vary respectively
 - pK_{lg} , pK_{nuc} : pK_a of leaving group and nucleophile respectively
 - breakpoint*: point of intersection of two linear relationships on a Brønsted or Hammett plot

- Brønsted anomalies*: see pp. 19–21
 β_{eq} or ρ_{eq} : Brønsted or Hammett slope of a calibrating equilibrium constant
standard equilibrium: ionization equilibrium against which β is measured
- 5 *Concerted, concertedness*: see p. 14
enforced concerted mechanism: see p. 14
synchronous concerted mechanism: see p. 17
balance: see p. 16
 - 6 *Effective charge* ε : see p. 6
 - 7 *Effective charge map*: see p. 13
 - 8 *Kreevoy's parameters*: identity reaction terminology (p. 26) includes
 k_{ii} : rate constant of the identity reaction
 β_{ii} : Brønsted slope of the dependence for k_{ii}
 τ : tightness parameter—see pp. 27–28
 δ : this equals $\beta_{\text{ii}}/\beta_{\text{eq}}$
 $\text{p}K_{\text{i}}$: $\text{p}K_{\text{a}}$ of the ligands in the identity reaction
ligand: this is used to refer collectively to the nucleophile or leaving group in a transfer reaction
tightness diagonal: this line on the reaction map (Fig. 4) represents the structures of all possible transition states of a concerted identity reaction
 - 9 *Leffler's parameters*: these are
 $a = \text{d log } k / \text{d log } K$: see p. 28
 a_{nuc} , a_{lg} : values of a for variation of nucleophile or leaving group respectively
 $a_{\text{formation}}$, a_{fission} : refer to a for formation or fission of a bond respectively
calibrating equilibrium: the equilibrium against which a substituent effect on a rate constant is compared; usually the equilibrium reaction is the same as that measured kinetically

References

- Al-Awadi, N. and Williams, A. (1990). *J. Org. Chem.* **55**, 2001, 4359
 Alborz, M. and Douglas, K. T. (1982). *J. Chem. Soc. Perkin Trans. 2*, 331
 Al-Rawi, H. and Williams, A. (1977). *J. Am. Chem. Soc.* **99**, 2671
 Anderson, E. and Fife, T. H. (1971). *J. Am. Chem. Soc.* **93**, 1791
 Anderson, B. M. and Jencks, W. P. (1960). *J. Am. Chem. Soc.* **82**, 1773

- Arnett, E. M. and Reich, R. (1980) *J. Am. Chem. Soc.* **102**, 5892
- Arora, M., Cox, B. G. and Sorensen, P. E. (1979). *J. Chem. Soc. Perkin Trans. 2*, 103
- Ba-Saif, S. and Williams, A. (1988). *J. Org. Chem.* **53**, 2204
- Ba-Saif, S., Luthra, A. K. and Williams, A. (1987). *J. Am. Chem. Soc.* **109**, 6362
- Ba-Saif, S., Davis, A. M. and Williams, A. (1989a). *J. Org. Chem.* **54**, 5483
- Ba-Saif, S., Luthra, A. K. and Williams, A. (1989b). *J. Am. Chem. Soc.* **111**, 2647
- Ba-Saif, S., Waring, M. A. and Williams, A. (1990). *J. Am. Chem. Soc.* **112**, 8115
- Bell, R. P. and Sorensen, P. E. (1976). *J. Chem. Soc. Perkin Trans. 2*, 1594
- Bender, M. L. and Nakamura, K. (1962). *J. Am. Chem. Soc.* **84**, 2577
- Bennet, A. J. and Sinnott, M. L. (1986). *J. Am. Chem. Soc.* **108**, 7287
- Bernasconi, C. F. (1987). *Acc. Chem. Res.* **20**, 301
- Bernasconi, C. F. and Killion, R. B. (1988). *J. Am. Chem. Soc.* **110**, 7506
- Bernasconi, C. F. and Killion, R. B. (1989). *J. Org. Chem.* **54**, 2878
- Bernasconi, C. F. and Leonarduzzi, G. D. (1982). *J. Am. Chem. Soc.* **104**, 5133
- Bernasconi, C. F. and Panda, M. (1987). *J. Org. Chem.* **52**, 3042
- Bernasconi, C. F. and Renfrow, R. A. (1987). *J. Org. Chem.* **52**, 3035
- Blackwell, L. F., Fischer, A., Miller, I. J., Topsom, R. D. and Vaughan, J. (1964). *J. Chem. Soc.*, 3588
- Bordwell, F. G. and Boyle, W. J. (1971). *J. Am. Chem. Soc.* **93**, 511
- Bordwell, F. G. and Boyle, W. J. (1972). *J. Am. Chem. Soc.* **94**, 3907
- Bordwell, F. G., Boyle, W. J., Hautala, J. A. and Yee, Y. C. (1969). *J. Am. Chem. Soc.* **91**, 4002
- Bourne, N. and Williams, A. (1984a). *J. Org. Chem.* **49**, 1200
- Bourne, N. and Williams, A. (1984b). *J. Am. Chem. Soc.* **106**, 7591
- Bourne, N., Chrystiuk, E., Davis, A. M. and Williams, A. (1988). *J. Am. Chem. Soc.* **110**, 1890
- Bover, W. J. and Zuman, P. (1973). *J. Chem. Soc. Perkin Trans. 2*, 786
- Burkey, T. J. and Fahey, R. C. (1983). *J. Am. Chem. Soc.* **105**, 868
- Burkhardt, G. N., Ford, W. G. K. and Singleton, E. (1936). *J. Chem. Soc.*, 17
- Burton, G. W., Sims, L. B., Wilson, J. C. and Fry, A. (1977). *J. Am. Chem. Soc.* **99**, 3371
- Burton, J. and Sinnott, M. L. (1983). *J. Chem. Soc. Perkin Trans. 2*, 359
- Chrystiuk, E. and Williams, A. (1987). *J. Am. Chem. Soc.* **109**, 3040
- Cevasco, G., Guanti, G., Hopkins, A., Thea, S. and Williams, A. (1985). *J. Org. Chem.* **50**, 479
- Cordes, E. H. and Bull, H. G. (1974). *Chem. Rev.* **74**, 581
- Cram, D. J. (1965) *Fundamentals of Carbanion Chemistry*. Academic Press, San Diego
- Craze, G. A. and Kirby, A. J. (1978). *J. Chem. Soc. Perkin Trans. 2*, 354
- Craze, G. A., Kirby, A. J. and Osborne, R. (1978). *J. Chem. Soc. Perkin Trans. 2*, 357
- Cullis, P. M. and Nicholls, P. (1987). *J. Chem. Soc. Chem. Commun.*, 783
- Cullis, P. M. and Rous, A. J. (1985). *J. Am. Chem. Soc.* **107**, 6721
- Davies, T. S., Feil, P. D., Kubler, D. G. and Wells, D. J. (1975). *J. Org. Chem.* **40**, 1478
- Davis, A. M., Hall, A. D. and Williams, A. (1988a). *J. Am. Chem. Soc.* **110**, 5105
- Davis, A. M., Regan, A. C. and Williams, A. (1988b). *Biochemistry* **27**, 904
- Davy, M. B., Douglas, K. T., Loran, J. S., Steltner, A. and Williams, A. (1977). *J. Am. Chem. Soc.* **99**, 1196
- Deacon, T., Farrar, C. R., Sikkell, B. J. and Williams, A. (1978) *J. Am. Chem. Soc.* **100**, 2525

- Dewar, M. J. S. (1984). *J. Am. Chem. Soc.* **106**, 209
- Dewar, M. J. S. (1969). *The Molecular Orbital Theory of Organic Chemistry*. McGraw-Hill, New York
- Dixon, J. E. and Bruice, T. C. (1971). *J. Am. Chem. Soc.* **93**, 3248
- do Amaral, L., Bastos, M. P., Bull, H. G., Ortiz, J. J. and Cordes, E. H. (1979). *J. Am. Chem. Soc.* **101**, 169
- Dunn, B. M. and Bruice, T. C. (1973). *Adv. Enzymol.* **37**, 1
- D'Rozario, P., Smyth, R. L. and Williams, A. (1984). *J. Am. Chem. Soc.* **106**, 5027
- Dyferman, A. and Lindberg, B. (1950). *Acta Chem. Scand.* **48**, 78
- Ferraz, J. P. and Cordes, E. H. (1979). *J. Am. Chem. Soc.* **101**, 1488
- Fersht, A. R. and Requena, Y. (1971). *J. Am. Chem. Soc.* **93**, 3499
- Fife, T. H. (1972). *Acc. Chem. Res.* **5**, 264
- Fife, T. H. and Jao, L. K. (1965). *J. Org. Chem.* **30**, 1492
- Fishbein, J. C. and Jencks, W. P. (1988). *J. Am. Chem. Soc.* **110**, 5075
- Frater, R., Pohl, E. R., Wilson, J. M. and Hupe, D. J. (1979). *J. Org. Chem.* **44**, 1771
- Freeman, S., Friedman, J. M. and Knowles, J. R. (1987). *J. Am. Chem. Soc.* **109**, 3166
- Friedman, J. M., Freeman, S. and Knowles, J. R. (1988). *J. Am. Chem. Soc.* **110**, 1268
- Gerstein, J. and Jencks, W. P. (1964). *J. Am. Chem. Soc.* **86**, 4655
- Gilbert, H. F. and Jencks, W. P. (1979). *J. Am. Chem. Soc.* **101**, 5774
- Greenzaid, P. (1973). *J. Org. Chem.* **38**, 3164
- Greenzaid, P., Luz, Z. and Samuel, D. (1967). *J. Am. Chem. Soc.* **89**, 749
- Grunwald, E. (1985). *J. Am. Chem. Soc.* **107**, 125
- Hall, C. R. and Inch, T. D. (1980). *Tetrahedron* **36**, 2059
- Hall, A. D. and Williams, A. (1986). *Biochemistry* **25**, 4784
- Hammett, L. P. (1937). *J. Am. Chem. Soc.* **59**, 96
- Hammett, L. P. and Pfluger, H. L. (1933). *J. Am. Chem. Soc.* **55**, 4079
- Hansch, C. (1969). *Acc. Chem. Res.* **2**, 232
- Hansch, C. (1978). *J. Org. Chem.* **43**, 4889
- Harvan, D. J., Hass, J. R., Busch, K. L., Bursey, M. M., Ramirez, F. and Meyerson, S. (1979). *J. Am. Chem. Soc.* **101**, 7409
- Hawkins, H. C. and Williams, A. (1976) *J. Chem. Soc. Perkin Trans. 2*, 723
- Henchman, M., Viggiano, A. A., Paulson, J. F., Freedman, A. and Wormhoudt, J. (1985). *J. Am. Chem. Soc.* **107**, 1453
- Hengge, A. C. and Cleland, W. W. (1990). *J. Am. Chem. Soc.* **112**, 7421
- Herschlag, D. and Jencks, W. P. (1986). *J. Am. Chem. Soc.* **108**, 7938
- Herschlag, D. and Jencks, W. P. (1989). *J. Am. Chem. Soc.* **111**, 7579
- Hill, S. V., Thea, S. and Williams, A. (1982). *J. Chem. Soc. Perkin Trans. 2*, 437
- Hine, J. (1960). *J. Am. Chem. Soc.* **82**, 4877
- Hopkins, A. R., Day, R. A. and Williams, A. (1983). *J. Am. Chem. Soc.* **105**, 6062
- Hopkins, A. R., Bourne, N. and Williams, A. (1985). *J. Am. Chem. Soc.* **107**, 4327
- Hupe, D. J. and Jencks, W. P. (1977). *J. Am. Chem. Soc.* **99**, 451
- Hupe, D. J. and Wu, D. (1980). *J. Org. Chem.* **45**, 3100
- Ingold, C. K. (1969). *Structure and Mechanism in Organic Chemistry*, 2nd edn. Cornell University Press, Ithaca, New York
- Jencks, W. P. (1971). *Cold Spring Harbor Symposia on Quantitative Biology* **36**, 1
- Jencks, W. P. (1972). *Chem. Rev.* **72**, 705
- Jencks, W. P. (1985). *Chem. Rev.* **85**, 511
- Jencks, W. P. (1988). *Bull. Soc. Chim. France* 218

- Jencks, D. A. and Jencks, W. P. (1977). *J. Am. Chem. Soc.* **99**, 7948
- Jencks, W. P., Brant, S. R., Gandler, J. R., Fendrick, G. and Nakamura, C. (1982). *J. Am. Chem. Soc.* **104**, 7045
- Jencks, W. P., Haber, M. T., Herschlag, D. and Nazaretian, K. L. (1986). *J. Am. Chem. Soc.* **108**, 479
- Jencks, W. P., Schaffhausen, B., Tornheim, K. and White, H. (1971). *J. Am. Chem. Soc.* **93**, 3917
- Jensen, J. L., Herold, L. R., Levy, P. A., Trusty, S., Sergi, V., Bell, K. and Rogers, P. (1979). *J. Am. Chem. Soc.* **101**, 4672
- Kanchuger, M. S. and Byers, L. D. (1979). *J. Am. Chem. Soc.* **101**, 3005
- Keesee, R. G. and Castleman, A. W. (1989). *J. Am. Chem. Soc.* **111**, 9015
- Keller, J. H. and Yankwich, P. E. (1973). *J. Am. Chem. Soc.* **95**, 4811, 7968
- Keller, J. H. and Yankwich, P. E. (1974). *J. Am. Chem. Soc.* **96**, 2303, 3721
- Kemp, D. S. and Casey, M. L. (1973). *J. Am. Chem. Soc.* **95**, 6670
- Kice, J. L. (1980). *Adv. Phys. Org. Chem.* **17**, 65
- Kirsch, J. F., Clewell, W. and Simon, A. (1968). *J. Org. Chem.* **33**, 127
- Kreevoy, M. M. and Lee, I. S. H. (1984). *J. Am. Chem. Soc.* **106**, 2550
- Kreevoy, M. M. and Taft, R. W. (1955). *J. Am. Chem. Soc.* **77**, 5590
- Kreevoy, M. M. and Truhlar, D. G. (1986). In *Investigations of Rates and Mechanisms of Reactions*, 4th edn (ed. C. F. Bernasconi), Part I, p. 13. Wiley-Interscience, New York
- Kwart, H. and Price, M. B. (1960). *J. Am. Chem. Soc.* **82**, 5123
- Ladd, M. F. C. and Palmer, R. A. (1977). *Structure Determination by X-ray Crystallography*. Plenum, New York
- Lahti, M. (1987). *Acta Chem. Scand.* **A41**, 93
- Lahti, M. and Kovero, E. (1988). *Acta Chem. Scand.* **A42**, 124
- Leffler, J. E. (1953). *Science* **117**, 340
- Leffler, J. E. and Grunwald, E. (1963). *Rates and Equilibria of Organic Reactions*, pp. 156ff. Wiley, New York
- Lee, I. (1990). *Chem. Soc. Rev.* **19**, 317
- Lee, I., Choi, Y. H., Rhyu, K. W. and Shin, C. S. (1989a). *J. Chem. Soc. Perkin Trans. 2*, 1881
- Lee, I., Shin, C. S. and Lee, H. W. (1989b). *J. Chem. Soc. Perkin Trans. 2*, 1205
- Lewis, E. S. and Hu, D. D. (1984). *J. Am. Chem. Soc.* **106**, 3292
- Lewis, E. S. and Kukes, S. (1979). *J. Am. Chem. Soc.* **101**, 417
- Lewis, E. S., Yousaf, T. I. and Douglas, T. A. (1987). *J. Am. Chem. Soc.* **109**, 2152
- Lonnberg, H. and Pohjola, V. (1976). *Acta Chem. Scand.* **A30**, 669
- Loudon, G. M. and Berke, C. (1974). *J. Am. Chem. Soc.* **96**, 4508
- Loudon, G. M., Smith, C. K. and Zimmerman, S. E. (1974). *J. Am. Chem. Soc.* **96**, 465
- Luthra, A. K., Ba-Saif, S., Chrystiuk, E. and Williams, A. (1988). *Bull. Soc. Chim. France* 391
- Maskill, H. (1985). *The Physical Basis of Organic Chemistry*. Oxford University Press
- McClelland, R. A. and Coe, M. (1983). *J. Am. Chem. Soc.* **105**, 2178
- McGowan, J. C. (1948). *Chem. Ind.* 632
- McGowan, J. C. (1960). *J. Appl. Chem.* **10**, 312
- More-O'Ferrall, R. A. (1970). *J. Chem. Soc. (B)*, 274
- Page, M. I. and Williams, A. (1987). *Enzyme Mechanisms*. Royal Society of Chemistry Special Publication

- Pople, J. A. and Beveridge, D. L. (1970). *Approximate Molecular Orbital Theory*. McGraw-Hill, New York
- Pross, A. (1983). *Tetrahedron Lett.* **24**, 835
- Pross, A. (1984). *J. Org. Chem.* **49**, 1811
- Ross, J. and Mazur, P. (1961). *J. Chem. Phys.* **35**, 19
- Satchell, D. P. N. and Satchell, R. S. (1990). *Chem. Soc. Rev.* **19**, 55
- Skoog, M. T. and Jencks, W. P. (1984). *J. Am. Chem. Soc.* **106**, 7597
- Stahl, N. and Jencks, W. P. (1986). *J. Am. Chem. Soc.* **108**, 4196
- Thatcher, G. R. J. and Kluger, R. (1989). *Adv. Phys. Org. Chem.* **25**, 99
- Thea, S. and Williams, A. (1986). *Chem. Soc. Rev.* **16**, 125
- Thea, S., Harun, M. G. and Williams, A. (1979). *J. Chem. Soc. Chem. Commun.*, 717
- Thea, S., Guanti, G., Petrillo, G., Hopkins, A. and Williams, A. (1982). *J. Chem. Soc. Chem. Commun.*, 577
- Thea, S., Cevasco, G., Guanti, G., Kashefi-Naini, N. and Williams, A. (1985). *J. Org. Chem.* **50**, 1867
- Van Etten, R. L., Sebastian, J. F., Clowes, G. A. and Bender, M. L. (1967). *J. Am. Chem. Soc.* **89**, 3242
- Vitullo, V. P., Pollack, R. M., Faith, W. C. and Keiser, M. L. (1974). *J. Am. Chem. Soc.* **96**, 6682
- Waring, M. A. and Williams, A. (1989). *J. Chem. Soc. Chem. Commun.* 1742
- Waring, M. A. and Williams, A. (1990). *J. Chem. Soc. Chem. Commun.* 173
- Westheimer, F. H. (1981). *Chem. Rev.* **81**, 313
- Williams, A. (1970). *Biochemistry* **9**, 3383
- Williams, A. (1972). *J. Chem. Soc. Perkin Trans. 2*, 808
- Williams, A. (1973). *J. Chem. Soc. Perkin Trans. 2*, 1244
- Williams, A. (1984a). In *The Chemistry of Enzyme Action* (ed. M. I. Page), pp. 127ff. Elsevier, Amsterdam
- Williams, A. (1984b). *Acc. Chem. Res.* **17**, 425
- Williams, A. (1989). *Acc. Chem. Res.* **22**, 387
- Williams, A. and Douglas, K. T. (1975). *Chem. Rev.* **75**, 627
- Williams, A. and Naylor, R. A. (1971). *J. Chem. Soc. (B)*, 1973
- Williams, A., Naylor, R. A. and Collier, S. G. (1973). *J. Chem. Soc. Perkin Trans. 2*, 25
- Williams, A. and Salvadori, G. (1971). *J. Chem. Soc. (B)*, 2401
- Williams, A. and Woolford, G. (1972). *J. Chem. Soc. Perkin Trans. 2*, 272
- Williams, A., Lucas, E. C. and Rimmer, A. R. (1972). *J. Chem. Soc. Perkin Trans. 2*, 621
- Williams, R. C. and Taylor, J. W. (1973). *J. Am. Chem. Soc.* **95**, 1710
- Williams, R. C. and Taylor, J. W. (1974). *J. Am. Chem. Soc.* **96**, 3721
- Williams, R. E. and Bender, M. L. (1971). *Can. J. Chem.* **49**, 210
- Wilson, D. J., Bayer, R. J. and Hupe, D. J. (1977). *J. Am. Chem. Soc.* **99**, 7922
- Wolfenden, R. and Jencks, W. P. (1961). *J. Am. Chem. Soc.* **83**, 2763
- Young, P. R. and Jencks, W. P. (1977). *J. Am. Chem. Soc.* **99**, 8238
- Young, P. R. and Jencks, W. P. (1979). *J. Am. Chem. Soc.* **101**, 3288

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Cross-interaction Constants and Transition-state Structure in Solution

IKCHOON LEE

Department of Chemistry, Inha University, Incheon, South Korea

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Glossary of abbreviations

BBS	benzyl benzenesulphonate
BEP	Bell-Evans-Polanyi
DMA	<i>N,N</i> -dimethylaniline
EBS	ethyl benzenesulphonate
EDS	electron-donating substituent
EWS	electron-withdrawing substituent
HFIP	hexafluoroisopropyl alcohol
IB	intrinsic barrier
IQ	increment quotient

KIE	kinetic isotope effect
LG	leaving group
MBS	methyl benzenesulphonate
MR	multiple regression
PAB	phenacyl benzenesulphonate
PES	potential energy surface
PPB	1-phenyl-2-propyl benzenesulphonate
QM	quantum mechanical
RSP	reactivity-selectivity principle
S _A N	nucleophilic addition-elimination
S _N i	intramolecular nucleophilic substitution
TB	thermodynamic barrier
TPB	thiophenyl benzoate
TS	transition state
VBCM	valence bond configuration mixing

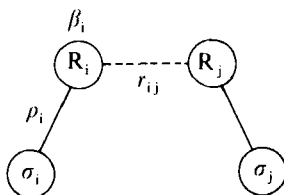
1 Introduction

Linear free energy relationships, notably the Hammett and Brønsted types, have long served as empirical means of characterizing transition-state (TS) structures, especially for reactions in solution (Chapman and Shorter, 1972, 1978; Lowry and Richardson, 1987a). The slopes, ρ_i and β_i , of these correlations are first derivatives of $\log k$, as shown in (1) and (2) respectively,

$$\rho_i = \partial \log k / \partial \sigma_i \quad (1)$$

$$\beta_i = \partial \log k / \partial pK_i \quad (2)$$

and reflect TS structures (e.g. the distance between two reaction centres, r_{ij} in Scheme 1) involved in a series of reaction with structural changes affecting reaction centre R_i (Scheme 1). However, ρ_i (or β_i) can be a measure of r_{ij}



Scheme 1

only when the other reaction centre, R_j , remains constant, because the efficiency of charge transmission between reaction centres R_i and R_j in bond

formation and cleavage may differ for different reaction series (McLennan, 1978; Poh, 1979; Lee *et al.*, 1987a). For example, it is well known that fluoride is a much worse leaving group (LG) compared with chloride owing to the weak electron-accepting ability of the C—F or S—F bond, and hence this leads to a tighter TS with a greater degree of bond formation in nucleophilic substitution reactions (Shaik and Pross, 1982). However, in the reactions of phenylmethanesulphonyl and benzenesulphonyl halides with anilines ($\text{XC}_6\text{H}_4\text{NH}_2$) (Lee *et al.*, 1987a, 1988d), the magnitude of ρ_x for fluoride is smaller ($\rho_{x(\text{F})} = -1.24$ and -1.31 respectively in MeOH) than that for chloride ($\rho_{x(\text{Cl})} = -3.23$ and -2.14 in MeOH), in contradiction to the greater magnitude of ρ_x normally expected for a greater degree of bond formation. This simply indicates that, owing to less effective charge transfer to S—F than to S—Cl, the $|\rho_x|$ -value for fluoride is smaller although bond formation is actually more advanced. Thus r_{ij} is a function not only of ρ_i (or β_i) but also of R_j (which in turn is dependent on σ_j), so that $r_{ij} = f(\rho_i, \sigma_j)$ and the $|\rho_i|$ -values for different reaction series cannot be directly compared to deduce changes in r_{ij} unless $R_j(\sigma_j)$ is constant (Lee *et al.*, 1988e).

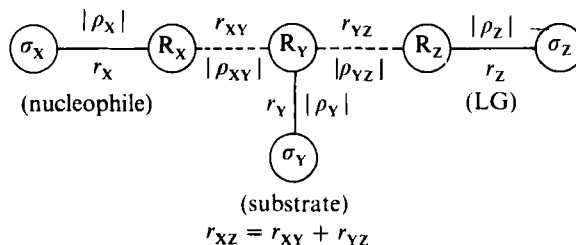
This shows that first-derivative parameters ρ_i and β_i have a serious limitation in their scope of application as a measure of TS structure. A simultaneous function of ρ_i and σ_j , $f(\rho_i, \sigma_j)$ [likewise $f(\beta_i, \text{p}K_j)$] is provided by a second derivative of $\log k$, the cross-interaction constant (ρ_{ij} or β_{ij}), which reflects the effect of a substituent in one reactant (σ_j) on a selectivity parameter for another reactant (ρ_i) (Dubois *et al.*, 1984; Jencks, 1985; Lee, 1990b). The magnitude $|\rho_{ij}|$ of these interaction constants does in fact represent the intensity of interaction between two substituents σ_i and σ_j through the two reaction centres R_i and R_j in the TS, and is inversely proportional to the distance r_{ij} between them (Lee, 1990b); reaction centres R_i and R_j interact more strongly with a greater $|\rho_{ij}|$ at a shorter distance in the rate-determining step. Recent systematic investigations (Dubois *et al.*, 1984; Jencks, 1985; Lee, 1990b) have shown that the cross-interaction constants resolve the limitation inherent in the first-derivative parameters and that the sign and magnitude are useful not only for characterizing TSs for various reactions but also for evaluating a change in the TS structure accompanying a structural change in the reactants (Lee, 1990b). The nature of these changes in TS structure has attracted considerable interest and provoked much controversy among chemists.

In this review theoretical as well as practical aspects of the cross-interaction constants will be presented, and their applications to characterization of TS structures will be considered for various types of reactions; for several examples the TS structures will be analysed in greater detail. Well-known rules, principles and equations will be used without detailed introduction.

2 Theoretical considerations

DERIVATION OF CROSS-INTERACTION CONSTANTS

Let us first introduce notation for describing TS structures. A typical reaction system will normally consist of an attacking group and a substrate with a LG. The most convenient system for this purpose is the S_N2 TS (Scheme 2). The attacking fragment is labelled as X and the substrate and LG are labelled as Y and Z respectively (Lee, 1990b). A similar notation can be adopted in the base-promoted β -elimination type of reaction, where the base catalyst that abstracts a proton from the substrate can now be labelled as X, etc. Substituent constants and reaction centres are denoted by σ_i and R_i respectively, and the distance between reaction centres by r_{ij} . Obviously the notation can be used flexibly for various other reaction systems within the basic framework adopted in Scheme 2.



Scheme 2 Typical S_N2 TS.

In the following derivations subscripts i and j represent X, Y or Z in Scheme 2. The structure of TSs (e.g. in Scheme 2) will be dependent on three fragments.

Let us suppose that we have determined the rate constants k_{ij} with substituents i and j in any two of the fragments. A Taylor series expansion of $\log k_{ij}$ (Wold and Sjöström, 1978) around $\sigma_i = \sigma_j = 0$ leads to (3), where k_{HH}

$$\log(k_{ij}/k_{HH}) = \rho_i \sigma_i + \rho_j \sigma_j + \rho_{ij} \sigma_i \sigma_j \quad (3)$$

is the rate constant with $\sigma_i = \sigma_j = H$. In this treatment we neglect third- and higher-derivative terms since they are normally too small to be taken into account in the actual determination. However, Ta-Shma and Jencks (1986) have considered the significances of third-derivative cross-interaction constants. There are cases where the first-derivative coefficients ρ_i in (1) are not constant, so that we must take into account pure second-derivative terms

$\sigma_i^2(\rho_{ii})$ and $\sigma_j^2(\rho_{jj})$, and even third-derivative terms like $\sigma_i^2\sigma_j(\rho_{ij})$ and $\sigma_i\sigma_j^2(\rho_{ij})$. A complete treatment should include all these terms, but they are usually too small and inaccurate to be significant, and in addition there are not enough experimental data for all these parameters to be accounted for meaningfully (Dubois *et al.*, 1984). We therefore settle simply with the *cross* second-derivative constant as a most practical and useful multiple substituent parameter. The second-derivative parameter ρ_{ij} can be expressed as a change in the first-derivative parameter ρ_i or ρ_j with a substituent σ_j or σ_i (4). Equation (4) shows that ρ_{ij} is a function of both ρ_i and σ_j (or ρ_j and

$$\rho_{ij} = \frac{\partial^2 \log k_{ij}}{\partial \sigma_i \partial \sigma_j} = \frac{\partial \rho_j}{\partial \sigma_i} = \frac{\partial \rho_i}{\partial \sigma_j} \quad (4)$$

σ_i), as required to reflect dependence on both reaction centres R_i and R_j , and reflects r_{ij} in the TS.

The series expansion of $\log k_{ij}$ can also be made around $\Delta pK_i = \Delta pK_j = 0$, where $\Delta pK_i = pK_i - pK_{i=H}$ and a Brønsted-type cross-interaction constant β_{ij} can be defined similarly as in (5a,b).

$$\log(k_{ij}/k_{HH}) = \beta_i \Delta pK_i + \beta_j \Delta pK_j + \beta_{ij} \Delta pK_i \Delta pK_j \quad (5a)$$

$$= \beta'_i pK_i + \beta'_j pK_j + \beta_{ij} pK_i pK_j + \text{Rem} \quad (5b)$$

$$\text{where } \beta_i = \partial \log k_{ij} / \partial \Delta pK_i, \quad \beta'_i = \partial \log k_{ij} / \partial pK_i.$$

Obviously these two are not the same, $\beta_i \neq \beta'_i$. However, the second-derivative constants in the two expressions (5a) and (5b) are equal: $\beta_{ij} = \beta_{ij}'$. The relations (6a,b,c) hold, where Rem is a remainder consisting of constant terms.

$$\beta'_i = \beta_i - \beta_{ij} pK_{j=H} \quad (6a)$$

$$\beta'_j = \beta_j - \beta_{ij} pK_{i=H} \quad (6b)$$

$$\text{Rem} = \beta_{ij} pK_{i=H} pK_{j=H} - \beta_i pK_{i=H} - \beta_j pK_{j=H} \quad (6c)$$

Again in terms of changes in the first-derivative constants, the second-derivative parameter becomes (7).

$$\beta_{ij} = \frac{\partial^2 \log k_{ij}}{\partial pK_i \partial pK_j} = \frac{\partial \beta_j}{\partial pK_i} = \frac{\partial \beta_i}{\partial pK_j} \quad (7)$$

Similarly, we can define a mixed Hammett/Brønsted-type cross-interaction constant λ_{ij} using (8a,b).

$$\log(k_{ij}/k_{HH}) = \beta_i \Delta pK_i + \rho_j \sigma_j + \lambda_{ij}^i \Delta pK_i \sigma_j \quad (8a)$$

$$= \rho_i \sigma_i + \beta_j \Delta pK_j + \lambda_{ij}^j \Delta pK_j \sigma_i \quad (8b)$$

$$\text{where} \quad \lambda_{ij}^i = \frac{\partial^2 \log k_{ij}}{\partial \Delta pK_i \partial \sigma_j} = \frac{\partial \beta_i}{\partial \sigma_j} = \frac{\partial \rho_j}{\partial \Delta pK_i}$$

Comparison of (3), (5) and (8) leads to the interrelationships between parameters given in (9)–(12).

$$\rho_i = \beta_i \rho_e^i, \quad \rho_j = \beta_j \rho_e^j \quad (9)$$

$$\rho_{ij} = \beta_{ij} \rho_e^i \rho_e^j = \lambda_{ij}^i \rho_e^i = \lambda_{ij}^j \rho_e^j \quad (10)$$

$$\lambda_{ij}^i = \beta_{ij} \rho_e^j = \frac{\rho_{ij}}{\rho_e^j}, \quad \lambda_{ij}^j = \beta_{ij} \rho_e^i = \frac{\rho_{ij}}{\rho_e^i} \quad (11)$$

$$\text{where} \quad \Delta pK_i = \rho_e^i \sigma_i, \quad \Delta pK_j = \rho_e^j \sigma_j \quad (12)$$

The second-derivative parameters ρ_{ij} , β_{ij} and λ_{ij} have variously been denoted by q , c or p by other authors (Miller, 1959; Cordes and Jencks, 1962; Dubois *et al.*, 1984) in this field. The parameters β_{ij} and λ_{ij} correspond to ρ_{xy} and ρ'_{xy} , respectively, which were introduced by Jencks (Jencks and Jencks, 1977). The interrelationships (9)–(12) allow us to deduce the mechanistic significance of these parameters based on accumulated knowledge concerning the interpretation of the sign and magnitude of the most widely studied Hammett-type cross-interaction constants ρ_{ij} .

Relations (10) and (11) show that $|\beta_{ij}|$ and $|\lambda_{ij}|$ are proportional to $|\rho_{ij}|$, the proportionality constants being ρ_e^i and ρ_e^j . Thus the greater the magnitude of β_{ij} and λ_{ij} , the stronger is the interaction between reaction centres R_i and R_j , and accordingly the shorter is the distance r_{ij} . Obviously the Brønsted-type parameter β_{ij} will be useful as a measure of the TS structure for a reaction series in which structural variations in the nucleophile and the LG do not involve substituent changes. It is worth noting that the use of pK_i rather than ΔpK_i in the Brønsted-type correlation (5) leads to the same cross-interaction constant β_{ij} , although β_i and β_j are different from β_i' and β_j' respectively. The mixed parameter λ_{ij} has potentially useful applications in a series of reactions in which only one fragment contains substituents, for example a series of reactions in which nucleophiles and substrate are varied but

substituents are only varied in the latter with different nucleophiles involving no substituents. Since the ρ_e -values are in general negative, ρ_{ij} and β_{ij} will have the same sign, while λ_{ij} may have a different sign. Normally, but not necessarily always, the magnitude of ρ_{ij} will be the greatest and that of β_{ij} will be the smallest, $|\rho_{ij}|$ being greater by the product of two constants $|\rho_e^i|$ and $|\rho_e^j|$ that represent the intensities of interaction between substituents (σ_i and σ_j) and respective reaction centres (R_i and R_j). Whenever practicable, determination of both ρ_{ij} and β_{ij} will be useful as a cross-check of the quantitative measure of the distance r_{ij} .

SIGNIFICANCE OF THE SIGN

As a typical example, let us consider the significance of the sign of the constants ρ_{ij} (similarly for β_{ij}) for nucleophilic substitution or group-transfer reactions. Charge development on R_i and the sign of ρ_i (or β_i) show a simple relationship in the bond-forming and bond-breaking steps; a more negative (positive) charge development at R_z (R_x) leads to a more positive ρ_z (a more negative ρ_x). Therefore a *negative* ρ_{xz} in (13) signifies that a more electron-

$$\rho_{xz} = \frac{\partial^2 \log k_{xz}}{\partial \sigma_x \partial \sigma_z} = \frac{\partial \rho_z}{\partial \sigma_x} = \frac{\partial \rho_x}{\partial \sigma_z} \quad (13)$$

donating substituent (EDS) in the nucleophile (i.e. a stronger nucleophile), $\delta \sigma_x < 0$, leads to a greater positive ρ_z , $\delta \rho_z > 0$ (a greater degree of bond breaking). If a more electron-withdrawing substituent (EWS) is present in the LG, $\delta \sigma_z > 0$ (i.e. a better LG), then a greater negative ρ_x , $\delta \rho_x < 0$ (a greater degree of bond formation) results. In effect, the negative ρ_{xz} value predicts a "later" TS for a stronger nucleophile or a better LG. This prediction is precisely what we should expect from the quantum mechanical (QM) model (Pross and Shaik, 1981; Mitchell *et al.*, 1985; Lee and Song, 1986) for the prediction of TS variation that has been shown to apply to the intrinsic-barrier- (IB-) controlled reaction series (Lee *et al.*, 1988b; Lee, 1989). Of the two factors comprising the free energy of activation of a reaction ($\Delta G^\ddagger$), the *intrinsic* ($\Delta G_0^\ddagger$) and the thermodynamic barriers (ΔG^0) in the Marcus equation (14) (Marcus, 1964, 1968; Cohen and Marcus, 1968;

$$\Delta G^\ddagger = \Delta G_0^\ddagger + \frac{1}{2} \Delta G^0 + (\Delta G^0)^2 / 16 \Delta G_0^\ddagger \quad (14)$$

Albery and Kreevoy, 1978; Wolfe *et al.*, 1981a,b; Murdock, 1983; Dodd and Brauman, 1984; Lewis and Hu, 1984; Yates, 1989), either can be dominant; for example, a reaction series will be IB-controlled when $\Delta G^0 = 0$, i.e. for a

thermoneutral reaction series, or when $\delta\Delta G^0 \approx 0$, i.e. for a reaction series for which the thermodynamic barrier (TB) is constant for all the members within the series. The Marcus equation (Marcus, 1964, 1968) has been shown to apply to a wide range of processes, including group-transfer (Albery and Kreevoy, 1978) and S_N2 reactions (Wolfe *et al.*, 1981a,b; Dodd and Brauman, 1984; Lewis and Hu, 1984; Lee *et al.*, 1986a), although originally it was derived for electron-transfer reactions in solution.

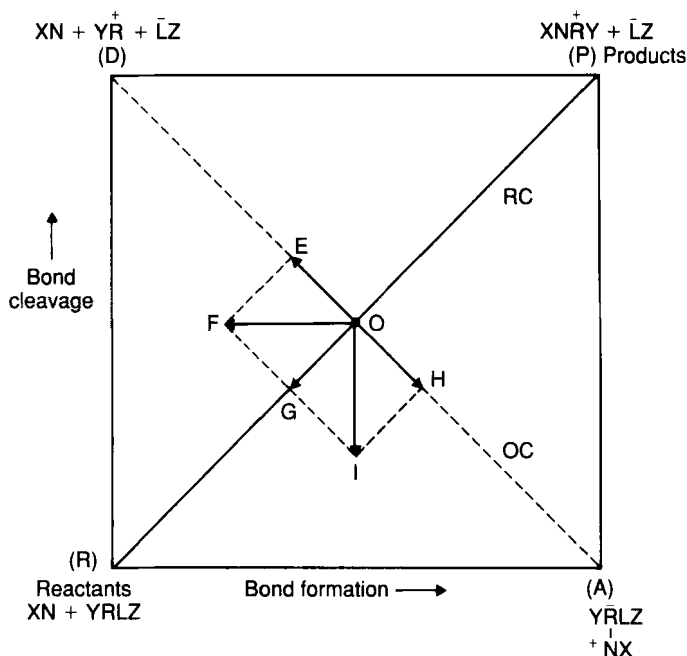


Fig. 1 Potential energy surface diagram for an S_N2 reaction. RC and OC stand for reaction coordinate and orthogonal coordinate diagonals.

Conversely, if the ρ_{xz} -value is *positive*, a stronger nucleophile and a better LG lead to an “*earlier*” TS with a lesser degree of bond breaking and bond formation. In this case the TS variation can be predicted from the potential energy surface (PES), or using a More O’Ferrall–Jencks diagram (More O’Ferrall, 1970; Jencks, 1972; Pross and Shaik, 1981; Mitchell *et al.*, 1985) such as that in Fig. 1; an EWS in the LG will stabilize the upper corners, D and P, in Fig. 1, so that the TS will shift to F, which is obtained as a sum of the two vectors, OG and OE, in accordance with the Hammond and anti-Hammond (or Thornton) rules (Hammond, 1955; Thornton, 1967). The bond formation is predicted to decrease. On the other hand, a strong

nucleophile will stabilize the right-hand corners, P and A, so that the TS is expected to shift to I, i.e. towards less bond breaking. These effects of substituents in the nucleophile and the LG on the TS variation are in complete agreement with what we should expect thermodynamically; a stronger nucleophile and a better LG will give thermodynamically more stable products, so that the reaction will become more exothermic. An increase in exothermicity will lead to an earlier TS according to the Hammond postulate (Hammond, 1955), which is also based on thermodynamic stabilities of reactants and products. Thus a reaction series becomes TB-controlled when the TS variation follows that predicted by the PES model.

Actually the PES diagram widely used for group-transfer and S_N -type reactions is so designed as to give secondary effects (effects of nucleophile on bond breaking and LG on bond formation) of structural changes of reactants (nucleophile or LG) on the TS variation in a *TB-controlled reaction series* by summing primary effects (effects of nucleophile on bond formation and LG on bond breaking) vectorially. This is really the same procedure of summing the IB and TB as in the Marcus equation. By assigning an effect due to the TB to the reaction coordinate diagonal and that due to the IB to the orthogonal coordinate diagonal (Fig. 1), we are tacitly assuming that the TB is dominant over the IB in the reaction series and hence the resultant TS variation becomes the thermodynamically correct (predicted) one (an earlier TS). Conversely, if we assign the IB effect to the reaction coordinate diagonal and the TB effect to the orthogonal coordinate diagonal, the resultant vector sum of the two effects will give the TS variations for the IB-controlled series, which will be exactly the same as those obtained by the QM model (a later TS). We should note in these procedures that, for a stronger nucleophile and/or a better LG, irrespective of whether the effect is primary or secondary, the TB always shifts the TS to an "earlier" position along the reaction coordinate whereas the IB shifts it to a "later" position. Thus the More O'Ferrall-Jencks diagram provides a qualitative prediction of the change in position of the barrier along the reaction coordinate whereas the Marcus equation provides a quantitative value of the barrier height.

For non-identity reactions, $X \neq Z$ in Scheme 2, a later (earlier) TS with a stronger nucleophile, $\delta\sigma_X < 0$, and a better LG, $\delta\sigma_Z > 0$, in an IB-controlled (TB-controlled) series should lead to the relations in (15), where $a, a' > 0$

$$\Delta r_{XY} = a\sigma_X: \Delta r_{YZ} = a'\sigma_Z \longrightarrow \text{primary effect} \quad (15)$$

$$\Delta r_{XY} = b\sigma_Z: \Delta r_{YZ} = b'\sigma_X \longrightarrow \text{secondary effect}$$

and $b, b' < 0$ for the IB-controlled reactions (and hence $\rho_{XY} < 0$ and

$\rho_{YZ} > 0$ when $\rho_{XZ} < 0$), whereas, for the TB-controlled reactions, $\rho_{XY} > 0$ and $\rho_{YZ} < 0$ when $\rho_{XZ} > 0$ (and hence they are reversed to $a, a' < 0$ and $b, b' > 0$). For the IB-controlled series, the QM model applies, while the PES model (with the TB effect as the reaction coordinate diagonal) applies to the TB-controlled reaction series. The following useful rules emerge:

- (i) an S_N2 or a group-transfer reaction series is IB-controlled if ρ_{XZ} is negative whereas it is TB-controlled if ρ_{XZ} is positive;
- (ii) a stronger nucleophile or a better LG always shifts the IB towards a later position and the TB towards an earlier position along the reaction coordinate;
- (iii) the TS moves in the direction determined by a combined effect of the two, IB and TB.

Naturally there will be cases where no clear-cut distinction of whether a reaction is IB- or TB-controlled can be made. The value of ρ_Y (or β_Y) for substituents on a central atom will depend on both bond-forming and bond-breaking processes, so that no simple general interpretation of the sign is possible; the signs of ρ_{XY} and ρ_{YZ} should therefore be interpreted for the specific case involved.

The reactivity-selectivity principle (RSP) (Pross, 1977; Buncl and Wilson, 1987; Lowry and Richardson, 1987a) asserts that more reactive reagents exhibit smaller selectivity and, conversely, that less reactive reagents exhibit greater selectivity. Thus if ρ_{XZ} is positive, (13) indicates that the RSP holds; if the nucleophile is a stronger, more reactive one ($\delta\sigma_X < 0$), the selectivity of the LG is less ($\delta\rho_Z < 0$), while more reactive, i.e. a better LG ($\delta\sigma_Z > 0$) leads to a less selective nucleophile ($\delta\rho_X > 0 \rightarrow \delta|\rho_X| < 0$, since ρ_X is negative). Conversely, however, when ρ_{XZ} is negative, the RSP will be violated. This means that the RSP holds only for the TB-controlled reaction series (Buncl and Wilson, 1987), and in the IB-controlled series it is violated, because the RSP is also a thermodynamically based principle, as is the Hammond postulate, or the Bell-Evans-Polanyi (BEP) principle (Dewar and Dougherty, 1975).

The significance of the sign of ρ_{XZ} should also apply to that of β_{XZ} , since the two have the same sign; in this sense λ_{XZ} has a sign that is opposite to that of these two parameters.

SIGNIFICANCE OF THE MAGNITUDE

The cross-interaction constant is a selectivity parameter dependent on both reacting centres R_i and R_j in Schemes 1 and 2, and represents the intensity of interaction between them. Since a selectivity parameter reflects the distance

of the TS along the reaction coordinate (Pross, 1977), the magnitude of the cross-interaction constant should also provide a measure of the TS structure. The magnitude of Hammett-type constant $|\rho_{ij}|$ represents the intensity of *indirect interaction* between two substituents σ_i and σ_j through the respective reaction centres R_i and R_j when the two fragments are involved in forming or breaking of a bond r_{ij} between the two reaction centres in the TS. Thus the $|\rho_{ij}|$ should be related inversely to the distance between the two substituents σ_i and σ_j , since the interaction will be stronger at a shorter distance; in fact it has been shown that the distance r_{ij} is related to $|\rho_{ij}|$ by (16) (Lee,

$$r_{ij} = a + \beta \log \frac{1}{|\rho_{ij}|} \quad (16)$$

1990b), where a and β are positive constants, assuming the rigidity of the fragment's skeleton in the reaction. The magnitude of ρ_{ij} is subject to fall-off by a factor of 2.4–2.8 (Charton, 1981; Lee *et al.*, 1988d; Siggel *et al.*, 1988) when a non-conjugating group, like CH_2 or CO , intervenes in one of the fragments (i) between the substituent σ_i and the reaction centre R_i , since normally each CH_2 group is known to reduce the magnitude of ρ_i in (4) by such an amount.

On the other hand, the magnitude of Brønsted-type constants $|\beta_{ij}|$ represents the intensity of *direct interaction* between the two reaction centres R_i and R_j , so that there will be no such complications arising from fall-off of the intensity of interaction due to any intervening groups between a substituent σ_i and its reaction centre R_i .

There are two types of extreme cases: in one case the cross-interaction constant nearly vanishes, $|\rho_{ij}| \approx 0$ (and $|\beta_{ij}| = |\lambda_{ij}| \approx 0$), and in the other the magnitude is abnormally large.

(a) *Weak or no interaction.* In the former case, there will be no interaction or weak interaction between the two reaction centres R_i and R_j . This situation will arise when the distance r_{ij} is very large between R_i and R_j so that the intensity of interaction will be negligible. It will also occur, however, when the two reaction centres are not involved in direct mutual interaction, so that a distance change Δr_{ij} does not occur in the rate-determining step. Thus there will be no interaction between R_Y and R_Z (and hence between σ_Y and σ_Z) in the rate-determining bond-formation step, since the bond length r_{YZ} remains the same in this step and ρ_Z (ρ_Y) is independent of σ_Y (σ_Z). This leads to the expression (17a).

$$\rho_{YZ} = \frac{\partial \rho_Z}{\partial \sigma_Y} \left(= \frac{\partial \rho_Y}{\partial \sigma_Z} \right) = 0 \quad (17a)$$

Likewise, in the rate-determining bond-breaking step, the bond length r_{XY} should not vary, leading to (17b). These two cases of no interaction can be

$$\rho_{XY} = \frac{\partial \rho_Y}{\partial \sigma_X} \left(= \frac{\partial \rho_X}{\partial \sigma_Y} \right) = 0 \quad (17b)$$

used for the characterization of S_N1 and $S_A N$ (addition–elimination) mechanisms: in the S_N1 TS, no bond formation occurs and only bond cleavage takes place, so that $|\rho_{XY}| = |\rho_{XZ}| \approx 0$ with only non-zero cross-interaction between σ_Y and σ_Z , $|\rho_{YZ}| \neq 0$. Likewise, in the addition–elimination mechanism $|\rho_{YZ}|$ will be zero if formation of the addition complex is rate-determining, whereas $|\rho_{XY}|$ will be zero if elimination from the addition complex is rate-limiting.

(b) *Strong interaction.* The magnitude of cross-interaction constants can be abnormally large when substituents or reaction centres interact through multiple routes.

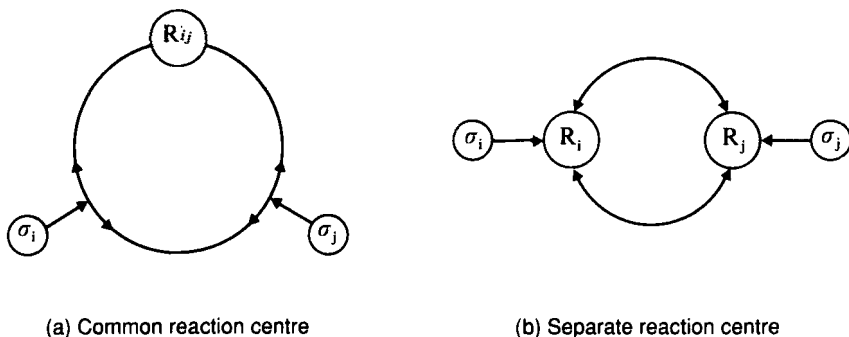
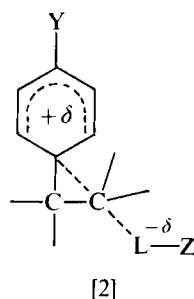
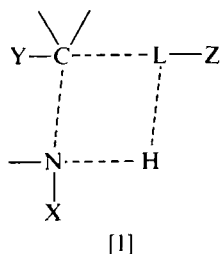


Fig. 2 Dual interaction routes.

There will be two types of manifold (two-fold) interactions, as shown in Fig. 2. In (a), two substituents, σ_i and σ_j , are both present in a single fragment, so that both interact with the common reaction centre R_{ij} via the two common routes, whereas in (b) the two routes interconnecting the two reaction centres R_i and R_j are separate, and the two substituents can interact through the two reaction centres simultaneously. These types of interaction are rather common, and especially useful in characterizing the TS structures. In [1] a hydrogen-bond bridge is formed (Lee *et al.*, 1987b, 1988c, 1990f), which provides an extra interaction route between two reaction centres N and L, and the interaction between substituents X and Z, $|\rho_{XZ}|$, will be exceptionally large. In another type of bridged structure [2] (Lee *et al.*,

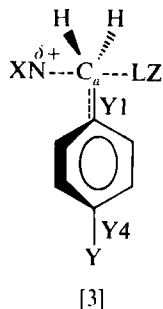


1988b, 1990i, j, k; Schadt *et al.*, 1978) the interaction between substituents Y and Z will be large and $|\rho_{YZ}|$ will also be abnormally great owing to the bypassing of an intervening CH_2 group ($|\rho|$ increases by a factor of 2.4–2.8) and a possible dual interaction. Characterization of TS structures like [1] and [2] using the magnitude of cross-interaction constants provides a novel approach to mechanistic investigations of organic reactions in solution.

(c) *Distance dependence.* It has been shown that the distance r_{ij} between the two substituents σ_i and σ_j is a logarithmic inverse function of $|\rho_{ij}|$; thus the relations (18) hold (Scheme 2). However, the distances r_X , r_Y and r_Z are

$$\begin{aligned} (r_X + r_Y) + r_{XY} &\propto \log(|\rho_{XY}|)^{-1} \\ (r_Y + r_Z) + r_{YZ} &\propto \log(|\rho_{YZ}|)^{-1} \end{aligned} \quad (18)$$

normally constant, and do not vary during reactions unless there is a structural change involving strong conjugation between the σ_i 's and R_i 's. The benzylic effect (King and Tsang, 1979), i.e. a conjugative interaction between the two bonds that are being formed and broken and the π -orbitals of the benzene ring, is known to contract the bond length of $\text{C}_a\text{—C}_{Y1}$ in [3] so that r_Y in such cases cannot be considered to be constant during such a



reaction. There will be other cases where an extra CH_2 group extends r_i , although r_i 's are constant within a series during the reaction, so that $|\rho_{ij}|$ will be reduced according to (18); this is reflected in the fall-off of $|\rho_{ij}|$ by a factor of 2.4–2.8 for each non-conjugating CH_2 or CO group between σ_i and R_i . The rigidity of skeletons, when held, simplifies the relationships (18) into that of equation (16).

Comparison of (15) and (16) leads to another useful set of relationships (19), where the signs of constants are now $A, A' < 0$ and $B, B' > 0$ for IB-

$$\Delta \log |\rho_{xY}| = A\sigma_X, \quad \Delta \log |\rho_{YZ}| = A'\sigma_Z \quad (19a)$$

$$\Delta \log |\rho_{XY}| = B\sigma_Z, \quad \Delta \log |\rho_{YZ}| = B'\sigma_X \quad (19b)$$

controlled reactions and $A, A' > 0$ and $B, B' < 0$ for TB-controlled reactions. Similar relationships to those given by (15), (16) and (19) are obtained using β_{ij} instead of ρ_{ij} with a different set of constants (a, β, a, A , etc.), which have the same signs as those for the corresponding constants for ρ_{ij} but different magnitudes.

3 Experimental determinations

METHODS

In order to obtain the cross-interaction constant ρ_{ij} for a given disubstituted (σ_i, σ_j) reaction system, the rate constants k_{ij} should be determined with as many different combinations of σ_i and σ_j as possible under set reaction conditions (at constant T, P and medium). For example, if we vary three substituents (excluding σ_i or $\sigma_j = \text{H}$) each in the two fragments i and j (Scheme 2), a total of nine k_{ij} -values for different sets of (σ_i, σ_j) combinations can be obtained. These k_{ij} -values are then subjected to multiple linear regression (MR) (Wold and Sjöström, 1978; Shorter, 1982) according to (3). In this equation, k_{HH} is a constant and does not in any way affect the calculated ρ_{ij} value. This method automatically supplies us ρ_i (at $\sigma_j = \text{H}$) and ρ_j (at $\sigma_i = \text{H}$) in addition to the cross-interaction constant ρ_{ij} . Since the ρ_i - or ρ_j -value can be obtained independently as a simple Hammett coefficient (1), agreement between the two, i.e. those obtained from (1) and (3), provides us with a convenient means to check accuracy or reliability and the self-consistency of the cross-interaction constant determined by this MR method. Another advantage of the MR method is that objective statistical analysis can be applied to test the reliability of the determined ρ_{ij} -values,

usually computing correlation coefficients of the multiple linear regression, standard deviations and confidence limits, etc. (Wold and Sjöström, 1978; Shorter, 1982).

Another experimental method for obtaining ρ_{ij} is to make use of (4) with increment quotients (IQ) rather than derivatives (Dubois *et al.*, 1984), as indicated in (20). Thus simple Hammett coefficients in (1), ρ_j 's (or ρ_i 's), are

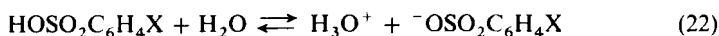
$$\begin{aligned} \rho_{ij} &= \frac{\partial \rho_j}{\partial \sigma_i} = \frac{\Delta \rho_j}{\Delta \sigma_i} \\ \text{or} \quad &= \frac{\partial \rho_i}{\partial \sigma_j} = \frac{\Delta \rho_i}{\Delta \sigma_j} \end{aligned} \quad (20)$$

experimentally obtained at least at two different σ_i 's (or σ_j 's), and the increment quotient (IQ) is determined as in (21), where $\rho_{i(1)}$ and $\rho_{j(2)}$

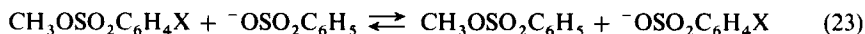
$$\rho_{ij} = \frac{\rho_{j(2)} - \rho_{j(1)}}{\sigma_{i(2)} - \sigma_{i(1)}} = \frac{\rho_{i(2)} - \rho_{i(1)}}{\sigma_{j(2)} - \sigma_{j(1)}} \quad (21)$$

represent ρ_i determined with $\sigma_{j(1)}$ and ρ_j with $\sigma_{i(2)}$ respectively. The IQ method may require fewer k_{ij} -values and hence is simpler, but the accuracy may be correspondingly less than the MR method. Objective statistical analysis of the accuracy and reliability of the determined ρ_{ij} -values cannot be carried out with this method. For a quantitative measure of the TS structure, accurate determinations of ρ_{ij} -values are essential, and in this respect the IQ method leaves much to be desired. On the other hand, however, much less effort is required in the experimental determination of rate constants; as few as four k_{ij} -values should be sufficient to arrive at a ρ_{ij} -value, which can be an advantage in view of its expediency.

For determination of β_{ij} , the multiple linear regression of k_{ij} is carried out according to either (5a) or (5b) using ΔpK or pK . In practice, the use of ΔpK_i ($= pK_i - pK_H$) is limited owing to the unavailability of pK_H , which is the pK_a -value for the unsubstituted ($i = H$) compound; this is because, when we are dealing with a series of nucleophiles or LGs that involve no substituent changes (e.g. alkylamines), there is no reference ($i = H$) compound. It is true that the β_{ij} -values obtained are dependent on the set of pK_a -values used in the correlation equations (5); according to (10), for a value of ρ_{ij} the β_{ij} -value will differ, depending on the value of ρ_e^i and/or ρ_e^j . For example, for the substituted benzenesulphonates $XC_6H_4SO_2O^-$, two types of pK_a -values have been used; (22) defines a pK_a -scale based on the conjugate acids of



benzenesulphonates (as nucleophiles or LGs), i.e. the proton acidity pK^{H^+} , whereas (23) introduces an entirely different pK_a -scale based on methyl



transfer reactions, pK^{Me} (Hoffman and Shankweiler, 1986), for which ρ_e -values are $\rho_e^{H^+} = -0.67$ and $\rho_e^{Me} = -2.99$. Some proton acidity ρ_e -values of interest in H_2O at $25^\circ C$ are -1.00 ($ArCOOH$), -1.06 ($ArCH_2NH_3^+$), -2.23 ($ArOH$), -2.2 ($ArSH$), -2.89 ($ArNH_3^+$), -3.46 ($ArN(CH_3)_2H^+$), -5.90 (pyridines), -4.28 (pyrroles) and -0.47 (cinnamic acids) (Dean, 1987; Lowry and Richardson, 1987d). This means that we need to adopt a standard procedure of using only the proton-acidity pK_a -values for the determination of β_{ij} (and λ_{ij}) in order that the magnitude of the β_{ij} - (and λ_{ij} -) values may serve as a quantitative measure of the TS structure. Another caveat in dealing with β_{ij} is that the pK_a -values are normally determined in water at $25^\circ C$, but in practice these values are applied to reactions carried out in other solvents and at other temperatures; the solvent and temperature effects on β_{ij} should not be ignored. In this respect, the temperature effect on ρ_{ij} may also be significant.

STATISTICAL PROBLEMS

Equations (3), (5) and (8) involve three variables, σ_i , σ_j and k_{ij} (or pK_i , pK_j and k_{ij}), and the task is to find the best correlation characterized by constants ρ_i , ρ_j and ρ_{ij} (or β_i , β_j and β_{ij}). This problem is directly related to the reality or the reliability of the determined cross-interaction constants. Multiple linear regression can be carried out routinely using computer programs devised for such purposes. The precision of the correlation is normally expressed by the multiple correlation coefficient r , the standard deviation of the estimate s , and the confidence level (Wold and Sjöström, 1978). It is highly desirable to have a large number n of data points (k_{ij} -values) for a reliable value of the cross-interaction constant; r increases with decreasing n , so that a large value of r (e.g. $r = 0.95$), which is highly significant if n is large ($n = 10$), is non-significant for a small n ($n = 4$). In general, a multiple linear regression with $n \geq 16$ is found to be sufficient for a reliable cross-interaction constant ρ_{ij} (or λ_{ij} or β_{ij}), when the multiple correlation coefficient ($r > 0.99$), standard deviation (e.g. for $\rho_{ij} \approx 0.10$, $SD \leq 0.01$) and confidence level ($> 99\%$) are within acceptable ranges.

This statistical analysis applies only to the MR method above; with the IQ method the reliability of the cross-interaction constants must be deemed less since this method is often used when there is insufficient data (k_{ij} -values) available. The ρ_{ij} -values in Tables 2–17 were obtained by the MR method

with $n \geq 16$, but the rest were derived mostly by the IQ method with n less than this.

The cross-interaction constants, being second-derivative parameters, are usually small in magnitude, $|\beta_{ij}|$ being smaller than $|\rho_{ij}|$. This means that the ρ_{ij} - and especially β_{ij} -values have to be reported to the third decimal place. It is, however, recommended to report at least two significant figures whenever it is warranted by the accuracy, especially if the magnitude is small and the value is of the order of 10^{-3} .

The magnitude of ρ_{ij} (or β_{ij}) is not necessarily smaller than the simple Hammett coefficients ρ_i (or β_i). There are cases when ρ_{ij} is greater than ρ_i or ρ_j , and in certain cases (normally for manifold interactions) (Dubois *et al.*, 1984) the magnitude of ρ_{ij} (or β_{ij}) becomes very large ($|\rho_{ij}| > 1.0$) and ρ_{ij} 's near unity are quite common.

4 Applications to TS structure

Applications of the various cross-interaction constants to the elucidation of reaction mechanisms will be presented in this section. The use of the sign and magnitude allows us to predict the reaction types (IB- or TB-controlled in group-transfer and nucleophilic displacement reactions) and TS structures semiquantitatively. One of the most extensively investigated reactions in chemistry is nucleophilic substitution (S_N). In addition, S_N -type reactions are most suitable for the application of cross-interaction constants as a measure of the TS structure. For these reasons, cross-interaction constants are determined and the TS structures are discussed for a large number of S_N reactions in greater detail. However, there is also a substantial amount of cross-interaction constant data available in the literature on various other types of reactions.

NUCLEOPHILIC SUBSTITUTION REACTIONS

Reactions with a vanishing cross-interaction constant

For S_N1 and S_{AN} (addition-elimination) mechanisms, no interaction between two fragments i and j (Scheme 2) with $\rho_{ij} = 0$ can be useful for the characterization of the TS structure. In the S_N1 TS no bond formation occurs, but only bond cleavage takes place, so that there will be no interaction between (substituents in) the nucleophile (X) and substrate (Y) or LG (Z); thus $|\rho_{XY}| = |\rho_{XZ}| \approx 0$ should hold, i.e. $\rho_{XY} = \partial\rho_Y/\partial\sigma_X = 0$ and $\rho_{XZ} = \partial\rho_Z/\partial\sigma_X = 0$ [see (4)], since ρ_Y and ρ_Z are independent of σ_X . Kevill *et*

al. (1973) reported that solvolysis of 2-adamantyl arenesulphonates have nearly constant ρ_Z ($= 1.60$) in EtOH and 70% EtOH, suggesting $|\rho_{XZ}| = 0$ for this S_N1 reaction.

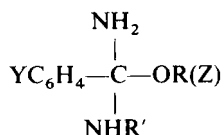
In the addition-elimination (S_{AN}) mechanism the reaction proceeds through an addition intermediate, and either the addition or the elimination step of the intermediate can be rate-limiting. The value of $|\rho_{YZ}|$ will be zero if the addition step is rate-limiting, whereas $|\rho_{XY}|$ will be zero if elimination is rate-limiting. On the other hand, a base-catalysed addition will result in a hydrogen-bond bridged structure providing twofold interaction pathways with very large $|\rho_{YZ}|$ values. Some examples are shown in Table 1. Reactions A and B are the reactions of phenyl benzoates with bases, OH^- and pyrrolidine, but in the former the addition step is rate-limiting ($\rho_{YZ} = 0$) whereas in the latter elimination from the addition intermediate is rate-limiting ($\rho_{YZ} > 0$); the two rate-determining steps are clearly distinguished by the magnitude of ρ_{YZ} .

Table 1 ρ_{ij} - (β_{ij} -) Values for reactions proceeding by the addition-elimination mechanism.

Class	Reactions	ρ_{ij} (β_{ij})
A	$OH^- + YC_6H_4COOC_6H_4Z$	$\rho_{YZ} = 0^a$
B	Pyrrolidine + $YC_6H_4COOC_6H_4Z$	(k_2 path) $\rho_{YZ} = -1.76^b$
		(k_3 path) $\rho_{YZ} = 9.33$
C	$RNH_2 + YC_6H_4NHCOOC_6H_4Z$	(k_2 path) $\rho_{YZ} = 1.02^c$
		(k_3 path) $\rho_{YZ} = -3.99$
D	$RNH_2 + YC_6H_4C(N=H)OR'Z$	$\rho_{YZ} = 0.70^d$ ($\beta'_{YZ} = -0.25$)
E	$XC_6H_4O^- + YC_6H_3(NO_2)Cl$	$\rho_{XY} = -1.41^e$

^a Kirsch *et al.* (1968). ^b Menger and Smith (1972). ^c Shawali *et al.* (1986). ^d Gilbert and Jencks (1982). ^e Knowles *et al.* (1961).

Both reactions B and C involve aminolysis with the rate-limiting collapse of addition intermediates. We note that the magnitude of ρ_{YZ} is very large for the third-order reaction pathway (k_3), i.e. for the base-catalysed mechanism in which the base, pyrrolidine and amine, forms a hydrogen-bond bridge between the base and the LG, providing an extra interaction route. The dual route (Fig. 2b) allows a stronger interaction with a large $|\rho_{YZ}|$. The magnitude of ρ_{YZ} for the latter (reaction C) is smaller since an extra intervening group, NH, is present between the two interacting substituents, Y and Z, in carbamates [cf. Section 2, p. 69]. Gilbert and Jencks (1982) reported on the mechanism of the aminolysis of alkyl benzimidates (reaction D). They gave



two rate data corresponding to the formation and decomposition of a tetrahedral intermediate. The breakdown of the intermediate correctly gave a relatively large β_{YZ} ($= 0.70$). The formation step is, however, a complex third-order process involving protonation on the imino group ($\text{C}=\text{NH}$) and the attack by the amine ($\text{R}'\text{NH}$) on the carbon atom. Thus no simple interpretation of $\beta'_{\text{YZ}} = -0.25$ is possible. Reaction E is an example of nucleophilic aromatic substitution (Knowles *et al.*, 1961). For this, the magnitude of ρ_{XY} was found to be large (-1.41), so that the reaction proceeds by rate-determining formation of the addition intermediate as the authors have concluded.

A notable example of no interaction can be found in the reactions of carbocations with nucleophiles. Ritchie (1972a, b, 1986; Isaacs, 1987) has shown that for a wide range of nucleophilic systems comprising nucleophile and solvent reacting with various types of organic cation, the reaction rates are correlated by the N^+ scale, defined in (24), where k_{XY} is the rate constant

$$\log(k_{\text{XY}}/k_0) = N_{\text{X}}^+ \quad (24)$$

for reaction of a given cation Y (e.g. triarylmethyl cations, tropylium ions and benzenediazonium ions) with a given nucleophilic system X, and k_0 is the rate constant of the reference reaction, which is the reaction of the cation with water in water. An interesting feature of this correlation is the absence of a susceptibility parameter corresponding to ρ_{Y} and ρ_{XY} (or β_{XY}), since N_{X}^+ is only dependent on the nucleophile, X. It is thought that the formation of an ion pair with solvent reorganization under electrostatic force is the slow step in this type of simple reaction. Equation (24) corresponds to $\rho_{\text{X}} = 1.0$, $\rho_{\text{Y}} = 0.0$ and $\rho_{\text{XY}} = 0.0$ (or $\beta_{\text{XY}} = 0$) in (3), so that there is *no cross-interaction* between the cations and nucleophiles. This means that, in this reaction, the rate-determining step has nothing to do with the actual (covalent) bond formation between the cations and nucleophiles, or alternatively bond formation occurs at an extremely early stage along the reaction coordinate so that the bond distance between the cation and nucleophile is very large; in either case the cross-interaction constant will vanish, $\rho_{\text{XY}} \approx 0$ (or $\beta_{\text{XY}} \approx 0$). This is another case of violation of the RSP, since the reactivity k_{XY} is independent of the selectivity ρ_{X} or ρ_{XY} .

Table 2 ρ_{XY} -Values for some nucleophilic substitution reactions.^a

Reactants		Temperature °C	ρ_X	ρ_Y	ρ_{XY}
Class I					
A	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{COC}\text{Cl}$	35.0	-2.24	2.17	-0.68
B	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{Cl}$	35.0	-0.98	-0.61	-0.77
C	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{Cl}$	35.0	-2.14	0.96	-0.70
D	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{Cl}$	25.0	-2.15	1.10	-0.75
E	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	35.0	-0.92	-0.75	-0.62
F	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{Br}$	35.0	-1.33	-0.67	-0.78
G	$\text{XC}_6\text{H}_4\text{S}^- + \text{YC}_6\text{H}_4\text{CH}_2\text{Cl}$	20.0	-0.58	0.58	-0.62
H	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	65.0	-1.14	-0.37	-0.77 ^b
Class II					
I	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{COF}$	55.0	-3.14	1.72	-1.67
J	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{F}$	45.0	-1.31	1.15	-1.07
K	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{COSC}_6\text{H}_4\text{Z}$	55.0	-5.11	1.41	1.48 ^c
Class III					
L	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{COCH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	45.0	-1.97	0.61	0.11
M	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{COCH}_2\text{Br}$	45.0	-1.81	0.61	0.11
N	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	60.0	-1.22	-0.15	-0.12
Class IV					
O	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{Cl}$	35.0	-1.38	1.51	-0.39
P	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{Br}$	45.0	-1.15	-0.46	-0.38
Q	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{F}$	45.0	-0.78	0.71	-0.66
R	$\text{XC}_6\text{H}_4\text{CO}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{Cl}$	30.0	-0.37	0.69	-0.37 ^d
S	$\text{XC}_6\text{H}_4\text{CHCHCO}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{Cl}$	30.0	-0.22	0.63	-0.22 ^d
Class V					
T	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}^e$	65.0	-0.58	1.18	-0.02 ^e
U	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{COCH}_2\text{Br}$	45.0	-0.88	0.37	0.05
V	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{COCH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	45.0	-0.74	0.54	0.03
W ^f	$\text{XC}_6\text{H}_4\text{CHCHCO}_2 + \text{YC}_6\text{H}_4\text{COCH}_2\text{Br}$		-0.22	1.07	-0.04
X ^g	$(\text{XC}_6\text{H}_4)_2\text{-C}\equiv\text{N}_2 + \text{YC}_6\text{H}_4\text{CO}_2\text{H}$	34.9	-1.70	2.22	-0.09
Y ^b	$\text{XC}_6\text{H}_4\text{SH} + \text{YC}_6\text{H}_4\text{C}\equiv\text{CCOOC}_6\text{H}_5$		-1.30	2.46	-0.32

^a References are cited in Lee *et al.* (1988d); in MeOH. ^b Lee *et al.* (1990k). ^c Lee *et al.* (1990n).^d Lee *et al.* (1990c). ^e In MeCN; Lee *et al.* (1990j). ^f In 9:1 Me₂CO-H₂O/MeCN. ^g In C₂H₅ONa/C₂H₅OH.

Bond tightness in TSs

The ρ_{XY} -values for some nucleophilic reactions are collected in Table 2. All except reaction G in class I involve anilines as nucleophiles and LGs of

relatively good leaving ability, Cl^- , Br^- and $\text{C}_6\text{H}_5\text{SO}_2\text{O}^-$. A striking feature for the class I reactions is that the ρ_{XY} -values, which are negative (suggesting an IB-controlled series), have a similar magnitude, $|\rho_{\text{XY}}| = 0.70 \pm 0.08$. Reactions in this class are considered to be good examples of the $\text{S}_{\text{N}}2$ type, and the similar size therefore provides evidence in support of a similar degree of bond formation, r_{XY} , in the TS.

Close examination of the ρ_{X} -values, however, reveals that the magnitude varies widely, $|\rho_{\text{X}}| = 0.58\text{--}2.24$, in contrast with the relatively constant $|\rho_{\text{XY}}|$ -values. This is a clear demonstration of variable charge transmission reflected in $|\rho_{\text{X}}|$, depending on the reaction centres, R_{X} and R_{Y} , although in reality a similar degree of bond formation, i.e. a similar value of r_{XY} , is involved in the TS of the reactions in this class, as the similar $|\rho_{\text{XY}}|$ -values indicate.

The LG for reactions in class II is fluoride and thiophenolate; as for reactions in class I, ρ_{X} and ρ_{XY} are both negative for the fluoride series but ρ_{XY} is positive for the reaction involving thiophenolate. This last reaction, K, is a TB-controlled series. However, a notable difference between the reactions in the two classes is the size of ρ_{XY} ; this is greater for the fluoride series by a factor of over 1.5 than that of the corresponding series with chloride LG in class I, and for the thiophenyl benzoate by a factor of *ca* 2.0 than those of the reactions in class I. It is well known that fluoride (and phenolates) is a much worse LG compared with chloride owing to the weak electron-accepting ability of the C—F or S—F bond (Shaik and Pross, 1982; Lee and Kang, 1987). The greater $|\rho_{\text{XY}}|$ -values for class II reactions indicate that a worse LG leads to a greater degree of bond formation, which is consistent with the predictions of TS variation by the PES model.

Comparison of reactions C and J indicates that $|\rho_{\text{X}}|$ is smaller for J despite the large $|\rho_{\text{XY}}|$ -value, supporting the contention that Hammett ρ_{X} -values are unreliable as a measure of bond tightness owing to variable charge transmission.

For reaction K, a more EWS in the LG ($\delta\sigma_{\text{Z}} > 0$) resulted in a decrease in ρ_{XY} ; hence *B* is negative and *b* is positive in (19b) and (15) respectively. This is the opposite trend to that found for reaction E, but in agreement with predictions by the PES model, and provides an example of a TB-controlled reaction series.

Substrates for reactions in class III are phenacyl and 2-phenylethyl derivatives. For the phenacyl systems, ρ_{XY} is positive, in contrast with those for the other reaction series in Table 2. For reactions of the 2-phenylethyl series, however, the sign of ρ_{XY} is negative and moreover *B* was found to be positive and hence *b* is negative (see below). It is to be noted that the magnitudes of ρ_{XY} for the phenacyl and 2-phenylethyl series are small but nearly the same (*ca* 0.11), despite the opposite signs of ρ_{XY} . One reason why

such smaller $|\rho_{XY}|$ -values are obtained relative to those in class I ($|\rho_{XY}| = 0.70$) is an intervening CO or CH₂ group in the substrate between the reaction centre carbon and the benzene ring. (For other reasons for the small $|\rho_{XY}|$ -values, see below.)

In classes IV and V the nucleophile changes to benzylamine, benzoates and cinnamates. Benzylamine is more basic than aniline, $\Delta pK_a \approx 5.0$, and hence is a stronger nucleophile, but it has an extra intervening CH₂ group; we note that the magnitudes of ρ_{XY} for reactions O–Q are slightly greater than half those for the corresponding reactions with anilines in classes I and II, but the signs of ρ_X , ρ_Y and ρ_{XY} agree. Comparison of reactions O, P and Q again shows that $|\rho_{XY}|$ is greater for the fluoride series (reaction Q) than those for the chloride and bromide series (reactions O and P), although $|\rho_X|$ is smaller for the fluoride series. For reaction R, $|\rho_{XY}|$ ($=0.37$) is slightly greater than half of that for reaction C ($|\rho_{XY}| \approx 0.70$), suggesting a somewhat greater degree of bond formation, if the fall-off by a factor of 2.4–2.8 due to an extra intervening carbon in the benzoate nucleophile is allowed for (Charton, 1981; Siggel *et al.*, 1988). Another intervening ethylene group (CH=CH) in the cinnamate (reaction S) seems to reduce $|\rho_{XY}|$ further (to $|\rho_{XY}| = 0.22$), but not as much as expected, indicating that for this case bond formation may be somewhat greater than that for benzoate nucleophile. The $|\rho_{XY}|$ -values for reactions U, V and W are approximately half those for reactions L and M, reflecting the fall-off due to an extra intervening CH₂ or CH=CH group in the nucleophiles. Reaction series X has a little larger $|\rho_{XY}|$ than expected, probably because of the twofold interaction between the two identical substituents X in the two phenyl groups and the substituent Y in the substrate acid. The relatively small $|\rho_{XY}|$ -value for the reaction of thiols with acetylenes, Y, seems to suggest an early TS for this reaction, or poor transmission of electronic effects by the triple bond.

Some mixed Hammett/Brønsted-type cross-interaction constants λ_{ij} are summarized in Tables 3 (λ_{XY}) and 4 (λ_{YZ}), together with the ρ_{XY} and ρ_{YZ} values. These parameters contain only one constant factor (ρ_e^i) corresponding to the interaction between substituent (σ_i) and reaction centre (R_i); the magnitudes are thus somewhat greater than the corresponding values of $|\beta_{ij}|$ but smaller than those of $|\rho_{ij}|$ with opposite sign; for example $\lambda_{XY} > 0$, whereas $\rho_{XY} < 0$ and $\beta_{XY} < 0$. As expected, the magnitude of λ_{XY} (0.20–0.27), which is a measure of bond formation in the TS, does not show much variation for typical S_N2 reactions with aniline nucleophiles (reactions A–E in Table 3); this is an indication of the nearly similar degree of bond formation, i.e. $r_{XY} \approx \text{constant}$ for S_N2 reactions A–E with aniline nucleophiles, as concluded from the nearly constant values of $|\rho_{XY}|$ for the reactions. The size of λ_{XY} for reactions G, J and N is greater by a factor of over two than that for the other reactions (A–E), indicating a much greater

Table 3 Mixed Hammett/Brønsted-type cross-interaction constants λ_{xy} for nucleophilic substitution reactions in methanol.^a

Reactions		Temperature				
		°C	β_x	ρ_y	λ_{xy}	ρ_{xy}
A	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_5$	35.0	0.30	-0.73	0.22	-0.62 ^b
B	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{Cl}$	35.0	0.72	0.91	0.20	-0.70
C	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{COCl}$	35.0	0.75	-2.18	0.23	-0.68
D	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{Cl}$	35.0	0.58	-0.64	0.27	-0.75 ^b
E	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{Br}$	35.0	0.47	-0.51	0.25	-0.78 ^b
F	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{F}$	45.0	0.48	1.15	0.39	-1.07
G	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{COF}$	55.0	1.14	1.73	0.61	-1.67
H	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{Cl}$	35.0	1.40	1.52	0.39	-0.39
I	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{Br}$	45.0	1.15	-0.41	0.26	-0.38
J	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{F}$	45.0	0.78	0.71	0.63	-0.67
K	$\text{XC}_6\text{H}_4\text{CO}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{Cl}$	30.0	0.38	0.69	0.33	-0.37
L	$\text{XC}_6\text{H}_4\text{CHCHCO}_2 + \text{YC}_6\text{H}_4\text{SO}_2\text{Cl}$	30.0	0.62	0.63	0.44	-0.22
M	$\text{XC}_6\text{H}_4\text{NH}_2 +$ $\text{YC}_6\text{H}_4\text{CH}_2\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_5$	65.0	0.41	-0.38	0.26	-0.71 ^c
N	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{COSC}_6\text{H}_5$	55.0	1.84	1.41	-0.54	1.48 ^d
O	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 +$ $\text{YC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_5$	65.0	0.58	-0.02	0.01	-0.02 ^e

^a Lee *et al.* (1989d). ^b Benzyl system fits better with σ^+ rather than σ due to substantial positive charge development in the TS. ^c Menger and Smith (1972). ^d Shawali *et al.* (1986). ^e Lee *et al.* (1990j).

Table 4 Mixed Hammett/Brønsted-type cross-interaction constants λ_{yz} for nucleophilic substitution reactions in methanol.^a

Reactions		Temperature				
		°C	ρ_y	β_z	λ_{yz}	ρ_{yz}
A	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	35.0	-0.80	-2.36	-0.18	0.11
B	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	25.0	-0.40	-1.63	-0.19	0.11
C	$\text{XC}_6\text{H}_4\text{N}(\text{Me})_2 + \text{YC}_6\text{H}_4\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	35.0	-0.45	-2.01	-0.26	0.13
D	$\text{MeOH} + \text{YC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	65.0	-0.43	-1.81	0.12	-0.07
E	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	60.0	-0.16	-1.73	-0.11	0.07
F	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{COCH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	45.0	0.65	-2.12	1.04	-0.62
G	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{COCH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	45.0	0.56	-1.77	0.82	-0.52
H	$\text{MeOH} + \text{YC}_6\text{H}_4\text{CH}_2\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	65.0	-0.45	-0.40	0.33	-0.21 ^b
I	$(\text{CF}_3)_2\text{CHOH} +$ $\text{YC}_6\text{H}_4\text{CH}_2\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	50.0	-3.07	-0.36	0.64	-0.41 ^c
J	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	65.0	-0.36	-1.84	0.15	-0.10 ^b

^a Lee *et al.* (1989d). ^b Excluding Y = *p*-NO₂. ^c Lee *et al.* (1990i).

degree of bond formation in the TS of the nucleophilic substitution reaction of a carbonyl compound with a worse LG, fluoride or thiophenolate ion. Similarly, a comparison of reaction B ($\lambda_{XY} = 0.20$) with F ($\lambda_{XY} = 0.39$) also shows an increase in the degree of bond formation with fluoride LG. A slight increase in the degree of bond formation is noted in S_N2 reactions with benzylamine nucleophiles (H–J); the increment of $|\lambda_{XY}|$ relative to the values for the reactions with anilines is seen to be inversely proportional to the nucleofugic power of the LG, i.e. the increase is in the order $\text{Br} < \text{Cl} < \text{F}$. This demonstrates an increase in bond formation in the TS with a stronger nucleophile, the increase being greater for the compounds with a worse LG. This sort of fine quantitative analysis is difficult with $|\rho_{XY}|$, since $|\rho_{XY}|$ is also dependent on the intervening group between substituent and reaction centre, which reduces it to an uncertain degree; one such group is known approximately to halve the magnitude of ρ_i or ρ_{ij} value in general. The λ_{XY} -values for anionic nucleophiles (K and L) are somewhat greater than those for the corresponding reactions with neutral nucleophiles (B and H), indicating a somewhat greater degree of bond formation.

The λ_{YZ} -values for reactions A–C in Table 4 range from 0.18 to 0.26 with negative signs; the magnitude of λ_{YZ} , which is a measure of bond breaking, does not differ much from that of $|\lambda_{XY}|$, a measure of bond formation, for S_N2 reactions A–E in Table 3, indicating that similar bond distances r_{XY} and r_{YZ} are involved in the TS for the S_N2 type of reaction. The magnitude of λ_{YZ} for reactions D and E are somewhat smaller, but those for reactions F and G are much greater than the $|\lambda_{YZ}|$ -values for reactions A–C. This difference is mainly due to an intervening non-conjugating CH_2 group present between substituent Y and the reaction centre at the α -carbon, and partially due to some aryl participation for reactions D and E, whereas for reactions F and G it is due to the minimal bond breaking involved in the TS. A small decrease in $|\lambda_{YZ}|$ for reaction of benzylamine (G) indicates that, as the nucleophilicity increases from anilines (F) to benzylamines (G), the degree of bond breaking in the TS is increased. Three types of reactions (H–J) of 1-phenyl-2-propyl benzenesulphonates (PPB) in Scheme 3 provide an interesting example of variations in bond-breaking. In the two direct back-side attack pathways, k_N and k_S , the nucleophilicity is greater in k_N , since aniline has a greater nucleophilicity than methanol, but the solvent ionizing power is the same since both reactions were conducted in MeOH (Scheme 3). A smaller magnitude of ρ_{YZ} and λ_{YZ} for k_N indicates that bond breaking is greater with a stronger nucleophile, i.e. in TS_N rather than in TS_S . Solvolysis of PPB in hexafluoroisopropanol (HFIP) proceeds by the aryl-assisted path, k_A (Lee *et al.*, 1990i). The large $|\rho_{YZ}|$ - and $|\lambda_{YZ}|$ -values obtained indeed support this mechanism since, by bridging C_α and C_{ipso} in TS_A (i.e. [2]), an intervening CH_2 group is bypassed, thereby allowing a short cut between

Table 5 Brønsted-type cross-interaction constants β_{XZ} for nucleophilic substitution reactions in methanol.^a

	Reactions	Temperature		β_X	β_Z	β_{XZ}	ρ_{XZ}
		°C					
A	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	35.0	0.28		-2.24	-0.06	-0.10
B	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	25.0	0.72		-1.60	-0.32	-0.56
						0.15 ^b	-0.25 ^b
						0.4 ^c	-0.8 ^c
C	$\text{XC}_6\text{H}_4\text{N}(\text{Me})_2 + \text{YC}_6\text{H}_4\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	35.0	0.50		-2.00	-0.11	-0.24 ^d
D	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{COCH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	45.0	0.73		-2.14	0.19	0.31
E	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{YC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	65.0	0.44		-1.79	-0.28	-0.45
F	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{YC}_6\text{H}_4\text{COCH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	45.0	0.73		-1.49	0.17	0.12
G	$\text{XC}_6\text{H}_4\text{N}(\text{Me})_2 + \text{CH}_3\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	65.0	0.66		-0.36	0.11	0.24
			0.62 ^e		-0.46 ^e	0.12 ^e	0.20 ^e
H	$\text{XC}_6\text{H}_4\text{N}(\text{Me})_2 + \text{C}_2\text{H}_5\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	65.0	0.63		-0.33	0.12	0.26
			0.63 ^e		-0.46 ^e	0.13 ^e	0.27 ^e
I	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{CH}_3\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	55.0	0.60		-0.39	0.18 ^f	0.30 ^f
			0.66 ^e		-0.45 ^e	0.20 ^{e,f}	0.32 ^{e,f}
J	$\text{XC}_6\text{H}_4\text{NH}_2 + \text{C}_2\text{H}_5\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	55.0	0.62		-0.37	0.19 ^f	0.33 ^f
			0.67 ^e		-0.44 ^e	0.21 ^{e,f}	0.34 ^{e,f}
K	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{CH}_3\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	55.0	0.89		-0.43	0.26 ^f	0.18 ^f
L	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 + \text{C}_2\text{H}_5\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	55.0	0.89		-0.42	0.28 ^f	0.19 ^f
M	X-amines + Y-  - $\text{SO}_2\text{Cl}(\text{F})$	55.0	0.17		-0.79	0.08 ^g	

^a Lee *et al.* (1989d). ^b Dissected value for back-side direct attack. ^c Dissected value for front-side attack involving a four-centre TS. ^d Lee *et al.* (1989b). ^e Values in MeCN; Lee *et al.* (1990m).

^f Lee *et al.* (1989a). ^g Arcoria *et al.* (1981).

substituents Y and Z, in addition to a possibility of dual interaction provided by the bridged structure.

Some β_{XZ} -values for $\text{S}_{\text{N}}2$ -type reactions calculated by multiple linear regression using (5a) are presented in Table 5. As expected (see Section 2, p. 66) the signs of β_{XZ} and ρ_{XZ} agree, and the magnitude of β_{XZ} is proportional to, but smaller than, that of ρ_{XZ} . For the phenacyl series (reactions D and F), however, $|\beta_{XZ}|$ is nearly constant, indicating that a similar bond distance r_{XZ} ($r_{XY} + r_{YZ}$ in Scheme 2) is involved in the TS. This is in contrast with the difference of $|\rho_{XZ}|$ by a factor of about two for the two phenacyl series due to a non-conjugating CH_2 group intervening between the benzene ring and the reaction centre N in the benzylamine nucleophiles, despite the fact that there is no significant change in the bond distance r_{XZ} in

reality. This demonstrates that the Brønsted-type cross-interaction parameter is a more direct measure of the TS structure, while the Hammett-type parameters are mixed with constant factors (ρ_e^i and ρ_e^j) corresponding to the interactions between substituents and reaction centres, which, for most practical purposes, can be considered to remain intact during the activation process.

In a dissociative S_N2 reaction, bond breaking is ahead of bond formation so that the TS is loose. Conversely in an associative S_N2 process, the opposite holds and the TS is tight.

The dissociative S_N2 reaction A has the smallest $|\beta_{xz}|$ of 0.06, whereas the S_N reactions with twofold interaction pathways between the nucleophile and the LG in the TS (reactions B and E) (see below) give considerably greater $|\beta_{xz}|$ -values (0.32), as has been shown to be the case with $|\rho_{xz}|$ -values. For the associative S_N2 reactions (D and F) (see below), the magnitude of β_{xz} (0.17–0.19) is more than three times greater than the value for the dissociative S_N2 reaction A, in addition to a change in the sign from negative to positive.

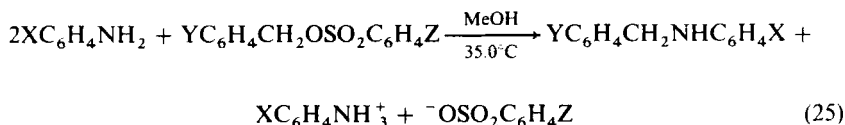
Another interesting application of cross-interaction constant is given for the reaction of 1-phenylethyl benzenesulphonates with anilines (B). This reaction is known to proceed by two discrete pathways, direct back-side attack (k_r) and front-side attack (k_f) involving a four-centre TS. In the four-centre TS [1], dual interaction routes are provided so that the magnitude of β_{xz} and ρ_{xz} is quite high (see below).

The aminolyses of methyl and ethyl benzenesulphonates (MBS and EBS) (reactions G–L) show that the TS is always tighter in MeCN than in MeOH, and tighter for EBS than for MBS. The size of β_{xz} indicates that the tightness of the TS with respect to amine decreases in the order benzylamine > aniline > *N,N*-dimethylaniline.

For reaction M, $|\beta_{xz}|$ obtained with $Z = F$ and Cl is relatively large (greater than that for reaction A) and this clearly indicates that the reaction proceeds by a concerted (S_N2) mechanism, not by an addition–elimination mechanism involving rate-limiting elimination of the intermediate with vanishing β_{xz} .

Dissociative and associative S_N2 reactions

The reaction of benzyl benzenesulphonates (BBS) with anilines. The ρ_{ij} -values determined for reaction (25) (Lee *et al.*, 1985, 1986b,c) are summar-



ized in Table 6. The sign of ρ_{XZ} is negative, so that the reaction is IB-controlled; in agreement with the predictions of (19b) ($B, B' > 0$) $|\rho_{XY}|$ and $|\rho_{YZ}|$ increase with a more positive σ_Z and σ_X respectively. In terms of bond lengths r_{XY} and r_{YZ} (Scheme 2), these trends correspond to a later TS for a stronger nucleophile and a better LG [$b, b' < 0$ in (15)]. There are anomalies for the electron-donating substituents in the nucleophile ($X = p\text{-MeO}$ and $p\text{-Me}$), for which strong conjugation between the reaction centre (R_Y) and the substrate (Y) ring is known to exist, so that the distance r_Y is compressed in the TS [3] (King and Tsang, 1979; Lynas and Stirling, 1984; Kost and Aviram, 1986; Amyes and Jencks, 1989; Lee *et al.*, 1990a) giving greater values for $|\rho_{YZ}|$. The size of ρ_{ij} is in the order $|\rho_{XY}| > |\rho_{YZ}| > |\rho_{XZ}|$, as expected from a dissociative S_N2 TS of somewhat advanced bond cleavage.

Table 6 ρ_{ij} -Values for reactions of benzyl benzenesulphonates with anilines in methanol at 30.0°C.^a

ρ_{XY}				ρ_{XZ}				ρ_{YZ}			
Z				X				Y			
<i>p</i> -Me	H	<i>p</i> -Cl	<i>m</i> -NO ₂	<i>p</i> -MeO	<i>p</i> -Me	H	<i>p</i> -Cl	<i>m</i> -NO ₂	H	<i>p</i> -Cl	<i>p</i> -NO ₂
-0.58	-0.62	-0.65	-0.72	0.35	0.20	0.11	0.13	0.14	-0.10	-0.19	-0.25

^a Lee *et al.* (1985, 1986b, c).

The kinetic isotope effects (KIE) involving both deuterated nucleophiles and substrate in Table 7 support the conclusions based on the sign and magnitude of ρ_{ij} regarding the TS structure and its variation with substituents X and Z.

Table 7 Kinetic isotope effects for reactions of $C_6H_5CH_2OSO_2C_6H_4Z$ with $XC_6H_4NH_2$ (AN) and $XC_6H_4CH_2NH_2$ (BA) in acetonitrile at 30.0°C.

X	Z	k_H/k_D		
		AN(D) + BBS ^a	BA(D) + BBS ^b	AN + BBS(D) ^c
<i>p</i> -MeO	<i>p</i> -NO ₂	0.89 ₈	0.94 ₀	1.10 ₂
<i>m</i> -NO ₂	<i>p</i> -NO ₂	0.95 ₁	0.95 ₃	1.09 ₅
<i>p</i> -MeO	<i>p</i> -Me	0.95 ₅	0.95 ₂	1.09 ₇
<i>m</i> -NO ₂	<i>p</i> -Me	0.97 ₃	0.96 ₆	1.08 ₉

^a With deuterated anilines; Lee *et al.* (1990d, f). ^b With deuterated benzylamines; Lee *et al.* (1990e). ^c With deuterated benzylic hydrogens; Lee *et al.* (1990h).

Replacement of both hydrogens on N in the nucleophile (aniline or benzylamine) leads to an inverse secondary α -deuterium KIE, $k_{\text{H}}/k_{\text{D}} < 1.0$ (in Table 7) as the two benzene rings on the nucleophile (X-ring) and substrate (Y-ring) are at an angle of about 150° , and the N—H and N—D bending vibrations are hindered in the TS relative to the initial state. The inverse secondary KIEs in Table 7 are in full accord with the trends expected from the negative ρ_{xz} -value observed, i.e. from an IB-controlled series, and (15) is seen to apply to this reaction with $b, b' < 0$; the inverse KIE is greater, i.e. $k_{\text{H}}/k_{\text{D}}$ is smaller, for the reaction with a better LG ($Z = p\text{-NO}_2$), indicating a higher degree of bond formation ($\Delta r_{\text{xy}} < 0$ since $\sigma_{\text{z}} > 0$ and $b < 0$). The trends are similar for both aniline and benzylamine nucleophiles, but the inverse secondary KIE is weaker ($k_{\text{H}}/k_{\text{D}}$ is greater) for the benzylamine nucleophile, indicating a lesser degree of hindrance in the TS, which in turn may result from a lesser degree of bond formation with benzylamines. Normal secondary deuterium KIEs ($k_{\text{H}}/k_{\text{D}} > 1.0$) are observed with substrate deuterated at the benzylic positions. A greater KIE with a stronger nucleophile ($X = p\text{-MeO}$) is again consistent with the predictions of the TS variation with $b, b' < 0$ in (15), i.e. IB-controlled with $\rho_{\text{xz}} < 0$. A greater $k_{\text{H}}/k_{\text{D}}$ -value is an indication of a lesser degree of congestion around the benzylic hydrogens, suggesting that a greater degree of bond breaking is achieved by a stronger nucleophile ($\Delta r_{\text{yz}} > 0$ since $\sigma_{\text{x}} < 0$ and $b' < 0$). Although a greater degree of bond formation is also expected from a stronger nucleophile, the TS is relatively loose, i.e. there is a dissociative $\text{S}_{\text{N}}2$ mechanism, so that a release of steric congestion by the more advanced bond cleavage of the LG can more than compensate for the increased congestion by the closer approach of a stronger nucleophile.

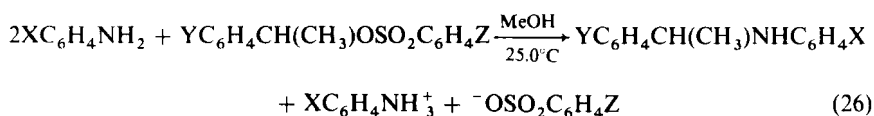
Table 8 Kinetic isotope effects for reactions of $\text{C}_6\text{H}_5\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{N}(\text{CH}_3)_2$ and $\text{C}_6\text{H}_4\text{CH}_2(\text{CH}_3)_2\text{NC}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{S}^-$.

X	Z	$k_{\text{H}}/k_{\text{T}}^a$	k^{14}/k^{15b}	$k_{\text{H}}/k_{\text{D}}^b$	ρ_{x}^b
<i>p</i> -MeO	<i>p</i> -Cl	1.06 ₁			
<i>p</i> -Me	<i>p</i> -Cl	1.05 ₅			
<i>p</i> -Me	H	1.04 ₃			
<i>p</i> -Me	<i>p</i> -MeO	1.03 ₅			
H	<i>p</i> -Cl	1.04 ₂			
H	<i>p</i> -MeO		1.0197	1.20 ₇	−1.54
H	H		1.0200	1.17 ₉	−1.70
H	<i>p</i> -Cl		1.0202	1.15 ₁	−1.83

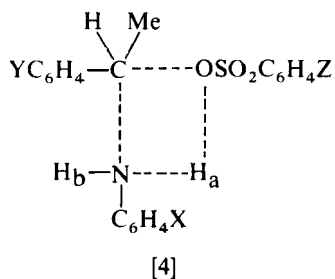
^a For the reactions of $\text{XC}_6\text{H}_4\text{N}(\text{CH}_3)_2$ with $\text{C}_6\text{H}_5\text{CH}_2^*\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$ (with tritiated benzylic hydrogens) in acetone at 35.0°C ; Ando *et al.* (1984). ^b For the reactions of $\text{XC}_6\text{H}_4\text{S}^-$ with $\text{C}_6\text{H}_5\text{CH}_2^*(\text{CH}_3)_2\text{N}^*\text{C}_6\text{H}_4\text{Z}$ in DMF at 0°C with $X = \text{H}$; Westaway and Ali (1979).

Similar KIE results are reported for the reactions of the benzyl system with *N,N*-dimethylanilines (DMA) (Ando *et al.*, 1984) and thiophenoxides (Westaway and Ali, 1979) in Table 8. The $k_{\text{H}}/k_{\text{T}}$, $k_{\text{H}}/k_{\text{D}}$ and k^{14}/k^{15} (nitrogen isotope effect) values shown in this table are all in agreement with the expected trends in the TS variation according to (15) for an IB-controlled reaction series ($\rho_{\text{XZ}} < 0$, $a, a' > 0$ and $b, b' < 0$). A stronger nucleophile ($\text{X} = p\text{-MeO}$, $\sigma_{\text{X}} < 0$) and a better LG ($\text{Z} = p\text{-Cl}$, $\sigma_{\text{Z}} > 0$) lead to a later TS; $k_{\text{H}}/k_{\text{T}}$ is greater, indicating $\Delta r_{\text{YZ}} = a'\sigma_{\text{Z}}$ and $\Delta r_{\text{YZ}} = b'\sigma_{\text{X}}$ with $a' > 0$ and $b' < 0$. Also k^{14}/k^{15} and $|\rho_{\text{X}}|$ are greater so that $\Delta r_{\text{YZ}} = a'\sigma_{\text{Z}}$ and $\Delta r_{\text{XY}} = b\sigma_{\text{Z}}$ with $a' > 0$ and $b < 0$, while $k_{\text{H}}/k_{\text{D}}$ (> 1.0) is smaller, i.e. $\Delta r_{\text{XY}} = b\sigma_{\text{Z}}$ with $b < 0$ as required by an IB-controlled reaction series.

The reactions of 1-phenylethyl benzenesulphonates (1-PEB) with anilines.
The cross-interaction constants for reaction (26) (Lee *et al.*, 1987b, 1988c)



are summarized in Table 9. The sign of ρ_{XZ} is again negative, so that the reaction is IB-controlled, and indeed (19a,b) are found to apply with $B, B' > 0$ as required. In the S_{N} -type reactions we should expect the $|\rho_{\text{XZ}}|$ -value to be the smallest among the three ρ_{ij} -values, as indeed was found in the reactions of BBS with anilines, since $r_{\text{XZ}} (= r_{\text{XY}} + r_{\text{YZ}})$ is normally longer than r_{XY} or r_{YZ} . In contrast, however, the $|\rho_{\text{XZ}}|$ in Table 9 is the greatest of the three. This unusual enhancement of the cross-interaction between substituents X and Z can only be rationalized by involvement of a four-centre TS, [4] (or [1]), i.e. by an intermolecular analogue of the S_{N}



mechanism (Gould, 1959). Two substituents X and Z in [4] can interact via two routes; an additional interaction route is provided by a bypass hydro-

gen-bond bridge so that the approach of the nucleophile aniline is restricted to the front side (k_f path), leading to retention of configuration in the amine product. One way of confirming the four-centre TS is to compare the $|\rho_{xz}|$ -values for a reaction with a nucleophile having no hydrogen atoms for bridge formation, e.g. *N,N*-dimethylaniline (DMA), with those in Table 9. Kinetic studies with DMAs conducted under the same conditions (Lee *et al.*, 1989b) gave markedly smaller values of $|\rho_{xz}|$, 0.23–0.25, less than half that for aniline. The impossibility of hydrogen-bond bridge formation is the main cause of the smaller $|\rho_{xz}|$.

Table 9 ρ_{ij} -Values for reactions of $\text{YC}_6\text{H}_4\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{NH}_2$ in methanol at 25.0°C.^a

Z	ρ_x	ρ_y	ρ_{xy}	X	ρ_y	ρ_z	ρ_{yz}	Y	ρ_x	ρ_z	ρ_{xz}
<i>p</i> -Me	-2.07	-0.39	-0.22	<i>p</i> -Me	-0.30	1.04	0.10	<i>p</i> -MeO	-2.11	0.91	-0.55
H	-2.20	-0.37	-0.21	H	-0.39	0.97	0.11	<i>p</i> -Me	-2.13	0.91	-0.55
<i>p</i> -Cl	-2.27	-0.34	-0.23	<i>p</i> -Cl	-0.45	0.78	0.13	H	-2.17	0.95	-0.56
<i>p</i> -NO ₂	-2.61	-0.25	-0.25	<i>m</i> -NO ₂	-0.50	0.56	0.14	<i>p</i> -Cl	-2.22	0.98	-0.56

^a Lee *et al.* (1987b, 1988c).

Table 10 Kinetic isotope effects for reactions of $\text{C}_6\text{H}_5\text{CH}(\text{Me})\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{NH}_2$ (D_2) at 30.0°C.^a

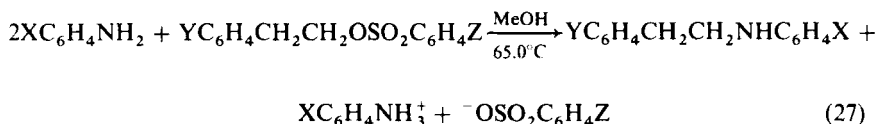
X	Z	k_H/k_D
<i>p</i> -MeO	<i>p</i> -Me	1.96 ₄
<i>p</i> -MeO	<i>p</i> -NO ₂	1.70 ₃
<i>m</i> -NO ₂	<i>p</i> -Me	2.58 ₃
<i>m</i> -NO ₂	<i>p</i> -NO ₂	2.34 ₈

^a Lee *et al.* (1990d, f).

There will be two significant vibrational changes involved in going from the reactants to TS [4]: N—H_a stretching and N—H_b bending. The former will result in a primary KIE, whereas the latter produces an inverse secondary KIE. These expectations are indeed borne out in the primary KIE observed in Table 10. The primary KIE in [4] is relatively small, since k_H/k_D is lowered (i) owing to the non-linear and unsymmetrical structure of N—H—O (Katz and Saunders, 1969; Melander and Saunders, 1980a,b; Kwart, 1982), (ii) by a concomitant inverse secondary KIE from the N—H_b bend-

ing vibration, (iii) by heavy atom (N and O) contribution to the reaction coordinate motion (Kaldor and Saunders, 1978; Melander and Saunders, 1980b), and, lastly and most importantly, (iv) owing to partial participation of the direct back-side attack pathway, k_r . A direct method of confirming the involvement of the four-centre TS is provided by optical rotation measurements of product stereochemistry. Such measurements for reaction of *p*-NO₂-1-PEB with *m*-NO₂-aniline in acetonitrile gave 9.3% net retention of product configuration (Lee *et al.*, 1990l). This means that the k_r (front-side attack) and k_t (back-side attack) pathways are approximately 55% (54.7%) and 45% (45.3%) respectively. Based on this, the ρ_{XZ} -value for TS_f becomes *ca* -0.8, assuming ρ_{XZ} for TS_r of -0.2 to -0.3. Likewise, the k_H/k_D -value corresponding to TS_f rises to *ca* 3.45, which is approximately half of the maximum primary KIE (k_H/k_D = 6–8) for a symmetrical linear three-centre TS (Westheimer, 1961). The abnormally large $|\rho_{XZ}|$ for reaction of 1-PEB with aniline proved to be a correct reflection of the involvement of the four-centre TS [4].

The reactions of 2-phenylethyl benzenesulphonates (2-PEB) with anilines. The cross-interaction constants (Lee *et al.*, 1988b) for reaction (27) are



summarized in Table 11. The reaction can proceed through two possible pathways in Scheme 3 (with the α -CH₃ group replaced by H). It has been shown that the k_s path does not interfere with the other two, aryl-assisted (k_A) and direct nucleophilic displacement (k_N) paths (Lee *et al.*, 1988b). A negative sign of ρ_{XZ} indicates that this reaction belongs to an IB-controlled series. The relations (19) are seen to hold, but $|\rho_{YZ}|$ behaves anomalously, i.e. $|\rho_{YZ}|$ decreases with a more EWS in the nucleophile ($\delta\sigma_X > 0$) instead of an increase expected from (19b). This could be attributed to a greater fraction *F* of the phenonium ion being captured by a stronger nucleophile. The values of $|\rho_{XY}|$ (0.10–0.17) are relatively small, in general slightly greater than half of the values for the 1-PEB reactions ($|\rho_{XY}|$ = 0.20–0.25) under similar reaction conditions. These rather unusually small $|\rho_{XY}|$ can be attributed to an extra CH₂ group in the substrate, which will reduce the intensity of interaction between substituent Y and reaction centre R_Y, and hence the $|\rho_{XY}|$ -values, by a factor of 2.4–2.8. Another reason for the small $|\rho_{XY}|$ -values is the participation of the aryl-assisted pathway, since the TS in this path, TS_Δ [2], does not include the nucleophile and constitutes an example of no

interaction, i.e. $\rho_{XY} = 0$ and $\rho_{XZ} = 0$. On the other hand, the $|\rho_{XZ}|$ -values are anomalously large, and similar to those for the reactions of 1-PEB. It is therefore likely that this reaction also proceeds by a four-centre TS, at least partially.

Table 11 ρ_{ij} -Values for reactions of $\text{YC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{NH}_2$ in methanol at 65.0°C.^a

Z	ρ_X	ρ_Y	ρ_{XY}	X	ρ_Y	ρ_Z	ρ_{YZ}	Y	ρ_X	ρ_Z	ρ_{XZ}
<i>p</i> -Me	-1.16	-0.17	-0.11	<i>p</i> -MeO	-0.11	1.17	0.10	<i>p</i> -MeO	-1.14	0.99	-0.38
H	-1.22	-0.15	-0.12	<i>p</i> -Me	-0.14	1.14	0.08	<i>p</i> -Me	-1.19	1.04	-0.45
<i>p</i> -Cl	-1.34	-0.12	-0.13	H	-0.16	1.03	0.07	H	-1.23	1.06	-0.45
<i>p</i> -NO ₂	-1.58	-0.10	-0.17	<i>p</i> -Cl	-0.18	0.96	0.07	<i>p</i> -Br	-1.26	1.08	-0.44
								<i>p</i> -NO ₂	-1.33	1.10	-0.49

^a Lee *et al.* (1988b).

In direct nucleophilic substitution, the N—H vibration, stretching as well as bending, within the aniline nucleophile will be sterically hindered to some extent relative to the ground-state aniline due to the steric crowding incurred by bond formation. Unlike the $\text{C}_\alpha\text{—H}$ vibration of a substrate molecule in an $\text{S}_\text{N}1$ reaction (Lowry and Richardson, 1987c), in no case will it become sterically relieved in the TS relative to the ground-state aniline; thus we should invariably observe an inverse secondary KIE ($k_\text{H}/k_\text{D} < 1.0$) with deuterated aniline nucleophiles, and there can be no possibility of observing normal KIE ($k_\text{H}/k_\text{D} > 1.0$), unless effects other than the steric inhibition are operative in the TS. One such possibility may be the N—H bond distension caused by hydrogen-bond formation of the H-atom toward another electronegative heteroatom in the TS leading to a weak primary KIE, such as $\text{N—H}_\text{a}\text{—O}$ in TS_f [4].

The KIEs observed for 2-PEB ($\text{R} = \text{H}$) are summarized in Table 12. We note that the k_H/k_D -values are near unity; the values are less than unity for a strong nucleophile ($\text{X} = \textit{p}\text{-MeO}$), whereas they are greater than unity for a weak nucleophile ($\text{X} = \textit{p}\text{-Cl}$). For this reaction, ρ_{XZ} is negative, so that the relations (15) with negative constants b and b' are expected to apply. This means that a stronger nucleophile leads to a greater degree of bond formation, and hence a greater steric hindrance will result in a greater inverse secondary KIE, i.e. k_H/k_D (< 1.0) will be smaller. Conversely, a weaker nucleophile ($\text{X} = \textit{p}\text{-Cl}$) should result in a lower inverse secondary KIE, i.e. k_H/k_D (< 1.0) will be larger, *but it can never be greater than unity in TS_r and/or TS_A* . This lends support to the probability of an involvement of

TS_f in the reactions with a weak nucleophile ($X = p\text{-Cl}$), since for $X = p\text{-Cl}$ the k_H/k_D -values are greater than unity. Indeed the unusually large magnitude of ρ_{XZ} for this reaction suggests a four-centre TS (TS_f) with a hydrogen-bond bridge $N-H_a-O$ providing an enhanced interaction due to an extra bypass interaction route between the substituents X and Z .

Table 12 Kinetic isotope effects for reactions of $YC_6H_4CH_2CH_2OSO_2C_6H_4Z$ with $XC_6H_4NH_2(D_2)$ in acetonitrile at 30.0°C .^a

X	Y	Z	k_H/k_D
<i>p</i> -MeO	H	<i>p</i> -NO ₂	0.97 ₆
<i>p</i> -MeO	<i>p</i> -NO ₂	<i>p</i> -NO ₂	0.97 ₅
<i>p</i> -MeO	<i>p</i> -MeO	<i>p</i> -Me	0.98 ₂
<i>p</i> -MeO	H	<i>p</i> -Me	0.96 ₁
<i>p</i> -Cl	H	<i>p</i> -NO ₂	1.03 ₁
<i>p</i> -Cl	H	<i>p</i> -Me	1.04 ₀

^a Lee *et al.* (1990g).

The same factors contribute to such a small primary KIE due to TS_f as for the reactions of 1-PEB with aniline. Since a stronger nucleophile ($X = p\text{-MeO}$) leads to a greater degree of bond formation in TS_f and TS_r , the inverse secondary effect ($k_H/k_D < 1.0$) can prevail over the primary KIE because the greater steric hindrance causes greater inverse effects, especially when the primary KIE is relatively small. In contrast, a weak nucleophile will result in less steric inhibition, causing a lower inverse effect; the primary KIE due to the $N-H_a$ distension in TS_f can then overwhelm the inverse secondary KIE. The balance of the two opposing KIEs can shift rather readily to either side of unity since the product of the two near-unity (primary and inverse secondary) effects is observed experimentally.

In this respect, relatively large primary KIEs observed for the 1-phenylethyl series, $k_H/k_D = 1.70\text{--}2.58$ (Table 10), can be taken as an indication of a large contribution of the k_f - compared with the k_r -path for the reactions of this series; the α -methyl group should sterically hinder the rear-side attack, diminishing the importance of the k_r -path. In addition, the k_Δ -path is not available for this compound, so that a greater role is played by the k_f -path. For this reaction series, ρ_{XZ} was also negative, and hence a greater degree of steric hindrance to the $N-H$ vibration of the aniline nucleophile in the two paths, k_f and k_r , by a stronger nucleophile and a better leaving group should cause a decrease in the primary KIE ($k_H/k_D > 1.0$), as indeed has been observed.

The aryl participation, k_Δ , is only conspicuous for a strong electron-

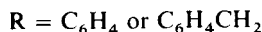
donating substituent in the substrate ($Y = p\text{-MeO}$); comparison of entries 3 and 4 in Table 12 indicates that k_H/k_D is greater (i.e. the inverse secondary effect is smaller) for $Y = p\text{-MeO}$ than for $Y = \text{H}$ owing to the relatively greater contribution of TS_A . A greater contribution of TS_A should reduce the steric hindrance of the N-H vibrations, leading to a lower inverse KIE, since in TS_A no bond formation occurs.

Table 13 Values ρ_{xz} and β_{xz} for reactions of $\text{ROSO}_2\text{C}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{NH}_2$ and $\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2$ in methanol and acetonitrile at 65.0°C ; $\text{R} = \text{Et}$ or Me .^a

R	ρ_{xz}			β_{xz}		
	$\text{XC}_6\text{H}_4\text{NH}_2$	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2$		$\text{XC}_6\text{H}_4\text{NH}_2$	$\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2$	
Et	0.33 ^b	0.34 ^c	0.19 ^c	0.19 ^b	0.21 ^c	0.28 ^c
Me	0.30 ^b	0.32 ^c	0.18 ^c	0.18 ^b	0.20 ^c	0.26 ^c

^a Lee *et al.* (1989a). ^b In methanol. ^c In acetonitrile.

The reactions of alkyl benzenesulphonates with anilines and benzylamines. The Hammett- and Brønsted-type cross-interaction constants ρ_{xz} and β_{xz} for reaction (28) are shown in Table 13 (Lee *et al.*, 1989a). The sign of



ρ_{xz} (and β_{xz}) is positive and the reactions are under TB control so that $a, a' < 0$ and $b, b' > 0$ in (15), and a stronger nucleophile ($\sigma_{\text{x}} < 0$) and a better LG ($\sigma_{\text{z}} > 0$) lead to an earlier TS, i.e. a smaller degree of bond formation ($\Delta r_{\text{xy}} > 0$) and bond breaking ($\Delta r_{\text{yz}} < 0$). The magnitude of ρ_{xz} (and β_{xz}) is slightly greater in MeCN than in MeOH, indicating that the TS is somewhat tighter in MeCN. The ρ_{xz} -value for benzylamine is smaller than that for aniline because of fall-off of the intensity of interaction by a factor of *ca* 2.4–2.8, caused by the intervening CH_2 group in benzylamine. In contrast, the β_{xz} -value is greater for benzylamine than for aniline, since the β_{ij} -values reflect the intensity of direct interaction between the two reaction centres, N and C_a , with no such fall-off effect due to the intervening group. Thus in fact the reaction of benzylamine leads to a tighter TS. It is rather unexpected to find that, for the ethyl compound (EBS), ρ_{xz} and β_{xz} are slightly greater, indicating a tighter TS than for the methyl compound

(MBS). The steric crowding in the TS for the ethyl system raises the activation energy and the rate is retarded; a later TS for bond formation, i.e. a tighter TS, is expected, in accordance with the Hammond postulate (Hammond, 1955; Lowry and Richardson, 1987b).

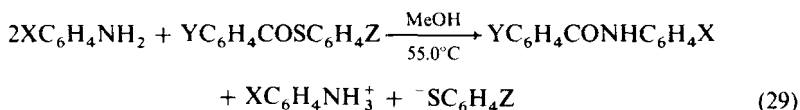
The magnitude of ρ_{xz} in Table 13 is about threefold greater than that for a typical dissociative S_N2 reaction ($\rho_{xz} = -0.10$ for the reaction of BBS with anilines), suggesting an associative S_N2 mechanism with a much tighter TS for the alkyl benzenesulphonates. The inverse secondary KIEs involving deuterated aniline nucleophiles also support this conclusion. The k_H/k_D -values in Table 14 are substantially smaller than those for the reactions of BBS (Table 7), correctly reflecting much steric congestion in the TS for the alkyl system. The magnitude of k_H/k_D predicts a TS variation that is in agreement with that based on the magnitude of ρ_{xz} (and β_{xz}); a stronger nucleophile ($X = p\text{-MeO}$) and a better LG ($Z = p\text{-NO}_2$) lead to a greater k_H/k_D -value, i.e. less crowding with a looser TS, as predicted by (15) for $\rho_{xz} > 0$ with $a, a' < 0$ and $b, b' > 0$. The results of similar α -deuterium secondary KIE studies by Ando *et al.* (1984) and Yamataka and Ando (1975, 1979, 1982) for the reactions of deuterated methyl benzenesulphonate ($Z = p\text{-Br}$) with p -substituted DMA are also in accord with the predictions of the TS variation for a TB-controlled system ($\rho_{xz} > 0$). In this case a stronger nucleophile ($X = p\text{-MeO}$) has a greater value of k_H/k_D , reflecting a smaller degree of bond formation, i.e. $\Delta r_{XY} > 0$ for $\sigma_X < 0$, since $a < 0$ for $\rho_{xz} > 0$ in (15). Consistent with this observation, an earlier TS for a stronger nucleophile was also reported by Ando *et al.* (1987) and Harris *et al.* (1981) in their KIE studies of the reaction of CH_3I with 3,5-disubstituted pyridines involving α -deuterium and carbon-13 isotopes in CH_3I ; with 3,5-dimethyl- and 3,5-dichloro-substitution in pyridine, $k^{12}/k^{13} = 1.063$ and 1.076 and $k_H/k_D = 0.908$ and 0.810 respectively, indicating a smaller degree of bond breaking and bond formation with the stronger nucleophile.

The reactions of thiophenyl benzoates with anilines. The cross-interaction constants ρ_{ij} and β_{xz} , determined for reaction (29) of thiophenyl benzoates

Table 14 Secondary kinetic isotope effects for reactions of $\text{CH}_3\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in acetonitrile at 65.0°C.

X	Z	k_H/k_D^a
<i>p</i> -MeO	<i>p</i> -NO ₂	0.86 ₉
<i>p</i> -MeO	<i>p</i> -Me	0.86 ₂
<i>m</i> -NO ₂	<i>p</i> -NO ₂	0.85 ₈
<i>m</i> -NO ₂	<i>p</i> -Me	0.85 ₁ (0.96 ₃) ^b

^a Lee *et al.* (1990f). ^b Values for reactions of $\text{CH}_3\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$.



(TPB) with anilines (Lee *et al.*, 1990n) are shown in Table 15. The sign of ρ_{xz} (and β_{xz}) is positive, so that this reaction series is again under TB control, and a stronger nucleophile and a better LG lead to an earlier TS. The magnitude of ρ_{xy} is very large, and, as discussed in Section 4 (p. 76), bond formation is very much advanced in the TS. The magnitude is also large for ρ_{yz} and ρ_{xz} (an associative $\text{S}_{\text{N}}2$ reaction), but in this case the LG has no extra intervening group between reaction centre S and substituent Z, in contrast with the benzenesulphonate, which does have such an intervening group, SO_2 , between reaction centre O and substituent Z. Thus, in comparing the magnitude of ρ_{yz} and ρ_{xz} between the two LGs $^-\text{SC}_6\text{H}_4\text{Z}$ and $^-\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$, we have to take a factor of 2.4–2.8 into consideration. The magnitude of the two will correspond to $|\rho_{\text{yz}}| \approx 0.5$ and $|\rho_{\text{xz}}| \approx 0.2$ when corrected for an intervening group, so that they can be compared with benzenesulphonates as a LG. The size of β_{xz} is not, however, affected by an intervening group and hence is directly comparable between different sets of systems irrespective of the intervening groups present in any reactant. We note that the size of the two cross-interaction constants, ρ_{xz} (≈ 0.2 , corrected) and β_{xz} ($= 0.085$), are smaller than those for methyl benzenesulphonates [$\rho_{\text{xz}} = 0.30$ and $\beta_{\text{xz}} = 0.18$ (Table 15)], but are greater than those for BBS [$|\rho_{\text{xz}}| = 0.10$ (Table 6) and $|\beta_{\text{xz}}| = 0.06$ (Table 5)]; the tightness of the TS will be intermediate between the two. The inverse secondary KIEs shown in Table 16 are also consistent with this conclusion, the $k_{\text{H}}/k_{\text{D}}$ -values being smaller than those for BBS but greater than those for EBS (after applying a temperature correction to $k_{\text{H}}/k_{\text{D}}$). According to the KIE, the TS is looser with a stronger nucleophile, as predicted by (15) for $\rho_{\text{xz}} > 0$. In contrast, the effect of LG seems very small as reflected in small changes in $|\rho_{\text{yz}}|$ as well as in $k_{\text{H}}/k_{\text{D}}$.

Table 15 Cross-interaction constants for reactions of $\text{YC}_6\text{H}_4\text{COSC}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{NH}_2$ in methanol at 55.0°C .^a

Z	ρ_{xy}	X	ρ_{yz}	Y	ρ_{xz}	β_{xz}
<i>p</i> -Me	1.49	<i>p</i> -MeO	−1.31	H	0.56	0.029
H	1.48	<i>p</i> -Me	−1.34	<i>p</i> -Cl	0.46	0.029
<i>p</i> -Cl	1.37	H	−1.38	<i>p</i> -NO ₂	0.43	0.021
<i>p</i> -NO ₂	1.35	<i>p</i> -Cl	−1.38			

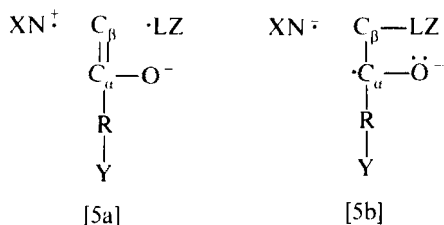
^a Lee *et al.* (1990n).

Table 16 Kinetic isotope effects for reactions of $C_6H_5COSC_6H_4Z$ with $XC_6H_4NH_2(D_2)$ in acetonitrile at $55.0^\circ C$.^a

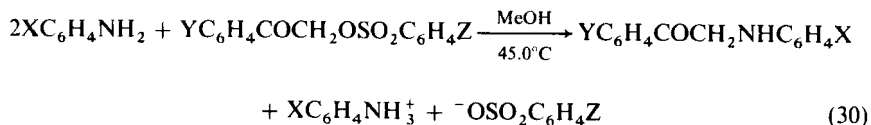
X	Z	k_H/k_D
<i>p</i> -MeO	<i>p</i> -NO ₂	0.89 ₉
<i>p</i> -MeO	<i>p</i> -Me	0.89 ₃
<i>p</i> -Cl	<i>p</i> -NO ₂	0.87 ₀

^a Lee *et al.* (1990m).

The reactions of phenacyl benzenesulphonates with anilines. The nucleophilic substitution reactions of α -carbonyl derivatives (Lee *et al.*, 1988e, 1989c) have attracted considerable interest from physical organic chemists in view of the rate-enhancing effect of the α -carbonyl group (Streitwieser, 1962). McLennan and Pross (1984) applied the valence bond configuration-mixing (VBCM) model to explain the mechanism of the α -carbonyl compounds and suggested the introduction of the enolate VB form of the carbanion [5] in



describing the TS structure. It is of interest to obtain experimental evidence for the involvement of such carbanion VB forms in the TS using the cross-interaction constants. The cross-interaction constants for reaction series (30)



are summarized in Table 17. The sign of ρ_{XZ} is positive, implying that this reaction is under TB control with $a, a' < 0$ and $b, b' > 0$ in (15). We note that $|\rho_{\text{XZ}}|$ is relatively large compared with those for dissociative $\text{S}_{\text{N}}2$ reactions of BBS and 1-PEB [$|\rho_{\text{YZ}}| = 0.11$ with $\text{X} = \text{H}$ (Tables 6 and 9)] and 2-PEB [$|\rho_{\text{YZ}}| = 0.07$ with $\text{X} = \text{H}$ (Table 11)], and with those for an associative $\text{S}_{\text{N}}2$ reaction of TPB [$|\rho_{\text{YZ}}| \approx 0.2$, corrected (Table 15)]. This shows that

Table 17 ρ_{ij} -Values for reactions of $\text{YC}_6\text{H}_4\text{COCH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{NH}_2$ in methanol at 45.0°C.^a

Z	ρ_X	ρ_Y	ρ_{XY}	X	ρ_Y	ρ_Z	ρ_{YZ}	Y	ρ_X	ρ_Z	ρ_{XZ}
<i>p</i> -Me	-2.06	0.71	0.14	<i>p</i> -MeO	0.60	1.14	-0.63	H	-2.01	1.24	0.32
H	-1.97	0.61	0.11	<i>p</i> -Me	0.64	1.17	-0.65	<i>p</i> -Cl	-1.96	1.09	0.31
<i>p</i> -Cl	-1.92	0.47	0.10	H	0.66	1.23	-0.66	<i>p</i> -NO ₂	-1.85	0.48	0.23
<i>m</i> -NO ₂	-1.77	0.18	0.07	<i>p</i> -Cl	0.67	1.30	-0.67				

^a Lee *et al.* (1988c, 1989c).

bond breaking has progressed very little in the TS for this reaction. The size of ρ_{XZ} is also relatively large, again indicating a small degree of bond cleavage in the TS. Two anomalies are noted in the size of ρ_{ij} in Table 17: (a) $|\rho_{XY}|$ is unusually small; and (b) $|\rho_{YZ}|$ increases in parallel with $|\rho_Y|$ and $|\rho_Z|$. The magnitude of ρ_{XY} for other $\text{S}_{\text{N}}2$ reactions under normal conditions with LGs comparable to benzenesulphonates was found to lie in the range 0.62–0.78 (Table 2), and hence $|\rho_{XY}|$ of 0.05–0.14 in Table 17 is abnormally small, even after allowing for the fall-off factor of 2.4–2.8 for an intervening CO group in phenacyl benzenesulphonates (PAB). This can be explained in fact by the involvement of an enolate VB structure [5a], in which the α -CO group provides a “shunt” or “leak” in the resonance between the reaction centre C_β and the substituent Y. Since charge transfer to the reaction centre from the nucleophile cannot be transmitted to substituent Y in structure [5], interaction between substituents X and Y is impossible, so that involvement of this structure in the TS would weaken the interaction, and hence $|\rho_{XY}|$ is decreased. This interpretation is supported by the second anomaly noted above: the parallel increase in the $|\rho_{YZ}|$ value with $|\rho_Y|$ and $|\rho_Z|$ as the substituent X becomes more electron-withdrawing (e.g. $\text{X} = \text{p-Cl}$). The increase in ρ_Z within a series of reactions is normally taken as an increase in bond cleavage, which should result in a decrease in the $|\rho_{YZ}|$ values, in contrast with the observed increase. This can be rationalized in terms of the enhanced contribution of the resonance “shunt”, [5a], by the α -CO group as charge transfer increases; this results in a resonance bond contraction of $\text{C}_\alpha\text{—C}_\beta$ (Lee, 1990a; Lee *et al.*, 1990a), and will give a larger observed $|\rho_{YZ}|$ because of the shorter distance r_Y in (18). If, however, the valence bond structure of the other enolate form, [5b], were involved in the TS, an abnormally small $|\rho_{XY}|$ would not have been observed, since the interaction between X and Y is possible in this form.

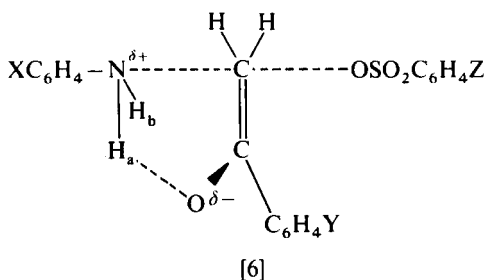
The involvement of structure [5a] in the TS is also supported by the primary KIE observed with deuterated aniline nucleophiles in Table 18. The

Table 18 Kinetic isotope effects for reactions of $\text{YC}_6\text{H}_4\text{COCH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$ with $\text{XC}_6\text{H}_4\text{NH}_2(\text{D}_2)$ in acetonitrile at 45.0°C .^a

X	Y	Z	$k_{\text{H}}/k_{\text{D}}$
<i>p</i> -MeO	H	<i>p</i> -NO ₂	1.02 ₉
<i>p</i> -MeO	H	<i>p</i> -Me	1.03 ₄
<i>m</i> -NO ₂	H	<i>p</i> -NO ₂	1.05 ₇
<i>m</i> -NO ₂	H	<i>p</i> -Me	1.07 ₈
<i>m</i> -NO ₂	<i>p</i> -NO ₂	<i>p</i> -Me	1.10 ₄

^a Lee *et al.* (1990f).

sign and magnitude of ρ_{XZ} for the reaction of PAB are remarkably similar to those of EBS (Table 14). In contrast with the similarity of the two reactions of PAB and EBS, the KIEs in Tables 18 and 14 exhibit a striking difference: the $k_{\text{H}}/k_{\text{D}}$ -values for the reactions of PAB are greater than unity ($k_{\text{H}}/k_{\text{D}} > 1.0$), in contrast with the inverse secondary KIE ($k_{\text{H}}/k_{\text{D}} < 1.0$) obtained for the reactions of EBS. Since the N—H or N—D stretching and/or bending vibrations in the aniline nucleophile can only result in hindrance (and never in a release of congestion) in bond formation (i.e. in the TS), a $k_{\text{H}}/k_{\text{D}}$ greater than unity can only be reconciled with the resonance “shunt” phenomenon of structure [5a]. In the TS [6] the N—H_a bond stretching



due to hydrogen bonding of H_a towards the carbonyl oxygen can give a primary KIE ($k_{\text{H}}/k_{\text{D}} > 1.0$) that will be reduced by a concomitant inverse secondary KIE ($k_{\text{H}}/k_{\text{D}} < 1.0$) of the N—H_b bending vibration. Since this reaction has a positive ρ_{XZ} , the TS variations with substituent changes are consistent with those predicted by a , $a' < 0$ and b , $b' > 0$ in equation (15); the bypass electron flow or leak from the aniline nucleophile to the carbonyl oxygen is expected to increase as the degree of bond formation increases (i.e. there is a decrease in the N—C_β distance) with a weaker nucleophile ($\text{X} = m\text{-NO}_2$) and a worse LG ($\text{Z} = p\text{-CH}_3$), which in turn result in a resonance

contraction of the $C_\alpha-C_\beta$ bond (Lee, 1990a; Lee *et al.*, 1990a). The decrease in the $N-C_\beta$ and $C_\alpha-C_\beta$ distances will not only transfer more negative charge to the carbonyl oxygen but will also contract the $O-H_a$ distance, enabling formation of a stronger hydrogen bond. Thus a greater stretching of $N-H_a$ with a greater primary KIE, k_H/k_D , will result, as has indeed been observed (Table 18). However, this primary KIE is small mainly due to the weak hydrogen bond formed between H_a and the relatively distant O; in addition, the bent and unsymmetrical structure of $N-H_a-O$ and the concomitant inverse secondary KIE of the $N-H_b$ bending vibration act to cancel out part of the primary KIE of $N-H_a$.

Group transfer reactions

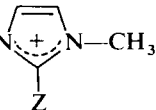
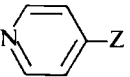
Although group (R) transfer reactions (31) really belong to S_N2 reactions, they have some interesting aspects of their own and have been extensively investigated in recent years. The most simple one in this category is the methyl ($R = CH_3$) transfer between identical fragments, $XN = LZ$, which may therefore be called an "identity-exchange reaction" (Pellerite and Brauman, 1980; Lewis and Hu, 1984; Lee, 1989, 1990c; Lee *et al.*, 1988a, 1990b). Since the two fragments, XN and LZ , are equal, the reaction is thermoneutral. This means that in the Marcus equation (14) the thermodynamic barrier (TB) ΔG^0 is zero, and the activation barrier $\Delta G^\ddagger$ is entirely represented by the intrinsic barrier (IB) $\Delta G_0^\ddagger$ in this type of reaction. The stereoelectronic origin of the IB has been discussed by Lee (1990c). The cross-interaction constants ρ_{xz} and β_{xz} in Table 19 provide information concerning the nature and the TS structure for selected group-transfer reactions.



For the identity exchange reactions, $\sigma_x = \sigma_z$, the variation of TS structure must follow (15) with $a, a' > 0$ and $b, b' < 0$, since for these types of reactions ρ_{xz} is normally negative. However, a conflict in the prediction arises between the primary and secondary effects of (15); for example, for a stronger nucleophile ($\sigma_x < 0$), the former predicts a tighter TS, i.e. $\Delta r_{xy} < 0$ and $\Delta r_{yz} < 0$, since $a, a' > 0$ and $\sigma_x = \sigma_z < 0$, whereas the latter predicts a looser TS, $\Delta r_{xy} > 0$ and $\Delta r_{yz} > 0$ since $b, b' < 0$ and $\sigma_x = \sigma_z < 0$. In practice, it was found that the latter prediction is correct and a stronger nucleophile (a worse LG since $\sigma_x = \sigma_z$) leads to a looser TS (Lee, 1990a,c).

In some cases, positive ρ_{xz} -values ($\rho_{xz} > 0$) are observed for the identity-exchange reactions, for which the TB is zero, and hence the reaction is necessarily under IB control. This is contrary to the classification applicable to non-identity reactions, $XN \neq LZ$ (i.e. non-thermoneutral reactions), since

Table 19 Cross-interaction constants for group-transfer reactions.

	Reactions	ρ_{ij} or β_{ij}	References
A	$\text{XC}_6\text{H}_4\text{OSO}_2 + \text{CH}_3\text{OSO}_2\text{C}_6\text{H}_4\text{Z}$	$\rho_{\text{xz}} = -0.003 \text{ (X=Z)}$	Lewis and Hu (1984)
B	$\text{XC}_6\text{H}_4\text{S}^- + \text{CH}_3\text{SC}_6\text{H}_4\text{Z}$	$\rho_{\text{xz}} = -0.001 \text{ (X=Z)}$	Lewis and Kukes (1979)
C	$\text{XC}_6\text{H}_4\text{Se}^- + \text{CH}_3\text{SeC}_6\text{H}_4\text{Z}$	$\rho_{\text{xz}} = -0.007 \text{ (X=Z)}$	Lewis <i>et al.</i> (1987)
D	$\text{XC}_6\text{H}_4\text{OSO}_2 + \text{C}_6\text{H}_5\text{COCH}_2\text{SO}_2\text{C}_6\text{H}_4\text{Z}$	$\rho_{\text{xz}} = 0.017 \text{ (X=Z)}$	Yousaf and Lewis (1987)
E	$\text{XC}_6\text{H}_4\text{O}^- + {}^-\text{SO}_3-\text{N}^+\langle\text{C}_6\text{H}_4\rangle\text{Z}$	$\beta_{\text{xz}} = 0.030$	Hopkins <i>et al.</i> (1983)
F	X-amines + ${}^-\text{PO}_3-\text{N}^+\langle\text{C}_6\text{H}_4\rangle\text{Z}$	$\beta_{\text{xz}} = 0.021$	Jameson and Lawlor (1970)
G	$\text{X}-\langle\text{C}_6\text{H}_4\rangle\text{N} + {}^-\text{PO}_3-\text{N}^+\langle\text{C}_6\text{H}_4\rangle\text{Z}$	$\beta_{\text{xz}} = 0.014$	Skoog and Jencks (1984)
H	$\text{XRO}^- + {}^-\text{PO}_3-\text{N}^+\langle\text{C}_6\text{H}_4\rangle\text{Z}$	$\beta_{\text{xz}} = 0.013$	Herschlag and Jencks (1989)
I	X-amines + $\text{SO}_2(\text{C}_6\text{H}_4\cdot\text{CH}_3)-\text{N}^+\langle\text{C}_2\text{H}_3\rangle\text{N}-\text{CH}_3$ 	$\beta_{\text{xz}} = 0.052$	Monjoint and Ruasse (1988)
J	X-amines + $\text{CH}_3\text{CO}-\text{N}\langle\text{C}_6\text{H}_4\rangle\text{Z}$ 	$\beta_{\text{xz}} = 0.059$	Fersht and Jencks (1970)
K	$\text{XC}_6\text{H}_4\text{O}^- + \text{CH}_3\text{COOC}_6\text{H}_4\text{Z}$	$\beta_{\text{xz}} = 0.17 \text{ (X=Z)}$	Ba-Saif <i>et al.</i> (1989)

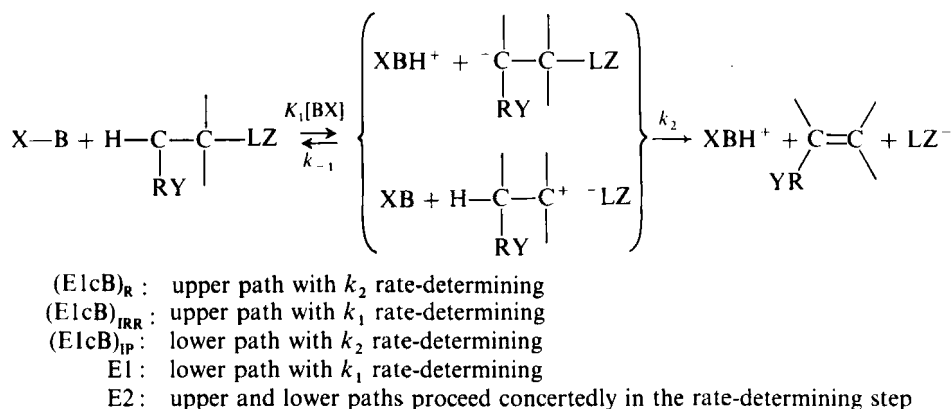
a positive ρ_{xz} for such reactions should indicate that the reaction is under TB control. In such identity-exchange reactions with a positive ρ_{xz} -value, the TS variation follows (15) with $a, a' < 0$. In other words, when $\rho_{xz} < 0$ the TS variation follows that expected from the secondary effect, whereas when $\rho_{xz} > 0$ the TS varies in accordance with that expected from the primary effect in (15). For identity exchanges, a negative ρ_{xz} (or β_{xz}) is usually associated with a loose TS in which bond breaking is ahead of bond cleavage, with positive charge development at the reaction centre, whereas a positive ρ_{xz} (or β_{xz}) is associated with a tight TS in which bond formation is ahead of bond breaking, with negative charge development at the reaction centre (Lee *et al.*, 1988e). Thus identity-exchange reactions are a special class of S_N2 reactions and must be excepted from the application of general rules (of non-identity reactions) for the prediction of the TS variations with substituents. The methyl transfer reactions A–C in Table 19 have quite small ρ_{xz} -values, indicating an open, “exploded” type of TS structure for these reactions. On the other hand, the phenacyl transfer reaction D has ρ_{xz} of about five times greater magnitude compared with that for reaction A (which can be directly compared since the two have the same NX^- or $LZ^- = XC_6H_4SO_2O^-$), in addition to its positive sign, which is in contrast with the negative ρ_{xz} -values for methyl transfer reactions; these observations suggest that the TS for the phenacyl transfer is much tighter than those for the methyl transfer.

β_{xz} -Values are smaller for the phosphoryl-transfer reactions F, G and H than for the sulphonyl-transfer reaction E, indicating the involvement of a very loose “exploded” TS structure for the phosphoryl transfer. The TS structure seems a little tighter for tosyl transfer I and acetyl transfer J than the sulphonyl transfer E. The greatest β_{xz} ($=0.17$), and hence the tightest TS, found so far is for acetyl transfer reactions between phenoxide anions, K. This is remarkable in view of the fact that the reaction is an identity exchange (i.e. $X = Z$) with a positive β_{xz} , and the aryloxide ions are displaced concertedly from phenyl acetates by phenoxide ions; the reaction does not proceed via a tetrahedral intermediate normally believed to be involved in carbonyl addition reactions (Bender, 1951; Patai, 1966). In this respect, the observation of non-zero cross-interaction constants, ρ_{xz} or β_{xz} , between the nucleophile (X) and LG (Z) itself constitutes strong evidence for concerted bond formation and bond breaking in the TS (Ba-Saif *et al.*, 1989; Williams, 1989).

β -ELIMINATION REACTIONS

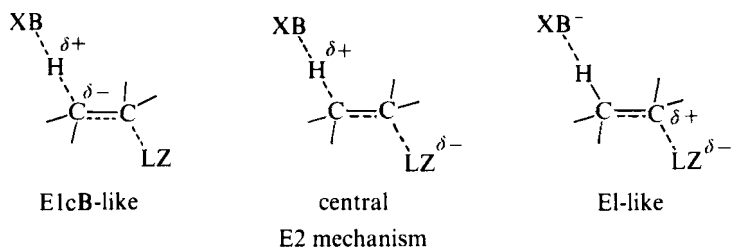
One of the most widely studied general class of organic reactions is the base-

promoted olefin-forming (including imine- and nitrile-forming) 1,2-elimination reaction (Saunders and Cockerill, 1973). Five distinct mechanisms are believed to exist in this type of reaction (Lowry and Richardson, 1987d), as concisely presented in Scheme 4. Considerations of interactions between the



Scheme 4

three fragments, X—B, R—Y and LZ in Scheme 4 in the TS provide experimental criteria for distinguishing between these mechanistic possibilities as summarized in Table 20. E2 is a one-step process involving the simultaneous removal of the β-hydrogen and an LG and formation of a double bond, but these bond interchanges need not be precisely synchronous. As a result, there is a continuous spectrum of E2 ranging from E1cB-like to E1-like, a completely concerted E2 in the centre (Scheme 5). Thus the



Scheme 5

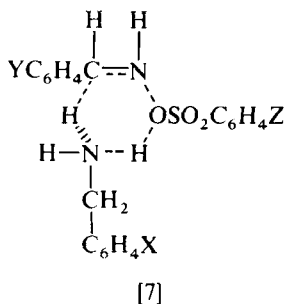
criteria for E2 have a range of magnitudes for various selectivity parameters shown in Table 20. For example, $|\rho_{\text{YZ}}|$ (or $|\beta_{\text{YZ}}|$) varies from a large magnitude for E1cB-like to a small value for E1-like, which may vanish in cases where bond breaking is much advanced in the TS. Some examples are shown in Table 21.

Table 20 Mechanistic criteria for β -elimination reactions based on cross-interaction constants. Simple Hammett and Brønsted coefficients are also included.^a

	(ElcB) _R	(ElcB) _{IRR}	(ElcB) _{IP}	E1	E2
ρ_Y	L (<0)	L (>0)	S (>0)	S (<0)	L - S (>0)
$\rho_X < 0$ (β_X)	0	L	L	0	L - M
$\rho_Z > 0$ (β_Z)	L	0	0	L	L - M
$ \rho_{XY} $	0	L	L	0	L - M
$ \rho_{YZ} $	M - S ^b	0	0	S ^b	M - S ^b
$ \rho_{XZ} $ ($ \beta_{XZ} $)	0	S	0	0	M - S ^b

^a L, M and S denote large, medium and small; these are only relative. ^b For an advanced degree of bond breaking, $|\rho_{YZ}| \approx$ zero.

We note that $|\rho_{YZ}|$ decreases as the TS structure for the E2 reaction is skewed more and more towards loss of LG. For reaction D, a hydrogen-bond bridged structure [7] was considered as a possibility for the TS. This,



however, is clearly untenable in view of the vanishing $|\rho_{YZ}|$ value since if this mechanism [7] occurred then $|\rho_{YZ}|$ would have been large instead of zero owing to strong interaction through dual interaction paths provided by an extra route of the hydrogen-bond bridge. Reaction E, (32), proceeds by an (ElcB)_R mechanism through carbanion intermediate [8], and the rate con-

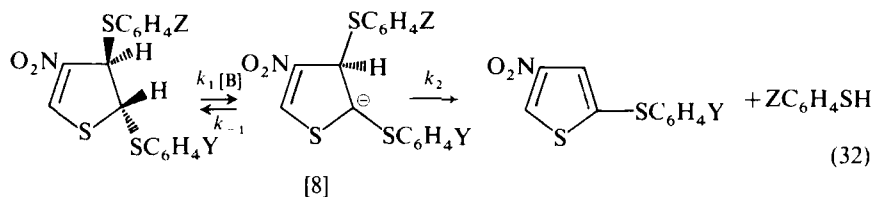
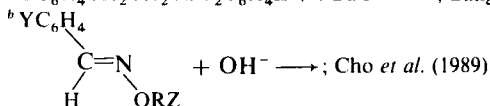


Table 21 Examples of some olefin-, imine- and nitrile-forming β -elimination reactions.

	Reactions				
	A ^a	B ^b	C ^c	D ^d	E ^e
ρ_Y	2.45	1.90	0.86	0.12	-0.28
ρ_Z	1.11	2.22	1.36	1.65	3.45
$-\beta_Z$	0.37	0.58	0.46	0.56	0.92
ρ_{YZ}	-0.50	-0.38	-0.34	0.00	0.00 ^f (0.01) ^g

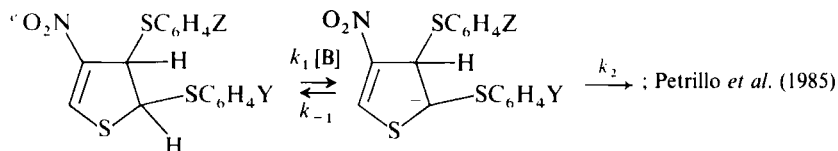
Mechanism	E2			(E1cB) _R
	E1cB-like	Central	E1-like	

^a $\text{YC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OSO}_2\text{C}_6\text{H}_4\text{Z} + \text{t-BuO}^- \longrightarrow$; Banger *et al.* (1971)



^c $\text{YC}_6\text{H}_4\text{CH}_2\text{NHOSO}_2\text{C}_6\text{H}_4\text{Z} + \text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 \xrightarrow[\text{THF-EtOAc}]{\text{H}_2\text{O}}$; Hoffman and Belfour (1979)

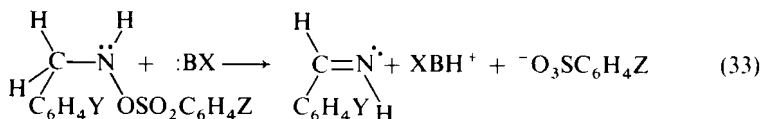
^d $\text{YC}_6\text{H}_4\text{CH}_2\text{NHOSO}_2\text{C}_6\text{H}_4\text{Z} + \text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2 \xrightarrow{\text{MeOH}}$; Hoffman and Belfour (1982)



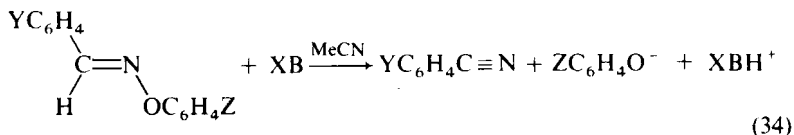
^f For the k_2 path. ^g For the $k' [=k_1/(k_{-1} + k_2)]$ path.

stants $k' [=k_1 k_2/(k_{-1} + k_2)]$, for the parallel processes of deprotonation and LG expulsion, and k_2 , for the process of LG expulsion, were reported. The magnitude of ρ_{YZ} , 0.01 for k' and zero for k_2 , does indeed agree with the putative mechanisms, since the degree of bond breaking is less in the former, k' , than in the latter, k_2 , for which bond cleavage has advanced very much as the extremely large magnitudes of ρ_Z and β_Z indicate. In the k_2 process, negative charge on C_2 is carried away by the LG in the TS, so that ρ_Y is negative.

Hoffman and Shankweiler (1986, 1988) reported on the TS structure of



imine-forming eliminations (33) in *N*-substituted *O*-(arylsulphonyl)hydroxylamines with amine bases BX. The λ_{XY} - and ρ_{YZ} -values calculated from their rate data are 0.10 and -0.08 respectively. The magnitude of λ_{XY} is relatively small (Table 3), indicating a relatively large $\text{C}_\beta\text{—H}$ bond cleavage in the TS. The magnitude of ρ_{YZ} is also small and similar to that for the dissociative $\text{S}_{\text{N}}2$ reaction of 2-phenylethyl benzenesulphonates with anilines in Table 11 ($\rho_{\text{YZ}} = 0.08$), suggesting an extensive degree of bond breaking in the TS. Taking these two values together, the TS for reaction (33) corresponds to that for an E1-like E2 mechanism, as the authors have correctly concluded. This assignment of the mechanism is also consistent with that based on the size of $|\rho_{\text{YZ}}|$ in Tables 20 and 21. Cho *et al.* (1988) reported similar studies of nitrile-forming elimination reactions (34) involving (*E*)-*O*-arylbenzaldox-



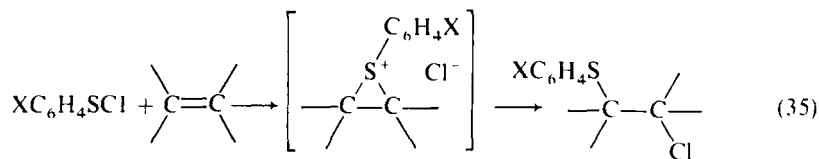
imes promoted by tertiary amines XB in acetonitrile. Their results have shown that a better LG, $\text{Z} = 2,4,6\text{-(NO}_2)_3$, leads to greater $\text{C}_\beta\text{—H}$ bond breaking (with $\lambda_{\text{XY}} = 0.08$) compared with $\text{Z} = 2,4\text{-(NO}_2)_2$ (with $\lambda_{\text{XY}} = 0.29$). A more EWS in the substrate ($\text{Y} = p\text{-NO}_2$) leads to an increase in β_{X} , i.e. an increase in $\text{C}_\beta\text{—H}$ bond cleavage, and a decrease in β_{Z} , i.e. a decrease in the N—OAr bond rupture. This, however, leads to a decrease in $|\beta_{\text{XZ}}|$ from 0.057 (for $\text{Y} = p\text{-MeO}$) to 0.010 (for $\text{Y} = p\text{-NO}_2$) and indicates that the increase in $\text{C}_\beta\text{—H}$ bond cleavage outweighs the relatively small decrease in the N—OAr bond rupture; thus a net increase in the distance between the amine base and the LG results. On the other hand, the ρ_{Y} -values decreased as the base strength decreased, indicating a gradual decrease in the TS carbanionic character with a weaker base. This is also accompanied by a decrease in β_{Z} [from -0.26 for Et_3N to -0.16 for $\text{N(CH}_2\text{CH}_2\text{OH)}_3$] as well as in λ_{YZ} [from 0.32 for Et_3N to 0.19 for $\text{N(CH}_2\text{CH}_2\text{OH)}_3$]. This parallel decrease in $|\rho_{\text{Y}}|$ with $|\beta_{\text{Z}}|$ implies a decrease in the charge development on C_β as well as on N, so that the triple bond character of the C=N bond also decreases (in the TS for a weaker base). The C=N bond should decrease in length from $1.32 \text{ \AA}$ (double bond) to $1.16 \text{ \AA}$ (triple bond), $\Delta d = 0.16 \text{ \AA}$, during the reaction, and this bond contraction is less with a weaker base in

the TS, which will result in a longer C=N bond and hence a decrease in λ_{VZ} between C_β and the LG for a weaker base, as observed. This type of bond-contraction effect is difficult to demonstrate with other selectivity parameters, and proves to be a useful application of cross-interaction constants to TS structure. When the structural changes lag behind the charge development, i.e. there is an imbalance (Jencks, 1985; Bernasconi, 1987),¹ the magnitude of cross-interaction constants can be a measure of the structural changes and will provide a useful method of studying such imbalance problems.

ELECTROPHILIC ADDITION AND SUBSTITUTION REACTIONS

Application of cross-interaction constants is also useful for the characterization of the TS structure for electrophilic substitution reactions. Some examples are listed in Table 22. The first three reactions, A–C, involve electrophilic aromatic substitution with two substituents Y and Y' in a single fragment interacting through a common reaction centre (Fig. 2a). As expected, the magnitude of $\rho_{\text{YY}'}$ is large owing to a strong interaction through dual interaction routes. Electrophilic vinylic addition reactions D–G also involve dual interaction pathways through formation of a bridged adduct in the TS. Reactions D and F are similar, but a common reaction centre is involved in the former whereas separate reaction centres are involved in the latter when the bromine adduct is formed in the TS. This could be the reason for a smaller $\rho_{\text{YY}'}$ for the latter reaction.

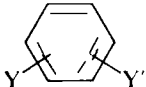
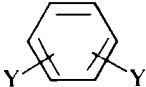
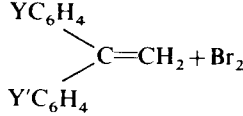
Reactions E and G are also similar, a sulphur bridge being formed in the TS in both reactions, providing dual interaction routes. In reaction G, (35),

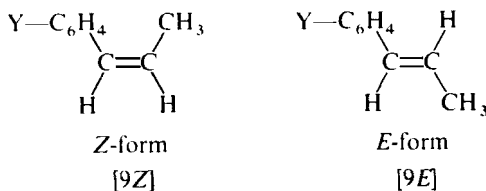


the *E*-form of the reactant [9*E*] gives rise to a stronger interaction, i.e. a greater $|p_{\text{XY}}|$ between the two substituents in the electrophile X and the substrate Y, due probably to a tighter sulphur adduct formation in the TS.

¹ This imbalance or non-perfect synchronization is the subject of the next contribution in this volume (p. 119).

Table 22 Cross-interaction constants for electrophilic reactions.

Reactions	Cross-interaction constants	References
A  + Br ₂	$\rho_{YY'} = -7.98$	Dubois <i>et al.</i> (1984)
B  + H ⁺	$\rho_{YY'} = -7.6$	Dubois <i>et al.</i> (1984)
C  + H ⁺	$\rho_{YY'} = -3.0$	Dubois <i>et al.</i> (1984)
D  + Br ₂	$\rho_{YY'} = -1.55$	Dubois <i>et al.</i> (1984)
E YC ₆ H ₄ -CH=CH ₂ + XC ₆ H ₄ SCl	$\rho_{YY'} = -1.02$	Dubois <i>et al.</i> (1984)
F YC ₆ H ₄ -C(Me)=CH-C ₆ H ₄ Y' + Br ₂	$\rho_{YY'} = -0.71$	Dubois <i>et al.</i> (1984)
G YC ₆ H ₄ -CH=CH-CH ₃ + XC ₆ H ₄ SCl	$\rho_{YY'} = -5.9$ (<i>E</i> -form) $= -2.0$ (<i>Z</i> -form)	Schmid and Garratt (1983)

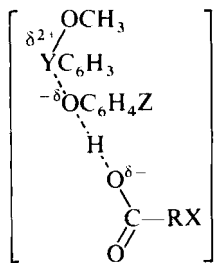


The *E*-form [9*E*] should be more congested, and hence there will be a greater steric hindrance for the approaching electrophile since bulky groups are on both sides, in contrast with the *Z*-form [9*Z*], in which the two groups are on one side. The Hammond postulate requires a later TS (i.e. a tighter TS) for bond formation along the reaction coordinate for the more sterically hindered process with the higher energy barrier (Hammond, 1955; le Noble and Asano, 1975; le Noble and Miller, 1979; Amyes and Jencks, 1989), as attested (Section 4; p. 91) by a tighter TS in the reactions of anilines with ethyl rather than methyl benzenesulphonates (Lee *et al.*, 1989a).

OTHER TYPES OF REACTIONS

Some examples of acid- and base-catalysed processes and a cycloaddition reaction are given in Table 23.

Reaction A is the general acid hydrolysis of benzaldehyde aryl methyl acetals, $\text{YC}_6\text{H}_3(\text{OCH}_3)\text{OC}_6\text{H}_4\text{Z}$. The TS structure proposed is shown in [10], which is consistent with the calculated values of $\lambda_{\text{XY}} (= -0.38)$ and λ_{XZ}

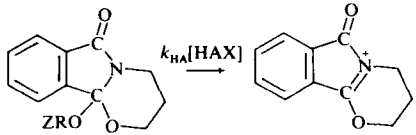
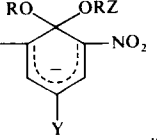
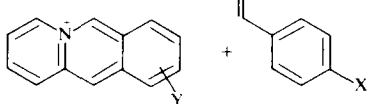


[10]

(=0.43); the distance between the two oxygen atoms, O(X) and O(Z) (interaction between X and Z), is shorter than that between O(X) and C(Y), so that $|\lambda_{\text{XZ}}| > |\lambda_{\text{XY}}|$. The different sign of the two λ_{ij} values is also consistent with the different charge development involved at the two reaction centres.

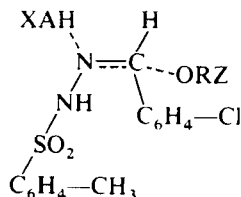
Reaction B is the general acid (HAX) catalysis of the methoxyaminolysis of alkyl benzimidates, $\text{YC}_6\text{H}_4\text{C}=(\text{NH})\text{OR}$. The substantial magnitude of

Table 23 Values of λ_{ij} and β_{ij} for various reactions.

	Reactions	λ_{ij} or β_{ij}	References
A	$\text{XRCO}_2\text{H} + \text{YC}_6\text{H}_3 \begin{array}{l} \nearrow \text{OCH}_3 \\ \searrow \text{OC}_6\text{H}_5\text{Z} \end{array}$	$\begin{cases} \lambda_{\text{XY}} = -0.38 \\ \lambda_{\text{XZ}} = 0.43 \end{cases}$	Capon and Nimmo (1975)
B	$\text{YC}_6\text{H}_5\text{C}(\text{NH})=\text{OR} + \text{HAX} (k_{\text{HA}})$	$\beta_{\text{XY}} = 0.065$	Gilbert and Jencks (1982)
C	$p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NHNHCH(ORZ)C}_6\text{H}_4\text{ } p\text{-Cl} + \text{HAX}$	$\beta_{\text{XZ}} = 0.036$	Sayer <i>et al.</i> (1973)
D	X-catalyst + Y-hydrazines → carbinolamine dehydration	$\begin{cases} (\text{GB}) \beta_{\text{XY}} = -0.02 \\ (\text{GA}) \beta_{\text{XY}} = 0.008 \end{cases}$	Sayer and Jencks (1977)
E	$\text{OH}^- + \text{Y-C}_6\text{H}_4\text{CH}_2\text{CO}_2\text{C}_6\text{H}_4\text{Z}$	$\lambda_{\text{YZ}} = -1.17$	Chandrasekar and Venkatasubramanian (1982)
F		+ ZROH $\beta_{\text{XZ}} = 0.07$	Gravity and Jencks (1974)
G	$\text{XAH} + \text{O}_2\text{N-C}_6\text{H}_3(\text{NO}_2)_2\text{-Y}$ 	$\beta_{\text{XZ}} = 0.12$	Bernasconi and Gandler (1978)
H		$\rho_{\text{XY}} = -0.37$	Porter <i>et al.</i> (1974)

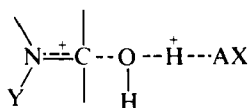
β_{XY} suggests a TS structure in which proton transfer from the acid, HAX, is well advanced.

Reaction C is the general acid (HAX) catalysis of tosylhydrazone formation from *o*-tosylhydrazino-*p*-chlorobenzyl alkylethers, *p*-CH₃C₆H₄SO₂-NHNHCH(ORZ)C₆H₄-*p*-Cl. The β_{XZ} -value of 0.036 calculated for this process agrees with the proposed TS structure for concerted N—H and C—O bond breaking [11].

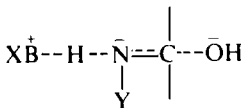


[11]

Reaction D is the general acid (HAX) and base (BX) catalysis for carbinolamine dehydration in imine formation from substituted hydrazines (Y-hydrazines). The two β_{XY} -values for the general acid- (GA) and base- (GB) catalysed dehydration, β_{XY} (GA) = 0.008 and β_{XY} (GB) = -0.02, are consistent with the proposed TSs for the concerted mechanisms [12] and [13] respectively.



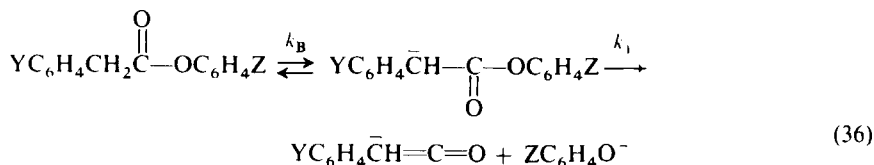
[12]



[13]

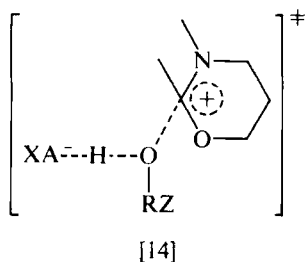
In the GA process [12] the two reaction centres, A(X) and N(Y), are farther apart because of an intervening $\text{—C} \cdots \text{O} \cdots$ linkage compared with those in the GB process, B(X) and N(Y) in [13], so that $|\beta_{XY}|$ is smaller; charge developments at the two reaction centres are also different, both positive in [12] and positive (B) and negative (N) in [13], so that the sign of β_{XY} differs in the two processes accordingly.

Reaction E is the alkaline hydrolysis of aryl phenylacetates, $\text{YC}_6\text{H}_4\text{CH}_2\text{—COOC}_6\text{H}_4\text{Z}$. This reaction has an unusually large λ_{YZ} -value (-1.17), which is in good accord with the proposed E1cB pathway (36), rather than a

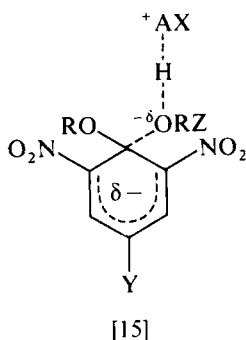


B_{AC2} process. In (36), the LG bond rupture from the carbanion intermediate is rate-limiting, and a strong interaction between the carbanion centre and the LG, phenoxide oxygen, is expected, as the large $|\lambda_{YZ}|$ indicates.

Reaction F is the acid-catalysed breakdown of alcohol adducts formed from *N,O*-trimethylene-phthalimidium cations. The reaction is believed to proceed concertedly involving the proton transfer to O and C—O bond breaking as shown in TS [14]. The magnitude of β_{XZ} ($=0.07$) is indeed consistent with this concerted mechanism.

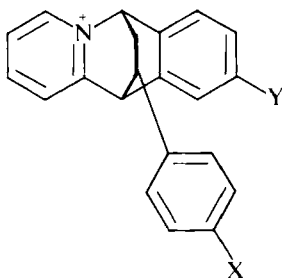


Reaction G is the acid-catalysed breakdown of Meisenheimer complexes. In this process the acid, XAH, interacts directly with the LG, ^-ORZ , so that the magnitude of β_{XZ} is fairly large ($=0.12$), as expected from TS [15].



This is also consistent with the expulsion of an alkoxide ion from an addition compound by a concerted, acid-catalysed pathway, such as alkoxide expulsion from the addition compound of a phthalimidium ion, reaction F. The difference in the magnitude of β_{XZ} between the two reactions, F and G, should reflect the difference in the degree of C—O bond rupture; in the acid-catalysed breakdown of the Meisenheimer complex G the alkoxide ion is farther away from the ring and the interaction between the two reaction centres, A^+ and O^- , is stronger.

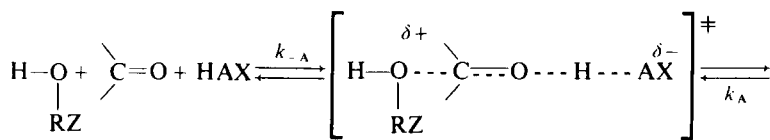
Reaction H is the cycloaddition of substituted acridizinium with *p*-substituted styrenes. In this process the cycloadduct [16] is formed and the



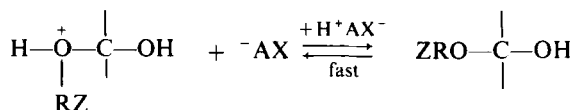
[16]

addition can be concerted or stepwise. The magnitude of $|p_{XY}|$ ($=0.37$) is, however, smaller than that expected for a concerted addition, since the bridged structure formed in the concerted process should provide dual interaction routes with a strong interaction so that the $|p_{XY}|$ -value should approach or exceed unity (see Tables 2 and 22). It is therefore most likely that the TS is formed by bond formation at position 6 preceding bond formation at position 11, i.e. the reaction of acridizinium with styrene proceeds by the stepwise mechanism.

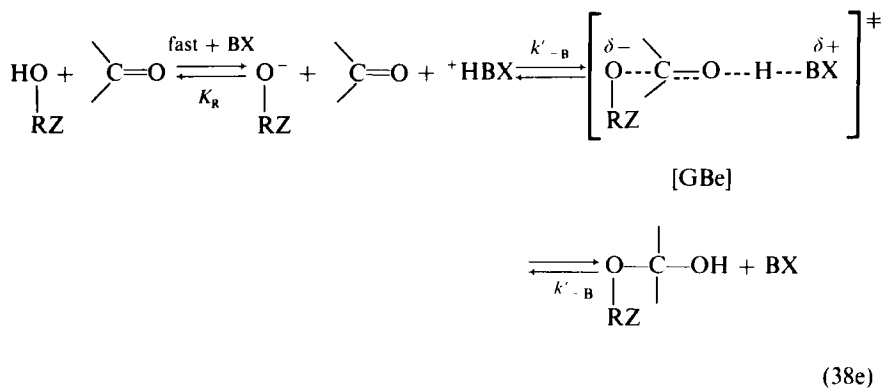
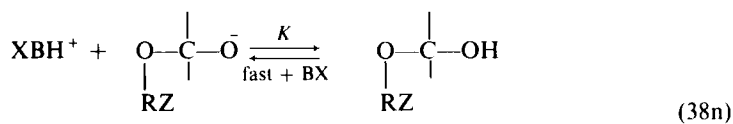
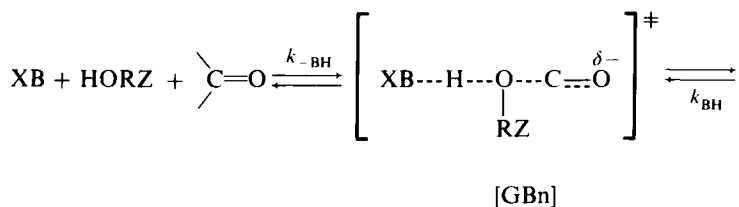
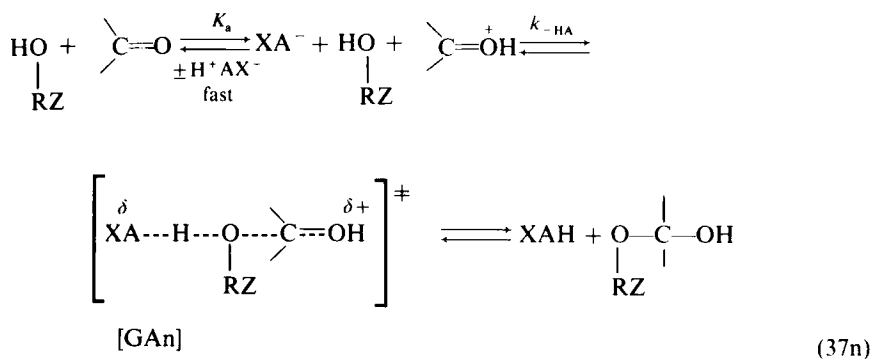
An interesting application of cross-interaction constants is given by Funderburk *et al.* (1978) to mechanisms of general acid (GA) and base (GB) catalysis of the reactions of water and alcohols with formaldehyde. For both general acid and base catalysis, two reaction pathways, class n and e mechanisms, are conceivable, as shown in (37) and (38).



[GAe]



(37e)



The TS structures in (37) and (38) indicate that the distance between X and Z is always shorter in the class n than in the class e mechanism, so that the magnitude of β_{xz} should be greater for the class n mechanism. The two β_{xz} -values obtained, 0.02 and 0.09 for general acid and base catalysis respectively, show that the general acid catalysis proceeds by the class e mechanism (β_{xz} is small) whereas the general base catalysis proceeds by the class n mechanism (β_{xz} is large).

5 Future developments

The applications of cross-interaction constants to TS structures presented in the previous section are limited to relatively few types of reaction at the present. Wider application to many more reactions should certainly give rise to a useful quantitative measure of TS structure, and, it is hoped, may lead to the generalization of such a measure.

For reaction series involving aliphatic compounds, (3), (5) and (8) can still be applied using Taft's substituent constants and pK_a -values. Such applications to TS structure should prove to be equally successful as with Hammett's σ -values, when sufficient rate data for such reaction series are available.

Another field of application of cross-interaction constants is to thermodynamic data. The definitions of cross-interaction constants for thermodynamic data are the same as (3), (5) and (8), except that the equilibrium constants K_{ij} are used instead of the rate constants k_{ij} . For example, for ρ_{ij} , the definition will become (39). Dubois *et al.* (1984) have in fact given some examples of the application of (39). These are not presented here, since this review is primarily concerned with the application of cross-interaction constants to TS structure. The magnitude of cross-interaction constants for thermodynamic data represents of course the change in the intensity of interaction between the two substituents involved from that in the reactant to that in the product instead of that in the TS.

$$\log(K_{ij}/K_{HH}) = \rho_i\sigma_i + \rho_j\sigma_j + \rho_{ij}\sigma_i\sigma_j \quad (39)$$

6 Limitations

As in any application of selectivity parameters from linear free energy relationships, cross-interaction constants reflect the TS structure only for the rate-determining step of a reaction. This means that interpretation of cross-interaction constants will not be clearcut and easy in a complex reaction,

which proceeds in many steps with no identifiable single rate-determining step (Section 4; p. 75).

Jencks and his coworkers (Funderburk *et al.*, 1978) have discussed the electrostatic interactions between two substituents that influence the magnitude of the cross-interaction constants. The resulting changes in ρ_{ij} or β_{ij} might be mistakenly interpreted as evidence for a change in TS structure. Thus, the cross-interaction constants determined may not be *directly* applicable to the TS structure in such reaction series with significant electrostatic interactions.

Finally, the problem of reality and accuracy of measured cross-interaction constants constitutes one of the most important aspects that should be carefully considered in any application. It is essential that the rate constants k_{ij} that are subjected to a multiple linear regression for the determination of cross-interaction constants are accurate. Often, inaccurate rate data produce the wrong sign of ρ_{ij} -values. Another way of improving the accuracy of determined ρ_{ij} -values would be to increase the number of rate data used in the regression. In most cases 16–20 data points are sufficient for a dependable value of ρ_{ij} (or β_{ij}) obtained by multiple regression provided that the rate constants k_{ij} are of sufficient accuracy.

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References

- Albery, W. J. and Kreevoy, M. M. (1978). *Adv. Phys. Org. Chem.* **16**, 87
- Amyes, T. L. and Jencks, W. P. (1989). *J. Am. Chem. Soc.* **111**, 7900
- Ando, T., Tanabe, H. and Yamataka, H. (1984). *J. Am. Chem. Soc.* **106**, 2084
- Ando, T., Kimura, T. and Yamataka, H. (1987). In *Nucleophilicity* (ed. J. M. Harris and S. P. McManus), pp. 103–114. Advances in Chemistry Series, Vol. 215, American Chemical Society, Washington, D.C.
- Arcoria, A., Ballestrei, F. P., Musumara, G. and Tomaselli, G. A. (1981). *J. Chem. Soc. Perkin Trans. 2*, 221
- Ba-Saif, S., Luthra, A. K. and Williams, A. (1989). *J. Am. Chem. Soc.* **111**, 2647
- Banger, J., Cockerill, A. F. and Davies, G. L. O. (1971). *J. Chem. Soc. (B)*, 498
- Bender, M. L. (1951). *J. Am. Chem. Soc.* **73**, 1626

- Bernasconi, C. F. (1987). In *Nucleophilicity* (ed. J. M. Harris and S. P. McManus), pp. 115–133. *Advances in Chemistry Series*, Vol. 215, American Chemical Society, Washington, D.C.
- Bernasconi, C. F. and Gandler, J. R. (1978). *J. Am. Chem. Soc.* **100**, 8117
- Buncel, E. and Wilson, H. (1987). *J. Chem. Educ.* **64**, 475
- Capon, B. and Nimmo, K. (1975). *J. Chem. Soc. Perkin Trans. 2*, 1113
- Chandrasekar, R. and Venkatasubramanian, N. (1982). *J. Chem. Soc. Perkin Trans. 2*, 1625
- Chapman, N. B. and Shorter, J. (eds.) (1972). *Advances in Linear Free Energy Relationships*. Plenum, London
- Chapman, N. B. and Shorter, J. (eds.) (1978). *Correlation Analysis in Chemistry*. Plenum, London
- Charton, M. (1981). *Prog. Phys. Org. Chem.* **13**, 119
- Cho, B. R., Kim, K. D., Lee, J. C. and Cho, N. S. (1988). *J. Am. Chem. Soc.* **110**, 6145
- Cho, B. R., Lee, J. C., Cho, N. S. and Kim, K. D. (1989). *J. Chem. Soc. Perkin Trans. 2*, 1741
- Cohen, A. O. and Marcus, R. A. (1968). *J. Phys. Chem.* **72**, 4249
- Cordes, E. H. and Jencks, W. P. (1962). *J. Am. Chem. Soc.* **84**, 4319
- Dean, J. A. (1987). *Handbook of Organic Chemistry*, Table 7-2. McGraw-Hill, New York
- Dewar, M. J. S. and Dougherty, R. C. (1975). *The PMO Theory of Organic Chemistry*, p. 212. Plenum, New York
- Dodd, J. A. and Brauman, J. I. (1984). *J. Am. Chem. Soc.* **106**, 5356
- Dubois, J.-E., Ruasse, M.-F. and Argile, A. (1984). *J. Am. Chem. Soc.* **106**, 4840
- Fersht, A. R. and Jencks, W. P. (1970). *J. Am. Chem. Soc.* **92**, 5442
- Funderburk, L. H., Aldwin, L. and Jencks, W. P. (1978). *J. Am. Chem. Soc.* **100**, 5444
- Gilbert, H. F. and Jencks, W. P. (1982). *J. Am. Chem. Soc.* **104**, 6769
- Gould, E. S. (1959). *Mechanism and Structure in Organic Chemistry*, p. 294. Holt, Rinehart and Winston, New York.
- Gravity, N. and Jencks, W. P. (1974). *J. Am. Chem. Soc.* **96**, 507
- Hammond, G. S. (1955). *J. Am. Chem. Soc.* **77**, 334
- Harris, J. M., Paley, M. S. and Prasthofer, T. W. (1981). *J. Am. Chem. Soc.* **103**, 5915
- Herschlag, D. and Jencks, W. P. (1989). *J. Am. Chem. Soc.* **111**, 7587
- Hoffman, R. V. and Belfour, E. L. (1979). *J. Am. Chem. Soc.* **101**, 5687
- Hoffman, R. V. and Belfour, E. L. (1982). *J. Am. Chem. Soc.* **104**, 2183
- Hoffman, R. V. and Shankweiler, J. M. (1986). *J. Am. Chem. Soc.* **108**, 5536
- Hoffman, R. V. and Shankweiler, J. M. (1988). *J. Am. Chem. Soc.* **110**, 4019
- Hopkins, A., Day, R. A. and Williams, A. (1983). *J. Am. Chem. Soc.* **105**, 6062
- Isaacs, N. S. (1987). *Physical Organic Chemistry*, p. 245. Longman, Harlow
- Jameson, G. W. and Lawlor, J. M. (1970). *J. Chem. Soc. (B)*, 53
- Jencks, D. A. and Jencks, W. P. (1977). *J. Am. Chem. Soc.* **99**, 7948
- Jencks, W. P. (1972). *Chem. Rev.* **72**, 705
- Jencks, W. P. (1985). *Chem. Rev.* **85**, 511
- Kaldor, S. B. and Saunders, W. H., Jr (1978). *J. Chem. Phys.* **68**, 2509
- Katz, A. M. and Saunders, W. H., Jr (1969). *J. Am. Chem. Soc.* **91**, 4469
- Kevill, D. N., Kolwyck, K. C., Shold, D. M. and Kim, C.-B. (1973). *J. Am. Chem. Soc.* **95**, 6022
- King, J. F. and Tsang, G. T. Y. (1979). *J. Chem. Soc. Chem. Commun.*, 1131
- Kirsch, J. F., Clewell, W. and Simon, A. (1968). *J. Org. Chem.* **33**, 127

- Knowles, J. R., Norman, R. O. C. and Prosser, J. H. (1961). *Proc. Chem. Soc.*, 341
- Kost, D. and Aviram, K. (1986). *J. Am. Chem. Soc.* **108**, 2006
- Kwart, H. (1982). *Acc. Chem. Res.* **15**, 401
- Lee, I. (1989). *J. Chem. Soc. Perkin Trans. 2*, 943
- Lee, I. (1990a). *Bull. Korean Chem. Soc.* **11**, 260
- Lee, I. (1990b). *Chem. Soc. Rev.* **19**, 317
- Lee, I. (1990c). *Chem. Soc. Rev.* **19**, 133
- Lee, I. and Kang, H. K. (1987). *Tetrahedron Lett.* **28**, 1183
- Lee, I. and Song, C. H. (1986). *Bull. Korean Chem. Soc.* **7**, 186
- Lee, I., Lee, H. W., Sohn, S. C. and Kim, C. S. (1985). *Tetrahedron* **41**, 2635
- Lee, I., Kim, C. K. and Song, C. H. (1986a). *Bull. Korean Chem. Soc.* **7**, 391
- Lee, I., Sohn, S. C., Kang, C. H. and Oh, Y. J. (1986b). *J. Chem. Soc. Perkin Trans. 2*, 1631
- Lee, I., Sohn, S. C., Oh, Y. J. and Lee, B. C. (1986c). *Tetrahedron* **42**, 4713
- Lee, I., Kang, H. K. and Lee, H. W. (1987a). *J. Am. Chem. Soc.* **109**, 7472
- Lee, I., Kim, H. Y. and Kang, H. K. (1987b). *J. Chem. Soc. Chem. Commun.*, 1216
- Lee, I., Cho, J. K. and Song, C. H. (1988a). *J. Chem. Soc. Faraday Trans. 84*, 1177
- Lee, I., Choi, Y. H., Lee, H. W. and Lee, B. C. (1988b). *J. Chem. Soc. Perkin Trans. 2*, 1537
- Lee, I., Kim, H. Y., Kang, H. K. and Lee, H. W. (1988c). *J. Org. Chem.* **53**, 2678
- Lee, I., Shim, C. S., Chung, S. Y., Kim, H. Y. and Lee, H. W. (1988d). *J. Chem. Soc. Perkin Trans. 2*, 1919
- Lee, I., Shim, C. S., Chung, S. Y. and Lee, H. W. (1988e). *J. Chem. Soc. Perkin Trans. 2*, 975
- Lee, I., Choi, Y. H., Rhyu, K. W. and Shim, C. S. (1989a). *J. Chem. Soc. Perkin Trans. 2*, 1881
- Lee, I., Kim, H. Y., Lee, H. W. and Kim, I. C. (1989b). *J. Phys. Org. Chem.* **2**, 35
- Lee, I., Shim, C. S. and Lee, H. W. (1989c). *J. Chem. Soc. Perkin Trans. 2*, 484
- Lee, I., Shim, C. S. and Lee, H. W. (1989d). *J. Chem. Soc. Perkin Trans. 2*, 1205
- Lee, I., Cho, J. K. and Kim, C. K. (1990a). Unpublished results
- Lee, I., Cho, J. K., Kim, H. S. and Kim, K. S. (1990b). *J. Phys. Chem.* **94**, 5190
- Lee, I., Koh, H. J., Huh, C. and Lee, H. W. (1990c). *J. Phys. Org. Chem.* **3**, 550
- Lee, I., Koh, H. J., Lee, B.-S. and Lee, H. W. (1990d). *J. Chem. Soc. Chem. Commun.*, 335
- Lee, I., Koh, H. J., Lee, H. W., Sohn, D. S. and Lee, B. C. (1990e). Unpublished results
- Lee, I., Koh, H. J. and Lee, H. W. (1990f). *J. Chem. Res. (S)*, 282; (*M*) 2177
- Lee, I., Koh, H. J. and Lee, H. W. (1990g). Unpublished results
- Lee, I., Koh, H. J. and Lee, H. W. (1990h). Unpublished results
- Lee, I., Lee, W. H., Lee, H. W. and Lee, B. C. (1990i). Unpublished results
- Lee, I., Lee, W. H. and Lee, H. W. (1990j). *J. Phys. Org. Chem.* **3**, 545
- Lee, I., Lee, W. H. and Lee, H. W. (1990k). Unpublished results
- Lee, I., Shim, C. S., Lee, H. W. and Lee, B.-S. (1990l). Unpublished results
- Lee, I., Shim, C. S., Rhyu, K. W. and Lee, H. W. (1990m). *J. Phys. Org. Chem.* **3**, 751
- Lee, I., Shim, C. S. and Lee, H. W. (1990n). Unpublished results
- Lewis, E. S. and Hu, D. D. (1984). *J. Am. Chem. Soc.* **106**, 3292
- Lewis, E. S. and Kukes, S. (1979). *J. Am. Chem. Soc.* **101**, 417
- Lewis, E. S., Yousaf, T. I. and Douglas, T. A. (1987). *J. Am. Chem. Soc.* **109**, 2152
- Lowry, T. H. and Richardson, K. S. (1987a). *Mechanism and Theory in Organic Chemistry*, 3rd edn, p. 148. Harper and Row, New York

- Lowry, T. H. and Richardson, K. S. (1987b). *Mechanism and Theory in Organic Chemistry*, 3rd edn, p. 212. Harper and Row, New York
- Lowry, T. H. and Richardson, K. S. (1987c). *Mechanism and Theory in Organic Chemistry*, 3rd edn, p. 238. Harper and Row, New York
- Lowry, T. H. and Richardson, K. S. (1987d). *Mechanism and Theory in Organic Chemistry*, 3rd edn, p. 309. Harper and Row, New York
- Lowry, T. H. and Richardson, K. S. (1987e). *Mechanism and Theory in Organic Chemistry*, 3rd edn, p. 588. Harper and Row, New York
- Lynas, J. I. and Stirling, C. J. M. (1984). *J. Chem. Soc. Chem. Commun.*, 483
- le Noble, W. J. and Asano, T. (1975). *J. Am. Chem. Soc.* **97**, 1778
- le Noble, W. J. and Miller, A. R. (1979). *J. Org. Chem.* **44**, 889
- Marcus, R. A. (1964). *Ann. Rev. Phys. Chem.* **15**, 155
- Marcus, R. A. (1968). *J. Phys. Chem.* **72**, 891
- McLennan, D. J. (1978). *Tetrahedron* **34**, 2331
- McLennan, D. J. and Pross, A. (1984). *J. Chem. Soc. Perkin Trans. 2*, 981
- Melander, L. and Saunders, W. H., Jr (1980a). *Reaction Rates of Isotopic Molecules*. Wiley, New York
- Melander, L. and Saunders, W. H., Jr (1980b). *Reaction Rates of Isotopic Molecules*, Chap. 6. Wiley, New York
- Menger, F. M. and Smith, J. H. (1972). *J. Am. Chem. Soc.* **94**, 3824
- Miller, S. I. (1959). *J. Am. Chem. Soc.* **81**, 101
- Mitchell, D. J., Schlegel, H. B., Shaik, S. S. and Wolfe, S. (1985). *Can. J. Chem.* **63**, 1642
- Monjoint, P. and Ruasse, M. F. (1988). *Bull. Soc. Chim. France*, 356
- More O'Ferrall, R. A. (1970). *J. Chem. Soc. (B)*, 274
- Murdoch, J. R. (1983). *J. Am. Chem. Soc.* **105**, 2660
- Patai, S. (ed.) (1966). *The Chemistry of the Carbonyl Group*. Interscience, New York
- Pellerite, M. J. and Brauman, J. I. (1980). *J. Am. Chem. Soc.* **102**, 5993
- Petrillo, G. P., Novi, M., Garbarino, G. and Dell'Erba, C. (1985). *J. Chem. Soc. Perkin Trans. 2*, 1741
- Poh, B.-L. (1979). *Can. J. Chem.* **57**, 255
- Porter, N. A., Westerman, I. J., Wallis, T. G. and Bradsher, C. K. (1974). *J. Am. Chem. Soc.* **96**, 5104
- Pross, A. (1977). *Adv. Phys. Org. Chem.* **14**, 69
- Pross, A. and Shaik, S. S. (1981). *J. Am. Chem. Soc.* **103**, 3702
- Ritchie, C. D. (1972a). *Acc. Chem. Res.* **5**, 348
- Ritchie, C. D. (1972b). *J. Am. Chem. Soc.* **94**, 4966
- Ritchie, C. D. (1986). *Can. J. Chem.* **64**, 2239
- Saunders, W. H., Jr and Cockerill, A. F. (1973). *Mechanism of Elimination Reactions*. Wiley, New York
- Sayer, J. M. and Jencks, W. P. (1977). *J. Am. Chem. Soc.* **99**, 464
- Sayer, J. M., Perkin, M. and Jencks, W. P. (1973). *J. Am. Chem. Soc.* **95**, 4277
- Schadt, F. L., III, Lancelot, C. J. and Schleyer, P. v. R. (1978). *J. Am. Chem. Soc.* **100**, 228
- Schmid, G. H. and Garrat, D. G. (1973). *Tetrahedron Lett.* **24**, 5299
- Shaik, S. S. and Pross, A. (1982). *J. Am. Chem. Soc.* **104**, 2708
- Shorter, J. (1982). *Correlation Analysis of Organic Reactivity*, Chap. 2. Research Studies Press, Chichester
- Shwali, A. S., Harhash, A., Sidky, M. M., Hassaneen, H. M. and Elkaabi, S. S. (1986). *J. Org. Chem.* **51**, 3498

- Siggel, M. R. F., Streitwieser, A., Jr and Thomas, T. D. (1988). *J. Am. Chem. Soc.* **110**, 8022
- Skoog, M. T. and Jencks, W. P. (1984). *J. Am. Chem. Soc.* **106**, 7597
- Streitwieser, A. (1962). *Solvolytic Displacement Reactions*, p. 28. McGraw-Hill, New York
- Ta-Shma, R. and Jencks, W. P. (1986). *J. Am. Chem. Soc.* **108**, 8040
- Thornton, E. R. (1967). *J. Am. Chem. Soc.* **89**, 2915
- Westaway, K. C. and Ali, S. F. (1979). *Can. J. Chem.* **57**, 1354
- Westheimer, F. H. (1961). *Chem. Rev.* **61**, 265
- Williams, A. (1989). *Acc. Chem. Res.* **22**, 387
- Wold, S. and Sjöström, M. (1978). In *Correlation Analysis in Chemistry* (ed. N. B. Chapman and J. Shorter), Chap. 1. Plenum, New York
- Wolfe, S., Mitchell, D. J. and Schlegel, H. B. (1981a). *J. Am. Chem. Soc.* **103**, 7692
- Wolfe, S., Mitchell, D. J. and Schlegel, H. B. (1981b). *J. Am. Chem. Soc.* **103**, 7964
- Yamataka, H. and Ando, T. (1975). *Tetrahedron Lett.* **16**, 1059
- Yamataka, H. and Ando, T. (1979). *J. Am. Chem. Soc.* **101**, 266
- Yamataka, H. and Ando, T. (1982). *Tetrahedron Lett.* **23**, 4805
- Yates, K. (1989). *J. Phys. Org. Chem.* **2**, 300
- Yousaf, T. I. and Lewis, E. S. (1987). *J. Am. Chem. Soc.* **109**, 6137

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The Principle of Non-perfect Synchronization

CLAUDE F. BERNASCONI

Department of Chemistry and Biochemistry, University of California at Santa Cruz, Santa Cruz, California 95064, USA

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1 Introduction

One of the most satisfying aspects of how the physical organic chemist deals with chemical reactivity is the use of models and explanations that are *qualitative* and *intuitive*. This is not to say that other, more quantitatively rigorous approaches such as quantum mechanics are less valuable; as a matter of fact, the two methods complement each other nicely, particularly in view of the recent progress made in *ab initio* calculations (Hehre *et al.*, 1986).

A well-known physical organic concept is the Hammond postulate (1955) and its various extensions summarized by the acronym Bema Hapothle (Jencks, 1985; see p. 21). It is our contention that the principle of non-perfect synchronization (PNS) is another prime example of a physical organic concept that deals with chemical reactivity in a qualitative or semiquantitative way. The basic idea of the PNS is to relate certain features of transition-state structure, deduced from substituent or solvent effects on rates and equilibria, to chemical reactivity. We begin by defining a few terms that will be used frequently throughout this review.

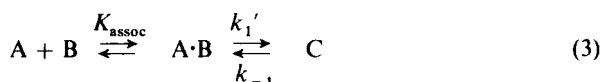
INTRINSIC BARRIERS AND INTRINSIC RATE CONSTANTS

The barrier of a reaction $\Delta G^\ddagger$, or its rate constant k , is essentially a function of two contributions. The first is the thermodynamic driving force ΔG^0 , the

second is a purely kinetic factor known as the intrinsic barrier $\Delta G_0^\ddagger$, or the intrinsic rate constant k_0 . For an elementary reaction such as (1), the intrinsic barrier is generally defined as $\Delta G_0^\ddagger = \Delta G_1^\ddagger = \Delta G_{-1}^\ddagger$ when $\Delta G^0 = 0$, and the intrinsic rate constant as $k_0 = k_1 = k_{-1}$ when $K_1 = k_1/k_{-1} = 1$. The same definitions apply to any elementary reaction in which the molecularities of the forward and reverse steps are the same.

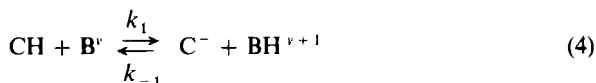


For a reaction such as (2), where the molecularities in the two directions are different, the above definitions are somewhat problematic, because k_1 and k_{-1} have different units and the value for ΔG^0 depends on the choice of standard state. A possible way of avoiding this complication was suggested by Hine (1971). It involves breaking down (2) into (3) in which $A \cdot B$ is an encounter complex, with K_{assoc} being the equilibrium constant for encounter-complex formation. The intrinsic barrier or intrinsic rate constant refers now to the unimolecular (in both directions) reaction $A \cdot B \rightleftharpoons C$ only, i.e. $k_0 = k_1' = k_{-1}$ when $K_1' = k_1'/k_{-1} = 1$. The relationships between the rate and equilibrium constants of (2) and (3) are $k_1' = k_1/K_{\text{assoc}}$ and $K_1' = K_1/K_{\text{assoc}}$ respectively.



Even though Hine's approach avoids the problem of the mismatched units for k_1 and k_{-1} , it has the clear disadvantage of requiring one to assume a value for the unknown K_{assoc} . We therefore prefer to use the same definition for k_0 and $\Delta G_0^\ddagger$ in (2) as in (1). As long as these quantities are used for comparison purposes in series of reactions of the type of (2) rather than as absolute values, the problem of different units is inconsequential.

When (1) refers to a proton transfer, it is good practice to introduce statistical factors. A common situation is the proton transfer from a carbon acid (CH) to a normal base, such as an oxyanion, amine or thiolate ion B^ν (with ν being the formal charge) as shown in (4). Here k_0 is defined as $k_1/q = k_{-1}/p$ when $pK_a^{\text{BH}} - pK_a^{\text{CH}} + \log(p/q) = \log K_1 + \log(p/q) = 0$; q is the number of equivalent basic sites on B^ν (e.g. 1 for RNH_2 , 2 for RCOO^-), while p is the number of equivalent protons on $\text{BH}^{\nu+1}$ (e.g. 3 for RNH_3^+ , 1



for RCOOH). The value of k_0 is found by interpolating or extrapolating a Brønsted plot of $\log(k_1/q)$ or $\log(k_{-1}/p)$ versus $\log K_1 + \log(p/q)$, generated by varying B^v (not CH), to $\log K_1 + \log(p/q) = 0$. Most k_0 -values for (4) reported in this review were obtained in this way.

When comparisons are being made between carbon acids that have different numbers of acidic protons, statistical factors for CH and C^- (Bell, 1973) may be included, so that $k_0 = k_1/qp' = k_{-1}/pq'$ when $pK_a^{\text{BH}} - pK_a^{\text{CH}} + \log(pq'/qp') = 0$, with p' the number of equivalent protons on CH and q' the number of equivalent basic sites on C^- . This latter practice is not very common and will not be adopted in this review.

The concept of the "intrinsic barrier" was introduced by Marcus (1956, 1957, 1964); it is now widely recognized as being a more meaningful reactivity parameter than the *actual* reaction barrier because it is a purely kinetic property of a reaction system and independent of its thermodynamic driving force. In other words, it is, at least in principle, a parameter that describes the reactivity of a whole reaction series, irrespective of the thermodynamics of a particular member in that series. Hence to understand the factors that affect intrinsic barriers is to understand a great deal about chemical reactivity.

Marcus (1956, 1957) developed a comprehensive theory of outer sphere electron transfer reactions which led to the well-known Marcus equations. The first, (5), relates the reaction barrier $\Delta G^\ddagger$ to the intrinsic barrier $\Delta G_0^\ddagger$

$$\Delta G^\ddagger = w_r + \Delta G_0^\ddagger \left(1 + \frac{\Delta G^0 - w_r + w_p}{4 \Delta G_0^\ddagger} \right)^2 \quad (5)$$

and the Gibbs free energy ΔG^0 . The equation includes "work terms" for bringing reactants together (w_r) and separating the products ($-w_p$). Originally developed for electron-transfer reactions, (5) has since been applied to numerous other types of reaction, including proton transfers (Marcus, 1968; Cohen and Marcus, 1968; Kresge, 1975a; Keeffe and Kresge, 1986), hydride transfers (Kreevoy and Lee, 1984; Lee *et al.*, 1988) and methyl transfers (Albery and Kreevoy, 1978; Albery, 1980; Lewis and Hu, 1984), as well as nucleophilic addition reactions (Hine, 1971). In many applications the work terms are typically neglected, especially when $\Delta G_0^\ddagger$ is high, which reduces (5) to (6).

$$\Delta G^\ddagger = \Delta G_0^\ddagger \left(1 + \frac{\Delta G^0}{4 \Delta G_0^\ddagger} \right)^2 = \Delta G_0^\ddagger + \frac{\Delta G^0}{2} + \frac{(\Delta G^0)^2}{16 \Delta G_0^\ddagger} \quad (6)$$

Equation (6) can provide a means to calculate $\Delta G_0^\ddagger$ when only a few experimental data points are available; in principle one $\Delta G^\ddagger$, ΔG^0 pair suffices. However, when an extended set of data is available, adherence to (6) is usually rather imperfect, which is the main reason why we generally prefer to determine k_0 directly by interpolating or extrapolating Brønsted plots as described above. In later sections we shall return to (5) and (6), deal with their limitations and discuss attempts at circumventing some of these limitations.

Marcus theory also relates intrinsic barriers of electron-, proton-, hydride- and methyl-transfer reactions to the intrinsic barriers of the corresponding "identity reactions". For a proton-transfer reaction such as (4) ("cross-reaction"), the corresponding identity reactions are given by (7) and (8), while the Marcus relationship between the various intrinsic barriers is shown in (9).



$$\Delta G_0^\ddagger(\text{CH/B}^v) = \frac{1}{2} [\Delta G_0^\ddagger(\text{CH/C}^-) + \Delta G_0^\ddagger(\text{BH}^{v+1}/\text{B}^v)] \quad (9)$$

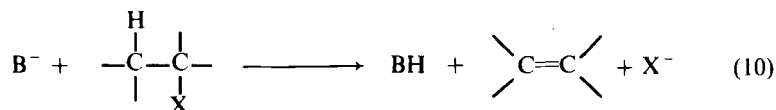
Furthermore, for electron transfers, Marcus theory provides a relationship between $\Delta G_0^\ddagger$ and properties of reactants and medium such as molecular size, charge and solvent polarity (Marcus, 1956, 1957), thereby making the Marcus approach a predictive and quantitative theory. This success can be traced to the simplicity of outer sphere electron transfers in which no bonds are being formed or cleaved. No such relationship has been found for the other reactions treatable by (6) and (9). In other words, even though equations such as (9) are quite successful in correlating or predicting intrinsic barriers in terms of other intrinsic barriers, they do not provide a molecular understanding of what determines the height of intrinsic barriers.

The same is true for (5) or (6): these equations interrelate $\Delta G^\ddagger$, ΔG^0 and $\Delta G_0^\ddagger$ and can also provide insights into why Brønsted-type plots ($\log k_1$ versus $\log K_1$) might show strong curvature when $\Delta G_0^\ddagger$ is small, but weak or no curvature when $\Delta G_0^\ddagger$ is large (see below). But this does not constitute "understanding at the molecular level". It is this molecular understanding that is our objective and that is at the core of the PNS.

TRANSITION-STATE IMBALANCES

The fundamental premise of the PNS is that there is a strong connection between intrinsic barriers and what Jencks and Jencks (1977) have called

transition-state imbalances. The transition state of the majority of chemical reactions has the potential for being imbalanced. In fact, whenever there is more than one process involved in a reaction, such as the formation or cleavage of a bond, development or destruction and localization or delocalization of a charge, development or destruction of π -overlap (resonance), solvation/desolvation, etc., there will be an imbalance if these processes have developed non-synchronously at the transition state (Bunnett, 1962; More O'Ferrall, 1970; Harris and Kurz, 1970; Jencks and Jencks, 1977; Harris *et al.*, 1979; Murdoch, 1983; Gajewski and Gilbert, 1984; Kreevoy and Lee, 1984; Lewis and Hu, 1984; Jencks, 1985). This phenomenon is nicely illustrated with the example of alkene-forming 1,2-eliminations (10). Figure



1 represents a More O'Ferrall-Jencks (More O'Ferrall, 1970; Jencks, 1972) diagram of this reaction, with separate axes for the proton transfer and for leaving-group departure. The reaction may proceed by two different stepwise mechanisms (E1 and E1cB), or by a concerted mechanism (E2) (Saunders and Cockerill, 1973; Gandler, 1989). For the E2 mechanism, there are essentially an infinite number of possible reaction coordinates, only one of which entails a completely synchronous development of proton transfer and leaving-group departure (balanced transition state), while all the others have imbalanced transition states. If proton transfer is ahead of leaving-group departure, the transition state is called "E1cB-like," if proton transfer lags behind leaving-group departure, it is called "E1-like."

It should be pointed out that, even though the representation of the E2 mechanism by two progress variables (B---H---C and C---X) on a three-dimensional More O'Ferrall-Jencks diagram is much more satisfactory than the use of a two-dimensional reaction profile with a single reaction coordinate, it does not take into account the possibility that C=C double bond formation may not be synchronized with either of the two other processes, and actually would require three independent reaction coordinates. The same problem arises in general acid-base-catalysed n- and e-type reactions (Jencks and Jencks, 1977; Palmer and Jencks, 1980). Most reactions to be dealt with in this review will involve fewer bond changes. The major emphasis will be on proton transfers from carbon acids and other carbanion-forming reactions. This is because they currently provide the most extensive data base relevant to the PNS. However, the PNS applies to any reaction that has an imbalanced transition state, and examples drawn from a variety of reaction classes will illustrate this claim.

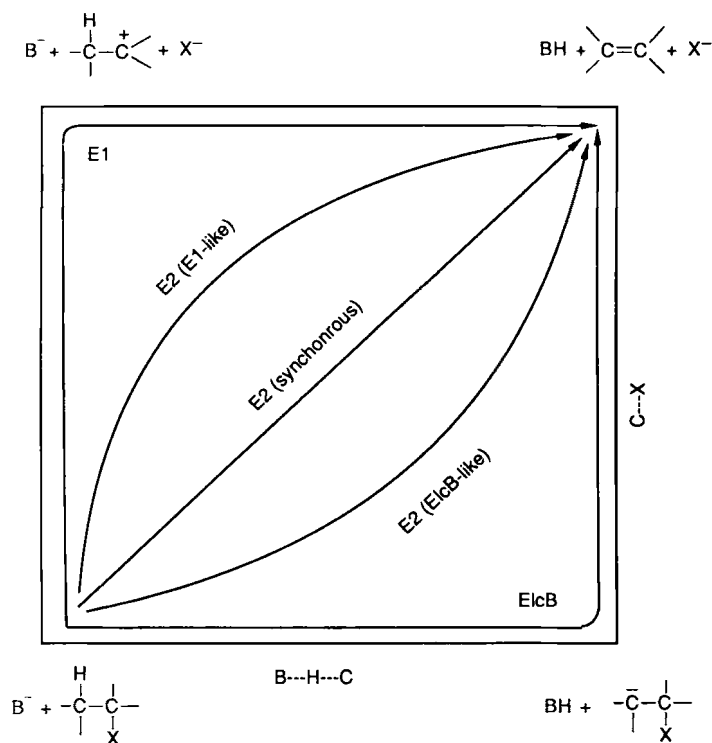
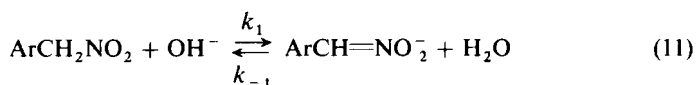


Fig. 1 More O'Ferrall-Jencks diagram for alkene-forming 1,2-eliminations. Paths along the edges of the diagram represent the stepwise E1 and E1cB mechanisms respectively. Paths through the inside of the diagram are for concerted E2 mechanisms, with the diagonal representing the synchronous case and the curved reaction coordinates the non-synchronous cases.

2 Imbalances in proton transfers

THE NITROALKANE ANOMALY

A reaction that has occupied centre stage in the development of the PNS is the deprotonation of arynitroalkanes (Bordwell and Boyle, 1972, 1975). For example, for the reaction of ArCH_2NO_2 with OH^- in water (11), the



Hammett ρ -value for the deprotonation rate, $\rho(k_1)$, is 1.28 while $\rho(K_1) = 0.83$ for the equilibrium constant (Bordwell and Boyle, 1972). What is unusual is that $\rho(k_1) > \rho(K_1)$, i.e. the rate of formation of $\text{ArCH}=\text{NO}_2^-$ is more sensitive to substituent effects than the equilibrium, implying that the transition state is subject to greater stabilization by electron-withdrawing substituents than is the product ion.

An equally unusual implication derives from $\rho(k_{-1})$ for the reaction in the reverse direction. From the relationship (12) we can calculate $\rho(k_{-1}) = 0.45$.

$$\rho(k_1) - \rho(k_{-1}) = \rho(K_1) \quad (12)$$

The fact that $\rho(k_{-1})$ is positive means that, like the forward reaction, the reverse reaction is accelerated by electron-withdrawing substituents, i.e. making $\text{ArCH}=\text{NO}_2^-$ less basic enhances the rate of its protonation by water. The same conclusions are reached from the *normalized* ρ -values, which are equivalent to Brønsted coefficients according to (13):¹ $a_{\text{CH}} > 1$ and

$$a_{\text{CH}} = \rho_n(k_1) = \rho(k_1)/\rho(K_1) = 1.28/0.83 = 1.54 \quad (13a)$$

$$\beta_{\text{C}} = -\rho_n(k_{-1}) = -\rho(k_{-1})/\rho(K_1) = -0.45/0.83 = -0.54 \quad (13b)$$

$\beta_{\text{C}} < 1$ are highly anomalous values in the context of the Leffler–Grunwald (1963) rate-equilibrium equation (14), according to which a is a measure of

$$\delta\Delta G^\ddagger = a\delta\Delta G^0 \quad (14)$$

reaction progress at the transition state, a point to which we shall return below. The above situation, called the “nitroalkane anomaly” (Kresge, 1974), is illustrated in Fig. 2.

These anomalous ρ - or a_{CH} -values are not restricted to (11). Values of a_{CH} for the deprotonation of ArCH_2NO_2 by morpholine and 2,4-lutidine are 1.29 and 1.30 respectively (Bordwell and Boyle, 1972), and those for the deprotonation of $\text{Z}(\text{CH}_2)_3\text{NO}_2$ by OH^- and pyridine are $a_{\text{CH}} = 1.67$ and 1.89 respectively (Bordwell *et al.*, 1978). On the other hand, the Brønsted β_{B} -values of *ca* 0.55 (variation of Bⁿ) for the deprotonation of 1-arylnitroethanes by a series of secondary alicyclic amines (Bordwell and Boyle, 1972) are in the normal range of $0 < \beta_{\text{B}} < 1$.

¹ Throughout this review, the symbols a_{CH} and β_{C} will be used for the Brønsted coefficients obtained by varying the acidity of the carbon acid, while keeping the base constant. They are to be distinguished from β_{B} and a_{BH} which refer to the Brønsted coefficients obtained by varying the acidity of BH^{++} [e.g. in (4)] while keeping the carbon acid constant.

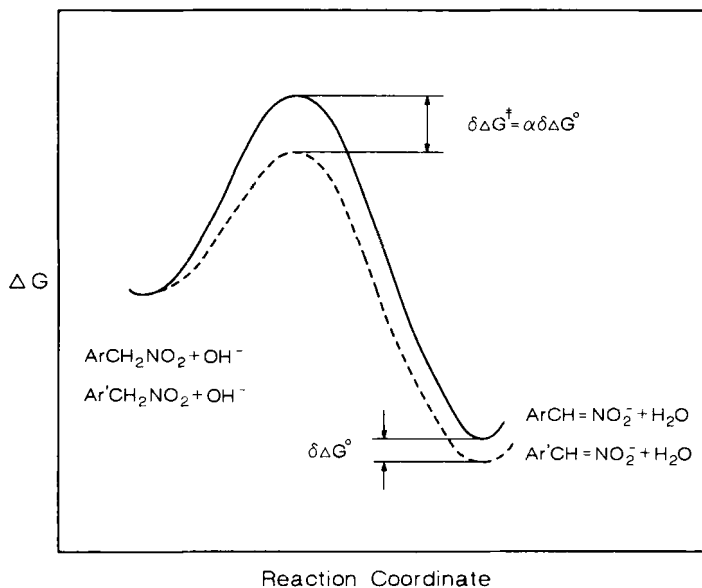
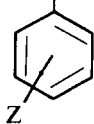
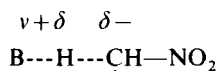
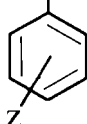


Fig. 2 Free energy versus reaction coordinate diagram for the deprotonation of aryl nitromethanes by OH^- . The effect of a polar substituent ($\text{Ar} \rightarrow \text{Ar}'$) on transition-state energy is larger than that on product energy, i.e. $\alpha > 1$ in (14).

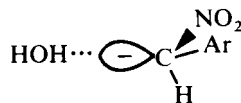
The most widely accepted explanation for the unusual ρ - or α_{CH} -values is that the transition state [1] is highly imbalanced in the sense that delocalization of the negative charge into the nitro-group lags strongly behind proton transfer. The representation in [1] that shows no charge on the nitro-group



[1]



[2]



[3]

may be an exaggeration, i.e. in reality there may be a small degree of charge transfer to the nitro-group with a concomitant small degree of $\text{C}=\text{N}$ double bond formation, but this modest degree of electronic reorganization must be smaller than the progress in the proton transfer to the base. Note that [1] also implies that the α -carbon essentially retains its sp^3 -hybridization.

The differences in the electronic structures between [1] and [2] can account for the fact that $\rho(k_1) > \rho(K_1)$, or $a_{\text{CH}} > 1$, as follows. In [2] there is a full negative charge, but the fact that it is located on the electronegative oxygens of the nitro-group and far removed from the aryl substituents tend to make $\rho(K_1)$ small. Hydrogen-bonding solvation by the aqueous solvent provides further stabilization of this charge and, with it, a further reduction in $\rho(K_1)$. In [1] the charge is located in close proximity to the aryl substituent, it is concentrated on carbon, which provides less internal stabilization than oxygen, and it is also less capable of being solvated by hydrogen bonding. All these factors tend to make $\rho(k_1)$ large despite the fact that there is only a partial charge.

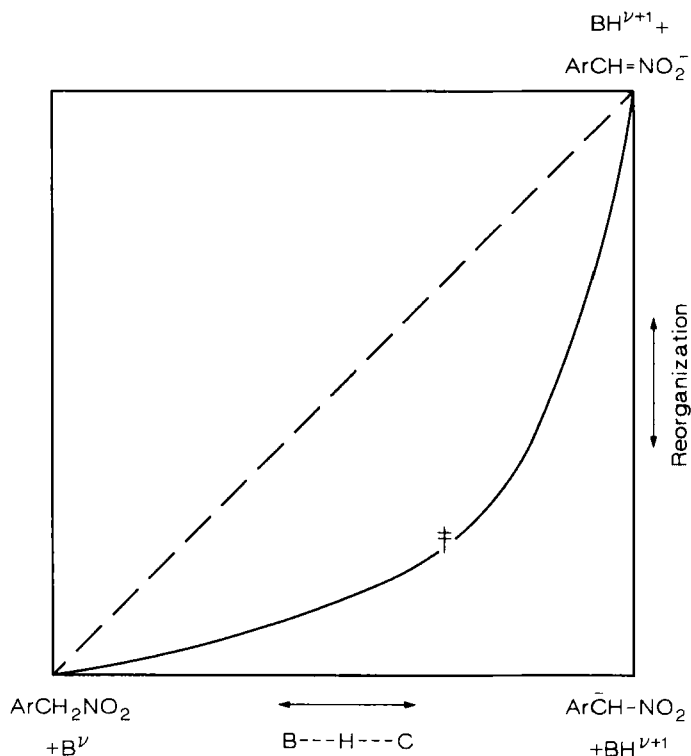


Fig. 3 More O'Ferrall-Jencks diagram for the deprotonation of phenylnitromethane. The curved line shows the reaction coordinate, with charge delocalization and solvation ("reorganization") lagging behind proton transfer.

The reaction coordinate that leads to a transition state such as [1] may be visualized by the More O'Ferrall-Jencks diagram of Fig. 3. The lower left corner represents the reactants, the upper right corner the products, while

the lower right corner is a hypothetical intermediate whose negative charge is localized on the sp^3 -hybridized carbon. At this point we shall leave the exact nature of the hypothetical intermediate in the upper left corner undefined; a possible structure would be the neutral nitroalkane that is in a solvent shell appropriate to the nitronate ion rather than the neutral nitro-compound (Albery *et al.*, 1988), a point to which we shall return in Section 4. The progress variables are the degree of proton transfer (horizontal axis), and the degree of charge delocalization into the nitro-group, with concurrent solvation (vertical axis), i.e. reorganization for short. A synchronous development of the two progress variables would correspond to the diagonal reaction coordinate (dashed line). The true reaction coordinate is shown by the curved line.

It should be noted that Bordwell and Boyle (1972, 1975) have suggested that the imbalance is so extreme as to lead to a two-step reaction with the formation of a tetrahedral intermediate [3] whose full negative charge on carbon may be stabilized by hydrogen bonding from the solvent. The formation of [3], which corresponds to the lower right corner in Fig. 3, is assumed to be rate-limiting. There is little experimental support for the presence of an intermediate, though, and a kinetic carbon isotope-effect study (Wilson *et al.*, 1980) seems to rule it out.

HOW TO MEASURE IMBALANCES

In the deprotonation of nitroalkanes the imbalance is so large that it is easily diagnosed on the basis of the anomalous Brønsted coefficients α_{CH} or β_C alone. Imbalances also occur in other proton transfers that involve charge delocalization in the carbanion, but they are less obvious because α_{CH} and β_C are in the "normal" range between zero and unity. In these cases an inequality between α_{CH} and β_B indicates the presence of a transition-state imbalance, and the difference $\alpha_{CH} - \beta_B$ serves as an approximate measure of the imbalance. The justification for this assumption is as follows. B^v in (4) is a base that, upon protonation, does not undergo major structural reorganization, which could potentially create its own imbalance. Hence β_B may be taken as a measure of the degree of proton transfer from CH to B^v or, better, of charge transfer from B^v to CH at the transition state (Leffler and Grunwald, 1963; Kresge, 1975b; Jencks, 1985). If CH were a carbon acid whose conjugate base is a non-delocalized carbanion, α_{CH} should be a measure of the same proton or charge transfer, i.e. the equality $\alpha_{CH} = \beta_B$ should hold since the amount of charge lost by B^v (β_B) is the same amount of charge received by CH (α_{CH}). On the other hand, if charge delocalization plays an important role in the stabilization of the carbanion and the

transition state is imbalanced, a_{CH} becomes distorted and is no longer a measure of charge or proton transfer at the transition state. As dramatically illustrated by the deprotonation of arylnitroalkanes, if charge delocalization lags behind proton transfer, a_{CH} will typically be exalted, and a_{CH} will be greater than β_{B} , although in certain cases discussed below one may have a_{CH} less than β_{B} .

It should be mentioned at this point that the notion that β_{B} is a measure of proton or charge transfer has been challenged (Pross, 1984; Bordwell and Hughes, 1985; Pross and Shaik, 1989) as well as defended (Jencks, 1985). We shall assume throughout this review that β_{B} is at least an approximate measure of charge transfer. The internal consistency of the conclusions reached on the basis of this assumption strongly supports it. In some cases, solvation effects may lead to distortions of β_{B} as a measure of charge transfer (Jencks *et al.*, 1982, 1986; Murray and Jencks, 1990). However, corrections can be applied to such β_{B} -values as discussed below.

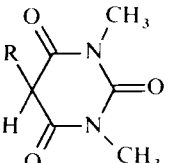
Representative a_{CH} - and β_{B} -values for a variety of proton-transfer reactions are summarized in Tables 1 and 2. Only examples in which a_{CH} was obtained by varying the acidity of CH by *polar* substituent effects² are included. As elaborated upon in a later section, *resonance* substituent effects can lead to gross distortions in a_{CH} that make the difference $a_{\text{CH}} - \beta_{\text{B}}$ unsuitable as a measure of the imbalance. All examples in Table 1 show a "positive" imbalance, i.e. $a_{\text{CH}} - \beta_{\text{B}} > 0$, while those in Table 2 have "negative" imbalances, i.e. $a_{\text{CH}} - \beta_{\text{B}} < 0$.

Do negative imbalances imply a transition state in which charge delocalization is ahead of proton transfer rather than lagging behind it? Such a notion appears intuitively unreasonable and is not necessary to explain why $a_{\text{CH}} - \beta_{\text{B}} < 0$. Whether the imbalance is positive or negative depends on the location of the carbon-acid substituent with respect to the site of charge development; a_{CH} will be increased, and hence $a_{\text{CH}} - \beta_{\text{B}} > 0$, if the substituent is closer to the site of negative charge in the transition state and more remote from the charge in the product, as is the case for all examples in Table 1 and illustrated in [1] and [2].

On the other hand, in the examples of Table 2 the substituent is closer to the charge in the product than in the transition state, as illustrated in [4] and [5], and hence, a_{CH} is decreased. The case of entry 4b in Table 2 is interesting because the carbanion is a resonance hybrid between [6a] and [6b]. If [6a] were the dominant form, an increased a_{CH} -value should be observed since the negative charge in the product is further away from Z than in the transition state, [7]. Since $a_{\text{CH}} - \beta_{\text{B}} < 0$, implying a decreased a_{CH} -value, it

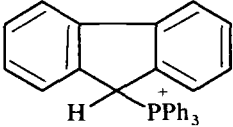
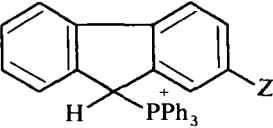
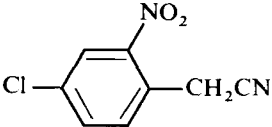
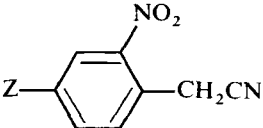
² Throughout this review, the term "polar effect" will be used for the combination of inductive and field effects.

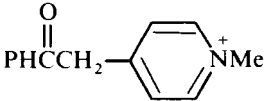
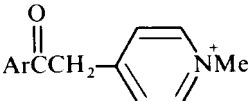
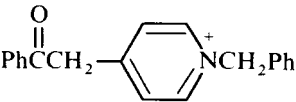
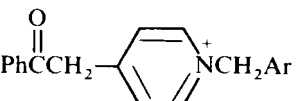
Table 1 Brønsted coefficients and imbalances $a_{\text{CH}} - \beta_{\text{B}}$ in the deprotonation of carbon acids by normal bases. Examples with $a_{\text{CH}} - \beta_{\text{B}} > 0$.

Entry	CH-Acid	Base	Solvent, T	β_{B}	a_{CH}	$a_{\text{CH}} - \beta_{\text{B}}$	Ref.
1a	$\text{PhCH}_2\text{CH}(\text{CN})_2$	RCOO^-	H_2O , 25°C	1.0 (≈ 0.83) ^a	0.98	0 (≈ 0.15) ^a	^b
1b	$\text{ArCH}_2\text{CT}(\text{CN})_2$	$\text{ClCH}_2\text{COO}^-$	H_2O , 25°C				^b
2a	PhCH_2CN	ArCH_2NH_2	Me_2SO , 25°C	0.67	0.71	0.04	^c
2b	ArCH_2CN	PhCH_2NH_2	Me_2SO , 25°C				^c
3a	$3\text{-ClC}_6\text{H}_4\text{CH}_2\text{CN}$	ArCH_2NH_2	Me_2SO , 25°C	0.61	0.74	0.13	^c
3b	ArCH_2CN	$4\text{-ClC}_6\text{H}_4\text{CH}_2\text{NH}_2$	Me_2SO , 25°C				^c
4a	$\text{PhCH}_2\text{CH}(\text{COMe})\text{COOEt}$	RCOO^-	H_2O , 25°C	0.44	0.76	0.32	^b
4b	$\text{ArCH}_2\text{CH}(\text{COMe})\text{COOEt}$	AcO^-	H_2O , 25°C				^b
5		H_2O	H_2O , 25°C		0.80		^d
6a	$3,5\text{-(NO}_2)_2\text{C}_6\text{H}_3\text{CH}_2\text{NO}_2$	ArCOO^-	CH_3CN , 25°C	0.56	0.82	0.26	^e
6b	ArCH_2NO_2	PhCOO^-	CH_3CN , 25°C				^e
7a	PhCH_2NO_2	ArCOO^-	Me_2SO , 25°C	0.55	0.92	0.37	^f
7b	ArCH_2NO_2	PhCOO^-	Me_2SO , 25°C				^f
8a	$\text{PhCH}(\text{CH}_3)\text{NO}_2$	R_2NH	H_2O , 25°C	0.55	0.94	0.39	^g
8b	$\text{ArCH}(\text{CH}_3)\text{NO}_2$	morpholine	H_2O , 25°C				^g
9a	PhCH_2NO_2	R_2NH	H_2O , 25°C	0.56	1.29	0.73	^h
9b	ArCH_2NO_2	morpholine	H_2O , 25°C				^g
10a	$4\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{NO}_2$	RS^-	H_2O , 25°C	0.43	1.32	0.89	^h
10b	ArCH_2NO_2	$\text{HOCH}_2\text{CH}_2\text{S}^-$	H_2O , 25°C				^h

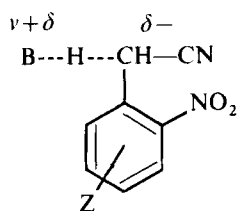
^a Corrected for the solvation of RCOOH , see p. 187. ^b Bell and Grainger (1976). ^c Bowden and Hirani (1990). ^d Buckingham *et al.* (1987). ^e Gandler and Bernasconi (1991). ^f Keeffe *et al.* (1979). ^g Bordwell and Boyle (1972). ^h Bernasconi and Wiersema (1992).

Table 2 Brønsted coefficients and imbalances $a_{\text{CH}} - \beta_{\text{B}}$ in the deprotonation of carbon acids by normal bases. Examples with $a_{\text{CH}} - \beta_{\text{B}} < 0$.

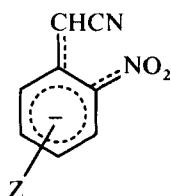
Entry	CH-Acid	Base	Solvent, T	β_{B}	a_{CH}	$a_{\text{CH}} - \beta_{\text{B}}$	Ref.
1a		R_2NH	50% Me_2SO , 20°C	0.49			^a
1b		morpholine	50% Me_2SO , 20°C		0.29	-0.20	^a
2a		R_2NH	90% Me_2SO , 20°C	0.64			^b
2b		morpholine	90% Me_2SO , 20°C		0.46	-0.20	^b

3a		RNH_2	H_2O , 25°C	0.55			^c
3b		$\text{PhCH}_2\text{CH}_2\text{NH}_2$	H_2O , 25°C		0.36	-0.19	^c
4a		RNH_2	H_2O , 25°C	0.55			^c
4b		$\text{PhCH}_2\text{CH}_2\text{NH}_2$	H_2O , 25°C		0.27	-0.28	^c

^a Bernasconi and Fairchild (1992). ^b Bernasconi and Wenzel (1992). ^c Stefanidis and Bunting (1990).



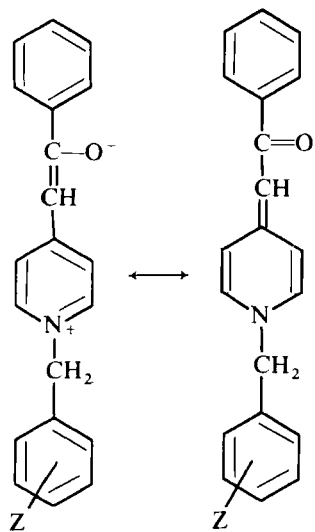
[4]



[5]

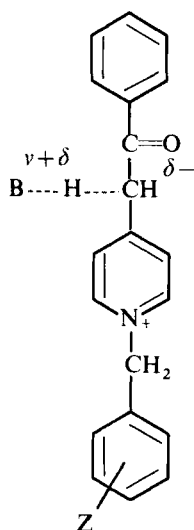
appears that [6b] is the dominant form. The low pK_a -values of [8] in the range of 7 (Stefanidis and Bunting, 1991), which are consistent with a strong resonance effect as implied in [6b], support this conclusion.

There is one result, entry 3b in Table 2, that is puzzling. The carbon acid [9] is very similar to [8] except that the substituents are located at the other end of the molecule. Hence, if the conjugate base of [9] is dominated by the neutral resonance form [10b], which is the analogue to [6b], a_{CH} should now be increased, i.e. $a_{CH} - \beta_B > 0$. Experimentally, $a_{CH} < \beta_B$ has been reported. This is difficult to explain and it may be advisable to repeat these measurements.

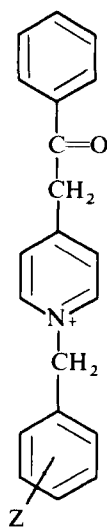


[6a]

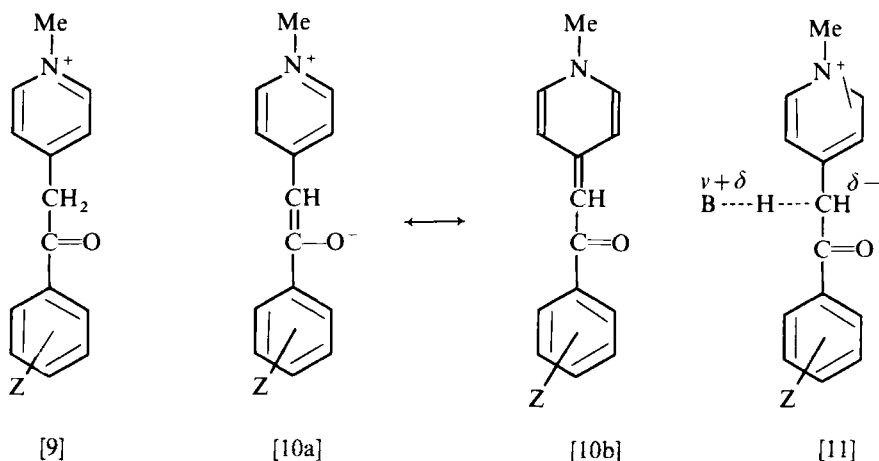
[6b]



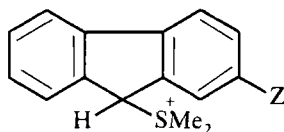
[7]



[8]



There exist other examples in the literature where both an α_{CH} and a β_{B} have been reported, but which have not been included in Tables 1 or 2. A prominent case is the reaction of [12] with carboxylate ions (Murray and



[12]

Jencks, 1990). The difficulty here is that β_{B} is so strongly dependent on Z ($\beta_{\text{B}} = 0.82, 0.76$ and 0.63 for $\text{Z} = \text{H}, \text{Br}$ and NO_2 respectively), and α_{CH} so strongly dependent on R in RCOO^- ($\alpha_{\text{CH}} = 0.68, 0.74, 0.84$ and 0.97 for $\text{R} = \text{CH}_3, \text{CH}_3\text{OCH}_2, \text{NCCH}_2$ and Cl_2CD respectively) that no meaningful $\alpha_{\text{CH}} - \beta_{\text{B}}$ can be calculated. These large variations in the Brønsted coefficients indicate a highly variable transition state, which renders an assessment of the imbalance difficult. We shall only deal with cases where the substituent dependence of α_{CH} and β_{B} is small or non-existent.

RELATION BETWEEN IMBALANCE AND DEGREE OF RESONANCE STABILIZATION OF THE CARBANION

The size of the transition-state imbalance in proton transfers measured by $\alpha_{\text{CH}} - \beta_{\text{B}}$ correlates with the degree of resonance stabilization of the carb-

anion. This is particularly apparent from the data reported in Table 1. At one extreme are the reactions of benzylmalononitriles and phenylacetone nitriles (Entries 1–3 in Table 1). The conjugate bases of these compounds derive most of their stabilization from the polar effect of the cyano group(s), while the resonance effect is relatively modest (Hine, 1977; Bell, 1973; Delbecq, 1984; Hoz *et al.*, 1985). Hence there is not much charge delocalization, and the charge distribution in the product ion is not very different from that in the transition state. This is reflected in relatively small imbalances. The size of the imbalance in the reaction of $\text{ArCH}_2\text{CH}(\text{CN})_2$ with RCOO^- reported in Table 1 is somewhat uncertain. The *experimental* β_{B} -value is 1.0, suggesting a zero imbalance, but there is evidence that high β_{B} -values obtained from reactions with carboxylate ions need a correction because of a solvation effect of the carboxylic acid (Murray and Jencks, 1990), a point to which we shall return later. The corrected β_{B} -value may be around 0.80–0.85, leading to $a_{\text{CH}} - \beta_{\text{B}} \approx 0.15\text{--}0.20$.

Intermediate sized imbalances are found with ketones or ketone derivatives, for example the reaction of $\text{ArCH}_2\text{CH}(\text{COMe})\text{COOEt}$ with carboxylate ions (Entry 4 in Table 1). For the reaction of 5-substituted barbituric acids with water (Entry 5 in Table 1), the rather high a_{CH} -value also suggests an appreciable imbalance, even though no β_{B} is available to evaluate the size of this imbalance. These intermediate sized imbalances are consistent with the notion that in these reactions the carbanion benefits appreciably from resonance that delocalizes the charge into the carbonyl groups.

At the other end of the spectrum are the aryl nitromethanes (Entries 9 and 10), whose conjugate bases are strongly resonance-stabilized, which leads to very large imbalances. It is noteworthy that the imbalance in the deprotonation of 1-arylnitroethanes (Entry 8) by amines is considerably smaller than for the deprotonation of aryl nitromethanes by the same amines (Bordwell and Boyle, 1972). This can be understood by the reduced resonance effect of the carbanion, owing to steric hindrance to optimal π -overlap by the methyl group in $\text{ArC}(\text{CH}_3)=\text{NO}_2^-$.

It is also significant that in the deprotonation of aryl nitromethanes the imbalance is much smaller in dipolar aprotic solvents such as Me_2SO (Entry 7) or acetonitrile (Entry 6). In water, the added stabilization of the negative charge of the nitronate ion by hydrogen-bonding solvation reduces the need for internal stabilization by the Z-substituent. This makes $\rho(K_1)$ relatively small, but has relatively little effect on $\rho(k_1)$ and is partially responsible for the high a_{CH} . Upon changing to a non-hydroxylic solvent, the loss in solvation of the nitronate ion is partially offset by increased internal stabilization, as reflected in an increase in $\rho(K_1)$ for (11) from 0.83 in water (Bordwell and Boyle, 1972) to 2.65 in Me_2SO (Keeffe *et al.*, 1979). Since the transition state is only minimally stabilized by hydrogen bonding, the

change in solvent has a smaller effect on $\rho(k_1)$, which only increases from 1.28 in water to *ca* 2.4 in Me_2SO . The result is a smaller $\alpha_{\text{CH}} = \rho(k_1)/\rho(K_1)$.

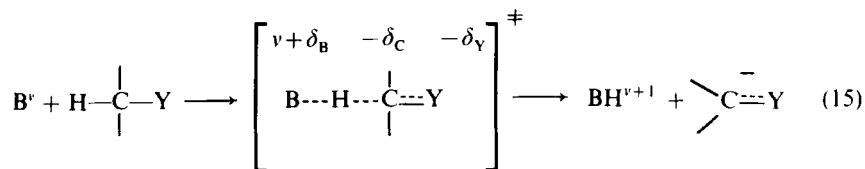
The above considerations demonstrate that solvation can be an important factor in creating imbalances. In cases such as nitronate ions, it is difficult to separate this solvation effect from the effect of charge delocalization. An interesting question is whether the lag in the development of this solvation is simply a consequence of the lag in charge delocalization, or whether there is an additional lag that arises solely from the solvent. In other words, if there were no lag in charge delocalization, would there still be a lag in this solvation? There exist numerous examples in which such a lag has been observed, as will be discussed in Section 5.

WHY DOES DELOCALIZATION LAG BEHIND CHARGE TRANSFER?

As will be discussed in a later section, the lag in charge delocalization, which is equivalent to a lag in resonance development, is responsible for the high intrinsic barrier of reactions that lead to resonance-stabilized products. This notion seems to contradict a basic law of nature according to which physical or chemical processes should always follow a path of minimum energy. The apparent contradiction is that the lag in resonance development creates a higher reaction barrier than would prevail if this resonance development were synchronous with charge transfer. Thus, one wonders why resonance does not develop synchronously with charge transfer.

Kresge's models

One of the intuitively most appealing explanations of this phenomenon has been put forward by Kresge (1974) in the context of the deprotonation of nitroalkanes, but his models are applicable to any reaction of type (15). The



basic idea is that the fraction of negative charge delocalized into Y depends on the fraction of π -bond formation between C and Y, and the fraction of π -bond formation in turn depends on the fraction of charge, δ_{B} , transferred from the base to the carbon acid. This means that the charge on Y in the

transition state, δ_Y , is a fraction of a fraction, and hence quite small. We shall discuss two models for calculating δ_Y .

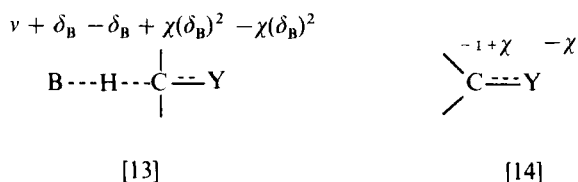
Model I. The first model assumes that the π -bond order of the C—Y bond is directly proportional to the transferred charge (i.e. $\pi_{b.o.} \propto \delta_B$), and that the fraction of δ_B delocalized into Y, δ_Y , is proportional to the π -bond order (i.e. $\delta_Y \propto \delta_B \pi_{b.o.}$). With these assumptions, δ_Y is given by (16), where χ is a proportionality constant. Note that δ_Y and δ_C (below) are defined as positive numbers; the fact that they refer to negative charges is indicated by minus signs in (15) and subsequent structures. The constant χ is found from (16) by setting $\delta_B = 1$, which yields $\delta_Y = \chi$, i.e. χ represents the amount of charge delocalized into Y in the product ion, and hence χ may also be equated with the C—Y π -bond order in the *product ion*.

$$\delta_Y = \chi(\delta_B)^2 \quad (16)$$

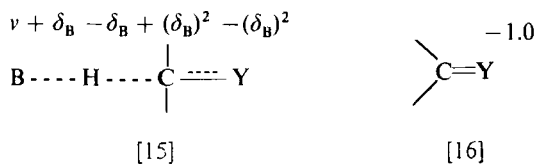
The charge that remains localized on the carbon, δ_C , is given by (17).

$$\delta_C = \delta_B - \delta_Y = \delta_B - \chi(\delta_B)^2 \quad (17)$$

Thus, the charge distribution in the transition state is represented by [13] and that in the product ion by [14].

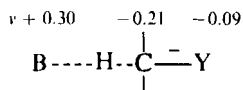


We now apply (16) and (17) to the situation where the π -bond in the product ion is fully developed, as is believed to be (approximately) the case with the nitroalkanes. This means $\chi = 1.0$, and hence $\delta_Y = (\delta_B)^2$ and $\delta_C = \delta_B - (\delta_B)^2$, so that [13] becomes [15] and [14] becomes [16].

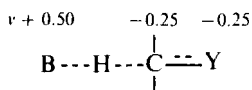


The reaction coordinate for this case is shown in Fig. 4, Curve I, which is equivalent to a More O'Ferrall-Jencks diagram with the horizontal axis

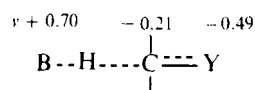
defined by δ_B and the vertical axis by $\delta_Y = (\delta_B)^2$. As indicated in Fig. 4, δ_B may also be equated with the Brønsted coefficient β_B . Structures [17]–[19]



[17]

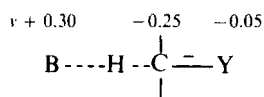


[18]

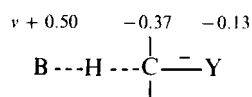


[19]

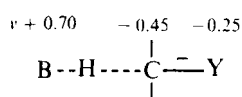
represent three transition states along the reaction coordinate of Fig. 4, with $\delta_B = 0.3, 0.5$ and 0.7 , respectively.³ When the π -bond in the product ion is less than fully developed, the situation changes to that shown in Fig. 5 (Curve 1). We shall discuss the specific case where $\chi = 0.5$. Transition states are shown in [20]–[22] for $\delta_B = 0.3, 0.5$ and 0.7 respectively, while for the product ion $\delta_Y = \delta_C = 0.5$.



[20]



[21]



[22]

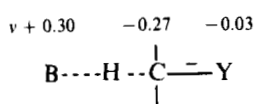
Model II. As pointed out by Kresge, the assumption that δ_Y is proportional to π -bond order and/or that π -bond order is proportional to charge transfer (δ_B) may not be quite correct. For example, charge delocalization might be a stronger or weaker function of π -bond order, and the same is possible for the dependence of π -bond order on charge transfer. If, for example, one assumes a quadratic dependence of charge delocalization on π -bond order (Kresge, 1974) and a linear dependence of π -bond order on charge transfer, (16) becomes (18), and (17) becomes (19). This is shown as

$$\delta_Y = \chi(\delta_B)^3 \quad (18)$$

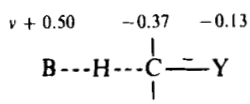
$$\delta_C = \delta_B - \delta_Y = \delta_B - \chi(\delta_B)^3 \quad (19)$$

Curve II in Figs. 4 and 5. Note that the meaning of χ is the same as in Model I. Structures [23]–[25] show representative transition-state charge distributions for $\chi = 1.0$ and $\delta_B = 0.3, 0.5$ and 0.7 respectively, while [26]–[28] refer to transition states for the same δ_B values and $\chi = 0.5$.

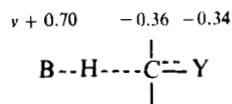
³ The varying number of dashes indicating partial bonds in [17]–[19] as well as in subsequent transition-state structures is meant to be a crude qualitative measure of how extensive the partial bond is.



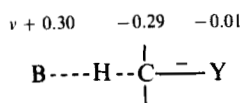
[23]



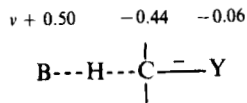
[24]



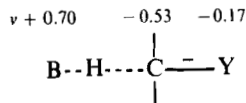
[25]



[26]



[27]



[28]

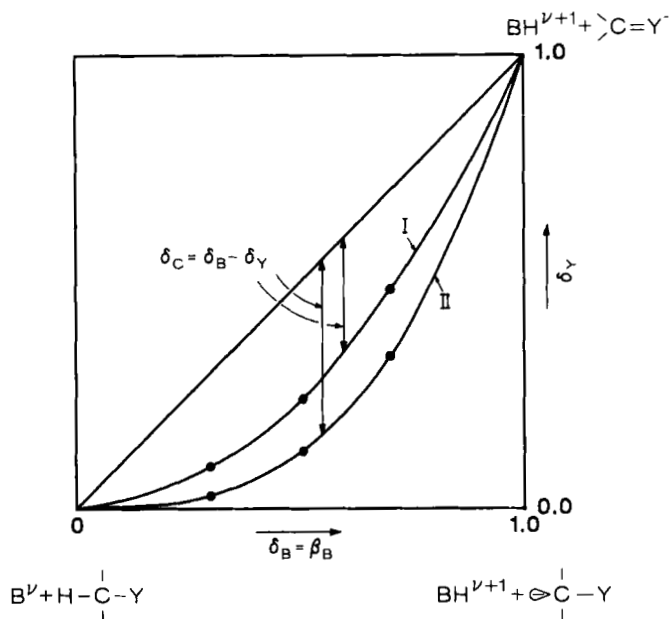


Fig. 4 More O'Ferrall-Jencks diagram for the deprotonation of a carbon acid that leads to a full C—Y π -bond in the product ion ($\chi = 1.0$). Axes are defined by $\delta_B = \beta_B$ and δ_Y respectively. Reaction coordinates I and II are calculated from (16) and (18) respectively. Highlighted points on the reaction coordinates represent transition states [17]–[19] on Curve I and [23]–[25] on Curve II respectively.

We have elaborated upon the Kresge models because many of our quantitative applications of the PNS formalism introduced in Section 3 will be based on them.

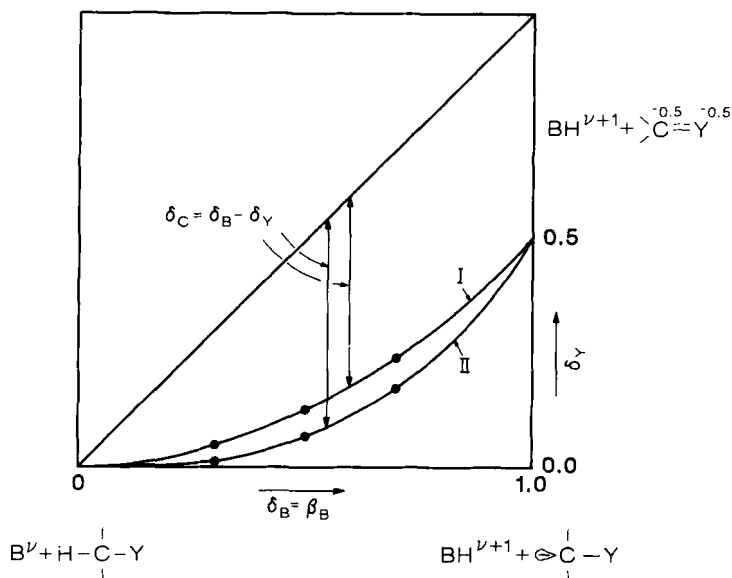
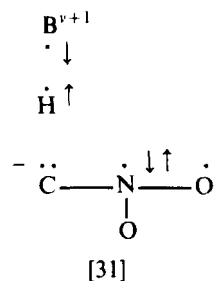
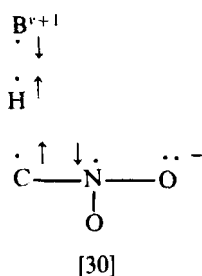
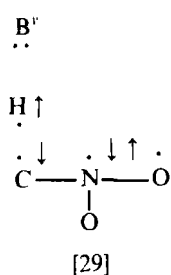


Fig. 5 More O'Ferrall-Jencks diagram for the deprotonation of a carbon acid that leads to a 50% development of the C—Y π -bond in the product ion ($\chi = 0.5$). Axes are defined by $\delta_B = \beta_B$ and δ_Y respectively. Reaction coordinates I and II are calculated from (16) and (18) respectively. Highlighted points on the reaction coordinates represent transition states [20]–[22] on Curve I and [26]–[28] on Curve II respectively.

The Shaik and Pross model

The imbalanced transition state in the deprotonation of nitroalkanes has also been discussed in the context of the valence bond configuration-mixing model (Pross and Shaik, 1982; Pross, 1985). In this model, the reactant and product configurations are represented by [29] and [30] respectively. As the



reaction progresses along the reaction coordinate, the energy of [29] increases because a repulsive $B \cdot H$ three-electron interaction is generated while the attractive $H \cdot \downarrow \uparrow C$ interaction is destroyed. In the early phases of the reaction coordinate, the product configuration [30] is of high energy since it can be regarded as generated from [29] by double electron excitation, but its energy drops fast along the reaction coordinate since the stable $B \cdot \downarrow \uparrow H$ interaction is generated. A third configuration, [31], with the negative charge on carbon contributes to the product, but less so than [30] since the negative charge prefers to be on oxygen. However, in the early phases, [31] is more stable than [30] since [31] is a monoexcited configuration while [30] is a diexcited configuration, and hence [31] makes a larger contribution to the transition-state structure than [30]. This is shown schematically in Fig. 6.

3 Effect of resonance on intrinsic rate constants of proton transfers

RELATIONSHIP BETWEEN IMBALANCE AND INTRINSIC RATE CONSTANTS: QUALITATIVE CONSIDERATIONS

There is a growing data base on intrinsic rate constants of proton transfers from carbon acids to a variety of bases, mainly amines and oxyanions. Representative examples are summarized in Table 3. The first part of the table reports data in water, 50% Me_2SO –50% water, and methanol, all of which typify strongly hydrogen-bonding media. The second part includes data in 90% Me_2SO –10% water, Me_2SO and CH_3CN as typical representatives of non-hydrogen-bonding (or weakly hydrogen-bonding in the case of 90% Me_2SO –10% water) solvents. The values of $\log k_0$ fall into four main clusters.

(1) The first cluster contains very high values, above 8.5, typical for reactions that are approaching the limit of diffusion-controlled reactions (Eigen, 1964; Ahrens and Maass, 1968). This group comprises two carbon acids (Entries 1 and 2), both of which lead to carbanions that are devoid of resonance effects and hence behave essentially like "normal acids", i.e. acids with the proton attached to oxygen, nitrogen or sulphur (Eigen, 1964).

(2) Values of $\log k_0$ between *ca* 6 and *ca* 7 for nitriles and malononitrile (Entries 3 and 31) fall in the second group. As pointed out earlier, even though the cyano-group is a π -acceptor that leads to some resonance

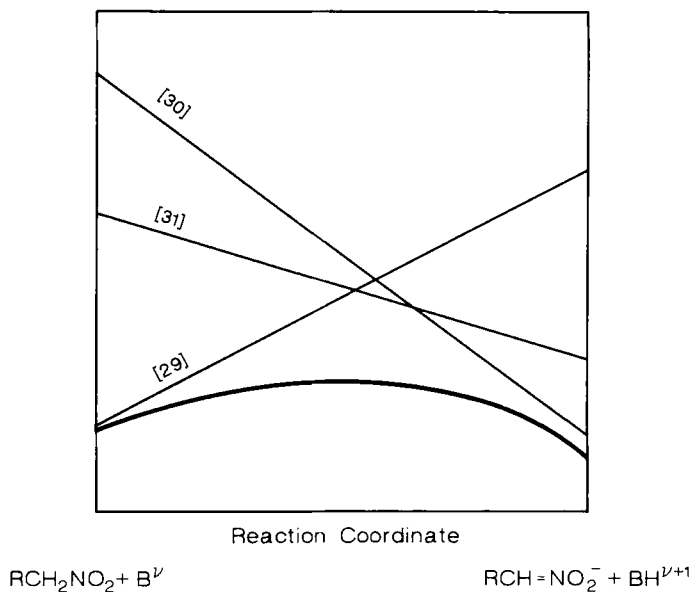
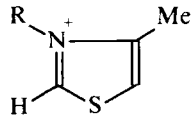
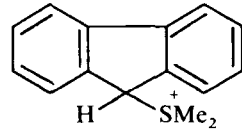
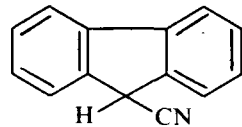
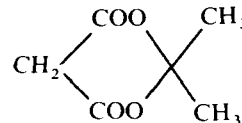


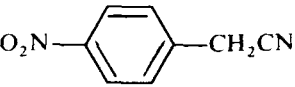
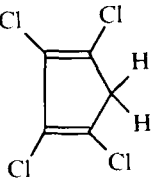
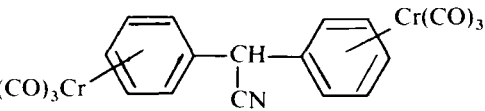
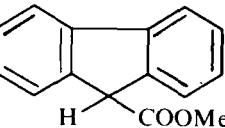
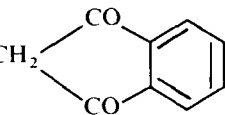
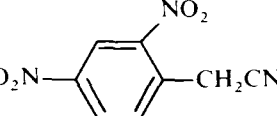
Fig. 6 Deprotonation of a nitroalkane: energy plot of reactant [29], product [30] and intermediate configuration [31] according to the Shaik and Pross valence bond configuration-mixing model. Adapted from Pross and Shaik (1982) with permission from the American Chemical Society.

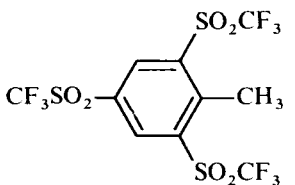
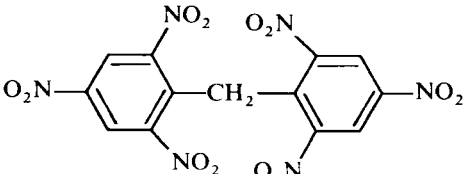
stabilization of the corresponding carbanions, this resonance effect is weaker than for the typical π -acceptors such as the carbonyl group or the nitro-group, and a large part of the electron-withdrawing capability of the cyano-group arises from its polar effect.

(3) The third cluster comprises $\log k_0$ -values between *ca* 2.5 and *ca* 5 and includes a large number of carbon acids (Entries 4–15 and 32–38). They are all compounds whose conjugate base is stabilized by moderately strong resonance effects as provided by carbonyl, fluorenyl, cyclopentadienyl and *p*-nitrophenyl groups, and some others, including arylnitroalkanes in Me_2SO or Me_2SO -rich solvents and CH_3CN . These carbon acids constitute a heterogeneous group, and hence an exact rank ordering according to the strength of the resonance effect is difficult to come by. This difficulty is compounded by the different effects of solvation on enolate or nitronate ions compared with, say, aromatic anions such as the fluorenyl ions, and the different solvents used. Nevertheless, there are several subgroups within this cluster that show a definite inverse correlation between $\log k_0$ and resonance.

Table 3 Intrinsic rate constants for proton transfers from carbon acids to normal bases.

Entry	CH-Acid	Solvent, <i>T</i>	pK_a^{CH}	$\log (k_0/M^{-1} s^{-1})$			Ref.
				pip/mor	RNH ₂	RCOO ⁻	
<i>In water, 50% Me₂SO-water, or MeOH</i>							
1		H ₂ O, 30°C	16.9–18.9			<i>ca</i> 9.0	<i>a</i>
2	HCN	H ₂ O, 20°C	9.0		<i>ca</i> 8.6	<i>ca</i> 9.1	<i>b</i>
3	CH ₂ (CN) ₂	H ₂ O, 25°C	11.2	<i>ca</i> 7.0			<i>c</i>
4		H ₂ O, 25°C	13.7		<i>ca</i> 4.0	<i>ca</i> 5.0	<i>d</i>
5	CH ₃ COCH ₂ ⁺ PPh ₃	50% Me ₂ SO, 20°C	7.21		3.93		<i>e</i>
6		50% Me ₂ SO, 20°C	9.53	4.58	3.76		<i>f</i>
7		50% Me ₂ SO, 20°C	4.70	3.90			<i>g</i>

8		50% Me ₂ SO, 20°C	12.62	3.70			<i>h</i>
9		50% Me ₂ SO, 20°C	8.32	3.59			<i>i</i>
10		50% Me ₂ SO, 20°C	10.26	3.30	2.94		<i>j</i>
11		50% Me ₂ SO, 20°C	10.97		2.84		<i>f</i>
12		50% Me ₂ SO, 20°C	6.35	3.13	2.44	3.18	<i>k</i>
13	CH ₂ (COCH ₃) ₂	50% Me ₂ SO, 20°C	9.12	2.75	2.06	3.80	<i>l</i>
14		50% Me ₂ SO, 20°C	8.06	2.75			<i>h</i>

	CH-Acid	Solvent, T	$\text{p}K_{\text{a}}^{\text{CH}}$	$\log (k_0/\text{M}^{-1} \text{ s}^{-1})$			Ref.
				pip/mor	RNH_2	RCOO^-	
15	$\text{CH}_2(\text{COCH}_3)_2$	H_2O , 20°C	9.11	2.60	1.90	2.89	^l
16	$\text{CH}_3\text{CH}(\text{NO}_2)_2$	50% Me_2SO , 20°C	5.00			1.70	^m
17	$\text{CH}_3\text{CH}(\text{NO}_2)_2$	H_2O , 25°C	<i>ca</i> 5.2			1.00	ⁿ
18	$(\text{CO})_5\text{Cr}=\text{C}\begin{matrix} \text{OMe} \\ \text{CH}_3 \end{matrix}$	H_2O , 20°C	12.3	<i>ca</i> 2.1			^o
19	CH_3NO_2	50% Me_2SO , 20°C	11.32	0.73			^p
20		MeOH , 25°C	9.46			0.38	^q
21		50% Me_2SO , 25°C	5.01			0.41	^r

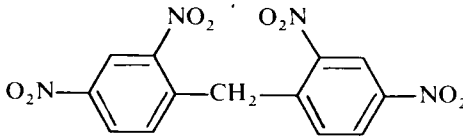
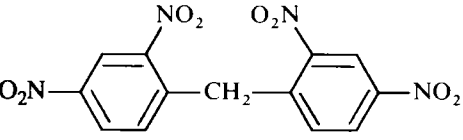
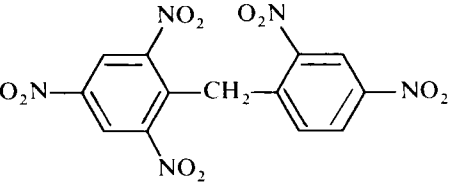
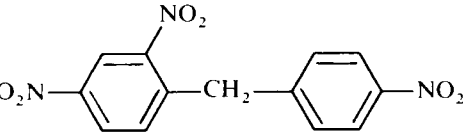
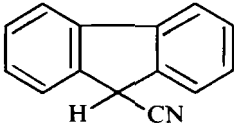
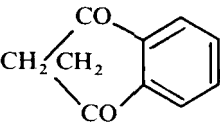
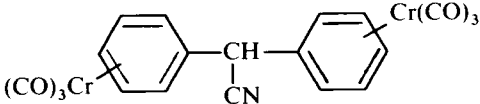
22		MeOH, 20°C	15.3			0.15	s
23	PhCH ₂ NO ₂	50% Me ₂ SO, 20°C	7.93	-0.25		ca -0.59	p
24	HOCH ₂ CH ₂ NO ₂	H ₂ O, 25°C	9.41	-0.45	-0.95	-1.00	t
25		50% Me ₂ SO, 25°C	10.9	-0.55		-0.60	r
26	CH ₃ NO ₂	H ₂ O, 20°C	10.28	-0.59			p
27		50% Me ₂ SO, 25°C	7.68			-0.68	r
28		50% Me ₂ SO, 25°C	12.19			-1.10	r

Table 3 (continued)

Entry	CH-Acid	Solvent, <i>T</i>	$\text{p}K_{\text{a}}^{\text{CH}}$	$\log (k_0/\text{M}^{-1} \text{s}^{-1})$			Ref.
				pip/mor	RNH ₂	RCOO [−]	
29	PhCH ₂ NO ₂	H ₂ O, 25°C	6.88	−0.86	−1.16		^u
30	PhCH ₂ NO ₂	H ₂ O, 20°C	6.77	−1.22		−2.10	^p
<i>In 90% Me₂SO, Me₂SO, or MeCN</i>							
31	PhCH ₂ CN	Me ₂ SO	9.81		6.38		^v
32	3,5-(NO ₂) ₂ C ₆ H ₃ CH ₂ NO ₂	CH ₃ CN	19.8			5.43	^w
33	3,5-(NO ₂) ₂ C ₆ H ₃ CH ₂ NO ₂	Me ₂ SO	8.56			4.09	^{w,x}
34		90% Me ₂ SO, 20°C	8.01	<i>ca</i> 4.4	3.57		^f
35		90% Me ₂ SO, 20°C	7.82	3.85	2.97	4.53	^k
36	CH ₂ (COCH ₃) ₂	90% Me ₂ SO, 20°C	11.10	3.64	2.91		^l

37	CH_3NO_2	90% Me_2SO , 20°C	14.80	3.06	2.77		^p
38		90% Me_2SO , 20°C	9.12	2.98	2.42	4.35	^j
39	PhCH_2NO_2	Me_2SO , 25°C	12.03			2.81	^x
40	PhCH_2NO_2	90% Me_2SO , 20°C	10.68	1.75	0.97	1.88	^p

^a Washabaugh and Jencks (1989). ^b Bednar and Jencks (1985). ^c Hibbert (1977). ^d Murray and Jencks (1990). ^e Bernasconi and Fairchild (1992). ^f Bernasconi and Terrier (1987). ^g Bernasconi and Oliphant (1992). ^h Bernasconi and Hibdon (1983). ⁱ Bernasconi and Stronach (1990). ^j Bernasconi *et al.* (1988a). ^k Bernasconi and Paschalis (1986). ^l Bernasconi and Bunnell (1985). ^m Bernasconi and Kanavarioti (1979). ⁿ Bell and Tranter (1974). ^o Gandler and Bernasconi (1989). ^p Bernasconi *et al.* (1988b). ^q Terrier *et al.* (1989). ^r Terrier *et al.* (1990). ^s Terrier *et al.* (1987). ^t Bernasconi and Panda (1992). ^u Bordwell and Boyle (1972). ^v Bowden and Hirani (1990). ^w Gandler and Bernasconi (1991). ^x Keffe *et al.* (1979).

For example, the increase in carbanion resonance for 2,4-dinitrophenylacetoneitrile (Entry 14) compared with 4-nitrophenylacetoneitrile (Entry 8) manifests itself in a decrease in $\log k_0$. Another relevant comparison is that of the two diketones 1,3-indandione and acetylacetone (Entries 12 and 13) with Meldrum's acid (Entry 7): the significantly higher $\log k_0$ for the latter is consistent with the fact that the high acidity of Meldrum's acid has much less to do with resonance than with a polar effect (Arnett and Harrelson, 1987; Wang and Houk, 1988; Wiberg and Laidig, 1988).

(4) The fourth group is mainly composed of nitroalkanes (Entries 16, 17, 19, 21–30 and 40) with $\log k_0$ -values less than 2, some being as low as -1 to -2 . These low values reflect the very strong resonance stabilization of the nitronate ions, particularly in water, where hydrogen-bonding solvation enhances this effect by several orders of magnitude. This solvation effect is seen even when changing from water to 50% Me_2SO (compare Entry 16 versus 17, 19 versus 26 and 23 versus 30) and dramatically manifests itself when comparing $\log k_0$ in water with the corresponding data in 90% Me_2SO , pure Me_2SO or CH_3CN . A similar but more modest enhancement in $\log k_0$ is apparent for acetylacetone when the solvent is changed from 50% Me_2SO to 90% Me_2SO (Entry 13 versus 36), or for 1,3-indandione in changing from 50% to 90% Me_2SO (Entry 12 versus 35). On the other hand, when hydrogen-bonding solvation is absent for lack of a good hydrogen-bond acceptor or because of strong charge dispersion over a large molecule, k_0 depends very little on the solvent (compare Entry 6 versus 34, 10 versus 38). These solvent effects will be discussed in more detail in a later section.

Comparison of PhCH_2NO_2 with CH_3NO_2 also suggests that resonance stabilization provided by the nitro-group is augmented by the phenyl group, since k_0 for PhCH_2NO_2 is significantly lower than for CH_3NO_2 in all solvents studied (Entry 19 versus 23, 26 versus 30, and 37 versus 40). On the other hand, the second nitro-group in $\text{CH}_3\text{CH}(\text{NO}_2)_2$ does not lead to a reduction of k_0 but to an increase (Entry 17 versus 24). This is consistent with the notion that steric crowding, which hinders coplanarity of both nitro-groups, prevents the second nitro-group from enhancing the overall resonance stabilization of the anion (more on this below).

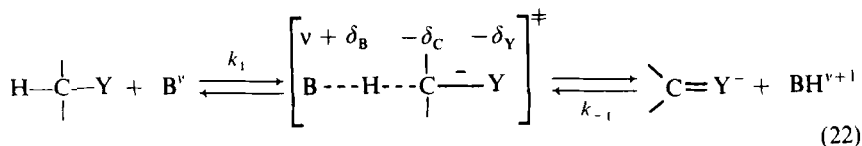
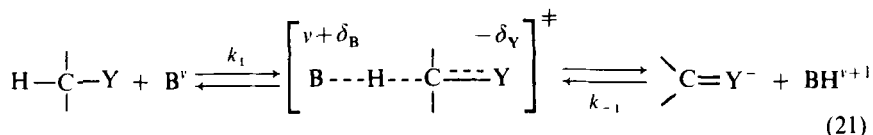
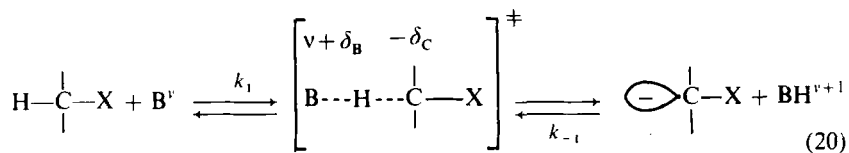
In conclusion, the data summarized in Table 3 leave little doubt about the inverse relationship between intrinsic rate constants and resonance stabilization of the carbanion, especially if the term "resonance" is understood to include hydrogen-bonding solvation where this is an important factor. This inverse relationship is not a new discovery and has been pointed out in several reviews (Eigen, 1964; Kresge, 1973, 1975a; Bell, 1973; Caldin and Gold, 1975; Hibbert, 1977; Bernasconi, 1982), but the recent addition of numerous examples (Table 3) has put this relationship on much firmer

ground. The question, then, is why is the creation of resonance-stabilized carbanions associated with low intrinsic rate constants or high intrinsic barriers?

There have been numerous suggestions that the increased structural and solvational reorganization that characterizes the formation of resonance-stabilized carbanions is the main contributor to the increased intrinsic barriers (Caldin, 1959; Eigen, 1964; Bell, 1973; Crooks, 1975; Hibbert, 1977; Ritchie, 1969a,b; Hine, 1977), although the lack of strong hydrogen bonding in the transition state of proton transfers involving carbon acids is also believed to play a role (Eigen, 1964; Hibbert, 1977; Bell, 1973; Ritchie, 1969a). Structural reorganization typically includes bond changes such as the conversion of single bonds to (partial) double bonds, or double bonds to single bonds, the shifting of negative charge from the site of proton abstraction to other parts of the molecule with a concomitant reorganization of the solvation shell, and also changes in bond angles and internal rotations. The notion that the intrinsic barrier increases with the degree of reorganization has generally been understood in the context of Hine's (1977) principle of least nuclear motion (PLNM), according to which the most favourable reaction is the one that requires the least amount of nuclear motion.

However, there are several problems with the PLNM. First, there exist only very few systems for which appropriate calculations have been performed, and the effect of solvation has not been included. Secondly, except for extreme cases such as the comparison between nitroalkanes and malononitriles, it is difficult to develop an intuitive or qualitative sense of the amount of reorganization involved in a given reaction. For example, it is not obvious why there should be so much less reorganization in the deprotonation of a β -diketone compared with a nitroalkane, as suggested by the much lower k_0 -value for the latter compounds. Indeed, Hine's calculations do not explain this large difference in k_0 ; similarly, PLNM calculations predict a smaller intrinsic barrier for 1,1-dinitroalkanes compared with β -diketones, but the opposite is observed.

A simpler and more direct way to understand why resonance leads to increased intrinsic barriers or low intrinsic rate constants is to realize that transition-state imbalances and depressed intrinsic rate constants are two manifestations of the same phenomenon, namely that the development of the resonance effect lags behind proton or charge transfer in the transition state. For a qualitative understanding of the connection between intrinsic barriers and the lag in resonance development, it is helpful to compare the energetics of the idealized reactions (20)–(22). Schematic free energy versus reaction coordinate profiles are shown in Fig. 7A for (20) and in Fig. 7B for (21) and (22). They refer to the case where the pK_a of the base is the same as that of the carbon acid so that $\Delta G^0 = 0$ and $\Delta G_1^\ddagger = \Delta G_{-1}^\ddagger = \Delta G_0^\ddagger$.



Reaction (20) leads to a carbanion that is devoid of resonance stabilization, i.e. X exerts only a polar effect, as for example, is the case with HCN. Since the polar effect presumably develops synchronously with the transfer of charge from the base to the carbon acid [i.e. it is proportional to δ_{B} (Taft and Topsom, 1987)], there is no transition-state imbalance in this reaction. Note that the intuitively reasonable assumption that polar effects develop synchronously with charge transfer will be used throughout this review.

In reactions (21) and (22), X has been replaced by the strong π -acceptor Y and it is assumed that in the product ion the charge is completely delocalized into Y. It is further assumed that substituting Y for X does not change the $\text{p}K_{\text{a}}$ of the carbon acid, i.e. the stabilization of the product ion by the combined polar and resonance effects of Y in (21) and (22) is equal to the stabilization exerted by the polar effect of X in (20). This implies that the polar effect of Y is smaller than that of X.

What distinguishes (21) from (22) is the transition state. In (21), which represents a hypothetical situation, it is assumed that charge delocalization is completely synchronous with charge transfer ($\delta_{\text{Y}} = \delta_{\text{B}}$). This means that the development of the resonance effect of Y is proportional to δ_{B} , just as is the case for its polar effect. This implies that the sum of the contributions from the polar and resonance effects of Y to the stabilization of the transition state of (21) is equal to the polar effect of X on the transition state of (20), just as is the case for the stabilization of the product ions in (21) and (20). $\Delta G^{\ddagger}_0$ should therefore be the same for the two reactions, as indicated in Fig. 7B. In (22), charge delocalization is assumed to have made little progress at the transition state, and hence resonance contributes less to its stabilization than in (21). This is symbolized by showing only one dash for

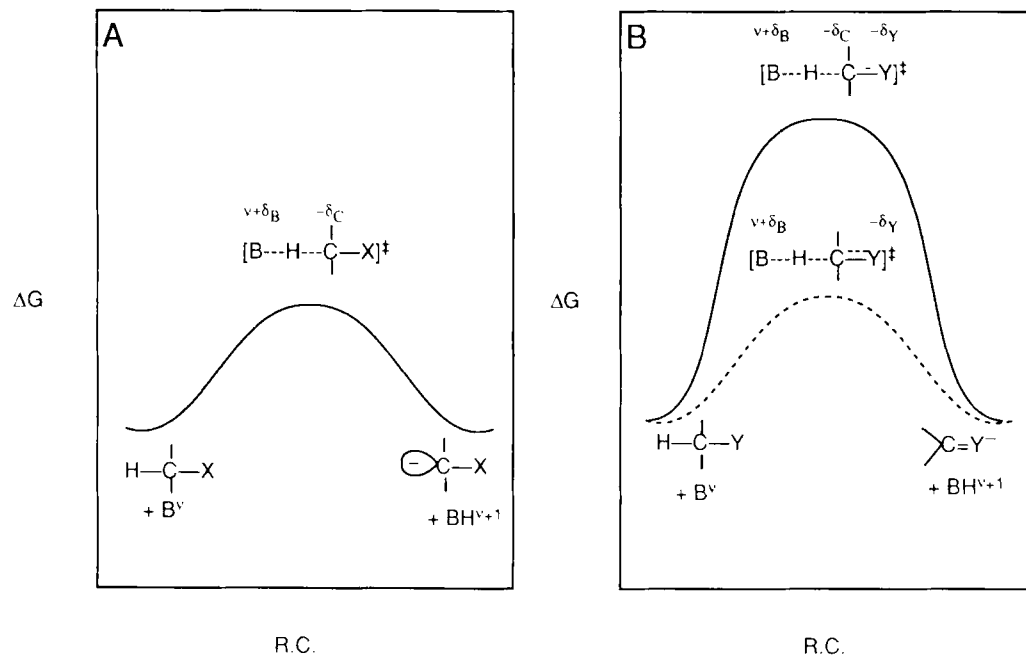


Fig. 7 Free energy versus reaction coordinate profiles for the deprotonation of carbon acids: (A) reaction (20); (B) reactions (21) (dashed line) and (22) (solid line).

the C-Y double bond and placing a negative charge on the carbon ($-\delta_C$). The consequence is that the main source of transition-state stabilization is the relatively weak polar effect of Y (weaker than that of X), which means less overall stabilization and a higher $\Delta G^\ddagger_0$ (Fig. 7B). A complementary way of looking at the situation is to consider the reaction in the reverse direction: $\Delta G^\ddagger_0$ is higher for (22) than for (21) because a larger fraction of the product resonance is lost in the transition state.

It should be noted that the assumption of equal acidity of the carbon acids in (20)–(22) was made for convenience but is not necessary for the argument. Typically a carbon acid with a π -acceptor Y will be more acidic than one that only carries a polar substituent. For example, the polar effects of X and Y may be of comparable magnitude, and the enhanced acidity of the Y-acid is the result of the resonance effect that is exerted on top of the polar effect. A case that may come close to this state of affairs is the comparison of nitromethane with acetonitrile. In this situation, a $\Delta G^\circ = 0$ in (21) and (22) will be achieved by using a weaker base, and the energy profiles will look the same as in Fig. 7.

RELATIONSHIP BETWEEN IMBALANCE AND INTRINSIC RATE CONSTANTS: A MATHEMATICAL FORMALISM

The qualitative notions discussed in the previous section can be cast into a mathematical formalism that relates the reduced intrinsic rate constants to the delay in the resonance development at the transition state. What is required is a parameter that measures the degree of resonance development, and a parameter that measures the degree of charge transfer, δ_B . As stated before, δ_B will be equated with the Brønsted β_B -value and corresponds to the horizontal axis in Figs. 4 and 5. For the progress in resonance development, we want a parameter that is a linear function of the resonance energy and varies between zero for the carbon acid and unity for the product ion. In previous papers we have used the symbol a_{res} or a_{res}^{C-} for this parameter (Bernasconi, 1985, 1987). Since a_{res}^{C-} was prone to confusion with the Brønsted coefficient a_{CH} , we shall henceforth use the symbol λ_{res} . There is in fact no simple mathematical relationship between λ_{res} and a_{CH} . That such a relationship cannot exist is perhaps most easily appreciated by recalling that the size of a_{CH} depends on the location of the Z-substituent in [1], [4], [7], etc., while λ_{res} is a function of Y and independent of the nature of Z or its location.

Let us now consider a comparison between a proton transfer, such as (20), in which the product ion is devoid of resonance, and a reaction that leads to a resonance-stabilized carbanion, such as (22). It is not necessary to assume

that the C—Y π -bond is fully developed in the product ion. We want to show that if both reactions have the same β_B -value, the difference between their intrinsic rate constants is given by (23), with $\log k_0(Y)$ referring to (22),

$$\log k_0(Y) - \log k_0(X) = \delta \log k_0^{\text{res}}(Y^-) = (\lambda_{\text{res}} - \beta_B) \delta \log K_1^{\text{res}}(Y^-) \quad (23)$$

$\log k_0(X)$ to (20). $\delta \log K_1^{\text{res}}(Y)$ represents the contribution of the resonance effect of Y to the overall equilibrium constant K_1 of (22), according to the breakdown of $\delta \log K_1(Y)$ into $\delta \log K_1^{\text{res}}(Y) + \delta \log K_1^{\text{pol}}(Y)$, with the latter being the contribution of the polar effect of Y. Equation (23) can be understood by considering the schematic Brønsted plots of Fig. 8, in which the variation of k_1 and K_1 is brought about by changing the $\text{p}K_a$ of the base. According to our definition of k_0 , $\log k_0$ is related to k_1 and K_1 by (24). This definition

$$\log k_0 = \log(k_1/q) - \beta_B [\log K_1 + \log(p/q)] \quad (24)$$

implies that any point on the Brønsted line is associated with the same k_0 , and any point that deviates from the line is associated with a different k_0 .

Assume now that the solid lines in Figs. 8A and 8B refer to reaction (20), i.e. a reaction without resonance effects. Assume further that X is replaced by Y, i.e. reaction (20) becomes (22), and that Y has the same polar effect as X. If B^v is kept the same, $\log K_1$ will increase by the amount $\delta \log K_1^{\text{res}}(Y)$, shown as horizontal arrows in Figs. 8A and 8B. The increase in K_1 should lead to an increase in k_1 , the magnitude of which depends on how far the resonance effect has developed at the transition state, i.e. on the size of λ_{res} . This increase in k_1 can be expressed by (25) and is indicated by the vertical arrows in Figs. 8A and 8B. Note that (25) provides the mathematical definition of λ_{res} .

$$\delta \log k_1^{\text{res}}(Y) = \lambda_{\text{res}} \delta \log K_1^{\text{res}}(Y) \quad (25)$$

Figure 8A shows the hypothetical scenario where $\lambda_{\text{res}} = \beta_B$. In this case, resonance develops synchronously with charge transfer, and the increase in K_1 induced by replacing X with Y has the same effect on k_1 as an equivalent increase in K_1 induced by a stronger base. Hence the point for the Y-acid ends up on the same Brønsted line as the X-acid, i.e. there is no change in k_0 . The same conclusion is reached from (23), which yields $\delta \log k_0^{\text{res}}(Y) = 0$.

Figure 8B shows the case for the imbalanced transition state, with $\lambda_{\text{res}} < \beta_B$. Here $\delta \log k_1^{\text{res}}(Y)$ is small and the point for the Y-acid falls below the Brønsted line of the X-acid, i.e. the intrinsic rate constant decreases, as reflected by $\delta \log k_0^{\text{res}}(Y) < 0$. The same conclusion is reached by consider-

ing the reverse reaction. In this case (23) becomes (26), where λ_{res} is a measure of the loss of resonance at the transition state ($\lambda_{-\text{res}} = 1 - \lambda_{\text{res}}$), a_{BH}

$$\delta \log k_0^{\text{res}}(Y) = (\lambda_{-\text{res}} - a_{\text{BH}}) \delta \log K_{-1}^{\text{res}}(Y) \quad (26)$$

is the Brønsted coefficient ($a_{\text{BH}} = 1 - \beta_{\text{B}}$) and $\delta \log K_{-1}^{\text{res}}(Y) = -\delta \log K_1^{\text{res}}(Y)$. Substituting $1 - \lambda_{\text{res}}$ for $\lambda_{-\text{res}}$, $1 - \beta_{\text{B}}$ for a_{BH} and $-\delta \log K_1^{\text{res}}(Y)$ for $\delta \log K_{-1}^{\text{res}}(Y)$ gives back (23). Since for the reverse reaction $\lambda_{-\text{res}} > a_{\text{BH}}$, the imbalance is in the direction of resonance loss being ahead of charge transfer.

It should be noted that the assumption that Y has the same polar effect as X, which was introduced in deriving (23) and (26), is convenient but not essential. Without it the change in $\log k_1$ brought about by the change from X to Y is given by (27). Since a given change in K_1 induced by the polar

$$\delta \log k_1 = \delta \log k_1^{\text{res}}(Y) + \delta \log k_1^{\text{pol}}(Y) = \lambda_{\text{res}} \delta \log K_1^{\text{res}}(Y) + \beta_{\text{B}} \delta \log K_1^{\text{pol}}(Y) \quad (27)$$

effect of Y [$\delta \log K_1^{\text{pol}}(Y)$] induces the same change of k_1 as an equivalent change in K_1 brought about by varying the base, k_0 remains unaffected.

APPLICATION OF MATHEMATICAL FORMALISM TO EXPERIMENTAL DATA

Equation (23) provides the mathematical formalism that relates the lowering of k_0 [$\delta \log k_0^{\text{res}}(Y)$] to the amount of resonance stabilization of the anion of the Y-acid [$\delta \log K_1^{\text{res}}(Y)$] and the degree by which the resonance development lags behind charge transfer in the transition state ($\lambda_{\text{res}} - \beta_{\text{B}}$). Assuming that $\lambda_{\text{res}} - \beta_{\text{B}}$ is independent of the Y-acid (it will be shown below that this is usually a good approximation), (23) may also be applied to the difference in $\log k_0$ between two Y-acids. This is shown as follows. Assume that (23) refers to the Y_1 -acid. A similar equation may be written for the Y_2 -acid. Subtracting the two equations from each other yields (28) or (29), with $\delta \log k_0^{\text{res}} = \delta \log k_0^{\text{res}}(Y_1) - \delta \log k_0^{\text{res}}(Y_2)$ and $\delta \log K_1^{\text{res}} = \delta \log K_1^{\text{res}}(Y_1) - \delta \log K_1^{\text{res}}(Y_2)$.

$$\begin{aligned} \log k_0(Y_1) - \log k_0(Y_2) &= \delta \log k_0^{\text{res}}(Y_1) - \delta \log k_0^{\text{res}}(Y_2) \\ &= (\lambda_{\text{res}} - \beta_{\text{B}})[\delta \log K_1^{\text{res}}(Y_1) - \delta \log K_1^{\text{res}}(Y_2)] \end{aligned} \quad (28)$$

$$\delta \log k_0^{\text{res}} = (\lambda_{\text{res}} - \beta_{\text{B}}) \delta \log K_1^{\text{res}} \quad (29)$$

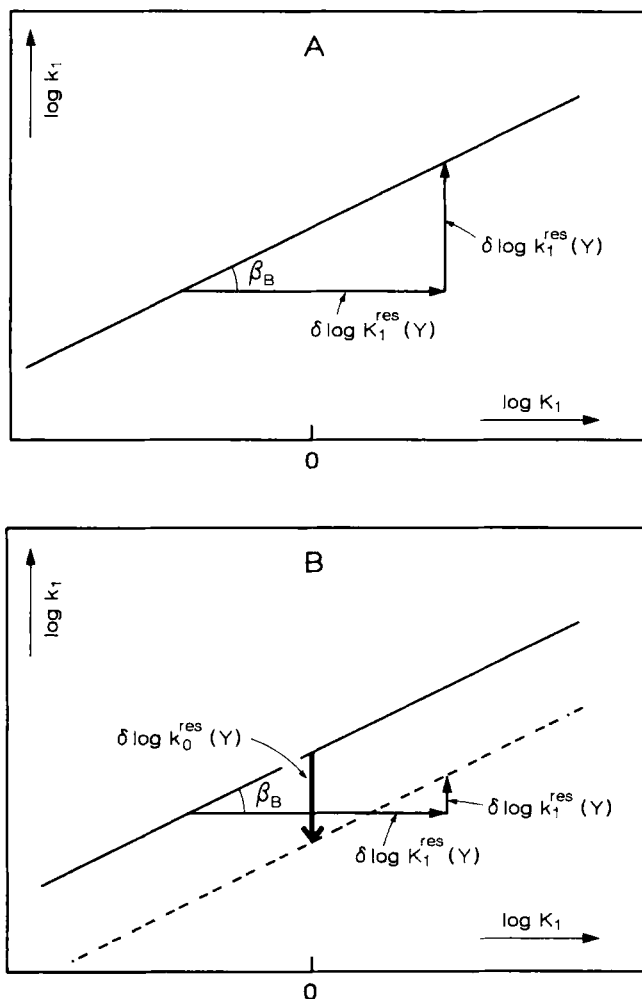


Fig. 8 The effect of replacing a polar group X by a π -acceptor Y on the Brønsted plot for the deprotonation of a carbon acid. Solid lines in A and B refer to the X-acid (20). If $\lambda_{\text{res}} = \beta_B$ then the change from X to Y does not affect k_0 (A), but if $\lambda_{\text{res}} < \beta_B$ then k_0 is decreased (B). Adapted from Bernasconi (1987) with permission from the American Chemical Society.

For the sake of simplicity, (29) from which the symbol “Y” has been deleted, will henceforth be used irrespective of whether two Y-acids are being compared or whether a Y-acid is compared with an X-acid.

As useful as (23) and (29) are in providing a *qualitative* insight into the effect of delayed resonance on k_0 , a test as to how *quantitatively* accurate these

equations are would be highly desirable. Such a test is difficult to come by because $\delta \log K_1^{\text{res}}$ values and λ_{res} are not known.

Regarding λ_{res} , Kresge's models developed in Section 2 (p. 137) may be used to estimate its value as follows. According to Model I, the amount of negative charge delocalized by Y was shown to be given by (30). We now

$$\delta_Y = \chi(\delta_B)^2 \quad (30)=(16)$$

assume that resonance is proportional to charge delocalization. Thus for the case where the C—Y π -bond order in the product ion, χ , is 1.0, we have (31); for the case where $\chi < 1.0$, we have (32), which follows from the requirement that $\lambda_{\text{res}} = 1.0$ for the product ion, irrespective of its π -order.

$$\lambda_{\text{res}} = \delta_Y \quad (31)$$

$$\lambda_{\text{res}} = \delta_Y/\chi \quad (32)$$

Combining (30) with (32) and equating δ_B with β_B leads to (33) and hence (34). This is an interesting and important result because it demonstrates that

$$\lambda_{\text{res}} = (\delta_B)^2 = (\beta_B)^2 \quad (33)$$

$$\lambda_{\text{res}} - \beta_B = (\beta_B)^2 - \beta_B \quad (34)$$

$\lambda_{\text{res}} - \beta_B$ only depends on β_B and not on the C—Y π -bond order χ . This is shown by the More O'Ferrall-Jencks diagram of Fig. 9, with the horizontal axis defined by $\beta_B (= \delta_B)$ and the vertical axis by $\lambda_{\text{res}} (= \delta_Y/\chi)$. Note that Fig. 9 is equivalent to Fig. 4, for which $\chi = 1.0$ since both the δ_Y and λ_{res} scales run from 0 to 1.0, but different from Fig. 5 ($\chi = 0.5$) because of different scales for δ_Y and λ_{res} .

With reference to Fig. 9, $|\lambda_{\text{res}} - \beta_B|$ corresponds to the vertical distance between the curved reaction coordinate and the reaction coordinate for the hypothetical synchronous reaction.

Combining (29) and (34) now affords (35).

$$\delta \log k_0^{\text{res}} = [(\beta_B)^2 - \beta_B] \delta \log K_1^{\text{res}} \quad (35)$$

If Model II is adopted, (30) is changed to (36), but (31) and (32) remain valid. Hence we may write (37), and (33) becomes (37), (34) becomes (38), while (35) becomes (39).

$$\delta_Y = \chi(\delta_B)^3 \quad (36)=(18)$$

$$\lambda_{\text{res}} = (\delta_B)^3 = (\beta_B)^3 \quad (37)$$

$$\lambda_{\text{res}} - \beta_B = (\beta_B)^3 - \beta_B \quad (38)$$

$$\delta \log k_0^{\text{res}} = [(\beta_B)^3 - \beta_B] \delta \log K_1^{\text{res}} \quad (39)$$

A noteworthy feature of (34) and (38) is that $\lambda_{\text{res}} - \beta_B$ is not very sensitive to the value of β_B as long as $0.35 < \beta < 0.65$ for (34), or $0.40 < \beta < 0.70$ for (38). This can be seen from the calculations in Table 4. This insensitivity to β_B allows flexibility in applying (35) or (39) to pairs of reactions with unequal β_B -values. We now apply (35) and (39) to the calculation of values of $\delta \log K_1^{\text{res}}$ in a few examples where the resonance contribution to the stabilization of the carbanion may be estimated independently. This should provide a test as to whether (35) or (39) are reasonable equations. A summary of relevant parameters is given in Table 5.

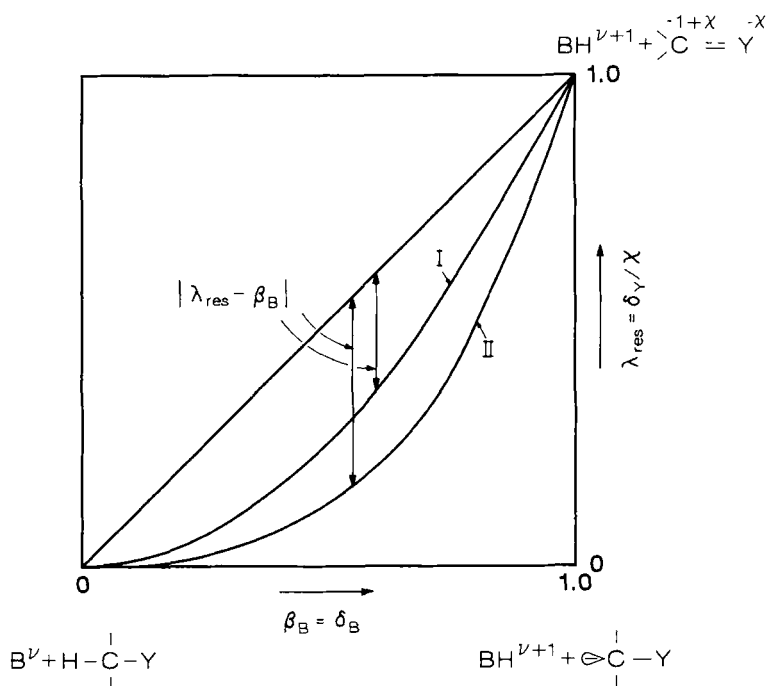


Fig. 9 More O'Ferrall-Jencks diagram for the deprotonation of a carbon acid, with axes defined by β_B and λ_{res} respectively. Reaction coordinates I and II are calculated from (33) and (37) respectively.

Table 4 Calculated values of $\lambda_{\text{res}} - \beta_{\text{B}}$ as a function of β_{B} according to (34) and (38).

β_{B}	$\lambda_{\text{res}} - \beta_{\text{B}} = (\beta_{\text{B}})^2 - \beta_{\text{B}}^a$	$\lambda_{\text{res}} - \beta_{\text{B}} = (\beta_{\text{B}})^3 - \beta_{\text{B}}^b$
0.20	-0.16	-0.19
0.30	-0.21	-0.27
0.35	-0.23	-0.32
0.40	-0.24	-0.34
0.50	-0.25	-0.37
0.60	-0.24	-0.38
0.65	-0.23	-0.37
0.70	-0.21	-0.36
0.80	-0.16	-0.29

^a Equation (34). ^b Equation (38).*1. Reaction of nitromethane with the piperidine/morpholine pair*

Using $\log k_0 = 9.0$ for the deprotonation of an X-acid, the $\log k_0$ -value of -0.59 for the deprotonation of nitromethane by the piperidine/morpholine pair in water (Entry 26 in Table 3) suggests a $\delta \log k_0^{\text{res}} \approx -9.6$. With $\beta_{\text{B}} = 0.59$ (Table 1), one calculates $(\beta_{\text{B}})^2 - \beta_{\text{B}} = -0.24$ and $(\beta_{\text{B}})^3 - \beta_{\text{B}} = -0.39$, which yields $\delta \log K_1^{\text{res}} \approx 40$ from (35) and $\delta \log K_1^{\text{res}} \approx 24.6$ from (39).

The $\text{p}K_{\text{a}}$ of methane is *ca* 56 (Bordwell, 1988) and that of nitromethane 10.28, indicating that the acidifying effect of the nitro-group is *ca* 46 $\text{p}K_{\text{a}}$ -units ($\Delta \text{p}K_{\text{a}}^{\text{CH}}$ in Table 5). If $\delta \log K_1^{\text{res}}$ were 40, from (35), this would mean that virtually the entire acidifying effect of the nitro-group is due to resonance, with only some 6 $\text{p}K_{\text{a}}$ -units accounted for by the polar effect. This is unreasonable.

On the other hand, if $\delta \log K_1^{\text{res}} \approx 24.6$, from (39), then only slightly more than half of the acidifying effect would be related to resonance, while the other half would come from the polar effect, a more reasonable result. Based on $\sigma_1 = 0.65$ and $\sigma_{\text{R}}^- = 0.46$ (Hine, 1975a), one would predict a ratio of resonance to polar effect of 0.71, i.e. the resonance effect is less than half of the entire substituent effect. The same prediction emerges from the ratio $(\sigma_{\text{p}}^- - \sigma_{\text{m}})/\sigma_{\text{m}} = 0.73$. However, σ_{R}^- or σ_{p}^- are likely to underestimate the resonance effect in $\text{CH}_2=\text{NO}_2^-$. This is because the nitro-group is directly attached to the reaction centre; not only does this enhance the inherent resonance effect, but owing to the strong delocalization of the charge into the nitro-group, there is further enhancement by the strong hydrogen-bonding solvation.

Be that as it may, the assumptions underlying (39) appear to be more realistic than those underlying (35). It is interesting to note that, based on arguments relating to the size of the Brønsted α_{CH} -value in the deprotonation

Table 5 Estimates of various parameters in (35) and (39) for seven selected systems.

Entry	Reaction	$\log k_0$	$\delta \log k_0^{\text{res}}$	$\text{p}K_{\text{a}}^{\text{CH}}$	$\Delta \text{p}K_{\text{a}}^{\text{CH}}$	β_{B}	$(\beta_{\text{B}})^2 - \beta_{\text{B}}$	$\delta \log K_1^{\text{res } c}$	$\delta \log K_1^{\text{pol } d}$	$(\beta_{\text{B}})^3 - \beta_{\text{B}}$	$\delta \log K_1^{\text{res } e}$	$\delta \log K_1^{\text{pol } d}$
1	$\text{CH}_3\text{NO}_2 + \text{pip}/\text{mor}$ in H_2O	-0.59	$ca - 9.6^a$	10.28	$ca 46.0^b$	0.59	-0.24	$ca 40.0$	$ca 6.0$	-0.39	$ca 24.6$	$ca 21.4$
2	$2,4-(\text{NO}_2)_2-$ $\text{C}_6\text{H}_3\text{CH}_2\text{CN}$ + pip/mor in 50% Me_2SO	2.75	-0.95^f	8.06	4.56^g	0.62	-0.24	3.96	0.60^d	-0.38	2.50	2.06^d
3	$\text{PhCH}_2\text{NO}_2 + \text{pip}/$ mor in H_2O	-1.22	-0.55^i	6.77	3.68^j	0.53^k	-0.25	2.20	1.48^d	-0.38	1.5	2.23^d
4	$\text{CH}_3\text{NO}_2 + \text{pip}/\text{mor}$ in 90% Me_2SO	3.06	3.65^l	$-\log \gamma^{90} = -6.70^m$		0.64^n	-0.23	-15.9		-0.38	-9.60	
5	$\text{PhCH}_2\text{CN} + \text{RNH}_2$ in Me_2SO	6.38	$ca - 2.6^a$	21.9	21.1^b	0.67	-0.22	$ca 11.8$	9.3	-0.37	$ca 7.0$	$ca 14.1$
6	$\text{CH}_2(\text{CN})_2 + \text{pip}/\text{mor}$ in H_2O	$ca 7.0$	$ca - 2.0^a$	11.0	$ca 45.0^b$	$ca 0.83$	-0.14	$ca 14.3$	$ca 30.7$	-0.24	$ca 7.7$	$ca 37.3$
7	$\text{CH}_2(\text{COCH}_3)_2 + \text{pip}/$ mor in H_2O	2.60	$ca - 6.4^a$	9.11	$ca 47.0^b$	0.37	-0.23	$ca 27.8$	$ca 19.2$	-0.32	$ca 20.0$	$ca 27.0$

^a Relative to $\log k_0(\text{X}) \approx 9.0$ in (23). ^b Relative to $\text{p}K_{\text{a}}^{\text{CH}} \approx 56$ for CH_4 . ^c $\delta \log K_1^{\text{res}}$ from (35). ^d $\delta \log K_1^{\text{pol}} = \Delta \text{p}K_{\text{a}} - \delta \log K_1^{\text{res}}$. ^e $\delta \log K_1^{\text{res}}$ from (39).

^f Relative to $\log k_0 = 3.70$ for $4\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{CN}$. ^g Relative to $\text{p}K_{\text{a}}^{\text{CH}}$ of $4\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{CN}$. ^h Average β_{B} for $4\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{CN}$ and $2,4\text{-(NO}_2)_2\text{-C}_6\text{H}_3\text{CH}_2\text{CN}$. ⁱ Relative to $\log k_0 = -0.67$ for CH_3NO_2 , statistically corrected. ^j Relative to $\text{p}K_{\text{a}}^{\text{CH}} = 10.45$ for CH_3NO_2 , statistically corrected. ^k Average β_{B} for CH_3NO_2 and PhCH_2NO_2 . ^l Relative to $\log k_0 = -0.59$ in H_2O . ^m Transfer activity coefficient for transfer of $\text{CH}_2=\text{NO}_2^-$ from H_2O in 90% Me_2SO .

ⁿ Average β_{B} in H_2O and 90% Me_2SO .

of CH_3NO_2 , $\text{CH}_3\text{CH}_2\text{NO}_2$ and $(\text{CH}_3)_2\text{CHNO}_2$, Kresge (1974) also reached the conclusion that in $\delta_Y = \chi(\delta_B)^n$, n should be greater than 2.

2. Reaction of 2-X-4-nitrophenylacetonitrile with the piperidine/morpholine pair

The reaction of 4-nitrophenylacetonitrile ($\text{p}K_a = 12.62$) with piperidine/morpholine in 50% Me_2SO –50% water has a $\log k_0 = 3.70$ and that of 2,4-dinitrophenylacetonitrile ($\text{p}K_a = 8.06$) a $\log k_0$ of 2.75 (Table 3, Entries 8 and 14). Hence $\delta\log k_0^{\text{res}} = -0.95$. The average β_B -value for these reactions is 0.62 (Bernasconi and Hibdon, 1983), which yields $(\beta_B)^2 - \beta_B = -0.24$ and $\delta\log K_1^{\text{res}} = 3.96$ from (35), or $(\beta_B)^3 - \beta_B = -0.38$ and $\delta\log K_1^{\text{res}} = 2.50$ from (39). Since the $\text{p}K_a^{\text{CH}}$ -difference is 4.56, $\delta\log K_1^{\text{res}} = 3.96$ suggests that virtually the entire acidifying effect of the 2-nitro-group is a resonance effect, while $\delta\log K_1^{\text{res}} = 2.50$ only assigns slightly more than half of the $\Delta\text{p}K_a^{\text{CH}}$ to resonance. This latter value is more reasonable and suggests that (39) provides a better model than (34), as was concluded for the reaction of nitromethane.

3. Reaction of phenylnitromethane with the piperidine/morpholine pair

Comparing the deprotonation of PhCH_2NO_2 by the piperidine/morpholine pair in water ($\log k_0 = -1.22$; Entry 30 in Table 3) with the analogous reaction of CH_3NO_2 ($\log k_0 = 0.59$; Entry 26) yields $\delta\log k_0^{\text{res}} = -0.63$ for the additional resonance effect by the phenyl group. With an average β_B -value of 0.53, we calculate $(\beta_B)^2 - \beta_B = -0.25$ and $\delta\log K_1^{\text{res}} = 2.20$ from (35), and $(\beta_B)^3 - \beta_B = -0.38$ and $\delta\log K_1^{\text{res}} = 1.45$ from (39). The $\text{p}K_a^{\text{CH}}$ of CH_3NO_2 is 10.28, that of PhCH_2NO_2 is 6.77, and thus $\Delta\text{p}K_a^{\text{CH}} = 3.51$. Again, $\delta\log K_1^{\text{res}} = 1.45$ estimated from (39) appears more reasonable than $\delta\log K_1^{\text{res}} = 2.20$ from (35), since it allows for more than half of the acidity enhancement to be a polar effect.

4. Solvent effect on reaction of nitromethane with the piperidine/morpholine pair

In 90% Me_2SO –10% water, $\log k_0 = 3.06$ for the title reaction (Entry 37 in Table 3) is 3.65 logarithmic units higher than in water (Entry 26). If this solvent effect is entirely attributed to the reduced resonance caused by the loss of hydrogen-bonding solvation of $\text{CH}_2=\text{NO}_2^-$, and the average β_B in the two solvents of 0.64 is used to calculate $\delta\log K_1^{\text{res}}$, we obtain $(\beta_B)^2 - \beta_B = -0.23$ and $\delta\log K_1^{\text{res}} = 15.9$ from (35), or $(\beta_B)^3 - \beta_B = -0.38$ and $\delta\log K_1^{\text{res}} = 9.6$ from (39). Once again, $\delta\log K_1^{\text{res}}$ estimated from (39) is more

realistic and is relatively close to the transfer activity coefficient (6.70) for the transfer of $\text{CH}_2=\text{NO}_2^-$ from water to 90% Me_2SO (Bernasconi and Bunnell, 1988). The remaining discrepancy between the calculated $\delta\log K_1^{\text{res}}$ and the transfer activity coefficient can largely be accounted for by the fact that solvation lags even farther behind charge transfer than resonance, as discussed in Section 5.

5. Reaction of PhCH_2CN with RNH_2 in Me_2SO

Based on the reference value of $\log k_0 = 9.0$ for an X-acid, the $\log k_0$ -value of 6.38 (Entry 31 in Table 3) for the title reaction implies $\delta\log k_0^{\text{res}} \approx -2.6$. With $\beta_{\text{B}} = 0.67$ (Entry 2a in Table 1), one obtains $(\beta_{\text{B}})^2 - \beta_{\text{B}} = -0.221$ and $\delta\log K_1^{\text{res}} \approx 11.8$ from (35), or $(\beta_{\text{B}})^3 - \beta_{\text{B}} = -0.37$ and $\delta\log K_1^{\text{res}} \approx 7.0$ from (39). The $\text{p}K_{\text{a}}^{\text{CH}}$ of PhCH_2CN in Me_2SO is 21.9, that of toluene about 43 (Bordwell, 1988); hence $\Delta\text{p}K_{\text{a}}^{\text{CH}} = 21.1$. With the estimate of 11.8 for $\delta\log K_1^{\text{res}}$, more than half of $\Delta\text{p}K_{\text{a}}^{\text{CH}}$ would have to be attributed to resonance while, with $\delta\log K_1^{\text{res}} \approx 7.0$, the resonance contribution is about one-third. This latter distribution reflects the relative sizes of $\sigma_1 = 0.57$ and $\sigma_{\text{R}}^- = 0.33$ of the cyano group (Hine, 1975a) fairly well. It is noteworthy that if $\delta\log K_1^{\text{res}} \approx 7.0$ is adopted, the calculated $\delta\log K_1^{\text{pol}}$ of about 14.0 yields $(\delta\log K_1^{\text{pol}})/\sigma_1 = 25.6$, which is quite similar to the corresponding ratio calculated for nitromethane ($\approx 21.7/0.68 \approx 31.9$).

6. Reaction of $\text{CH}_2(\text{CN})_2$ with the piperidine/morpholine pair in water

For this reaction, $\log k_0 \approx 7.0$ (Entry 3 in Table 3), and hence $\delta\log k_0^{\text{res}} \approx -2.0$. If one uses a corrected β_{B} (more on this correction in Section 5) of 0.83, we obtain $(\beta_{\text{B}})^2 - \beta_{\text{B}} = -0.14$ and $\delta\log K_1^{\text{res}} \approx 14.3$ from (35), or $(\beta_{\text{B}})^3 - \beta_{\text{B}} = -0.26$ and $\delta\log K_1^{\text{res}} \approx 7.7$ from (39). These $\delta\log K_1^{\text{res}}$ -values for substituting two hydrogens of methane by two cyano-groups are only slightly larger than those calculated above for one cyano-group in converting PhCH_3 to PhCH_2CN . This suggests a surprisingly strong saturation of the resonance effect, especially if the second estimate ($\delta\log K_1^{\text{res}} \approx 7.7$) is adopted, without a corresponding saturation of the polar effect. The polar effect would account for about 29.4 $\text{p}K_{\text{a}}$ -units of the difference between the $\text{p}K_{\text{a}}^{\text{CH}}$ of methane (≈ 56) and malononitrile (11.0) if $\delta\log K_1^{\text{res}} \approx 14.3$, and for 36.5 units if $\delta\log K_1^{\text{res}} = 7.7$. If σ_1 for two CN-groups can be equated with $2\sigma_1$ for one cyano-group, these numbers translate into $(\delta\log K_1^{\text{pol}})/\sigma_1 \approx 28.8$ and 32.0, respectively, which are similar to $(\delta\log K_1^{\text{pol}})/\sigma_1 \approx 24.6$ estimated from the reaction of PhCH_2CN with RNH_2 .

The case of malononitrile is of particular interest because $\log k_0$ is substantially higher than one might have anticipated on the basis of the

resonance effect of the cyano-group, even if saturation of this resonance effect plays an important role. The key to understanding the high intrinsic rate constant is the high β_B -value, which makes $\lambda_{\text{res}} - \beta_B$ much smaller than in all the other examples, and hence makes $|\delta \log k_0^{\text{res}}|$ much smaller than it would otherwise be.

7. Reaction of acetylacetone with the piperidine/morpholine pair in water

Again using $\log k_0 \approx 9.0$ for the reference X-acid, one obtains $\delta \log k_0^{\text{res}} = -6.40$ from $\log k_0 = 2.60$ (Entry 15 in Table 3). The $\text{p}K_{\text{a}}^{\text{CH}}$ of acetylacetone is 9.11, and hence the acidifying effect of the two CH_3CO groups is some 48 $\text{p}K_{\text{a}}$ -units relative to methane. From $\beta_B = 0.37$ (Table 1), one calculates $(\beta_B)^2 - \beta_B = -0.23$ and $\delta \log K_1^{\text{res}} = 27.8$ from (35), or $(\beta_B)^3 - \beta_B = -0.32$ and $\delta \log K_1^{\text{res}} \approx 20.0$ from (39). Thus, in the first case, the contribution of the polar effect is *ca* 19.5 $\text{p}K_{\text{a}}$ -units, in the second it is *ca* 27 $\text{p}K_{\text{a}}$ -units. In this reaction, the first set, based on (35), seems to give a more reasonable result. With $\sigma_1 = 0.29$ and, just as for malononitrile, assuming no saturation of the polar effect, we calculate $\delta \log K_1^{\text{pol}}/2\sigma_1 = 33.1$, which is similar to what was obtained for the cyano- and nitro-groups. This contrasts with $\delta \log K_1^{\text{pol}}/2\sigma_1 = 46.6$ from the second set, which seems too high. Furthermore, the ratio $\sigma_{\text{R}}^-/\sigma_1 = 0.47/0.29 = 1.62$ suggests that $\delta \log K_1^{\text{res}}/\delta \log K_1^{\text{pol}}$ should be greater than unity even if resonance is subject to a saturation effect. This is the case with the first set with $\delta \log K_1^{\text{res}}/\delta \log K_1^{\text{pol}} = 1.45$, but not with the second, where $\delta \log K_1^{\text{res}}/\delta \log K_1^{\text{pol}} = 0.74$.

The seven examples discussed above demonstrate that (29) provides a useful mathematical formalism for evaluating the effect of resonance stabilization of the carbanion on intrinsic rate constants. It seems safe to assume that the same formalism should apply to the many cases that are not as easily tested. It is also interesting that our approximation of $\lambda_{\text{res}} - \beta_B$ with $(\beta_B)^3 - \beta_B$ and hence (39) leads consistently to more reasonable $\delta \log K_1^{\text{res}}$ values than the approximation with $(\beta_B)^2 - \beta_B$, at least for the first five cases. For the last two examples, the approximation by $(\beta_B)^2 - \beta_B$ seems to provide a better estimate for $\delta \log K_1^{\text{res}}$. It may or may not be a coincidence that these last two cases refer to carbon acids of the type H_2CY_2 with two strongly electron-withdrawing Y-groups, whereas in the first five cases, there is only one strong electron-withdrawing Y-group attached to the central carbon, phenyl being considered a weak group.

GENERALIZATIONS: THE PRINCIPLE OF NON-PERFECT SYNCHRONIZATION

Delayed resonance development in proton transfers is only one example of a transition-state imbalance that can affect the intrinsic rate constants of

reactions. In later sections, similar imbalances between resonance and bond changes that occur in other types of reactions, and different kinds of imbalances, such as delayed solvation, intramolecular hydrogen bonding, and others will be discussed. The principle by which these imbalances affect k_0 is the same as that discussed for the resonance stabilization of carbanions. This has led to a rule that we have called the "principle of non-perfect synchronization" (PNS). The PNS may be stated as follows.

A product-stabilizing factor (e.g. resonance) that develops late along the reaction coordinate always lowers k_0 , whereas a product-stabilizing factor that develops early increases k_0 . "Early" and "late" are defined in relation to the "main process" along the reaction coordinate, which is usually equated with a bond change or charge transfer.

As will become apparent throughout the remainder of this review, late development of product stabilizing factors is much more common than early development, and hence imbalances most often lead to a lowering of k_0 .

Since late (early) development in the forward direction implies early (late) loss in the reverse direction, the PNS may also be formulated by the following corollary.

A reactant-stabilizing factor that is lost early always lowers k_0 , while a reactant-stabilizing factor that is lost late always increases k_0 .

For product- or reactant-destabilizing factors, all the predictions are reversed, i.e. a product-destabilizing factor that develops late enhances k_0 , etc. Equation (29) may thus be generalized to become (40), where "f" stands

$$\delta \log k_0^f = (\lambda_f - \beta_M) \delta \log K_1^f \quad (40)$$

for any factor that affects the free energy of a reactant or product and $\delta \log K_1^f$ is the change in the equilibrium constant of the reaction induced by introduction of this factor. If "f" is in a product, λ_f measures the progress in the development of "f" at the transition state; if "f" is in a reactant, λ_f measures how much of it has been lost at the transition state. In (40), β_M is the progress variable of the main process of the reaction. Note that the limiting case $\lambda_f = 0$ will usually mean that the factor develops (is lost) in a post-equilibrium, while $\lambda_f = 1$ implies the factor is developed (lost) in a pre-equilibrium. Note also that, when several factors "f" are involved, each contributes a term, given by (40), to the overall change in k_0 , i.e. (41) prevails.

$$\delta \log k_0 = \sum_{i=1}^n \delta \log k_0^{f_i} = \sum_{i=1}^n (\lambda_{f_i} - \beta_{M_i}) \delta \log K_1^{f_i} \quad (41)$$

PROTON TRANSFER FROM CARBON TO CARBON

In contrast with the extensive literature on proton transfers from carbon acids to normal bases B' , only a few systematic studies of proton transfer from carbon acids to carbanions have been reported. In hydroxylic solvents, it is virtually impossible to measure the kinetics of such reactions because their rates are too slow to compete with the proton transfer to or from the solvent, the lyate ion and the lyonium ion. However, in non-hydroxylic solvents the proton transfer between a carbon and a carbanion is, in principle, easily measured.

The results of two reaction series that are relevant to this review have recently been reported (Bernasconi and Ni, 1992). One refers to the deprotonation of 9-cyanofluorene, 1,3-indandione, 4-nitrophenylacetone, 3-nitrophenylnitromethane and 4-nitrophenylnitromethane by substituted benzylmalononitrile anions in 90% Me_2SO –10% water (v/v), the other to the reaction of phenylnitromethane with the anions of 9-cyanofluorene, 1,3-indandione, 4-nitrophenylacetone, Meldrum's acid and nitromethane in the same solvent. Intrinsic rate constants and intrinsic barriers are summarized in Table 6 for the first series and in Table 7 for the second series. They were estimated from the measured rate (k_1) and equilibrium constants (K_1) as $\log k_0 = \log k_1 - \beta \log K_1$, with β arbitrarily assumed to be 0.5; interestingly, Brønsted plots constructed by varying Z in $4-Z-C_6H_4CH_2C(CN)_2$ in the first series yielded $\beta = 0.50 \pm 0.02$ for all carbon acids. Note that for the reactions of phenylnitromethane with the anions of 1,3-indandione, Meldrum's acid and CH_3NO_2 , proton transfer may occur either at the carbon or the oxygen of the enolate ions or of $CH_2NO_2^-$. It was demonstrated that the reported k_0 -values refer to the former.

The results listed in Tables 6 and 7 show that k_0 is substantially lower for carbon-to-carbon proton transfer than for carbon-to-nitrogen transfer. In the reactions of the various carbon acids with $ArCH_2C(CN)_2^-$ (Table 6), $\log k_0$ is on the average 1.77 logarithmic units lower ($\Delta G_0^\ddagger$ 2.36 kcal mol⁻¹ higher) than for the reactions of the same carbon acids with the piperidine/morpholine pair, while in the reactions of $PhCH_2NO_2$ with the various carbanions, $\log k_0$ is between 1.47 and 2.79 logarithmic units lower ($\Delta G_0^\ddagger$ between 1.97 and 3.74 kcal mol⁻¹ higher) than for the reaction of $PhCH_2NO_2$ with the piperidine/morpholine pair. These reduced k_0 -values reflect the fact that in reactions of type (42) there will be two PNS effects related to resonance; one for its late development in Y, the other for its early

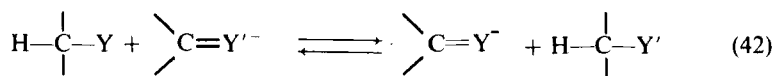


Table 6 Intrinsic rate constants $\log k_0$ and intrinsic barriers $\Delta G_0^\ddagger$ for the deprotonation of various carbon acids by the anions of benzylnitriles and the piperidine/morpholine pair in 90% Me₂SO–10% water at 20°C.^a

Substrate	ArCH ₂ C(CN) ₂ [–]		pip/mor		$\Delta \log (k_0/\text{M}^{-1} \text{s}^{-1})^b$	$\Delta \Delta G_0^\ddagger / \text{kcal mol}^{-1}$
	$\log (k_0/\text{M}^{-1} \text{s}^{-1})$	$\Delta G_0^\ddagger / \text{kcal mol}^{-1}$	$\log (k_0/\text{M}^{-1} \text{s}^{-1})$	$\Delta G_0^\ddagger / \text{kcal mol}^{-1}$		
9-Cyanofluorene	2.70	13.46	<i>ca</i> 4.39	<i>ca</i> 11.21	<i>ca</i> –1.69	<i>ca</i> 2.25
1,3-Indandione	2.21	14.12	3.85	11.92	–1.64	2.20
4-Nitrophenylacetonitrile	1.87	14.57	3.84	11.94	–1.97	2.63
3-Nitrophenylacetonitrile	0.32	16.63				
4-Nitrophenylnitromethane	0.24	16.74				
Phenylnitromethane ^d	<i>ca</i> –0.02	<i>ca</i> 17.08	1.75	14.72	<i>ca</i> –1.77	<i>ca</i> 2.36

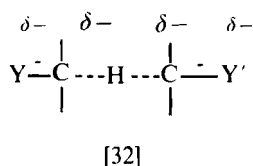
^a Bernasconi and Ni (1992). ^b $\log k_0(\text{ArCH}_2\text{C(CN)}_2^-) - \log k_0(\text{pip/mor})$. ^c $\Delta G_0^\ddagger(\text{ArCH}_2\text{C(CN)}_2^-) - \Delta G_0^\ddagger(\text{pip/mor})$. ^d Results for this compound are extrapolated.

Table 7 Intrinsic rate constants $\log k_0$ and intrinsic barriers $\Delta G_0^\ddagger$ for the deprotonation of PhCH_2NO_2 by the anions of various carbon acids in 90% Me_2SO –10% water at 20°C.^a

CH-Acid	$\log (k_0/\text{M}^{-1} \text{s}^{-1})$	$\Delta G_0^\ddagger/\text{kcal mol}^{-1}$
9-Cyanofluorene	0.01	17.1
4-Nitrophenylacetonitrile	−0.33	17.5
1,3-Indandione	0.28	16.7
Meldrum's acid	−0.24	17.4
Nitromethane	−1.04	18.5

^a Bernasconi and Ni (1992).

loss from Y' . Accordingly, the transition state should be represented by [32]



and the total $\delta \log k_0^{\text{res}}$ given by (43), where β and a stand for the degrees of proton transfer at the transition state. They do not correspond to *measured*

$$\begin{aligned} \delta \log k_0^{\text{res}} &= \delta \log k_0^{\text{res}}(\text{Y}) + \delta \log k_0^{\text{res}}(\text{Y}') \\ &= [\lambda_{\text{res}}(\text{Y}) - \beta] \delta \log K_1^{\text{res}}(\text{Y}) + [\lambda_{\text{res}}(\text{Y}') - a] \delta \log K_{-1}^{\text{res}}(\text{Y}') \end{aligned} \quad (43)$$

Brønsted α - or β -values, since such coefficients would be distorted by the resonance effect regardless of whether they were obtained from the variation of the Y -acid or the Y' -base. Since it was shown that for reactions such as (15) or (22) $\lambda_{\text{res}} - \beta_{\text{B}}$ is quite independent of β_{B} over a wide range of β_{B} (Table 4), we shall assume the same to be true for $\lambda_{\text{res}}(\text{Y}) - \beta$ and $\lambda_{-\text{res}}(\text{Y}') - a$ and use the relationship (44). As a result, (43) is simplified to (45).

$$\lambda_{\text{res}}(\text{Y}) - \beta = -[\lambda_{-\text{res}}(\text{Y}') - a] = \varepsilon_{\text{res}} \quad (44)$$

$$\delta \log k_0^{\text{res}} = \varepsilon_{\text{res}} [\delta \log K_1^{\text{res}}(\text{Y}) - \delta \log K_{-1}^{\text{res}}(\text{Y}')] \quad (45)$$

What is a likely value for ε_{res} ? In a first approximation, one may assume that ε_{res} is of similar magnitude to $\lambda_{\text{res}} - \beta_{\text{B}}$ in the reactions with normal bases. If $|\varepsilon_{\text{res}}|$ were much smaller than $|\lambda_{\text{res}} - \beta_{\text{B}}|$ then $\delta \log k_0^{\text{res}}$ in (45) would

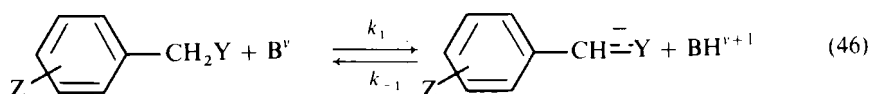
not be more negative than in (29), and hence k_0 for carbon-to-carbon proton transfer would not be lower than for carbon-to-oxygen or carbon-to-nitrogen proton transfer. On the other hand, if $|\epsilon_{\text{res}}|$ were substantially larger than $|\lambda_{\text{res}} - \beta_{\text{B}}|$ then k_0 for the carbon-to-carbon proton transfer would be even lower than observed and would have been difficult to measure owing to competition from the reaction with the solvent, H^+ and OH^- . A more detailed analysis (Bernasconi and Ni, 1992) suggests that $|\epsilon_{\text{res}}|$ is just slightly lower than $|\lambda_{\text{res}} - \beta_{\text{B}}|$.

4 Substituent effects on intrinsic rate constants of proton transfers

The discussion of the PNS in proton transfers has thus far focused on the effect of π -acceptors directly attached to the central carbon, which provide the major source of resonance stabilization of the carbanion. We now address the effect of substituents, remote as well as directly attached to the central carbon, which only act through a *polar* effect.

POLAR EFFECT OF REMOTE SUBSTITUENTS

Let us consider a reaction of type (46), where Y is a π -acceptor leading to



resonance in the carbanion, and Z is a remote substituent that exerts only a polar effect. Reaction (46) thus represents a case where $\alpha_{\text{CH}} > \beta_{\text{B}}$, for which a number of examples have been summarized in Table 1. A consequence of the inequality between α_{CH} and β_{B} is that each $\text{ZC}_6\text{H}_4\text{CH}_2\text{Y}$ is characterized by its own Brønsted plot ($\log k_1$ as a function of $\text{p}K_{\text{a}}^{\text{B}^v}$), i.e. the intrinsic rate constant depends not only on Y and the phenyl group, but on Z as well. This dependence on Z can be expressed by (47). This equation can be understood

$$\log k_0(\text{Z}) - \log k_0(\text{H}) = \delta \log k_0^{\text{pol}}(\text{Z}) = (\alpha_{\text{CH}} - \beta_{\text{B}}) \delta \log K_1^{\text{pol}}(\text{Z}) \quad (47)$$

by considering the schematic Brønsted plot (variation of B^v) for the parent compound ($\text{Z} = \text{H}$) shown in Fig. 10. Introduction of an electron-withdrawing Z while keeping B^v constant will increase $\log K_1$ by $\delta \log K_1^{\text{pol}}(\text{Z})$, shown as the horizontal arrow in Fig. 10, and increase $\log k_1$ by $\delta \log k_1^{\text{pol}}(\text{Z})$, shown

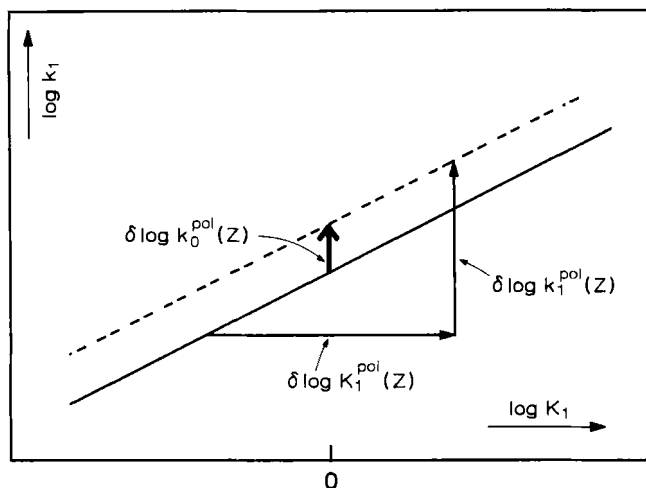


Fig. 10 The effect of an electron-withdrawing polar substituent Z on the Brønsted plot for the deprotonation of a carbon acid activated by a π -acceptor Y. The dashed line shows the Brønsted plot for the Z-substituted derivative.

as the vertical arrow. These quantities are related by a_{CH} via (48). The resulting

$$\delta \log k_1^{\text{pol}}(\text{Z}) = a_{\text{CH}} \delta \log K_1^{\text{pol}}(\text{Z}) \quad (48)$$

$\log k_1$ -value for the Z-compound ends up above the Brønsted line for the H-compound. Assuming that β_{B} does not change with Z, the Brønsted plot for the Z-compound is represented by the dashed line. The increase in $\log k_0$ is given by (47). Since a_{CH} , β_{B} and $\delta \log K_1^{\text{pol}}(\text{Z})$ are all experimentally accessible, $\delta \log k_0^{\text{pol}}(\text{Z})$ may be determined accurately without further assumptions.

From (48), it is evident that, whenever $a_{\text{CH}} > \beta_{\text{B}}$, which is the case for all examples reported in Table 1, k_0 increases when Z is made more electron-withdrawing, and decreases for electron-donating substituents. On the other hand, for the cases reported in Table 2, where $a_{\text{CH}} < \beta_{\text{B}}$, the opposite is true. This substituent dependence of k_0 can be understood as follows. An electron-withdrawing Z helps stabilize the negative charge in the carbanion and, in the reaction shown in (46), reduces the demand for resonance stabilization by Y. This reduced resonance stabilization reduces $\delta \log K_1^{\text{res}}$ in (29) and with it the k_0 -lowering PNS effect; this results in a higher k_0 . It is important to realize that the substituent effects on k_0 have nothing to do with any special characteristics of Z. They are simply a consequence of the transition-state imbalance, a phenomenon caused by Y, not by Z.

The effect of Z on k_0 , even though significant, is typically small compared

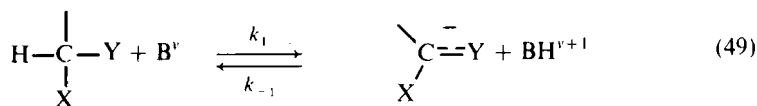
to the influence of Y. A few examples will serve to illustrate this point. For the deprotonation of $ZC_6H_4CH_2NO_2$ by morpholine in water, $a_{CH} = 1.29$, while $\beta_B = 0.56$ (Table 1). The change from $Z = H$ ($pK_a^{CH} = 7.39$) to $Z = m\text{-NO}_2$ ($pK_a^{CH} = 6.67$) corresponds to $\delta \log K_1^{pol} = 0.72$, and thus (47) yields $\delta \log k_0(m\text{-NO}_2) = (1.29 - 0.56)0.72 = 0.53$. Compared with the effect of the α -nitro-group ($\delta \log k_0^{res}(Y) \approx -9.6$, Table 5, Entry 1), this is a modest change.

In Me_2SO , where the substituent effect on pK_a^{CH} is much larger than in water ($pK_a^{CH} = 12.03$ for $Z = H$ and 10.04 for $Z = m\text{-NO}_2$), the value of $\delta \log k_0^{pol}(Z) = (0.92 - 0.55)1.99 = 0.74$ in the reaction with benzoate ion is also larger but not in proportion to the increased pK_a -difference, since $a_{CH} - \beta_B$ is smaller in Me_2SO . For $3,5\text{-(NO}_2)_2C_6H_3CH_2NO_2$, $pK_a = 8.56$ in Me_2SO , which leads to $\delta \log k_0^{pol}(Z) = 1.28$ and makes k_0 for this compound substantially higher than for $PhCH_2NO_2$.

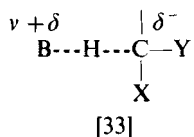
Most other reactions show smaller $\delta \log k_0^{pol}(Z)$ values. For example, in the reaction of $ArCH_2CH(COMe)COOEt$ with $RCOO^-$ in water, $\delta \log k_0^{pol}(Z) = (0.76 - 0.44)0.75 = 0.24$ for $Z = p\text{-nitro}$. When the substituent is as remote as in [8], the effect becomes almost negligible: $\delta \log k_0^{pol}(Z) = (0.27 - 0.55)0.32 = -0.09$ when $Z = m\text{-nitro}$. Note that here the electron-withdrawing substituent *reduces* k_0 because $a_{CH} < \beta_B$.

POLAR EFFECT OF ADJACENT SUBSTITUENTS

The situation to be discussed here is represented by a reaction such as (49),



where Y is again a π -acceptor while X acts only through a polar effect. An electron-withdrawing group X will lead to an increase in K_1 and k_1 , but, just as with a remote polar substituent Z, the increase in k_1 will be disproportionately large because in the transition state X is directly adjacent to the site of negative charge development [33], where it can be more effective in stabilizing the negative charge than in the product ion. The consequence is again an increase in k_0 .



There are only a few examples in Table 3 that show this effect unequivocally, because in most systems studied the second group attached to the α -carbon is also a π -acceptor. However, when steric crowding prevents the two groups from being coplanar, one of them may act mainly through its polar effect. The larger k_0 -value for the deprotonation of 2,2',4,4',6,6'-hexanitrodiphenylmethane ($\log k_0 = 0.41$; Entry 21 in Table 3) compared to that of 2,2',4,4',6-pentanitrodiphenylmethane ($\log k_0 = -0.68$; Entry 27) is a case in point. On the basis of nmr evidence (Simonnin *et al.*, 1989), it was shown that π -overlap with the central carbon in the carbanion is only possible with one of the rings (the picryl ring in the case of 2,2',4,4',6-pentanitro-derivative), while the other ring is turned out of the plane. In other words, these compounds behave as α -(2,4,6-trinitrophenyl)- and α -(2,4-dinitrophenyl)-substituted 2,4,6-trinitrotoluenes rather than polynitrodiphenylmethanes. Hence the larger k_0 for the hexanitro-derivative can be understood as being caused by the strong electron-withdrawing polar effect of the 2,4,6-trinitrophenyl group.

The fact that $\log k_0$ for the deprotonation of $\text{CH}_3\text{CH}(\text{NO}_2)_2$ by RCOO^- in water ($\log k_0 = 1.0$; Entry 17 in Table 3) is 2 logarithmic units higher than for the deprotonation of $\text{HOCH}_2\text{CH}_2\text{NO}_2$ ($\log k_0 = -1.0$; Entry 24) may have a similar explanation. The two nitro-groups in the anion cannot both be coplanar. If both nitro-groups were turned out of the plane of the central carbon, the increased k_0 would have to be a consequence of the reduced resonance effect of these groups. More specifically, the resonance effect of the two nitro-groups, $\delta \log K_1^{\text{res}}$, would have to be smaller than the resonance effect of only one nitro-group in $\text{HOCH}_2\text{CH}_2\text{NO}_2$ or CH_3NO_2 , so as to make $\delta \log k_0^{\text{res}}$ less negative. A different explanation is that one of the nitro-groups has strong π -overlap with the central carbon of the nitronate ion, while the second one is turned out of the plane and acts mainly through its polar effect, thereby enhancing k_0 . Perhaps the most satisfactory interpretation is that both of these factors contribute to the enhanced k_0 .

RESONANCE EFFECT OF REMOTE SUBSTITUENTS

π -Acceptor substituents that contribute to the stabilization of the product ion may affect k_0 through a PNS effect of their own. The deprotonation of $\text{ZC}_6\text{H}_4\text{CH}_2\text{NO}_2$ by PhCOO^- in Me_2SO provides a good example (Keeffe *et al.*, 1979). A Brønsted plot for the p - CH_3 , H, p -Br, m - NO_2 , p -CN, p - NO_2 and 3,5-(NO_2)₂ derivatives is shown in Fig. 11. The points for p -CN and p - NO_2 are seen to deviate negatively from the line by nearly 0.6 and 1.1 logarithmic units respectively, which implies an equivalent reduction of k_0 .

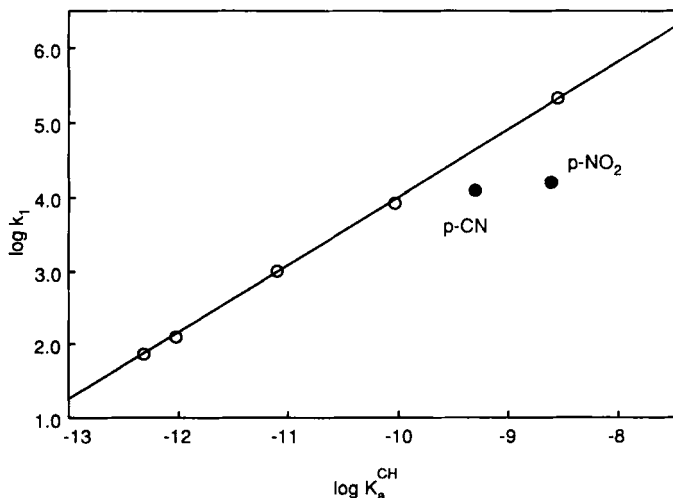
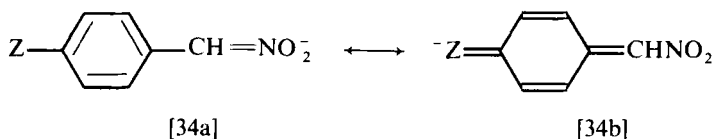


Fig. 11 Brønsted plot of the deprotonation of ArCH_2NO_2 by PhCOO^- in Me_2SO . Adapted from Keeffe *et al.* (1979) with permission from the American Chemical Society.

This reduction arises from a delayed development of the resonance effect that is associated with a contribution of [34b] and counteracts the increase in k_0 that stems from the *polar* effect of the *p*-Z groups. If the polar effect of the



p-NO₂ group is assumed to be the same as that of the *m*-NO₂ group, the value of $\delta \log k_0^{\text{pol}}(\text{Z}) = 0.74$ calculated earlier for the *m*-NO₂ group is reduced by about 1.1 logarithmic units (the deviation from the Brønsted line) so that $\log k_0$ for the *p*-NO₂ derivative is about 0.36 logarithmic units lower than that for the parent PhCH_2NO_2 .

It is interesting that the negative deviation for the *p*-NO₂ compound is significantly stronger in Me_2SO than in water (Fig. 12).⁴ A possible explanation is that in water the solvational stabilization of the α -nitro-group in the nitronate ion is so strong that the contribution by the resonance effect of the *p*-nitro-group is relatively inconsequential. On the other hand, the

⁴ The positive deviation of the *o*-methyl derivative will be discussed on p. 177.

resonance effect of the *p*-nitro-group becomes more important in Me₂SO, where solvation of the α -nitro-group is weaker. Solvation of the aryl π -acceptor substituents adds another layer of complexity to the problem, as has been shown by comparisons between the gas phase and Me₂SO. This phenomenon has been called the substituent-solvation-assisted-resonance (SSAR) effect (Fujio *et al.*, 1981; Taft, 1983; Mashima *et al.*, 1984).

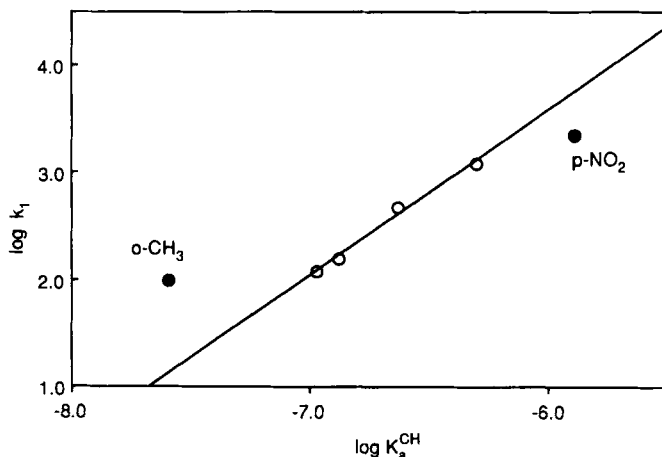
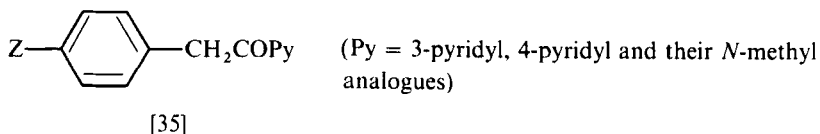


Fig. 12 Brønsted plot of the deprotonation of ArCH₂NO₂ by HO⁻ in water. Data from Bordwell and Boyle (1972).

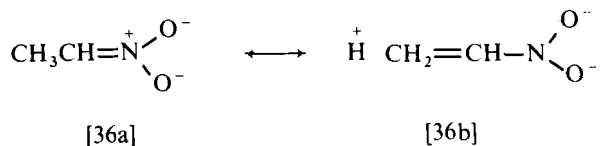
Other examples where π -acceptor substituents in the *p*-position show negative deviations from Brønsted plots include the reaction of piperidine with 2-nitro-4-*Z*-phenylacetonitriles in 50% Me₂SO–50% water (Bernasconi and Wenzel, 1992) and the reactions of various substrates of type [35] with OH⁻ (Bunting and Stefanidis, 1988) and amines (Stefanidis and Bunting, 1991).



HYPERCONJUGATION: NITROALKANE ANOMALY OF THE SECOND KIND

The reaction of CH₃NO₂, CH₃CH₂NO₂ and (CH₃)₂CHNO₂ with OH⁻ is subject to hyperconjugation effects (Kresge, 1974). Rate and equilibrium data are summarized in Table 8. The results are unusual in that k_{OH}

decreases with *increasing* acidity of the nitroalkane. This translates into $a_{\text{CH}} = -0.5 \pm 0.1$. The increase in acidity on substituting hydrogen for methyl has been attributed to the hyperconjugative stabilization of the nitronate ion, e.g. [36b]. The reason why the rate constants do not follow the



trend of the acidity constants is that hyperconjugation is poorly developed at the transition state, and hence k_{OH} is mainly governed by the electron-releasing *polar* effect of methyl groups. This, then, constitutes another example of a PNS effect where a late-developing, product-stabilizing factor (hyperconjugation) lowers k_0 .

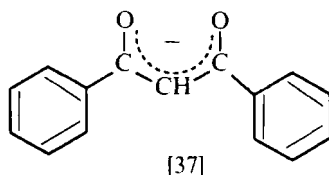
Table 8 Rate and equilibrium data for deprotonation of nitroalkanes by hydroxide ion in water at 25°C.^a

CH-Acid	$\text{p}K_{\text{a}}^{\text{CH}}$	$k_{\text{OH}}/\text{M}^{-1} \text{s}^{-1}$
CH_3NO_2	10.22	27.6
$\text{CH}_3\text{CH}_2\text{NO}_2$	8.60	5.19
$(\text{CH}_3)_2\text{CHNO}_2$	7.74	0.316

^a Kresge (1974).

π -OVERLAP WITH REMOTE PHENYL GROUPS

A recent study of the deprotonation of dibenzoylmethane by piperidine and morpholine revealed a $\log k_0$ -value (1.56) that is about 0.5 logarithmic units lower than that for the reactions of acetylacetone, 3,5-heptanedione or 2,4-dimethyl-3,5-heptanedione with the same amines (Bernasconi and Stronach, 1991b). A steric effect could be excluded as the cause for the depressed k_0 . It was suggested that the overlap between the π -electrons of the phenyl groups of the enolate [37] with the π -system involved in the

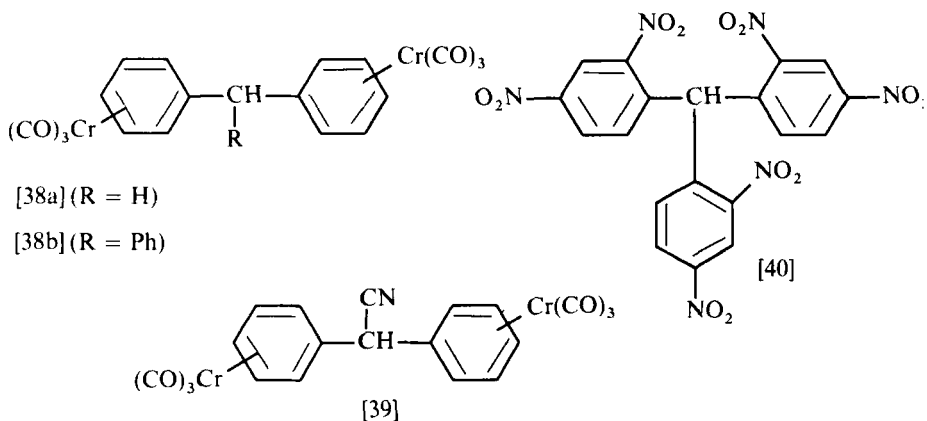


delocalization of the charge is responsible for the low k_0 . Inasmuch as the development of this overlap depends on the delocalization of the charge, the lag in the delocalization behind charge transfer also implies a lag in the development of the π -overlap. Since π -overlap is product-stabilizing, k_0 is reduced.

STERIC EFFECTS

Intrinsic rate constants of proton transfers can be significantly affected by steric effects. One type of steric effect that always lowers k_0 is crowding in the transition state, which prevents the base from approaching the proton efficiently. Well-documented examples include the reactions of 2-nitropropane with 2,6-dimethyl-, 2,4,6-trimethyl- and 2-*t*-butyl-pyridine (Lewis and Funderburk, 1967), of isobutyraldehyde with 2,6-dimethyl- and 2,4,6-trimethyl-pyridine (Hine *et al.*, 1965), and the reactions of several ketones with the same hindered pyridine derivatives (Feather and Gold, 1965). In each of these cases, the rate reductions manifest themselves by a negative deviation from a Brønsted plot defined by pyridine derivatives lacking *ortho*-substituents. Reductions of up to more than 100-fold have been observed.

Steric hindrance has also been postulated in the reactions of MeO^- with [38] (Terrier *et al.*, 1985a), and of amines with [39] (Bernasconi *et al.*, 1988a) and [40] (Farrell *et al.*, 1990). For [40], k_0 for deprotonation by piperidine



and morpholine is about 0.8 logarithmic units lower than for the deprotonation by primary amines, which contrasts with the general observation that $\log k_0$ for deprotonation of carbon acids by the piperidine/morpholine pair is usually 0.7–1.0 logarithmic units *higher* than with primary aliphatic amines

(Bernasconi and Hibdon, 1983; Bernasconi and Bunnell, 1985; Bernasconi and Paschalis, 1986; Bernasconi and Stronach, 1991b). Using the same criterion for [39] indicates a much smaller steric effect since $\log k_0(\text{pip}/\text{mor}) - \log k_0(\text{RNH}_2) = 0.4$ is not much lower than for sterically unhindered systems.

In all the examples cited above, the steric effect operates exclusively in the transition state; there is no counterpart in either the reactants or products, and hence the reduction in k_0 has nothing to do with the PNS. However, steric factors can affect k_0 by a PNS effect in an indirect way when a bulky group hinders π -overlap in the carbanion, thereby reducing $\delta \log K_1^{\text{res}}$ in (29). Two examples, the deprotonation of 1,1-dinitroethane and of 2,2',4,4',6,6'-hexanitrodiphenylmethane, have been discussed earlier. Since the groups that lead to steric inhibition in these examples also contribute to the enhanced k_0 by their electron-withdrawing polar effect, it is difficult to assess how much of the increase in k_0 may be attributed to the steric effect. An example where there is no such polar effect is the reaction of *o*-methylphenylnitromethane with OH^- in water (Bordwell and Boyle, 1972). Figure 12 shows that the point for this compound deviates 0.8 logarithmic units positively from the Brønsted line defined by *m*-Me-, H-, *m*-Cl- and *m*-NO₂-substituted phenylnitromethane, i.e. k_0 is enhanced by 0.8 logarithmic units owing to steric hindrance of the coplanarity of the α -nitro-group in $\text{ArCH}=\text{NO}_2^-$ by the *o*-methyl group.⁵ It is interesting that Bordwell and Boyle (1972) did not show this Brønsted plot in their paper and did not comment on the reaction of the *o*-methyl derivative.

Another example where steric inhibition of resonance has been invoked to explain enhanced proton transfer rates is in the proton exchange of 1,3-dimethyl-2-iminoimidazolin-4-one with benzoate ions (Srinivasan and Stewart, 1976). *Ortho*-substituted benzoate ions were found to deviate positively from a Brønsted plot. Steric inhibition of resonance or of the solvation of the neutral carboxylic acid, coupled with the assumption that these resonance and solvation effects are poorly developed in the transition state, can account for these observations. This, then, is again a PNS effect, although the authors did not phrase it in these terms.

TREATMENT OF SUBSTITUENT EFFECTS USING MODIFIED MARCUS EQUATIONS

As is well known, the parameter that is at the centre of the PNS is the intrinsic barrier or intrinsic rate constant, concepts originally introduced by Marcus (1956, 1957, 1964, 1968). However, the equations

⁵ The negative deviation of the *p*-nitro-derivative has been discussed on p. 173.

developed by Marcus, (5) or (6), are not easily applied to reactions with imbalanced transition states because the theory is based on a description of reactions by a single progress variable, implying a balanced transition state. The breakdown of the Marcus equations when applied to reactions with imbalanced transition states manifests itself in a particularly obvious way when dealing with substituent effects. Let us use the example of equation (46). On the basis of (5) or (6) one predicts the equalities in (50), i.e. $d\Delta G^\ddagger/d\Delta G^0$ is the same regardless of whether ΔG^0 is varied by a change in the substituent of the base or the carbon acid, in stark contrast with experimental observations (Tables 1 and 2). For (50) to be valid would require $\Delta G_0^\ddagger$ to

$$\frac{d \log k_1}{d \log K_1} = \frac{d\Delta G^\ddagger}{d\Delta G^0} = 0.5 \left(1 + \frac{\Delta G^0}{4\Delta G_0^\ddagger} \right) = \beta_B = a_{CH} \quad (50)$$

be independent of the substituent in both the carbon acid and the base. This is approximately true for the base, and hence (50) often gives a reasonable approximation of β_B , but it is clearly not the case for the carbon acid, as discussed in detail above. As we have shown, the degree by which a_{CH} differs from β_B is actually a measure of how strongly k_0 or $\Delta G_0^\ddagger$ depend on the substituent as expressed in (47).

Attempts have been made to modify the Marcus equation so as to make it applicable to reactions with imbalanced transition states. These attempts are now briefly discussed.

Marcus' approach

The problem of substituent dependent intrinsic barriers and their effect on a_{CH} was already recognized by Marcus (1969), who suggested a modification of (50) for a_{CH} in the form of (51). Marcus did not elaborate further and did

$$a_{CH} = 0.5 \left(1 + \frac{\Delta G^0}{4\Delta G_0^\ddagger} \right) + \left[1 - \left(\frac{\Delta G^0}{4\Delta G_0^\ddagger} \right)^2 \right] \frac{d\Delta G_0^\ddagger}{d\Delta G^0} \quad (51)$$

not specify an analytical expression for $d\Delta G_0^\ddagger/d\Delta G^0$. However, if we assume that β_B is given correctly by (50), subtraction of (50) from (51) yields (52) which, for ΔG^0 close to zero, simplifies to (53). Note that (53) is completely

$$a_{CH} - \beta_B = \left[1 - \left(\frac{\Delta G^0}{4\Delta G_0^\ddagger} \right)^2 \right] \frac{d\Delta G_0^\ddagger}{d\Delta G^0} \quad (52)$$

$$a_{\text{CH}} - \beta_{\text{B}} \approx \frac{d\Delta G_0^*}{d\Delta G^0} \quad (53)$$

analogous to (47) since (47) may be rearranged to (54). The only difference

$$\frac{\delta \log k_0^{\text{pol}}(Z)}{\delta \log K_1^{\text{pol}}(Z)} = \frac{d\Delta G_0^*}{d\Delta G^0} = a_{\text{CH}} - \beta_{\text{B}} \quad (54)$$

between the Marcus and the PNS approach is that, in the latter, a_{CH} and β_{B} are determined empirically and ΔG_0^* is obtained by linear interpolation or extrapolation of the β_{B} -Brønsted plot, while in the former β_{B} and a_{CH} are calculated via (50) and (51), respectively, with ΔG_0^* being obtained by solving (5) or (6).

Bunting's approach

Bunting and Stefanidis (1988) have proposed a similar analysis of substituent effects in the context of the Marcus equation. As implied by (47) or (54), ΔG_0^* is a linear function of ΔG^0 when ΔG_0^* is determined by interpolation or extrapolation of linear β_{B} -Brønsted plots. This should also be true when ΔG_0^* is obtained from (5) or (6), at least as long as ΔG^0 is close to zero. This was explicitly shown to be the case in the deprotonation of a series of benzylic ketones of the general structure [35] by OH^- (Bunting and Stefanidis, 1988). This linear function was expressed by (55).

$$\Delta G_0^* = A + B \Delta G^0 \quad (55)$$

Note that comparing (55) with (53) implies that $B \approx a_{\text{CH}} - \beta_{\text{B}}$. Inserting (55) into (6) leads to (56).

$$\Delta G^* = (A + B \Delta G^0) \left(1 + \frac{\Delta G^0}{4(A + B \Delta G^0)} \right)^2 \quad (56)$$

By fitting the observed dependence of ΔG^* on ΔG_0^0 within each series of benzylic ketones, best values for A and B were obtained. These parameters were then used to calculate a_{CH} according to (57), which is strictly analogous

$$a_{\text{CH}} = \frac{d\Delta G^*}{d\Delta G^0} = 0.5 \left[1 + \frac{\Delta G^0}{4(A + B \Delta G^0)} \right] + B \left[1 - \left(\frac{\Delta G^0}{4(A + B \Delta G^0)} \right)^2 \right] \quad (57)$$

to (51) proposed by Marcus. Table 9 summarizes A , B , a_{CH} ($\Delta G^0 = 0$) and ranges of a_{CH} corresponding to the experimental range of ΔG^0 for the four

Table 9 A , B and a_{CH} calculated from the Bunting equations (55) and (57) for the reaction of benzylic ketones of the general structure [35] with OH^- .^a

CH-Acid ^b	$A/\text{kcal mol}^{-1}$	B	ΔG^0 range/ kcal mol^{-1}	Calculated a_{CH} range	Observed a_{CH}
[35a]	16.0	0.18	−1.04 to −4.45	0.64 to 0.67	0.66
[35b]	16.7	0.22	−2.08 to −5.65	0.67 to 0.70	0.68
[35c]	17.4	0.28	−4.82 to −7.93	0.71 to 0.74	0.73
[35d]	18.9	0.32	−6.49 to −9.35	0.73 to 0.77	0.76

^a Bunting and Stefanidis (1988). ^b [35a], 3-pyridyl; [35b], 4-pyridyl; [35c], *N*-methyl-3-pyridyl; [35d], *N*-methyl-4-pyridyl.

benzylic ketones. The agreement between the ranges of a_{CH} and the a_{CH} -values determined from the slope of Brønsted plots is very close, indicating that it makes little difference whether $\Delta G_0^\ddagger$ is calculated from (6) or determined from the β_{B} -Brønsted plot.

Equations (56) and (57) have recently been applied to numerous other proton transfers (Bunting and Stefanidis, 1989). For example, for the reaction of ArCH_2NO_2 with morpholine in water, $B = 0.80 \pm 0.09$ whereas $a_{\text{CH}} - \beta_{\text{B}} = 0.73$ (Table 1), and for the reaction of $\text{ArCH}(\text{CH}_3)\text{NO}_2$ with the same amine $B = 0.44 \pm 0.01$ whereas $a_{\text{CH}} - \beta_{\text{B}} = 0.31$. In both cases, the agreement between B and $a_{\text{CH}} - \beta_{\text{B}}$ is reasonably close. For the reaction of ArCH_2NO_2 with OH^- , a_{CH} calculated from (57) is 1.54, equal to the observed a_{CH} . Bunting and Stefanidis (1989) have also extended their treatment to the calculations of β_{B} by an equation analogous to (57).

Grunwald's approach

Grunwald's (1985) approach is illustrated for the deprotonation of ArCH_2NO_2 by OH^- . The reaction-coordinate diagram, as proposed by Grunwald, is shown in Fig. 13. The process connecting the reactants with the products, ($r \rightarrow p$), is called the "main reaction", the one connecting the two hypothetical intermediates, ($i \rightarrow h$), is called the "disparity reaction". The position of the transition state is defined by a progress variable x along the main reaction coordinate, and a progress variable y along the disparity reaction coordinate ($y = 0$ for i , $y = 1.0$ for h).

Energy parameters for the main reaction are ΔG^0 , $\Delta G^\ddagger$ and $\gamma = \Delta G_0^\ddagger$. The corresponding parameters for the disparity reaction are $\Delta G'$, $\Delta W^\ddagger$ and μ . $\Delta G'$ is defined as $G(h) - G(i)$ and $\Delta W^\ddagger$ as $G^\ddagger - G(i)$. Note that the reaction coordinate for the disparity reaction represents an energy well and hence $\Delta W^\ddagger$ is a negative number. The parameter μ is called the intrinsic well depth and is defined as $\mu = -\Delta W^\ddagger$ for $\Delta G' = 0$, i.e. it is a positive number.

The energy surface is modelled by an equation of the general form (58),

$$G = c + ax(1 - x) + bx + dy(1 - y) + ey \quad (58)$$

and the various parameters are related to the energy parameters introduced above by applying Marcus theory and appropriate boundary conditions. This gives $a = 4\gamma$, $b = \Delta G^0$, $d = -4\mu$ and $e = \Delta G'$, while c is a constant depending on the choice of the zero energy level. From the condition $\partial G / \partial x = \partial G / \partial y = 0$ at the transition state, one obtains the transition-state coordinates in (59) and (60),

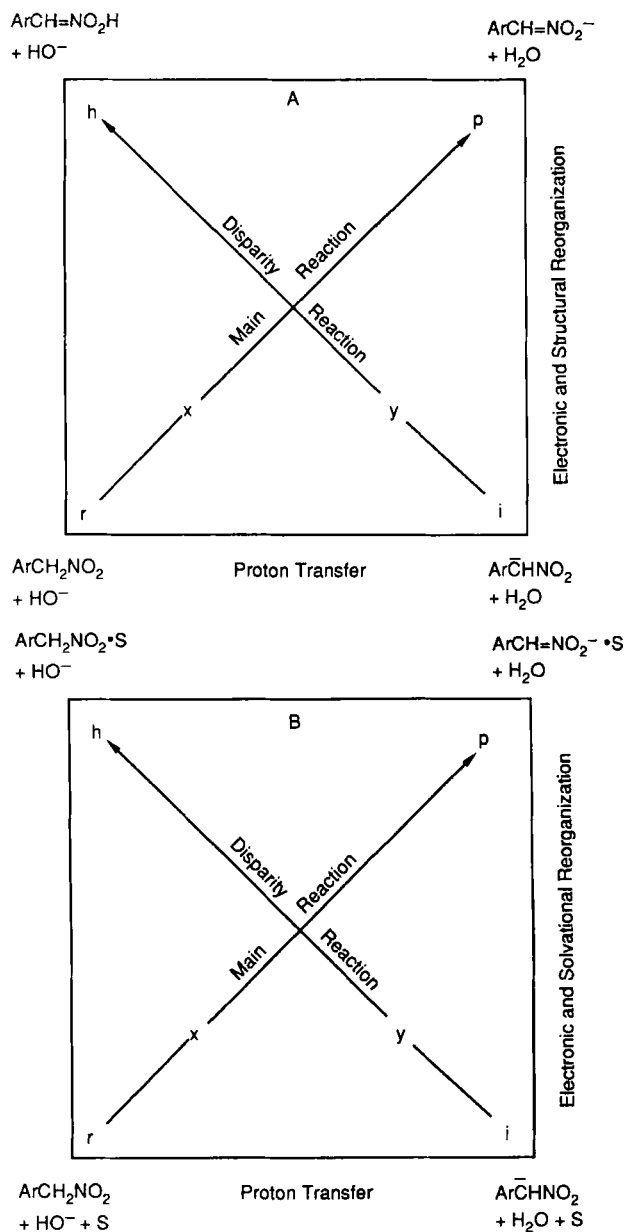


Fig. 13 Grunwald diagrams for the deprotonation of ArCH_2NO_2 by HO^- , showing the main and disparity reactions: (A) upper left corner as suggested by Grunwald (1985); (B) upper left corner as suggested by Albery *et al.* (1988). Adapted from Grunwald (1985) and Albery *et al.* (1988) with permission of the American Chemical Society and of John Wiley & Sons respectively.

$$x^* = \frac{1}{2} + \Delta G^0/8\gamma \quad (59)$$

$$y^* = \frac{1}{2} - \Delta G'/8\mu \quad (60)$$

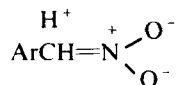
which leads to (61).

$$\Delta G^* = \gamma + \frac{\Delta G^0}{2} + \frac{(\Delta G^0)^2}{16\gamma} - \frac{(\Delta G')^2}{16\mu} \quad (61)$$

After introducing some additional assumptions and using the experimental $\Delta G^0 = -9.71 \text{ kcal mol}^{-1}$ and $\Delta G^* = 14.42 \text{ kcal mol}^{-1}$ for the reaction of PhCH_2NO_2 with OH^- , Grunwald was able to estimate $\gamma = 22 \text{ kcal mol}^{-1}$ and $\Delta G'/8\mu = 0.41$; no estimates for $\Delta G'$ and μ separately were obtained. Solving (59) and (60) afforded $x^* = 0.45$ and $y^* = 0.09$; this would correspond to 0.86 progress along the horizontal axis of the energy surface, which measures proton transfer (β_B in Fig. 9), and 0.04 progress along the vertical axis, which measures electronic reorganization (λ_{res} in Fig. 9). These parameters, then, indicate a transition state in which the negative charge is virtually completely localized on the carbon, more so than our own analysis suggests.

Grunwald's choice of the nitronic acid as the intermediate in the h-corner of the diagram has been criticized (Albery *et al.*, 1988). Albery *et al.* estimated $\Delta G^0 \leq -24.2 \text{ kcal mol}^{-1}$ for the process $i \rightarrow p$, i.e. $\text{Ar}\bar{\text{C}}\text{HNO}_2 \rightarrow \text{ArCH}=\text{NO}_2^-$, and $\Delta G^0 \leq -10.4 \text{ kcal mol}^{-1}$ for the disparity reaction $i \rightarrow h$, i.e. $\text{Ar}\bar{\text{C}}\text{HNO}_2 + \text{H}_2\text{O} \rightarrow \text{ArCH}=\text{NO}_2\text{H} + \text{OH}^-$. This latter estimate makes the disparity reaction an exoergic process and implies that the transition state should be closer to the h-corner than the i-corner in Fig. 13A (Thornton, 1967; More O'Ferrall, 1970; Jencks, 1972), i.e. delocalization would be ahead of proton transfer, contradicting all experimental evidence. In view of this criticism, the numerical estimates for λ , $\Delta G'/8\mu$, x^* and y^* given by Grunwald should be regarded with caution.

Albery *et al.* (1988) suggested a remedy by having the vertical axes not only represent electronic rearrangement but include solvent reorganization, as shown in Fig. 13B. This is in keeping with the strong coupling between resonance and solvational stabilization of the nitronate ion discussed earlier. The h-corner would then be represented by a nitroalkane molecule with a solvation shell appropriate to a nitronate ion rather than a neutral nitroalkane. This species could possibly be thought of as also having an *electronic* structure more appropriate to a nitronate ion, e.g. [41]. Such a species would



probably be sufficiently unstable to make the disparity reaction strongly endoergic, thereby placing the transition state well below the diagonal of the main reaction.

What is the relationship between the PNS formalism and the Grunwald approach? In terms of visualization of transition-state imbalances, they are quite equivalent since the same kind of energy surfaces are used to describe the reaction (Fig. 13 versus 3 and 4). Thus the progress variables in the PNS formalism, β_B for proton transfer and λ_{res} for electronic reorganization (Fig. 9), are easily transformed into Grunwald's progress variables along the main (x) and the disparity reaction (y) through (62) and (63). The main virtue of

$$x = \frac{1}{2}(\beta_B + \lambda_{res}) \quad (62)$$

$$y = \frac{1}{2}(\lambda_{res} - \beta_B) + \frac{1}{2} \quad (63)$$

the Grunwald approach is that it makes the Marcus equation applicable to reactions with imbalanced transition states by adding a term for the disparity reaction. However, just as in the case with the original Marcus equation, (61) is only a rate/equilibrium relationship, which does not provide insight, on the molecular level, into the factors that determine intrinsic barriers, and hence cannot be regarded as a substitute for the PNS formalism.

A somewhat similar approach in dealing with imbalanced transition states was proposed by Kreevoy and Lee (1984) for hydride transfer reactions, where the disparity reaction is called the "tightness parameter". Work by Lewis *et al.* (1987a,b) is also relevant here.

5 Solvation effects on intrinsic rate constants of proton transfers

Most reactions in solution are affected by solvation effects, and proton transfers are no exception. Inasmuch as solvation of products and/or desolvation of reactants may be out of step with the main process of the reaction, intrinsic rate constants will be affected according to the rules of the PNS. Since solvation of each product (carbanion and BH^{v+1}) and desolvation of each reactant (carbon acid and B^v) may contribute a PNS-effect to k_0 , a quantitative treatment of these effects is difficult. Nevertheless, a mathematical formalism based on (41) has been developed and will be detailed below. We start our discussion with qualitative considerations.

SOLVATION/DESOLVATION OF IONS

As discussed earlier, resonance and solvation effects of the carbanion are difficult to separate from each other, especially in cases where the negative charge is concentrated on oxygen atoms that are subject to strong hydrogen bonding solvation. As a matter of convenience, the two factors were therefore lumped together, i.e. $\delta \log k_1^{\text{res}}$, $\delta \log K_1^{\text{res}}$ and $\delta \log k_0^{\text{res}}$ in (25) and (29) refer to the combined effect of resonance and solvation on the respective parameters.

An alternative approach is to separate the two factors and express the overall effect of resonance and solvation as sum of two terms, as in (64),

$$\begin{aligned} \delta \log k_0^{\text{res}' + \text{sol}} &= \delta \log k_0^{\text{res}'} + \delta \log k_0^{\text{sol}} \\ &= (\lambda_{\text{res}'} - \beta_{\text{B}}) \delta \log K_1^{\text{res}'} + (\lambda_{\text{sol}} - \beta_{\text{B}}) \delta \log K_1^{\text{sol}} \end{aligned} \quad (64)$$

where the meaning of $\delta \log K_1^{\text{res}'}$ and $\delta \log k_0^{\text{res}'}$ is somewhat different from that in (29) since they refer to resonance only. This is symbolized by a prime (res'). If $\lambda_{\text{sol}} = \lambda_{\text{res}'}$, then (64) is equivalent to (29) with $\lambda_{\text{res}'} = \lambda_{\text{res}}$, but not if $\lambda_{\text{sol}} \neq \lambda_{\text{res}'}$. Hence the main advantage of (64) over (29) is that it allows for the possibility that $\lambda_{\text{sol}} \neq \lambda_{\text{res}'}$.

It is reasonable to assume that $\lambda_{\text{sol}} < \lambda_{\text{res}'}$, i.e. solvation of the developing carbanion lags farther behind charge transfer than resonance stabilization. The justification for assuming an additional lag is that solvation of the developing ions lags behind charge transfer even when there is no charge delocalization, as for oxyanions or ammonium ions. Hence, when delocalization is involved, the lag in the solvation is on top of the lag in the delocalization.

Evidence for non-synchronous solvation of oxyanions comes from the frequently reported negative deviation of highly basic oxyanions from Brønsted plots in proton transfers and nucleophilic reactions in aqueous media (Kresge, 1973; Hupe and Jencks, 1977; Hupe and Wu, 1977; Pohl *et al.*, 1980; Jencks *et al.*, 1982; Bernasconi and Bunnell, 1985; Terrier *et al.*, 1988). This effect, which implies a reduced intrinsic rate constant, arises from the (partial) desolvation of the oxyanion being ahead of charge transfer or bond formation in the transition state. In the reverse direction, this is equivalent to a late solvation of the developing oxyanion. This can be expressed by (65), with $\delta \log K_1^{\text{des}}(\text{B}^-)$ being the reduction in $\log K_1$ brought

$$\delta \log k_0^{\text{des}}(\text{B}^-) = (\lambda_{\text{des}}^{\text{B}^-} - \beta_{\text{B}}) \delta \log K_1^{\text{des}}(\text{B}^-) \quad (65)$$

about by the solvation of B^- . Since a reduction in K_1 implies $\delta \log K_1^{\text{des}}(B^-) < 0$ and early desolvation means $\lambda_{\text{des}}^{B^-} > \beta_B$, we obtain $\delta \log k_0^{\text{res}}(B^-) < 0$. It needs to be stressed, though, that for a negative deviation from a straight line Brønsted plot to occur, $\delta \log K_1^{\text{res}}(B^-)$ has to be a stronger than linear function of pK_a^{BH} , otherwise the early desolvation would only change the slope of the entire Brønsted plot. Evidence indicating disproportionately strong solvation of highly basic oxyanions has been summarized by Jencks *et al.* (1982).

A recent kinetic isotope effect study of methoxide ion addition to phenylacetate in methanol leads to similar conclusions (Huskey and Schowen, 1987). The secondary β -hydrogen isotope effect indicates a progress of approximately 0.15 in the bond formation between the nucleophile and the acyl carbon at the transition state, while the solvent isotope effect is consistent with a *ca* 0.68 progress in the desolvation of MeO^- .

It has been suggested (Jencks *et al.*, 1982) that desolvation may be completely uncoupled from the bond changes and should be treated as a pre-equilibrium. In such a case, (65) simplifies to (66), i.e. $\lambda_{\text{des}}^{B^-} = 1.0$. The isotope

$$\delta \log k_0^{\text{des}}(B^-) = (1 - \beta_B) \delta \log K_1^{\text{des}}(B^-) \quad (66)$$

effect study mentioned above as well as solvent-effect studies discussed below are more consistent with $\lambda_{\text{des}} < 1$, though.

Non-synchronous solvation/desolvation is not restricted to anions. The solvation of developing ammonium ions typically lags behind charge transfer. This manifests itself in the frequent observation that, for a given amine pK_a , the reactivity order is $\text{RR}'\text{R}''\text{N} > \text{RR}'\text{NH} > \text{RNH}_2 > \text{NH}_3$ in proton transfers and nucleophilic reactions (Bell, 1973; Bernasconi and Hibdon, 1983; Bernasconi and Bunnell, 1985; Terrier *et al.*, 1985b; Bernasconi and Paschalis, 1986; Bernasconi and Terrier, 1987). This reactivity order is a consequence of the increasingly stronger solvation of the protonated amines in the order $\text{NH}_4^+ > \text{RNH}_3^+ > \text{RR}'\text{NH}_2^+ > \text{RR}'\text{R}''\text{NH}^+$, coupled with the assumption of late development of this solvation (Jencks, 1968; Bell, 1973; Bernasconi, 1985). The mathematical description is shown in (67), where NH^+ symbolizes the protonated amine, $\delta \log K_1^{\text{sol}}(\text{NH}^+)$ is the

$$\delta \log k_0^{\text{sol}}(\text{NH}^+) = (\lambda_{\text{sol}}^{\text{NH}^+} - \beta_B) \delta \log K_1^{\text{sol}}(\text{NH}^+) \quad (67)$$

increase in equilibrium constant due to its solvation and $\lambda_{\text{sol}}^{\text{NH}^+}$ is the progress of this solvation at the transition state.

SOLVATION/DESOLVATION OF CARBOXYLIC ACIDS, AMINES AND CARBON ACIDS

With respect to how strongly k_0 may be affected by non-synchronous solvation/desolvation, the contributions from the carbanion, from B' when $\nu = -1$, and BH^{v+1} when $\nu = 0$, are generally the most important ones. However, non-synchronous solvation/desolvation of neutral reactants and products also needs to be considered. Brønsted coefficients β_B close to unity or close to zero have been interpreted in terms of solvational imbalances of carboxylic acids and amines. For example, the deprotonation of dimethyl-9-fluorenylsulphonium tetrafluoroborate by carboxylate ions has $\beta_B = 1.0$, and hence $a_{BH} = 0$ for the reverse reaction (Murray and Jencks, 1988, 1990). According to these authors, solvation of $RCOOH$ by hydrogen bonding to the water, $RCOOH \cdot OH_2$, is substantial and increases with the acidity of $RCOOH$, an increase that may be described by a Brønsted $a_{sol} = d \log K_{sol} / d \log K_a$ estimated to be about 0.2. Before protonation of the carbon by $RCOOH$ can occur, this hydrogen bond needs to be broken. This reduces the rate constant, more so with increasing acidity of $RCOOH$, thereby reducing the "true" a_{BH} by $a_{sol} \approx 0.2$. In other words, the true a_{BH} is given by $a_{BH,obsd} + ca\ 0.2 \approx 0.2$, and, by virtue of the relationship $a_{BH} + \beta_B = 1.0$, the "true" β_B is $\beta_{B,obsd} - ca\ 0.2 \approx 0.8$. It is these "true" or corrected a_{BH} - and β_B -values that should be taken as measures of charge or proton transfer.

For less extreme values of a_{BH} and β_B , the need for desolvation of $RCOOH$ has a decreasing impact on the true Brønsted coefficients. Jencks *et al.* (1986) suggest (68) and (69) to calculate the true or corrected Brønsted

$$a_{BH,corr} = (a_{BH,obsd} + a_{sol}) / (1 + a_{sol}) \quad (68)$$

$$\beta_{B,corr} = \beta_{B,obsd} / (1 + a_{sol}) \quad (69)$$

coefficients. In the light of Murray and Jenck's conclusions, many β_B - and a_{BH} -values in the literature should probably be corrected, at least when β_B approaches 1.0 and a_{BH} approaches 0. We have used (69) to estimate $\beta_{B,corr}$ for the reaction of $PhCH_2CH(CN)_2$ with $RCOO^-$ reported in Table I (Entry 1a).

A similar imbalance between desolvation and bond formation has also been found with quinuclidine bases acting as nucleophiles in phosphoryl transfer reactions (Jencks *et al.*, 1986). Negative β_{nuc} -values were attributed to the requirement of desolvation of the amine prior to the nucleophilic attack, presumably by way of a pre-equilibrium. A negative β_{nuc} was also reported by Richard (1987) in the reaction of 1-(4-methylthiophenyl)-2,2,2-trifluoroethyl

carbocation with amines and this was explained in terms of a rate-limiting desolvation of the amine.

Within the PNS formalism, the above solvation/desolvation effects of carboxylic acids and amines will lead to a contribution to k_0 that is of the form of (70) and (71) respectively, with $\delta \log K_1^{\text{sol}}(\text{BH})$ being the increase in

$$\delta \log k_0^{\text{sol}}(\text{BH}) = (\lambda_{\text{sol}}^{\text{BH}} - \beta_{\text{B}}) \delta \log K_1^{\text{sol}}(\text{BH}) \quad (70)$$

$$\delta \log k_0^{\text{des}}(\text{N}) = (\lambda_{\text{des}}^{\text{N}} - \beta_{\text{B}}) \delta \log K_1^{\text{des}}(\text{N}) \quad (71)$$

K_1 brought about by the solvation of BH, $\delta \log K_1^{\text{des}}(\text{N})$ being the decrease in K_1 brought about by the solvation of N, and $\lambda_{\text{sol}}^{\text{BH}} (< \beta_{\text{B}})$ and $\lambda_{\text{des}}^{\text{N}} (> \beta_{\text{B}})$ measuring the progress of the solvation of BH and the desolvation of N, respectively.

It is likely that the partial desolvation of the carbon acid should also play a role. Hence, when dealing with solvation/desolvation PNS effects, a term for this process should be included in the form of (72). Since the evidence

$$\delta \log k_0^{\text{des}}(\text{CH}) = (\lambda_{\text{des}}^{\text{CH}} - \beta_{\text{B}}) \delta \log K_1^{\text{des}}(\text{CH}) \quad (72)$$

indicates that desolvation for all other species is ahead of proton transfer, we assume the same to be true for the carbon acid, i.e. $\lambda_{\text{des}}^{\text{CH}} > \beta_{\text{B}}$.

WHY IS SOLVATION/DESOLVATION NON-SYNCHRONOUS WITH CHARGE TRANSFER OR BOND CHANGES?

According to Kurz (1989a,b), the reason for this asynchrony is the existence of dynamic solvent effects that result from the disparity between the natural time scales of the various processes that change charge distributions and reorient the solvent molecules. Let us consider the solvation of a developing charge in a transition state. The changing charge leads to a polarization of the solvent in such a way as to minimize free energy. There are two main mechanisms available for the solvent to attain optimal interaction with the charge. The first is electronic (possibly including vibrational) polarization, which is rapid enough to keep pace with changes in the charge. This electronic polarization is always in equilibrium with the internal charge distribution of the transition state and cannot be the source of non-synchronous solvation effects.

The second mechanism is the rotation of the solvent molecules that brings their dipoles into the correct orientation with respect to the charge. This rotation is relatively slow; it cannot keep pace with changes in the charge,

and is therefore not in equilibrium with these charges. This slow reorientation is believed to be the source of non-synchronous solvation effects and leads to an increase in the free energy of the transition state. These qualitative arguments have been confirmed by molecular dynamics calculations, most recently on a model S_N2 reaction, $Cl^- + CH_3Cl$ (Gertner *et al.*, 1991), for which solvent reorganization occurs ahead of the change in charge distribution of the reactants, or lags behind this change in the incipient products.

It should be noted that dynamic solvent effects may also affect the rate of a reaction in a different way, i.e. not through an increase in the free energy of the transition state by non-equilibrium solvation, but by a reduction of the transmission coefficient κ in the Eyring equation. This dynamic solvent effect "of the second kind" is presumably caused by slow solvent relaxation when the solvent is "in flight" (Kurz and Kurz, 1985). The question whether a dynamic solvent effect of the second kind occurs in proton transfers will be taken up in a later section.

SOLVENT EFFECTS: QUALITATIVE CONSIDERATIONS

Equations such as (64), (65), (67) and (70)–(72) are difficult to apply in a quantitative assessment of the various solvation/desolvation effects on k_0 . Even if the solvation energies of the various species were known, estimates for $\delta \log K_1^{sol}(C^-)$, $\delta \log K_1^{des}(B^-)$, $\delta \log K_1^{sol}(NH^+)$, $\delta \log K_1^{des}(N)$, $\delta \log K_1^{sol}(BH)$ and $\delta \log K_1^{des}(CH)$ would be hard to come by. For example, the desolvation necessary for a reactant to react does not involve complete removal of all surrounding solvent molecules; in the case of a product, solvation starts with an already partially solvated state. A second difficulty is that $\lambda_{sol}^{C^-}$, $\lambda_{des}^{B^-}$, $\lambda_{sol}^{NH^+}$, λ_{sol}^{BH} , λ_{des}^N and λ_{des}^{CH} are not known, although they can be estimated as discussed below.

Equations (64), (65), (67) and (70)–(72) are more easily applied to evaluating how k_0 is affected by a *change* in solvent. Let us develop the formalism for the contribution of the late solvation of the carbanion to the solvent effect on k_0 . According to (64), we can write (73) in solvent I (e.g. water) and (74) in solvent II (e.g. Me_2SO or Me_2SO –water). The effect of

$$\delta \log k_0^{sol}(C^-)_I = (\lambda_{sol}^{C^-} - \beta_B)_I \delta \log K_1^{sol}(C^-)_I \quad (73)$$

$$\delta \log k_0^{sol}(C^-)_{II} = (\lambda_{sol}^{C^-} - \beta_B)_{II} \delta \log K_1^{sol}(C^-)_{II} \quad (74)$$

changing I to II is then given by (75). If we approximate $(\lambda_{sol}^{C^-} - \beta_B)_{II} \approx (\lambda_{sol}^{C^-} - \beta_B)_I \approx (\lambda_{sol}^{C^-} - \beta_B)$ then (75) simplifies to (76). Note that the

$$\delta_{C^-} = \delta \log k_0^{\text{sol}}(C^-)_{\text{II}} - \delta \log k_0^{\text{sol}}(C^-)_{\text{I}} \\ = (\lambda_{\text{sol}}^{C^-} - \beta_{\text{B}})_{\text{II}} \delta \log K_1^{\text{sol}}(C^-)_{\text{II}} - (\lambda_{\text{sol}}^{C^-} - \beta_{\text{B}})_{\text{I}} \delta \log K_1^{\text{sol}}(C^-)_{\text{I}} \quad (75)$$

$$\delta_{C^-} \approx (\lambda_{\text{sol}}^{C^-} - \beta_{\text{B}}) [\delta \log K_1^{\text{sol}}(C^-)_{\text{II}} - \delta \log K_1^{\text{sol}}(C^-)_{\text{I}}] \quad (76)$$

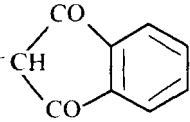
above approximation does not require that $\lambda_{\text{sol}}^{C^-}$ and β_{B} be individually solvent-independent, only that their difference be insensitive to the solvent change, i.e. the lag in solvation is assumed to be solvent-independent. The term in square brackets can be written as (77), and hence (76) simplifies to (78). The term ${}^{\text{I}}\delta^{\text{II}} \log K_1^{\text{sol}}(C^-)$ is the change in the equilibrium constant

$$\delta \log K_1^{\text{sol}}(C^-)_{\text{II}} - \delta \log K_1^{\text{sol}}(C^-)_{\text{I}} = {}^{\text{I}}\delta^{\text{II}} \log K_1^{\text{sol}}(C^-) = -\log {}^{\text{I}}\delta_{\text{C}^-}^{\text{II}} \quad (77)$$

$$\delta_{C^-} \approx (\lambda_{\text{res}}^{C^-} - \beta_{\text{B}}) {}^{\text{I}}\delta^{\text{II}} \log K_1^{\text{sol}}(C^-) = (\lambda_{\text{res}}^{C^-} - \beta_{\text{B}}) (-\log {}^{\text{I}}\gamma_{\text{C}^-}^{\text{II}}) \quad (78)$$

brought about by the change in the solvation of C^- ; it is essentially the same as the solvent activity coefficient for the transfer of C^- from I to II, ${}^{\text{I}}\gamma_{\text{C}^-}^{\text{II}}$, except that the logarithm of the latter is defined with a minus sign (Parker, 1969).

Table 10 Transfer activity coefficients for the transfer of ions from water to 90% Me_2SO -10% water ($\log {}^{\text{w}}\gamma^{90}$) and from 50% Me_2SO -50% water to 90% Me_2SO -10% water ($\log {}^{50}\gamma^{90}$).

Ion	$\log {}^{\text{w}}\gamma^{90}$	$\log {}^{50}\gamma^{90}$	Ref.
$\text{CH}_2=\text{NO}_2^-$	6.70	3.83	^a
$\text{PhCH}=\text{NO}_2^-$	4.09	2.10	^a
$\text{CH}(\text{COCH}_3)_2^-$	5.03	2.67	^a
	1.79 ^e	1.38	^a
2- NO_2 -4-Cl- $\text{C}_6\text{H}_3\text{CHCN}^-$		-2.01	^b
2,4-(NO_2) ₂ - $\text{C}_6\text{H}_3\text{CHCN}^-$	-3.24	-2.48	^b
9-COOMe-FI ^{-d}		-2.12	^a
9-CN-FI ^{-d}	-4.02 ^e	-2.65	^a
AcO^-	<i>ca</i> 6.50 ^f (<i>ca</i> 5.38) ^e	<i>ca</i> 3.42	^c
$\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2^+$	<i>ca</i> -2.80 ^f (<i>ca</i> -2.40) ^e	<i>ca</i> -0.99	^c
H^+	-3.05 ^f (-2.57) ^e	-1.12	^c

^a Bernasconi and Bunnell (1988). ^b Gandler and Bernasconi (1991). ^c Wells (1979). ^d FI = fluorene. ^e Solvent I = 10% Me_2SO -90% water. ^f Extrapolated from data in Wells (1979).

Values of $\log \gamma_{C^-}^{\text{II}}$ with I = water and II = 90% Me₂SO–10% water ($\log {}^w\gamma^{90}$), and with I = 50% Me₂SO–50% water and II = 90% Me₂SO ($\log {}^{50}\gamma^{90}$) for representative carbanions are summarized in Table 10. A positive value means the carbanion is less well solvated in Me₂SO than in water while a negative value means the opposite. Inspection of Table 10 confirms the well-known fact that the carbanions with concentrated charge are less stable in Me₂SO (Parker, 1969; Buncel and Wilson, 1977). This leads to $\delta_{C^-} > 0$, since both $\lambda_{\text{res}}^{C^-} - \beta_B$ and $-\log \gamma_{C^-}^{\text{II}}$ are negative. On the other hand, carbanions with a highly dispersed charge are more stable in Me₂SO, leading to $\delta_{C^-} < 0$. These predictions conform to the PNS since a product–destabilizing factor ($\log \gamma_{C^-}^{\text{II}} < 0$) that develops late should increase k_0 .

Equations for the contribution from early desolvation of an anionic base, δ_{B^-} , an amine, δ_N , and the carbon acid, δ_{CH} , or the contribution from the late solvation of a protonated amine, δ_{NH^+} , or the neutral acid BH, δ_{BH} , can be derived in a similar way as for δ_{C^-} . They are shown as (79)–(83). Note that in (79)–(81) logarithms of the transfer activity coefficients are associated with a positive sign since B[−], N and CH are reactants; when the transfer activity coefficient is for a product (C[−], NH⁺, BH), it has a minus sign.

$$\delta_{B^-} \approx (\lambda_{\text{des}}^{B^-} - \beta_B) \log \gamma_{B^-}^{\text{II}} \quad (79)$$

$$\delta_N \approx (\lambda_{\text{des}}^N - \beta_B) \log \gamma_N^{\text{II}} \quad (80)$$

$$\delta_{CH} \approx (\lambda_{\text{des}}^{CH} - \beta_B) \log \gamma_{CH}^{\text{II}} \quad (81)$$

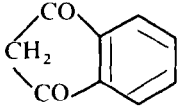
$$\delta_{NH^+} \approx (\lambda_{\text{sol}}^{NH^+} - \beta_B)(-\log \gamma_{NH^+}^{\text{II}}) \quad (82)$$

$$\delta_{BH} \approx (\lambda_{\text{sol}}^{BH} - \beta_B)(-\log \gamma_{BH}^{\text{II}}) \quad (83)$$

$\log \gamma_{B^-}^{\text{II}}$ and $\log \gamma_{NH^+}^{\text{II}}$ values for a representative carboxylate ion and protonated amine respectively are included in Table 10. The positive value of $\log \gamma_{B^-}^{\text{II}}$ reflects mainly the loss of hydrogen-bonding solvation in Me₂SO, while the negative value of $\log \gamma_{NH^+}^{\text{II}}$ indicates the well-known stronger solvating power of Me₂SO for cations and hydrogen-bond donors (Parker, 1969; Buncel and Wilson, 1977; Abraham *et al.*, 1989). Equation (79) predicts $\delta_{B^-} > 0$, while (82) suggests $\delta_{NH^+} < 0$.

The $\log \gamma_{CH}^{\text{II}}$ values for various carbon acids, along with $\log \gamma_{BH}^{\text{II}}$ for AcOH and $\log \gamma_N^{\text{II}}$ for *n*-propylamine, are summarized in Table 11. The value of $\log \gamma_N^{\text{II}}$ is close to zero for the two solvent changes of interest, and hence $\delta_N \approx 0$; $\log \gamma_{CH}^{\text{II}}$ and $\log \gamma_{BH}^{\text{II}}$ are negative, indicating stronger solvation in the more organic solvent. This is expected for CH; in the case of BH, the stronger solvation by Me₂SO may be attributed to its superior hydrogen-bond acceptor ability (Buncel and Wilson, 1977; Abraham *et al.*, 1989). The negative values of $\log \gamma_{CH}^{\text{II}}$ and $\log \gamma_{BH}^{\text{II}}$ lead to $\delta_{CH} < 0$ and $\delta_{BH} < 0$.

Table 11 Transfer activity coefficients for the transfer of neutral molecules from water to 90% Me₂SO–10% water (log ^wγ⁹⁰) and from 50% Me₂SO–50% water to 90% Me₂SO–10% water (log ⁵⁰γ⁹⁰).

Compound	log ^w γ ⁹⁰	log ⁵⁰ γ ⁹⁰	Ref.
CH ₃ NO ₂	−0.87	−0.77	^a
PhCH ₂ NO ₂	−2.86	−1.75	^a
CH ₂ (COCH ₃) ₂	−0.22	−0.43	^a
	−1.67 ^e	−1.21	^a
2-NO ₂ -4-Cl-C ₆ H ₃ CH ₂ CN	−2.73	−1.88	^b
2,4-(NO ₂) ₂ -C ₆ H ₃ CH ₂ CN	−2.28	−1.54	^b
9-COOMe-Fl ^d	−4.14 ^e	−2.24	^a
9-CN-Fl ^d	−3.88	−2.24	^a
AcOH	ca−1.50 (−1.93) ^e	−1.44	^c
CH ₃ CH ₂ CH ₂ NH ₂	ca−0.09 (−0.03) ^e	ca 0.26	^c

^a Bernasconi and Bunnell (1988). ^b Gandler and Bernasconi (1991). ^c Bernasconi (1985). ^d Fl = fluorene. ^e Solvent I = 10% Me₂SO–90% water.

For the overall solvent effect on k_0 , we can now write (84) for the reaction with a carboxylate ion, or (85) for the reaction with an amine. These

$${}^{\text{I}}\delta^{\text{II}}\log k_0(\text{CH}/\text{B}^-) = \delta_{\text{C}^-} + \delta_{\text{B}^-} + \delta_{\text{CH}} + \delta_{\text{BH}} + \delta_{\text{TS}(\text{B})} \quad (84)$$

$${}^{\text{I}}\delta^{\text{II}}\log k_0(\text{CH}/\text{N}) = \delta_{\text{C}^-} + \delta_{\text{NH}^+} + \delta_{\text{CH}} + \delta_{\text{N}} + \delta_{\text{TS}(\text{N})} \quad (85)$$

equations include an additional term, $\delta_{\text{TS}(\text{B})}$ in (84) and $\delta_{\text{TS}(\text{N})}$ in (85),⁶ which accounts for possible effects not related to late solvation/early desolvation of the various parts of the transition state and whose origin will be discussed below.

Equations (84) and (85) differ somewhat from similar expressions proposed earlier (Bernasconi, 1987; Bernasconi and Terrier, 1987). In the earlier treatment, ${}^{\text{I}}\delta^{\text{II}}\log k_0(\text{CH}/\text{B}^-)$ was expressed as $\delta_{\text{C}^-} + \delta_{\text{B}^-} + \delta_{\text{SR}}$ and ${}^{\text{I}}\delta^{\text{II}}\log k_0(\text{CH}/\text{N})$ as $\delta_{\text{C}^-} + \delta_{\text{NH}^+} + \delta_{\text{SR}}$, i.e. $\delta_{\text{CH}} + \delta_{\text{BH}}$ (84) or $\delta_{\text{CH}} + \delta_{\text{N}}$ (85) were not explicitly shown but included in a δ_{SR} term that corresponds to

⁶ The subscripts TS(B) and TS(N) stand for transition-state solvation in the oxyanion (B[−]) and amine (N) reactions.

$\delta_{\text{TS(B)}} + \delta_{\text{CH}} + \delta_{\text{BH}}$ or $\delta_{\text{TS(N)}} + \delta_{\text{CH}} + \delta_{\text{N}}$ respectively. Equations (84) and (85) allow a more detailed quantitative treatment, which is discussed in the next section.

Equations (84) and (85) account quite satisfactorily for the solvent effects observed for the reactions summarized in Table 12, at least qualitatively. Three main points can be made regarding these data.

- (1) $^1\delta^{\text{H}}\log k_0(\text{CH/B}^-)$ and $^1\delta^{\text{H}}\log k_0(\text{CH/N})$ are largest (positive) for reactions leading to carbanions with large positive values of $\log \gamma_{\text{C}^-}^{\text{H}}$, and becomes small or even slightly negative when $\log \gamma_{\text{C}^-}^{\text{H}} \approx 0$ or < 0 , respectively. This reflects the dependence of the δ_{C^-} term in (84) and (85).
- (2) We find that the $^1\delta^{\text{H}}\log k_0(\text{CH/B}^-) > ^1\delta^{\text{H}}\log k_0(\text{CH/N})$ in all reported cases. This reflects the fact that $\delta_{\text{B}^-} + \delta_{\text{BH}} > 0$ in (84) while $\delta_{\text{NH}^+} + \delta_{\text{N}} < 0$ in (85).
- (3) In the reactions of 9-X-fluorenes and 2-NO₂-4-X-phenylacetonitriles, the combination of strongly negative values of δ_{C^-} and δ_{CH} with a negative δ_{NH^+} should add up to a substantial decrease in k_0 in 90% Me₂SO. The fact that k_0 depends little on the solvent suggests that a positive $\delta_{\text{TS(N)}}$ term contributes significantly to $^1\delta^{\text{H}}\log k_0(\text{CH/N})$.

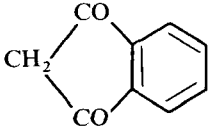
One factor that contributes to $\delta_{\text{TS(N)}}$ must be the equilibrium solvation of the transition state, a potentially important contribution that originates in the electronic polarization of the solvent discussed earlier and that forms the basis of "classical" solvent effects. For a transition state with a well-dispersed charge, as in reactions leading to fluorenyl ions, Me₂SO provides better stabilization than water, and should lead to a positive $\delta_{\text{TS(N)}}$ -term.

Another factor suggested previously (Bernasconi and Terrier, 1987) is a dynamic solvent effect of the "second kind", which reduces the transmission coefficient κ in the Eyring equation (Kurz and Kurz, 1985), as discussed earlier. If the reduction of κ were stronger in water than in Me₂SO, this would contribute to a positive $\delta_{\text{TS(N)}}$ -term. However, the quantitative analysis discussed in the next section suggests that this latter effect is probably quite small and perhaps negligible. Thus $\delta_{\text{TS(N)}}$ and, by analogy, $\delta_{\text{TS(B)}}$ must refer mainly to classical solvent effects.

QUANTITATIVE TREATMENT OF SOLVENT EFFECTS

In this section, we estimate approximate values for δ_{C^-} , δ_{NH^+} , δ_{B^-} , δ_{N} , δ_{BH} , δ_{CH} , $\delta_{\text{TS(N)}}$ and $\delta_{\text{TS(B)}}$ in (84) and (85) after introducing a few assumptions. The first assumption is that for a given carbon acid, δ_{C^-} and δ_{CH} are independent

Table 12 Solvent effects on the intrinsic rate constants of the reaction of carbon acids with $B^- = RCOO^-$, $N =$ primary amines and $N =$ piperidine/morpholine.

CH-Acid	Solvent		$^1\delta^{II}\log k_0(CH/B^-)$ $B^- = RCOO^-$	$^1\delta^{II}\log k_0(CH/N)$ $N = RNH_2$	$^1\delta^{II}\log k_0(CH/N)$ $N = \text{pip}/\text{mor}$	Ref.
	I	II				
CH_3NO_2	H_2O	90% Me_2SO			3.65	^a
	50% Me_2SO	90% Me_2SO			2.33	^a
$PhCH_2NO_2$	H_2O	Me_2SO	<i>ca</i> 4.9			^{b,c}
	H_2O	90% Me_2SO	3.98		2.97	^a
	50% Me_2SO	90% Me_2SO			2.00	^a
$CH_2(COCH_3)_2$	H_2O	90% Me_2SO	<i>ca</i> 2.13	1.01	1.04	^d
	50% Me_2SO	90% Me_2SO	<i>ca</i> 1.47	0.85	0.89	^d
	10% Me_2SO	90% Me_2SO	1.89	0.70	0.88	^e
	50% Me_2SO	90% Me_2SO	1.35	0.53	0.72	^e
2- NO_2 -4-Cl- $C_6H_3CH_2CN$	50% Me_2SO	90% Me_2SO			-0.02	^f
2,4-(NO_2) ₂ - $C_6H_3CH_2CN$	H_2O	90% Me_2SO			-0.28	^f
	50% Me_2SO	90% Me_2SO			-0.18	^f
9-COOMe-Fl ^h	50% Me_2SO	90% Me_2SO		0.25		^g
9-CN-Fl ^h	10% Me_2SO	90% Me_2SO		-0.05		^g
	50% Me_2SO	90% Me_2SO		-0.19		^g

^a Bernasconi *et al.* (1988b). ^b Bordwell and Boyle (1972). ^c Keeffe *et al.* (1979). ^d Bernasconi and Bunnell (1985). ^e Bernasconi and Paschalis (1986).

^f Bernasconi and Wenzel (1992). ^g Bernasconi and Terrier (1987). ^h Fl = fluorene.

of the base (B^- or N) used. The second is that $|\lambda_{des}^{B^-} - \beta_B| = |\lambda_{des}^N - \beta_B| = |\lambda_{sol}^{BH^+} - \beta_B| = |\lambda_{sol}^{NH^+} - \beta_B|$ and that these differences are independent of the carbon acid. Subtracting (85) from (84) yields (86).

$$\begin{aligned} {}^1\Delta^H \log k_0 &= {}^1\delta^H \log k_0(CH/B^-) - {}^1\delta^H \log k_0(CH/N) \\ &= \delta_{B^-} + \delta_{BH} - \delta_{NH^+} - \delta_N + \delta_{TS(B)} - \delta_{TS(N)} \end{aligned} \quad (86)$$

$${}^1\Delta^H \log k_0 = (\lambda_{des}^{B^-} - \beta_B)(\log \gamma_{B^-}^{II} + \log \gamma_{BH}^{II} - \log \gamma_{NH^+}^{II} - \log \gamma_N^{II}) + \delta_{TS(B)} - \delta_{TS(N)} \quad (87)$$

With the second assumption above, (86) may be recast into the form (87). Even though $\delta_{TS(B)}$ and $\delta_{TS(N)}$ probably depend on the carbon acid, their *difference* is assumed to be constant. Hence a plot of ${}^1\Delta^H \log k_0$ versus $(\log \gamma_{B^-}^{II} + \log \gamma_{BH}^{II} - \log \gamma_{NH^+}^{II} - \log \gamma_N^{II})$ should yield a straight line of slope $\lambda_{des}^{B^-} - \beta_B$ and intercept $\delta_{TS(B)} - \delta_{TS(N)}$. Figure 14 shows such a plot for the reactions of $PhCH_2NO_2$, acetylacetone and 1,3-indandione, the only examples for which data with both types of bases are available. The plot yields an approximate straight line, an encouraging fact that suggests that our assumptions may not be far off the mark. From the slope and intercept, we obtain $\lambda_{des}^{B^-} - \beta_B \approx 0.09$ and $\delta_{TS(B)} - \delta_{TS(N)} \approx 0.36$, respectively. In conjunction with (79), (80), (82) and (83), δ_{B^-} , δ_{BH} , δ_{NH^+} and δ_N can now be calculated for different solvent changes. They are summarized in Table 13.

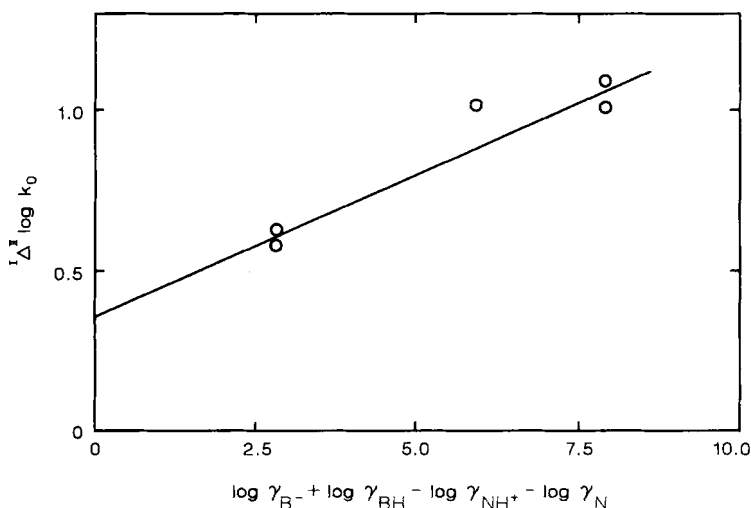


Fig. 14 Plot according to (87), giving a slope $\lambda_{des}^{B^-} - \beta_B$ and an intercept $\delta_{TS(B)} - \delta_{TS(N)}$.

Table 13 Estimates for δ_B^- , δ_{BH} , δ_{NH}^+ and δ_N .^a

Solvent change	δ_B^-	δ_{BH}	δ_{NH}^+	δ_N
H ₂ O→90% Me ₂ SO	0.59	-0.14	-0.25	-0.01
10% Me ₂ SO→90% Me ₂ SO	0.48	-0.17	-0.22	0
50% Me ₂ SO→90% Me ₂ SO	0.31	-0.13	-0.09	0.02

^a Calculated from (79), (80), and (83), respectively, with $\lambda_{des}^{B-} - \beta_B = -(\lambda_{sol}^{BH} - \beta_B) = -(\lambda_{sol}^{NH^+} - \beta_B) = \lambda_{des}^N - \beta_B = 0.09$.

In order to estimate δ_{C^-} and δ_{CH} , assumptions must be made regarding $\lambda_{sol}^{C^-} - \beta_B$ and $\lambda_{des}^{CH} - \beta_B$. For $\lambda_{des}^{CH} - \beta_B$, we set a value of 0.09, the same as for $\lambda_{des}^{B-} - \beta_B = \lambda_{des}^N - \beta_B$. For $|\lambda_{sol}^{C^-} - \beta_B|$, a much larger value needs to be chosen since, as argued earlier, the lag in the solvation is on top of the lag in the charge delocalization. We shall assume that the two lags are additive, and hence $\lambda_{sol}^{C^-} - \beta_B = \lambda_{res'} - \beta_B - 0.09$. Approximating $\lambda_{res'}$ [see (64)] by λ_{res} [see (29)], this yields $\lambda_{sol}^{C^-} - \beta_B \approx (\beta_B)^3 - \beta_B - 0.09$ from (38) and $\approx (\beta_B)^2 - \beta_B - 0.09$ from (34). Values of δ_{CH} and δ_{C^-} are summarized for eight carbon acids in Table 14; the table also includes $\delta_{TS(N)}$ values, calculated from (88).

$$\delta_{TS(N)} = {}^I\delta_{\log}^{\text{II}} \log k_0(\text{CH/N}) - \delta_{C^-} - \delta_{CH} - \delta_{NH^+} - \delta_N \quad (88)$$

Before commenting on the various δ_{C^-} , δ_{CH} , δ_{NH^+} , δ_N and $\delta_{TS(N)}$ terms reported in Tables 13 and 14, a word of caution is in order. All these terms are associated with considerable uncertainties because they depend on our estimates of $\lambda_{sol}^{C^-} - \beta_B$, $\lambda_{des}^{CH} - \beta_B$, etc., whose potential errors are unknown. The term with the largest uncertainty is $\delta_{TS(N)}$, since it contains the cumulative errors of δ_{C^-} , δ_{CH} , δ_{NH^+} and δ_N . Despite these caveats, a few conclusions may be drawn that confirm and expand on those made on p. 193.

- (1) δ_N is virtually zero because the small $\log {}^I\gamma_{\text{N}}^{\text{II}}$ -values are combined with a small $\lambda_{des}^N - \beta_B$.
- (2) Both δ_{CH} and δ_{NH^+} tend to depress k_0 (CH/N) in Me₂SO, but the effect is modest in most cases. For I = water or 10% Me₂SO, and II = 90% Me₂SO, $\delta_{CH} + \delta_{NH^+}$ varies from -0.27 (acetylacetone) to -0.60 (9-cyanofluorene); for I = 50% Me₂SO and II = 90% Me₂SO, it varies from -0.13 (acetylacetone) to -0.29 (9-cyanofluorene). The relative smallness of δ_{CH} and δ_{NH^+} , irrespective of the size of $\log {}^I\gamma_{\text{CH}}^{\text{II}}$ or $\log {}^I\gamma_{\text{NH}^+}^{\text{II}}$, is a consequence of the small $|\lambda_{des}^{CH} - \beta_B|$ and $|\lambda_{sol}^{NH^+} - \beta_B|$ values (0.09).

Table 14 Estimates for δ_{C^-} , δ_{CH} and $\delta_{\text{TS(N)}}$ for various carbon acids.

CH-Acid	H ₂ O → 90% Me ₂ SO					50% Me ₂ SO → 90% Me ₂ SO				
	β_{B}	$\lambda_{\text{sol}}^{\text{C}^-} - \beta_{\text{B}}$	$\delta_{\text{C}^-}^a$	δ_{CH}^b	$\delta_{\text{TS(N)}}^c$	β_{B}	$\lambda_{\text{sol}}^{\text{C}^-} - \beta_{\text{B}}$	$\delta_{\text{C}^-}^a$	δ_{CH}^b	$\delta_{\text{TS(N)}}^c$
CH ₃ NO ₂	0.64	−0.47	3.15	−0.08	0.84	0.66	−0.46	1.76	−0.07	0.71
PhCH ₂ NO ₂	0.59	−0.47	1.91	−0.26	1.57	0.61	−0.47	0.99	−0.16	1.24
CH ₂ (COCH ₃) ₂	0.44	−0.34	1.71	−0.02	−0.39	0.47	−0.34	0.91	−0.04	0.09
1,3-Indandione	0.44	−0.34	0.61	−0.15	0.67	0.44	−0.34	0.47	−0.11	0.43
2-NO ₂ -4-Cl-C ₆ H ₃ CH ₂ CN				−0.26		0.62	−0.47	−0.94	−0.17	1.16
2,4-(NO ₂) ₂ -C ₆ H ₃ CH ₂ CN	0.48	−0.46	−1.49	−0.21	1.68	0.52	−0.47	−1.17	−0.14	1.20
9-COOMe-Fl ^d				−0.37		0.55	−0.47	−1.00	−0.20	1.52
9-CN-Fl ^d	0.56	−0.47	−1.89	−0.35	2.45	0.53	−0.47	−1.25	−0.20	1.33

^a Calculated from (78) with $\lambda_{\text{sol}}^{\text{C}^-} - \beta_{\text{B}} = (\beta_{\text{B}})^3 - \beta_{\text{B}} - 0.09$ or $(\beta_{\text{B}})^2 - \beta_{\text{B}} - 0.09$ (see pp. 160–164). ^b Calculated from (81) with $\lambda_{\text{des}}^{\text{CH}} - \beta_{\text{B}} = 0.09$.

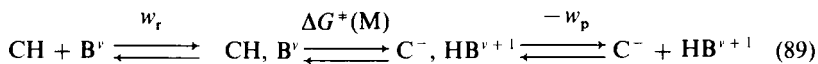
^c Calculated from (88). ^d Fl = fluorene.

- (3) For the nitro-compounds and the diketones, δ_{C}^- is the dominant factor in enhancing k_0 (CH/N) in Me_2SO , except for 1,3-indandione, where $\delta_{\text{TS(N)}}$ contributes about equally. The large δ_{C}^- -values are due to the large $|\lambda_{\text{sol}}^{\text{C}^-} - \beta_{\text{B}}|$, coupled with substantial values of $\log \gamma_{\text{C}}^{\text{II}}$. The $\delta_{\text{TS(N)}}$ -term reinforces the effect of δ_{C}^- except for acetylacetone; the negative value of $\delta_{\text{TS(N)}}$ in this latter case is suspect and warrants a redetermination of some of the experimental parameters.
- (4) For the phenylacetonitriles and the 9-substituted fluorenes, δ_{C}^- and δ_{SN} are of comparable absolute magnitude but unequal sign; hence their effects tend to cancel. This explains the small solvent effect on k_0 (CH/N), since the other factors (δ_{CH} , δ_{NH^+} and δ_{N}) are minor.
- (5) With the exception of the reaction of acetylacetone mentioned above, $\delta_{\text{TS(N)}}$ is always positive and of significant magnitude. This term tends to be higher for systems that lead to carbanions with more dispersed negative charge (phenylacetonitrile and fluorene derivatives), and lower when the carbanion has the charge concentrated on oxygen atoms. PhCH_2NO_2 takes an intermediate position, presumably because the anion is able to disperse some of its negative charge into the phenyl group. These trends are consistent with our conclusion reached on p. 193, according to which a major component of $\delta_{\text{TS(N)}}$ must be due to the preferential equilibrium solvation of the transition state by Me_2SO , an effect that increases in importance for transition states with a more diffuse charge as in the formation of fluorenyl ions.

This conclusion regarding $\delta_{\text{TS(N)}}$ contrasts with one reached earlier (Bernasconi and Terrier, 1987), where a major component of $\delta_{\text{TS(N)}}$ was attributed to a dynamic solvent effect (of the second kind) that reduces the transmission coefficient κ more in water than in Me_2SO . In the earlier work, $\lambda_{\text{sol}}^{\text{C}^-} - \beta_{\text{B}}$ was estimated to be -0.15 , a much less negative value than our current estimates of -0.34 to -0.47 (Table 14). This leads to much smaller δ_{C}^- and hence much larger $\delta_{\text{TS(N)}}$ -values for the nitroalkanes, and much less negative δ_{C}^- and much smaller δ_{SN} -values for the fluorenes. Thus the order of the $\delta_{\text{TS(N)}}$ -values was reversed, with the highest values for the nitroalkanes, and much lower values for the other compounds. Since the reduction of κ by the dynamic solvent effect should increase with increasing charge density (Kurz and Kurz, 1972; Van der Zwan and Hynes 1982), it was concluded that $\delta_{\text{TS(N)}}$ reflects, at least in part, this kind of dynamic solvent effect. The results of the current analysis no longer require the assumption of such a dynamic solvent effect although they do not exclude it. This conclusion is in agreement with a theoretical analysis by Kurz (1989a) that is discussed in detail in the next section.

THE KURZ MODEL

Kurz (1989a) recently proposed a theoretical model that deals with the solvent effects on k_0 . Just as in our approach, a major premise of the model is that non-equilibrium solvation of the transition state makes a significant contribution to the solvent effect, and some of the quantitative predictions made by this model come close to ours. Kurz uses the Marcus (1956, 1957, 1964, 1968) relationship as the basis of his model. According to Marcus (1968), a proton transfer may be broken down into three steps: the rapid formation of a precursor complex PC, associated with the work term w_r , the actual proton transfer with the activation barrier $\Delta G^*(M)$, and the breakdown, in a post-equilibrium, of the successor complex, as shown in (89).



The observed activation barrier is given by (90), while the observed free energy of reaction is given by (91), with $\Delta G^0(M)$ referring to the free energy of the reaction $\text{CH} \cdots \text{B}^\nu \rightleftharpoons \text{C}^- \cdots \text{HB}^{\nu+1}$.⁷

$$\Delta G^* = w_r + \Delta G^*(M) \quad (90)$$

$$\Delta G_{\text{obsd}}^0 = w_r + \Delta G^0(M) - w_p \quad (91)$$

The intrinsic barrier, $\Delta G_0^*(M)$ as defined by Marcus, is equal to $\Delta G^*(M)$ when $\Delta G^0(M) = 0$. For the systems modelled by Kurz where $\text{B}^\nu = \text{RCOO}^-$, and C^- has a similar charge distribution as RCOO^- (e.g. nitronate or enolate ions), the approximation $w_r = w_p$ is reasonable, so that $\Delta G^0(M)$ becomes equal to ΔG_{obsd}^0 . Even with this approximation, there remains a difference between the Marcus definition of the intrinsic barrier, $\Delta G_0^*(M)$, and the operational one that we have used and defined as ΔG_{obsd}^* when $\Delta G_{\text{obsd}}^0 = 0$. The relationship between the two is given by (92).

$$\Delta G_{\text{obsd}}^* = w_r + \Delta G_0^*(M) \quad (92)$$

In the w_r process, both initial and final states are assumed to have equilibrated solvation, i.e. w_r contains no contribution from non-synchronous solvation/desolvation effects. These latter only affect the conversion of the precursor complex into the transition state, and hence are all contained in $\Delta G_0^*(M)$. By breaking down $\Delta G_0^*(M)$ into a component for "internal" terms, $\Delta G_{0\text{int}}^*(M)$, one for equilibrium solvation, $\Delta G_{0\text{eq}}^*(M)$, and one for non-

⁷ (M) in $\Delta G^*(M)$, $\Delta G^0(M)$ and $\Delta G_0^*(M)$ refers to Marcus; Kurz (1989a) uses the symbols ΔG_{tr}^* , ΔG_{tr}^0 and ΔG_0^* respectively.

$$\Delta G_0^+(\text{obsd}) = w_r + \Delta G_{0\text{int}}^+(\text{M}) + \Delta G_{0\text{eq}}^+(\text{M}) + \Delta G_{0\text{non-eq}}^+(\text{M}) \quad (93)$$

equilibrium solvation, $\Delta G_{0\text{non-eq}}^+(\text{M})$, (92) becomes (93). The relationship between the solvent effect on the intrinsic rate constant, ${}^1\delta^{\text{II}}\log k_0$, and the Marcus parameters is then given by (94). Note that $\Delta G_{0\text{int}}^+(\text{M})$ is solvent-independent (Kurz, 1989a) and hence cancels in (94).

$$-2.203RT^{\text{I}}\delta^{\text{II}}\log k_0 = {}^1\delta^{\text{II}}\Delta G_0^+(\text{obsd}) = {}^1\delta^{\text{II}}w_r + {}^1\delta^{\text{II}}\Delta G_{0\text{eq}}^+(\text{M}) + {}^1\delta^{\text{II}}\Delta G_{0\text{non-eq}}^+(\text{M}) \quad (94)$$

The $\Delta G_{0\text{eq}}^+(\text{M})$ term reflects primarily the rapidly relaxing electronic components of solvent polarization. This polarization is fast enough to keep pace with the changes in charge distribution during formation of the transition state, and hence is in equilibrium with this internal charge distribution. In contrast, the $\Delta G_{0\text{non-eq}}^+(\text{M})$ term reflects the slower orientational component of solvent polarization, which solvates the charges by rotational motion of the solvent molecules. Since this rotation is too slow to keep pace with changes in internal charge distribution, the resulting solvation is not in equilibrium with internal charge distribution.

To estimate w_r , $\Delta G_{0\text{eq}}^+(\text{M})$ and $\Delta G_{0\text{non-eq}}^+(\text{M})$, Kurz modelled the reactants, precursor complex and transition state as charges imbedded in spherical (reactants) or ellipsoidal cavities (PC and TS) in dielectric continua, as shown in Fig. 15 for the precursor complex and the transition state. The values of w_r , $\Delta G_{0\text{eq}}^+(\text{M})$ and $\Delta G_{0\text{non-eq}}^+(\text{M})$ depend on cavity size (R_{PC} and R_{TS} respectively) and the extent of solvational imbalance at the transition state. The dependence of $\Delta G_{0\text{non-eq}}^+(\text{M})$ on this imbalance was formulated as the product of a Hooke's law force constant F_s and the square of the displacement from charge/solvation equilibrium (Kurz and Kurz, 1972, 1985), as shown in (95) and (96); z_{TS} , assumed to be -0.5 , is the fraction of

$$\Delta G_{0\text{non-eq}}^+(\text{M}) = \frac{1}{2} F_s (m - z_{\text{TS}})^2 \quad (95)$$

$${}^1\delta^{\text{II}}\Delta G_{0\text{non-eq}}^+(\text{M}) = \frac{1}{2} (F_s^{\text{II}} - F_s^{\text{I}})(m - z_{\text{TS}})^2 \quad (96)$$

an electronic charge that is located at each of the foci of the transition state ellipsoid (Fig. 15), while m is the value of the hypothetical fraction of the electronic charge at each focus that would be in equilibrium with the real, slowly relaxing component of the solvent polarization. The magnitude of the difference between the real and hypothetical charges, $|m - z_{\text{TS}}|$ thus measures the extent of charge/solvation disequilibrium.

The results of the calculations are summarized in Table 15 for water, Me_2SO and acetonitrile. According to Kurz, the "best guesses" for R_{PC} and R_{TS} are 4.0 and 2.4 Å respectively (the first row in Table 15). We now

estimate some solvent effects based on these best guesses. For $I = \text{H}_2\text{O} \rightarrow \text{II} = \text{Me}_2\text{SO}$, we obtain ${}^1\delta''w_r$ between -1.89 and $-2.92 \text{ kcal mol}^{-1}$ and ${}^1\delta''\Delta G_{0\text{ eq}}^*(M) = -0.97 \text{ kcal mol}^{-1}$, for a total contribution to ${}^1\delta''\Delta G_{0\text{ obsd}}^*$ of -2.86 to $-3.89 \text{ kcal mol}^{-1}$ by equilibrium solvation/desolvation effects. ${}^1\delta''\Delta G_{0\text{ non-eq}}^*(M)$ is given by $-54.4(m - z_{\text{TS}})^2$, which yields ${}^1\delta''\Delta G_{0\text{ non-eq}}^*(M) = -0.54, -1.22, -2.18, -3.40$ and $-4.90 \text{ kcal mol}^{-1}$ for $|m - z_{\text{TS}}| = 0.10, 0.15, 0.20, 0.25$ and 0.30 respectively.

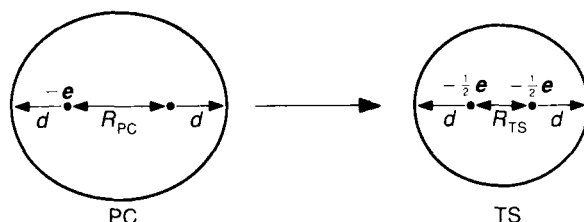


Fig. 15 Model for the conversion of the precursor complex (PC) to the transition state (TS). Proportions of the ellipsoids correspond to the best guess values of $R_{\text{PC}} = 4.0 \text{ \AA}$, $R_{\text{TS}} = 2.4 \text{ \AA}$ and $d = 2.19 \text{ \AA}$. Reprinted from Kurz (1989a) with permission from the American Chemical Society.

How do these estimates compare with the PNS terms of (84) reported in Tables 13 and 14? In (84), the $\delta_{\text{TS(B)}}$ term contains the contribution from equilibrium solvation of reactants and transition state, and hence corresponds to ${}^1\delta''w_r + {}^1\delta''\Delta G_{0\text{ eq}}^*(M)$ in (94); the sum of $\delta_{\text{C}^-} + \delta_{\text{B}^-} + \delta_{\text{CH}} + \delta_{\text{BH}}$ in (85) includes all non-equilibrium solvation/desolvation effects and is the counterpart of ${}^1\delta''\Delta G_{0\text{ non-eq}}^*(M)$ in (94). Hence we obtain (97) and (98).

$$-2.303RT \delta_{\text{TS(B)}} \approx {}^1\delta''w_r + {}^1\delta''\Delta G_{0\text{ eq}}^*(M) \quad (97)$$

$$-2.303RT(\delta_{\text{C}^-} + \delta_{\text{B}^-} + \delta_{\text{CH}} + \delta_{\text{BH}}) \approx {}^1\delta''\Delta G_{0\text{ non-eq}}^*(M) \quad (98)$$

From Table 14, we see that $\delta_{\text{TS(N)}}$ for the nitro-compounds and diketones, the compounds modelled by Kurz, range from 0.67 to 1.57 for $I = \text{H}_2\text{O}$, $\text{II} = 90\% \text{ Me}_2\text{SO}$ (excluding acetylacetone). Since $\delta_{\text{TS(B)}} = \delta_{\text{TS(N)}} + 0.36$, $\delta_{\text{TS(B)}}$ ranges from 1.03 to 1.93, which translates into a range from -1.40 to $-2.62 \text{ kcal mol}^{-1}$ for ${}^1\delta''w_r + {}^1\delta''\Delta G_{0\text{ eq}}^*(M)$. This is very close to the range from -1.89 to $-2.92 \text{ kcal mol}^{-1}$ obtained from the Kurz model for $I = \text{H}_2\text{O}$ and $\text{II} = \text{Me}_2\text{SO}$, and would probably be even closer if our solvent II were pure Me_2SO .

For $\delta_{\text{C}^-} + \delta_{\text{B}^-} + \delta_{\text{CH}} + \delta_{\text{BH}}$, we have 0.91, 2.11 and 3.52 for 1,3-indandione, PhCH_2NO_2 and CH_3NO_2 respectively, which corresponds to ${}^1\delta''\Delta G_{0\text{ non-eq}}^*(M)$ of $-1.24, -2.87$ and $-4.79 \text{ kcal mol}^{-1}$ respectively. These

Table 15 Values of w_r , $\Delta G_{0\text{ eq}}^{\ddagger}(\text{M})$ and F_s in different solvents, calculated for different sizes of the precursor complex and transition state.^a

$R_{\text{PC}}/\text{\AA}$	$R_{\text{TS}}/\text{\AA}$	H_2O			Me_2SO			CH_3CN		
		w_r	$\Delta G_{0\text{ eq}}^{\ddagger}(\text{M})$	F_s	w_r	$\Delta G_{0\text{ eq}}^{\ddagger}(\text{M})$	F_s	w_r	$\Delta G_{0\text{ eq}}^{\ddagger}(\text{M})$	F_s
		kcal mol ⁻¹	kcal mol ⁻¹	kcal mol ⁻¹	kcal mol ⁻¹	kcal mol ⁻¹	kcal mol ⁻¹	kcal mol ⁻¹	kcal mol ⁻¹	kcal mol ⁻¹
4.0	2.4	^b	1.58	226.2	^c	0.61	117.4	^d	0.48	143.6
2.4	2.4	^b	3.21	226.2	^c	1.88	117.4	^d	1.66	143.6
4.38	2.4	10.47	1.34	226.2	7.55	0.41	117.4	6.90	0.30	143.6
1.23	1.23	6.17	1.41	264.8	4.28	1.21	137.4	3.88	0.72	168.2
2.4	1.23	^b	-0.99	264.8	^c	-0.96	137.4	^d	-0.91	168.2

^a Kurz (1989a). ^b 10.47 > w_r > 6.17. ^c 7.55 > w_r > 4.28. ^d 6.90 > w_r > 3.88.

values are within the range predicted by the Kurz model for values of $|m - z_{TS}|$ between 0.15 and 0.30

The good agreement between the predictions made by the Kurz model and our dissection of the experimental data into PNS-effects is perhaps surprising because there are some important differences in the two approaches. They can be briefly summarized as follows.

- (1) The charge/solvation disequilibrium is measured differently: $\lambda_{sol}^{C^-} - \beta_B$, $\lambda_{des}^B - \beta_B$ etc. in the PNS approach; $m - z_{TS}$ in the Kurz model. The former are fractions of free energy changes; for example, $\lambda_{des}^B - \beta_B = 0.09$ means that the non-synchronous desolvation of B^- increases $\Delta G_0^\ddagger$ (obsd) by 0.09 times the energy of transfer of B^- from I to II. On the other hand, $m - z_{TS}$ measures the difference between the real charge in the foci of the transition state cavity and the charge me that would be in equilibrium with the prevailing solvation shell around the transition state.
- (2) In the PNS equations, the increase in the intrinsic barrier caused by non-equilibrium solvation/desolvation is directly proportional to the disequilibrium parameters, but proportional to the *square* of $m - z_{TS}$ in the Kurz model.
- (3) Kurz separates equilibrium solvation into a work term and an activation term, while the PNS treatment lumps them together. However, this has no effect on the numerical analysis.
- (4) Kurz makes a clear distinction between the rapidly and slowly relaxing components of solvent polarization, which identifies the source of the various terms in (94) and provides a physical explanation for the solvational disequilibrium of the transition state, i.e. slow rotational reorientation of the solvent molecules. This distinction is not made explicitly in the PNS approach but it is implied in the separation of the $\delta_{TS(B)}$ and $\delta_{TS(N)}$ terms from the other terms in (84) and (85).

Which approach is "better"? This is probably the wrong question to ask. Both approaches have strengths and weaknesses, but they essentially complement each other. The Kurz model is well grounded in electrostatic theory and provides a clear physical picture of the reasons for the non-synchronous solvation/desolvation effects. On the other hand, in its current form, it is restricted to reactions that lead to carbanions with a highly concentrated charge. The PNS approach is not subject to this restriction and also allows for the important assumption that the solvation disequilibrium on the carbanion side of the transition state is larger than on the base side

($|\lambda_{\text{sol}}^{\text{C}^-} - \beta_{\text{B}}| > |\lambda_{\text{des}}^{\text{B}^-} - \beta_{\text{B}}|$), and that neutral reactants and products are also subject to non-synchronous solvation/desolvation effects, an aspect ignored in the Kurz model.

How do these two approaches compare with respect to their predictive capabilities? Kurz suggested that his model could be tested by comparing k_0 in acetonitrile with k_0 in Me_2SO . This is because when $\text{I} = \text{Me}_2\text{SO}$ and $\text{II} = \text{CH}_3\text{CN}$, ${}^1\delta''\Delta G_{0\text{ non-eq}}^*(\text{M})$ has a different sign from ${}^1\delta''w_r + {}^1\delta''\Delta G_{0\text{ eq}}^*(\text{M})$. Hence, if $|{}^1\delta''\Delta G_{0\text{ non-eq}}^*(\text{M})| > |{}^1\delta''w_r + {}^1\delta''\Delta G_{0\text{ eq}}^*(\text{M})|$, the direction of the solvent effect would be determined by the non-equilibrium term and directly prove the existence of such non-equilibrium solvation; such unequivocal proof is not possible when $\text{I} = \text{H}_2\text{O}$ and $\text{II} = \text{Me}_2\text{SO}$ because all terms in (94) have the same sign. From the first row in Table 15 and $\text{I} = \text{Me}_2\text{SO}$, $\text{II} = \text{CH}_3\text{CN}$, we obtain a ${}^1\delta''w_r$ between -0.40 and $-0.65 \text{ kcal mol}^{-1}$ and ${}^1\delta''\Delta G_{0\text{ eq}}^*(\text{M}) = -0.13 \text{ kcal mol}^{-1}$, for a total contribution of between -0.53 and $-0.78 \text{ kcal mol}^{-1}$ coming from equilibrium solvation effects. For the non-equilibrium solvation, we have ${}^1\delta''\Delta G_{0\text{ non-eq}}^*(\text{M}) = 26.2 (m - z_{\text{TS}})^2$ which yields $0.26, 0.59, 1.05, 1.64$ and $2.36 \text{ kcal mol}^{-1}$ for $|m - z_{\text{TS}}| = 0.10, 0.15, 0.20, 0.25$ and 0.30 respectively. These calculations show that for $|m - z_{\text{TS}}| \geq 0.10$ – 0.15 , the contribution from the non-equilibrium term becomes dominant and makes ${}^1\delta''\Delta G_0^*(\text{obsd}) > 0$.

Values of $|m - z_{\text{TS}}|$ may be estimated from data on the reactions in water and Me_2SO . For example, with PhCH_2NO_2 , ${}^1\delta''\Delta G_{0\text{ non-eq}}^*(\text{M})$ calculated from (98) is $-2.87 \text{ kcal mol}^{-1}$ which corresponds to a $|m - z_{\text{TS}}|$ -value of between 0.20 and 0.25 . Using the same $|m - z_{\text{TS}}|$ for the comparison between CH_3CN and Me_2SO suggests ${}^1\delta''\Delta G_{0\text{ non-eq}}^*(\text{M})$ is between 1.05 and $1.64 \text{ kcal mol}^{-1}$, and ${}^1\delta''\Delta G_0^*(\text{obsd})$ between 0.27 and $1.11 \text{ kcal mol}^{-1}$ or ${}^1\delta''\log k_0$ of -0.20 to -0.82 .

A recent determination of k_0 for the reactions of 3-nitro- and 4-nitro-phenylnitromethane with ArCOO^- in Me_2SO and CH_3CN (Gandler and Bernasconi, 1991) yielded ${}^1\delta''\log k_0 = 1.43$ and 1.70 respectively, a result that is quite different from the predicted one, since it shows an increase rather than decrease of k_0 in CH_3CN . This result suggests that the combined uncertainties in the F_s -values of the two solvents are about as large as, or even larger than, their difference, which is not too surprising since F_s is not much different in CH_3CN than in Me_2SO . This problem does not exist when Me_2SO and water are compared, since here the difference between the F_s -values is quite large.

An analysis of the ${}^1\delta''\log k_0$ -values ($\text{I} = \text{Me}_2\text{SO}$, $\text{II} = \text{CH}_3\text{CN}$) according to (84) is presented in Table 16. It suggests that, in contrast with the Kurz model, the terms for the non-equilibrium solvation ($\delta_{\text{C}^-} + \delta_{\text{B}^-} + \delta_{\text{CH}} + \delta_{\text{BH}}$) and the contribution from equilibrium solvation ($\delta_{\text{TS(B)}}$) have the same sign but that the latter is dominant. A point of particular interest is that

δ_{BH} is the largest non-equilibrium term for the 3-nitro- and the second largest for the 4-nitro-phenylnitromethane reaction. This is because $\log {}^{\text{I,II}}\gamma_{\text{BH}}$ is quite large, owing to the loss of the strong hydrogen bonding of RCOOH to Me_2SO (Buncel and Wilson, 1977; Abraham *et al.*, 1989) when the solvent is changed to CH_3CN . The neglect of this contribution to ${}^{\text{I}}\delta^{\text{II}}\Delta G_{0 \text{ non-eq}}^{\ddagger}(\text{M})$ may, in part, be responsible for the wrong sign in the solvent effect predicted by the Kurz model.

Table 16 Solvent-effect parameters for the reactions of 3-nitro- and 4-nitro-phenylnitromethane with benzoate ions: I = Me_2SO , II = MeCN , 20°C .^a

	3- NO_2 - $\text{C}_6\text{H}_4\text{CH}_2\text{NO}_2$	4- NO_2 - $\text{C}_6\text{H}_4\text{CH}_2\text{NO}_2$
$\log {}^{\text{I,II}}\gamma_{\text{C}}^-$	0.28	0.66
$\log {}^{\text{I,II}}\gamma_{\text{CH}}$	0.18	0.16
$\log {}^{\text{I,II}}\gamma_{\text{B}}^-$	-0.25	-0.25
$\log {}^{\text{I,II}}\gamma_{\text{BH}}$	1.90	1.90
β_{B}^b	<i>ca</i> 0.56	<i>ca</i> 0.56
$\lambda_{\text{sol}}^{\text{C}} - \beta_{\text{B}}^c$	-0.47	-0.47
$\lambda_{\text{des}}^{\text{B}} - \beta_{\text{B}}^d$	0.09	0.09
δ_{C}^-	0.13	0.31
δ_{CH}	0.02	0.01
δ_{B}^-	-0.02	-0.02
δ_{BH}	0.17	0.17
${}^{\text{I}}\delta^{\text{II}}\log k_0$	1.45	1.93
$\delta_{\text{TS(B)}}$	1.15	1.46

^a Gandler and Bernasconi (1991). ^b β_{B} from the reaction of 3,5-dinitrophenylnitromethane.

^c $(\beta_{\text{B}})^3 - \beta_{\text{B}} - 0.09$. ^d $\lambda_{\text{des}}^{\text{B}} - \beta_{\text{B}} = \lambda_{\text{des}}^{\text{CH}} - \beta_{\text{B}} = -(\lambda_{\text{sol}}^{\text{BH}} - \beta_{\text{B}})$.

6 Nucleophilic addition to olefins

CORRELATION OF INTRINSIC RATE CONSTANTS IN OLEFIN ADDITIONS AND PROTON TRANSFERS

Over the past several years, kinetic studies of nucleophilic addition reactions of the type shown in (99) have been reported and recently reviewed

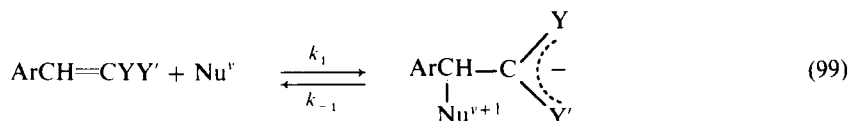


Table 17 Intrinsic rate constants $\log k_0$ for nucleophilic addition of the piperidine/morpholine pair and OH^- to $\text{PhCH}=\text{CYY}'$ and deprotonation of $\text{CH}_2\text{YY}'$ by the piperidine/morpholine pair in 50% Me_2SO –50% water at 20°C .

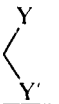
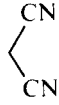
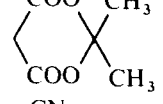
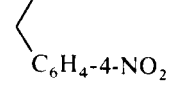
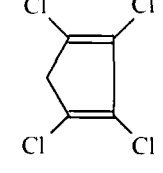
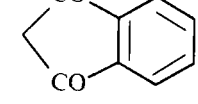
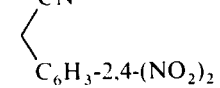
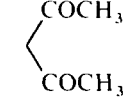
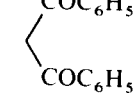
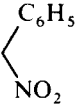
Entry		$\text{PhCH}=\text{CYY}'$ + R_2NH	$\text{PhCH}=\text{CYY}'$ + OH^-	$\text{CH}_2\text{YY}'$ + R_2NH
1		4.94 ^a	<i>ca</i> -0.20 ^b	<i>ca</i> 7.0 ^c
2		4.10 ^d		3.90 ^e
3		<i>ca</i> 3.35 ^f		<i>ca</i> 3.70 ^g
4		3.34 ^h		3.59 ^h
5		4.2 ⁱ	<i>ca</i> -2.05 ^b	3.13 ^j
6		2.65 ^f		2.75 ^g
7		0.30 ^k		2.75 ^l
8		0.08 ⁱ		2.36 ^m
9		2.55 ⁿ	<i>ca</i> -4.03 ^b	0.73 ^o

Table 17 (continued)

Entry		$\text{PhCH}=\text{CYY}' + \text{R}_2\text{NH}$	$\text{PhCH}=\text{CYY}' + \text{OH}^-$	$\text{CH}_2\text{YY}' + \text{R}_2\text{NH}$
10		1.42 ^p		-0.25 ^o

^a Bernasconi *et al.* (1980). ^b Bernasconi *et al.* (1985). ^c In water; Hibbert (1977). ^d Bernasconi and Fornarini (1980). ^e Bernasconi and Oliphant (1992). ^f Bernasconi *et al.* (1983). ^g Bernasconi and Hibdon (1983). ^h Bernasconi and Stronach (1990). ⁱ Bernasconi and Stronach (1991a). ^j Bernasconi and Paschalis (1986). ^k Bernasconi and Kanavarioti (1986). ^l Bernasconi and Bunnell (1985). ^m Bernasconi and Stronach (1991b). ⁿ Bernasconi *et al.* (1986). ^o Bernasconi *et al.* (1988b). ^p Bernasconi and Renfrow (1987).

(Bernasconi, 1989). Typical nucleophiles used are OH^- , H_2O , ArO^- , RS^- , and amines. The most systematic work has been with amine nucleophiles, in particular the piperidine/morpholine pair. Table 17 presents intrinsic rate constants for reactions with OH^- and the piperidine/morpholine pair in 50% Me_2SO –50% water (v/v) at 20°C. The k_0 -values for the amine additions were obtained from Brønsted-type plots of $\log k_1$ versus $\log K_1$ by interpolation or extrapolation to $\log K_1 = 0$, i.e. $\log k_0$ is given by (100),

$$\log k_0 = \log k_1 - \beta_{\text{nuc}}^n \log K_1 \quad (100)$$

with β_{nuc}^n being the slope of these plots. In the case of OH^- addition no β_{nuc}^n is available, and the $\log k_0$ -values were estimated as $\log k_0 \approx \log k_1 - 0.5 \log K_1$, i.e. by arbitrarily assuming $\beta_{\text{nuc}}^n = 0.5$, making these $\log k_0$ -values somewhat uncertain.

Table 17 includes $\log k_0$ -values for the deprotonation of carbon acids of the type $\text{CH}_2\text{YY}'$ by the piperidine/morpholine pair in the same solvent. The most noteworthy feature of Table 17 is that, with a few exceptions, k_0 for the addition reactions shows the same qualitative dependence on YY' as k_0 for proton transfers, i.e. a decrease in k_0 with increasing π -acceptor ability of YY' . Inasmuch as the carbanion formed in (99) is very similar to the one generated by the deprotonation of $\text{CH}_2\text{YY}'$, this result is not surprising and shows the same PNS-effect of late developing resonance at work as with the proton transfers. This is expressed by (101), which is analogous to (102) =

$$\delta \log (k_0^{\text{res}})_{\text{N}} = (\lambda_{\text{res}} - \beta_{\text{nuc}}^n) \delta \log (K_1^{\text{res}})_{\text{N}} \quad (101)$$

$$\delta \log (k_0^{\text{res}})_{\text{P}} = (\lambda_{\text{res}} - \beta_{\text{B}}) \delta \log (K_1^{\text{res}})_{\text{P}} \quad (102)$$

(29) for proton transfer, except that β_{nuc}^n , the normalized β_{nuc} , replaces β_{B} as a measure of charge transfer or bond formation in the transition state. The subscripts N (nucleophile) and P (proton) are used to distinguish between the two types of reactions.

Despite the qualitative similarities, there are *quantitative* differences between nucleophilic additions and proton transfers that are best illustrated by the plot of $(\log k_0)_N$ for amine addition versus $(\log k_0)_P$ for proton transfer in Fig. 16. One major difference is that the sensitivity of $\log(k_0)_N$ to the resonance effect of YY' is strongly attenuated, as indicated by the small slope of the plot; excluding the points for benzylideneacetylacetone, benzylidenedibenzoylmethane, and benzylidene-1,3-indandione (filled squares), this slope is 0.46 ± 0.07 .

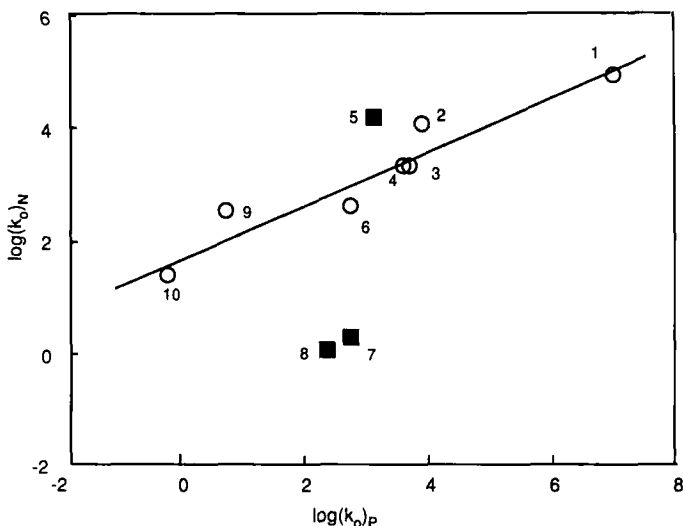


Fig. 16 Plot of $\log(k_0)_N$ for nucleophilic addition of piperidine/morpholine to $\text{PhCH}=\text{CYY}'$ versus $\log(k_0)_P$ for deprotonation of $\text{CH}_2\text{YY}'$ by piperidine/morpholine in 50% Me_2SO -50% water. The slope of the least squares line through the open circles is 0.46 ± 0.07 . Numbering corresponds to that in Table 17.

The attenuation indicates that $|\delta \log(k_0^{\text{res}})_N|$ is smaller than $|\delta \log(k_0^{\text{res}})_P|$ and should be reflected in smaller transition-state imbalances. Such imbalances are measured by $\alpha_{\text{nuc}}^n - \beta_{\text{nuc}}^n$, with α_{nuc}^n defined as $d \log k_1 / d \log K_1$ obtained by varying the substituent in the Ar-group of substrates such as $\text{ArCH}=\text{CYY}'$ in (99) or $\text{PhCH}=\text{C(Y)Ar}$. Representative values of α_{nuc}^n , β_{nuc}^n and $\alpha_{\text{nuc}}^n - \beta_{\text{nuc}}^n$ are summarized in Table 18. Even though only a few cases allow a direct comparison with a corresponding proton transfer, i.e. those

Table 18 Brønsted coefficients and imbalances $a_{\text{nuc}}^{\text{n}} - \beta_{\text{nuc}}^{\text{n}}$ for nucleophilic additions to olefins in water and 50% Me₂SO–50% water.

Olefin	Nucleophile	Solvent, <i>T</i>	$a_{\text{nuc}}^{\text{n}}$	$\beta_{\text{nuc}}^{\text{n}}$	$a_{\text{nuc}}^{\text{n}} - \beta_{\text{nuc}}^{\text{n}}$	Ref.
ArCH=C(CN) ₂	R ₂ NH ^{<i>a</i>}	H ₂ O, 20°C	0.55 ^{<i>b</i>}	0.35	0.20	^{<i>c</i>}
ArCH=C(CN) ₂	R ₂ NH ^{<i>a</i>}	50% Me ₂ SO, 20°C	0.56 ^{<i>b</i>}	0.42	0.14	^{<i>c</i>}
ArCH=C(COO) ₂ C(CH ₃) ₂	R ₂ NH ^{<i>a</i>}	H ₂ O, 20°C	0.24 ^{<i>b</i>}	0.08	0.17	^{<i>d</i>}
ArCH=C(COO) ₂ C(CH ₃) ₂	R ₂ NH ^{<i>a</i>}	50% Me ₂ SO, 20°C	0.25 ^{<i>b</i>}	0.15	0.10	^{<i>d</i>}
ArCH=CHNO ₂	R ₂ NH ^{<i>a</i>}	H ₂ O, 20°C	0.51 ^{<i>b</i>}	0.25	0.26	^{<i>e</i>}
PhCH=C(Ar)NO ₂	R ₂ NH ^{<i>a</i>}	50% Me ₂ SO, 20°C	0.67 ^{<i>b</i>}	0.37	0.30	^{<i>f</i>}
PhCH=C(Ar)NO ₂	RS [−]	50% Me ₂ SO, 20°C	0.87	0.19	0.68	^{<i>g</i>}

^{*a*} Piperidine/morpholine. ^{*b*} $a_{\text{nuc}}^{\text{n}}$ (corr), see text. ^{*c*} Bernasconi and Killion (1989). ^{*d*} Bernasconi and Panda (1987). ^{*e*} Bernasconi *et al.* (1986). ^{*f*} Bernasconi and Renfrow (1987). ^{*g*} Bernasconi and Killion (1988).

where YY' and the solvent are the same in both types of reaction, the values of $\alpha_{\text{nuc}}^{\text{n}} - \beta_{\text{nuc}}^{\text{n}}$ appear to be significantly smaller than those of $\alpha_{\text{CH}} - \beta_{\text{B}}$. The most clear-cut examples are the reactions of the nitro-compounds with amines, where $\alpha_{\text{nuc}}^{\text{n}} - \beta_{\text{nuc}}^{\text{n}} = 0.26\text{--}0.30$, while $\alpha_{\text{CH}} - \beta_{\text{B}} = 0.89$ in water. On the other hand, $\alpha_{\text{nuc}}^{\text{n}} - \beta_{\text{nuc}}^{\text{n}}$ is about the same as $\alpha_{\text{CH}} - \beta_{\text{B}}$ in the reactions with nitriles, a finding that seems puzzling and will be discussed below. Another unusual result is the large $\alpha_{\text{nuc}}^{\text{n}} - \beta_{\text{nuc}}^{\text{n}}$ of 0.68 in the reaction of thiolate ions with $\text{PhCH}=\text{CHNO}_2$; it reflects the high polarizability of thiolate ions as will be detailed later.

How can the smaller imbalances and smaller $|\delta \log(k_0^{\text{res}})_{\text{N}}|$ be understood? One extreme view is that they are entirely due to $(\lambda_{\text{res}} - \beta_{\text{nuc}}^{\text{n}})_{\text{N}}$ in (101) being only 0.46 times (0.46 is the slope of the line in Fig. 16) as large as $(\lambda_{\text{res}} - \beta_{\text{B}})_{\text{P}}$ in (102). This view implies that $\delta \log(K_1^{\text{res}})_{\text{N}}$ and $\delta \log(K_1^{\text{res}})_{\text{P}}$ are the same but that the lag in the development of the resonance behind charge transfer is much smaller in the addition reactions. At the other extreme is the notion that it is $(\lambda_{\text{res}} - \beta_{\text{nuc}}^{\text{n}})_{\text{N}}$ and $(\lambda_{\text{res}} - \beta_{\text{B}})_{\text{P}}$ that are the same, while $\delta \log(K_1^{\text{res}})_{\text{N}}$ is only 0.46 as large as $\delta \log(K_1^{\text{res}})_{\text{P}}$. The true state of affairs is probably somewhere in the middle, i.e. $|(\lambda_{\text{res}} - \beta_{\text{nuc}}^{\text{n}})_{\text{N}}|$ is somewhat smaller than $|(\lambda_{\text{res}} - \beta_{\text{B}})_{\text{P}}|$, and $\delta \log(K_1^{\text{res}})_{\text{N}}$ is somewhat smaller than $\delta \log(K_1^{\text{res}})_{\text{P}}$. It is easily shown (Bernasconi and Stronach, 1990) that if this is the case then the slope of the straight line in Fig. 16 is the product of the attenuation of $(\lambda_{\text{res}} - \beta_{\text{nuc}}^{\text{n}})_{\text{N}}$ and the attenuation of $\delta \log(K_1^{\text{res}})_{\text{N}}$, i.e. slope = ab , with a and b given by (103) and (104) respectively.

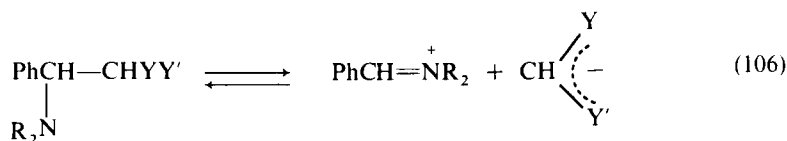
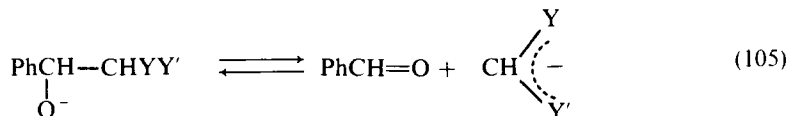
$$a = (\lambda_{\text{res}} - \beta_{\text{nuc}}^{\text{n}})_{\text{N}} / (\lambda_{\text{res}} - \beta_{\text{B}})_{\text{P}} \quad (103)$$

$$b = \delta \log(K_1^{\text{res}})_{\text{N}} / \delta \log(K_1^{\text{res}})_{\text{P}} \quad (104)$$

A reduction in $\delta \log(K_1^{\text{res}})_{\text{N}}$ for the olefin adducts is likely to arise from a steric effect that hinders optimal π -overlap with the YY' groups. A direct manifestation of this effect can be seen from comparisons of equilibrium constants for addition to olefins, $(K_1)_{\text{N}}$, with $\text{p}K_{\text{a}}$ -values of the corresponding carbon acids. For example, $(K_1)_{\text{N}}$ for piperidine addition to α -cyano-2,4-dinitrostilbene is only 36.1 times larger than $(K_1)_{\text{N}}$ for piperidine addition to α -cyano-4-nitrostilbene (Bernasconi *et al.*, 1983), while the acidity constants of 2,4-dinitrophenylacetonitrile and 4-nitrophenylacetonitrile differ by a factor of 3.63×10^4 (Bernasconi and Hibdon, 1983). Similar conclusions can be reached when comparing $(K_1)_{\text{N}}$ for piperidine addition to β -nitrostyrene (Bernasconi *et al.*, 1986) and α -nitrostilbene (Bernasconi and Renfrow, 1987) with the $\text{p}K_{\text{a}}$ difference between nitromethane and phenyl-nitromethane (Bernasconi *et al.*, 1988b).

Regarding the lag in resonance development, there are two factors that

can make $(\lambda_{\text{res}} - \beta_{\text{nuc}})_{\text{N}}$ smaller than $(\lambda_{\text{res}} - \beta_{\text{B}})_{\text{P}}$. The first is the sp^2 -hybridization of the procarbanionic carbon in the olefin, which facilitates π -overlap with YY' in the transition state and hence reduces the lag in resonance development. Evidence for this effect comes from a study of reactions such as (105) and (106). These reactions bear a greater similarity to the deprotonation of $\text{CH}_2\text{YY}'$ than to (99), because the procarbanionic carbon



in the reactant is sp^3 -hybridized, just as in $\text{CH}_2\text{YY}'$. Hence the imbalance and sensitivity of k_0 to YY' should be closer to those in proton transfers. There are no accurate data available on k_0 for reactions such as (105) and (106), but estimates for *ratios* of k_0 -values do exist. For example when $\text{YY}' = (\text{CN})_2 = \text{I}$ is being compared with $\text{YY}' = \text{H}$, $\text{NO}_2 = \text{II}$, we find $\log k_0^{\text{I}} - \log k_0^{\text{II}}$ is approximately 6.3, 3.9 and 2.6 for the proton transfer, reaction (105) and reaction (99) with $\text{Nu}^{\text{v}} = \text{OH}^-$ respectively (Bernasconi, 1987). For $\text{YY}' = (\text{CN})_2 = \text{I}$ and $\text{YY}' = \text{CN}$, $4\text{-NO}_2\text{-C}_6\text{H}_4 = \text{II}$, $\log k_0^{\text{I}} - \log k_0^{\text{II}}$ is approximately 3.0, 2.7 and 1.6 for the proton transfer, reaction (106) and reaction (99) with $\text{Nu}^{\text{n}} = \text{R}_2\text{NH}$ respectively (Bernasconi, 1987). These estimates indicate that the sensitivity of k_0 to YY' in (105) and (106) is indeed higher than in the nucleophilic additions, but not as high as in the proton transfers, suggesting that differences in the hybridization are not the only factors that determine relative sensitivities of k_0 to YY' .

A second factor that can enhance the sensitivity of k_0 to YY' in proton transfers is hydrogen bonding in the transition state (Bernasconi and Paschalis, 1989). Since the hydrogen bond would be stronger in a reaction where the negative charge is more localized on the carbon (Bednar and Jencks, 1985), the reactions where YY' are weak π -acceptors will benefit the most from this hydrogen-bonding stabilization; this increases k_0 . With strong π -acceptors in YY' , this effect becomes small or disappears altogether, i.e. k_0 is only subject to the depressing effect of the delayed resonance development. Hydrogen bonding thus leads to a wider spread in k_0 -values between the carbon acids with strong π -acceptors and those with weak π -acceptors.

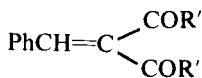
A complementary view of this phenomenon is to understand it as a consequence of a reduced imbalance when YY' are poor π -acceptors. Hydrogen bonding and resonance represent competing interaction mechanisms for the stabilization of the transition state. When there is resonance, negative charge is removed from the carbon, which reduces its capability as a hydrogen-bond acceptor. With poor π -acceptors, there is little resonance in the product ion and virtually none in the transition state. In this case, hydrogen bonding is quite effective to begin with, and further helps in keeping the charge on the carbon, thereby reducing the imbalance; this increases k_0 . With good π -acceptors, there is more charge delocalization in the transition state, hydrogen bonding is relatively ineffective to begin with, and hence cannot affect the imbalance in a major way. The fact that $(a_{CH} - \beta_B)_P$ is so much larger than $(a_{nuc}^n - \beta_{nuc}^n)_N$ with strong π -acceptors, especially in nitro-compounds, but about the same as $(a_{nuc}^n - \beta_{nuc}^n)_N$ with weak π -acceptors, particularly in nitriles, fits very well with this notion.

EFFECTS OF INTRAMOLECULAR HYDROGEN BONDING, STERIC CROWDING AND ENFORCED π -OVERLAP ON INTRINSIC RATE CONSTANTS

Intramolecular hydrogen bonding

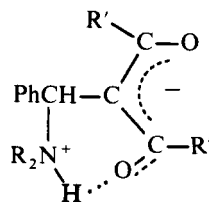
The points for benzylideneacetylacetone [42a] and benzylidenedibenzoylmethane [42b] show negative deviations of about 2.5 logarithmic units from the straight line in Fig. 16. Similar deviations have also been reported for the reactions of benzylidene-3,5-heptanedione ($R' = Et$) and benzylidene-2,6-dimethyl-3,5-heptanedione [$R' = (CH_3)_2CH$] (Bernasconi and Stronach, 1991a). Two major factors, both PNS-effects, are believed to be responsible for the lowering of $(k_0)_N$ in these reactions. The first is intramolecular hydrogen bonding, and the second is steric congestion.

The amine adducts of benzylideneacetylacetone or derivatives thereof, [43], are unique in that they have a very strong intramolecular hydrogen



[42a] $R' = \text{Me}$

[42b] $R' = \text{Ph}$



[43]

bond. This manifests itself in unusually high pK_a -values of the NH^+ in [43] (Bernasconi and Kanavarioti, 1986; Bernasconi and Stronach, 1991a). The intramolecular hydrogen bond adds stability to the adduct, and hence a late development would decrease and early development would increase k_0 according to (107). $\delta \log K_1^{Hb}$ is the increase in $\log K_1$ brought about by the

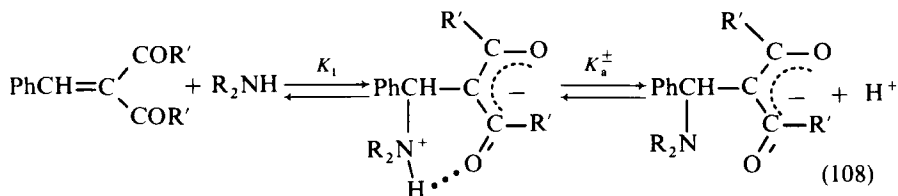
$$\delta \log k_0^{Hb} = (\lambda_{Hb} - \beta_{nuc}^n) \delta \log K_1^{Hb} \quad (107)$$

hydrogen bond and λ_{Hb} the progress of the hydrogen bond in the transition state. It is likely that $\lambda_{Hb} < \beta_{nuc}^n$ and hence $\delta \log k_0^{Hb} < 0$ for two reasons.

- (1) The strength of the hydrogen bond should be roughly proportional to the product of the positive charge on the amine nitrogen and the negative charge on the enolate portion of the adduct. If $|\delta^+| = |\delta^-| = 0.5$, this product is only one-quarter of that in the adduct. A similar argument may be made in terms of the Hine equation (Hine, 1972; Funderburk and Jencks, 1978) for hydrogen-bonded complexes, as elaborated upon by Bernasconi and Kanavarioti (1986).
- (2) The distance between the donor and acceptor atoms is larger in the transition state than in the adduct because of incomplete C—N bond formation and incomplete delocalization of the negative charge into the enolate oxygen. With $\delta \log K_1^{Hb}$ estimated at about 4 (Bernasconi and Kanavarioti, 1986), and assuming $\lambda_{Hb} - \beta_{nuc}^n \approx -0.35$, hydrogen bonding could account for $\delta \log k_0^{Hb} \approx -1.4$, which is about half of the negative deviations shown in Fig. 16.

Steric effects

The effect of steric hindrance on K_1 is difficult to evaluate directly because intramolecular hydrogen bonding in [43] opposes the expected decrease in K_1 . However, a comparison of equilibrium constants for the formation of the *deprotonated* adduct, $K_1 K_a^\pm$ in (108), with that in systems less



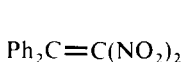
prone to steric hindrance can give a quantitative measure of this steric effect. Such comparisons suggest that K_1 for piperidine/morpholine addition to

$\text{PhCH}=\text{C}(\text{COR}')_2$ is depressed by 3–4 orders of magnitude (Bernasconi and Kanavarioti, 1986; Bernasconi and Stronach, 1991a). If this steric effect were to develop ahead of bond formation, it would lead to lowering of k_0 according to (109) because $\lambda_{\text{st}} > \beta_{\text{nuc}}^{\text{n}}$ and $\delta \log K_0^{\text{st}} \approx -3$ to -4 . A value of

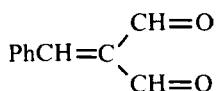
$$\delta \log k_0^{\text{st}} = (\lambda_{\text{st}} - \beta_{\text{nuc}}^{\text{n}}) \delta \log K_0^{\text{st}} \quad (109)$$

$\lambda_{\text{st}} - \beta_{\text{nuc}}^{\text{n}}$ of about 0.35 would yield $\delta \log k_0^{\text{st}} \approx -0.95$ to -1.4 , enough to explain the difference between the negative deviations from the plot in Fig. 16 and $\delta \log k_0^{\text{Hb}}$.

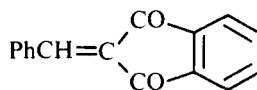
The steric effect in these reactions is probably a composite of several factors that act in concert. One factor is F-strain (Brown *et al.*, 1944; Brown, 1946), i.e. direct frontal repulsion between the nucleophile and the electrophile. This F-strain is clearly seen in the reactions of amines with [44]



[44]



[45]



[46]

(Bernasconi and Carré, 1979), a particularly bulky olefin: with piperidine as nucleophile, $K_1 K_{\text{a}}^{\pm}$ is only 3.07×10^{-4} times as large as $K_1 K_{\text{a}}^{\pm}$ with the sterically less demanding *n*-butylamine. This contrasts with the reaction of the much smaller [45], where $K_1 K_{\text{a}}^{\pm}$ is about the same for piperidine and *n*-butylamine (Bernasconi and Stronach, 1991a).

Does F-strain develop ahead of bond formation? Kinetic data on amine addition to [44] and [45] suggest an affirmative answer: The difference in $\log k_0$ values for piperidine/morpholine and 1-*n*-alkylamines, $\log k_0(\text{pip}/\text{mor}) - \log k_0(1^\circ \text{RNH}_2)$, which for [45] is about 1.7 is reduced to about 0.3 in the reaction of [44], suggesting a $\delta \log k_0^{\text{st}} < 0$ and $\lambda_{\text{st}} > \beta_{\text{nuc}}^{\text{n}}$. Incidentally, the generally observed positive difference of $\log k_0(\text{pip}/\text{mor}) - \log k_0(1^\circ \text{RNH}_2)$ is reminiscent of the same general observation in proton transfers, and must have the same origin, i.e. a PNS effect of the late solvation of the developing ammonium ion.

A second steric factor is hindrance to coplanarity of the two $\text{R}'\text{CO}$ -groups, which affects both the olefin and the adduct. The effect on the adduct is to reduce its resonance stabilization, which should lead to an increase in k_0 . The effect on the olefin is to reduce π -overlap of the $\text{R}'\text{CO}$ -groups with the $\text{C}=\text{C}$ double bond. Since π -overlap between YY' and the $\text{C}=\text{C}$ double bond is one of the reasons why $|(\lambda_{\text{res}} - \beta_{\text{nuc}}^{\text{n}})|$ in additions to

olefins are smaller than $|(\lambda_{\text{res}} - \beta_{\text{B}})_{\text{P}}|$ in proton transfers, a reduction in this overlap will tend to increase $|(\lambda_{\text{res}} - \beta_{\text{nuc}})_{\text{N}}|$ and, with it, the k_0 -lowering PNS effects. These considerations suggest that steric hindrance to coplanarity in the olefin and in the adduct have opposite effects on k_0 , which may approximately cancel each other. Hence the main source of $\delta \log k_0^{\text{st}}$ in (109) appears to be F-strain.

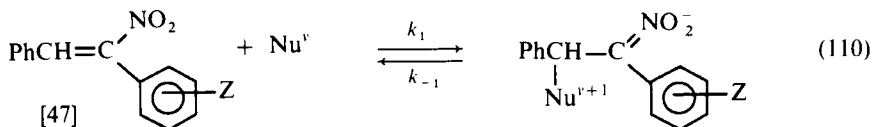
Enforced π -overlap

The point for [46] shows a positive deviation of approximately 1.0 logarithmic units from the line in Fig. 16. That this enhanced $(\log k_0)_{\text{N}}$ value is not simply the result of the absence of significant steric effects is evident from the fact that $(\log k_0)_{\text{N}}$ for piperidine/morpholine addition to [46] is 0.6 logarithmic units higher than for the reaction of the same amines with the least bulky diketone derivative [45] (Bernasconi and Stronach, 1991a). The most plausible explanation of the enhanced $(k_0)_{\text{N}}$ is that the cyclic structure of [46] assures that the π -overlap of the CO-groups with the C=C double bond is already maximally developed in the olefin. This should reduce $|(\lambda_{\text{res}} - \beta_{\text{nuc}})_{\text{N}}|$ in (101), thereby reducing $|(\delta \log k_0^{\text{res}})_{\text{N}}|$. Note that this is the opposite of how steric effects that hinder coplanarity of the R'CO-groups in [42] affect $|(\lambda_{\text{res}} - \beta_{\text{nuc}})_{\text{N}}|$.

Closer inspection of Fig. 16 reveals that $(k_0)_{\text{N}}$ for benzylidene Meldrum's acid is also somewhat increased, but less so than for [46]; a similar interpretation is called for. The effect is smaller here, presumably because resonance is not as important in the stabilization of Meldrum's acid anions (Arnett and Harrelson, 1987; Wang and Houk, 1988; Wiberg and Laidig, 1988) and/or because the ring structure is less rigid than in [46].

POLAR EFFECTS OF REMOTE SUBSTITUENTS

The polar effects of remote substituents (Z) as well as of substituents (X) directly attached to the carbanionic centre in (PhCH=CXY) are qualitatively similar to those in proton transfers. Most substituent effects reported to date are for reactions of the type shown in (99), with Z being in a phenyl ring attached to the benzylic carbon, but nitroolefins offer the possibility of varying Z in the α -phenyl ring as well (110). Since $a_{\text{nuc}}^{\text{n}} > \beta_{\text{nuc}}^{\text{n}}$ in all reactions



reported so far, a more electron-withdrawing substituent Z always enhances k_0 according to (111), which is analogous to (47). The size of $\delta \log k_0^{\text{pol}}(Z)$ is generally smaller in the addition reactions because $a_{\text{nuc}}^n - \beta_{\text{nuc}}^n < a_{\text{CH}} - \beta_{\text{B}}$. On the other hand, $\delta \log K_1^{\text{pol}}(Z)$ in (111) is typically not very different from

$$\delta \log k_0^{\text{pol}}(Z) = (a_{\text{nuc}}^n - \beta_{\text{nuc}}^n) \delta \log K_1^{\text{pol}}(Z) \quad (111)$$

the same parameter in (47), or sometimes even larger, despite the much greater distance of Z from the site of negative charge in the adduct of (99) than in the carbanion generated by proton transfer (46). For example, for a p -nitro group, $\delta \log K_1^{\text{pol}}(Z) = 1.20$ in the OH^- -addition to β -nitrostyrene in 50% Me_2SO –50% water (Bernasconi and Paschalis, 1989), while in the deprotonation of ArCH_2NO_2 , $\delta \log K_1^{\text{pol}}(Z) = 0.56$ for the m -nitro group and 0.99 for the p -nitro group (Bordwell and Boyle, 1972). In this latter case, 0.99 is actually an overestimate of $\delta \log K_1^{\text{pol}}(Z)$ because of the resonance effect of the p -nitro-group.

The large substituent effect on K_1 cannot be solely due to the stabilization of the negative charge in the adduct, but must reflect an enhanced reactivity of the olefin. This enhanced reactivity must be due to the destabilizing effect of electron-withdrawing substituents on the sp^2 -carbon, which is more electronegative than the sp^3 -carbon in the adduct.

In reactions with amine nucleophiles, the substituent effects on K_1 as well as on k_1 are attenuated by the development of the positive charge on the amine nitrogen. This attenuation is especially significant when Z is in the phenyl group attached to the electrophilic centre (99), but by no means negligible when it is in an α -phenyl ring (110). For example, in the reaction of piperidine with substituted β -nitrostyrenes in water, $\rho(K_1) = -0.06$ and $\rho(k_1) = 0.33$ (Bernasconi *et al.*, 1986). These small ρ -values contrast with $\rho(K_1 K_a^\pm) = 1.09$ for the formation of the deprotonated (anionic) adduct. In the reaction of piperidine with α -nitrostilbenes (Z in α -phenyl group), $\rho(K_1) = 0.88$, $\rho(k_1) = 0.90$ and $\rho(K_1 K_a^\pm) = 1.90$ (Bernasconi and Renfrow, 1987). The attenuation of the substituent effects by the positive charge distorts $a_{\text{nuc}}^n = \rho(k_1)/\rho(K_1) = d \log k_1 / d \log K_1$ and makes it unsuitable as a measure, in the form of $a_{\text{nuc}}^n - \beta_{\text{nuc}}^n$, of transition-state imbalances. However, the attenuation can be corrected for, as illustrated for the α -nitrostilbene reaction.

We first correct for the contribution of the positive charge to $\rho(K_1)$ by expressing $\rho(K_1)$ as the sum of two terms (112). Here $\rho_{\text{eq}}(\text{C}^-)$ and $\rho_{\text{eq}}(\text{NH}^+)$

$$\rho(K_1) = \rho_{\text{eq}}(\text{C}^-) + \rho_{\text{eq}}(\text{NH}^+) = 0.88 \quad (112)$$

are the responses to the negative and positive charges respectively; in the

reaction of β -nitrostyrenes, $\rho_{\text{eq}}(\text{C}^-)$ would also include the response to the rehybridization of the electrophilic carbon. The value of $\rho_{\text{eq}}(\text{NH}^+)$ may be approximated by the ρ -value for $\text{p}K_{\text{a}}^{\pm}$, which is -1.02 (Bernasconi and Renfrow, 1987). Solving (112) for $\rho_{\text{eq}}(\text{C}^-)$ affords (113).

$$\rho_{\text{eq}}(\text{C}^-) = 0.88 + 1.02 = 1.90 \quad (113)$$

In analogy to (112), we express $\rho(k_1)$ by (114). The ratio $\rho_{\text{kin}}(\text{NH}^+)/\rho_{\text{eq}}(\text{NH}^+)$ can be regarded as a measure of the progress of positive charge development on the amine nitrogen in the transition state, as seen by the phenyl substituent, while $\beta_{\text{nuc}}^{\text{n}}$ is assumed to measure the same process as seen by the amine substituent. Hence we set them equal and obtain (115) and (116).

$$\rho(k_1) = \rho_{\text{kin}}(\text{C}^-) + \rho_{\text{kin}}(\text{NH}^+) = 0.90 \quad (114)$$

$$\rho_{\text{kin}}(\text{NH}^+)/\rho_{\text{eq}}(\text{NH}^+) = \beta_{\text{nuc}}^{\text{n}} = 0.37 \quad (115)$$

$$\rho_{\text{kin}}(\text{NH}^+) = 0.37(-1.02) = -0.38 \quad (116)$$

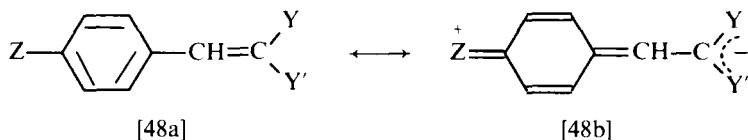
Insertion into (114) leads to (117), and hence the corrected $a_{\text{nuc}}^{\text{n}}$ is given by (118). Note that it is $a_{\text{nuc}}^{\text{n}}(\text{corr})$ that is reported in Table 18.

$$\rho_{\text{kin}}(\text{C}^-) = 0.90 + 0.38 = 1.28 \quad (117)$$

$$a_{\text{nuc}}^{\text{n}}(\text{corr}) = \rho_{\text{kin}}(\text{C}^-)/\rho_{\text{eq}}(\text{C}^-) = 1.28/1.90 = 0.67 \quad (118)$$

π -DONOR EFFECTS: PNS OR RADICALOID TRANSITION STATE?

π -Donor substituents in the *para*-position of $\text{ArCH}=\text{CYY}'$ lead to interesting effects on k_0 that we have interpreted within the framework of the PNS, but which have also been explained by an alternative model to be described below. π -Donors stabilize the olefin, which is best understood in terms of the resonance structure [48b]. This reduces the equilibrium constant for



nucleophilic addition, and manifests itself by negative deviations of $\log K_1$ or $\log K_1 K_{\text{a}}^{\pm}$ from Hammett plots. With $p\text{-Me}_2\text{N}$ and, occasionally, with $p\text{-OMe}$ this negative deviation persists even when σ^+ is used as the substi-

tuent constant. Representative examples include piperidine and morpholine addition to benzylidene Meldrum's acids (Bernasconi and Panda, 1987) and to benzylidenemalononitriles (Bernasconi and Killion, 1989), piperidine addition to β -nitrostyrenes (Bernasconi *et al.*, 1986) and also OH^- and thiolate ion ($\text{HOCH}_2\text{CH}_2\text{S}^-$ and $\text{MeO}_2\text{CCH}_2\text{S}^-$) addition to β -nitrostyrenes (Bernasconi *et al.*, 1992; Bernasconi and Schuck, 1992).

The effect of the resonance stabilization of the olefin on k_0 varies with YY' and the solvent. For example, in the reactions of piperidine with benzylidenemalononitriles in 50% Me_2SO (Bernasconi and Killion, 1989), or the reactions of piperidine or morpholine with benzylidene Meldrum's acids in water and in 50% Me_2SO –50% water (Bernasconi and Panda, 1987), k_0 for the $p\text{-Me}_2\text{N}$ derivatives is somewhat depressed, as indicated by a negative deviation from a plot of $\log k_1$ versus $\log K_1$. These deviations are quite small, however—in some cases as small as 0.2–0.3 logarithmic units, and hence could possibly be interpreted as experimental scatter.

A lowering of k_0 is consistent with the PNS. Since resonance development in reactions is invariably found to lag behind charge transfer or bond changes, the loss of the olefin resonance should be ahead of such changes, and hence should lower k_0 . However, a detailed analysis (Bernasconi and Killion, 1989) suggests that a stronger reduction in k_0 than the typical 0.2–0.3 logarithmic units should have been observed. This implies the presence of a compensating factor that tends to enhance k_0 . Indeed, in reactions of β -nitrostyrenes with nucleophiles, this compensating factor is so strong as to lead to *positive* deviations from Brønsted plots for $p\text{-Me}_2\text{N}$ and $p\text{-MeO}$. For example, in 50% Me_2SO –50% water, the positive deviation for the $p\text{-Me}_2\text{N}$ derivative is 0.4 logarithmic units when the nucleophile is OH^- , and 0.7 when it is $\text{HOCH}_2\text{CH}_2\text{S}^-$ in water (Bernasconi *et al.*, 1992). The corresponding deviations for the $p\text{-MeO}$ derivatives are 0.25. In 90% Me_2SO –10% water, the points for $p\text{-Me}_2\text{N}$ and $p\text{-MeO}$ show no deviation at all. For the reactions of β -nitrostyrenes with piperidine in water (Bernasconi *et al.*, 1986) a Brønsted plot is meaningless because K_1 is virtually independent of substituents that are not π -donors, i.e. $\rho \approx 0$. In this case, the increase in k_0 is seen in the fact that both k_1 and k_{-1} are enhanced for the π -donors, as shown in the Hammett plots of Fig. 17.

A further example is the addition of CN^- to 1,1-diaryl-2-nitroethylenes (Gross and Hoz, 1988), for which small positive deviations from a Hammett plot were reported in water for the 4-methoxy (+0.08 logarithmic units) and 4,4'-dimethoxy (+0.15 logarithmic units) derivatives; in Me_2SO , no deviations were observed. These findings are very similar to those reported for the β -nitrostyrene reactions, although the absence of equilibrium constants does not allow one to firmly establish whether the positive deviations really reflect enhanced k_0 -values.

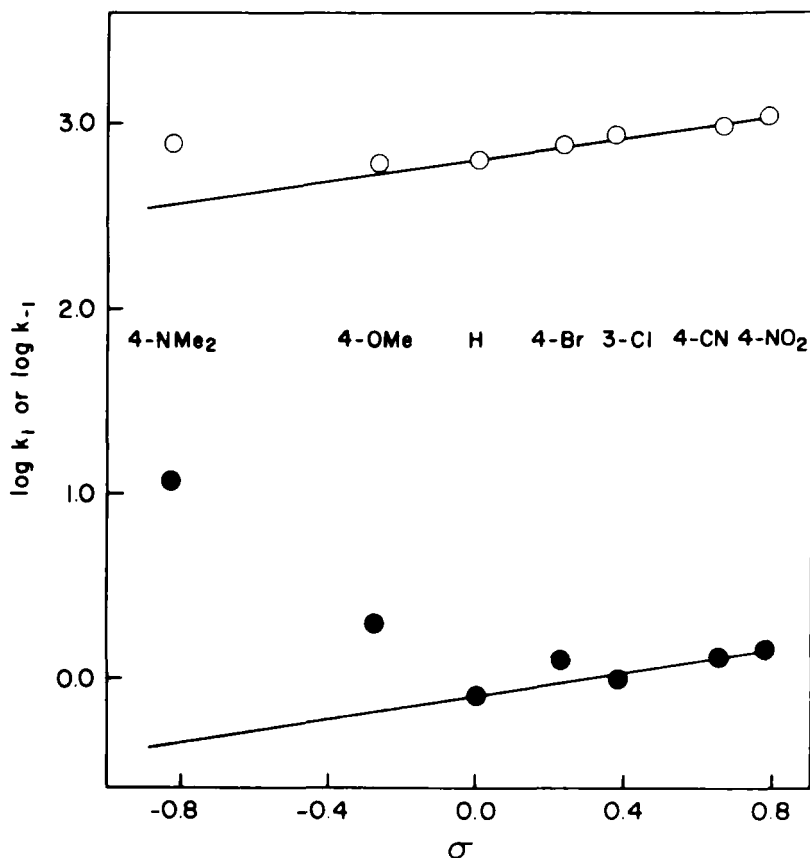
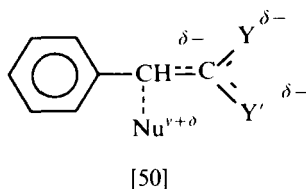
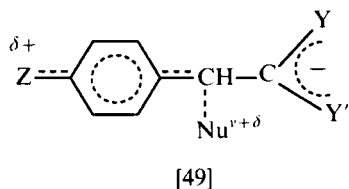


Fig. 17 Hammett plots (standard σ -values) for k_1 (open circles) and k_{-1} (filled circles) in the reaction of piperidine with substituted β -nitrostyrenes in water. Reprinted from Bernasconi *et al.* (1986) with permission from the American Chemical Society.

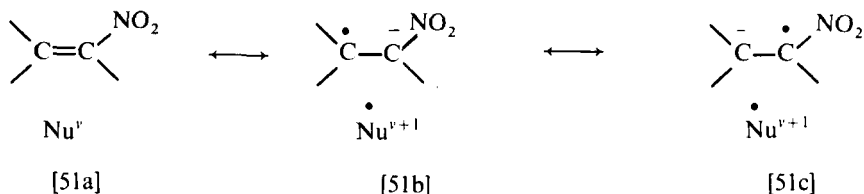
All the above results can be rationalized in terms of a transition state that, in exaggerated form, may be represented by [49]. The major difference between [49] and [50] for substrates without a π -donor is that in [49] the



charge is extensively delocalized into YY' because this delocalization is already built into the olefin [48b]. This reduces the detrimental PNS-effect of delayed charge delocalization and increases k_0 . The impact of this built-in delocalization is strongest for reactions with large $|\delta \log (k_0^{\text{res}})_N|$. This explains why, in the reactions of the nitro-activated olefins in water or 50% Me_2SO , this effect overrides the reduction in k_0 from the early loss of the olefin resonance, but not in the reactions of benzyldenemalononitriles and benzyldiene Meldrum's acids. Intermediate cases are the reactions of the β -nitrostyrenes in 90% Me_2SO and the 1,1-diaryl-2-nitroethylenes in Me_2SO , for which $|\delta \log (k_0^{\text{res}})_N|$ is smaller than in the more aqueous media.

Our explanation of the k_0 -enhancing effect in terms of charge delocalization already built into the olefin is somewhat analogous to the explanation of the enhanced k_0 for nucleophilic addition to benzyldiene-1,3-indandione. In this latter case, delocalization of the negative charge in the transition state is enhanced by strong π -overlap between the CO-groups and the $\text{C}=\text{C}$ double bond built into the olefin because of the cyclic structure.

An alternative interpretation of the enhanced reactivity of nitro-olefins with π -donor substituents was offered by Gross and Hoz (1988). According to their model, these reactions have some characteristics of an electron transfer from the nucleophile to the olefin, i.e. the transition state has some radicaloid character, which can be understood as a resonance hybrid of [51a-c]. In water, [51b] is a major resonance form, and rate enhancements



arise from mesomeric stabilization of the lone electron on the benzylic carbon by p -MeO or p -Me₂N. In Me_2SO , [51c] becomes favoured, and hence there is no special acceleration by the p -MeO or p -Me₂N groups.

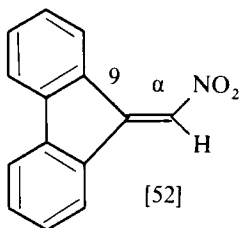
We suggest that the explanation based on the PNS is to be preferred over that offered by Gross and Hoz for two reasons.

- (1) If there were a radicaloid transition state then the use of a nucleophile with a lower oxidation potential, such as a thiolate ion, should enhance the radical character of the transition state, thereby magnifying the positive deviations of the p -Me₂N and p -MeO derivatives. However, no such enhancement was found with $\text{HOCH}_2\text{CH}_2\text{S}^-$ or $\text{MeO}_2\text{CCH}_2\text{S}^-$ as nucleophiles (Bernasconi and Schuck, 1992), de-

spite the large difference expected in the oxidation potentials ($E^0 = 0.9$ V for EtS^- , and 1.9 V for OH^- and CN^- ; Eberson, 1987).

- (2) With a radicaloid transition state, substituents that are strong mesomeric stabilizers of radicals should lead to particularly strong positive deviations, whereas substituents that destabilize radicals should lead to negative deviations. *p*-MeS and *p*-CN belong to the former (Creary, 1980) and *m*-CN to the latter category (Dust and Arnold, 1983), but neither displays the predicted behaviour for a radicaloid transition state in the reactions of β -nitrostyrenes with $\text{HOCH}_2\text{CH}_2\text{S}^-$ or $\text{MeO}_2\text{OCCH}_2\text{S}^-$ (Bernasconi and Schuck, 1992), even though these substituent effects should have been magnified because of the use of the thiolate ion nucleophiles.

Another observation that has been interpreted in terms of [51a–c] is the ambident behaviour of [52]: in water, [52] is attacked by CN^- at the 9-position, but in Me_2SO and DMF, reaction occurs mainly at the α -position



(Hoz and Speizman, 1983). MNDO calculations suggest that in water the spin population shifts from the α -carbon [51c] to the 9-position [51b] (Hoz and Speizman, 1983). Assuming that bond formation with Nu^{v+1} is most likely with the carbon with the most radical character, the change in positional selectivity with the solvent is easily understood.

The interpretation of the ambident nature of [52] in terms of a radicaloid transition state is not as easily discarded as that of the enhanced reactivity of the *p*- Me_2N and *p*-MeO derivatives of nitro-olefins. However, the following more “classical” interpretation seems just as satisfactory. Attack at the 9-position creates a nitronate ion that is less stable in a dipolar aprotic solvent than in water (Table 10). This should lower the rate of nucleophilic attack, even though this reduction will be somewhat attenuated by an increase in the intrinsic rate constant. In contrast, attack at the α -position leads to a highly dispersed fluorenyl anion that is more stable in a dipolar aprotic solvent (Table 10). This will be reflected in an increased rate for nucleophilic addition—an effect not counteracted by changes in k_0 since in such systems k_0 is virtually independent of solvent. Hence the solvent effect on the

positional selectivity of [52] is easily explained by a relative decrease in k for attack at the 9-position coupled with an increase for attack at the α -position. Note, though, that the above discussion ignores the expected increase in nucleophilic reactivity of CN^- in the dipolar aprotic solvents. This is justified, since this factor should affect both reactions in a similar way.

CAN A PRODUCT STABILIZING FACTOR DEVELOP AHEAD OF BOND FORMATION? REACTIONS OF THIOLATE IONS AS NUCLEOPHILES

Thiolate ions are known to be excellent nucleophiles, and superior to oxyanions or amines of comparable $\text{p}K_{\text{a}}$ in many nucleophilic addition reactions (Friedman *et al.*, 1965; Ladkani and Rappoport, 1974; Rosenberg *et al.*, 1987; Rappoport, 1987; Rappoport and Topol, 1989; Bernasconi, 1989). One of the reasons for this high reactivity is their high carbon basicity, i.e. the high equilibrium constants for nucleophilic addition (Hine and Weimar, 1965; Sander and Jencks, 1968; Hine, 1975b; Bone *et al.*, 1983). Within the framework of hard-soft acid-base interactions (Pearson and Songstad, 1967; Pearson, 1969), this can be understood as the soft (polarizable) electrophile (e.g. alkene) having a stronger affinity for the soft sulphur bases than for the hard nitrogen or oxygen bases.

It was shown recently (Bernasconi and Killion, 1988) that the high thermodynamic affinity cannot fully explain the high nucleophilicity of thiolate ions. An important contribution comes from an enhanced intrinsic rate constant. This was demonstrated for the reaction of thiolate ions with α -nitrostilbene [47] ($\text{Z} = \text{H}$) in 50% Me_2SO -50% water, for which $\log k_0 = 3.43$ is much higher than $\log k_0 = 1.43$ for the reaction of piperidine/morpholine with the same substrate (Bernasconi and Renfrow, 1987). A similar comparison for the reaction of β -nitrostyrene shows $\log k_0 = 3.50$ for thiolate ion (Bernasconi and Schuck, 1992) and 2.10 for amine addition (Bernasconi *et al.*, 1986). An attractive explanation for the enhanced k_0 -value is that the soft acid-soft base interaction that is responsible for the high thermodynamic stability of the thiolate ion adduct develops ahead of C-S bond formation. This is interesting because it contrasts with most other product-stabilizing factors (e.g. resonance, solvation, intramolecular hydrogen bonding and hyperconjugation) whose development typically lags behind bond formation at the transition state, thereby lowering k_0 .

How can we understand these contrasting patterns? A common characteristic of product-stabilizing factors such as resonance, solvation or intramolecular hydrogen bonding is that they are "created" by the reaction, i.e. they would not exist in the absence of bond formation. For example, in a proton

transfer, resonance in the carbanion could not develop if the proton transfer did not occur and so make an electron pair available to be delocalized into the activating π -acceptor. In other words, at best these factors could conceivably develop synchronously with bond formation but not possibly ahead of it; in fact, they lag behind for reasons discussed earlier. In contrast, soft-soft interactions are rooted in the polarizability of the interacting molecules and may not require a substantially developed bond for them to make themselves felt. It is therefore not unreasonable that they could be more advanced at the transition state than bond formation.

In view of the many unanswered questions regarding nucleophilic reactivity (Bordwell and Hughes, 1982, 1983; Ritchie, 1983; Shaik, 1985; Harris and McManus, 1987; Lewis *et al.*, 1987a; Bordwell *et al.*, 1987; Jencks, 1987; Ritchie, 1987; Hoz, 1987) and the fact that the reactions under discussion represent only two examples, our interpretation should be regarded as tentative, and there may be other factors that contribute to the enhanced intrinsic rate constant for thiolate ion nucleophiles. None the less, the Brønsted coefficients α_{nuc}^n and β_{nuc}^n are consistent with the notion of a PNS effect brought about by early development of the soft-soft interactions. They are $\alpha_{\text{nuc}}^n = 0.87$, obtained for the reaction of $\text{HOCH}_2\text{CH}_2\text{S}^-$ with variously substituted [47], and $\beta_{\text{nuc}}^n = 0.19$, determined for the reaction of [47] ($Z = \text{H}$) with a number of RS^- (Table 18). These coefficients reveal an imbalance, $\alpha_{\text{nuc}}^n - \beta_{\text{nuc}}^n = 0.68$, which is much larger than $\alpha_{\text{nuc,corr}}^n - \beta_{\text{nuc}}^n = 0.51 - 0.25 = 0.26$ for the reaction of [47] with piperidine and morpholine (Bernasconi *et al.* 1988). A major reason for the large α_{nuc}^n -value in the thiolate ion reaction may be related to the above-mentioned disproportionately large progress in the soft-soft interactions at the transition state. The strong polarizability of the thiolate ion would allow substantial negative charge density to develop in the α -carbon (large α_{nuc}^n) without extensive bond formation (low β_{nuc}^n).

7 Other reactions that show PNS effects

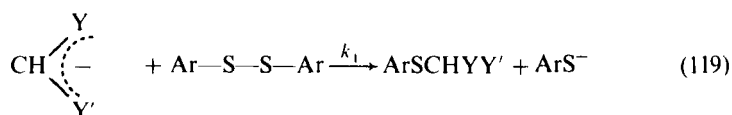
Proton transfers at carbon and nucleophilic addition to activated olefins provide most examples that illustrate the various aspects of PNS. In this section, we shall discuss PNS effects in other types of reaction. The number of such examples is at present relatively small, even though the principle should be applicable to any process in which stabilizing or destabilizing factors develop (are lost) non-synchronously with charge transfer or bond changes. Reasons for the smaller number of examples include lack of systematic studies, difficulty in determining both rate and equilibrium constants of reactions, and the likelihood that numerous structure-reactivity

correlations may not have been recognized as reflecting PNS-effects at the time they were reported.

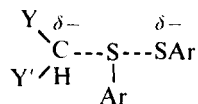
REACTIONS INVOLVING CARBANIONS

In the section on nucleophilic addition to olefins (p. 211) two reactions involving carbanion nucleophiles, (105) and (106), were briefly mentioned. Approximate *ratios* of k_0 indicated that expulsion of $\text{CH}(\text{CN})_2^-$ has a much higher k_0 than expulsion of $\text{CH}_2=\text{NO}_2^-$ in (105), and expulsion of $\text{CH}(\text{CN})_2^-$ has a much higher k_0 than that of $4\text{-NO}_2\text{C}_6\text{H}_4\text{CHCN}^-$ in (106).

Gilbert (1980) reported on the reaction of diaryl disulphides with carbanions such as 1,3-dicarbonyl carbanions, cyanocarbon anions and nitronate ions (119). Plots of $\log k_1$ versus $\text{p}K_{\text{a}}^{\text{CH}_2\text{YY}'}$ indicated that k_0 (cyano-



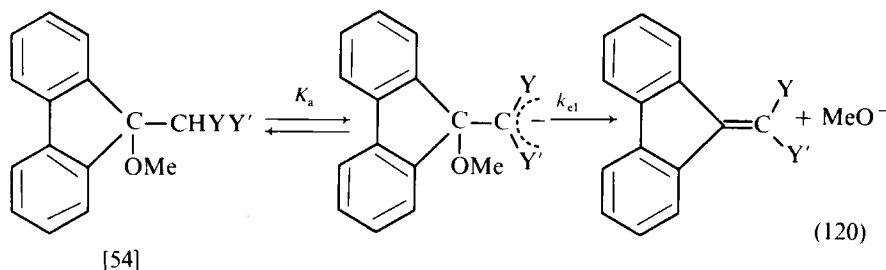
carbon anions) $> k_0$ (1,3-dicarbonyl anions) $\gg k_0$ (nitronate ions) in water. He also showed that, upon transfer from water to Me_2SO , there was little effect on k_0 for the cyanocarbon anions, but a significant increase in k_0 for 1,3-dicarbonyl anions and a dramatic increase in k_0 for nitronate ions. All these observations parallel those made for proton transfers involving the same carbanions, and indicate a transition state with a substantial fraction of the negative charge shifted away from YY' to the carbon as shown in [53].



[53]

PNS patterns have recently been observed in the reaction of carbanions with 1,3,5-trinitrobenzene and 2,4,6-trinitrotoluene to form Meisenheimer complexes (Cox *et al.*, 1988). In methanol, the following values of $\log k_0$ were reported: 4.40 ($\text{CH}(\text{CN})_2^-$), -0.66 (MeCHNO_2^-), and -0.74 (CH_2NO_2^-).

Hoz *et al.* (1985) studied the E1cB elimination reaction from [54] in 25% sulpholane-75% water at 25°C. They estimated $k_{\text{el}}(\text{YY}' = (\text{CN})_2) \geq 10^7 k_{\text{el}}(\text{YY} = \text{H}, \text{NO}_2)$. Since the $\text{p}K_{\text{a}}$ -values of $\text{CH}_2(\text{CN})_2$ and CH_3NO_2 are quite similar, it may be assumed that the equilibrium constants for the



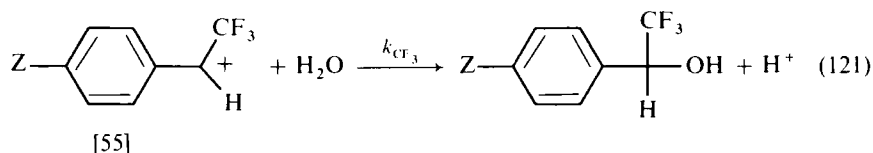
k_{el} process should also be similar with $YY' = (\text{CN})_2$ and H, NO_2 . This implies that the k_{el} -ratio will be a good approximation for the k_0 -ratio. In the light of the results reported in the section on nucleophilic additions to olefins (p. 211), the estimated ratio of greater than 10^7 seems to be high, although there can be no doubt about the qualitative result that $k_0(\text{CN})_2 \gg k_0(\text{H}, \text{NO}_2)$.

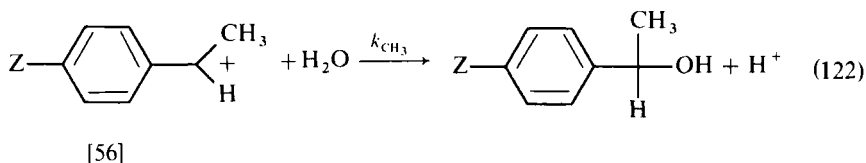
Hoz *et al.* (1985) did not interpret their results in the context of the PNS, but invoked Klopman's (1974) theory of orbital-controlled reactions. It was argued that the HOMO coefficients are larger on the α -carbon in the cyano-derivative than in the nitro-derivative, and therefore the cyano-derivative should react faster. A second factor deemed to be important is the HOMO-LUMO energy gap between the reacting groups, which is larger for $\text{CH}(\text{CN})_2^-$ than for CH_2NO_2^- , and should again make the cyano-derivative more reactive.

A PNS effect induced by resonance in remote substituents was reported by Bordwell *et al.* (1985). The $\text{S}_{\text{N}}2$ reaction of a series of 19 carbanions of the type ArCHSO_2Ph with *n*-butyl chloride was studied in Me_2SO . A plot of $\log k$ versus the $\text{p}K_{\text{a}}$ of $\text{ArCH}_2\text{SO}_2\text{Ph}$ yielded a good straight line with $\beta_{\text{nuc}} = 0.40$, but π -acceptor substituents in the *para*-position such as NO_2 , CN , SO_2Ph and COPh showed marked negative deviations from the plot. These deviations are strictly analogous to those in the deprotonation of ArCH_2NO_2 for *p*-CN and *p*- NO_2 (Fig. 11).

REACTIONS INVOLVING CARBOCATIONS

Richard (1989) reported that the rate constants for water addition to 1-aryl-2,2,2-trifluoroethyl carbocations [55] are about the same as for addition to





1-arylethyl carbocations [56]. This is surprising because [55] is at least 8 kcal mol⁻¹ less stable than [56]. Apparently the much larger thermodynamic driving force of (121) is not reflected in an increased rate. Later work (Richard *et al.*, 1990) showed that steric hindrance by the CF₃ group accounts for only a fraction of the effect. Hence these results imply that k_0 for (121) is lower than that for (122). Inasmuch as resonance plays a major role in the stabilization of these carbocations, k_0 for both reactions must be subject to a rate-reducing PNS effect from early loss of this resonance. The lower k_0 for (121) must mean more resonance stabilization in [55] than in [56], because the electron-withdrawing polar effect of the CF₃ group enhances the demand for resonance stabilization. However, the polar effect of the CF₃ group is stronger than the enhancement of the resonance effect, which explains why [55] is less stable than [56].

Richard (1989) expresses the competition between the resonance and polar effects on rate and equilibrium constants in terms of (123). Here $(K_{\text{CF}_3}/K_{\text{CH}_3})_{\text{I}}$ represents the degree by which the inductive (I) effect of the CF₃

$$\log(k_{\text{CF}_3}/k_{\text{CH}_3}) = \rho_{\text{nor}}^{\text{I}} \log(K_{\text{CF}_3}/K_{\text{CH}_3})_{\text{I}} + \rho_{\text{nor}}^{\text{R}} \log(K_{\text{CF}_3}/K_{\text{CH}_3})_{\text{R}} \quad (123)$$

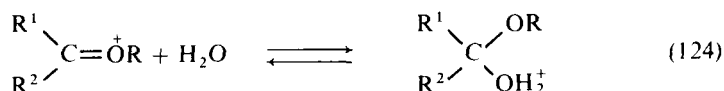
group increases the equilibrium constant of (121) relative to that of (122), while $(K_{\text{CF}_3}/K_{\text{CH}_3})_{\text{R}}$ represents the reduction of the equilibrium constant by the resonance effect. Note that, since the equilibrium constant for (121) is larger than for (122), we have $(K_{\text{CF}_3}/K_{\text{CH}_3})_{\text{I}} \gg 1$ and $(K_{\text{CF}_3}/K_{\text{CH}_3})_{\text{R}} < 1$. The factors $\rho_{\text{nor}}^{\text{I}}$ and $\rho_{\text{nor}}^{\text{R}}$ measure how much of the inductive and resonance effects are expressed at the transition state. In order for $\log(k_{\text{CF}_3}/k_{\text{CH}_3})$ to reflect the experimental value (≈ 0), the relationship $\rho_{\text{nor}}^{\text{R}} > \rho_{\text{nor}}^{\text{I}}$ is required, implying that loss of resonance stabilization is ahead of loss of the inductive stabilization. From an analysis of substituent effects on rate and equilibrium constants, $\rho_{\text{nor}}^{\text{I}} = 0.42$ and $\rho_{\text{nor}}^{\text{R}} = 0.53$ were calculated, consistent with the above requirement.

Richard's analysis is consistent with the PNS formalism. Since inductive effects develop (or are lost) synchronously with charge transfer or bond changes, loss of resonance that is ahead of loss of an inductive effect implies that loss of resonance is also ahead of C—O bond formation. The only difference between Richard's example and the reactions with carbanions is that, in the latter, bond formation is usually measured by polar substituent

effects on a different molecule (β_B , β_{nuc}^n) while in the present example bond formation is measured by polar substituent effects within the same molecule (ρ_{nor}^1). We note that (123) is quite similar to (27), except that (27) refers to the formation rather than destruction of a carbanion.

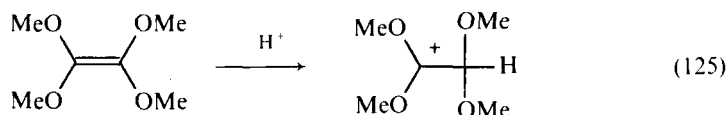
A further analogy between the situation for resonance-stabilized cations and anions can be seen if the change induced by substituting CH_3 for CF_3 is treated as a polar substituent effect on k_0 . We recall that polar substituents increase k_0 in reactions involving carbanions if the substituents help in stabilizing the carbanion, because they reduce the demand for resonance stabilization; they decrease k_0 if they oppose and thereby enhance demand for the resonance effect. The same is true for cations, with [55] and [56] providing an example where the substituent (CF_3) opposes the resonance effect, thereby lowering k_0 .

Further examples of imbalances between resonance and polar effects in reactions of carbocations have been reported by Richard *et al.* (1984, 1990) and McClelland *et al.* (1989). Furthermore, Amyes and Jencks (1989) describe analogous findings for the reaction of oxocarbenium ions with water (124). By analysing the effect of changing substituents on rate and



equilibrium constants of (124), they concluded that the fraction of polar effect ($\text{R}^1=\text{H}\rightarrow\text{CH}_3$) expressed in the transition state is 0.27, that of the resonance effect ($\text{R}^1=\text{CH}_3\rightarrow\text{Ph}$) 0.37. In other words, loss of resonance stabilization of the oxocarbenium ions is ahead of the polar effect, just as in the previous example.

A recent study of the protonation of tetramethoxyethene to form the corresponding carbocation (125) shows another type of PNS-effect (Kresge

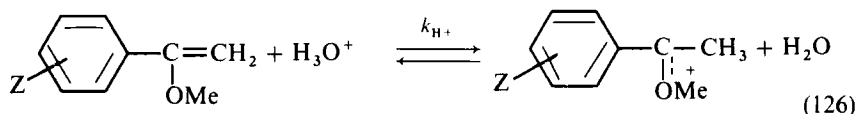


and Leibovitch, 1990). The rate constant for (125) is about 10^6 -fold lower than for the protonation of 1,1-dimethoxyethane, which was attributed to stabilization of the tetramethoxyethene by conjugation of the π -bond with the two extra methoxy groups. However, this rate reduction was shown to be about 600-fold stronger than expected on the basis of an estimated 10.4 kcal mol⁻¹ stabilization of the alkene and a degree of proton transfer at the transition state of about 0.42 calculated from a Brønsted α_{BH} -value ($\text{BH} = \text{RCOOH}$). It was concluded that the stronger than expected rate reduction is

probably a PNS effect whereby the loss of conjugation of the methoxy groups with the π -bond is ahead of the proton transfer.

AN EXAMPLE OF PERFECT SYNCHRONIZATION?

An interesting case is the protonation of α -methoxystyrenes to form alkoxy-carbocations according to (126) (Toullec, 1989). A plot of $\log k_{H^+}$ versus the



$\text{p}K_{\text{a}}$ for the oxocarbenium ion is shown in Fig. 18. By treating $\log k_{H^+}$ and $(\text{p}K_{\text{a}})_{\text{oxo}}$ by the Young-Jencks equation (Young and Jencks, 1977) shown in (127), the following parameters were obtained: $\rho^n(k_{H^+}) = -2.33$, $\rho^n(\text{p}K_{\text{a}})_{\text{oxo}} = -3.41$, $\rho^r(k_{H^+}) = -0.97$ and $\rho^r(\text{p}K_{\text{a}})_{\text{oxo}} = -2.28$. From these parameters, one calculates $\rho^n(k_{H^+})/\rho^n(\text{p}K_{\text{a}})_{\text{oxo}} = 0.68$, which expresses the degree of polar effect development in the transition state and which may be taken as a measure of charge or proton transfer, and $\rho^r(k_{H^+})/\rho^r(\text{p}K_{\text{a}})_{\text{oxo}} = 0.43$, which expresses the degree of resonance effect developed at the transition state. Resonance development again lags behind charge transfer or bond formation.

Curiously, after offering this analysis, Toullec discards it and suggests a new analysis based on the version (128) of the Marcus equation with $\Delta G_{\text{R}}^0 = \Delta G_{\text{obsd}}^0 - w_{\text{r}} + w_{\text{p}}$. The dashed line in Fig. 18 was calculated from (128)

$$\log k \text{ or } \log K = \rho^n \sigma^n + \rho^r(\sigma^+ - \sigma_n) + \text{constant} \quad (127)$$

$$\Delta G^\ddagger = w_{\text{r}} + \Delta G_0^\ddagger + \frac{\Delta G_{\text{R}}^0}{2} + \frac{(\Delta G_{\text{R}}^0)^2}{16 \Delta G_0^\ddagger} \quad (128)$$

with $\Delta G_0^\ddagger = 3.59 \text{ kcal mol}^{-1}$, $w_{\text{r}} = 10.64 \text{ kcal mol}^{-1}$ and $w_{\text{p}} = 12.43 \text{ kcal mol}^{-1}$. A value of β_{s} (in our terminology, this would be β_{C}) was then determined for each point according to (129), which yielded $\beta_{\text{s}} = 0.48, 0.53,$

$$\beta_{\text{s}} = \frac{\text{d}\Delta G^\ddagger}{\text{d}\Delta G_{\text{R}}^0} = 0.5 + \frac{\Delta G_{\text{R}}^0}{8 \Delta G_0^\ddagger} \quad (129)$$

0.56, 0.59, 0.64 and 0.68 for Z = 4-MeO, 4-Me, H, 4-Cl, 3-Cl and 3-NO₂ respectively. Now applying the Young-Jencks equation to $\log k_{H^+}$ by setting

$\rho^n(k_{H^+})\sigma^n = \rho^n(pK)_{\text{oxo}}\beta_s\sigma^n = -3.41\beta_s\sigma^n$, affords $\rho^r(k_{H^+}) = -1.04$ and hence $\rho^r(k_{H^+})/\rho^r(pK_a)_{\text{oxo}} = 0.46$. This value is relatively close to $\beta_s = 0.48$ and 0.53 for $Z = 4\text{-MeO}$ and 4-Me respectively, from which Toullec draws the conclusion that "there is a perfect agreement between calculated ρ^n and ρ^r data and those expected when one assumes a perfect balance between polar and resonance effects at the transition state, due to a synchronization between proton transfer and positive charge delocalization."

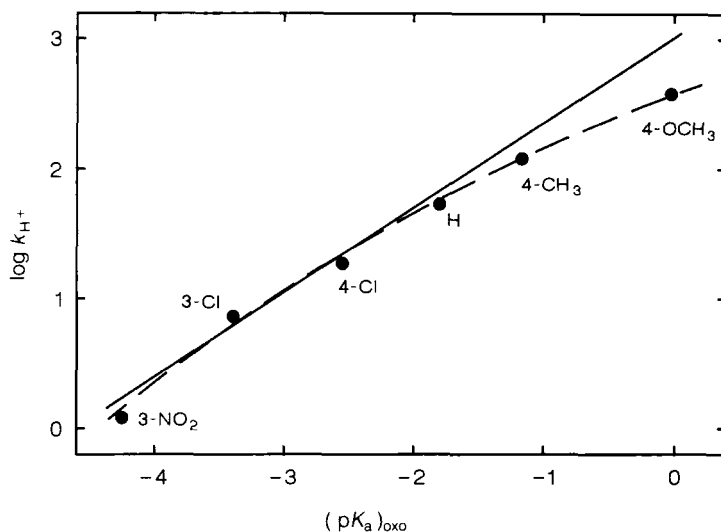


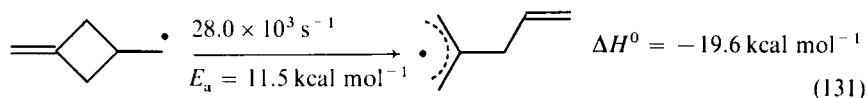
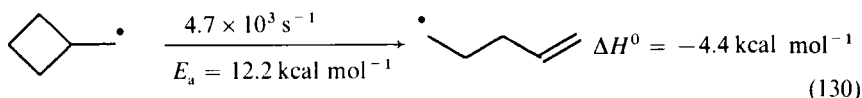
Fig. 18 Brønsted plot for the protonation of α -methoxystyrenes by H_3O^+ [reaction (125)]. The dashed line is calculated from (127); the solid line of slope 0.66 is the best straight line through the first four points. Adapted from Toullec (1989) with permission from the Royal Society of Chemistry, London.

Our view is that Toullec's analysis is not convincing, because it depends on the probably faulty premise that the Marcus equation accurately reproduces the data. Specifically, the implication that the curvature of the plot of $\log k_{H^+}$ versus $(pK_a)_{\text{oxo}}$ represents "Marcus curvature" seems problematic. For illuminating comments regarding the suitability (or lack thereof) of the Marcus equation in relating intrinsic barriers and curvatures in structure-reactivity plots, see Murdoch (1983). A more cogent interpretation of the Brønsted plot is that it represents a straight line with slope β_s of 0.66 defined by the electron-withdrawing substituents (solid line), while the π -donors (4-Me and 4-MeO) show the expected negative deviation caused by a PNS effect due to the enhanced resonance stabilization of the oxocarbenium ions.

The slope of the solid line is close to $\rho^n(k_{\text{H}^+})/\rho^n(\text{p}K_{\text{a}})_{\text{oxo}} = 0.68$ afforded by the original analysis.

REACTIONS INVOLVING FREE RADICALS

That radical reactions can be subject to PNS effects has recently been shown by Walton (1989). The reactions involved ring opening by β -scission of cyclic radicals as shown in (130)–(132). The exothermicity of the reaction increases



dramatically from (130) to (131) and (132) owing to the resonance stabilization of the products in (131) and (132). This contrasts with a very modest increase in the rate constant and a virtually unchanged activation energy. These results indicate a strongly imbalanced transition state with little resonance stabilization. MNDO calculations suggest that bond cleavage is about 85% and resonance development about 10% complete at the transition state.

If these estimates of bond cleavage and resonance development are correct, they would imply that this latter follows a much steeper function of bond order than in proton transfers. For example, for a $\beta_{\text{B}} = 0.85$ in a proton transfer, (33) predicts $\lambda_{\text{res}} = 0.72$ and (37) leads to $\lambda_{\text{res}} = 0.61$. For λ_{res} to become as low as 0.10, it would have to follow an approximate $(\beta_{\text{B}})^{14}$ law. Walton has suggested that the extreme imbalance may be due to the need for a flattening of C_γ and a rotation of 90° before maximum π -overlap is achieved in (131), and the need for flattening at both C_β and C_γ and rotation at both C_β and C_γ in (132), processes that can only occur after virtually complete bond cleavage.

The above example is probably the best documented case for the PNS at work in a free radical reaction, but there have been previous suggestions of

similarly imbalanced transition states in such reactions (Tedder and Walton, 1978, 1980). The fact that the addition of radicals such as $\text{H}\cdot$, $\text{CH}_3\cdot$ or $\text{CF}_3\cdot$ to 1,3-butadiene is only about tenfold faster than addition to ethylene (Cvetanović and Irwin, 1967), despite the strong allylic stabilization in the products derived from 1,3-butadiene, also suggests a PNS effect of delayed resonance development (Walton, 1989).

8 Concluding remarks

Originally the PNS was called the principle of *imperfect* synchronization (Bernasconi, 1985), a name borrowed from Hine (1977), who used the expression in the context of interpreting exceptions to the Leffler–Grunwald principle (Leffler and Grunwald, 1963). To quote: “Many of the exceptions may be explained in terms of (a) the principle of least motion or (b) imperfect synchronization of the various changes that take place during the reaction (which in some cases results in non-monotonic changes in structural or other features with progress along the reaction coordinate).” Curiously, Hine left it there without further elaboration or explanations.

The meaning I have given to the term PNS is that it describes the relationship between intrinsic rate constants and transition-state imbalances, as expressed in (40) or (41) (Bernasconi, 1985, 1987, 1989). On the other hand, the credit for recognizing the existence of transition-state imbalances in numerous reactions, either by calling them imbalances or describing the phenomenon in different terms, clearly goes to others (Bunnett, 1962; More O’Ferrall, 1970; Harris and Kurz, 1970; Bordwell and Boyle, 1972, 1975; Jencks and Jencks, 1977; Harris *et al.*, 1979; Murdoch, 1983; Gajewski and Gilbert, 1984; Kreevoy and Lee, 1984; Lewis and Hu, 1984).

I hope this review has demonstrated the power of the PNS as a conceptual framework aimed at understanding structure–reactivity relationships in chemical reactions using the language of the physical organic chemist. Its greatest usefulness is probably in providing a qualitative understanding of such relationships, but an accumulating data base, particularly for carb-anion-forming reactions, shows that it may become a fairly reliable (semi)-quantitative tool as well.

A major strength of the PNS that distinguishes it from other “principles” such as the reactivity–selectivity principle (Pross, 1977; Giese, 1977; Rappoport, 1985; Bunzel and Wilson, 1987) or the Bema Hapothle (Hammond, 1955; Leffler and Grunwald, 1963; Jencks, 1985) is that it is very general and, within the constraints of the definitions of the progress variables [β_{M} and λ_{f} in (40)], mathematically provable. In other words, if β_{M} is a true measure of a bond change or charge-transfer process and λ_{f} a measure of the progress in

the stabilizing or destabilizing "factor" at the transition state then (40) always gives the correct description of the change in k_0 , without exception. This infallibility contrasts with, for example, the reactivity-selectivity principle, for which so many exceptions have been reported (Johnson, 1975, 1980; Young and Jencks, 1979; Arnett and Reich, 1980; Bordwell and Hughes, 1980, 1982; Arnett and Molter, 1986) that it has been suggested that it be abandoned as a general principle.

The infallible adherence to (40) might also be viewed as a weakness of the PNS: since in most cases λ_f cannot be measured directly, any trend in k_0 could be "explained" by arbitrarily choosing the appropriate magnitude of λ_f . However, the arbitrariness is more apparent than real because one can usually infer from *independent* experiments and/or from theoretical considerations whether λ_f should be greater or less than β_M . For example, late development of resonance and solvation in carbanion-forming reactions is not only inferred from the low k_0 -value, but there is direct evidence for it from the imbalances in the Brønsted coefficients ($a_{CH} > \beta_B$). At the same time, there is considerable theoretical support for the notion that resonance should develop late (Pross and Shaik, 1982; Dewar, 1984; Jencks, 1985; Williams *et al.*, 1985). In fact, with respect to resonance effects, it is safe to conclude that their development *always* lags behind charge transfer. This means that not only is (29) a good description of the situation but we can state that λ_{res} is always smaller than β_B in equations such as (23), (26) or (29), i.e. k_0 is always decreased by resonance effects. By implication, the internal consistency of these results also supports the notion that β_B is a reasonably good measure of charge transfer at the transition state.

Other factors whose development seems invariably to lag behind charge transfer or bond changes and hence lower k_0 include solvation, intramolecular hydrogen bonding and π -overlap with remote phenyl groups, e.g. [37]. Again, there is good theoretical support for such lags, especially for lagging solvation. In fact, among the PNS factors identified thus far, the only ones that appear to develop ahead of bond formation are the soft acid-soft base interaction between a nucleophile and electrophile in thiolate ion additions to olefins, and steric effects (F-strain). However, more examples are needed to test the generality of this conclusion. One might also be tempted to view polar effects that enhance k_0 as a product-stabilizing factor that develops early (PNS-effect), but, as was discussed in Section 4, this enhancement of k_0 is not a phenomenon caused by the polar substituent but is a consequence of the imbalanced transition state. In other words, the polar substituent effect is only ahead of the resonance effect, but is synchronous with charge transfer or bond formation, and hence this is not a PNS-effect caused by the polar substituent.

In view of the universality of the PNS, one would expect that it also

operates in enzyme-catalysed reactions. One generally recognized factor responsible for the efficiency of enzymes is that certain functional groups of the enzyme are optimally positioned with respect to the reaction centre. If, for example, the purpose of such a group is to solvate a developing charge in a reaction product, the optimal positioning may lead to solvation that is essentially synchronous with charge development. This would translate into a circumvention of the typical k_0 -lowering PNS effect of late solvation in solution reactions. Another important mechanism used by enzymes is to desolvate reactants by virtue of binding them into a cavity from which the solvent is excluded (Gilbert, 1981; Dewar and Storch, 1985). Part of the resulting acceleration may simply be a consequence of an increase in the equilibrium constant of the reaction, as recently discussed by Gilbert (1981). However, a considerable fraction of the acceleration may again be an effect on k_0 resulting from the avoidance of the k_0 -lowering PNS of early desolvation. No systematic studies have been performed in the area of enzyme reactions that would specifically address the contribution to the rate by the avoidance of PNS effects. Clearly this is an area in need of attention.

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References

- Abraham, M. H., Grellier, P. L., Prior, D. V., Morris, J. J., Taylor, P. J., Laurence, C. and Berthelot, M. (1989). *Tetrahedron Lett.* **30**, 2571
Ahrens, M.-L. and Maass, G. (1968). *Angew. Chem. Int. Ed. Engl.* **7**, 818
Albery, W. J. (1980). *Annu. Rev. Phys. Chem.* **31**, 227
Albery, W. J. and Kreevoy, M. M. (1978). *Adv. Phys. Org. Chem.* **16**, 87.
Albery, W. J., Bernasconi, C. F. and Kresge, A. J. (1988). *J. Phys. Org. Chem.* **1**, 29
Amyes, T. L. and Jencks, W. P. (1989). *J. Am. Chem. Soc.* **111**, 7888
Arnett, E. M. and Harrelson, J. A. (1987). *J. Am. Chem. Soc.* **109**, 809
Arnett, E. M. and Molter, K. E. (1985). *Acc. Chem. Res.* **18**, 339
Arnett, E. M. and Molter, K. E. (1986). *J. Phys. Chem.* **90**, 383
Arnett, E. M. and Reich, R. (1980). *J. Am. Chem. Soc.* **102**, 5892
Bednar, R. A. and Jencks, W. P. (1985). *J. Am. Chem. Soc.* **107**, 7117, 7126
Bell, R. P. (1973). *The Proton in Chemistry*, 2nd edn, Chap. 10. Cornell University Press, Ithaca, New York.
Bell, R. P. and Grainger, S. (1976). *J. Chem. Soc. Perkin Trans. 2*, 1367
Bell, R. P. and Tranter, R. L. (1974). *Proc. R. Soc. Lond.* **A337**, 517

- Bergman, N.-A., Saunders, W. J., Jr and Melander, L. (1972). *Acta Chem. Scand.* **26**, 1130
- Bernasconi, C. F. (1982). *Pure Appl. Chem.* **54**, 2335
- Bernasconi, C. F. (1985). *Tetrahedron* **41**, 3219
- Bernasconi, C. F. (1987). *Acc. Chem. Res.* **20**, 301
- Bernasconi, C. F. (1989). *Tetrahedron* **45**, 4017
- Bernasconi, C. F. and Bunnell, R. D. (1985). *Isr. J. Chem.* **26**, 420
- Bernasconi, C. F. and Bunnell, R. D. (1988). *J. Am. Chem. Soc.* **110**, 2900
- Bernasconi, C. F. and Carré, D. J. (1979). *J. Am. Chem. Soc.* **91**, 2698
- Bernasconi, C. F. and Fairchild, D. E. (1992). Unpublished results
- Bernasconi, C. F. and Fornarini, S. (1980). *J. Am. Chem. Soc.* **102**, 5329
- Bernasconi, C. F. and Hibdon, S. A. (1983). *J. Am. Chem. Soc.* **105**, 4343
- Bernasconi, C. F. and Kanavarioti, A. (1979). *J. Org. Chem.* **44**, 4829
- Bernasconi, C. F. and Kanavarioti, A. (1986). *J. Am. Chem. Soc.* **108**, 7744
- Bernasconi, C. F. and Killion, R. B., Jr (1988). *J. Am. Chem. Soc.* **110**, 7506
- Bernasconi, C. F. and Killion, R. B., Jr (1989). *J. Org. Chem.* **54**, 2878
- Bernasconi, C. F. and Ni, J. X. (1992). Unpublished results
- Bernasconi, C. F. and Oliphant, N. (1992). Unpublished results
- Bernasconi, C. F. and Panda, M. (1987). *J. Org. Chem.* **52**, 3042
- Bernasconi, C. F. and Panda, M. (1992). Unpublished results
- Bernasconi, C. F. and Paschalis, P. (1986). *J. Am. Chem. Soc.* **108**, 2969
- Bernasconi, C. F. and Paschalis, P. (1989). *J. Am. Chem. Soc.* **111**, 5893
- Bernasconi, C. F. and Renfrow, R. A. (1987). *J. Org. Chem.* **52**, 3035
- Bernasconi, C. F. and Schuck, D. F. (1992). Unpublished results
- Bernasconi, C. F. and Stronach, M. W. (1990). *J. Am. Chem. Soc.* **112**, 8448
- Bernasconi, C. F. and Stronach, M. W. (1991a). *J. Am. Chem. Soc.* **113**, 2222
- Bernasconi, C. F. and Stronach, M. W. (1991b). *J. Org. Chem.* **56**, 3016
- Bernasconi, C. F. and Terrier, F. (1987). *J. Am. Chem. Soc.* **109**, 7115
- Bernasconi, C. F. and Wenzel, P. J. (1992). Unpublished results
- Bernasconi, C. F. and Wiersema, D. (1992). Unpublished results
- Bernasconi, C. F., Fox, J. P. and Fornarini, S. (1980). *J. Am. Chem. Soc.* **102**, 2810
- Bernasconi, C. F., Murray, C. J., Fox, J. P. and Carré, D. J. (1983). *J. Am. Chem. Soc.* **105**, 4349
- Bernasconi, C. F., Laibelman, A. and Zitomer, J. L. (1985). *J. Am. Chem. Soc.* **107**, 6563
- Bernasconi, C. F., Renfrow, R. A. and Tia, P. R. (1986). *J. Am. Chem. Soc.* **108**, 4541
- Bernasconi, C. F., Bunnell, R. D. and Terrier, F. (1988a). *J. Am. Chem. Soc.* **110**, 6514
- Bernasconi, C. F., Kliner, D. A. V., Mullin, A. S. and Ni, J. X. (1988b). *J. Org. Chem.* **53**, 3342
- Bernasconi, C. F., Schuck, D. F. and Zitomer, J. L. (1992). Unpublished results
- Bone, R., Cullis, P. and Wolfenden, R. (1983). *J. Am. Chem. Soc.* **105**, 1339
- Bordwell, F. G. (1988). *Acc. Chem. Res.* **21**, 457
- Bordwell, F. G. and Boyle, W. J., Jr (1972). *J. Am. Chem. Soc.* **94**, 3907
- Bordwell, F. G. and Boyle, W. J., Jr (1975). *J. Am. Chem. Soc.* **97**, 3447
- Bordwell, F. G. and Hughes, D. H. (1980). *J. Org. Chem.* **45**, 3314
- Bordwell, F. G. and Hughes, D. H. (1982). *J. Org. Chem.* **47**, 3224
- Bordwell, F. G. and Hughes, D. L. (1983). *J. Org. Chem.* **48**, 2206
- Bordwell, F. G. and Hughes, D. L. (1985). *J. Am. Chem. Soc.* **107**, 4737
- Bordwell, F. G., Bartmess, J. E. and Hautala, J. A. (1978). *J. Org. Chem.* **43**, 3107

- Bordwell, F. G., Branca, J. C. and Cripe, T. A. (1985). *Isr. J. Chem.* **26**, 357
- Bordwell, F. G., Cripe, T. A. and Hughes, D. L. (1987). *Adv. Chem. Ser.* **215**, 137
- Bowden, K. and Hirani, S. I. J. (1990). *J. Chem. Soc. Perkin Trans. 2*, 885
- Brown, H. C. (1946). *Science* **103**, 385
- Brown, H. C., Taylor, M. D., Gerstein, M. and Bartholomay, H. (1944). *J. Am. Chem. Soc.* **66**, 431
- Buckingham, D. A., Clark, C. R., McKeown, R. H. and Wong, O. (1987). *J. Am. Chem. Soc.* **109**, 466
- Buncel, E. and Wilson, H. (1977). *Adv. Phys. Org. Chem.* **14**, 133
- Buncel, E. and Wilson, H. (1987). *J. Chem. Ed.* **64**, 475
- Bunnett, J. F. (1962). *Angew. Chem. Int. Ed. Engl.* **1**, 225
- Bunting, J. W. and Stefanidis, D. (1988). *J. Am. Chem. Soc.* **110**, 4008
- Bunting, J. W. and Stefanidis, D. (1989). *J. Am. Chem. Soc.* **111**, 5834
- Caldin, E. F. (1959). *J. Chem. Soc.*, 3345
- Caldin, E. F. and Gold, V. (eds.) (1975). *Proton Transfer Reactions*. Wiley, New York
- Cohen, A. O. and Marcus, R. A. (1968). *J. Phys. Chem.* **72**, 4249
- Cox, J. P. L., Crampton, M. R. and Wright, P. (1988). *J. Chem. Soc. Perkin Trans. 2*, 25
- Creary, X. (1980). *J. Org. Chem.* **45**, 280
- Crooks, J. E. (1975). In *Proton Transfer Reactions* (ed. E. F. Caldin and V. Gold), p. 153. Wiley, New York
- Cvetanović, R. J. and Irwin, R. S. (1967). *J. Chem. Phys.* **46**, 1694
- Delbecq, F. (1984). *J. Org. Chem.* **49**, 4838
- Dewar, M. J. S. (1984). *J. Am. Chem. Soc.* **106**, 209
- Dewar, M. J. S. and Storch, D. M. (1985). *Proc. Natl Acad. Sci. USA* **82**, 2225
- Dust, J. M. and Arnold, D. R. (1983). *J. Am. Chem. Soc.* **105**, 1221
- Eberson, L. (1987). *Electron Transfer Reactions in Organic Chemistry*, p. 46. Springer, New York
- Eigen, M. (1964). *Angew. Chem. Int. Ed. Engl.* **3**, 1
- Farrell, P. G., Terrier, F., Xie, H.-Q. and Boubaker, T. (1990). *J. Org. Chem.* **55**, 2546
- Feather, J. A. and Gold, V. (1965). *J. Chem. Soc.*, 1752
- Friedman, M., Cavins, J. F. and Wall, J. S. (1965). *J. Am. Chem. Soc.* **87**, 3672
- Fujio, M., McIver, R. I. and Taft, R. W. (1981). *J. Am. Chem. Soc.* **103**, 4017
- Funderbunk, L. H. and Jencks, W. P. (1978). *J. Am. Chem. Soc.* **100**, 6708
- Gajewski, J. J. and Gilbert, K. E. (1984). *J. Org. Chem.* **49**, 11
- Gandler, J. R. (1989). In *The Chemistry of Double-Bonded Functional Groups* (ed. S. Patai), p. 733. Wiley, New York
- Gandler, J. R. and Bernasconi, C. F. (1989). *Organometallics* **8**, 2282
- Gandler, J. R. and Bernasconi, C. F. (1991). *J. Am. Chem. Soc.* **113**, in press
- Gertner, B. J., Whitnell, R. M., Wilson, K. R. and Hynes, J. T. (1991). *J. Am. Chem. Soc.* **113**, 74
- Giese, B. (1977). *Angew. Chem. Int. Ed. Engl.* **16**, 125
- Gilbert, H. F. (1980). *J. Am. Chem. Soc.* **102**, 7059
- Gilbert, H. F. (1981). *Biochemistry* **20**, 5643
- Gross, Z. and Hoz, S. (1988). *J. Am. Chem. Soc.* **110**, 7489
- Grunwald, E. (1985). *J. Am. Chem. Soc.* **107**, 125
- Hammond, G. S. (1955). *J. Am. Chem. Soc.* **77**, 334
- Harris, J. C. and Kurz, J. L. (1970). *J. Am. Chem. Soc.* **92**, 349
- Harris, J. M. and McManus, S. P. (1987). *Adv. Chem. Ser.* **215**, 23

- Harris, J. M., Shafer, S. G., Moffatt, J. R. and Becker, A. R. (1979). *J. Am. Chem. Soc.* **101**, 3295
- Hehre, W. J., Radom, L., Schleyer, P. v. R. and Pople, J. A. (1986). *Ab Initio Molecular Orbital Theory*. Wiley, New York
- Hibbert, F. (1977). *Compr. Chem. Kinet.* **8**, 97
- Hine, J. (1971). *J. Am. Chem. Soc.* **93**, 3701
- Hine, J. (1972). *J. Am. Chem. Soc.* **94**, 5766
- Hine, J. (1975a). *Structural Effects on Equilibria in Organic Chemistry*, Chap. 3. Wiley, New York
- Hine, J. (1975b). *Structural Effects on Equilibria in Organic Chemistry*, p. 225. Wiley, New York
- Hine, J. (1977). *Adv. Phys. Org. Chem.* **15**, 1
- Hine, J. and Weimar, R. D., Jr (1965). *J. Am. Chem. Soc.* **87**, 3387
- Hine, J., Houston, J. G. and Mulders, J. (1965). *J. Am. Chem. Soc.* **87**, 5050
- Hoz, S. (1987). *Adv. Chem. Ser.* **215**, 181
- Hoz, S. and Speizman, D. (1983). *J. Org. Chem.* **48**, 2904
- Hoz, S., Gross, Z. and Cohen, D. (1985). *J. Org. Chem.* **50**, 832
- Hupe, D. J. and Jencks, W. P. (1977). *J. Am. Chem. Soc.* **99**, 451
- Hupe, D. J. and Wu, D. (1977). *J. Am. Chem. Soc.* **99**, 7653
- Huskey, W. P. and Schowen, R. L. (1987). *Gazz. Chim. Ital.* **117**, 409
- Jencks, D. A. and Jencks, W. P. (1977). *J. Am. Chem. Soc.* **99**, 7948
- Jencks, W. P. (1968). *Catalysis in Chemistry and Enzymology*, p. 178. McGraw-Hill, New York
- Jencks, W. P. (1972). *Chem. Rev.* **72**, 705
- Jencks, W. P. (1985). *Chem. Rev.* **85**, 511
- Jencks, W. P. (1987). *Adv. Chem. Ser.* **215**, 155
- Jencks, W. P., Brant, S. R., Gandler, J. R., Fendrich, G. and Nakamura, C. (1982). *J. Am. Chem. Soc.* **104**, 7045
- Jencks, W. P., Haber, M. T., Herschlag, D. and Nazaretian, K. L. (1986). *J. Am. Chem. Soc.* **108**, 479
- Johnson, C. D. (1975). *Chem. Rev.* **75**, 755
- Johnson, C. D. (1980). *Tetrahedron* **36**, 3461
- Keeffe, J. R. and Kresge, A. J. (1986). In *Investigation of Rates and Mechanisms of Reactions*, Part I (ed. C. F. Bernasconi), p. 747. Wiley, New York
- Keeffe, J. R., Morey, J., Palmer, C. A. and Lee, J. C. (1979). *J. Am. Chem. Soc.* **101**, 1295
- Klopman, G. (1974). *Chemical Reactivity and Reaction Paths*. Wiley, New York
- Kreevoy, M. M. and Lee, I.-S. H. (1984). *J. Am. Chem. Soc.* **106**, 2550
- Kresge, A. J. (1973). *Chem. Soc. Rev.* **2**, 475
- Kresge, A. J. (1974). *Can. J. Chem.* **52**, 1897
- Kresge, A. J. (1975a). *Acc. Chem. Res.* **8**, 354
- Kresge, A. J. (1975b). In *Proton Transfer Reactions* (ed. E. F. Caldin and V. Gold), p. 179. Wiley, New York
- Kresge, A. J. and Leibovitch, M. (1990). *Can. J. Chem.* **68**, 1786
- Kurz, J. L. (1989a). *J. Am. Chem. Soc.* **111**, 8631
- Kurz, J. L. (1989b). Personal communication
- Kurz, J. L. and Kurz, L. C. (1972). *J. Am. Chem. Soc.* **94**, 4451
- Kurz, J. L. and Kurz, L. C. (1985). *Isr. J. Chem.* **26**, 339
- Ladkani, D. and Rappoport, Z. (1974). *Chem. Ser.* **5**, 124
- Lee, I.-S. H., Ostović, D. and Kreevoy, M. M. (1988). *J. Am. Chem. Soc.* **110**, 3989
- Leffler, J. E. and Grunwald, E. (1963). *Rates and Equilibria of Organic Reactions*, p. 156. Wiley, New York

- Lewis, E. S. and Funderbunk, L. H. (1967). *J. Am. Chem. Soc.* **89**, 2322
- Lewis, E. S. and Hu, D. D. (1984). *J. Am. Chem. Soc.* **106**, 3292
- Lewis, E. S., Douglas, T. A. and McLaughlin, T. A. (1987a). *Adv. Chem. Ser.* **215**, 35
- Lewis, E. S., Yousaf, T. I. and Douglas, T. A. (1987b). *J. Am. Chem. Soc.* **109**, 2152
- McClelland, R. A., Kanagasabapathy, V. M., Banait, N. S. and Steenken, S. (1989). *J. Am. Chem. Soc.* **111**, 3966
- Marcus, R. A. (1956). *J. Chem. Phys.* **24**, 966
- Marcus, R. A. (1957). *J. Chem. Phys.* **26**, 867
- Marcus, R. A. (1964). *Annu. Rev. Phys. Chem.* **15**, 155
- Marcus, R. A. (1968). *J. Phys. Chem.* **72**, 891
- Marcus, R. A. (1969). *J. Am. Chem. Soc.* **91**, 7224
- Mashima, M., McIver, R. I., Taft, R. W., Bordwell, F. G. and Olmstead, W. N. (1984). *J. Am. Chem. Soc.* **106**, 2717
- More O'Ferrall, R. A. (1970). *J. Chem. Soc. (B)*, 274
- Murdoch, J. R. (1983). *J. Am. Chem. Soc.* **105**, 2159, 2600
- Murray, C. J. and Jencks, W. P. (1988). *J. Am. Chem. Soc.* **110**, 7561
- Murray, C. J. and Jencks, W. P. (1990). *J. Am. Chem. Soc.* **112**, 1880
- Palmer, J. L. and Jencks, W. P. (1980). *J. Am. Chem. Soc.* **102**, 6472
- Parker, A. J. (1969). *Chem. Rev.* **69**, 1
- Pearson, R. G. (1969). *Surv. Prog. Chem.* **5**, 1
- Pearson, R. G. and Songstad, J. (1967). *J. Am. Chem. Soc.* **89**, 1827
- Pohl, E. R., Wu, D. and Hupe, D. J. (1980). *J. Am. Chem. Soc.* **102**, 2759
- Pross, A. (1977). *Adv. Phys. Org. Chem.* **16**, 69
- Pross, A. (1984). *J. Org. Chem.* **49**, 1811
- Pross, A. (1985). *Adv. Phys. Org. Chem.* **21**, 99
- Pross, A. and Shaik, S. S. (1982). *J. Am. Chem. Soc.* **104**, 1129
- Pross, A. and Shaik, S. S. (1989). *Nouv. J. Chim.* **13**, 427
- Rappoport, Z. (ed.) (1985). *Isr. J. Chem.* **26**, 303-428 (reactivity-selectivity issue)
- Rappoport, Z. (1987). *Adv. Chem. Ser.* **215**, 399
- Rappoport, Z. and Topol, A. (1989). *J. Org. Chem.* **54**, 5967
- Richard, J. P. (1987). *J. Chem. Soc. Chem. Commun.*, 1768
- Richard, J. P. (1989). *J. Am. Chem. Soc.* **111**, 1455
- Richard, J. P., Amyes, T. L., Bei, L. and Stubblefield, V. (1990). *J. Am. Chem. Soc.* **112**, 9513
- Richard, J. P., Rothenberg, M. E. and Jencks, W. P. (1984). *J. Am. Chem. Soc.* **106**, 1361
- Ritchie, C. D. (1969a). In *Solute-Solvent Interactions* (ed. J. F. Coetzee and C. D. Ritchie), p. 219. Dekker, New York
- Ritchie, C. D. (1969b). *J. Am. Chem. Soc.* **91**, 6749
- Ritchie, C. D. (1983). *J. Am. Chem. Soc.* **105**, 7313
- Ritchie, C. D. (1987). *Adv. Chem. Ser.* **215**, 169
- Rosenberg, M., Balaz, S., Sturdik, E. and Kucher, A. (1987). *Collect. Czech. Chem. Commun.* **52**, 425.
- Sander, E. G. and Jencks, W. P. (1968). *J. Am. Chem. Soc.* **90**, 6154
- Saunders, W. H., Jr and Cockerill, A. F. (1973). *Mechanisms of Elimination Reactions*. Wiley, New York
- Shaik, S. S. (1985). *Prog. Phys. Org. Chem.* **15**, 197
- Simonnin, M. P., Xie, H. Q., Terrier, F., Lelièvre, J. and Farrell, P. G. (1989). *J. Chem. Soc. Perkin Trans. 2*, 1553
- Srinivasan, P. and Stewart, R. (1976). *J. Chem. Soc. Perkin Trans. 2*, 674
- Stefanidis, D. and Bunting, J. W. (1991). *J. Am. Chem. Soc.* **113**, 991
- Taft, R. W. (1983). *Prog. Phys. Org. Chem.* **14**, 247

- Taft, R. W. and Topsom, R. D. (1987). *Prog. Phys. Org. Chem.* **16**, 1.
- Tedder, J. M. and Walton, J. C. (1978). *Adv. Phys. Org. Chem.* **18**, 51
- Tedder, J. M. and Walton, J. C. (1980). *Tetrahedron* **36**, 701
- Terrier, F., Farrell, P. G., Lelièvre, J., Top, S. and Jaouen, G. (1985a). *Organometallics* **4**, 1291
- Terrier, F., Lelièvre, J., Chatrousse, A.-P. and Farrell, P. (1985b). *J. Chem. Soc. Perkin Trans. 2*, 1479
- Terrier, F., Lelièvre, J., Chatrousse, A.-P., Schaal, R. and Farrell, P. (1987). *Can. J. Chem.* **65**, 1980
- Terrier, F., Degorre, F., Kiffer, D. and Laloi, M. (1988). *Bull. Soc. Chim. France*, 415
- Terrier, F., Chatrousse, A.-P., Kizilian, E., Ignateu, N. V. and Yagupolskii, L. M. (1989). *Bull. Soc. Chim. France*, 627
- Terrier, F., Xie, H.-Q. and Farrell, P. G. (1990). *J. Org. Chem.* **55**, 2610
- Toullec, J. (1989). *J. Chem. Soc. Perkin Trans. 2*, 167
- Van der Zwan, G. and Hynes, J. T. (1982). *J. Chem. Phys.* **76**, 2993
- Walton, J. C. (1989). *J. Chem. Soc. Perkin Trans. 2*, 173
- Wang, X. and Houk, K. N. (1988). *J. Am. Chem. Soc.* **110**, 1870
- Washabaugh, M. W. and Jencks, W. P. (1989). *J. Am. Chem. Soc.* **111**, 674, 683
- Wells, C. F. (1979). *Adv. Chem. Ser.* **177**, 53
- Wiberg, K. B. and Laidig, K. E. (1988). *J. Am. Chem. Soc.* **110**, 1872
- Williams, I. H., Spangler, D., Maggiora, G. M. and Schowen, R. L. (1985). *J. Am. Chem. Soc.* **107**, 7717
- Wilson, J. C., Källsson, I. and Saunders, W. H., Jr (1980). *J. Am. Chem. Soc.* **102**, 4780
- Young, P. R. and Jencks, W. P. (1977). *J. Am. Chem. Soc.* **99**, 8238
- Young, P. R. and Jencks, W. P. (1979). *J. Am. Chem. Soc.* **101**, 3288

Solvent-induced Changes in the Selectivity of Solvolyses in Aqueous Alcohols and Related Mixtures

RACHEL TA-SHMA and ZVI RAPPOPORT

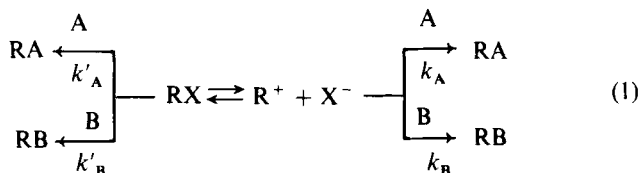
Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel

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1 Introduction

Solvolysis is an important reaction in organic chemistry. Its mechanism has been extensively investigated using a variety of tools, such as kinetics, stereochemistry, nature of products, structural and medium changes, isotope effects and many others (see, for example, Streitwieser, 1962; Olah and Schleyer, 1968, 1976; Vogel, 1985; Lowry and Richardson, 1987). The solvolysis of an alkyl halide or sulphonate is frequently conducted in a binary aqueous-organic medium, and when the organic component of the mixture is also a nucleophile capable of forming a stable product, the reaction can give, in the absence of additional features such as rearrangement, two substitution products derived from both solvent components. The term "selectivity" relates to the ability of the covalent precursor, or of a cationic intermediate derived from it, to react preferentially with one of the binary mixture components, and is experimentally reflected in the product mixture.

This review deals with the selectivity of an electrophilic carbon centre carrying a nucleofuge (RX) or of a solvolytically generated carbocation species (R^+) towards the two nucleophilic solvent components. Selectivities in solvolysis of acyl derivatives RCOX (e.g. Bentley and Koo, 1989) and in deamination reactions are excluded. Most generally, the reaction can be written as in (1), where both a concerted and a stepwise route are depicted,



and R^+ represents an intimate ion pair (IIP), a solvent-separated ion pair (SSIP) or a free carbocation according to Winstein's solvolysis scheme (Winstein *et al.*, 1965; Raber *et al.*, 1974). The selectivity is usually expressed by the ratio k_A/k_B (or k'_A/k'_B), where A and B are the two nucleophilic solvents. One of them is nearly always water (W) and the other is an alcohol (SOH) [the most frequently used are ethanol (E), methanol (M) and trifluoroethanol (TFE)]. The selectivity is calculated from the observed ratio of the product concentrations $[RA]/[RB]$ and from the concentrations of the two nucleophiles according to (2), in deriving which it is assumed that

$$S = \frac{k_A}{k_B} \quad \text{or} \quad \frac{k'_A}{k'_B} = \frac{[RA][B]}{[RB][A]} \quad (2)$$

the product ratio is the ratio of the two second-order rates for the reaction of the electrophilic species (RX or R^+) with the two nucleophiles.

The selectivity values thus calculated should be constant at different solvent compositions for a reaction proceeding through any single electrophilic species in the ideal case when the solvent composition does not affect the ratio of the individual rate constants. If this is indeed the case, the knowledge is important if the selectivity ratios are to be used as a mechanistic probe, since they are mostly obtained in a single binary mixture, which may differ for different substrates.

For demonstration, we list in Table 1 several selectivity values for various systems calculated by us or by the authors from the product ratios. Product ratios are abundant in the literature, but they, or the selectivity ratios derived from them, are not always expressed explicitly. More frequently, they are buried in the experimental section and their accuracy is mostly unknown. Moreover, some of the values in the presence of an added base

Table 1 k_E/k_W Ratios from the solvolysis of a variety of solvolysing systems in aqueous ethanol.

Solvolysing system	$T/^\circ\text{C}$	%EtOH (v/v)	k_E/k_W	Reference
Et_2CHBr	80	60	0.71 ± 0.06	Hudson and Ragoonanan (1970)
$\text{Et}_2\text{CHBr}/0.24 \text{ M KOH}$	80	60	1.06^a	Hudson and Ragoonanan (1970)
$\text{Et}_2\text{CHBr}/1.3 \text{ M KOH}$	80	60	1.52^a	Hudson and Ragoonanan (1970)
Cyclopropylcyclopropyl-OTs ^b	25	50	1.15	Howell and Jewett (1975)
	25	80	0.70 ± 0.01	Howell and Jewett (1975)
2-Octyl-OBs	54	70	$0.80(0.56^c)$	Gregoriou and Varveri (1978)
	73	70	$0.77(0.52^c)$	Gregoriou and Varveri (1978)
1-Chloro-1,2-dimethylcyclohexane ^d	70	80		Becker and Grob (1973)
			0.45^e ; 0.54^f	Becker and Grob (1973)
			0.63^e ; 0.40^f	Becker and Grob (1973)
			0.41^e ; 0.45^f	Becker and Grob (1973)
			0.59^e ; 0.27^f	Becker and Grob (1973)
<i>cis</i> -				
<i>trans</i> -				
<i>cis</i> - (+ AgNO ₃)				
<i>trans</i> - (+ AgNO ₃)				
<i>threo</i> -3-Phenyl-2-butyl-OTs	25	50	0.93 ; 0.89^g ; 0.92^h	Cramer and Jewett (1972)
4-Tricycl-OTf/0.06 M Et ₃ N	232.8	66	0.84	Sherrod <i>et al.</i> (1972)
Apocamphyl-OTf/0.06 M Et ₃ N	99	66	1.27	Sherrod <i>et al.</i> (1972)
1-Methyl-4-tricyclo[2.2.2.0 ^{2,6}]-octyl-OTf/0.06 M Et ₃ N	41	66	0.97	Sherrod <i>et al.</i> (1972)
1-Adamantyl-OTs	25	80	0.42	Meyer and Martin (1976)
	25	80	0.33	Kevill <i>et al.</i> (1970)
3-Bromo-1-adamantyl-OTs	60	80	0.54	Meyer and Martin (1976)
3-Cyano-2-oxa-1-adamantyl-OTs	120	80	0.51	Meyer and Martin (1976)
<i>N</i> -Methyl-3-cyano-2-aza-1-adamantyl-OTs	45	80	0.27	Meyer and Martin (1976)
3-Cyano-1-adamantyl-OTs	80	80	0.36	Meyer and Martin (1976)
2-Oxa-1-adamantyl-OTs	60	80	0.55	Meyer and Martin (1976)

Table 1 (continued)

Solvolyzing system	T/°C	%EtOH (v/v)	k _E /k _W	Reference
1-R-3-Br-adamantane R = CH ₂ =C(Me)	70	80	0.54	Fischer and Grob (1978)
Ph	70		0.54	Fischer and Grob (1978)
OH	70		0.78	Fischer and Grob (1978)
SH	70		0.59	Fischer and Grob (1978)
<i>p</i> -HOC ₆ H ₄	70		0.81	Fischer and Grob (1978)
<i>p</i> -MeOC ₆ H ₄	70		0.54	Fischer and Grob (1978)
<i>p</i> -H ₂ NC ₆ H ₄	70		0.49	Fischer and Grob (1978)
<i>p</i> -MeC ₆ H ₄	70		0.54	Fischer and Grob (1978)
<i>p</i> -O ₂ NC ₆ H ₄	70		0.44	Fischer and Grob (1978)
MeCCH ₂ CH ₂	70		0.54	Fischer and Grob (1978)
<i>cis</i> -4- <i>t</i> -Butylcyclohexyl-OBs/ CaCO ₃	45	60	0.59 ⁱ	Shiner and Jewett (1964)
<i>trans</i> -4- <i>t</i> -Butylcyclohexyl-OBs/ CaCO ₃	reflux	50	0.72 ^j	Shiner and Jewett (1965)
7-Methyl-7-norbornyl-OTs	40	80	0.42(1.02 ^k)	Fisher <i>et al.</i> (1975)
<i>endo</i> -Bicyclo[3.2.1]octan-3-yl- OTs ^l	36	50	0.74	Banks and Maskill (1976)
	60	98	0.54	Banks and Maskill (1976)
<i>exo</i> -Bicyclo[3.2.1]octan-3-yl- -OTs ^l	36	50	0.62	Banks and Maskill (1976)
	60	98	0.51	Banks and Maskill (1976)
<i>exo</i> -2-Norbornyl-OTs	55	80	0.64 ^f	McManus <i>et al.</i> (1988a)
<i>endo</i> -2-Norbornyl-OTs	55	80	0.74 ^e	McManus <i>et al.</i> (1988a)

^a These values probably result from reaction with the anions HO⁻ and EtO⁻ rather than with the neutral solvents. ^b The rearranged product (CH₂=C(CH₂OR)-C₃H₅-c) and the unrearranged product have similar selectivities. ^c For the 3-substituted product. ^d Low percentage of substitution product (2–10%) was observed, and elimination is the main reaction. ^e Inverted product. ^f Retained product. ^g The 1- α -d derivative. ^h The 1- β -d derivative. ⁱ 79% inverted. ^j 94% inverted. ^k The value for the 7-CD₃ derivative. ^l Only ratios for inversion products are given.

such as HO^- or Et_3N are certainly due to reaction with the conjugate bases (HO^- , EtO^-) of the solvent components and are not true $k_{\text{E}}/k_{\text{W}}$ -values. Careful analysis is therefore required. After obtaining the appropriate ratios, the major problem is whether one can deduce something about the details of the solvolysis mechanism or about the stability and lifetime of the intermediate from these data.

Two questions should be answered in this connection. First, is it at all possible that the selectivity will be constant for a single system, taking into account the complex nature of aqueous alcohol mixtures (Franks and Ives, 1966; Blandamer, 1977), the possibility of solvent sorting around the cation or the solvolytic transition state, and the expected dependence of $k_{\text{A}}/k_{\text{B}}$ on the solvent polarity? Secondly, is it justified, considering these complexities and the large excess of the solvent compared with the substrate, to calculate selectivities using the bulk molar ratio of the solvent components as in (2)? Although these or similar questions have been discussed several times in the literature (McLennan and Martin, 1982; Ta-Shma and Rappoport, 1983; Allard and Casadevall, 1985), they have remained unanswered.

By inspection of the experimental data, it was found that the selectivity constants of (2) change almost always with the solvent composition (see Tables 2–8 and Figs. 1–4). Although these changes are not large and seldom exceed a factor of three in the range of solvent mixtures investigated, the interest in them stems from three main reasons. First, the selectivity values themselves are not spread in an excessively large range around unity. For instance, the $k_{\text{E}}/k_{\text{W}}$ -values range between 7.0 and 0.3, while most of them are between 4.0 and 0.5 (see Tables 2 and 3 and Fig. 1). Against the background of such moderate changes, the effect of altering the solvent composition is remarkable, and in some systems like 1-adamantyl bromide (Rappoport and Kaspi, 1980) or tosylate (Allard and Casadevall, 1985) in TFE–W, the preference of the cation for one of the solvent components is reversed at some solvent compositions. While TFE is the better nucleophile below 60% v/v TFE, water is the better nucleophile above 80% v/v TFE. The second reason is the regularity and generality of such changes. In aqueous methanol (M–W), ethanol (E–W) or trifluoroethanol (TFE–W), the $k_{\text{ROH}}/k_{\text{W}}$ -ratios generally decrease when the alcohol volume percentage (%v) increases, while the $k_{\text{E}}/k_{\text{TFE}}$ ratios in E–TFE usually show an overall increase or remain nearly constant on increasing the volume percentage of ethanol (Tables 2–8). The third reason has already been mentioned: there is a large body of information derived from different solvent compositions in different single binary (e.g. E–W) mixtures, and it is important to know whether comparisons of values obtained at different compositions is meaningful.

The generality of these phenomena, at least qualitatively, for systems solvolysing by different mechanisms indicates that they are mainly due to the

Table 2 Selectivity ratios k_E/k_W for reactions of the first group in EtOH–H₂O mixtures.^a

System	Nucleofuge	$T/^{\circ}\text{C}$	k_E/k_W in % EtOH (v/v)						Reference
			50	60	70	80	90	95	
1-Adamantyl	Br	25			0.85 ^b	0.74 ^b			McManus and Zutaut (1985)
	Br	75 ^c	0.61	0.57	0.55	0.53	0.56	0.58	Karton and Pross (1978)
	Br	100	0.49			0.48	0.45	0.45	Luton and Whiting (1979)
	Cl	100	0.55	0.51	0.50	0.51	0.53 ^d	0.56 ^d	Karton and Pross (1978)
	OTs	100	0.60			0.47	0.38	0.40	Luton and Whiting (1979)
	SMe ₂ ⁺	71	0.87	0.83	0.82	0.78	0.74	0.79	Kevill and Anderson (1986)
2-Adamantyl	Br	100	0.62	0.59	0.56	0.56	0.61	0.64	Karton and Pross (1978)
	OTs	100		0.57 ^d	0.53	0.49	0.49	0.50	Karton and Pross (1978)
	OCIO ₃ ^e	25	0.62	0.55	0.52	0.52	0.64	0.61	Kevill <i>et al.</i> (1984)
2- <i>exo</i> -Norbornyl	Cl	100 ^f	0.94	0.82	0.82	0.84	0.79		Harris <i>et al.</i> (1974)
2-Methyl-2-adamantyl	Cl	25	0.31 ^g		0.44 ^g	0.43 ^g			Fisher <i>et al.</i> (1975)
	Br	25	0.39			0.44			Fisher <i>et al.</i> (1975)
1-Ph-c-C ₆ H ₉ O ^{h,i}		25	1.48	1.27	1.07 ^j		0.79	0.66	Battistini <i>et al.</i> (1977)

^a For definition of reactions of the first group, see text. ^b $k_M/k_W = 1.1$ and 0.93 in the corresponding M–W mixtures. ^c Very similar values at 50°C and at 100°C . ^d At 75°C . ^e The solvent mixture includes 9% dioxane; very similar results are obtained at 0°C . ^f Very similar results at 125°C and 150°C . ^g Values for the corresponding 2-CD₃ derivative are 0.37, 0.36 and 0.34 in 50, 70 and 80% E respectively. ^h 1-Phenylcyclohexene oxide. ⁱ For the *syn*-isomer in the acid-catalysed solvolysis. At 40% and 30% E $k_E/k_W = 1.61$ and 1.50 respectively, and lower values were observed at lower E percentages. In water-rich mixtures, the values are unreliable since the reaction was carried out on a suspension of the substrate in the solvent. ^j In 76% E.

Table 3 Selectivity ratios k_E/k_W for reactions of the second group in solvolysis of RX .^a

R	X	T/°C	k_E/k_W in % EtOH (v/v)						Reference
			50	60	70	80	90	95	
(4-MeC ₆ H ₄) ₂ CH	OPNB	100	7.0	5.79	4.91	4.10	3.05		McLennan and Martin (1982)
(4-MeC ₆ H ₄)CHPh	Cl	25			4.66	3.93	3.54	3.32	Karton and Pross (1977)
Ph ₂ CH	Cl ^b	25			3.25	2.78	2.54	2.32	Karton and Pross (1977)
	OPNB ^c	100	3.79	3.22	2.82	2.25			McLennan and Martin (1982)
4-ClC ₆ H ₄ CHPh	Cl	25			2.87	2.49	2.14	2.03	Karton and Pross (1977)
(4-ClC ₆ H ₄) ₂ CH	Cl	25 ^d			2.75	2.41	2.03	1.93	Karton and Pross (1977)
	OPNB	100	3.66	3.04	2.47	1.92			McLennan and Martin (1982)
4-MeOC ₆ H ₄ CH ₂	Cl	75	3.81	3.24	2.78	2.46	2.15	2.22 ^e	Aronovitch and Pross (1978)
4-MeC ₆ H ₄ CH ₂ ^f	Cl	75	2.00	1.96	2.07	2.07	2.05	1.91	Aronovitch and Pross (1978)
PhCH ₂	Cl ^g	75	3.33	3.09	2.87	2.45	2.17	1.86	Aronovitch and Pross (1978)
4-ClC ₆ H ₄ CH ₂	Cl	75	3.23	2.98	2.67	2.33	1.86	1.67	Aronovitch and Pross (1978)
1-n-C ₈ H ₁₇	Cl ^h	120	1.97	1.74	1.53	1.32	1.06	0.97	Pross <i>et al.</i> (1978)
1-n-C ₄ H ₉	Br	75	1.51 ⁱ		1.28 ^j		0.59		Bird <i>et al.</i> (1943)
c-C ₅ H ₉	OBs	40			0.99 ^k	1.02 ^k	1.00 ^k	1.08 ^{k,l}	Humski <i>et al.</i> (1973)
2-n-C ₈ H ₁₇	Cl	120	0.88	0.83	0.86	0.79	0.73	0.67	Pross <i>et al.</i> (1978)
	casilate ^m			1.03		0.74	0.65		McManus <i>et al.</i> (1982)
1-Phenyl-c-C ₆ H ₉ O ^{n,o}		25	1.17	1.01		1.00 ^p	0.89	0.88	Battistini <i>et al.</i> (1977)

^a For definition of reactions of the second group, see text. ^b With Br as nucleofuge, k_E/k_W -ratios decrease from 4.13 to 3.09 in the same solvent range.

^c With Cl as nucleofuge, k_E/k_W -ratios decrease from 3.76 to 2.16 in 50–90% E. With ODNB (3,5-dinitrobenzoate) as nucleofuge, k_E/k_W -ratios decrease from 3.79 to 2.18 in 50–80% E. ^d At 75°C, k_E/k_W -ratios are the same within experimental accuracy. ^e The lack of decrease in this k_E/k_W -ratio is attributed to increased product formation through intimate ion-pair (Aronovich and Pross, 1978). For the same system at 25°C, Bentley and Beaman (1991) obtained k_E/k_W -values decreasing from 4.4 to 1.7 on increasing E from 20% to 90%. ^f The constancy, rather than decrease, of the selectivity values is attributed to increase in the percentage of product formation from intimate ion-pair on increasing the E %v. In the solvolysis of the corresponding bromide, the values decreased from 2.61 to 1.99 in the same solvent range (Aronovich and Pross, 1978). ^g With Br as nucleofuge, k_E/k_W -ratios decrease from 3.61 to 1.80 in the same solvent range. ^h Very similar values were obtained for Br and OTs as nucleofuges. ⁱ In 54% EtOH (v/v). ^j In 72% EtOH (v/v). ^k The corresponding values for the β -d₄ derivative are 0.94, 1.03, 0.96 and 0.98 in 70, 80, 90 and 96% E respectively. ^l In 96% EtOH (v/v). ^m Camphor-10-sulphonate at unspecified temperature. ⁿ 1-Phenylcyclohexene oxide. ^o For the *anti*-isomers in the acid-catalysed solvolysis. At 40% and 30% ethanol, k_E/k_W = 1.11 and 0.99 respectively, and lower values were observed at lower E percentage. In water-rich mixtures, the values are unreliable since the reaction was carried out on a suspension of the substrate in the solvent. ^p In 76% EtOH (v/v).

Table 4 Selectivity ratios k_M/k_W for reactions of the second group.^a

System	Nucleofuge	k_M/k_W in % MeOH (v/v)									Reference
		10	20	30	40	50	60	70	80	90	
1-(4-Methoxyphenyl)ethyl ^b	X ^c	10.3	10.6	11.0	9.3	9.0	8.3	7.0	6.0		Richard <i>et al.</i> (1984)
1-(4-Methylphenyl)ethyl ^b	Cl					2.44	2.24	2.0	1.74	1.62	Richard <i>et al.</i> (1984)
1-(4-Fluorophenyl)ethyl ^b	Cl		2.3	2.15	1.9	1.8	1.7	1.5	1.37		Richard and Jencks (1984b)
1-(3-Methoxyphenyl)ethyl ^b	Cl	2.6	2.6	2.5	2.4	2.2					Richard and Jencks (1984b)
1-Butyl	Br ^d						1.57	1.48	1.14	1.20	Bird <i>et al.</i> (1943)
4-Methoxybenzyl	Cl ^e		6.4		5.8		4.8		3.8	3.6	Bentley and Beaman (1991)

^a For definition of reactions of the second group, see text. ^b At $22 \pm 2^\circ\text{C}$. ^c X = $\text{CH}_2\text{ClCOO}^-$ for 10% and 20% MeOH; X = $3,5\text{-(O}_2\text{N)}_2\text{C}_6\text{H}_3\text{-COO}^-$ for other % of MeOH. ^d At 59°C . The exact % MeOH values (v/v) in increasing order are 60, 71, 83, 93. ^e At 25°C .

Table 5 Selectivity ratios $k_{\text{TFE}}/k_{\text{w}}$ for reactions of $\text{XC}_6\text{H}_4\dot{\text{C}}\text{HCH}_3$ ions belonging to the second group at 22°C.^a

X	Nucleofuge	$k_{\text{TFE}}/k_{\text{w}}$ in % TFE (v/v)							Reference
		40	50	60	70	80	90	97	
4-MeO	Y ^b	0.581	0.520	0.457	0.383	0.313	0.254		Richard <i>et al.</i> (1984)
4-Me	Cl		0.75	0.67	0.58	0.55	0.50	0.45	Richard <i>et al.</i> (1984)
4-F	Cl		0.65	0.60		0.52	0.50		Richard and Jencks (1984b)
3-MeO	Cl		1.14	1.03	0.93	0.88	0.83		Richard and Jencks (1984b)

^a $\pm 2^\circ\text{C}$; for definition of reactions of the second group, see text. ^b The average value obtained with $\text{X} = 4\text{-O}_2\text{NC}_6\text{H}_4\text{COO}^-$ and $\text{X} = 3,5\text{-(O}_2\text{N)}_2\text{C}_6\text{H}_3\text{COO}^-$ was taken.

Table 6 Selectivity ratios $k_{\text{TFE}}/k_{\text{w}}$ for reactions of the first group in TFE-H₂O mixtures.^a

System	Nucleofuge	$T/^{\circ}\text{C}$	$k_{\text{TFE}}/k_{\text{w}}$ in % TFE (w/w)						Reference
			50	60	70	80	90	97	
1-Adamantyl	Br	35	1.32		1.12	1.00	1.01	0.97	Allard and Casadevall (1985)
	OTs	35	2.08		1.28	1.09	0.82	0.67	Allard and Casadevall (1985)
	Br	35	2.04	1.51	0.88	0.78	0.76	0.49	Rappoport and Kaspi (1980)
2-Adamantyl	OTs	^b		1.24 ^c		0.89 ^d		0.87	Conner and Maskill (1988)
	azoxytosylate			2.22 ^c		1.08 ^d		0.94	Conner and Maskill (1988)
7-Methyl-7-norbornyl	OTs	20				0.96		0.98	Fisher <i>et al.</i> (1975)

^a For definition of reactions of the first group, see text. ^b Not specified. ^c At 58% TFE w/w. ^d At 85% TFE w/w.

Table 7 Selectivity ratios k_E/k_{TFE} for reactions of the first group in EtOH–TFE mixtures.^a

System	Nucleofuge	$T/^\circ\text{C}$	k_E/k_{TFE} in % EtOH (v/v)								Reference
			10	20	30	40	50	60	70	80	
1-Adamantyl	Br	35	0.38	0.70	0.84	1.20	1.11	1.09	0.81	0.71	Rappoport and Kaspi (1980)
	Br	25		0.60				0.75			McManus and Zutaut (1985)
	Br ^b	35	0.46	0.51	0.61	0.63	0.66	0.69	0.65	0.56	Allard and Casadevall (1985)
	OTs ^b	35	0.46	0.51	0.55	0.53	0.54	0.61	0.62	0.56	Allard and Casadevall (1985)
	OCOC1	25			0.61			0.71		0.88	Kevill <i>et al.</i> (1989)
	SMe ₂ ⁺	200			1.10				1.10		McManus <i>et al.</i> (1988b)
Cyclooctyl	OBs ^c	35				0.67	0.76	1.28			Nordlander <i>et al.</i> (1982)
α -D-Glucopyranosyl	F ^d	100	0.61 ^d	0.66	0.80	0.91		0.80	0.82		Sinnott and Jencks (1980)

^a For definition of reactions of the first group, see text. ^b % EtOH (v/v) in increasing order: 8.4, 16, 30, 43, 54, 64, 72, 80. ^c Fully retained products and very similar k_E/k_{TFE} -ratios for the unrearranged and rearranged products (1→5 H-shift) prove substitution through collapse of a solvent-separated ion-pair (Nordlander *et al.*, 1982). ^d Selectivity ratios for the retained products, which are probably formed from collapse of solvent-separated ion-pair (Amyes and Jencks, 1989). However, retained products from β -D-glucopyranosyl fluoride give k_E/k_{TFE} -ratios between 1.6 and 2.4 in the same solvent range.

Table 8 Selectivity ratios k_E/k_{TFE} for reactions of the second group in EtOH–TFE mixtures.^a

System	Nucleofuge	T/°C	k_E/k_{TFE} in EtOH % (v/v)										Reference
			5	10	15	20	30	40	45	50	60	70	
4,4'-Dichlorobenzhydryl	Cl	25	58	41		39 ± 6	37 ± 8^b	31 ± 9^b					Rappoport <i>et al.</i> (1978)
α -D-Glucopyranosyl ^c	F	100			19	15	16		20 ± 3		20	15	Sinnott and Jencks (1980)
β -D-Glucopyranosyl ^c	F	100			4.1	5.0	4.4		4.7 ± 0.7		5.2	5.0	Sinnott and Jencks (1980)
4-Methylbenzyl	Br	85				4.6^d				19			da Roza <i>et al.</i> (1973)

^a For definition of reactions of the second group, see text. ^b The extent of product formation from the free carbocation is estimated to be greater than 20% and is higher at lower EtOH %. ^c For the inverted product. ^d Benzyl bromide gave $k_E/k_{TFE} = 21.5$.

effect of the mixed solvent on the relative nucleophilicity of its components. They cannot result from changes in the stability of the electrophile, which affects its selectivity according to the reactivity-selectivity principle, as was suggested by several authors (Battistini *et al.*, 1977; Tarnus *et al.*, 1988), because this does not agree with the behaviour of a free carbocation in aqueous alcohol, as demonstrated by data for the two first systems in Tables 3–5, which are displayed in Fig. 2. It is true that raising the W %v in E–W and M–W, which results in a consequent increase in the “ionizing power” of the medium and the stability of the carbocation, does seem to increase the preference of the latter for the better nucleophile, i.e. the alcohol. However, a parallel increase in W %v in TFE–W results in an opposite effect, and the preference for water, which is the better nucleophile in this mixture, decreases when its %v increases.

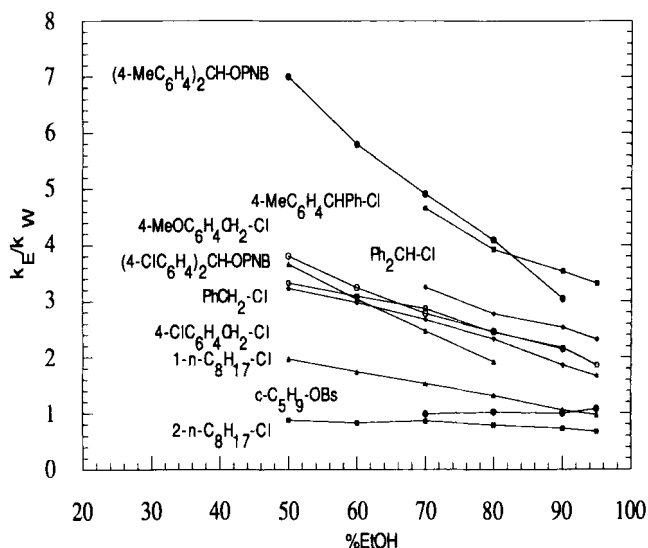


Fig. 1 Selectivity ratios k_E/k_W for solvolysis of several RX systems in E–W. Data from Table 3.

The possibility that the change in selectivity can be attributed to a change in the nature of the reactive cationoid species should be considered. Indeed, this can be the largest obstacle to any generalization regarding the selectivity. Harris *et al.* (1974), addressing the question of stability-selectivity relationships in solvolytic displacement reactions of alkyl derivatives, concluded that each of the electrophilic species in the complex Winstein solvolysis scheme (Winstein *et al.*, 1965; Raber *et al.*, 1974) except for the solvent-separated ion-pair has a constant selectivity despite changes in

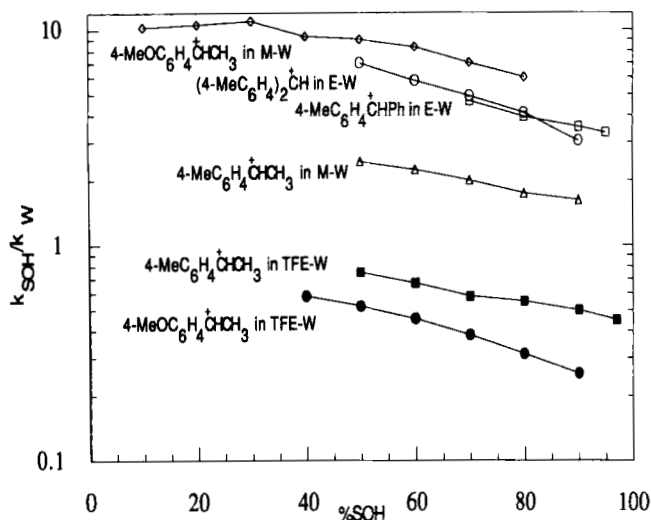


Fig. 2 Selectivity ratios $k_{\text{SOH}}/k_{\text{W}}$ for solvolysis of free carbocations in SOH-W mixtures. SOH = ethanol, methanol or trifluoroethanol. Data from Tables 3-5.

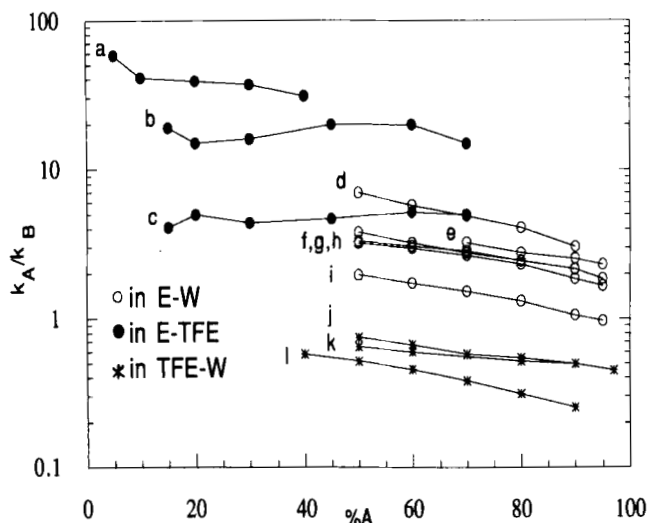


Fig. 3 Selectivity ratios $k_{\text{A}}/k_{\text{B}}$ for reactions of the second group in three binary mixtures: (a) (4-ClC₆H₄)₂CHCl; (b) α -D-glucopyranosyl-F; (c) β -D-glucopyranosyl-F; (d) (4-MeC₆H₄)₂CHOPNB; (e) Ph₂CHCl; (f,g,h) 4-XC₆H₄CH₂Cl (X = MeO, H, Cl); (i) 1-n-C₆H₁₇Cl; (j,k,l) 4-XC₆H₄CH(CH₃)Y (X = Me, F, MeO; Y = Cl, OPNB). Data from Tables 3, 5 and 7.

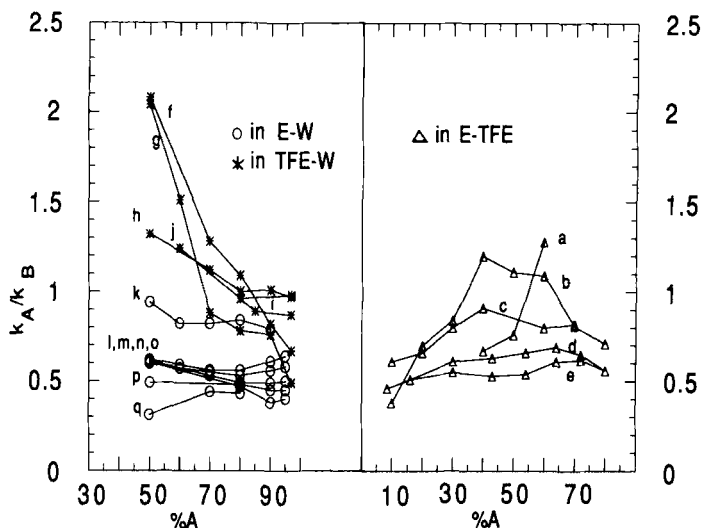


Fig. 4 Selectivity ratios k_A/k_B for reactions of the first group in three binary mixtures: (a) *c*-octyl-OBs; (b,d,g,h,m,p) 1-adamantyl-Br; (c) *α*-D-glucopyranosyl-F; (e,f,o) 1-adamantyl-OTs; (i) 7-methyl-7-norbornyl-OTs; (j,n) 2-adamantyl-OTs; (k) 2-*exo*-norbornyl-Cl; (l) 2-adamantyl-Br; (q) 2-methyl-2-adamantyl-Cl. Data from Tables 2, 6 and 7.

stability. So, those relationships resulted from different blends of the separate selectivities. We think that, although a change of the reactive species when changing the solvent composition may occur for certain specific cases (Bentley and Koo, 1989; Aronovich and Pross, 1978), it is excluded here as a general explanation since it cannot explain the results for free carbocations in Tables 3–5 mentioned above. In addition, it cannot explain the change in selectivity for the 1-adamantyl system in TFE–W, since this system solvolyses only via the SSIP (Rappoport and Kaspi, 1980; Allard and Casadevall, 1985; cf. Table 6).

A specific solvent effect on the nucleophilicity of E–W mixtures was proposed by Karton and Pross (1978) in order to explain the influence of added acetone on k_E/k_W selectivity values. In a previous discussion of their results, Ta-Shma and Rappoport (1990) suggested that the influence of acetone is mainly due to the changes that its addition imposes on the kinetic activity coefficients of W and E. By “kinetic activity coefficients”, we mean those terms that should multiply the molarities of E and W in (2) in order to obtain “solvent-free” selectivities. These kinetic activity coefficients cannot be measured independently, but interactions affecting them such as dipole–dipole interactions, hydrogen bonding, dispersion forces and structure making or breaking (Parker, 1969) are also reflected in the partial vapour

pressures of the solvent components, and in the Raoult's law activity coefficients of E and W (γ_E and γ_W) calculated from them. Therefore changes in the kinetic activity coefficients can be deduced from changes in γ_E and γ_W . However, the influence of acetone stems also from its action as a basic cosolvent towards both E and W according to Symons' proposals (Symons, 1981, 1983, 1989; Symons, *et al.*, 1981). Acetone can form hydrogen bonds with the free OH groups (OH_f) of E and W and thus increase the concentration of their free nucleophilic lone pairs (LP_f) and hence their basicities. This effect, together with the effect of the activity coefficients, could account for all the changes observed upon the addition of acetone to E-W mixtures (Ta-Shma and Rappoport, 1990). Symons (1981) found that M added to water acted also as an OH_f scavenger, and the same behaviour must apply to E in W, while the opposite should be observed for TFE in W, since the former is more acidic. In the present review, we shall try to show that in binary mixtures of M-W, E-W, TFE-W and E-TFE the mutual operation of the kinetic activity coefficients and the basicity (or acidity) of the nucleophilic solvent components leads to the observed changes in the selectivity values S when the binary solvent composition is changed. In addition, we believe that these two factors can account for the following four other related phenomena, which in our opinion have not hitherto received a proper explanation.

- (a) A lack of increase, and actually even a small decrease, of the pseudo-first-order rate constant $k_s (= k_w[W]/s^{-1})$ found by McClelland *et al.* (1989) for several relatively stable diarylmethyl carbocations in acetonitrile-water mixtures, when the water %v increased above 20%. The value of k_s increased steeply on addition of up to 5% water, but then levelled off, and above 20% it started to decrease.
- (b) The constancy of ratios $(k_{Az}/k_s)/M^{-1}$ (where k_{Az} is the second-order rate constant for the reaction of N_3^- with the electrophilic species) for the reaction of oxocarbenium ions in varying MeCN-W mixtures found by Amyes and Jencks (1989), and the inherently similar constancy of $[RN_3]/[ROH]$ ratios found by Bateman *et al.* (1940) and Golomb (1959) for the reaction of 4,4'-dimethylbenzhydryl chloride in varying acetone-water mixtures. Both features (a) and (b) are relevant to the unsolved problem concerning the validity of using bulk molar concentrations to calculate selectivities, as applied in deriving (2).
- (c) The remarkable spread in the k_{Az}/k_w -ratios for 1-(4-methoxyphenyl)-ethyl carbocation in different 50:50 water-organic cosolvent mixtures; values range from 3300 in TFE-W to 220 in DMSO-W (Richard *et al.*, 1984).

- (d) The significantly lower $k_{\text{TFE}}/k_{\text{W}}$ -ratio for reactions of relatively stable carbocations calculated from the separate rate constants with pure trifluoroethanol or pure water than the $k_{\text{TFE}}/k_{\text{W}}$ -ratio calculated for different cations of comparable stability according to (2) from the product concentrations in TFE-W mixtures. In contrast, the $k_{\text{M}}/k_{\text{W}}$ ratios calculated in the pure solvents on the one hand and measured in mixtures as explained above on the other, are lower in the mixtures (see Section 5).

Although solvent structure is certainly important in solvolysis reactions, as shown, for example, by Winstein's (Winstein and Fainberg, 1957) and Arnett's (Arnett *et al.*, 1965) work, we do not intend to consider the maxima in properties that they observed in our discussion of the selectivity. This is because of our inability to do it, as well as our feeling that a more simplified model (see Section 5) qualitatively explains most of the phenomena. Future reviews may be able to tackle this problem successfully.

2 Summary of solvent-related changes in $k_{\text{A}}/k_{\text{B}}$

Before dealing with the above-mentioned phenomena, we should like to summarize in an organized way the available systematic data for the changes in $k_{\text{A}}/k_{\text{B}}$ -ratios caused by the solvent in the four solvent systems M-W, E-W, TFE-W and E-TFE. Inspection of the data reveals that selectivity values can be divided roughly into two groups. To the first group belong selectivity ratios resulting mainly from front-side collapse of SSIP, where the products are formed by capture of the carbocation moiety by a solvent molecule that is interposed between the cation and the anion in the ion-pair. The formation of this ion-pair is the product-determining step. Consequently, the steric parameters of the nucleophiles and their ability to stabilize the SSIP through hydrogen bonds to the nucleofuge are important in determining the selectivity (Karton and Pross, 1977; Luton and Whiting, 1979). The second and much larger group includes the selectivity values resulting mainly from direct nucleophilic attack of a solvent molecule on the electrophilic carbon centre in the neutral substrate, the IIP, the SSIP or the free carbocation formed from it.

The first group includes systems that are sterically hindered to back-side attack and yet cannot sustain a free carbocation; examples are 1-adamantyl and 2-adamantyl-X (X = Cl, Br, OTs and other nucleofuges), 2-methyl-2-adamantyl chloride and bromide, *exo*-2-norbornyl chloride and a few other systems (Tables 2, 6 and 7 and Fig. 4). These systems exhibit $k_{\text{E}}/k_{\text{W}}$ -ratios less than unity since a water molecule is less bulky and forms hydrogen

bonds better than an ethanol molecule. The ratios decrease by no more than 15% when the E %v increases from 50 to 90% (Table 2). Consequently, the values can be averaged in most cases within $\pm 10\%$. An exception is the 1-phenylcyclohexene oxide system (Battistini *et al.*, 1977), where the k_E/k_W -values for the *syn*-isomer decrease from 1.6 at 40% to 0.66 at 95% E. We shall refer to this system later.

In TFE-W, the k_{TFE}/k_W -ratios for systems belonging to this group are higher than the corresponding k_E/k_W -ratios, and are greater than unity in most cases. This is probably due to the better ability of TFE compared with water to solvate the nucleofuge in spite of its bigger size (Allard and Casadevall, 1985; Rappoport and Kaspí, 1980). The decrease of the k_{TFE}/k_W -values on increasing the TFE %v is much more marked and seems to depend on the nucleofuge (Table 6).

The k_E/k_{TFE} -values in E-TFE are usually less than unity, and for 1-adamantyl bromide or tosylate they cover the same range as the corresponding k_E/k_W -values, i.e. the preference for reaction with E over W or TFE is usually found to be between 0.4 and 0.7 (Tables 2 and 7 and Fig. 4). However, while the k_E/k_W -ratios decrease slightly on increasing the E %v, the k_E/k_{TFE} -ratios clearly increase, at least up to 60% E.

The selectivity values for a second group of solvolysis reactions are summarized in Tables 3, 4, 5 and 8 and Fig. 3. This group consists of systems of a large structural and mechanistic variety. At one extreme are the benzydrylic, the 1-(4-methoxyphenyl)ethyl and the 1-(4-methylphenyl)ethyl systems, where the solvolysis products are mainly derived from reaction of the solvent molecules with the free carbocation (Karton and Pross, 1977, 1978; McLennan and Martin, 1982; Richard *et al.*, 1984; Rappoport *et al.*, 1978). At the other extreme, we find the aliphatic 1-butyl, 1-octyl and 2-octyl systems, which form products by solvent attack on the neutral RX (Pross *et al.*, 1978; Bird *et al.*, 1943; McManus *et al.*, 1982). Systems intermediate in behaviour include the benzylic systems (da Roza *et al.*, 1973; Aronovitch and Pross, 1978), 1-(3-methoxyphenyl)ethyl and 1-(4-fluorophenyl)ethyl systems (Richard and Jencks, 1984b), glucopyranosyl fluoride (Sinnott and Jencks, 1980) and cyclopentyl brosylate (Humski *et al.*, 1973, 1976); products are believed to be formed mainly through back-side attack on the intimate or solvent separate ion-pair or on both. Common to all the solvolysis reactions of this group is the need for a basic nucleophile having a free lone pair of electrons which will attack the positive centre. Electrophilic interactions with the nucleofuge are less important, and steric considerations are less imposing, although they definitely exist and are probably the cause of the higher k_M/k_W - than k_E/k_W -ratios found for 4-methoxybenzyl chloride (Bentley and Beaman, 1991), 2-octyl camphor-10-sulphonate (McManus *et al.*, 1982) and several 1-arylethyl systems (Richard and Jencks, 1984a).

In this group, the k_E/k_W -values in E-W and the k_M/k_W -values in M-W are greater than unity (Tables 3 and 4), as expected from the better nucleophilicity of these alcohols relative to water. Exceptions showing values less than unity are the 2-octyl system, where a crowded S_N2 transition state was suspected (McManus *et al.*, 1982), *exo*- and *endo*-bicyclo[3.2.1]octan-3-yl tosylate (Banks and Maskill, 1976) and *endo*-2-norbornyl tosylate (McManus *et al.*, 1988a). Since the three systems still gave only inverted products, steric factors seem to be the reason for this behaviour. The selectivity values generally decrease with decrease in the stability of the carbocationic moiety; for example, at 70%E they decrease from 4.9 for 4,4'-dimethylbenzhydryl carbocation to 0.99 for cyclopentyl brosylate, which reacts through an intimate ion-pair (Humski *et al.*, 1973). The k_E/k_W -ratios usually decrease much more markedly than those for systems of the first group, by approximately twofold when the E %v increases from 50% to 95% (compare Tables 2 and 3 and Figs. 1 and 4). The limited data in M-W exhibit the same trend, but the decrease seems to be more moderate (Table 4).

There are not many data on selectivity ratios in TFE-W. Richard's measurements for α -arylethyl systems (Richard *et al.*, 1984) are summarized in Table 5, and we can add to them three additional values found for benzyl systems: $k_{TFE}/k_W = 0.5$ for 4-methoxybenzyl chloride (Amyes and Richard, 1990) in 50:50 TFE-W at 22°C, 0.83 for benzyl tosylate (Maskill, 1986) in 58:42 TFE-W at 25°C, and 0.25 for 4-(trifluoromethyl)benzyl with methyl 4-nitrophenyl sulphide ion as the nucleofuge in 58:42 TFE-W at 40°C (Dietze and Jencks, 1989). In contrast with the values for reactions of the first group in Table 6, the k_{TFE}/k_W -ratios for reactions of the second group are nearly always less than unity, in agreement with the greater basicity of water. Only 1-(3-methoxyphenyl)ethyl chloride gives k_{TFE}/k_W -ratios of 1.14 and 1.03 in 50% and 60% TFE respectively, and relatively high values, although less than unity, at higher TFE percentages. This might reflect a considerable extent of product formation by front-side collapse of an SSIP for this relatively unstable carbocation [$k_s = 10^{11} \text{ s}^{-1}$ in 50% TFE (Richard *et al.*, 1984)]. Indeed, 1-phenylethyl chloride, for which k_s is similar, gives above 25% of retained products in E-W mixtures (Okamoto *et al.*, 1966). As far as can be judged from the limited data in Tables 5 and 6, k_{TFE}/k_W decreases similarly for both groups.

The most notable difference between the selectivity values of the two groups is in the k_E/k_{TFE} -ratios. For the first group, they are usually less than unity and tend to increase with the E %v (Table 7). However, they are much greater than unity (4-58) for the second group, and they seem to remain constant within the experimental error when the E %v increases (Table 8). It is worthwhile to mention here Richard and Jencks' data for the same 1-arylethyl systems that appear in Tables 4 and 5 and which were investi-

gated in the single solvent mixture, 5:45:50 E-TFE-W at 22°C. The k_E/k_{TFE} -values are 30, 5.1, 3.7 and 2.3 for the 4-methoxy, 4-methyl, 4-fluoro and 3-methoxyphenylethyl systems respectively (Richard and Jencks, 1984a). Amyes and Jencks (1989) found that k_E/k_{TFE} -ratios in 5:45:50 E-TFE-W and in 50:50 E-TFE were the same for the 1-methoxy-3-(4-methoxyphenyl)-1-propyl cation and twice as large in the binary mixture for the 2-methoxy-4-(4-methoxyphenyl)-2-butyl cation, so that Richard and Jencks' results (1984a) are in agreement with those in Table 8.

Table 9 summarizes briefly and qualitatively the main features of the selectivity values demonstrated in Tables 2-8 and Figs. 3 and 4.

Table 9 Selectivity values and the way in which they change when the volume percentage of A increases.

k_A/k_B	First group	Second group
k_E/k_W	lower than 1; small decrease	higher than 1; considerable decrease ^a
k_{TFE}/k_W	equal or higher than 1; considerable decrease	lower than 1; considerable decrease
k_E/k_{TFE}	lower than 1; small increase	much higher than 1; no change

^a This applies to k_M/k_W as well.

As can be seen from Table 9, the pattern of selectivity values and their solvent-induced changes differ considerably for the two groups of reactions. These differences can themselves serve as a mechanistic tool, provided that data are available in several mixtures of differing solvent compositions.

It is unfortunate that no reliable selectivity data exist for the t-butyl cation, a central species in solvolysis studies. In Ingold's experiments in M-W and E-W more than half a century ago (Bateman *et al.*, 1938), the ethers were isolated by an inaccurate extraction procedure and both the alcohols and the elimination products were determined indirectly. Frisone and Thornton (1968) obtained in 54% E a k_E/k_W -value of 0.89, which is twice as large as Ingold's value of 0.47 in 60% E, but both groups used no buffering base in order to capture the HCl formed. Shiner *et al.* (1969) determined the products by ¹H nmr spectroscopy in TFE-W containing a two- to threefold excess of pyridine buffer in order to prevent reactions of the products. However, their results are somewhat puzzling since they obtained $k_{TFE}/k_W \approx 0.5$ between 60% and 94% TFE but no ether at all below 60% TFE.

The selectivity values of the various systems displayed in Tables 2–8 generally fit our expectations based on their assigned solvolysis mechanisms. Consequently, we feel that the changes in these values with the solvent composition should also be accounted for by these mechanisms. We suggested that these changes are governed by both the kinetic activity coefficients of the nucleophilic solvent components as modelled by their Raoult's law activity coefficients and by their basicity or acidity according to Symons' proposals (Symons, 1981, 1983, 1989; Symons *et al.*, 1981).

Let us look more closely at the relevant changes in the activity coefficients. The activity coefficients discussed here were usually calculated by us from partial vapour pressures given in the literature. Those for the TFE–W and E–TFE mixtures were calculated using the Hansen–Miller equation (Smith *et al.*, 1981). In aqueous methanol, ethanol or trifluoroethanol, the activity-coefficient ratio $\gamma_{\text{ROH}}/\gamma_{\text{W}}$ decreases when the alcohol %v increases. In the commonly used range of 50–95% alcohol, the $\gamma_{\text{ROH}}/\gamma_{\text{W}}$ -ratios decrease by 1.9-fold (from 1.46 to 0.75) in M–W at 40°C and by 4.2-fold (from 1.83 to 0.44) in E–W at 40°C (Washburn, 1928a), whereas the $\gamma_{\text{TFE}}/\gamma_{\text{W}}$ -ratios (Smith *et al.*, 1981) decrease by 4.6-fold (from 2.12 to 0.46) in TFE–W at 25°C. In contrast, in E–TFE mixtures at 25°C, the $\gamma_{\text{E}}/\gamma_{\text{TFE}}$ -ratios increase with the E %v from 0.43 at 10% E to 2.2 at 80% E (Smith *et al.*, 1981). Moderate temperature differences should not significantly affect the relative ratios (Ta-Shma and Rappoport, 1990).

The changes in the activity coefficients described above fit qualitatively the trends in Table 9 and especially the singular increase of $k_{\text{E}}/k_{\text{TFE}}$ -ratios with the increase in %E found for reactions of compounds belonging to the first group. The values above also explain the more moderate decrease of $k_{\text{M}}/k_{\text{W}}$ than of $k_{\text{E}}/k_{\text{W}}$ for reactions of compounds in the second group (Tables 3 and 4). On the whole, the selectivity changes are smaller than the activity changes, and they differ for the two groups. Luton and Whiting (1979) investigated the solvolysis of several 1-adamantyl derivatives in 50–95% E–W and observed “a good linear relationship” between the $k_{\text{W}}/k_{\text{E}}$ -values and the activity-coefficient ratio $\gamma_{\text{W}}/\gamma_{\text{E}}$, with slopes ranging from 0.1 for the bromide as nucleofuge to 0.6 for the tosylate. The values of the slopes were taken as measuring “the need during the formation of the solvent-separated ion-pair to isolate the interstitial solvent molecule from the rest of the solvent”. Different needs might cause different trends in the values of the two groups. However, it is not clear why such a need should be higher in E–W for a back-side attack of a solvent molecule than for a front-side attack leading to the formation of a SSIP, or why it should be higher in TFE–W compared with E–W for a front-side attack, as can be inferred from the trends in Table 9.

Like Whiting, we also think that the variations in the selectivity ratios do

not completely represent those of the activity coefficients, so that there is no reason to replace the molarities in (2) by activities. It is also reasonable that the extent to which the changes in the activity coefficients are reflected in the rate constants depends on the reaction. However, in our opinion, an additional factor is the basicity or acidity of the nucleophilic solvent components, which depends mainly on the concentration of the free lone pairs (LP_f) or free hydrogen-bonding groups (OH_f) of each component according to Symons' proposals (Symons *et al.*, 1981; Symons, 1981, 1983, 1989). This factor changes for each solvent component when the composition of the binary mixture is changed. Its effect on the selectivity depends on whether the reaction belongs to the first or the second group, and it might strengthen or weaken the effect of the activity coefficients. For instance, when %E increases in E-W, γ_E goes down while γ_W goes up. The basicity of both E and W increases (more LP_f), but not necessarily to the same extent, so that the total effect of changing the solvent composition on k_E/k_W is composite. It is quite clear that the effect of the solvent on the separate rate constants (k_E , k_W , k_{TFE} and k_M) can be highly informative in testing the applicability of our hypothesis (see also Section 5). In Section 3 we analyse the available literature data in this respect.

3 Individual rate constants and the effect of the solvent on the diffusion-controlled reaction of azide ion

The individual rate constants for the reaction of a nucleophilic component of a solvent mixture with an electrophilic centre were measured directly until very recently only in aqueous acetonitrile (MeCN-W) and only for relatively stable triarylmethyl and diarylmethyl carbocations. The values were first measured by Ivanov *et al.* (1972) and more recently and comprehensively by McClelland, Steenken and coworkers (McClelland *et al.*, 1989). In the latter work, it was found that all the systems investigated showed very similar behaviour. The first-order rate constants k_s/s^{-1} for the reaction of these ions with water were linear in [W] up to 1–2% W, but on further increase in W% they increased in a hyperbolic fashion, reached a shallow maximum around 20% W and finally decreased linearly up to 80% and even 100% W, by a factor of 1.3–1.5 (McClelland *et al.*, 1989).

The first case in which individual rate constants for the reaction of an alcohol and water with the same cation were separated is recent work by Mathivanan *et al.* (1991). The data, for which we are grateful to Professor McClelland, are as yet unpublished, and neither experimental details, nor a discussion by the authors are available. These very important data, which may require rethinking of some of the generalizations suggested in this

review, are given in Table 10 and their main features are described below. However, since it is not clear how general these new results are, we shall defer a detailed analysis at this stage.

McClelland and coworkers solvolysed dianisylmethyl *p*-nitrobenzoate in the complete range of aqueous ethanol and aqueous methanol, and measured the overall pseudo-first-order rate constants of decay (presumably capture by the solvent) of the formed dianisylmethyl cation (An_2CH^+). A combination of these values and the independently determined alcohol/ether product ratios gave the pseudo-first-order rate constants for the individual solvent components. The second-order constants and the selectivity constants based on them were then calculated using the molarities of the solvent components. The changes of the various parameters in aqueous ethanol and aqueous methanol mixtures were similar, showing the following features.

- (a) The overall first-order rate of capture of the cation increases by 54.5- and 75-fold respectively on changing the solvent from W to pure E and M. This increase is not linear with the concentration of added alcohol, and only 10.5–11% of it is achieved by addition of 50% of the alcohol.
- (b) The first-order rate constants for the water reaction in both E–W and M–W decrease on increasing the water content. The 1.5-fold decrease between 80 and 20% M is similar to that found for the same cation in MeCN–W. The decrease in E–W is larger, being threefold between 80 and 20% E.
- (c) Both individual second-order rate coefficients k_w and k_{SOH} increase strongly with alcohol content. Their ratio, i.e. the selectivity, is almost always greater than unity, but the values change with the solvent composition in an inverted unsmooth parabolic fashion. In E–W, the value increases from 1.4 at 5% EtOH to 4.5 at 15% EtOH, remains nearly constant at 15–50% EtOH, and then decreases to 0.7 at 95% EtOH. In M–W, the value increases from 2.2 at 5% MeOH to 7.9 at 40% MeOH, is nearly constant at 40–70% MeOH, and decreases to 3.2 in 90% EtOH.
- (d) The second-order rate constant for the reaction of the cation with water in water is 167- and 177-fold lower than the corresponding rate constants with methanol and ethanol in the corresponding alcohols respectively.

The selectivities of An_2CH^+ seem too low by comparison with other systems. That in 70% MeOH (7.5) resembles that for $\text{An}\overset{+}{\text{C}}\text{HMe}$ (7), although the k_s -values in TFE differ by four orders of magnitude (14 for

Table 10 Individual rate constants and selectivity values for the reaction of dianisylmethyl cation (R^+) in EtOH-H₂O and MeOH-H₂O.^a*(a) Ethanol-water*

% EtOH (v/v)	$10^{-5} k_{\text{decay}}^b$ /s ⁻¹	$\frac{[\text{ROH}]^c}{[\text{ROEt}]}$	$10^{-5} k_w[\text{W}]^d$ /s ⁻¹	$10^{-5} k_E[\text{EtOH}]^d$ /s ⁻¹	$10^{-3} k_w^e$ /M ⁻¹ s ⁻¹	$10^{-3} k_E^e$ /M ⁻¹ s ⁻¹	k_E/k_w
0	1.01	—	1.01	—	1.83	—	—
5	1.18	44.1	1.15	0.026	2.19	3.09	1.4
10	1.35	16.1	1.27	0.079	2.54	4.66	1.8
12.5	1.45	12.2	1.34	0.11	2.76	5.18	1.8
15	1.57	4.09	1.26	0.31	2.67	12.1	4.5
20	1.81	2.90	1.35	0.46	3.03	13.7	4.5
30	2.7	1.67	1.69	1.01	4.35	19.9	4.6
40	3.8	1.06	1.96	1.84	5.87	27.2	4.6
50	5.8	0.73	2.46	3.34	8.85	39.5	4.5
70	10.8	0.409	3.13	7.67	18.8	64.6	3.4
75	13	0.414	3.81	9.19	27.4	72.3	2.6
80	16	0.344	4.10	11.9	36.9	87.8	2.4
90	29	0.306	6.79	22.2	122	146	1.2
95	42.2	0.266	8.82	33.2	318	206	0.7
100	55	—	—	55	—	324	—

(b) Methanol-water

% MeOH (v/v)	$10^{-5} k_{\text{decay}}^b$ /s ⁻¹	$\frac{[\text{ROH}]^c}{[\text{ROME}]}$	$10^{-5} k_w[\text{W}]^d$ /s ⁻¹	$10^{-5} k_M[\text{MeOH}]^d$ /s ⁻¹	$10^{-3} k_w^e$ /M ⁻¹ s ⁻¹	$10^{-3} k_M^e$ /M ⁻¹ s ⁻¹	k_M/k_w
0	1.01	—	1.01	—	1.83	—	—
5	1.29	19.5	1.23	0.062	2.33	5.02	2.2
10	1.68	4.59	1.38	0.30	2.75	12.2	4.4
20	2.54	1.90	1.66	0.88	3.70	17.5	4.7
30	3.71	1.085	1.93	1.78	4.85	23.5	4.8
40	5.42	0.427	1.62	3.80	4.73	37.2	7.9
50	8.32	0.292	1.88	6.44	6.55	50.3	7.7
60	12.0	0.199	2.00	10.0	8.66	65	7.5
70	18.6	0.129	2.13	16.5	12.2	91.5	7.5
80	28.9	0.098	2.6	26.3	22.2	130	5.9
90	48.5	0.077	3.5	45.0	61.3	199	3.2
100	75.4	—	—	75.4	—	305	—

^a Data of Mathivanan *et al.* (1991) for the solvolysis of dianisylmethyl *p*-nitrobenzoate. ^b Overall rate of decay of the ion. ^c Product ratio. ^d First-order individual rate constants, calculated from k_{decay} and $[\text{ROH}]/[\text{ROS}]$ (S = Me, Et). ^e Second-order individual rate constants.

An_2CH^+ , 3.5×10^5 for $\text{An}\dot{\text{C}}\text{HMe}$) (Richard *et al.*, 1984; McClelland *et al.*, 1988). Likewise, at 70% E, the selectivity of An_2CH^+ (3.3) resembles that of Ph_2CH^+ (3.4) (Karton and Pross, 1977), while the k_s -values in TFE are 14 and 3.2×10^6 respectively (McClelland *et al.*, 1988). The anticipated selectivity for An_2CH^+ from a $\sigma^+ \rho^+$ correlation in 70% E for benzhydryls is 16 (Karton and Pross, 1977).

Regardless of the explanation for this behaviour, an important conclusion emerges from the data. The selectivity values for a single system reacting by a single mechanism can increase, remain constant or decrease in different ranges of solvent composition. Consequently, explanations based on the changes in a restricted range of solvent composition (which indeed relate to most of the data reported in the literature) should be regarded with caution.

Apart from these results, all the other available and relevant literature data are either in the form of the $(k_{\text{Az}}/k_s)/\text{M}^{-1}$ or $k_{\text{Az}}/k_{\text{SOH}}$ selectivity ratios or as product ratios $[\text{RN}_3]/[\text{ROS}]$, from which the selectivity ratios can be calculated (Richard *et al.*, 1984; Amyes and Jencks, 1989; Bateman *et al.*, 1940; Golomb, 1959; Ta-Shma and Jencks, 1986; Amyes and Richard, 1990, 1991).

When calculating k_s/s^{-1} or $k_{\text{SOH}}/\text{M}^{-1} \text{s}^{-1}$ from the $k_{\text{Az}}/k_{\text{SOH}}$ ratios, it is assumed that k_{Az} is a diffusion-controlled rate constant for a reaction between N_3^- and the carbocation, and we have to assign its proper value. This should depend on the viscosity and the dielectric constant of the medium. This N_3^- -carbocation reaction has been extensively used as a "clock" to determine the carbocation reactivity (Ta-Shma and Rappoport, 1983; Richard *et al.*, 1984; Richard and Jencks, 1984b; Ta-Shma and Jencks, 1986; Richard, 1989; Amyes and Jencks, 1989; Amyes and Richard, 1990, 1991), so that a somewhat extended discussion on the correct k_{Az} value in different solvents is worthwhile. Recently McClelland *et al.* (1988) measured k_{Az} -values directly for several diarylmethyl cations in water and in TFE, methanol and 20% MeCN (v/v). Their important results will be discussed later and will serve to check our suggested method of estimating k_{Az} in the different solvent systems of interest.

Literature values of diffusion-controlled rate constants of any ion in mixed aqueous solvents are rare. However, the diffusion-controlled reaction of solvated electrons e_s with neutral or charged solutes in binary alcohol-water mixtures was investigated in some detail (Maham and Freeman, 1988; Mićić and Čerček, 1977; Barat *et al.*, 1973), and hence served us to establish a general treatment for estimating k_{Az} -values. For that reaction, the Debye equation (Debye, 1942) was usually applied as a basis for discussing solvent effects. According to this equation, the rate constant for a diffusion-controlled reaction between species A and B at zero ionic strength (k_{diff}) is given by (3) (Barat *et al.*, 1973), where N is the Avogadro number, D_A and

D_B are the diffusion coefficients and r_A and r_B are the reaction radii of the two species. The second factor in (3) results from the Coulombic interaction

$$k_{\text{diff}} = \frac{4N(D_A + D_B)(r_A + r_B)}{1000} \frac{Q}{e^Q - 1} \quad (3)$$

between the reactants that affects their probability to attain the required reaction distance, and Q is a complex expression that depends on whether the reactants are ions, polar or non-polar solutes (Maham and Freeman, 1988). A change in the medium composition is accompanied by changes in both its viscosity and dielectric constant, affecting all the variables in (3). The diffusion coefficients of an ion in dilute solutions are directly related to its molar limiting conductance λ , and they therefore change when the medium viscosity η and, to a lesser extent, its dielectric constant ϵ are changed (Spiro, 1973). The radii of the reacting species depend on their solvation, and the expression for Q includes the dielectric constant. For a reaction between ions $Q = NZ_A Z_B e^2 / \epsilon (r_A + r_B) RT$, where Z_A and Z_B are the ionic charges and e is the electronic charge (Barat *et al.*, 1973). For oppositely charged ions $Q < 0$ and $e^Q \ll 1$ so that k_{diff} will be roughly proportional to $1/\epsilon$ and will decrease when ϵ increases. For a reaction between two anions, $Q > 0$ and $e^Q \gg 1$ and, since Q increases when ϵ decreases, k_{diff} will decrease as well.

Barat *et al.* (1973) successfully correlated the rate constant for the reaction of e_s^- with NO_3^- in EtOH-H₂O mixtures with the dielectric constant of the medium using (3). The value of $D(\text{NO}_3^-)$ was calculated from $\lambda(\text{LiNO}_3)$, and $D(e_s^-)$ was calculated from the reaction of e_s^- with PhNO_2 in the same solvent system. The failure of a parallel treatment for the reaction of e_s^- with H^+ was ascribed to a non-diffusion-controlled reaction in water-rich mixtures. Maham and Freeman (1988) analysed the reactions of e_s^- with PhNO_2 in several pure alcohols by (3), using a slightly different expression for Q for the reaction of an ion and a polar solute. They avoided the need to know the D -values in the different solvents by assuming a Stokes correlation (Watts, 1973) between D and the viscosity of the solvent (i.e. $\eta D = \text{constant}/r_s$, where r_s is the effective radius for diffusion). Although in this case the expected dependence of k_{diff} on the dielectric constant was roughly observed, for the reaction of e_s^- with PhNO_2 , CCl_4 , p -benzoquinone, O_2 or H_2O_2 in aqueous EtOH or MeOH a similar treatment yielded no simple dependence, mainly because the limiting molar conductivity λ^0 of e_s^- and therefore $D(e_s^-)$ in the aqueous alcohols do not obey the Stokes correlation in all the solvent compositions (Maham and Freeman, 1988; Mićić and Čerček, 1977). The latter phenomenon is common to all ions investigated in aqueous mixtures (Tissier and Douheret, 1978; Kay and Broadwater, 1970, 1971, 1976), and

hence the actual changes in the D -values of the ions rather than in the medium viscosity should be used when estimating changes in k_{diff} . It is clear that the shortcomings of the Stokes correlation result from the effects of the ionic charge on its immediate vicinity, and several models were proposed to account for these effects (Spiro, 1973; Watts, 1973; Kay *et al.*, 1976). The most widely used model is that of Zwanzig (1963), which considers the retarding force imposed on the moving ion by the oriented solvent dipoles in its vicinity. The success of this model is very limited (Covington and Dickinson, 1973).

The above examination leads us to suggest that in the diffusion-controlled reactions of N_3^- with carbocations (C^+) k_{Az} -values in different solvent mixtures will be proportional to the $(D_{\text{Az}} + D_{\text{C}^+})/\epsilon$ values in these mixtures. The required D -values, or the conductivity values directly related to them through the Nernst equation (Moore, 1965), are unknown. N_3^- could be modelled by Cl^- , which has a similar size (Huheey, 1983), and the conductivity changes for a relatively large organic carbocation usually containing one or two aryl rings, which because of resonance has low surface charge density, may be modelled by Et_4N^+ . There are relatively extensive literature data on the conductivity of Cl^- and Et_4N^+ in various organic solvents and in aqueous mixtures (Spiro, 1973; Tissier and Douheret, 1978; Kay and Broadwater, 1970, 1971, 1976). Consequently, the preferred way for calculating k_{Az} in any solvent [$k_{\text{Az}}^0(\text{sol})$] from k_{Az} in water [$k_{\text{Az}}^0(\text{w})$] would be from (4), where the zero superscript on the k 's and λ 's indicates limiting rate constants and conductivities at a zero ionic strength.

$$\frac{k_{\text{Az}}^0(\text{sol})}{k_{\text{Az}}^0(\text{w})} = \frac{\lambda^0(\text{Et}_4\text{NCl})(\text{sol})}{\lambda^0(\text{Et}_4\text{NCl})(\text{w})} \frac{\epsilon_{\text{w}}}{\epsilon_{\text{sol}}} \quad (4)$$

The applicability of (4) can be tested for the data of McClelland *et al.* (1988). The calculations are summarized in Table 11. McClelland *et al.* measured k_{Az} -values of $(6.8 \pm 0.5) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for five diarylmethyl carbocations in 1:4 MeCN-W (v/v). The 3,4'-dimethoxybenzhydryl cation was also investigated in pure water, giving a k_{Az} -value of $(7.2 \pm 0.5) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. This small difference is as expected according to (4). For $p\text{-An}\dot{\text{C}}\text{HCH}_3$ in TFE, McClelland *et al.* found $k_{\text{Az}} = (5.6 \pm 0.5) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. This value does not differ much from that in water, in line with (4), but it does not fit a simpler estimate based only on viscosity considerations ($\eta_{\text{TFE}}/\eta_{\text{W}} = 2.0$ at 25°C). The calculated k_{Az} -value for 50:50 TFE-W is $0.737 \times 7 \times 10^9 \text{ M}^{-1} \text{ s}^{-1} = 5.1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, which, surprisingly, is identical with Jencks' estimate of $5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, which he and others used for a vast range of systems in H_2O and 50:50 TFE-W (Amyes and Jencks, 1989; Ta-Shma and Jencks, 1986; Ta-Shma and Rappo-

port, 1983; Amyes and Richard, 1990, 1991). For $p\text{-Ar}_2\text{CH}^+$ in 1:4 MeCN-W, $k_{\text{Az}} = (4.2 \pm 0.2) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, while in MeOH $k_{\text{Az}} = (9.0 \pm 0.3) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. This more than twofold increase in k_{Az} is as expected from (4). However, both values are slightly lower than found for diffusion-controlled reactions in water or in methanol. Ritchie and Virtanen (1972a) gave $k_{\text{diff}} \approx 10^{10}$ for the reaction of benzenediazonium cation with N_3^- in methanol. Milosavijevic and Mićić (1978) found k_{diff} -values of $(2.0\text{--}2.35) \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ for the reactions of the solvated electron with PhNO_2 , CCl_4 or O_2 in MeOH. This might indicate that the reaction of N_3^- with the relatively stable $p\text{-Ar}_2\text{CH}^+$ is not strictly diffusion-controlled in both water and methanol.¹

Table 11 Calculated $k_{\text{Az}}^0(\text{sol})/k_{\text{Az}}^0(\text{w})$ -ratios for some solvent systems, where $k_{\text{Az}}^0(\text{sol})$ was measured by McClelland and coworkers.^a

Solvent	ϵ^b	$\lambda^0(\text{Et}_4\text{NCl})$ $/\text{cm}^2 \Omega^{-1} \text{ mol}^{-1} \text{ }^b$	$\frac{k_{\text{Az}}^0(\text{sol})}{k_{\text{Az}}^0(\text{w})}$
H_2O	78.54 ^c	109 ^d	1.000
80 : 20 $\text{H}_2\text{O} : \text{MeCN}$ (v/v)	72.2 ^e	94.7 ^f	0.945
TFE	26.67 ^g	37.0 ^h	1.00
MeOH	32.6 ⁱ	112 ^d	2.47
50 : 50 TFE : H_2O (v/v)	52.2 ^g	53.4 ^j	0.737

^a McClelland *et al.* (1988). ^b Values at 25°C. ^c Weast (1989b). ^d Tissier and Douheret (1978). ^e Moreau and Douheret (1976). ^f Calculated from the ratio of $\lambda^0(\text{Bu}_4\text{NBr})$ in water to $\lambda^0(\text{Bu}_4\text{NBr})$ in 80 : 20 $\text{H}_2\text{O} : \text{MeCN}$ (Schiavo and Scrosati, 1976) and $\lambda^0(\text{Et}_4\text{NCl})$ in water (Tissier and Douheret, 1978). These two salts exhibit very similar behaviour in $\text{EtOH} : \text{H}_2\text{O}$ (Kay and Broadwater, 1976). ^g Murto and Heino (1966). ^h Evans and Nadas (1971). ⁱ Adhadow (1981a). ^j Calculated from λ^0 -values in water assuming Stokes correlation. This solvent was not investigated by McClelland *et al.*

¹ Very recently, after this work was submitted for publication, McClelland *et al.* (1991) published kinetic results for the reaction of N_3^- with substituted diaryl- and triaryl-methyl carbocations in 0–99% MeCN (v/v). They found that the diffusion-controlled k_{Az} -values remained practically constant between 0 and 50% MeCN (being $ca\ 7.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for Ar_2CH^+ and $ca\ 5.1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for Ar_3C^+) but then increased by (2.2–2.5)-fold on proceeding to 99% MeCN. In order to calculate diffusion-controlled k_{Az} -values in water and in 99% MeCN (v/v) for comparisons with experimental values, they applied an essentially identical theoretical treatment to (3). Their assumptions regarding the unknown diffusion constants for N_3^- and the carbocation are remarkably parallel to ours. However, unlike us, they did take into account the solid angle of approach through which encounter of the two ions leads to reaction. They concluded that this angle differs for diaryl- and triaryl-methyl carbocations. This, however, is irrelevant to our work, where comparison is made for the same, or for very similar, systems in different solvent mixtures. The trend of McClelland's experimental k_{Az} -values for the diffusion-controlled reaction of Ar_2CH^+ in 0–93% MeCN fits nicely with our predictions, which are based on (4). The only exception is the measured value in 99% MeCN, which is lower than that at 93% MeCN and lower than expected from the theoretical treatment.

We believe that (4) could be applied in calculating k_{ROH} -values from the $k_{\text{Az}}/k_{\text{ROH}}$ selectivity ratios ($R = \text{H}, \text{CH}_3, \text{CF}_3\text{CH}_2$) given by Richard *et al.* (1984). These values for 1-(4-methoxyphenyl)ethyl and 1-(4-methylphenyl) ethyl carbocations were calculated from the product ratios in several aqueous methanol (M-W) and aqueous trifluoroethanol (TFE-W) mixtures (Richard *et al.*, 1984) and for the former cation also in several 50:50 (v:v) H_2O :organic cosolvent mixtures (Table 12) (Richard *et al.*, 1984). The necessary limiting conductivities of Et_4NCl in M-W and E-W are available (Tissier and Douheret, 1978; Kay and Broadwater, 1976), but they are unknown for the range of TFE-W mixtures studied and for some of the solvent systems given in Table 12. Values of $\lambda^0(\text{Bu}_4\text{NBr})$ in aqueous MeCN, DMSO and acetone are known (Schiavo and Scrosati, 1976) and, since Et_4N^+ and Bu_4N^+ on the one hand and Br^- and Cl^- on the other, are similar in nature and exhibit very similar conductivity patterns in aqueous organic solvents (Tissier and Douheret, 1978; Kay and Broadwater, 1971, 1976), the ratio of the known $\lambda^0(\text{Bu}_4\text{NBr})$ -values in different solvent mixtures can be used to calculate the required $\lambda^0(\text{Et}_4\text{NCl})$ -values. From conductivity measurements in aqueous methanol (Tissier and Douheret, 1978) and ethanol (Kay and Broadwater, 1976), it can be seen that, in mixtures containing up to 50% alcohol, Stokes correlation for $\lambda^0(\text{Et}_4\text{NCl})$ holds quite well and the deviation from the predicted value is less than 4%. Deviations of less than 10% were found for Bu_4NCl in the same range of dioxane: H_2O mixtures (Kay and Broadwater, 1971) and for Bu_4NBr in the same range of DMSO- H_2O and acetone- H_2O mixtures (Schiavo and Scrosati, 1976). At higher organic cosolvent percentages, Stokes correlation predicts much higher values than those found experimentally (up to 70% higher near the pure organic solvent) (Tissier and Douheret, 1978; Kay and Broadwater, 1971, 1976; Schiavo and Scrosati, 1976). Consequently, for aqueous TFE or DMF, which show viscosity patterns similar to those of aqueous ethanol, methanol, acetone, dioxane and DMSO with a maximum around $x_w \approx 0.8 \pm 0.1$ (Washburn, 1928b; Kay and Broadwater, 1971; Murto and Heino, 1966; Blankenship and Clampitt, 1950; Cowie and Toporowski, 1961; Weast, 1989c), we have calculated $\lambda^0(\text{Et}_4\text{NCl})$ values up to 50:50 solution by multiplying $\lambda^0(\text{Et}_4\text{NCl})(w)$ by the viscosity ratio $\eta_{\text{solution}}/\eta_w$. However, for 50:50 aqueous ethylene glycol, which has a different viscosity pattern (Weast, 1989c), we preferred to multiply $\lambda^0(\text{Et}_4\text{NCl})(w)$ by the ratio of $\lambda^0(\text{KNO}_3)$ in 50:50 ethylene glycol: H_2O (Sesta and Berardelli, 1972) and its value in water (Weast, 1989a). For aqueous TFE mixtures containing more than 50% TFE, we have calculated $\lambda^0(\text{Et}_4\text{NCl})$ values by interpolating between the calculated value at 50% TFE and the known value in pure TFE (Evans and Nadas, 1971).

An additional problem when estimating k_{SOH} -values using (4) is that the

Table 12 Solvent effect on relative k_w -values for the 1-(4-methoxyphenyl)ethyl carbocation in 50% (v/v) water:cosolvent mixtures.

Cosolvent	ϵ^a	$\lambda^0(\text{Et}_4\text{NCl})$ $/\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$ at 25°C	$\left(\frac{k_{Az}}{k_w} \right)^b$	$k_{Az}(\text{W}; \mu = 0.5)^c$ $k_w(50\% \text{ sol}; \mu = 0.5)$	$k_w(50\% \text{ sol}; \mu = 0.5)$ $k_w(50\% \text{ TFE}; \mu = 0.5)$	$\gamma_w(50\% \text{ TFE})^d$ $\gamma_w(50\% \text{ sol})$	$k_w(50\% \text{ sol})/$ $\gamma_w(50\% \text{ sol})$
TFE	52.2 ^e	53.4 ^f	3300	6740	1	1	1
MeOH	59	60 ^g	950	1730	3.90	1.25 ^h	4.89
EtOH	52.8	42.5 ⁱ	570	1460	4.62	1.05 ^h	4.87
HOCH ₂ CH ₂ OH	63.9	34.9 ^j	560	1750	3.85	1.23 ^k	4.75
Me ₂ CO	53.18	67.1 ^l	470	763	8.82	0.93 ^h	8.21
CH ₃ CN	58.6	97.5 ^m	860	961	7.01	0.97 ⁿ	6.80
DMF	65.2	44.0 ^f	260	644	10.5	1.20 ^o	12.6
DMSO	74.9	30.2 ^p	220	794	8.49	1.34 ^q	11.4
H ₂ O	78.5	109 ^g	2720 ^r	2720	2.5	1.16	2.87

^a Adhador (1981); data at 25°C. ^b Ratios given by Richard *et al.* (1984) at $\mu = 0.5$. ^c Calculated from $(k_{Az}/k_w)/(\lambda_{\text{sol}}/\lambda_w)$ (see text). ^d γ -Values are at 25°C, except for E-W and M-W at 40°C. γ -Values change very little in this temperature range (Ta-Shma and Rappoport, 1990); the γ_w -value at 50% TFE is from Smith *et al.* (1981). The use of the γ -ratio assumes that this ratio is not significantly different at $\mu = 0$ and 0.5. ^e Murto and Heino (1966). ^f Calculated from λ^0 in water assuming Stokes correlation. ^g Tissier and Douheret (1978). ^h Washburn (1928a). ⁱ Kay and Broadwater (1976). ^j Calculated from λ^0 (KNO₃) in 50:50 W:ethylene glycol (Sesta and Berardelli, 1976) and in water (Weast, 1989a) assuming the same ratio for Et₄NCl. Stokes correlation would give $\lambda(\text{Et}_4\text{NCl}) = 29.6 \Omega^{-1} \text{ cm}^2$. ^k Trimble and Potts (1935). ^l Like footnote *f* in Table 11, but for 50:50 Me₂CO:H₂O. ^m Like footnote *f* in Table 11 but for 50:50 MeCN:H₂O. ⁿ Treiner *et al.* (1976). ^o Lipsztajn *et al.* (1974). ^p Like footnote *f* in Table 11, but for 50:50 DMSO:H₂O. ^q Lam and Benoit (1974). ^r Ratios given by Richard *et al.* (1984) at $\mu = 1$ (NaClO₄). The difference between this value and that at 0.5 M should not exceed 12% as calculated from (6).

equation applies strictly only to reaction at zero ionic strength μ , while the experimental k_{Az}/k_{SOH} -ratios were not measured at $\mu = 0$. The ionic strength affects the value of the diffusion-controlled k_{Az} electrostatically by "shielding" the two ionic reactants, and its effect depends on the dielectric constant ϵ of the solution. In order to deal with the effect of μ on k_{Az} [i.e. to obtain k_{Az}^0 from $k_{Az}(\mu)$], we use (5), adapted from Barat *et al.* (1973), which is

$$\log \left(\frac{k_{Az}(\mu)}{k_{Az}^0} \right) = - \frac{2B\mu^{1/2}}{1 + ag\mu^{1/2}} \quad (5)$$

based on the Debye-Hückel theory as applied to ionic reactions. In (5), a is the distance of closest approach of the ions, and B and g are functions of the dielectric constant and temperature and include the basic electric charge, π , N and the Boltzmann constant. If α is expressed in Ångström units then (Kortum, 1965) these constants become $B = 1.824 \times 10^6/(\epsilon T)^{3/2}$ and $g = 50.29/(\epsilon T)^{1/2}$. Solving for 22°C [the temperature used by Richard *et al.* (1984)] and rearranging (5), we obtain (6). Whereas the experimental data are insufficient for checking the validity of (6) in the systems of Richard *et al.*

$$\log \left(\frac{k_{Az}(\mu)}{k_{Az}^0} \right) = - \frac{720}{\epsilon[(\epsilon/\mu)^{1/2} + 2.93a]} \quad (6)$$

(1984) and for obtaining a , the limited data show that (6) correctly predicts the strong influence of ϵ on $k_{Az}(\mu)/k_{Az}^0$. On changing from water ($\epsilon = 78.5$) containing 0.01 M NaN_3 to $\text{H}_2\text{O}/0.01 \text{ M } \text{NaN}_3/1 \text{ M } \text{NaClO}_4$, the k_{Az}/k_W values decreased by 1.3-fold, while, on changing from 50:50 TFE-W ($\epsilon = 52.2$) (Moreau and Douheret, 1976) containing 0.005 M NaN_3 to 50% TFE-W/0.005 M $\text{NaN}_3/0.5 \text{ M } \text{NaClO}_4$, the k_{Az}/k_W -values decreased already by 1.6-fold. Note that k_W -values should not be affected by the addition of NaClO_4 .

We tried to use (6) in a semiquantitative way in order to evaluate the effect of ϵ on the $k_{Az}(\mu)/k_{Az}^0$ -term in the range of ϵ 's and μ 's of interest given by Richard *et al.* (1984). Two experimental situations exist: (a) k_{Az}/k_W -ratios for $p\text{-An}\dot{\text{C}}\text{HCH}_3$ were measured in 50:50 v/v water-organic cosolvent at $\mu = 0.5$ maintained with NaClO_4 (Richard *et al.*, 1984); (b) k_{Az}/k_{SOH} -ratios for $p\text{-An}\dot{\text{C}}\text{HCH}_3$ and $p\text{-Tol}\dot{\text{C}}\text{HCH}_3$ were measured in M-W and TFE-W mixtures where μ decreased with the water volume percentage, since aqueous NaClO_4 ($\mu = 1$) was diluted with alcohol (Richard *et al.*, 1984).

In situation (a) where $\mu = 0.5$ the term in square brackets in the denominator of (6) becomes $(2\epsilon)^{1/2} + 2.93a$. If we use 5 Å as a reasonable estimate for a , since the radius of N_3^- is 1.8 Å (Huheey, 1983), when ϵ changes between 52.2 and 74.9 (cf. Table 12) the expression in square brackets has a nearly constant value of 26 ± 1 . Consequently, (7) applies. In the range of ϵ

$$k_{Az}^0/k_{Az}(\mu) = 10^{(28 \pm 1)/\varepsilon} \quad (7)$$

concerned, ε is 2–3 times larger than 28, and, for these ε -values, $\varepsilon \times 10^{(28 \pm 1)/\varepsilon} = 175 \pm 2 = \text{constant}$. This conclusion is valid within $\pm 10\%$ for any a between 4 and 10 Å, although the value of the constant is different in each case. Since the exact value of a is unknown, we shall not use the numerical value of the constant, although (8) still applies. On dividing (8) for the

$$k_{Az}^0/k_{Az}(\mu) = \text{constant}/\varepsilon \quad (8)$$

reaction in water by (8) as it applies for any of the solutions (sol) in Table 12, we obtain (9). By using (5) for the ratio of the rate constants at $\mu = 0$, we obtain (10). This means that at $\mu = 0.5$ in the above range of dielectric

$$\frac{k_{Az}(\text{sol}, \mu = 0.5)}{k_{Az}(\text{w}, \mu = 0.5)} = \frac{k_{Az}^0(\text{sol})}{k_{Az}^0(\text{w})} \frac{\varepsilon_{\text{sol}}}{\varepsilon_{\text{w}}} \quad (9)$$

$$k_{Az}(\text{sol}, \mu \approx 0.5)/k_{Az}(\text{w}, \mu = 0.5) = \lambda^0(\text{sol})/\lambda^0(\text{w}) \quad (10)$$

constants, the expected higher k_{Az} at higher ε , through the influence of ε on the effect of μ , is cancelled by the inverse dependence of k_{Az} on ε through its effect on the Coulombic interaction term Q in (3) (i.e. lower k_{Az} at higher ε). Consequently, the k_{Az} -values in the different mixtures relate to one another as the λ^0 's of N_3^- and the carbocation (which are modelled by Et_4NCl). This conclusion is now exploited to transfer the ratios $k_{Az}(\text{sol}, \mu = 0.5)/k_{\text{w}}(\text{sol})$ given by Richard *et al.* (1984) to ratios $k_{Az}(\text{w}, \mu = 0.5)/k_{\text{w}}(\text{sol})$, which differ only in the denominator and hence exhibit the influence of the organic cosolvent on k_{w} . These latter ratios are presented in Table 12 together with the relative k_{w} -values calculated from them.

In situation (b), μ decreases on decreasing the water percentage, and in M–W mixtures $(\varepsilon/\mu)^{1/2}$ increases when ε decreases, from 8.86 in H_2O ($\varepsilon = 78.5$, $\mu = 1$) to 19.7 in 90% MeOH ($\varepsilon = 38.9$, $\mu = 0.1$). This causes a smaller decrease in the denominator in (6) than the decrease in ε . We found that in the range of ε 's and μ 's concerned and assuming that $a = 5$ Å, (6) gives (11), and therefore equation (12) applies. Here also we find that in the range of $\varepsilon^{1/2}$ concerned (8.9–6.2), (13) holds.

$$\log \left(\frac{k_{Az}(\mu)}{k_{Az}^0} \right) = \frac{-720}{(200 \pm 10) \varepsilon^{1/2}} = \frac{-3.6}{\varepsilon^{1/2}} \quad (11)$$

$$k_{Az}^0/k_{Az}(\mu) = 10^{3.6/\varepsilon^{1/2}} \quad (12)$$

$$\varepsilon^{1/2} \times 10^{3.6/\varepsilon^2} = 23 \pm 1 = \text{constant} \quad (13)$$

Calculations show that this conclusion is valid within $\pm 10\%$ for any a between 4 and 10 Å, with a different constant in each case. We therefore avoid again using the numerical value of the constant, and shall use (14). Application of a similar treatment to TFE–W mixtures between 0 and 90% TFE gives the same conclusion, with the constant equal to 28 ± 1 . When (14) for the reaction in water, $\mu = 1$, is divided by (14) for the reaction in any other mixture of Tables 13–15, (15) is obtained. Using (5) again for the ratio of k_{Az} -values at $\mu = 0$, we finally obtain (16). This equation suggests that for the four sets of data taken from Richard *et al.* (1984) and presented in Tables 13–15, the effect of ε on k_{Az} through the expression for the Coulombic interaction Q in (3) is only partially balanced by its effect on the contribution by μ (6).

$$k_{\text{Az}}^0/k_{\text{Az}}(\mu) = \text{constant}/\varepsilon^{1/2} \quad (14)$$

$$\frac{k_{\text{Az}}(\text{sol}, \mu)}{k_{\text{Az}}(\text{w}, \mu = 1)} = \frac{k_{\text{Az}}^0(\text{sol})}{k_{\text{Az}}^0(\text{w})} \quad (15)$$

$$\frac{k_{\text{Az}}(\text{sol}, \mu)}{k_{\text{Az}}(\text{w}, \mu = 1)} = \frac{\lambda^0_{\text{sol}}}{\lambda^0_{\text{w}}} \frac{\varepsilon_{\text{sol}}^{1/2}}{\varepsilon_{\text{w}}^{1/2}} \quad (16)$$

Equation (16) was used by us to transfer ratios $k_{\text{Az}}(\text{sol}, \mu)/k_{\text{SOH}}(\text{sol})$ from Richard *et al.* (1984) to ratios $k_{\text{SOH}}(\text{sol})/k_{\text{Az}}(\text{w}, \mu = 1)$, which differ in the denominator only. These ratios are given in Tables 13–15. For the 1-(4-methoxyphenyl)ethyl cation, we also multiplied them by the appropriate water concentration.

The latter ratios are actually the required individual first-order rate constants for each of the nucleophilic solvent components divided by the same constant value ($k_{\text{Az}}(\text{w}, \mu = 1)$). Their most interesting behaviour is that in M–W the values of $k_{\text{w}}[\text{W}] \text{ s}^{-1}$ were nearly constant and even increased slightly with decreasing water percentage in the range 10–80% M, but in 20–90% TFE these values decreased 21-fold on decreasing the water percentage. The behaviour of water towards this free carbocation in M–W but not in TFE–W is thus reminiscent of its behaviour towards the free and relatively stable carbocations investigated by McClelland *et al.* (1989, 1991) in MeCN–W. Since the selectivity values for the unstable 1-(4-methylphenyl)ethyl cation varied only slightly when varying the solvent composition, they were not analysed in this way.

Table 13 Effect of changes in solvent composition on the separate rate constants for the reaction of 1-(4-methoxyphenyl)ethyl carbocation in M-W.

% MeOH	$\lambda(\text{Et}_4\text{NCl})^a$ $/\Omega^{-1} \text{ cm}^{-1} \text{ mol}^{-1}$	$\epsilon^{1/2}{}^b$	$\left(\frac{k_{\text{Az}}}{k_{\text{w}}}\right)_{\text{R}}^c$	$\frac{10^4 k_{\text{w}}(\text{sol})^d}{k_{\text{Az}}(\mu = 1; \text{w})}$	$\left(\frac{k_{\text{Az}}}{k_{\text{MeOH}}}\right)_{\text{R}}^c$	$\frac{10^4 k_{\text{M}}(\text{sol})^d}{k_{\text{Az}}(\mu = 1; \text{w})}$	$\frac{10^2 k_{\text{w}}(\text{sol})[\text{H}_2\text{O}]}{k_{\text{Az}}(\mu = 1; \text{w})}$
0	109	8.86	2720	3.68	—	—	2.04
10	91.5	8.66	2680	3.20	260	33.0	1.60
20	78	8.45	2260	3.32	213	35.2	1.48
30	68	8.23	1870	3.59	170	39.5	1.40
40	62	7.96	1300	4.87	140	45.2	1.62
50	60	7.68	1000	6.35	111	57.2	1.76
60	60.5	7.35	840	7.96	104	64.3	1.77
70	63.2	7.04	660	11.06	95	76.8	1.84
80	69.5	6.66	540	15.7	90	94.2	1.75
90	82.5	6.24	—	—	—	—	—

^a Graphically interpolated values using data at 25°C in other MeOH : H₂O mixtures (Tissier and Douheret, 1978). ^b Calculated from the dielectric constant at 25°C (Adhadov, 1981). ^c Product ratios and reactant concentrations at 22 ± 2°C from Richard *et al.* (1984); R stands for Richard.

^d Calculated as $(\lambda_{\text{sol}}\epsilon_{\text{w}}^{1/2}/\lambda_{\text{w}}\epsilon_{\text{sol}}^{1/2})/(k_{\text{Az}}/k_{\text{SOH}})_{\text{R}}$, see text.

Table 14 Effect of changes in solvent composition on the separate rate constants for the reaction of the 1-(4-methoxyphenyl)ethyl carbocation in TFE-W.

% TFE	$\lambda(\text{Et}_4\text{NCl})^a$ $/\Omega^{-1} \text{ cm}^{-1} \text{ mol}^{-1}$	$\epsilon^{1/2}{}^b$	$\left(\frac{k_{\text{Az}}}{k_{\text{W}}}\right)_{\text{R}}^c$	$\frac{10^4 k_{\text{W}}(\text{sol})^d}{k_{\text{Az}}(\mu = 1; \text{w})}$	$\left(\frac{k_{\text{Az}}}{k_{\text{TFE}}}\right)_{\text{R}}^c$	$\frac{10^4 k_{\text{W}}(\text{sol})^d}{k_{\text{Az}}(\mu = 1; \text{w})}$	$\frac{10^2 k_{\text{W}}(\text{sol})}{k_{\text{Az}}(\mu = 1; \text{w})} / \text{M}$
0	109	8.86	2720	3.68	—	—	204
20	69.9	8.32	2640	2.59	—	—	115
30	59.9	7.84	2670	2.33	—	—	90.6
40	55.3	7.57	3020	1.97	5200	1.14	65.7
50	53.4	7.22	3070	1.96	5900	1.02	54.4
60	52.6	6.83	3470	1.80	7600	0.824	40.0
70	48.7	6.43	3910	1.58	10200	0.604	26.3
80	44.8	6.02	4790	1.26	15300	0.396	14.0
90	40.9	5.61	6060	0.978	23900	0.248	5.43

^a Calculated from λ^0 -values at 25°C in water and TFE, see text. ^b Calculated from the dielectric constants at 25°C given by Murto and Heino (1966).

^c Calculated from product ratios and reactant concentrations at $22 \pm 2^\circ\text{C}$ from Richard *et al.* (1984); R stands for Richard. ^d Calculated as $(\lambda_{\text{sol}}\epsilon_{\text{W}}^{1/2}/\lambda_{\text{W}}\epsilon_{\text{sol}}^{1/2})/(k_{\text{Az}}/k_{\text{SOH}})_{\text{R}}$, see text.

Table 15 Effect of changes in solvent composition on the separate rate constants for the reaction of the 1-(4-methylphenyl)ethyl carbocation in M-W and TFE-W.*(a) Methanol-water*

% MeOH v/v	$\left(\frac{k_{Az}}{k_W}\right)_R^a$	$\frac{10^2 k_W(sol)^b}{k_{Az}(\mu = 1; w)}$	$\left(\frac{k_{Az}}{k_M}\right)_R^a$	$\frac{10^2 k_M(sol)^b}{k_{Az}(\mu = 1, w)}$
50	66	0.962	27	2.35
60	65	1.03	29	2.31
70	68	1.07	34	2.15
80	75	1.13	43	1.97
90	91	1.18	56	1.92

(b) 2,2,2-Trifluoroethanol-water

% TFE v/v	$\left(\frac{k_{Az}}{k_W}\right)_R^a$	$\frac{10^2 k_W(sol)^b}{k_{Az}(\mu = 1; w)}$	$\left(\frac{k_{Az}}{k_{TFE}}\right)_R^a$	$\frac{10^2 k_{TFE}(sol)^b}{k_{Az}(\mu = 1, w)}$
50	38	1.58	51	1.18
60	38	1.65	57	1.10
70	37	1.66	64	0.962
80	41	1.48	75	0.793
90	44	1.35	88	0.674

^a Product ratios and reactant concentrations at $22 \pm 2^\circ\text{C}$ from Richard *et al.* (1984); R stands for Richard. ^b Calculated as $(\lambda_{sol} \epsilon_W^{1/2} / \lambda_W \epsilon_{sol}^{1/2}) / (k_{Az} / k_{SOH})_R$.

There are two more relevant cases. Amyes and Jencks (1989) gave a graphical representation of k_{Az}/k_S -values for two relatively stable oxycarbocation ions having k_S -values of 5×10^7 – $2 \times 10^9 \text{ s}^{-1}$ in MeCN-W. For the 1-methoxy-1-phenylethyl carbocation they obtained a straight line through all the points between 30 and 70% MeCN, whereas for the 2,4-dimethoxy-2-butyl cation the value at 40% MeCN was lower by *ca* 35% than the value in pure water. Since the exact k_{Az}/k_S -values are unknown, and the ionic strength was only specified to be between 0.5 and 2, a full analysis similar to that given above is impossible. However, in the range of ϵ 's and μ 's concerned [for 70% MeCN, $\epsilon = 49$ (Adhadov, 1981)], we can conclude that k_{Az} changes mainly by the changes in the conductivity of the ions. The conductivity of Bu_4NBr decreases by 15% between 0% and 40% MeCN and then increases, regaining its former value at 70% MeCN (Schiavo and Scrosati, 1976). Consequently, the behaviour of the k_{Az}/k_S -ratios in the range 0–70% MeCN suggests an increase around 30% for the k_S -values

when the MeCN %v increases, in good agreement with the results of McClelland *et al.* (1989).

The solvolysis of $(4\text{-CH}_3\text{C}_6\text{H}_4)_2\text{CHCl}$ in acetone–water (A–W) mixtures containing 0.05 M NaN_3 was studied by two groups, which obtained slightly different results. The product ratios yielded invariant $k_{\text{Az}}/k_{\text{W}}[\text{W}]$ -values between 50 and 90% A according to one (Bateman *et al.*, 1940), or increased by less than 50% when the [W] term decreased fourfold between 50 and 87.5% A according to the other (Golomb, 1959). We believe that the experimental accuracy of these old data does not justify an extensive analysis. However, taking into account the twofold increase in the conductivity of Bu_4NBr in this range (Schiavo and Scrosati, 1976), the relatively low dielectric constants [$\epsilon = 53.2$ for 50% A and 27.4 for 90% A (Adhadov, 1981)] and the low but significant μ (0.05), we can estimate that k_{Az} -values would certainly not decrease when [W] decreases between 50 and 90% A. They might even increase slightly which means that $k_{\text{W}}[\text{W}]$ -values between 50 and 90% A will increase slightly when [W] decreases. This is similar to the behaviour of the $k_{\text{W}}[\text{W}]$ -value for the same carbocation in MeCN–W (McClelland *et al.*, 1989).

In summary we now have information on the behaviour of $k_{\text{W}}[\text{W}]$ -values in five cases.

- (a) For eight diarylmethyl and triarylmethyl cations in MeCN–W, these values first increase when increasing the W %v, but then level off, and above 20% MeCN they even slightly decrease (McClelland *et al.*, 1989).
- (b) Two α -oxocarbenium ions show similar behaviour in 30–70% or 60–100% W in MeCN–W (Amyes and Jencks, 1989).
- (c) For the 1-(4-methoxyphenyl)ethyl carbocation, $k_{\text{W}}[\text{W}]$ -values in M–W are quite constant, and even decrease slightly when W %v increases from 20 to 90%, but in TFE–W they increase 21-fold when W %v increases from 10 to 80% (Richard *et al.*, 1984).
- (d) For the 4,4'-dimethylbenzhydryl carbocation in A–W, the azide/water product ratios strongly suggest unchanged or slightly decreasing $k_{\text{W}}[\text{W}]$ -values when W %v increases from 10 to 50% (Bateman *et al.*, 1940; Golomb, 1959).
- (e) The recent data of Mathivanan *et al.* (1991) show that in the reaction of An_2CH^+ in M–W and especially in E–W, $k_{\text{W}}[\text{W}]$ -values decrease substantially when the W %v increases. These results, which were obtained by direct measurements, do not fit the very slight decrease found for $\text{An}\overset{+}{\text{C}}\text{HMe}$ in M–W [cf. (c) above], and may suggest that the

behaviour of $k_w[W]$ depends on the system or that our method of estimation is deficient.

Solvent sorting around the reacting carbocation might be a possible explanation for some of these phenomena. This is discussed in the following section.

4 The possibility of solvent sorting

McClelland *et al.* (1989) offered "solvation, changing water structure and even the formation of water pools" as an explanation for the behaviour of k_s -values in the reactions of their carbocations with the solvent. The first two factors are too broad for a useful discussion. As to "water pools", Ivanov *et al.* (1972), to whom McClelland refers, explains that "a hydrated ion is formed ... and its reaction with water does in fact take place within the solvate". A similar idea was raised earlier by Ingold (1969) in order to explain the independence of $[RN_3]/[ROH]$ on $[W]$ for the reaction of $(4-CH_3C_6H_4)_2CH^+ (= R^+)$ in A-W mixtures. In his words: "Provided sufficient water is present for the purpose, the first formed carbonium ion is solvated by a shell of a fixed composition so that the rates at which the ion covalently unites with one of the solvating water molecules is independent of the composition of the bulk of the medium." In essence, these authors assume extensive solvent sorting around the carbocation. The possibility that solvent sorting around the reactive electrophile in E-W mixtures was responsible, at least in part, for the measured k_E/k_W -values and for their change with the solvent, was invoked and rejected by both Karton and Pross (1977) and by Harris *et al.* (1974). This was mainly because the change of the selectivity values was independent of the identity of the leaving group in the solvolysis of octyl derivatives (Pross *et al.*, 1978) and because of the insensitivity of the selectivity values to temperature changes (Harris *et al.*, 1974). Harris concluded that solvent sorting was unimportant for alkyl halides in aqueous ethanol. However, McManus and Zutaut (1985) again raised this possibility for the solvent-related changes in the selectivity values of 1-adamantyl bromide that they found in several binary mixtures of alcohols, fluoroalcohols and organic acids.

"Solvent sorting", also called "preferential solvation" in physical chemistry, assumes a different macroscopic and microscopic distribution of the solvent components around stable ions in mixed solvents. If it is significant and products are formed by reaction of a carbocation with the immediate neighbouring solvent molecules, the assumption used for calculation of the selectivity according to (2) becomes invalid. This phenomenon

is well established experimentally (Schneider, 1976; Langford and Tong, 1977), and has lately been the subject of a thorough theoretical investigation (Marcus, 1988, 1989; Ben-Naim, 1988, 1990). A variety of thermodynamic, electrochemical and spectroscopic methods, mainly nmr spectroscopy, were used in order to establish and determine the extent of preferential solvation around ions. Simple anions in aqueous ethanol, methanol, acetone or acetonitrile were found to be preferentially solvated by water, while the situation varies for cations (Schneider, 1976).

Langford and Tong (1977) stressed the need to know the preferential solvation curve of any solute undergoing reaction with a solvent molecule in a mixture. Their view is that it is meaningless to calculate a second-order rate constant for a solvolysis reaction by using only bulk molarities, as in (2). They present the convincing example of the hydrolysis of $\text{Cr}(\text{NCS})_6^{3-}$ to $\text{Cr}(\text{NCS})_5\text{OH}_2^-$ in MeCN-W mixtures. The observed first-order rate constant decreased dramatically on adding small amount of MeCN to pure water, resulting in a very curved k_1 versus mole fraction x_w or $[\text{W}]$ plot. However, the same rate constants are linearly correlated with n/n_0 -values (measured through nmr relaxation times), which express the ratio of the number of W-molecules in encounter with $\text{Cr}(\text{NCS})_6^{3-}$ in the mixed solvent to their number in pure water. The n/n_0 -ratio fell from 1 to 0.55 when only 10% MeCN was added to water. Such surprising preference for MeCN was also shown by $\text{Cr}(\text{NH}_3)_2(\text{NCS})_4^-$ (Langford and Tong, 1977), an ion that also preferred acetone to water (Langford and White, 1967). Watts (1973) ascribes this to a rejection of the cosolvent MeCN or acetone by the bulk water structure rather than to a predominance of any ion-solvent interaction.

Medda *et al.* (1988) investigated the energy of the solvent-sensitive charge-transfer absorbance band ($E_{\text{T}}^{\text{max}}$) of the 3-cyano-*N*-ethylpyridinium iodide intimate ion-pair in several binary aqueous mixtures. Whereas in aqueous methanol, ethanol or propanol, $E_{\text{T}}^{\text{max}}$ was linearly proportional to x_w , and thus no specific solvation of the ion-pair is indicated, in aqueous acetone or in aqueous MeCN, $E_{\text{T}}^{\text{max}}$ -values were higher than expected, indicating a substantial preferential solvation by the water.

Marcus (1988) developed a quasi-lattice-quasi-chemical theory that enabled him to calculate the amount of preferential solvation of an ion X in any binary mixture of solvents S_1 and S_2 . The only data required are the two standard Gibbs free energies of transfer of the ion from the reference solvent, usually W, to S_1 and S_2 in their pure states, $\Delta G_i^0(\text{W}, \text{W} \rightarrow S_1)$ and $\Delta G_i^0(\text{X}, \text{W} \rightarrow S_2)$, and the excess Gibbs free energy of mixing for the equimolar mixture of S_1 and S_2 G_{12}^E ($x = 0.5$). He calculated preferential solvation curves, which gave the local composition of the solvent around Na^+ , Ag^+ and Cl^- in MeCN-W and DMSO-W mixtures as a function of x_w . From

these curves, it can be deduced that for binary systems for which G^E -values are small (1.32 and $-1.23 \text{ kJ mol}^{-1}$ respectively) compared with the ΔG_i^0 -values (which are between 13 and 42 kJ mol^{-1}), the local composition of the solvent around the ion is mainly determined by the ΔG_i^0 -values. However, G_{12}^E is very important in determining the general shape of the preferential solvation curve, and when we analysed those curves we concluded that the sign of G^E determines the direction of the change of the composition ratio $(x_w/x_s)_{\text{bulk}}/(x_w/x_s)_{\text{local}}$ when x_w changes (x_s is the mole fraction of the cosolvent). When $G_{12}^E > 0$, as in MeCN, the mutual rejection of the two solvents increases the accumulation of the preferred solvent around the ion, especially when its molar fraction is low. Therefore, when water is sorted preferentially (as for Cl^-), $(x_w/x_{\text{MeCN}})_{\text{bulk}}/(x_w/x_{\text{MeCN}})_{\text{local}}$ will increase from its lowest value at $x_w \rightarrow 0$ to unity at $x_w = 1$. When MeCN is preferred (as for Ag^+), the composition ratio is greater than unity, and it will change in the opposite way, being highest at low x_{MeCN} (high x_w). Consequently, this composition ratio will always increase with the W molar fraction. The reverse applies for solvent systems with $G_{12}^E < 0$, exemplified by DMSO-W. Using the preferential solvation curves given by Marcus (1988), we calculated changes between 30 and 50% in the composition ratios for the ions mentioned above, in solvent systems when the water volume percentage changed from 50 to 90%.

The reason for applying this analysis is that all the alcohol-water mixtures considered by us have positive and low $G_{\text{SOH-W}}^E$ values that are not far from that of MeCN-W; $G_{\text{M-W}}^E = 0.3 \text{ kJ mol}^{-1}$ (Marcus, 1988), $G_{\text{E-W}}^E = 0.73 \text{ kJ mol}^{-1}$ (Marcus, 1989) and $G_{\text{TFE-W}}^E = 0.83 \text{ kJ mol}^{-1}$, as calculated from activity coefficients (Smith *et al.*, 1981). If the reactive solute (either neutral or a cationoid species) in SOH-W mixtures is subject to a preferential solvation similar to that of an ion in MeCN-W, it means that the k_{SOH}/k_w -values calculated according to (2) using bulk molarities will always increase with x_w even when the "true" selectivities are constant. This is so because, by dividing (17) by (18), which gives the calculated and the true selectivity ratios respectively, we obtain (19). Note that k_{SOH}/k_w increases

$$\left(\frac{k_{\text{SOH}}}{k_w}\right)_{\text{calc}} = \frac{[\text{ROS}]}{[\text{SOH}]} \left(\frac{x_w}{x_{\text{SOH}}}\right)_{\text{bulk}} \quad (17)$$

$$\left(\frac{k_{\text{SOH}}}{k_w}\right)_{\text{true}} = \frac{[\text{ROS}]}{[\text{SOH}]} \left(\frac{x_w}{x_{\text{SOH}}}\right)_{\text{local}} \quad (18)$$

$$\frac{(k_{\text{SOH}}/k_w)_{\text{calc}}}{(k_{\text{SOH}}/k_w)_{\text{true}}} = \frac{(x_w/x_{\text{SOH}})_{\text{bulk}}}{(x_w/x_{\text{SOH}})_{\text{local}}} \quad (19)$$

with x_W for almost all systems. In addition, we calculated from the activity-coefficient data of Smith *et al.* (1981) a G_{E-TFE}^E -value of $-0.73 \text{ kJ mol}^{-1}$ for E-TFE mixtures. Hence the preferential solvation situation in E-TFE resembles that in DMSO-W, and k_E/k_{TFE} -values calculated from bulk molarities will tend to decrease when x_{TFE} increases, as was indeed found for reactions of compounds of the first group shown in Table 7. Consequently, preferential solvation can explain, at least partially, the observed trends in the selectivity values. Moreover, since the change in the composition ratio is determined by G_{12}^E which is directly related to the activity coefficients of the solvent components, it might be concluded that the preferential solvation of the reactive solutes is the reason for the dependence of the selectivity ratios on the activity coefficient ratios.

However, caution is required in applying the Marcus treatment to aqueous alcohols, since two of its basic assumptions are the independence of the separate interaction energies between X and S1, X and S2 and S1 and S2, and that the entropy of mixing is ideal ($S_{12}^E = 0$). Indeed, the macroscopic G -values are understood to express the microscopic interaction energies. These assumptions do not fit the complex nature of aqueous solutions, where cooperative forces between water molecules and their effect on entropy changes are very important (Franks and Ives, 1966). In addition, in aqueous alcohols, the positive sign of G_{W-SOH}^E results from a more negative TS^E - than H^E -term (Franks and Ives, 1966; Treiner *et al.*, 1976). Likewise, ΔG_i^0 -values for transferring ions from water to an organic solvent are mainly governed by the entropy changes involved (Cox *et al.*, 1974).

Hence, when regarding the question of preferential solvation, the change in the separate rate constants will be instructive. For instance, if we ascribe to preferential solvation the near constancy of $k_W[W]/s^{-1}$ in MeCN-W above 20% W found by McClelland *et al.* (1989), we have to assume a nearly constant local x_W around the carbocation. This environment surrounds the ion all the way up to pure water, and hence this $x_W(\text{local})$ must be unity, i.e. the organic cations prefer water almost exclusively over MeCN. Such total preference was not found even for Cl^- (Marcus, 1988). Moreover, a ΔG_i^0 -value of 0.73 kJ mol^{-1} was calculated for the transfer of phenyltropylium perchlorate from W to M (Hopkins and Alexander, 1976). Since for ClO_4^- , $\Delta G_i^0 = 5.9 \text{ kJ mol}^{-1}$ for the same transfer (Cox *et al.*, 1974), for the transfer of the phenyltropylium cation from W to M, $\Delta G_i^0 = -5.13 \text{ kJ mol}^{-1}$, a value that definitely does not agree with an almost exclusive preference of water over MeCN. Certainly, the preferential solvation cannot explain the actual small decrease observed above 20% W in $k_W[W]$ when the W %v increased in all the systems investigated (McClelland *et al.*, 1989). Likewise, the slight decreases found also in A-W and M-W are sufficient to eliminate the possibility that preferential solvation is an important contributor to the

behaviour of the $k_w[W]$ -values. Moreover, the substantial and even outstanding increase of $k_w[W]$ in TFE-W also does not agree with preferential solvation. There is no reason why the carbocation should prefer water over methanol, acetonitrile and acetone but not over trifluoroethanol. Finally, the regular increase of both the first-order $k_w[W]$ and $k_M[M]$ in M-W and $k_w[W]$ and $k_E[E]$ in E-W for An_2CH^+ on increasing the alcohol %v in these solvents (Mathivanan *et al.*, 1991), is inconsistent with specific solvation by water.

5 The mutual role of activity coefficients and basicity (or acidity) of the nucleophilic solvent components

Fifteen years ago, Langford and Tong (1976) jokingly termed aqueous solutions the "kineticist's troubled water". Since then the situation has not improved much, and the exact structure of liquid water and aqueous solutions is still very much unknown (Symons, 1989). Consequently, the identity of the reactive species (monomers or oligomers) is unclear, and speculations and broad generalizations govern much of the discussion in the field. Nevertheless, by analysing the changes in k_w and k_{SOH} ($SOH = M, E, TFE$) in binary mixtures as due to changes in both the activity coefficients and the basicity or acidity of the binary solvent components, we obtain a coherent picture that also enables us to explain the various trends in k_A/k_B -values summarized in Table 9 as well as in the k_w -values given in Table 12.

We shall start with k_w for diarylmethyl and triarylmethyl carbocations in MeCN-W, for which abundant, directly measured data are available. In the range of water mole fraction $x_w = 0-0.2$ that corresponds to 0-10% W, the activity of water rises steeply and then remains quite constant (0.75-0.80) between $x_w = 0.2$ and 0.7 (10 and 45% W), where the decrease of the W activity coefficients from $\gamma_w = 3.75$ to 1.15 balances the increase in its mole fraction (Behrendt *et al.*, 1969). This alone is almost sufficient to explain the shape of the $\log k_s$ versus W %v plots below $x_w = 0.7$. Above this value and up to pure water, γ_w decreases only by 10%, so that the activity increases by 20%. That the $k_w[W]$ -values in this range do not increase but rather decrease can stem from the accompanying lowering of the mole fraction of MeCN, which is known to act as a basic cosolvent in aqueous solutions (Symons, 1981, 1983). MeCN can bind free OH groups (OH_f) and thus increase the number of W free lone pairs (LP_f), which amount to *ca* 10% in pure water (Symons, 1989) and which are the actual nucleophiles in the mixtures. We suggest that, when MeCN is added to water, the k_w -term increases more than the [W]-term decreases, and therefore $k_s = k_w[W]$ increases gradually. Since the reaction between the weak base MeCN and bulk water to form the LP_f is an equilibrium process, this effect contributes

less at high MeCN levels, where the activity coefficients play the main part in shaping the k_s -values. The relatively constant k_s -values for the solvolysis of $(4\text{-CH}_3\text{C}_6\text{H}_4)_2\text{CHCl}$ in acetone–water can be explained similarly. When the A %v increases, the combination of increased activity coefficients (Washburn, 1928a) and increased number of W LP_f keeps k_s from decreasing despite the dwindling [W].

By examining k_w - and k_M -values for the 1-(4-methoxyphenyl)ethyl carbocation in M–W [by looking at the ratios $k_{\text{SOH}}(\text{sol})/k_{\text{AZ}}(\mu = 1, w)$ in Table 13], we see that when the M %v increases between 10% and 80% both rate constants increase substantially. For the former cation, k_w increases 4.9-fold and k_M 2.9-fold. The increase in k_M despite the twofold decrease in γ_M in this range (Washburn, 1928a) shows that the basicity of M increases considerably when M replaces W, probably because lowering of the total number of OH_f groups in the medium increases the total number of M lone pairs (either free or bonded to the M polymeric chain). There is also an increase in the number of W LP_f, which must be more influential in raising k_w than the modest increase of 30% in γ_w (Washburn, 1928a). The near constancy of $k_w[\text{W}]$ -values for An $\dot{\text{C}}\text{HMe}$ is then interpreted as a fortuitous compensation between increase of k_w and decrease of [W]. The greater increase of k_w than of k_M , which is the cause of the diminished preference for M as its %v increases, results mainly from changes in the γ 's in opposite directions rather than from the change in the same direction in the LP_f. It is conceivable that the lack of decrease of k_M/k_w at less than 30 M %v (Table 4) is due to the irregular decrease of γ_w between 0 and 20% M (Wrewsky, 1913).

In TFE–W mixtures between 40 and 90% TFE, both k_w and k_{TFE} for the 1-(4-methoxyphenyl)ethyl cation decrease: k_w by 2.0-fold and k_{TFE} by 4.6-fold (Table 12). The decrease in k_w despite the 1.8-fold increase in γ_w points to the significance of lowering the W basicity by adding TFE, as suggested previously for this reaction (Richard *et al.*, 1984; Ta-Shma and Jencks, 1986). Owing to the low pK_a of TFE (12.4) (Murto and Heino, 1966), it acts as an acidic cosolvent for W, the hydrogen bonds to the W LP_f decreasing the W nucleophilicity. The decrease in k_{TFE} when TFE replaces W is more than the 3.3-fold lowering of γ_{TFE} between 40 and 90% TFE. It is not very probable that the total number of TFE LP's decreases significantly when the %v of TFE increases, but it may well be that the lone pair in self-associated TFE is much less basic than the TFE lone pair in the complex with W. We note that water was found to fit a Brønsted plot for general base catalysis of the reaction of this cation with TFE that included several substituted acetates (Ta-Shma and Jencks, 1986). In TFE–W as in M–W, the increasing preference of the carbocation for W when its %v decreases is mainly due to changes of the activity coefficients in opposite directions.

The variation of the rate constants for the 1-(4-methylphenyl)ethyl carbocation is small (Table 15), and their mechanistic significance relies strongly

on the validity and accuracy of our treatment regarding k_{Az} -values. Nevertheless, the noticeable trends are very reasonable. Between 50 and 90% M, k_w increases 1.2-fold and k_M decreases 1.2-fold. These small identical opposite changes probably reflect the similar opposite changes of the activity coefficients of a 1.39-fold decrease of γ_w and a 1.34-fold increase of γ_M (Washburn, 1928a). Similarly k_{TFE} decreases 1.8-fold when γ_{TFE} decreases 2.4-fold (Smith *et al.*, 1981) between 50 and 90% TFE. Only the k_w -values in TFE-W remain practically unchanged, despite the 1.7-fold increase of γ_w . Consequently, for the 1-(4-methylphenyl)ethyl carbocation, only the water reaction in TFE is affected by changing the basicity of the nucleophile. The general insensitivity of the cation to the change fits its relative instability ($k_s = 4 \times 10^9 \text{ s}^{-1}$ in 50% TFE) (Richard *et al.*, 1984). Some contribution to the selectivity values could also arise from front-side collapse of solvent-separated ion pairs. About 27% reaction through unspecified ion pairs was proposed for the solvolysis of 1-(4-methylphenyl)ethyl chloride by Richard and Jencks (1984a).

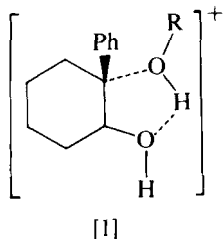
We conclude that for nucleophilic attacks on phenylethyl free carbocations in M-W and TFE-W, the k_{SOH}/k_w -values decrease when the alcohol %v increases, since the γ 's change in opposite directions. The changes in the basicity of the nucleophiles, which significantly alter the separate rate constants, mostly cancel out when comparing the selectivity ratios. Considering the above-mentioned numerical changes of the rate constants and the activity coefficients, there is some evidence that adding TFE to TFE-W solution lowers the basicity of water more than it lowers the basicity of TFE. The same conclusion also fits experiments showing that k_w increased more than k_{TFE} when 5–20% of a less acidic alcohol was substituted for TFE in 50% TFE (Ta-Shma and Jencks, 1986).

We believe that we can adapt these conclusions to all the reactions belonging to the second group in aqueous ethanol, methanol or trifluoroethanol. The similar decrease of k_E/k_w observed for almost all the systems in Table 3 suggests that the effect of the activity coefficients is not very sensitive to the nature of the electrophile. We note, however, that, for the reactions of An_2CH^+ in M-W and E-W, k_{SOH} increases more than k_w until 40% ROH, with a consequent increase in the k_{SOH}/k_w selectivity values (Mathivanan *et al.*, 1991). This is in spite of the decrease in γ_{SOH} in this range.

These conclusions also seem to hold for reactions of systems of the first group in TFE-W. In this case, the acidity of the nucleophile, as determined by the number of its OH_f groups, is important. When the TFE %v increases, both its acidity and the acidity of water increase, so that again the activity coefficients play the main role in determining the changes in the selectivity ratios, which therefore do not differ much for the two groups. However, the situation in E-W is different, since k_E/k_w -values for reactions of the first

group decrease much less than for reactions of the second group. If our general scheme holds, that means that the acidity changes for the former compensate for the decrease in γ_E/γ_W when the E %v goes up. This will happen if the decrease in the acidity of W resulting from replacing W with E is significantly larger than the decrease in the acidity of E itself. On examining possible structures in aqueous ethanol, this seems reasonable. Water has no need to hydrogen bond to the LP_f of E, and statistically most of it will be bound to the lone pairs of the polymeric E. Therefore it has very little effect on the equilibrium of $E LP_f$ with $E OH_f$ and on the concentration of the latter. On the other hand, as all the hydrogen bonds formed by W use its OH_f , an increase in the E %v will markedly decrease the water acidity and therefore its reactivity. This will compensate for the decrease of γ_E/γ_W and lead to an overall small effect of the change in the E %v on the selectivity values.

In this regard, it is worthwhile to mention the k_E/k_W -values of the *syn*-isomers in the acid-catalysed solvolysis of 1-phenylcyclohexene oxide (Battistini *et al.*, 1977). They are believed to arise from front-side collapse of the carbocation [1]. In contrast with other systems belonging to the first



group, these selectivity values are greater than unity below 80% E, and decrease significantly when E %v is increased (Table 2). The authors ascribed the increase in selectivity values, when the W %v increased, to an increased stability of the ion with the consequent increase in solvent polarity. However, they also suggested that k_E/k_W -values greater than unity resulted from "a preference for solvation by ethanol, a better and more easily polarized nucleophile than water". These arguments seem to us internally inconsistent. We suggest that the different behaviour of the selectivity values here stems from the different nucleofuge, which, in contrast with most solvolysis reactions, is a neutral OH, rather than anionic, and which remains covalently bonded to the carbocation. Hence electrophilic assistance to the formation of the latter is much less important, resulting in k_E/k_W -values greater than unity. Their decrease at higher E %v is due to a decrease in the γ_E/γ_W -ratio, which is not compensated here by a decrease in the acidity of water.

E-TFE mixtures show negative deviation from Raoult's law. Consequently, the activity-coefficient ratios γ_E/γ_{TFE} increase with the increase in E %v (Smith *et al.*, 1981), implying a consequent increase in k_E/k_{TFE} -ratios. Although the data in Tables 7 and 8 are limited, small increases were found for reactions of the first group, but not for those of the second group. TFE-E mixtures must be structurally different from the aqueous alcohol mixtures because mutual associations in them are much preferred over self-association, as deduced by a variety of measurements including the boiling points, viscosities and ir spectra (Smith *et al.*, 1981; Mukherjee and Grunwald, 1958). In the associative complex, TFE will donate the OH and E the LP. We therefore suggest that adding E to an excess of TFE will only strengthen the basicity of TFE without improving that of the E itself, until [E] will become large enough to give oligomers containing more than one or two E molecules (at least above 45% E, which is an equimolar mixture). For reactions of the second group, this effect can compensate for the increase in γ_E/γ_{TFE} -values so that k_E/k_{TFE} -values could remain nearly constant up to 70% E, as was found experimentally (Table 8). For reactions of the first group, a similar approach will lead to the conclusion that, at least up to 45% E, the acidity of TFE decreases much more than that of E, and therefore k_E/k_{TFE} -ratios should increase. It is noteworthy that the increase in the k_E/k_{TFE} ratios in Table 7 does seem to reach a shallow maximum between 40–60% E.

Table 16 gives the k_{TFE}/k_W and k_M/k_W selectivity ratios for relatively stable carbocations, which were calculated from the separate rate constants k_W , k_{TFE} and k_M in the pure solvents. Comparison shows that the k_{TFE}/k_W -values in Table 16 are much lower than the k_{TFE}/k_W -values derived from the product ratios in binary mixtures (Table 5). It could be argued that this is a reflection of reactivity-selectivity behaviour, where the more stable cations in Table 16 show greater discrimination between TFE and W than the less stable cations in Table 5. However, this cannot be the main reason for the discrepancy, as shown by the following data: (a) $4\text{-Me}_2\text{NC}_6\text{H}_4\dot{\text{C}}\text{HCH}_3$ should be at least as stable as An_2CH^+ , judged by the calculated solvolysis rates of their precursor chlorides (Ta-Shma and Rappoport, 1983), yet its selectivity value in 50% TFE (v/v) is already 0.33 (Richard *et al.*, 1984); (b) $\text{An}\dot{\text{C}}\text{HCH}_3$ ($k_{TFE} = 2.6 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$; McClelland *et al.*, 1988) has a comparable reactivity to $\text{ToI}\dot{\text{C}}\text{HPh}$ ($k_{TFE} = 2.0 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$; Table 16), yet the former ($k_{TFE}/k_W = 0.58\text{--}0.25$ in 40–90% TFE; Richard *et al.*, 1984) is two orders of magnitude less selective than the latter ($k_{TFE}/k_W = 0.0093$; Table 16); (c) AnCH_2^+ , $\text{ToI}\dot{\text{C}}\text{HCH}_3$ and Ph_2CH^+ are comparable in reactivity, judging from the solvolysis rates of the precursor chlorides (Ta-Shma and Rappoport, 1983), but the corresponding k_{TFE}/k_W -values differ—they are respect-

ively 0.5 at 50% TFE (Amyes and Richard, 1990), 0.75–0.50 in 50–90% TFE (Richard *et al.*, 1984), and 0.014 (Table 16).

Consequently, the difference in the apparent nucleophilicity between TFE and W and the dependence of this difference on the stability of the carbocation are much smaller when the nucleophiles react competitively in their mixture than when they react independently.

Table 16 Selectivity ratios for relatively stable carbocations calculated from the separate second-order rate constants in the pure solvents.

(a) *Trifluoroethanol–water*^a

Carbocation	$10^{-3}k_W/M^{-1} s^{-1}$	$k_{TFE}^b/M^{-1} s^{-1}$	$\frac{10^4 k_{TFE}}{k_W}$
An ₂ CH ⁺	1.8 ^c	1.0	5.6
AnTolCH ⁺	14 ^d	20	15
AnPhCH ⁺	34 ^e	88	26
Tol ₂ CH ⁺	54 ^d	1.8×10^3	32
TolPhCH ⁺	2.3×10^3 ^f	2.0×10^4	93
Ph ₂ CH ⁺	1.64×10^4 ^f	2.3×10^5	140

(b) *Methanol–water*

Carbocation	$k_W^g/M^{-1} s^{-1}$	$k_M^h/M^{-1} s^{-1}$	$\frac{k_M}{k_W}$
<i>p</i> -O ₂ N-MG ⁱ	2.5×10^{-6} ^j	2.2×10^{-5}	6.8
<i>p</i> -Me ₂ NC ₆ H ₄ -Tr ⁺ ^k	3.6×10^{-4}	8.9×10^{-3}	25
<i>p</i> -An-Tr ⁺ ^k	4.9×10^{-3}	0.53	108
Ph-Tr ⁺ ^k	1.8×10^{-2}	2.9	160
4-ClC ₆ H ₄ -Tr ⁺ ^k	2.2×10^{-2}	3.7	170
Tr ⁺ ^k	4.7×10^{-2}	6.07	130
An ₂ CH ⁺ ^{c,l}	1.83×10^{-3}	3.05×10^5	167

^a At 20 ± 1°C. ^b McClelland *et al.* (1988). ^c Mathivanan *et al.* (1991). ^d Calculated, using linear extrapolation from the k_S -value at <80% W in MeCN–W (McClelland *et al.*, 1989). ^e Calculated from the k_S -value at 80% W in MeCN–W (McClelland *et al.*, 1989) using the same extrapolation as in (d) above. ^f Calculated from k_W in MeCN–W at very low W %v using a $k_W(\text{low W \%v})/k_W(W)$ ratio that can be calculated from the data for Tol₂CH⁺ (McClelland *et al.*, 1989). ^g Calculated from k_S -values in water (Ritchie and Fleischhauer, 1972). ^h Calculated from k_S -values in MeOH at 23 ± 1°C (Ritchie and Virtanen, 1972b). ⁱ MG = malachite green. ^j Calculated from the k_S -value in water (Ritchie and Virtanen, 1972c). ^k Tr = Tropylium. ^l In EtOH, $k_E = 3.24 \times 10^5 M^{-1} s^{-1}$ and $k_E/k_W = 177$ (Mathivanan *et al.*, 1991).

This discrepancy cannot result from the change in the activity coefficient ratio between the pure solvent and the mixture. At the highest percentage of water (60% W) used in TFE-W, the $\gamma_{\text{TFE}}/\gamma_{\text{W}}$ -ratio is only 3.1 (Smith *et al.*, 1981). So it cannot explain the greater than 30-fold increase in the $k_{\text{TFE}}/k_{\text{W}}$ -ratio.

We suggest that extensive hydrogen bonding between the free lone pairs of water and the free OH-groups of TFE takes place when both components are mixed. The consequent combination of higher basicity of TFE in the presence of water and lower basicity of W in the presence of TFE increase $k_{\text{TFE}}/k_{\text{W}}$ appreciably in the mixture, and this accounts for the discrepancy between the magnitudes of the selectivities in Tables 5 and 16.

The selectivity values of 7–16 for the stable carbocations investigated by Ritchie and Virtanen (1972a–c) in W and in pure M (Table 16) are significantly higher, with the exclusion of the value for *p*-nitromalachite green, than the values calculated in M-W or E-W mixtures from the product distributions for less stable carbocations (Tables 3 and 4). Among the cations of Table 16, the more stable ones show somewhat lower selectivity. As in TFE-W, the selectivity differences displayed in Tables 3 and 4 and in Table 16 are not due to reactivity-selectivity behaviour, since the effect is observed even for a single cation. For An_2CH^+ , McClelland and coworkers' (Mathivanan *et al.*, 1991) k_{M} -, k_{E} - and k_{W} -values measured in the pure solvents led to $k_{\text{M}}/k_{\text{W}} = 167$ and $k_{\text{E}}/k_{\text{W}} = 177$, whereas the $k_{\text{M}}/k_{\text{W}}$ - and $k_{\text{E}}/k_{\text{W}}$ -selectivities calculated from the product ratios in M-W and E-W mixtures were much lower, respectively 2.2–7.9 and 6.7–4.6 (Table 10).

Again, the effect is not mainly due to a change in the activity-coefficient ratios between the pure solvents and the mixtures. When substituting M or E for W, $\gamma_{\text{ROH}}/\gamma_{\text{W}}$ -ratios are greater than unity up to 70% ROH (R = M, Et), and even at 95% E the ratio is still 0.44 (Washburn, 1928a).

Our explanation resembles that given above for TFE-W mixtures. Extensive hydrogen bonding takes place between the OH_f groups of water and the MeOH or EtOH lone pairs (free or on the polymeric chain) on mixing. Hence the water basicity is greatly enhanced in the presence of ROH, and that of the ROH is greatly reduced in the presence of W. The consequent reduced $k_{\text{M}}/k_{\text{W}}$ - and $k_{\text{E}}/k_{\text{W}}$ -values in the mixtures account for the different magnitude of the values in Tables 3 and 4 and in Table 16.

We shall conclude this discussion by looking at the k_{W} -values in Table 12, which clearly demonstrate the effect of a basic cosolvent on the reactivity of W toward a free carbocation. The ratios of the k_{W} -values in various 50:50 mixtures to those at 50% TFE vary considerably, and it is gratifying that these variations exactly fit the hydrogen-bonding ability of the cosolvents as determined by Symons *et al.* from ir and nmr measurements (Symons, 1981, 1983, 1989; Symons *et al.*, 1981). This trend becomes even clearer after

correcting for the moderate differences in γ_w . We can see that M, E and ethylene glycol affect water similarly. The diminished basicity of ethylene glycol is probably compensated for by its extra lone pairs. Acetone is more basic than MeCN, and DMSO and especially DMF are the most basic cosolvents. We feel that the results in Table 12 serve as an excellent example of the action of basic cosolvents in aqueous mixtures.

6 Epilogue

In this review we have summarized and tried to interpret the solvent-induced changes in the selectivity values k_A/k_B in A-B mixtures (A and B being W, M, E or TFE). We posed several questions, and we feel that we have given some, albeit incomplete, answers. We found that the selectivity of a single electrophilic species usually varies when the solvent composition is changed, owing to different responses of the individual rate constants k_A and k_B to the composition change. Solvent sorting around the electrophile does not seem to explain the trends found for the variations of the individual rate constants. Consequently, it cannot be the major factor responsible for the selectivity changes. Although this conclusion may not be valid at low alcohol percentages in water, data for evaluating this question are almost non-existent in this solvent range, because of the solubility problems.

We have not found support for the possibility that k_A and k_B respond differently to the polarity of the solvent through its effect on the stability of the electrophile. However, we have been able to explain the different dependences of the nucleophilicities of A and B on the solvent composition in terms of changes in the activity coefficients and in the basicity (or acidity) of A and B, resulting from their mutual interactions. The latter factor, but not the former, is strongly system-dependent. Our explanation gives a coherent picture that qualitatively fits almost all of the data. Consequently, we believe that selectivity values derived from product ratios using bulk molar concentrations of the nucleophiles, as well as the solvent-dependent changes in these selectivity values, can be used, with caution, as mechanistic tools.

A proper analysis of changes in k_A/k_B must be in terms of the changes in the individual rate constants. Indeed, since the selectivities are derived parameters, the importance of their solvent-induced changes as mechanistic probes will decrease if the values of the individual rate constants at various solvent compositions are known. A large part of the present review has been devoted to extracting these constants from related data, for example from experiments using the "azide clock". This is justified mainly because individual rate constants in the media of interest are still unavailable (or at least

unpublished), and it will be very difficult, if not altogether impossible, to obtain them for most of the systems, considering the very short lifetimes of the carbocations involved.

As authors and reviewers, we obviously hope that our conclusions will be verified by directly measured k_A - and k_B -values. We believe, however, that the important thing is that values such as k_W , k_M and k_E are now being accumulated (cf. Table 10), and this will lead to better understanding of the medium effect on the product-determining step in solvolysis reactions.

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References

- Adhadov, Y. Y. (1981). *Dielectric Properties of Binary Solutions*, (a) p. 274; (b) pp. 277–281. Pergamon, Oxford
- Allard, B. and Casadevall, E. (1985). *Nouv. J. Chim.* **9**, 725
- Amyes, T. L. and Jencks, W. P. (1989). *J. Am. Chem. Soc.* **111**, 7888
- Amyes, T. L. and Richard, J. P. (1990). *J. Am. Chem. Soc.* **112**, 9507
- Amyes, T. L. and Richard, J. P. (1991). *J. Chem. Soc. Chem. Commun.*, 200
- Arnett, E. M., Bentrude, W. G., Burke, J. J. and Duggleby, P. M. (1965). *J. Am. Chem. Soc.* **87**, 1541
- Aronovitch, H. and Pross, A. (1978). *J. Chem. Soc. Perkin Trans. 2*, 540
- Banks, R. M. and Maskill, H. (1976). *J. Chem. Soc. Perkin Trans. 2*, 1506
- Barat, F., Griller, L., Hickel, B. and Lesigne, B. (1973). *J. Phys. Chem.* **77**, 1711
- Bateman, L. C., Hughes, E. D. and Ingold, C. K. (1938). *J. Chem. Soc.*, 881
- Bateman, L. C., Hughes, E. D. and Ingold, C. K. (1940). *J. Chem. Soc.*, 974
- Battistini, C., Berti, G., Crotti, P., Ferretti, M. and Macchia, F. (1977). *Tetrahedron* **33**, 1629
- Becker, K. B. and Grob, C. A. (1973). *Helv. Chim. Acta* **56**, 2723
- Behrendt, S., Langford, C. H. and Frankel, L. S. (1969). *J. Am. Chem. Soc.* **91**, 2236
- Ben-Naim, A. (1988). *Cell Biophys.* **12**, 255
- Ben-Naim, A. (1990). *Pure Appl. Chem.* **62**, 25
- Bentley, T. W. and Beaman, N. (1991). Unpublished results (we are grateful to Dr Bentley for communicating his results to us)
- Bentley, T. W. and Koo, I. S. (1989). *J. Chem. Soc. Perkin Trans. 2*, 1385
- Bird, M. L., Hughes, E. D. and Ingold, C. K. (1943). *J. Chem. Soc.*, 255
- Blandamer, M. J. (1977). *Adv. Phys. Org. Chem.* **14**, 203
- Blankenship, F. and Clampitt, B. (1950). *Proc. Oklahoma Acad. Sci.*, 106
- Conner, J. K. and Maskill, H. (1988). *Bull. Soc. Chim. France*, 342

- Cox, B. G., Hedwig, G. R., Parker, A. J. and Watts, D. W. (1974). *Aust. J. Chem.* **27**, 477
- Cowie, J. M. C. and Toporowski, P. M. (1961). *Can. J. Chem.* **39**, 2240
- Covington, A. K. and Dickinson, T. (eds.) (1973). *Physical Chemistry of Organic Solvent Systems*. Plenum, London
- Cramer, J. A. and Jewett, J. G. (1972). *J. Am. Chem. Soc.* **85**, 1377
- da Roza, D. A., Andrews, L. J. and Keefer, R. M. (1973). *J. Am. Chem. Soc.* **95**, 7003
- Debye, P. (1942). *Trans. Electrochem. Soc.* **82**, 265
- Dietze, P. E. and Jencks, W. P. (1989). *J. Am. Chem. Soc.* **111**, 340
- Evans, D. F. and Nadas, J. A. (1971). *J. Phys. Chem.* **75**, 1708
- Fischer, W. and Grob, C. A. (1978). *Helv. Chim. Acta* **61**, 1588
- Fisher, R. D., Seib, R. C., Shiner, V. J., Jr, Szele, I., Tomic, M. and Sunko, D. E. (1975). *J. Am. Chem. Soc.* **97**, 2408
- Franks, F. and Ives, D. J. G. (1966). *Quart. Rev.* **20**, 1
- Frisone, G. J. and Thornton, E. R. (1968). *J. Am. Chem. Soc.* **90**, 1211
- Golomb, D. (1959). *J. Chem. Soc.*, 1334
- Gregoriou, G. A. and Varveri, F. S. (1978). *Tetrahedron Lett.*, 291
- Harris, J. M., Clark, D. C., Becker, A. and Fagan, J. F. (1974). *J. Am. Chem. Soc.* **96**, 4478
- Hopkins, H. P., Jr and Alexander, C. J. (1976). *J. Sol. Chem.* **5**, 249
- Howell, B. A. and Jewett, J. G. (1975). *J. Am. Chem. Soc.* **93**, 798
- Hudson, H. R. and Ragoonanan, D. (1970). *J. Chem. Soc. (B)*, 1755
- Huheey, J. E. (1983). *Inorganic Chemistry*, 3rd edn, Chap. 3. Harper and Row, San Francisco
- Humski, K., Sendjarevic, V. and Shiner, V. J., Jr (1973). *J. Am. Chem. Soc.* **95**, 7722
- Humski, K., Sendjarevic, V. and Shiner, V. J., Jr (1976). *J. Am. Chem. Soc.* **98**, 2865
- Ingold, C. K. (1969). *Structure and Mechanism in Organic Chemistry*, 2nd edn, Chap. 7. Cornell University Press, Ithaca, New York
- Ivanov, V. B., Ivanov, V. L. and Kuzmin, M. G. (1972). *Zh. Org. Khim.* **8**, 621. [Engl. Transl. (1972) *J. Org. Chem. (USSR)* **8**, 626]
- Karton, Y. and Pross, A. (1977). *J. Chem. Soc. Perkin Trans. 2*, 1860
- Karton, Y. and Pross, A. (1978). *J. Chem. Soc. Perkin Trans. 2*, 595
- Kay, R. L. and Broadwater, T. L. (1970). *J. Phys. Chem.* **74**, 3802
- Kay, R. L. and Broadwater, T. L. (1971). *Electrochimica Acta* **16**, 667
- Kay, R. L. and Broadwater, T. L. (1976). *J. Sol. Chem.* **5**, 57
- Kay, R. L., Evans, D. F. and Matesick, M. A. (1976). In *Solute-Solvent Interaction*, Vol. 2 (ed. J. F. Coetzee and C. D. Ritchie), Chap. 10, pp. 138-147. Dekker, New York
- Kevill, D. N. and Anderson, S. W. (1986). *J. Am. Chem. Soc.* **108**, 1580
- Kevill, D. N., Kolowych, K. C. and Weitz, F. L. (1970). *J. Am. Chem. Soc.* **92**, 7300
- Kevill, D. N., Bahari, M. S. and Anderson, S. W. (1984). *J. Am. Chem. Soc.* **106**, 2895
- Kevill, D. N., Kyong, J. B. and Weitz, F. L. (1989). ESOR 2nd Conference, Padova, 1989, Abstract C6
- Kortum, G. (1965). *Treatise on Electrochemistry*, pp. 180, 186. Elsevier, Amsterdam
- Lam, S. Y. and Benoit, R. L. (1974). *Can. J. Chem.* **52**, 718
- Langford, C. H. and White, J. F. (1967). *Can. J. Chem.* **45**, 3049
- Langford, C. H. and Tong, J. P. K. (1977). *Acc. Chem. Res.* **10**, 258
- Lipsztajn, M., Krygowsky, T. M. and Galus, Z. (1974). *Electroanal. Chem.* **49**, 17

- Lowry, T. H. and Richardson, K. S. (1987). *Mechanism and Theory in Organic Chemistry*, 3rd edn, Chap. 4, pp. 327–423. Harper and Row, New York
- Luton, P. R. and Whiting, M. C. (1979). *J. Chem. Soc. Perkin Trans. 2*, 646
- McClelland, R. A., Kanagasabapathy, V. M. and Steenken, S. (1988). *J. Am. Chem. Soc.* **110**, 6914
- McClelland, R. A., Kanagasabapathy, V. M., Banait, N. S. and Steenken, S. (1989). *J. Am. Chem. Soc.* **111**, 3966
- McClelland, R. A., Kanagasabapathy, V. M., Banait, N. S. and Steenken, S. (1991). *J. Am. Chem. Soc.* **113**, 1009
- McLennan, D. J. and Martin, P. L. (1982). *J. Chem. Soc. Perkin Trans. 2*, 1009
- McManus, S. P. and Zutaut, S. E. (1985). *Isr. J. Chem.* **26**, 400
- McManus, S. P., Roberts, F. E., Lam, D. H. and Hovans, B. (1982). *J. Org. Chem.* **47**, 4387
- McManus, S. P., Smith, M. R., Shankweiler, J. M. and Hoffman, R. V. (1988a). *J. Org. Chem.* **53**, 141
- McManus, S. P., Crutcher, T., Naumann, R. W., Tate, K. L., Zutaut, S. E., Katritzky, A. R. and Kevill, D. N. (1988b). *J. Org. Chem.* **53**, 4401
- Maham, Y. and Freeman, G. R. (1988). *J. Phys. Chem.* **92**, 1506
- Marcus, Y. (1988). *J. Chem. Soc. Faraday Trans. 1*, **84**, 1465
- Marcus, Y. (1989). *J. Chem. Soc. Faraday Trans. 1*, **85**, 3819
- Maskill, H. (1986). *J. Chem. Soc. Perkin Trans. 2*, 1242
- Mathivanan, N., McClelland, R. A. and Steenken, S. (1991). Unpublished results
- Medda, K., Pal, M. and Bagchi, S. (1988). *J. Chem. Soc. Faraday Trans. 1*, **84**, 1501
- Meyer, W. P. and Martin, J. C. (1976). *J. Am. Chem. Soc.* **98**, 1231
- Mičić, O. I. and Čerček, B. (1977). *J. Phys. Chem.* **81**, 833
- Milosavijevic, B. H. and Mičić, O. I. (1978). *J. Phys. Chem.* **82**, 1359
- Moore, W. J. (1965). *Physical Chemistry*, p. 340. London, Longmans
- Moreau, C. and Douheret, G. (1976). *J. Chem. Thermodyn.* **8**, 403
- Mukherjee, L. M. and Grunwald, E. (1958). *J. Phys. Chem.* **66**, 1311
- Murto, J. and Heino, E. L. (1966). *Suomen Kemistilehti* **B39**, 263
- Nordlander, J. C., Owuor, P. O., Cabral, D. J. and Haky, J. E. (1982). *J. Am. Chem. Soc.* **104**, 201
- Okamoto, K., Uchida, N., Saito, S. and Shingu, H. (1966). *Bull. Chem. Soc. Japan* **39**, 307
- Olah, G. A. and Schleyer, P. v. R. (1968). *Carbonium Ions*, Vols 1–4. Wiley, Chichester
- Olah, G. A. and Schleyer, P. v. R. (1976) *Carbonium Ions*, Vol. 5. Wiley, Chichester
- Parker, A. J. (1969). *Chem. Rev.* **69**, 1
- Pross, A., Aronovitch, H. and Koren, R. (1978). *J. Chem. Soc. Perkin Trans. 2*, 197
- Raber, D., Harris, J. M. and Schleyer, P. v. R. (1974). In *Ions and Ion Pairs in Organic Reactions*, Vol. 2 (ed. M. Szwarc), p. 247. Wiley, New York
- Rappoport, Z., Ben-Yacov, H. and Kaspi, J. (1978). *J. Org. Chem.* **43**, 3678
- Rappoport, Z. and Kaspi, J. (1980). *J. Am. Chem. Soc.* **102**, 3829
- Richard, J. P. (1989). *J. Am. Chem. Soc.* **111**, 1455
- Richard, J. P. and Jencks, W. P. (1984a). *J. Am. Chem. Soc.* **106**, 1373
- Richard, J. P. and Jencks, W. P. (1984b). *J. Am. Chem. Soc.* **106**, 1383
- Richard, J. P., Rothenberg, M. E. and Jencks, W. P. (1984). *J. Am. Chem. Soc.* **106**, 1361
- Ritchie, C. D. and Fleischhauer, H. (1972). *J. Am. Chem. Soc.* **94**, 3481
- Ritchie, C. D. and Virtanen, P. O. I. (1972a). *J. Am. Chem. Soc.* **94**, 1589

- Ritchie, C. D. and Virtanen, P. O. I. (1972b). *J. Am. Chem. Soc.* **94**, 4963
- Ritchie, C. D. and Virtanen, P. O. I. (1972c). *J. Am. Chem. Soc.* **94**, 4966
- Schiavo, S. and Scrosati, B. (1976). *Z. Phys. Chem.* **102**, 9
- Schneider, H. (1976). In *Solute-Solvent Interactions*, Vol. 2 (ed. J. F. Coetzee and C. D. Ritchie), Chap. 11, pp. 166-169. Dekker, New York
- Sesta, B. and Berardelli, M. L. (1972). *Electrochim. Acta* **17**, 915
- Sherrod, S. A., Bergman, R. G., Gleicher, C. J. and Morris, D. G. (1972). *J. Am. Chem. Soc.* **94**, 4615
- Shiner, V. J., Jr and Jewett, J. G. (1964). *J. Am. Chem. Soc.* **96**, 945
- Shiner, V. J., Jr and Jewett, J. G. (1965). *J. Am. Chem. Soc.* **97**, 1383
- Shiner, V. J., Jr, Dowd, W., Fisher, R. D., Hartshorn, S. R., Kessick, M. A., Milakofsky, L. and Rapp, M. W. (1969). *J. Am. Chem. Soc.* **91**, 4838
- Sinnott, M. L. and Jencks, W. P. (1980). *J. Am. Chem. Soc.* **102**, 2026
- Smith, L. S., Tucker, E. E. and Christian, S. D. (1981). *J. Phys. Chem.* **85**, 1120
- Spiro, M. (1973). In *Physical Chemistry of Organic Solvent Systems* (ed. A. K. Covington and T. Dickinson), Chap. 5, part 3, and Appendices, p. 635. Plenum, London
- Streitwieser, A., Jr (1962). *Solvolytic Displacement Reactions*. McGraw-Hill, New York
- Symons, M. C. R. (1981). *Acc. Chem. Res.* **14**, 179
- Symons, M. C. R. (1983). *Chem. Soc. Rev.* **12**, 1
- Symons, M. C. R. (1989). *Chem. Brit.*, 491
- Symons, M. C. R., Thomas, V. K., Fletcher, N. J. and Pay, N. G. (1981). *J. Chem. Soc. Faraday Trans. 1*, **77**, 1899
- Tarnus, C., Muller, M. H. and Shuber, F. (1988). *Bioorg. Chem.* **16**, 38
- Ta-Shma, R. and Jencks, W. P. (1986). *J. Am. Chem. Soc.* **108**, 8040
- Ta-Shma, R. and Rappoport, Z. (1983). *J. Am. Chem. Soc.* **105**, 6082
- Ta-Shma, R. and Rappoport, Z. (1990). *J. Phys. Org. Chem.* **3**, 503
- Tissier, M. and Douheret, G. (1978). *J. Sol. Chem.* **7**, 87
- Treiner, C., Tzias, P., Chemla, M. and Poltoratskii, G. M. (1976). *J. Chem. Soc. Faraday Trans. 1*, **72**, 2007.
- Trimble, H. M. and Potts, W. (1935). *Ind. Engng Chem.* **27**, 66
- Vogel, P. (1985). *Carbocation Chemistry*. Elsevier, Amsterdam
- Washburn, E. W. (ed.) (1928). *International Critical Tables*, (a) Vol. 3, p. 290; (b) Vol. 5, p. 22. US National Research Council/McGraw-Hill, New York
- Watts, D. W. (1973). In *Physical Chemistry of Organic Solvent Systems* (ed. A. K. Covington and T. Dickinson), Chap. 6, p. 716. Plenum, London
- Weast, R. C. (ed.) (1989). *Handbook of Chemistry and Physics*, (a) D-16; (b) E-50; (c) D-228-238. CRC Press, Boca Raton, Florida
- Winstein, S. and Fainberg, A. H. (1957). *J. Am. Chem. Soc.* **79**, 5937
- Winstein, S., Appel, B., Baker, R. and Diaz, A. (1965). *Chem. Soc. Special Publ.* **19**, 109.
- Wrewsky M. (1913). *Z. Phys. Chem.* **81**, 1
- Zwanzig, R. (1963). *J. Chem. Phys.* **38**, 1603

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p. 234

Structure [37'] is a dication

p. 237; lines 12, 13 should be:

The quintet was later found to be the ground state of the two interacting triplets (Murai *et al.*, 1988).

p. 244; line 7 should be:

in the range $+150 \sim -500 \text{ cm}^{-1}$. Therefore, when the radicals bind with

p. 250; The following reference should be inserted:

Murai, H., Safarik, I., Torres, M. and Strausz, O. P. (1988). *J. Am. Chem. Soc.* **110**, 1025.