to be stable relative to the neutral molecule for bond angles less than about 140°. Moreover, it possesses a shallow minimum near 135°. The lifetime of the anion will depend on the Franck–Condon overlap of its vibrational wavefunctions with those of the neutral molecule. The situation is similar to that for the CO_2^- anion.[40] The lifetime of this anion is sufficiently long that it can be observed mass spectroscopically. We have also found[39] that bent MgF_2^- is stable by 0.5 eV. The greater stability of MgF_2^- compared to BeF_2^- can be largely ascribed to the smaller bending force constant of MgF_2 compared to BeF_2.

I have benefited from discussions with many colleagues working in the area of electron–polar molecule interactions. In particular, I wish to thank Professors A. Herzenberg and W. C. Lineberger. I also wish to acknowledge the contributions of my co-workers, Drs. Blickensderfer, Luken, Seeger, Simons, and Wendoloski.

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Initial-State and Transition-State Solvent Effects on Reaction Rates and the Use of Thermodynamic Transfer Functions

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The past few years have seen greatly increased interest in the use of thermodynamic transfer functions by organic chemists. Their use to elucidate transition-state behavior started in the 1960s, on the one hand with Arnett's work[2] aimed to explain the serpentine variation of the hydrolysis of *tert*-butyl chloride in alcohol–water mixtures and on the other with Parker's studies[3] of bimolecular nucleophilic substitution reactions in dipolar aprotic solvents. The latter were found to have very large rate-enhancing properties in many instances as compared with hydroxylic solvents.[4]

Our own work with dipolar aprotic media[5] also started with the aim of bringing about certain reactions which could not readily be accomplished in hydroxylic solvents. Thus we found that deuterioxide-catalyzed H/D exchange in 1,3,5-trinitrobenzene occurred readily in dimethylformamide (DMF) rich media (e.g., 90:10 v/v $DMF–D_2O$),[6] whereas exchange by NaOD in D_2O alone was negligible. Some years later it became apparent to us that serendipity had played its role, as it was found that a competing equilibrium, σ-complex formation, was also greatly enhanced by the dipolar aprotic medium (vide infra).

An equal challenge was to find an explanation for the failure of an anticipated large rate increase to materialize. The OH^- catalyzed isotopic exchange of D_2 in $Me_2SO–H_2O$ mixtures might have been expected to result in very large rate increases. However, the observed[7] rate increase on changing the solvent from aqueous to 99.6 mol % Me_2SO was only 10^4, whereas the basicity of the medium as measured by the H_- function increases by 14 logarithmic units over this range.[8]

In this Account, we examine systematically the various possible outcomes of medium changes on rate processes as approached from the viewpoint of thermodynamic transfer functions.[9] This approach is highly informative concerning transition-state structure in a variety of processes, enabling one to deduce subtle effects of charge distribution, etc., and the correlation between medium effects and structure–reactivity relationships. Medium effects are generalized here in the widest sense, including, for example, the variation of acid concentration for reactions occurring in moderately concentrated acid media. Our purpose is not only to highlight recent developments but also to point to some future directions for the application of this method so as to provide an impetus for further research. Espe-

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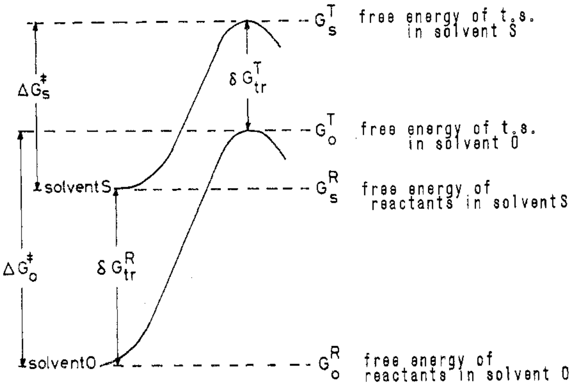

Figure 1. Illustration of relationship between the transfer free energies of reactants and of the transition state, and the free energies of activation, for a reaction occurring in two solvent systems.

cially noteworthy in this regard are the concept of a variable transition state as the medium is changed and the use of synergistic and antagonistic effects as probes for changing transition states.

Thermodynamic Transfer Functions

The free energy of activation for a reaction in a particular standard solvent 0, and in a solvent S, may be expressed by eq 1 and 2 where T refers to the transition state and R to the reactants. Simple subtraction yields eq 3. If the standard free energy of transfer between solvents 0 and S is defined according to eq 4, then (5) can be derived from (3). A pictorial representation of these relationships is shown in Figure 1.

$$\Delta G_0^{‡} = G_0^{\mathrm{T}} - G_0^{\mathrm{R}} \tag{1}$$

$$\Delta G_{\mathrm{S}}^{‡} = G_{\mathrm{S}}^{\mathrm{T}} - G_{\mathrm{S}}^{\mathrm{R}} \tag{2}$$

$$\Delta G_{\mathrm{S}}^{‡} - \Delta G_0^{‡} = (G_{\mathrm{S}}^{\mathrm{T}} - G_0^{\mathrm{T}}) - (G_{\mathrm{S}}^{\mathrm{R}} - G_0^{\mathrm{R}}) \tag{3}$$

$$\delta G_{\mathrm{tr}}^{\mathrm{i}} = G_{\mathrm{S}}^{\mathrm{i}} - G_0^{\mathrm{i}} \tag{4}$$

$$\delta G_{\mathrm{tr}}^{\mathrm{T}} = \delta G_{\mathrm{tr}}^{\mathrm{R}} + \Delta G_{\mathrm{S}}^{‡} - \Delta G_0^{‡} = \delta G_{\mathrm{tr}}^{\mathrm{R}} + \delta \Delta G^{‡} \tag{5}$$

From eq 5 it is apparent that $\delta G_{\mathrm{tr}}^{\mathrm{T}}$ can be evaluated from calculated values of the transfer free energies of stable solute species, $\delta G_{\mathrm{tr}}^{\mathrm{R}}$, in conjunction with the measured kinetic activation parameters, $\delta \Delta G^{‡}$. The required transfer free energies $\delta G_{\mathrm{tr}}^{\mathrm{R}}$ can readily be obtained from activity coefficient measurements using eq 6 in which γ refers to solute activity coefficients in the different solvents (γ_{S} and γ_0 are referred to the same standard state in solvents S, 0 or any other medium). Methods used to obtain these activity coefficients have included vapor pressure, solubility, and distribution coefficient measurements.[10]

$$\delta G_{\mathrm{tr}}^{\mathrm{i}} = -RT \ln \frac{\gamma_{\mathrm{S}}}{\gamma_0} \tag{6}$$

By analogy it is apparent that for the equilibrium situation the transfer free energy relationship will be given by eq 7 where $\delta G_{\mathrm{tr}}^{\mathrm{P}}$ is the transfer free energy of the products and $\delta \Delta G_{\mathrm{tr}}$ is the difference in the standard free energies of reaction between the two solvents.

$$\delta \Delta G_{\mathrm{tr}} = \delta G_{\mathrm{tr}}^{\mathrm{P}} - \delta G_{\mathrm{tr}}^{\mathrm{R}} \tag{7}$$

Transfer functions can also be defined for the other thermodynamic state functions. Since enthalpy changes are often conveniently measurable, the transfer enthalpy, $\delta H_{\mathrm{tr}}^{\mathrm{i}}$, is perhaps the most widely used function. From the second law of thermodynamics, the transfer entropy function is given by eq 8. Thus if both transfer free energies and enthalpies are available it should be possible to achieve complete dissection of the effect of solvent on the various thermodynamic parameters.

$$\delta G_{\mathrm{tr}}^{\mathrm{i}} = \delta H_{\mathrm{tr}}^{\mathrm{i}} - T \delta S_{\mathrm{tr}}^{\mathrm{i}} \tag{8}$$

Other potentially useful transfer functions[11] are the transfer heat capacity,[12] $\delta C_{\mathrm{tr}}^{\mathrm{i}}$, the transfer volume,[13] $\delta V_{\mathrm{tr}}^{\mathrm{i}}$, and the transfer internal energy,[14] $\delta U_{\mathrm{tr}}^{\mathrm{i}}$. At present, measurements of these transfer functions are available for only a few systems, but they can in certain instances be predicted using scaled-particle theory.[15]

Classification of Rate Profile–Medium Effect Reaction Types

By combination of thermodynamic and kinetic measurements one can obtain values for $\delta G_{\mathrm{tr}}^{\mathrm{T}}$, which in conjunction with $\delta G_{\mathrm{tr}}^{\mathrm{R}}$ values can be used to pinpoint the cause of rate change with changing solvent. A number of different types can be envisaged. The $\delta G_{\mathrm{tr}}^{\mathrm{T}}$, $\delta G_{\mathrm{tr}}^{\mathrm{R}}$ terms can be positive (destabilization), negative (stabilization), or zero (no effect). When both terms have the same sign we call it a balancing situation, and with opposite sign a reinforcing situation. The rate effects are expected to be largest in the reinforcing situation and smallest in the balancing situation.

In Table I we summarize the various possibilities and identify the reaction types in terms of positive (negative), initial-state (transition-state) control. For example, case 3 can be described as a "positive transition-state control" reaction type, and so on. Not all of these situations have been observed so far. It would be of interest to design appropriate reactions to complete this classification.

In Figure 2 are shown a few examples of reactions[16,17] (see also ref 18, 19) under these types, some of which will be referred to again subsequently. It may be noted that only in example D is the ground-state effect zero. In the general case, however, the rationalization of medium effects on reaction rates requires knowledge of the pertinent transfer function data for the reactants; these are now becoming increasingly available for neutral molecules as well as ionic reagents.[10,20–23] In the case of transfer functions for ionic reagents it has been customary to estimate thermodynamic quantities for single ions by use of extrathermodynamic as-

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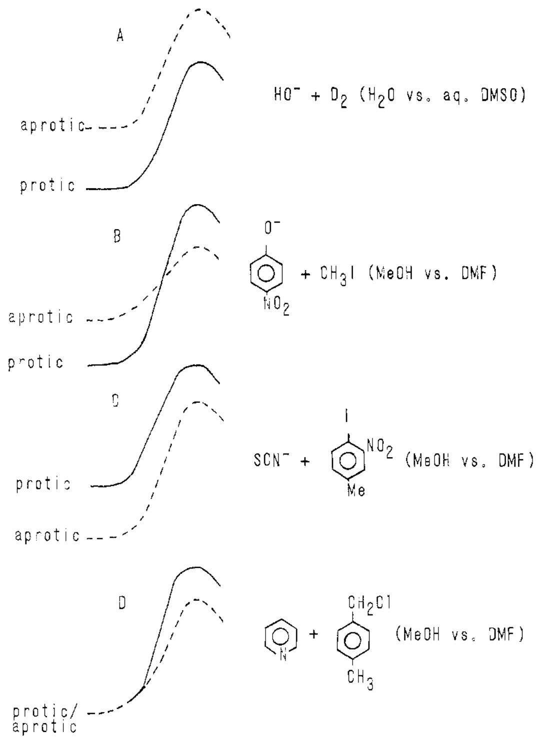

Figure 2. Reaction profile illustrations of solvent effects on the rates of some representative reactions for changes from protic to dipolar aprotic media, showing enthalpy as the ordinate.[16,17] Using the classification in Table I, cases A and C represent balancing situations, B positively reinforced, D negative transition-state control.

Table I
Transfer Free Energies of Reactants (δG_{tr}^R) and Transition States (δG_{tr}^T) and Solvent Effects on Reaction Rates. Classification of Reaction Types

case	δG_{tr}^R	δG_{tr}^T	effect on rate[a]	reaction type
1	−	−	+, 0, or −	balanced
2	+	−	+	positively reinforced
3	0	−	+	positive transition-state control
4	−	0	−	negative initial-state control
5	+	0	+	positive initial-state control
6	0	0	0	solvent independent
7	−	+	−	negatively reinforced
8	+	+	+, 0, or −	balanced
9	0	+	−	negative transition-state control

[a] The plus sign refers to rate acceleration, the minus sign to rate retardation, and zero to no effect.

sumptions, such as $\delta\Delta G_{tr}(Ph_4P^+) = \delta\Delta G_{tr}(BPh_4^-)$. These methods are open to criticism, but in certain instances they can be avoided by use of appropriate thermochemical cycles.[24]

Analogous considerations are applicable in principle to certain excited-state processes. The blue shift of n → π* transitions on going to more polar solvents was recently analyzed in this manner by Haberfield and co-workers for a number of ketones and azo compounds.[25] According to the terminology given in Table I, with substitution of the excited state for the transition state, the commonly observed blue shift for ketones on transfer from a nonpolar solvent to a hydrogen bonding solvent falls under the category of a negatively reinforced type of process.

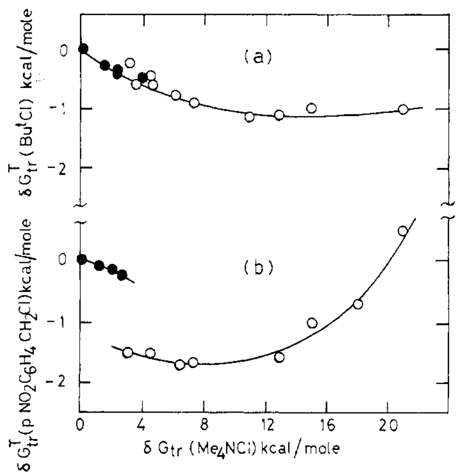

Figure 3. Plot of (a) δG_{tr}^T(*t*-BuCl) and (b) δG_{tr}^T(*p*-$NO_2C_6H_4CH_2Cl$) against $\delta G_{tr}(Me_4NCl)$ for various solvents at 25 °C.[10]

Transfer Functions and the Transition State

Since in the derivation of δG_{tr}^T no assumption was made concerning the transition state, the derived δG_{tr}^T values can by themselves yield no information about its nature. In order to deduce transition-state properties some extrathermodynamic method must be used. One such method is to compare values of δG_{tr}^T to corresponding values for various stable solutes. If the values match, the assumption is made that the transition state is similar in nature to the chosen solute. Abraham[10] has used tetraalkylammonium salts as models for polar but electrically neutral transition states, as, for example, in reactions of tertiary amines with alkyl halides or in solvolytic processes. Plotting δG_{tr}^T against $\delta G_{tr}(R_4NX)$ can then lead to several types of behavior proposed to have mechanistic significance. (1) If a linear relationship is observed for δG_{tr} values covering both hydroxylic and aprotic solvents it is concluded that the transition state resembles the chosen ion pair. (2) If a single curve of slightly negative slope is obtained the transition state resembles a nonpolarizable nonelectrolyte. (3) If a double curve is obtained the transition state resembles a polarizable nonelectrolyte. These relationships, shown in Figure 3, represent extreme examples, and intermediate behavior is also to be expected. Thus for the reaction of Et_3N with EtI the conclusion is drawn that the transition state lies between the reactants and the product ion pair, being rather closer to the reactants.[26] A related study shows that the pair of ions ($Me_4N^+ + Cl^-$) is not a suitable model for the *tert*-butyl chloride solvolysis transition state.[27]

Another possible probe of transition-state structure is found in the application of reaction field theory to solvent effects on reaction rates.[28,29] In essence the

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theory evaluates $E_V - E_S$, the energy of transfer of a solute from a solvent (S) to the vapor (V). This is calculated for the reactants and some proposed transition-state structure. Data required for the calculation include the dipole moment (μ), quadrupole moment, molar volume (M_v), and refractive index (η) of the solute, and the dielectric constant (ϵ) of the solvent. In the case of the transition state the values of M_v, η, and the geometry are considered fixed, and the dipole moment is left as the only adjustable parameter. A transfer function δE_{tr}^{i} from reference solvent to solvent S, defined by (9) and (10), can be evaluated for both

$$\delta E_{tr}^{i} = E_S^{i} - E_0^{i} = (E_V^{i} - E_0^{i}) - (E_V^{i} - E_S^{i}) \qquad (9)$$

$$\delta E_{tr}^{T} = \delta E_{tr}^{R} - \delta \Delta E^{\ddagger} \qquad (10)$$

the reactants (δE_{tr}^{R}) and the transition state (δE_{tr}^{T}), and consequently $\delta\Delta E^{\ddagger}$, can be calculated. It is suggested that the values of $\delta\Delta E^{\ddagger}$ calculated from reaction field theory should be directly comparable to the observed values of $\delta\Delta G^{\ddagger}$.

Transition-state dipole moments were obtained by this procedure for the solvolysis of *tert*-butyl chloride and for the reaction of tri-*n*-propylamine with methyl iodide. For the "Onsager liquids"[30] there is good agreement between $\delta\Delta E^{\ddagger}$ and $\delta\Delta G^{\ddagger}$; specific solvent effects appear to be nonexistent, and reaction field theory is applicable. However, agreement is poor in hydroxylic, polyhalogenated, and aromatic solvents where other effects (marked solute–solvent interactions), not taken into consideration by the theory, may partially determine the free energy of the transition state.

Reactions in Aqueous Mineral Acid Solvents. The transfer function approach has been applied, with considerable success, to the phenomenon of the marked increase in acidity of aqueous media with increase in acid concentration. That the stoichiometric concentration of H^+ does not account for the intrinsic acidity of moderately concentrated acids has been known for some time.[31,32] A number of acidity functions H_X have been operationally defined according to eq 11 as a

$$H_X = -\log \frac{a_{H^+} f_X}{f_{XH^+}} \qquad (11)$$

measure of the ability of the medium to protonate a given basic species X. A dissection of the individual contributions to the total acidity function behavior has been made by determining the activity coefficients for transfer of the various pertinent species, from their solutions in water to that in an acid solvent, over a range of acid concentrations.[33] In Figure 4 are presented the relevant plots for the H_0 and H_A functions in the sulfuric acid system.[34] It is seen that although the f_{H^+} term is dominant, f_{XH^+} can have strong moderating influence on the magnitude of the acidity function. Transfer free energies, enthalpies, and entropies, from water to aqueous sulfuric and perchloric acid solutions, have been determined for a number of stable solutes.[35,36]

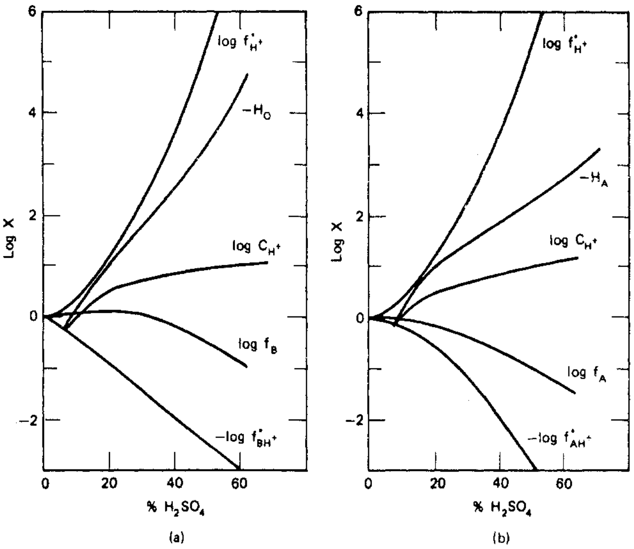

Figure 4. Analysis of individual contributions to total acidity function behavior: (a) H_0 (primary aromatic amines), (b) H_A (aromatic amides). The activity coefficient terms for the ionic species are expressed relative to $f(Et_4N^+)$.[33]

There now exists a fund of data of transfer activity coefficients of stable species to various acidic media. This can be used for elucidation of transition-state structures in a variety of acid-catalyzed reactions. Considering a reaction symbolized as in eq 12 and 13

$$S + H^+ \rightleftarrows SH^+ \qquad (12)$$

$$SH^+ + H_2O \xrightarrow{k_0} S^{\ddagger} \qquad (13)$$

and assuming the limiting case where $[SH^+] \simeq 0$ (see also ref 31 and 32), one obtains from transition-state theory expression 14 for the pseudo-first-order rate

$$k_\psi = \frac{k_0 f_S a_{H^+}}{K_{SH^+} f_{S^{\ddagger}}} \qquad (14)$$

constant. The acidity dependence of k_ψ is thus determined by that of the variables f_S, a_{H^+}, and $f_{S^{\ddagger}}$. Many treatments make rather risky assumptions concerning these quantities with a view of cancellation of terms involving $f_{S^{\ddagger}}$ which is experimentally undeterminable. However, it has been shown[37] that $f_{S^{\ddagger}}$ can be calculated via eq 15, which is derived from (14). The $a_{H^+}{}^*$ term

$$\log (f_{S^{\ddagger}}{}^*/k_0) = -\log k_\psi - \log k_{SH^+} + \log f_S + \log a_{H^+}{}^* \qquad (15)$$

represents the activity of the proton relative to the standard ion Et_4N^+, and similarly $f_{S^{\ddagger}}{}^* = f_{S^{\ddagger}}/f_{Et_4N^+}$. Since $\log f_{S^{\ddagger}}{}^* \rightarrow 0$ in dilute acid solutions, plotting $\log (f_{S^{\ddagger}}{}^*/k_0)$ vs. the acid concentration will yield $-\log k_0$ as the intercept. The medium variation of the transition-state activity coefficient (relative to a standard ion) can hence be evaluated and compared with the behavior of stable species (cf. Abraham, vide supra). The method has been applied to ester and amide hydrolyses, aromatic hydrogen exchange, and protodealkylation.[38] It is

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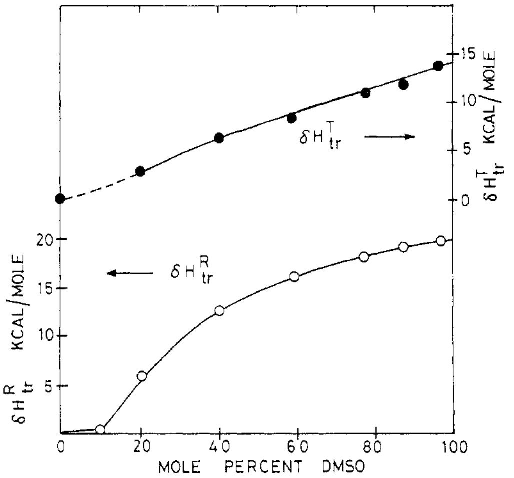

Figure 5. Plot of $\delta H_{tr}{}^{R}$ and $\delta H_{tr}{}^{T}$ against mole per cent Me_2SO for D_2–OH^- exchange in aqueous Me_2SO.[16]

apparent that $\log f_{S^{\ddagger}}{}^{*}$ will be a useful mechanistic criterion. These studies may aid also in differentiating between the several treatments that have been proposed for the analysis of reactions occurring in strongly acidic media which specifically invoke activity coefficient behavior in explaining the rate–acidity dependence.[39-45]

Exchange of Dihydrogen. For illustration of the use of transition-state models in interpreting $\delta H_{tr}{}^{T}$ values, an interesting system is isotopic exchange between molecular hydrogen (deuterium) and a hydroxylic solvent under base catalysis.[7,16,46-49] On theoretical grounds the hydride (deuteride) ion mechanism of eq 16 and 17 has been disfavored and the addition complex

$$HO^- + D\text{–}D \xrightarrow{\text{slow}} HOD + D^- \qquad (16)$$

$$D^- + HOD \xrightarrow{\text{fast}} DH + OH^- \qquad (17)$$

mechanism of eq 18 and 19 advanced,[47] while yet other

$$HO^- + D\text{–}D \xrightarrow{\text{slow}} [HO\text{–}D\text{–}D]^- \qquad (18)$$

$$[HO\text{–}D\text{–}D]^- + HOH \xrightarrow{\text{fast}} HOD + DH + OH^- \qquad (19)$$

mechanisms (e.g., involving electrophilic assistance) are possible. A recent investigation of the reaction in the Me_2SO–water system has given the results shown in Figure 5.[16] It is seen that the reaction is characterized by large positive $\delta H_{tr}{}^{T}$ values. In 99.6 mol % Me_2SO, $\delta H_{tr}{}^{T}$ = 13.7 kcal/mol, which compares with the $\delta H_{tr}{}^{T}$ value for hydroxide ion of 17.5 kcal/mol in this medium.[50] Noting that $\delta H_{tr}(OH^-)$ is the major component of $\delta H_{tr}{}^{R}$ in the Me_2SO-rich media, since $\delta H_{tr}(D_2)$ is small,[51] it is apparent that the destabilization of hydroxide ion is largely retained in the transition state. These results point to a rate-determining transition state with considerable charge localization on electronegative atom(s). Any proposed mechanism must be in accord with this conclusion.[16,49]

Future Directions

There are numerous major areas in which the application of the transfer function approach can be of value. To demonstrate the usefulness of this method, we now indicate its applicability to two current problems. The first concerns nucleophile–electrophile combination reactions—central to understanding of nucleophilic reactivity. We then examine the problem of the variety of processes in the interaction of nitroaromatic compounds with bases, which have been under investigation in our laboratory, and elsewhere, for some time.

Nucleophile–Electrophile Combination Reactions. The remarkable correlation given in eq 20 was

$$\log k = \log k_0 + N_+ \qquad (20)$$

discovered by Ritchie[52] (see also ref 53–56) for the reaction of nucleophiles with electrophiles of widely varying structure (organic cations, esters, etc.). In eq 20, k is the measured second-order rate constant for reaction of an electrophile with a given nucleophilic system (nucleophile plus solvent), k_0 is characteristic of the electrophile, and N_+ is a parameter characteristic of the nucleophilic system. The most striking feature of this correlation is that it represents a failure of the reactivity–selectivity principle[57] since the N_+ value for a given nucleophilic system does not change with different electrophiles, i.e., electrophiles of widely different reactivity exhibit constant selectivity.

Ritchie's results could find explanation in the hypothesis that the nucleophile and the electrophile are completely separated in the transition state and that electrophile desolvation has not begun. The electrophile is then similarly solvated in the reactant and transition states. An alternative explanation has been proposed by Pross,[58] who suggests that the constant selectivity results from cancellation of two opposing effects. (i) A reactive electrophile is strongly solvated, a factor that would tend to increase its selectivity. (ii) For a reactive electrophile the transition state is "reactant-like", resulting in a decrease in selectivity. The opposite is suggested to hold for an unreactive electrophile.

Determination of $\delta G_{tr}(E_i)$ values, where E_i represents the electrophilic species, would appear central to the

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problem, but the available δG_{tr} data are difficult to reconcile with the medium effect results. The relative reactivities of several cations with given nucleophiles are *not* solvent dependent. The rate constant ratio k_{MeO^-}/k_{HO^-} in methanol and water is virtually identical for crystal violet cation and phenyltropylium ion[59] even though the free energies of transfer for these cations from water to methanol solution differ by at least 4 kcal/mol.[60]

In contrast, the relative reactivities of the two electrophiles 2,4-dinitrofluorobenzene (DNFB) and (*p*-(dimethylamino)phenyl)tropylium ion (DMAPTr$^+$) have been found to be solvent dependent.[61] The 0.7 log unit separating the water and methanol lines in the log *k*(DNFB) vs. log *k*(DMAPTr$^+$) plots for reaction with various nucleophiles corresponds to an energy difference of almost 1 kcal/mol. Noting that $\delta G_{tr}(H_2O \rightarrow MeOH)$ is −5.75 kcal/mol for DNFB and −2.9 kcal/mole for DMAPTr$^+$, it follows that of the 2.9 kcal/mol difference in free energies of transfer of the reactants 1.9 kcal/mol remains at the transition states for reactions with these nucleophilic systems.

These separate observations concerning medium effects, which at present appear at variance, could have another explanation. Thus it is conceivable that the electrophilic centers of various electrophiles could be similarly solvated and that differences in δG_{tr} arise from solvation at sites removed from the electrophilic center.[61] If that were the case, then in principle it may be possible to obtain information concerning the specific contribution of the reaction center solvation to transfer free energies by utilizing the additivity of group contributions to the thermodynamic transfer function.[62-64] However further measurements of transfer quantities will be required before the group additivity approach can be applied in these systems. Once these data were available, if this explanation should thereby be found unsatisfactory, an alternative possibility would be that the one extraordinary degree of freedom of transition states (i.e., the reaction coordinate) could entail specific solvation requirements. A related aspect concerning unusual transition-state properties is broached in the last section of this Account.

Nitroaromatic/Base Interactions. Our investigation of the interactions of bases with nitroaromatic compounds have revealed several unexpected solvent effects. Typical of these are the results obtained for the reactions of alkoxide ions with 1,3,5-trinitrobenzene, which participates in an equilibrium to yield a σ complex adduct, concurrently with proton abstraction leading to isotopic exchange when the experiment is performed in deuterated solvent.[65] The two processes exhibit a different response to medium change, and other nitroaromatic base combinations show varying behaviors. *m*-Dinitrobenzene in Me_2SO–methanolic sodium methoxide[66] shows a different response to that in aqueous alkaline DMF.[67] Moreover, trinitrobenzene in aqueous alkaline solution is reported not to undergo exchange.[68] These separate observations, which at present appear to be somewhat puzzling, could be rationalized if transfer functions for the σ complex and alkoxide ion were determined in the media of interest.

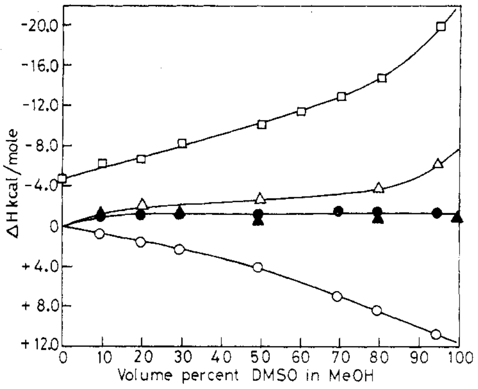
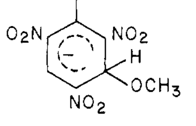


Figure 6. The enthalpy of transfer of 2,4,6-trinitroanisole (●), sodium methoxide (○), the 2,4,6-trinitroanisole–methoxide σ complex (△), and sodium picrate (▲) from methanol to methanol-Me_2SO mixtures; and the enthalpy of reaction (□) between 2,4,6-trinitroanisole and NaOMe to give the σ complex.[77]

The interaction of 2,4,6-trinitrotoluene (TNT) with base also leads to concurrent σ-complex formation (**1**)



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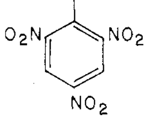

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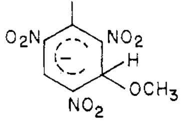

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and proton abstraction to give the anion **2**.[69-72] The two processes compete to different extents in various alcoholic solvents (EtOH, *i*-PrOH, *t*-BuOH). Moreover analysis of the equilibria and rate data points to increased importance of ion-pair mechanisms along the series of alcoholic solvents. Thus evaluation of thermodynamic transfer functions would yield information not only relating to equilibrium complex formation and proton abstraction but also on the ion-pairing phenomenon. To the authors' knowledge no measurement of transfer functions for carbanion reactions in which ion-pair mechanisms are known to be important have so far been reported.[73-75]

By the use of high-resolution NMR in flowing systems[76] the dianion **3** was detected when TNT was treated with excess methoxide in a high Me_2SO content

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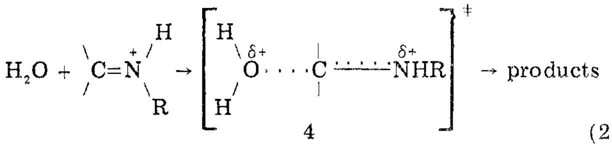
Me_2SO/CH_3OH solvent. Thus the species **1**, **2**, and **3** can be generated under different solvent conditions. These species are closely related, and it would be intriguing to evaluate the factors stabilizing one relative to the others; transfer function data would aid in such an analysis. Measurement of transfer functions for such unstable species (or related more stable species) poses quite a problem, but some progress is being made in this area.

Enthalpies of transfer for the methoxide adduct of 2,4,6-trinitroanisole in Me_2SO/methanol have already been determined[77] (see also ref 78). Figure 6 shows the results and includes also the δH_{tr} data for other pertinent species (trinitroanisole, picrate ion, and sodium methoxide) as well as the enthalpy of formation of the σ complex from the reactants. The increased stabilization of the σ complex compared to trinitroanisole or picrate ion is noteworthy and may have as origin interaction by London dispersion forces between the polarizable σ complex and Me_2SO solvent.[79,80]

Changing Transition States. Normal interpretation of δG_{tr}^{T} values assumes that the measured quantity refers to the difference in free energy of the transition state in the two solvents. It is implicitly assumed that the transition state is the same species in the two media. This is not necessarily so. It is conceivable that there are two or more paths from reactants to products[81] and that the preferred path may change on solvent change. In such an instance δG_{tr}^{T} is measuring the difference in free energy of two *different* species. The differences between these transition states may be quite subtle. Thus one may resemble an intimate ion pair and the other a solvent-separated ion pair. Alternatively the two competing transition states could differ in their interaction with solvent; electrophilic or nucleophilic interaction of solvent is possible at various sites. Obviously a change in transition state makes interpretation of δG_{tr}^{T} values more complex, though potentially of greater interest.

A change in transition state for a reaction on solvent change could in principle be revealed by synergistic or antagonistic effects. Detection of these effects requires that one other factor which affects the rate of reaction (e.g., a substituent effect) be considered in conjunction with solvent change. The effect of each factor on the rate is measured separately, and then the two effects are combined. If there is no change in transition state, the rate enhancement produced by the combined effects will be the product of the separate rate enhancements. If the rate observed is higher (synergistic) or lower (antagonistic) than expected, it is an indication of a possible change in transition state.

A marked synergism has been detected in Schiff base hydrolysis.[82] A combination of general base catalysis in chloroacetate buffers with solvent change, from water to 70% aqueous dioxane, produces a 350-fold rate enhancement. The solvent effect (11-fold) and the effect of general base catalysis (2.5-fold) would predict a rate increase of approximately 28. The total observed rate enhancement is substantially greater than expected from the individual effects. Inspection of the probable transition states for the two competing processes suggests an explanation for the synergism. Attack by H_2O on the protonated substrate leads to transition state **4** (eq 21)



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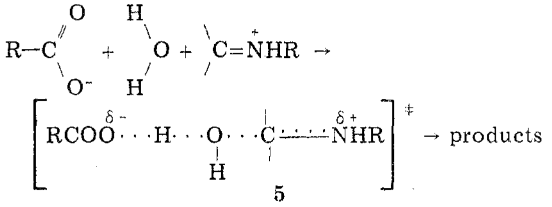
with delocalization of the positive charge and a predicted[83] rate increase as solvent polarity is lowered. However, the transition state **5** formed in general base catalysis by carboxylate ion (eq 22)



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(22)

is expected to show a much greater solvent dependence since charge is destroyed in this case.

In the above example the competing transition states are quite different. One can speculate as to whether these effects will be detectable in cases where the differences in the transition states will be more subtle. We propose this as a problem for future application of this method, noting that common mechanistic criteria do not shed light on this aspect of the transition state.

Changes in transition-state stucture can also be detected using kinetic isotope effects.[84,85] Recently heavy atom leaving group KIE's have been used to determine how the structure of an S_N2 transition state is affected by solvent change.[64] This is based on the reasonable proposition that if the leaving group KIE changes markedly when the solvent is changed then the transition state must be changing. Such a result was observed for the reaction of EtO^- with Me_3S^+ in $EtOH-Me_2SO$ mixtures.[86] Conversely, no change in isotope effect was observed for the reaction of PhS^- with *n*-BuCl with change in solvent.[87] It remains to be clarified in future applications of the KIE criterion whether the change in isotope effect with solvent change would reflect merely a subtle change in the original transition state or the increased importance of an alternative pathway (vide supra).

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