

## PROTIC-DIPOLAR APROTIC SOLVENT EFFECTS ON RATES OF BIMOLECULAR REACTIONS

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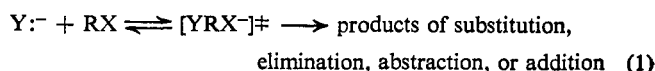
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### I. Introduction

#### A. PURPOSE AND SCOPE

Bimolecular reactions (see eq 1 below) between anions and uncharged species, as well as some bimolecular reactions of other charge types, are often very much faster in dipolar aprotic than in protic solvents.<sup>1,2</sup> On the other hand, many dissociative reactions and rearrangements, as well as bimolecular solvolyses of RX, are slower in dipolar aprotic than in protic solvents. Rates of competing homolytic processes, oxidations, and reductions are often rather independent of solvents.<sup>2,3</sup> This simple observation has been helpful to



those concerned with shortening reaction times, increasing yields, and decreasing contamination by side reactions in some of the most common of organic reactions.<sup>3-10</sup>

The purposes of this review are twofold: firstly, to show more clearly why dipolar aprotic solvents are such excellent media for many organic and inorganic reactions and, secondly, to encourage an approach toward the study of mechanisms, which originated in 1935 with Wynne-Jones and Eyring.<sup>11</sup> This was developed quantitatively by Fainberg and Winstein<sup>12</sup> and qualitatively by Hughes and Ingold<sup>13</sup> and has been popularized by the lucid and entertaining papers of

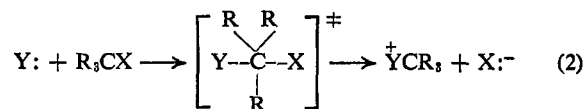
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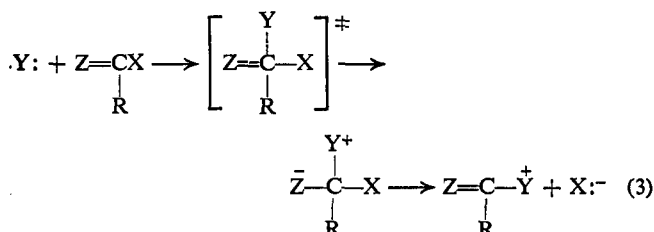
Arnett and his coworkers.<sup>14,15</sup> The approach, which uses  $\delta_s \log k$ , *i.e.*, the change in rate constant with solvent transfer, to obtain information about charge distribution and structure in the transition state,<sup>12,14-23</sup> has been most often applied to the less useful solvolysis reactions.<sup>24</sup> Here it is applied to reactions represented by eq 1.

This review will concentrate on the progress which has been made since 1961<sup>1</sup> in the interpretation of protic-dipolar aprotic solvent effects on the rates of three types of bimolecular reaction. These are the one-step substitution (SN2) reactions at saturated carbon (eq 2), the two-step addition-elimination reactions (eq 3) such as the substitution reactions of carbonyl, aryl, and vinyl compounds, and the one-step  $\beta$  elimination (E2) reactions (eq 4).<sup>25</sup> Reactions of various charge types<sup>26</sup> will be considered, but in eq 2-4 the signs only indicate that the base Y becomes one unit more positive and the leaving group X becomes one unit more negative, from reactants to products. The reactions chosen have no monopoly on the basic principles outlined, which apply equally well to all those "slow" inorganic and organic bimolecular reactions whose transition state structure is essentially unchanged (*i.e.*, mechanism is unchanged) with transfer from protic to dipolar aprotic solvent. The solvent effect on very fast (*e.g.*, diffusion controlled) reactions is not dealt with.

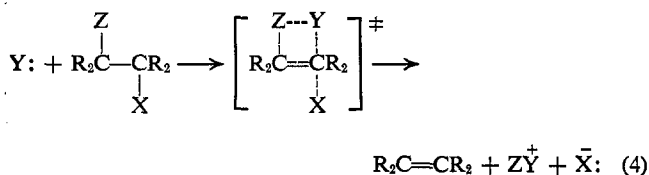
Substitution (SN2)



Addition-elimination (SN2)



Elimination (E2)



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## B. CLASSIFICATION OF SOLVENTS AND THEIR PROPERTIES

Protic solvents, such as fluoro alcohols, hydrogen fluoride, water, methanol, formamide, and ammonia are strong hydrogen-bond donors. Dipolar aprotic solvents are highly polar but are no more than very weak hydrogen-bond donors.<sup>4</sup> A simple rule of thumb guiding this classification is that solvents with hydrogen bound only to carbon are at best poor hydrogen-bond donors; they are very weakly acidic and exchange very slowly, if at all, with D<sub>2</sub>O. Solvents with hydrogen bound to more electronegative atoms, such as oxygen or nitrogen, exchange rapidly and form strong hydrogen bonds with suitable acceptors. Erythrosin fluorescence is said to be quenched according to solvent proticity.<sup>27</sup> Only solvents of dielectric constant greater than *ca.* 15 are considered when making the distinction between protic and dipolar aprotic solvent. This arbitrary choice<sup>4</sup> is made because in solvents of lower dielectric constant ion aggregation is so extensive that it becomes very difficult to observe the behavior of solvent-separated ions. Common dipolar aprotic solvents<sup>2-5,9,24,28</sup> are dimethylformamide (DMF), dimethylacetamide (DMAC), dimethyl sulfoxide (DMSO),<sup>7,8,10</sup> hexamethylphosphoramide (HMPT),<sup>6</sup> acetone, nitromethane, nitrobenzene, acetonitrile, benzonitrile, sulfur dioxide, propylene carbonate,<sup>29</sup> and N-methyl-2-pyrrolidone (NMePy).<sup>30</sup> This range is extended if substances like sulfolane (TMS) and dimethyl sulfone, which melt above room temperature, or if mixtures of dipolar aprotic compounds (*e.g.*, dimethyl sulfone in DMSO) are considered. The dipolar aprotic solvents often recommended<sup>8</sup> as reaction media for reactions (eq 1) are DMF, DMAC, DMSO, and acetone. This is because they are cheap, readily available, and water miscible, allowing ready isolation of products. However, most reactions (eq 1) are even faster and cleaner in N-methyl-2-pyrrolidone or hexamethylphosphoramide as solvent.

The distinction between protic and dipolar aprotic solvents, in so far as they influence rates of reaction (eq 1), is a sharp one.<sup>31</sup> Thus although N-methylformamide is one of the less protic of solvents and nitromethane is one of the less dipolar aprotic, many reactions (eq 1) are more than 100 times faster in nitromethane than in N-methylformamide.<sup>2</sup> The classification suggests that hydrogen bonding will be an important interaction in determining protic-dipolar aprotic solvent effects on rates and so it is, but other factors, such as dispersion forces, ion-dipole and dipole-dipole interactions, which overlap the protic-dipolar aprotic division, must be taken into account. The degree of solvent structure is often related to the ability of the solvent molecules to donate and accept hydrogen bonds, so that structure-making and structure-breaking interactions may be indirectly responsible for some of the protic-dipolar aprotic solvent effect on rate.

The dielectric constants and other physical constants of common protic and dipolar aprotic solvents are in Table I.

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Table I  
Properties of Solvents

	HOH	H <sub>2</sub> COH	HCONH <sub>2</sub>	HCO- N(CH <sub>3</sub> ) <sub>2</sub>	H <sub>2</sub> CCO- N(CH <sub>3</sub> ) <sub>2</sub>	(H <sub>3</sub> C) <sub>2</sub> SO	H <sub>3</sub> CCN	[(CH <sub>3</sub> ) <sub>2</sub> N] <sup>+</sup> PO	NMePy	H <sub>3</sub> CNO <sub>2</sub>
Bp, °C <sup>a</sup>	100	65.0	193	152.5	165.5	189	80.1	235 <sup>b</sup>	202	100.8
Mol wt ( <i>M</i> )	18	32	45	73.1	87.1	78	41	179	99.1	61
Density, <i>d</i> <sup>20</sup> <sub>4</sub> , g/cm <sup>3</sup> <sup>a</sup>	0.9982	0.7914	1.134	0.9445 <sup>d</sup>	0.9366 <sup>d</sup>	1.1014	0.7856	1.0253 <sup>b</sup>	1.0327 <sup>a</sup>	1.1354
Dielectric con- stant, ε (25°)	78.5 <sup>a</sup>	32.6 <sup>a</sup>	109.5 <sup>a</sup>	36.7 <sup>p</sup>	37.8 <sup>a</sup>	48.9 <sup>f,g</sup>	37.5 <sup>a,g</sup>	29.6 <sup>b</sup>	31.5 <sup>a</sup>	38.6 <sup>a,g</sup>
Molar polariza- tion, cm <sup>3</sup> <sup>i</sup>	17.3	36.9	38.8	71.3	85.2	66.7	48.4	158.0	87.2	49.2
Refractive index, <i>n</i> <sup>20</sup> <sub>D</sub> <sup>a</sup>	1.333	1.3288	1.4453	1.4269 <sup>d</sup>	1.4351 <sup>d</sup>	1.4783 <sup>f</sup>	1.3441	1.4582 <sup>b</sup>	1.4706 <sup>a</sup>	1.3935
Molecular polar- izability, 10 <sup>-24</sup> cm <sup>3</sup> <sup>j</sup>	1.477	3.24	4.219	7.91	9.65	7.97	4.45	18.8	10.3	4.95
Dipole moment, D	1.84 <sup>a,i</sup>	1.70 <sup>a,i</sup>	3.25 <sup>a,i</sup>	3.82 <sup>k,o</sup>	3.79 <sup>k,o</sup>	4.3 <sup>f,o</sup>	3.84 <sup>a,i</sup>	5.37 <sup>b,n</sup>	4.09 <sup>m,o</sup>	3.44 <sup>a,i</sup>
Viscosity (25°), cP	1.00 <sup>a</sup>	0.547 <sup>a</sup>	3.31 <sup>p</sup>	0.796 <sup>p</sup>	0.919 <sup>p</sup>	2.000 <sup>b</sup>	0.345 <sup>a</sup>	3.34 <sup>a,r</sup>	1.83 <sup>a</sup>	0.62 <sup>a</sup>
Surface tension (20°), dynes cm <sup>-1</sup>	72.8 <sup>a</sup>	22.6 <sup>a</sup>	58.2 <sup>a</sup>	35.2 <sup>d,h</sup>	...	46.2 <sup>f</sup>	29.3 <sup>a</sup>	...	...	36.8 <sup>a</sup>
Structure: Trou- ton, <sup>s</sup> cal deg <sup>-1</sup> mole <sup>-1</sup>	26.0 <sup>a</sup>	25.0 <sup>p</sup>	37.3 <sup>t</sup>	23.3 <sup>u</sup>	22.2 <sup>a</sup>	29.6 <sup>f</sup>	20.2 <sup>a</sup>	...	...	22.0 <sup>a</sup>
Basicity: Δδ, ppm <sup>w</sup>	...	...	...	0.78	...	1.05	0.31	1.89	...	...
Polarity: <sup>e</sup>										
Z <sup>z</sup> , kcal mole <sup>-1</sup>	94.6	83.6	83.3	68.5	...	71.1	71.3	62.8 <sup>r</sup>	...	...
E <sub>T</sub> <sup>v</sup> , kcal mole <sup>-1</sup>	63.1	55.5	56.6	43.8	...	45.0	46.0	...	...	46.3
Log <i>k</i> <sub>ion</sub> <sup>t</sup>	-1.180	-2.796	...	-4.298	...	-3.738	-4.221	...	...	-3.921

<sup>a</sup> "Handbook of Chemistry and Physics," 47th ed, Chemical Rubber Co., Cleveland, Ohio, 1966-1967. <sup>b</sup> Reference 6. <sup>c</sup> Reference 30. <sup>d</sup> At 25°. <sup>e</sup> References 24 and 33. <sup>f</sup> Reference 7. <sup>g</sup> At 20°. <sup>h</sup> At 30°, ref 30. <sup>i</sup> [(ε - 1)/(ε + 2)](M/d). <sup>j</sup> [(n<sup>2</sup> - 1)/(n<sup>2</sup> + 2)](M/d)(3/4πN) for sodium D-line. Correction to R<sub>∞</sub> would give similar relative values: cf. ref 47. <sup>k</sup> Reference 3. <sup>l</sup> Gas phase. <sup>m</sup> E. Fischer, *J. Chem. Soc.*, 1382(1955). <sup>n</sup> Liquid. <sup>o</sup> Dilute solution in benzene or carbon tetrachloride. <sup>p</sup> Reference 53. <sup>q</sup> At 30°. <sup>r</sup> J. E. Dubois and A. Bienvenue, *Tetrahedron Letters*, 1809 (1966). <sup>s</sup> Trouton constant calculated from latent heat of vaporization at boiling point and boiling point (°K), using data from references indicated. <sup>t</sup> "Formamide," E. I. du Pont de Nemours Co., Wilmington, Del., 1961. <sup>u</sup> "DMF and DMAC Product Information," E. I. Du Pont de Nemours Co., Wilmington, Del., 1961. <sup>v</sup> "Organic Solvents," Vol. VII, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1955. <sup>w</sup> Nmr chemical shifts of CHCl<sub>3</sub> at infinite dilution in these solvents; cf. J. J. Delpuech, *Tetrahedron Letters*, 2111 (1965). <sup>x</sup> Molar transition energies of 1-ethyl-4-methoxycarbonylpyridinium iodide in these solvents at 25°. <sup>y</sup> Molar transition energies of pyridinium N-phenol betaines in these solvents at 25°. <sup>z</sup> Ionization rates of *p*-methoxyneophyl tosylate at 75°.

It must be stated firmly at the outset that, except in very limited circumstances, the macroscopic solvent dielectric constant recorded in Table I gives no indication of protic-dipolar aprotic solvent effects on rate. Many reactions are over a million times faster in dipolar aprotic solvents (e.g., DMF) than in protic solvents of much the same dielectric constant<sup>21</sup> (e.g., MeOH and MeOH-H<sub>2</sub>O). Thus we cannot use, in the present situation, the plausible theories of solvent effects,<sup>22</sup> which are convincingly documented for a very limited range of solvents but are based on electrostatics in a dielectric continuum. It is equally difficult to see any correlation of δ<sub>s</sub> log *k* with properties such as the refractive index, viscosity, dipole moment, or density. The qualitative interpretation in terms of our classification is clear: reactions (eq 1) are considerably faster in any dipolar aprotic solvent than in any protic solvent. Once this major division has been made, into solvents which can donate hydrogen bonds and those which cannot, then other solvent properties can sometimes be used to interpret δ<sub>s</sub> log *k* for transfer within each solvent class.

Empirical parameters of solvent polarity<sup>24,33</sup> are also in

Table I. Solvent polarity has so far eluded exact definition, although it has immediate meaning for the properly developed intuition.<sup>14</sup> The parameters are useful when the solvent effect on one process, even one so removed as an electronic transition, proves, for one reason or another, to be a model for the solvent effect on the free-energy difference between a particular reactant and transition state.<sup>24,33</sup> The parameters are at least qualitatively related to δ<sub>s</sub> log *k* for bimolecular reactions (eq 1). The Hughes-Ingold solvent theory<sup>18</sup> predicts a rate decrease for transfer of such reactions to more "polar" solvents, and these parameters of polarity show that protic solvents are more polar than dipolar aprotic solvents.

Other properties in Table I, such as the molar polarization, the molecular polarizability, the Trouton constant, and the basicity of solvents, will be referred to in the sections dealing with solute-solvent interactions. Agami<sup>34</sup> has suggested a

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"solvating power" for carbon-metal bonds of DMSO > HMPT. Solvent basicity has been interpreted in a variety of ways<sup>3,6,7,35,36</sup> and most authors agree that DMSO is a quite powerful Lewis base.<sup>3,4</sup> Isaacs<sup>37</sup> has suggested that the excitation energy of the hexamethylbenzene-tetracyanoethylene donor-acceptor system gives a guide to solvent polarizability, but few measurements in dipolar aprotic solvents have been reported.

## II. Solvation

### A. SOLVENT ACTIVITY COEFFICIENTS

Solvent effects on rate are best treated in terms of the thermodynamics of a hypothetical equilibrium between reactants and transition state, *i.e.*, in terms of the absolute rate theory rather than the collision theory.<sup>2,33,38,39</sup> The specific rate of a chemical reaction depends on the standard free-energy difference between reactants and the transition state, so the first step in solving the problem of the influence of solvent on reaction rates is therefore the determination of the standard chemical potentials of the reactants and transition state in various solvents.<sup>18</sup> Additional information comes from the enthalpies and entropies of solvation of reactants and transition state.<sup>14,15</sup> Our discussion will therefore start with solvent activity coefficients,  ${}^0\gamma_i^S$ , of reactants. Solvent activity coefficients<sup>2</sup> have been called "medium effects" by Bates,<sup>40</sup> "distribution coefficients" by Kolthoff,<sup>41</sup> and "degenerate activity coefficients" by Grunwald.<sup>42</sup> They are defined as in eq 5 such that  ${}^0\gamma_i^S$  is proportional to the change in the standard chemical potential,  $\bar{\mu}_i$ , of a solute, *i* (hypothetically ideal, in respect to Henry's law, unimolar solution), on transfer from an arbitrarily chosen reference solvent, 0 (*i.e.*, the standard state), to another solvent, *S*, at a temperature *T*.

$$\bar{\mu}_i^S = \bar{\mu}_i^0 + RT \ln {}^0\gamma_i^S \quad (5)$$

Variations from nonideality within each solvent system, due to changes in ionic strength, can be accommodated by including in eq 5 the more familiar "ionic strength activity coefficients"  $\gamma_i$ , referred to infinite dilution in each solvent.<sup>40,42</sup> Allowance also must sometimes be made for ion association, using  $\alpha$ , the degree of dissociation of the electrolyte. In many of the studies of protic-dipolar aprotic solvent effects on rate which have been made,<sup>21</sup> values of  $\alpha$  and of  $\gamma_i$  do not change appreciably with solvent transfer and are much the same in each solvent or are much closer to 1 than are the values of  ${}^0\gamma_i^S$ . Concentrations have been usually *ca.*  $10^{-2}$  *M* in solvents of dielectric constant between 30 and 40, and electrolytes were often the strong tetraalkylammonium salts. For this reason, values of  $\alpha$  and  $\gamma_i$  were rarely taken into account, although clearly they should be when more

precise data are needed. The question arises of a molar, molal, or mole fraction scale of concentrations. The molar scale is used here because it is the most common in kinetic studies, but solvent activity coefficients are readily converted from one scale to another.<sup>43</sup>

### B. THE ACTIVITY COEFFICIENT RATE EQUATION

The rate constant for a bimolecular reaction (eq 1) in a solvent, *S*, is related to the rate constant in the reference solvent, 0, through the appropriate solvent activity coefficients, as in eq 6. This is derived<sup>2,39</sup> from the absolute rate theory and is valid for measurements at a single temperature (commonly 25°).

$$\log k^S/k^0 = \log {}^0\gamma_{Y^-}^S + \log {}^0\gamma_{RX}^S - \log {}^0\gamma_{YRX^\ddagger}^S \quad (6)$$

Equation 6 shows to what extent solvent effects on the rate of reaction (eq 1) are due to changes in the solvation of reactant anion,  $Y^-$ , of reactant nonelectrolyte,  $RX$ , and of anionic transition state,  $YRX^\ddagger$ . As will be shown, linear free-energy relationships (eq 7), having a limited number of constants, *C*, follow from eq 6. These allow prediction of rate constants in solvents, *S*, from rate constants in the reference solvent, but more important, deviations from these relationships hint at any unusual feature of the reaction mechanism.

$$\log k^S/k^0 = \log {}^0\gamma_{Y^-}^S + C \quad (7)$$

Perhaps the most useful application of eq 6 is that it provides information about the structure and charge distribution of transition states. Values of  $\log {}^0\gamma_{YRX^\ddagger}^S$  from eq 6 are compared with  $\log {}^0\gamma_i^S$  for solutes, or for other well-established transition states, whose structure and charge distribution are such that they might act as models for the various transition states,  $YRX^\ddagger$ , under consideration. That model whose  $\log {}^0\gamma_i^S$  value is most like  $\log {}^0\gamma_{YRX^\ddagger}^S$  is used as a guide to the structure and charge distribution in  $YRX^\ddagger$ .<sup>21,22</sup>

This type of investigation has been applied profitably to the solvolysis of *t*-butyl halides in protic solvents<sup>14</sup> and of methyl halides<sup>16,19</sup> and of esters<sup>17</sup> in water and water-DMSO mixtures. It shows,<sup>44</sup> for example, that isomerization and solvolysis of *cis*- and *trans*-dichlorobis(ethylenediamine)-cobalt(III) cations in methanol, DMF, DMAC, sulfolane, and DMSO have different rate-determining steps. Negative charge is not highly localized on chlorine in all the solvents.

It must be realized that comparisons of solvation of transition states with solvation of model solutes rest on the assumption that *transition states are in equilibrium with their surroundings*. Ritchie, Skinner, and Badding<sup>45</sup> have recently emphasized that there is solvent reorganization during progress from reactant to transition state. The main justification for this assumption is that it leads to a consistent and reasonable picture for solvent effects on reaction rates. The solvent activity coefficients of transition states, for reactions whose mechanisms are well established, are exactly as expected for species in equilibrium with their environment.

Transition state structures may change more drastically

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(44) W. R. Fitzgerald, A. J. Parker, and D. W. Watts, *J. Am. Chem. Soc.*, **90**, 5744 (1968).

(45) C. D. Ritchie, G. A. Skinner, and V. G. Badding, *ibid.*, **89**, 2063 (1967).

with solvent transfer than do the shape and the partition functions of real species.<sup>21</sup> A transition state can, in principle, exist at any point along the reaction coordinate. Its position will surely change with solvent transfer. It seems legitimate, however, to take model structures for bimolecular transition states and discuss expected solvent effects on the basis of these structures, provided that the reaction has the same basic mechanism (*e.g.*, SN<sub>2</sub>, E2) in each solvent considered. After all, "real solutes" also change their structure and partition functions with solvent transfer, or from crystal to gas phase, as evidenced, for example, by changes in their spectra. Nevertheless, chemists still use the same representation for these species in all environments. In reactions where each solvent is part of the composition of the transition state, *i.e.*, the solvents are undergoing covalency change in the transition state, as in bimolecular solvolyses, equations like (6) cannot be usefully applied to rate data, because the solvolysis is a bimolecular reaction with two different reagents.<sup>44</sup>

Before we can use eq 6 properly, we need to understand how solvent activity coefficients of anions, cations, and non-electrolytes are influenced by solute-solvent interactions.

### C. SOLUTE-SOLVENT INTERACTIONS

The data in Table I provide information on which qualitative discussion of the interactions between solutes and solvent can be based. Attention is focused on four types of interaction: electrostatic (ion-dipole or dipole-dipole), hydrogen bonding, dispersion forces, and structure making or breaking. Complexing of donors with acceptors, *e.g.*, iodine with DMSO, silver cation with acetonitrile, is considered whenever it is relevant.

The dielectric constant, molar polarization, and dipole moment of a solvent show how strongly it may interact electrostatically with a solute. We might therefore expect to find that electrostatic interactions with a polar solute decrease in the order HMPT > NMePy  $\approx$  DMAC > DMF > DMSO > CH<sub>3</sub>NO<sub>2</sub>  $\approx$  CH<sub>3</sub>CN > HCONH<sub>2</sub> > H<sub>2</sub>O > CH<sub>3</sub>OH. However, we must consider whether the solvent can effectively align its dipolar molecules in positions for maximum interaction with the solute.<sup>1</sup> A positive charge localized on hydrogen, as in water, fits more closely about a negative center than would the positive charge localized on, for example, the nitrogen in DMF. The negative center in DMSO is on a less hindered oxygen and interacts more strongly with positive centers than does the negative oxygen of methanol. The "hydrogen-bonding" interaction of protic solvents with anions, which we discuss below, is an extreme case of an anion-dipole electrostatic interaction, where the positive center of the solvent is in a most favorable atom. In most cases it is not seen as a specific 1:1 interaction like that in HF<sub>2</sub><sup>-</sup> and HCl<sub>2</sub><sup>-</sup>.

Dispersion interactions<sup>46</sup> or mutual polarizability<sup>4</sup> are indicated by the molecular polarizability of the solvent<sup>47</sup> and will decrease in the order of solvents: HMPT  $\gg$  NMePy  $\approx$  DMAC > DMSO, DMF > CH<sub>3</sub>NO<sub>2</sub>  $\approx$  CH<sub>3</sub>CN  $\approx$  HCONH<sub>2</sub> > CH<sub>3</sub>OH > H<sub>2</sub>O.

Solvent structure is difficult to estimate precisely, although a well-established property,<sup>15,48-52</sup> but should be developed

most in those solvents, like water, which are both strong hydrogen-bond donors and acceptors.<sup>52</sup> An interesting discussion of the solvent structure of amides has been given by Dawson.<sup>53</sup> Millen<sup>54</sup> has calculated a solvent structure parameter for protic and dipolar aprotic solvents, by considering the work of creating a liquid surface equal to the surface of a spherical solute of radius  $\gamma$ . The free energy in making this hole is then  $\Delta G_h^\circ = 4\pi r^2\sigma$ , where  $\sigma$  is the free energy per square centimeter of liquid surface and is calculated from the temperature coefficient of the surface tension and the latent heat of vaporization of the solvent. Millen's calculations work well for water,<sup>55</sup> and the limited data available for dipolar aprotic solvents suggest<sup>54</sup> that solvent ordering decreases: HCONH<sub>2</sub>  $\approx$  H<sub>2</sub>O > DMSO > DMF > DMA. High Trouton constants are thought to indicate well-developed solvent structure, but, despite the high value in Table I for DMSO, it is hard to accept a structure for DMSO quite as strongly developed as is that of water. Structure-breaking interactions should be much weaker than in water for solvents like DMF, CH<sub>3</sub>CN, CH<sub>3</sub>NO<sub>2</sub>, and HMPT, which are not held together by hydrogen bonds between small solvent molecules, as in water. The "structure" of methanol<sup>52</sup> involves small clusters of only a few molecules and is less strongly developed than is that of water or formamide. Structure-breaking solute-solvent interactions may be smaller in methanol than in, for example, DMSO, because the inert gases are much less soluble in DMSO than in methanol (*cf.* Table II).

By definition and as can be seen from their formulas in Table I, protic solvents are strong hydrogen-bond donors, whereas dipolar aprotic solvents are not. Protic solvents will interact strongly with solutes which are strong H-bond acceptors. Many dipolar aprotic solvents, *e.g.*, DMF, DMSO, and HMPT, are powerful bases and hydrogen-bond acceptors, so that they have strong interactions with solutes which are strong hydrogen-bond donors.<sup>4,6,7</sup> They interact quite strongly, for example, with chloroform and this interaction, as reflected by nmr chemical shifts, is a measure of solvent basicity.<sup>4</sup>

Although one must be cautious in assigning a single interaction mechanism<sup>88</sup> to an observed solvent activity coefficient, there is some value in a qualitative interpretation of solvation by considering separately each of the interactions described above. It is possible to predict behavior in new situations, and the principles are useful when we consider solvation of transition states.

### D. SOLVATION OF NONELECTROLYTES

Solvent activity coefficients of some representative non-electrolytes, referred to a standard state of hypothetically ideal unimolar solution in methanol at 25°, are in Table II. They come from measurements, in methanol (M) and in other solvents (S), of solubilities, *S*, mole l.<sup>-1</sup>, as in eq 8 of Henry's law constants, *h/c* mm l. mole<sup>-1</sup>, as in eq 9, or of

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(47) R. J. W. Le Fevre, *Advan. Phys. Org. Chem.*, **3**, 1 (1965).

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(52) F. Franks and D. J. G. Ives, *Quart. Rev. (London)*, **20**, 1 (1966).

(53) L. R. Dawson in "Chemistry in Non-Aqueous Ionizing Solvents," Vol. IV, Interscience Publishers, New York, N. Y., 1963.

(54) W. A. Millen, Ph.D. Thesis, University of Western Australia, 1967.

(55) W. A. Millen and D. W. Watts, *J. Am. Chem. Soc.*, **89**, 6051 (1967).

Table II  
Solvent Activity Coefficients of Nonelectrolytes at 25°<sup>a</sup> (Reference Solvent: Methanol)

Solute RX	$-\log {}^M\gamma_{RX}^S \text{ for } S =$						
	H <sub>2</sub> O	HCONH <sub>2</sub>	DMF	DMSO	CH <sub>3</sub> CN	HMPT	NMePy
Neon	0.6 <sup>b</sup>	...	...	+0.6 <sup>c</sup>	...	...	...
Krypton	0.6 <sup>b</sup>	...	...	+0.6 <sup>c</sup>	...	...	...
Xenon	1.7 <sup>b</sup>	...	...	+1.1 <sup>c</sup>	...	...	...
Ethane	1.7 <sup>b</sup>	...	...	+0.6 <sup>c</sup>	...	...	...
Ethylene	1.3 <sup>b</sup>	...	0.0	-0.1	...	...	...
Ethylene oxide	0.4 <sup>d</sup>	...	...	-0.3 <sup>d</sup>	...	...	...
CH <sub>3</sub> Cl	0.9	0.1	-0.4	...	...	...	...
CH <sub>3</sub> Br	1.2	0.2	-0.3	...	...	...	...
CH <sub>3</sub> I	1.4	0.5	-0.5	-0.5	-0.4	-0.7	-0.7
<i>n</i> -BuBr	...	0.5	-0.1	+0.1	-0.2	-0.4	...
<i>t</i> -BuCl	3.0 <sup>e</sup>	...	-0.2 <sup>f</sup>	+0.1 <sup>f</sup>	...	...	0.0 <sup>f</sup>
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl	...	...	+0.1	...	...	...	...
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br	...	...	-1.2	...	...	...	...
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> I	...	0.4	-1.2	-1.1	-0.4	-1.5	-1.4
2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> Cl	4.2	...	<-1	...	...	...	...
[2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> S] <sub>2</sub>	...	...	-2.3	-2.1	-0.9	...	...
(C <sub>6</sub> H <sub>5</sub> ) <sub>4</sub> C	...	...	-1.6	...	-0.5	...	...
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> Fe	3.6	...	...	...	-0.3	...	...
I <sub>2</sub>	2.3	0.5	-1.8	-4.1	-0.2	...	...

<sup>a</sup> Data from ref 21 unless stated otherwise. <sup>b</sup> H. Stephen and T. Stephen, "Solubilities of Inorganic and Organic Compounds," Pergamon Press, London, 1963. <sup>c</sup> Reference 58. <sup>d</sup> Reference 62 at 40°. <sup>e</sup> Reference 12. <sup>f</sup> E. C. Ko and A. J. Parker unpublished work.

distribution coefficients with a third immiscible solvent, such as decalin or cyclohexane. A positive value of  $\log {}^M\gamma_{RX}^S$  means that RX is more solvated by methanol than by S; a negative value means that RX is more solvated by S.

$$\log S^M - \log S^S = \log {}^M\gamma_{RX}^S \quad (8)$$

$$\log \left(\frac{h}{c}\right)^S - \log \left(\frac{h}{c}\right)^M = \log {}^M\gamma_{RX}^S \quad (9)$$

Polar solutes, especially those which are very polarizable, like nitro-substituted aromatics, are usually much more soluble in polar and polarizable dipolar aprotic solvents (*cf.* Table I) than in methanol. This may be because dipole-dipole interactions and dispersion forces are stronger in the former solvents. Polar solutes are much less soluble in water<sup>56</sup> and formamide than in methanol, so that  $\log {}^M\gamma_{RX}^W$  becomes quite positive with increasing size of RX. Structure-breaking interactions decrease solvation of large solutes by water and formamide, and mutual polarizability interactions favor solvation by methanol. Nonpolar solutes, such as alkanes,<sup>57</sup> inert gases,<sup>58</sup> and weakly polar species, like the higher homologs of the alkyl halides, are very slightly soluble in water and not very soluble in dipolar aprotic solvents,<sup>4</sup> so that  $\log {}^M\gamma_{RX}^S$  is often positive. Structure breaking,<sup>57,59,60</sup> in the absence of other strong interactions, must be considered. Solutes which are strong hydrogen-bond donors are often more solvated by the more strongly basic HMPT, DMF, DMSO, and formamide than by methanol. A solute which is a hydrogen-bond-acceptor, like ethylene oxide, is only slightly

less solvated by water than by DMSO, but ethylene and methyl iodide, which are not acceptors, are much less solvated by water than by DMSO. The data for the inert gases show the importance of solvent structure in water and DMSO, relative to methanol. The less positive value of  $\log {}^M\gamma_{RX}^S$  for xenon in DMSO than in water could be due to less structure of DMSO and/or greater polarizability of DMSO, but the difference is surprisingly small.

Changes in solvation with transfer of nonelectrolytes from water to DMSO-water mixtures are shown in Table III.

Table III

Solvent Activity Coefficients of Nonelectrolytes in DMSO-Water Mixtures (Reference Solvent: Water at 25°)

Mole fraction of DMSO	$-\log {}^W\gamma_{RX}^S \text{ for } RX =$				
	CH <sub>3</sub> I <sup>a</sup>	CH <sub>3</sub> CH(OEt) <sub>2</sub> <sup>b</sup>	EtOAc <sup>b</sup>	<i>t</i> -BuOAc <sup>b</sup>	H <sub>2</sub> O <sup>b</sup>
0.00	0.0	0.00	0.00	0.00	0.00
0.10	...	0.139	0.088	0.010	-0.025
0.20	...	0.309	0.105	-0.110	-0.032
0.30 <sup>c</sup>	-0.7	0.345	0.024	-0.272	-0.148
0.40	...	0.205	-0.134	-0.465	-0.229
0.50	...	0.043	-0.270	-0.690	-0.305
0.60	...	-0.126	-0.421	-0.925	-0.374
0.70	-1.1	-0.289	-0.567	-1.138	-0.436
0.80	...	-0.450	-0.675	-1.315	-0.493
0.90	...	-0.599	-0.755	-1.492	-0.553

<sup>a</sup> A. J. Parker, unpublished work. <sup>b</sup> Reference 17. <sup>c</sup> This composition is very close to a 2:1 ratio of water to DMSO and corresponds to maxima in viscosity and structure for DMSO-water mixtures; *cf.* ref 143.

(56) C. Hansch, J. E. Quinlan, and G. L. Laurence, *J. Org. Chem.*, **33**, 347 (1968).

(57) C. McAuliffe, *J. Phys. Chem.*, **70**, 1267 (1966).

(58) J. H. Dymond, *ibid.*, **71**, 1829 (1967).

(59) C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **84**, 822 (1962).

(60) F. H. Long and W. F. McDevit, *Chem. Rev.*, **51**, 119 (1952).

Mixtures of DMSO with water show interesting changes in structure, as shown by maxima in viscosity and thermo-

dynamic properties at mole fraction *ca.* 0.32 in DMSO.<sup>7,16,46,61</sup> Acetal and ethyl acetate, which are hydrogen-bond acceptors, are more soluble in water than in DMSO-water of low DMSO content. Competition by DMSO for hydrogen bonds donated by water and the well-developed structure of these mixtures might be the reason. Methyl iodide is more solvated in the mixtures than in water, at all concentrations of DMSO, and shows a much bigger difference on transfer from water to 0.70 mole fraction DMSO-water than does ethyl acetate, which is a stronger hydrogen-bond acceptor. *t*-Butyl acetate, which is large, is better solvated in DMSO-water mixtures than in water. The rational solvent activity coefficients for water in DMSO-water mixtures<sup>17</sup> cover a remarkably small range. Hydrogen-bond donation and acceptance, with accompanying structural changes, might be compensating each other.

Virtanen has discussed the solvation of ethylene oxide<sup>62</sup> and of methyl iodide<sup>16</sup> in DMSO-water mixtures at 40°. He, like Cox and McTigue,<sup>17</sup> emphasizes a point, which is apparent from Tables II and III, that solvation of the uncharged substrate is sometimes a significant factor in determining rate, especially when rates in water are involved. One cannot consider only ion solvation. Although ions have much greater solvation energies than nonelectrolytes for transfer from vacuum to solvent, the changes in chemical potential of nonelectrolytes may be greater than the changes in chemical potential of electrolytes for transfer between solvents of comparable dielectric constant, as is the case for protic to dipolar aprotic transfer. However, nonelectrolyte solvation is often not an important factor in  $\delta_S \log k$ . In many cases,  $\log {}^0\gamma_{RX}^S$  is close to zero, and, even when it is large, many of the interactions causing this large value, such as mutual polarizability or structure breaking, are still present to much the same extent in the transition state,  $YRX^\ddagger$ . Thus the term of  $\log {}^0\gamma_{RX}^S - \log {}^0\gamma_{YRX}^S$  in eq 6 is not large, or, when it is large, this is due almost entirely to predictable changes caused by charge distribution at the reaction center in the transition state. However, it is always necessary to estimate or measure  $\log {}^0\gamma_{RX}^S$  when considering solvent effects on rate of reaction (eq 1).

## E. SOLVATION OF ELECTROLYTES

It will forever be impossible to determine single ion solvent activity coefficients.<sup>40-43,63-66</sup> This may be one reason why eq 6 has not been used as much as it might have been. Many values of  $({}^0\gamma_{M^+}^S)({}^0\gamma_{Y^-}^S)$  are available from solubilities of salts, MY, in a reference solvent and other solvents S,<sup>63</sup> but they cannot be split into thermodynamically acceptable values of  ${}^0\gamma_{Y^-}^S$  or of  ${}^0\gamma_{M^+}^S$ . We have two alternatives. The first is to choose an anion or cation (*e.g.*,  $X^-$ ) as a reference ion and to set its solvent activity coefficient at unity. Pseudo-solvent activity coefficients,  ${}_Y-{}^0\gamma_{M^+}^S$ , relative to  ${}^0\gamma_{X^-}^S$ , are then calculated as in eq 10 from the solubility products, expressed as

molar concentration products, of MX in the two solvents. Pseudo-solvent activity coefficients,  ${}_X-{}^0\gamma_{Y^-}^S$ , for anions  $Y^-$  are given by  $\log ({}^0\gamma_{M^+}^S)({}^0\gamma_{Y^-}^S) - \log {}_X-{}^0\gamma_{M^+}^S$ . This procedure

$$\log \frac{K^0}{K^S}(\text{MX}) = \log {}^0\gamma_{M^+}^S + \log {}^0\gamma_{X^-}^S = \log {}_X-{}^0\gamma_{M^+}^S \quad (10)$$

has been used,<sup>63</sup> with thiocyanate ion as reference ion, to give *P* values (*i.e.*,  $\log {}_{\text{NCS}^-}^W\gamma_{Y^-}^S$ ) for anions on transfer from water to dipolar aprotic solvents at 25°. *P* values lead to the same conclusions about protic-dipolar aprotic solvent effects on  $\log {}^0\gamma_{Y^-}^S - \log {}^0\gamma_{YRX}^S$  in rate eq 6, as does the extrathermodynamic alternative, discussed below, but they are clumsy, discussion of effects becomes unnecessarily long, and some interesting (although nonthermodynamic) features of solvent effects on rate are obscured.<sup>21</sup>

The second procedure, which uses extrathermodynamic assumptions to split the product  $({}^0\gamma_{M^+}^S)({}^0\gamma_{Y^-}^S)$ , seems preferable.<sup>64,65</sup> Even if the assumptions are not valid, the solvent activity coefficients so obtained are always relative to some reference point<sup>65</sup> (*e.g.*, an assumed liquid junction potential, assumed solvation of a tetraphenylboride anion, solvation of the ferrocene-ferricinium couple, etc.; *vide infra*) so that they give as much information as do the pseudo-solvent activity coefficients, described above. If the assumptions have any validity, they then give more information, so that one has nothing to lose and much to gain by this procedure. The original extrathermodynamic assumptions must always be remembered though. If, as has been observed,<sup>65</sup> a number of independent extrathermodynamic assumptions lead to much the same single ion solvent activity coefficients, then one has some confidence in those values.

## F. EXTRATHERMODYNAMIC ASSUMPTIONS

Parker and Alexander,<sup>65</sup> Strehlow,<sup>43</sup> Kolthoff and Thomas,<sup>67</sup> and Bates<sup>40</sup> have compared a number of extrathermodynamic assumptions proposed for splitting  $({}^0\gamma_{M^+}^S)({}^0\gamma_{Y^-}^S)$ . Those which lead to much the same single ion solvent activity coefficients, when applied to solubilities of electrolytes in protic and in dipolar aprotic solvents, are discussed below. Of course, other assumptions have been made,<sup>65</sup> but each gives a different solvent activity coefficient, so they are less convincing.

### 1. The Tetraphenylarsonium Tetraphenylboride Assumption

The assumption is that  ${}^0\gamma_{\text{Ph}_4\text{As}^+}^S = {}^0\gamma_{\text{Ph}_4\text{B}^-}^S$ . Grunwald, Baughman, and Kohnstam<sup>66</sup> first argued convincingly in favor of this assumption and it has proved popular.<sup>49,64,68</sup> Structural effects are assumed cancelled, because the cation and anion are symmetrical species of much the same size and shape, but the fact that solvent orientation about an anion is different from that about a cation is ignored. Electrostatic interactions are small, because the charge is "buried" under an insulating layer of phenyl groups, but there is some leakage to the phenyl groups in the tetraphenylarsonium cation. In any case, the Born equation, (11), suggests that electrostatic interactions will be much the same in solvents of equivalent

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(63) R. Alexander, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Am. Chem. Soc.*, **89**, 3703 (1967).

(64) R. Alexander and A. J. Parker, *ibid.*, **89**, 5549 (1967).

(65) R. Alexander and A. J. Parker, *ibid.*, **90**, 3313 (1968).

(66) E. Grunwald, G. Baughman, and G. Kohnstam, *ibid.*, **82**, 5801 (1960).

(67) I. M. Kolthoff and F. G. Thomas, *J. Phys. Chem.*, **69**, 3049 (1965).

(68) E. M. Arnett and D. R. McKelvey, *J. Am. Chem. Soc.*, **88**, 2598 (1966).

Table IV

Extrathermodynamic Assumptions for Single-Ion Solvent Activity Coefficients of Silver Cation (Reference Solvent: Methanol at 25°)<sup>a</sup>

Assumptions <sup>b</sup>	Uncertainty	Log <sup>M</sup> γ <sup>S</sup> <sub>Ag<sup>+</sup></sub> for S =												
		H <sub>2</sub> O	HCONH <sub>2</sub>	DMF	DMAC	DMSO	<sup>0.32</sup> DMSO-W <sup>c</sup>	CH <sub>3</sub> CN	HMPT	CH <sub>3</sub> NO <sub>2</sub>	TMS	NMePy	<sup>80</sup> DMSO-M <sup>d</sup>	
1. <sup>0</sup> γ <sup>S</sup> <sub>Ph<sub>4</sub>As<sup>+</sup></sub> = <sup>0</sup> γ <sup>S</sup> <sub>Ph<sub>4</sub>B<sup>-</sup></sub>	±0.2	-1.3	-3.8	-5.3	-6.6	-7.8	-5.6	-6.3	-7.8	...	-3.6	...	...	
2. <sup>0</sup> γ <sup>S</sup> <sub>Ph<sub>4</sub>C</sub> = <sup>0</sup> γ <sup>S</sup> <sub>Ph<sub>4</sub>B<sup>-</sup></sub>	±0.5	...	...	-5.6	-6.6	...	...	-6.2	...	...	...	...	...	
2. <sup>0</sup> γ <sup>S</sup> <sub>I<sub>2</sub></sub> = <sup>0</sup> γ <sup>S</sup> <sub>I<sub>2</sub><sup>-</sup></sub>	±0.4	-0.8	-3.2	-5.3	-6.7	-8.2	-5.4	-6.6	...	+1.4	-2.8	-6.8	-7.2	
2. <sup>0</sup> γ <sup>S</sup> <sub>ArX</sub> = <sup>0</sup> γ <sup>S</sup> <sub>ArXY<sup>-</sup></sub> ≠	±0.3	...	-3.7	-4.6	-5.4	-8.5	...	-5.4	-9.5	+2.8	-1.1	-5.8	...	
3. <sup>0</sup> γ <sup>S</sup> <sub>F</sub> = <sup>0</sup> γ <sup>S</sup> <sub>F<sup>+</sup></sub>	...	+0.8	-2.7	...	...	...	...	-6.1	...	...	...	...	...	
4. <sup>0</sup> γ <sup>S</sup> <sub>Rb<sup>+</sup></sub> = <sup>0</sup> γ <sup>S</sup> <sub>Cs<sup>+</sup></sub> = 1	...	-2.1	-1.5 <sup>e</sup>	-2.0 <sup>e</sup>	...	...	...	-6.3	...	...	...	...	...	
4. Pleskov-Strehlow	...	-0.4	-1.9	...	...	...	...	-6.9	...	...	...	...	...	
5. No E <sub>LJ</sub>	±0.3	-1.5	-3.6	-5.5	-6.8	-8.8	...	(-6.3) <sup>f</sup>	-9.7	+1.6	-1.1	...	-7.8	
6. <sup>0</sup> γ <sup>S</sup> <sub>±</sub> = 1	±0.3	-0.2	-4.0	-5.1	-6.5	-8.5	-5.5	-5.8	-10.3	+2.6	...	-7.3	-7.7	
Parker-Alexander	...	-0.8	-3.7	-5.1	-6.6	-8.2	-5.5 <sup>e</sup>	-6.3	-10	+1.7	-2	-6.8	-7.4	

<sup>a</sup> Data from ref 65 unless stated otherwise. <sup>b</sup> Numbers and symbols are as used in the text. <sup>c</sup> 0.321 mole fraction of DMSO-water; S. H. Tay and A. J. Parker, unpublished work. <sup>d</sup> 80% v:v DMSO-methanol. <sup>e</sup> From formal solubilities of cesium and silver halides given in ref 63. <sup>f</sup> Assumed value: other solvent activity coefficients in this row for dipolar aprotic solvents are actual values, relative to the value assumed for acetonitrile (see text).

dielectric constant, as is the case for the protic and dipolar aprotic solvents that we are considering. Specific interactions between the solvent and the well-insulated arsenic or boron

$$\log {}^0\gamma^S_i = \frac{NZ_1^2e^2}{4.606RT\epsilon} \left( \frac{1}{\epsilon_S} - \frac{1}{\epsilon_0} \right) \quad (11)$$

do not occur, and short-range dispersion forces should be as for four tetrahedrally arranged phenyl groups, in both anion and cation. For these reasons, the assumption expressed in eq 12 is made, where  $K$  is the solubility product, as a molar concentration product, of tetraphenylarsonium tetraphenylboride in each solvent.

$$\log {}^0\gamma^S_{Ph_4As^+} = \log {}^0\gamma^S_{Ph_4B^-} = \frac{1}{2} \log (K^0/K^S) (Ph_4AsBPh_4) \quad (12)$$

Solvent activity coefficients for silver ion, calculated from the tetraphenylarsonium tetraphenylboride assumption, are in Table IV, with methanol at 25° as reference solvent.<sup>64</sup> The value for water is uncertain, because the solid "AgBPh<sub>4</sub>" precipitated from water may be a different species from that precipitated from saturated solutions in other solvents.<sup>65,64</sup>

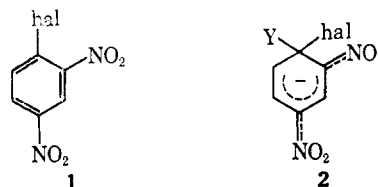
Popovych<sup>69</sup> has made a closely related assumption about the solubilities of triisooamylbutylammonium tetraphenylboride. He obtains much the same value for log <sup>M</sup>γ<sup>W</sup><sub>Ag<sup>+</sup></sub> as is shown in Table IV. He, too, encountered difficulties with tetraphenylborides in water.

## 2. The Large Anion-Large Molecule

Assumption: <sup>0</sup>γ<sup>S</sup><sub>B<sup>-</sup></sub> = <sup>0</sup>γ<sup>S</sup><sub>C</sub>

The solutes B<sup>-</sup> and C are chosen<sup>65</sup> so that all their interactions with any one solvent, other than electrostatic, may be the same. Values of <sup>0</sup>γ<sup>S</sup><sub>C</sub> can be obtained without recourse to any assumption. The anion B<sup>-</sup> is preferably very large, with negative charge "buried" beneath ligands or well dispersed. Thus, for transfer through solvents of much the same dielectric constant, the electrostatic interactions of B<sup>-</sup> will not change appreciably (cf. eq 11). Some suitable large anion-large molecule pairs are tetraphenylmethane-tetraphenylboride anion (<sup>0</sup>γ<sup>S</sup><sub>Ph<sub>4</sub>C</sub> = <sup>0</sup>γ<sup>S</sup><sub>Ph<sub>4</sub>B<sup>-</sup></sub>),<sup>66</sup> iodine-triiodide ion

(<sup>0</sup>γ<sup>S</sup><sub>I<sub>2</sub></sub> = <sup>0</sup>γ<sup>S</sup><sub>I<sub>2</sub><sup>-</sup></sub>),<sup>66</sup> and 2,4-dinitrohalobenzene (structure 1) or 4-halonnitrobenzene-SNAr transition state anion (structure 2)<sup>66</sup> (i.e., <sup>0</sup>γ<sup>S</sup><sub>ArX</sub> = <sup>0</sup>γ<sup>S</sup><sub>ArYX<sup>-</sup></sub>). This assumption, in conjunction with the one below, partly answers the criticisms about leakage of positive charge in the Ph<sub>4</sub>As<sup>+</sup> cation and differences in solvent orientation about anions and cations, which were applied to the preceding assumption. The results of



these assumptions, expressed as single-ion solvent activity coefficients for silver, with methanol as reference solvent at 25°, are in Table IV.

## 3. The Large Cation-Large Molecule

Assumption: <sup>0</sup>γ<sup>S</sup><sub>F</sub> = <sup>0</sup>γ<sup>S</sup><sub>F<sup>+</sup></sub>

The reasoning is the same as in section 2 above. Suitable pairs are ferrocene (F)-ferricinium cation (F<sup>+</sup>) and cobaltocene-cobalticinium.<sup>48,67,70</sup> One might expect that the orientation of solvent dipoles about a cation would be different from the orientation about an anion, also that anions might be more polarizable than cations. This would lead to differences, but it is reassuring that the large cation-large anion assumption (1), the large anion-large molecule assumption (2), and the large cation-large molecule assumption (3) lead to much the same value for log <sup>0</sup>γ<sup>S</sup><sub>Ag<sup>+</sup></sub>, as shown in Table IV. The ferrocene-ferricinium redox system is an excellent vehicle for this assumption, because liquid junction potentials and single-ion solvent activity coefficients can be estimated electrochemically. Strehlow,<sup>48</sup> Kolthoff and Thomas,<sup>67</sup> and Iwamoto and



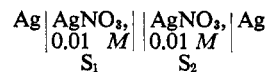
Nelson<sup>70</sup> have used this assumption and give some justification for it.

#### 4. Modifications of the Born Equation (Eq 11)

Pleskov<sup>48,71</sup> suggested that large alkali metal cations, such as cesium and rubidium, which do not have specific interactions with solvents and are not very polarizable, will have  $\log \gamma_{M^+}^S$  close to zero, particularly if the two solvents have similar dielectric constants. Izmailov<sup>48,72,73</sup> has extrapolated data for pairs of cations to cations of infinite size, which have zero solvation energy (eq 11). Strehlow,<sup>48</sup> Coetzee and Campion,<sup>74,75</sup> and Feakins and Watson<sup>76</sup> have made some modifications to this simple approach, but, as de Ligny and Alfenaar<sup>77</sup> have noted, their procedure does not allow for effects due to structure making or breaking by the large cations. Solutes like methane or the inert gases (*cf.* Table II) have been used as models for such structural effects.<sup>77</sup> These assumptions are only likely to be valid (*cf.* Table VII) if the two solvents are of comparable structure.<sup>65</sup> Values of  $\log \gamma_{Ag^+}^S$ , calculated *via* modifications of the Born equation, are in Table IV. Only the value for transfer of silver cation from methanol to acetonitrile is in agreement with other assumptions, and the value for transfer to DMF is very different from other values in Table IV.

#### 5. Negligible Liquid Junction Potential

This assumption<sup>65,78,79</sup> is applied to cells like A, where the salt bridge of saturated tetraethylammonium picrate in either solvent  $S_1$  or solvent  $S_2$  is chosen because picrate and  $NEt_4^+$  have similar ionic mobilities.<sup>4</sup> Solvents  $S_1$  and  $S_2$  must both be dipolar aprotic. Dipolar aprotic solvents, although miscible in all proportions, are not expected to have the strong interactions with each other, which a strong hydrogen-bond donor like water and a strong acceptor like DMSO<sup>4,80</sup> have. There does seem to be a significant liquid junction potential between protic and dipolar aprotic solvents.<sup>65</sup> This assumption accommodates liquid junction potentials of  $\pm 20$  mV between dipolar aprotic solvents. Its only justification is the similar mobilities of the bridge ions and the agreement with other assumptions. Acetonitrile is the reference solvent. Solvent activity coefficients for silver cation, with methanol as reference solvent, come from the further assumption that  $\log \gamma_{Ag^+}^{M, CH_3CN}$  is  $-6.3$ , which is in line with values, from other assumptions, for  $\log \gamma_{Ag^+}^{M, CH_3CN}$  in Table IV. The  $\log \gamma_{Ag^+}^S$  values for water or formamide in Table IV are calculated on the assumption<sup>65</sup> that there is a negligible liquid junction potential between methanol and these solvents in cell A.



$$\Delta E = 0.0591 \log \gamma_{S_1} \gamma_{S_2}^{Ag^+} - E_{LJ} \text{ (assume } E_{LJ} = 0)$$

#### 6. The SN2 Transition State Assumption: $\gamma_{\pm}^S = 1$

This assumption<sup>65,78</sup> is applied to large tight transition state anions ( $\pm -$ ) for one-step SN2 reactions, which do not have specific interactions, such as hydrogen bonding, with either solvent. Reactions of primary alkyl iodides with large anions, such as thiocyanate or iodide ion, are well suited. In one sense, this assumption, for a large anion with well-dispersed charge, is like those in assumption 4 for the large alkali metal cations, which are based on the Born equation, (11). It might apply for transfer through a series of solvents of much the same dielectric constant, but it is remarkable that, despite the disregard of differences in dispersion forces and structure-breaking interactions, there is excellent agreement with the other assumptions for  $\log \gamma_{Ag^+}^S$  shown in Table IV. The supposition about the large halonitrobenzenes and the SNAr transition state anion given in assumption 2 seems more reasonable. It may be, of course, that synchronous SN2 transition states change their structure (their position along the reaction coordinate) so that they are similarly solvated in each solvent; *i.e.*, they are in the lowest possible energy state in each solvent, consistent with structure, charge distribution, and solvation. However, a large number of transition states do not have solvent activity coefficients of unity,<sup>21</sup> so that such behavior is not general.

Parker and Alexander's estimates<sup>65</sup> of  $\log \gamma_{Ag^+}^S$  at 25° are included in Table IV. Roughly the same values as the estimates are obtained from the assumption that  $\gamma_{I_2}^S = \gamma_{I_3^-}^S$ , so that the estimated  $\log \gamma_{Ag^+}^S$  is in fact  $\log \gamma_{Ag^+}^S - \log \gamma_{I_2}^S + \log \gamma_{I_3^-}^S$ . All values of  $\log \gamma_{Y^-}^S$  for anions in Table V and throughout this review are actually  $\log \gamma_{Y^-}^S + \log \gamma_{I_2}^S - \log \gamma_{I_3^-}^S$ . When solvation of one anion (*e.g.*, a reactant) is compared with solvation of another (*e.g.*, a transition state), the  $\gamma_{I_2}^S$  and  $\gamma_{I_3^-}^S$  terms cancel, so that thermodynamic differences are obtained.

Many nucleophiles,  $Y^-$  in eq 1, form slightly soluble silver salts, so that the solubility products of  $AgY$ , as molar concentration products,<sup>63</sup>  $K$ , combined with  $\log \gamma_{Ag^+}^S$  from Table IV, give  $\log \gamma_{Y^-}^S$ , as in eq 13.<sup>21,65</sup>

$$\log \frac{K^0}{K^S} (AgY) = \log \gamma_{Ag^+}^S + \log \gamma_{Y^-}^S \quad (13)$$

#### G. SOLVATION OF ANIONS

Solvent activity coefficients for transfer of anions from reference solvent methanol to other solvents at 25° are in Tables V and VI. The effect of transfer from a protic solvent, methanol, to a dipolar aprotic solvent, DMF, of much the same dielectric constant is interpreted qualitatively in Figure 1. The variables in the anion, which are represented in Tables V and VI, are the size of the anion, its polarizability, and its charge dispersal, but we cannot completely isolate the effect of any one variable. Charge dispersal is only considered qualitatively but is of the type well understood by physical organic chemists,<sup>13</sup> *i.e.*,  $SCN^- > SC_6H_5^-$ , and picrate  $\gg 4-NO_2C_6H_4O^- > C_6H_5O^- > CH_3CO_2^- > CH_3O^-$ . The effect of charge dispersal on solvent activity coefficients is shown in Table VI. Size and polariz-

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(72) N. A. Izmailov, *Dokl. Akad. Nauk SSSR*, **126**, 1033 (1959).

(73) N. A. Izmailov, *ibid.*, **127**, 104 (1959).

(74) J. F. Coetzee and J. J. Campion, *J. Am. Chem. Soc.*, **89**, 2513 (1967).

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(77) C. L. de Ligny and M. Alfenaar, *Rec. Trav. Chim.*, **84**, 81 (1965).

(78) A. J. Parker, *J. Chem. Soc.*, **A**, 220 (1966).

(79) F. K. V. Koch, *ibid.*, 269 (1928).

(80) J. J. Lindberg and J. Kenttämä, *Suomen Kemistilehti*, **B33**, 104 (1960).

Table V  
Solvent Activity Coefficients of Anions (Reference Solvent: Methanol at 25°)<sup>a</sup>

Anion	Polarizability, <sup>b</sup> cm <sup>3</sup> mole <sup>-1</sup>	r, <sup>c</sup> Å	Log $\gamma_{Y^-}^S \pm 0.3$ for $S^e =$													
			H <sub>2</sub> O	HCO-NH <sub>2</sub>	DMF	DMAC	DMSO	MeCN	HMPT	MeNO <sub>2</sub>	NMePy	TMS	PC <sup>f</sup>	80 D-M	0.32 D-W <sup>g</sup>	0.697 D-W <sup>g</sup>
Cl <sup>-</sup>	9.07	1.81	-2.5	0.0	6.5	7.8	5.5	6.3	8.8	4.9	8.1	5.8	7.8	4.2	1.9	...
Br <sup>-</sup>	12.66	1.95	-2.1	-0.1	4.9	5.9	3.6	4.2	7.1	...	6.1	...	...	...	...	...
I <sup>-</sup>	19.21	2.16	-1.5	-0.1	2.6	3.0	1.3	2.4	...	2.6	3.0	2.4	3.0	1.5	0.8	1.0
N <sub>3</sub> <sup>-</sup>	...	...	-1.8	0.2	4.9	6.2	3.5	4.7	7.2	4.6	6.3	5.4	...	...	1.9	...
CN <sup>-</sup>	8.34	...	-1.5	0.4	6.2	...	...	...	...	...	...	...	...	...	2.1 <sup>h</sup>	2.9 <sup>h</sup>
SCN <sup>-</sup>	16.54	...	-1.2	-0.3	2.7	3.2	1.4	2.6	3.4	2.4	2.9	2.6	3.4	1.6	1.2	1.3
BPh <sub>4</sub> <sup>-</sup>	...	4.2 <sup>d</sup>	4.1	-0.1	-2.7	-2.7	-2.6	-1.6	-2.7	...	...	-2	-2.0	-2.2	0.3	...
OAc <sup>-</sup>	...	...	-2.9	0.6	9.2	10.2	6.5	7.8	...	...	...	...	...	...	...	4.4 <sup>h</sup>
OMe <sup>-</sup>	...	...	...	...	...	...	...	...	...	...	...	...	...	4.0	...	...
ClO <sub>4</sub> <sup>-</sup>	13.24	2.00	-1.9	...	-0.4	...	-0.3	...	...	...	...	...	...	...	...	...
Pic <sup>-</sup>	...	...	0.6	-0.6 <sup>f</sup>	-0.4	...	...	1.1 <sup>f</sup>	...	...	...	...	...	...	...	...
AgCl <sub>2</sub> <sup>-</sup>	...	...	-3.3	...	-0.5	-0.3	-1.3	-0.2	-2.6	-0.5	-0.3	-1.9	...	...	...	...
AgBr <sub>2</sub> <sup>-</sup>	...	...	-1.8	...	-1.2	-1.0	-2.3	-0.8	-3.8	...	...	...	...	...	...	...
AgI <sub>2</sub> <sup>-</sup>	...	...	-0.2	...	-2.7	-3.1	-2.7	-2.2	...	-1.5	-3.5	-2.9	-1.8	...	...	...
I <sub>3</sub> <sup>-</sup>	...	...	+2.2	1.0	-2.0	-3.0	-3.6 <sup>f</sup>	-0.4	...	...	...	...	...	...	...	...

<sup>a</sup> Data from ref 21, unless stated otherwise. <sup>b</sup> Refractions measured in aqueous solution: Landolt-Bornstein, "Atoms and Ions," Vol. 1, Part 1, Springer-Verlag, Berlin, 1950. <sup>c</sup> Ionic radius from L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1944. <sup>d</sup> Reference 66. <sup>e</sup> Abbreviations not in text are: TMS = tetramethylene sulfone; PC = propylene carbonate; 80-D-M 80% v: v DMSO-methanol; 0.32D-W = 0.32 mole fraction of DMSO-water; 0.697D-W = 0.697 mole fraction of DMSO-water. <sup>f</sup> R. Alexander, Ph.D. Thesis, University of Western Australia, 1968. <sup>g</sup> A. J. Parker and S. H. Tay, unpublished work. <sup>h</sup> Derived from a linear free-energy relationship (eq 7), rough values only.

Table VI

Solvent Activity Coefficients of Anions for Transfer from Methanol to DMF at 25°. Effect of Charge Dispersal on Anion

Anion, Y <sup>-</sup>	CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	C <sub>6</sub> H <sub>5</sub> O <sup>-</sup>	C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> O <sup>-</sup>	
Log $\gamma_{Y^-}^{DMF}$	9.2	7.7	4.9	4.1	
Anion, Y <sup>-</sup>	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>3</sub> <sup>-</sup>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> S <sup>-</sup>	SCN <sup>-</sup>	Pic <sup>-b</sup>	ClO <sub>4</sub> <sup>-</sup>
Log $\gamma_{Y^-}^{DMF}$	3.5	2.9	2.7	-0.4	-0.4

<sup>a</sup> Reference 21. <sup>b</sup> Picrate ion.

ability effects are also present. The solvent variables which we will consider are their ability to donate hydrogen bonds, their polarizability, their dielectric constants, and their structure. These have been discussed already, by reference to Table I. They, too, can rarely be treated rigidly as independent variables.

### 1. Hydrogen Bonding<sup>4</sup>

A negative charge on small atoms, especially first-row atoms, which do not have electron-withdrawing substituents attached to them, produces anions (e.g., F<sup>-</sup>, OR<sup>-</sup>, Cl<sup>-</sup>, NR<sub>2</sub><sup>-</sup>, R<sub>3</sub>C<sup>-</sup>) which are strong hydrogen-bond acceptors. Such anions have strong general, hydrogen-bonding interactions, rather than specific 1:1 interactions, with protic solvents.<sup>81</sup> This interaction is absent in dipolar aprotic solvents. Hydrogen bonding is the major reason why such anions are much more solvated by protic than by dipolar aprotic solvents, i.e., why log  $\gamma_{Y^-}^S$  is very positive when the solvent O is protic and S is dipolar aprotic (cf. Table V).

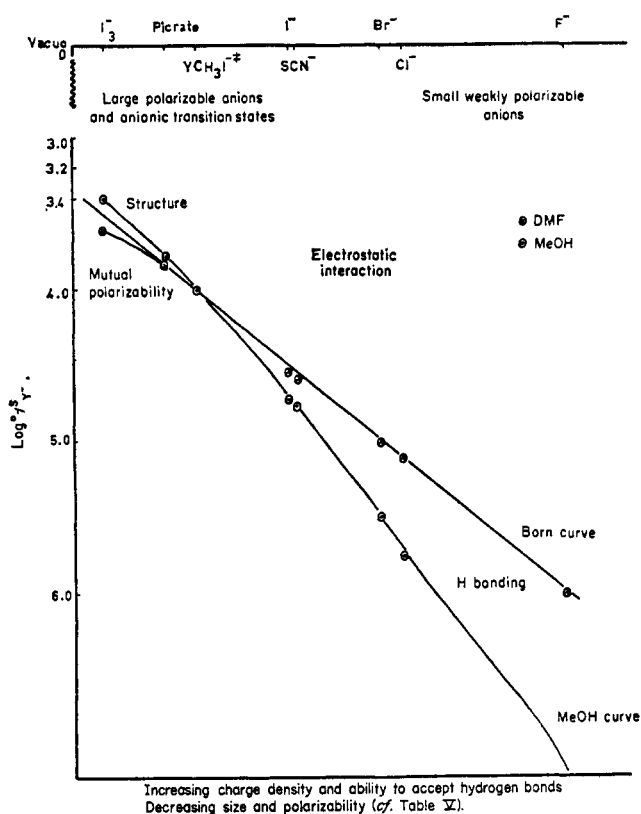
Dispersal of charge by electron-withdrawing groups, as in picrate, thiocyanate, triphenylmethide, silver dichloride, and perchlorate anions, or localization of charge on large atoms,

e.g., I<sup>-</sup>, produces an anion which is a weak hydrogen-bond acceptor. Such anions are not significantly more solvated by protic than by dipolar aprotic solvents (Tables V and VI). Many tight transition state anions, YRX<sup>-‡</sup>, for eq 1, have dispersed negative charge, so that they too are weak hydrogen-bond acceptors and are not particularly well solvated by protic solvents.

In Figure 1, small anions are shown as being more solvated in methanol than would be expected from their charge density and from the solvent dielectric constant, i.e., more than expected from the Born equation, (11). This deviation from the "Born curve" is due to hydrogen-bond donation by methanol. No such deviation is shown for small anions in aprotic DMF, which has the same Born curve as methanol, being of much the same dielectric constant.

### 2. Mutual Polarizability

Dipolar aprotic solvents, especially HMPT, are much more polarizable than protic solvents (cf. Table I), so that this interaction is strong for polarizable anions, e.g., I<sup>-</sup>, I<sub>3</sub><sup>-</sup>, SCN<sup>-</sup>, ClO<sub>4</sub><sup>-</sup> (cf. Table V) in dipolar aprotic solvents. This is one reason why some polarizable anions (e.g., picrate) are more solvated by dipolar aprotic than by protic solvents. In Figure 1, polarizable anions are shown as being more solvated than predicted by the "Born curve" because of this



**Figure 1.** A qualitative representation (as  $\log {}^0\gamma_{Y^-}$ ) of the effect of electrostatic, hydrogen-bonding, mutual polarizability, and structural interactions, between anion and solvent, on the standard chemical potential of anions, on transfer from vacuum to methanol and DMF at 25°. The Born curve is drawn with the distance between the halide ions, on the ordinate, corresponding to the solvation free energies calculated by R. H. Stokes, *J. Am. Chem. Soc.*, **86**, 979 (1964), for a solvent of dielectric constant 9. The positions of other anions on the Born curve are very rough estimates. The methanol curve is drawn on the assumption that  $I_3^-$  is virtually not a hydrogen-bond acceptor and that structure-breaking interactions, which raise the free energy of the anion, slightly outweigh mutual polarizability interactions between  $I_3^-$  and methanol. The position of  $I_3^-$  in methanol is thus slightly above the Born curve. The DMF curve is located by assuming that fluoride ion is virtually nonpolarizable and "fits" readily into the solvent structure of DMF so its position in DMF is close to the Born curve. Mutual polarizability and structural effects are thought to roughly cancel for the smaller anions in DMF, so the DMF curve and the Born curve are coincident in this region. Polarizability is significant for the large anions. The distances between the DMF and the methanol curves on the ordinate are taken from  $\log {}^M\gamma_{Y^-}^{DMF}$  in Table V. The abscissa is drawn intuitively, with guidance from anion size and polarizability, so that this figure is only a qualitative expression of some ideas about solvation.

interaction. Many transition state anions, especially for  $S_NAr$  reactions, are expected to be highly polarizable and will have strong interactions with solvents like HMPT, DMSO, and DMF.

### 3. Structure

This is particularly important when comparing solvation in water and formamide with that in the other solvents of Table V. Large anions, like  $BPh_4^-$ ,  $I_3^-$ , and some "organic" transition states, fit poorly into highly structured solvents whose molecules are small.<sup>82</sup> Dipolar aprotic solvents, and

especially methanol, have less structure, as indicated in Table I. This interaction accounts in part for the positive solvent activity coefficients of large anions in water and formamide, when methanol or dipolar aprotic solvents are the reference solvent. It is difficult to separate "structure" interactions from mutual polarizability, but the poor solvation of large solutes by highly structured solvents is observed also for cations (Table VII) and nonelectrolytes (Table II) where polarizability is less important. In Figure 1, effects of solvent structure for methanol and DMF are thought to be comparable, so a minor deviation from the Born curve is shown, but, if water and DMF were compared, in this type of figure, then large anions would be shown as considerably less solvated in water than predicted by the Born curve (structural effect) and more solvated than predicted in DMF (polarizability effect).

### 4. Ion-Dipole Electrostatic Interactions

We assume with Born<sup>83</sup> that ion-dipole interactions are related to the solvent dielectric constant and the charge density on the anion. Small anions with localized charge are more solvated, relative to the gas phase, than are large anions, especially those with dispersed charge (e.g., picrate) in all the solvents of Tables V and VI. Water and formamide will tend to solvate all anions more strongly than will the other solvents of lower dielectric constant, but this will be modified by the factors discussed above. This electrostatic interaction is shown as being the same for methanol and DMF in Figure 1, because these solvents have much the same dielectric constant and hence have the same Born curve.

Figure 1 has no quantitative significance. It is merely a convenient way of illustrating one interpretation of the solvent activity coefficients in Tables V and VI. The representative anions have been arranged in Figure 1 in an intuitive order<sup>4</sup> by considering their size, polarizability, charge density, and ability of the negative atom in the anion to accept hydrogen bonds.

## H. SOLVATION OF CATIONS

Solvent activity coefficients for some cations, with methanol as reference solvent at 25°, are in Table VII. Cations are generally smaller and less polarizable than anions and are not hydrogen-bond acceptors.<sup>4</sup> Some cations (e.g.,  $Ag^+$ ,  $Co^{2+}$ ) are Lewis acids and the solvent behaves as a basic ligand toward them: a few others (e.g.,  $R_3NH^+$ ) are hydrogen-bond donors, but the common interactions to be considered are cation-dipole and structure making or breaking. Small "closed-shell" cations, like  $Na^+$ ,  $K^+$ , and  $Me_3S^+$ , are very much more solvated by HMPT, DMF, and DMSO<sup>84</sup> and are more solvated by acetonitrile, formamide, propylene carbonate, and water than by methanol. These solvents have the negative end of their solvent dipole on an atom which is less sterically hindered, is more basic, and has charge more localized than on the oxygen of methanol.<sup>1</sup> Note that  $\log {}^0\gamma_{Co^{2+}}$  is not zero, as required by Pleskov.<sup>71</sup> Silver cation (Table IV) apparently has specific interactions with  $\pi$ -electron donors, such as N-methylpyrrolidone, formamide, DMF, DMSO,  $CH_3CN$ , DMAC, and HMPT. These must be much stronger than interactions of  $Ag^+$  with methanol, because  $\log {}^M\gamma_{Ag^+}^S$  is very negative.

(83) M. Born, *Z. Physik.*, [I] 45 (1920).

(84) J. M. Crawford and R. P. H. Gasser, *Trans. Faraday Soc.*, **63**, 2758 (1967).

(82) B. E. Conway and R. E. Verrall, *J. Phys. Chem.*, **70**, 1473 (1966).

Table VII  
Solvent Activity Coefficients for Cations (Reference Solvent: Methanol at 25°)<sup>a</sup>

Cation	$r, \text{Å}$	Polarizability, <sup>g</sup> $\text{cm}^3 \text{mole}^{-1}$	$\text{Log } {}^m\gamma_{\pm}^S \text{ for } S =$								
			H <sub>2</sub> O	HCONH <sub>2</sub>	DMF	DMAC	DMSO	CH <sub>3</sub> CN	HMPT	CH <sub>2</sub> NO <sub>2</sub>	PC <sup>b,c</sup>
Ag <sup>+</sup>	1.26	4.79	-0.8	-3.7	-5.1	-6.6	-8.2	-6.3	-10	1.7	-1.0
Na <sup>+</sup>	0.95	0.20	...	...	-3.9	...	-3.6	+1.4	-6.3	...	...
K <sup>+</sup>	1.33	2.25	-1.5	-2.8 <sup>c</sup>	-3.7	...	-4.5	-0.8 <sup>c</sup>	-4.8	...	-1.7
Me <sub>2</sub> S <sup>+</sup>	...	...	...	...	-3.1	-3.6	...	-1.6	...	-2.0	...
Cs <sup>+</sup>	1.67	6.53	-1.1	-2.1	-3.3	-4.2 <sup>c</sup>	-4.3 <sup>c</sup>	-1.3 <sup>c</sup>	...	...	...
NBu <sub>4</sub> <sup>+</sup>	...	...	3.7	...	...	...	...	-1.5	...	...	...
Ph <sub>4</sub> As <sup>+</sup>	...	...	4.1	-0.1	-2.7	-2.7	-2.6	-1.6	-2.7	...	-2.2
4-Cl-3-NO <sub>2</sub> C <sub>6</sub> H <sub>2</sub> - N <sup>+</sup> Me <sub>2</sub>	...	...	...	...	-4.6	...	...	...	...	...	...
<i>cis</i> -[Co(en) <sub>2</sub> Cl <sub>2</sub> ] <sup>+</sup> <sup>d</sup>	...	...	-2.2	...	-6.0	-6.2	-6.8	...	...	...	...
<i>trans</i> -[Co(en) <sub>2</sub> Cl <sub>2</sub> ] <sup>+</sup> <sup>d</sup>	...	...	-0.9	...	-4.2	-4.2	-4.7	...	...	...	...

<sup>a</sup> Reference 21, unless stated otherwise. <sup>b</sup> Propylene carbonate. <sup>c</sup> R. Alexander, Ph.D. Thesis, University of Western Australia, 1968. <sup>d</sup> Reference 44. <sup>e</sup> From solubility of CsCl in DMSO; J. N. Butler, *J. Electroanal. Chem.*, **14**, 89 (1967). <sup>f</sup> Ionic radius from L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1944. <sup>g</sup> Refractions measured in aqueous solution; Landolt-Bornstein, "Atoms and Ions," Vol. 1, Part 1, Springer-Verlag, Berlin, 1950.

Interactions of Ag<sup>+</sup> with water, propylene carbonate, sulfolane, or nitromethane are very much weaker than with the  $\pi$ -electron donors. Structure effects are apparent, in that large "organic" cations (NBu<sub>4</sub><sup>+</sup>, Ph<sub>4</sub>As<sup>+</sup>), like large anions and non-electrolytes, are considerably less solvated by water than by methanol. Such cations are more solvated by dipolar aprotic solvents than by methanol. Cations which are hydrogen-bond donors, such as *cis*-[Co(en)<sub>2</sub>Cl<sub>2</sub>]<sup>+</sup>, are much more solvated by DMF, DMSO, DMAC, and water than by methanol. The effect is less pronounced with *trans*-[Co(en)<sub>2</sub>Cl<sub>2</sub>]<sup>+</sup>, which is a weaker hydrogen-bond donor.<sup>44</sup>

### III. Solvation of Transition States

#### A. ANIONIC TRANSITION STATES FOR SUBSTITUTION

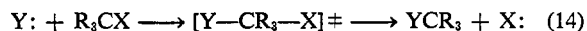
Solvent activity coefficients for transition states of bimolecular reactions can be calculated from eq 6. The protic-dipolar aprotic solvent effects on the rates (*i.e.*,  $\delta_s \log k^S/k^0$ ) of some bimolecular substitution reactions between anions and molecules are analyzed<sup>21,22</sup> for reactant and transition state solvation in Table VIII. The reactions are faster in dipolar aprotic solvents because the reactant anion, Y<sup>-</sup>, is much more solvated by protic than by dipolar aprotic solvents and this outweighs any effects due to transition state anion or reactant molecule solvation. The corresponding transition state anion has a value of  $\log {}^0\gamma_{\text{YRX}}^{\ddagger}$  which is less positive than is  $\log {}^0\gamma_{\text{Y}^-}$  when the reference solvent is protic and the other solvent is dipolar aprotic. This follows the pattern shown in Table V and Figure 1 for two anions, one of which, YRX<sup>-</sup>, is large and polarizable, the other, Y<sup>-</sup>, being smaller, less polarizable, and of greater charge density. Differences in solvation of the uncharged reactants, RX, as already noted, are often small, and, even when  $\log {}^0\gamma_{\text{RX}}^S$  is large, this effect is usually transferred to the transition state so that  $\log {}^0\gamma_{\text{RX}}^S/{}^0\gamma_{\text{YRX}}^{\ddagger}$  is fairly constant (*cf.* Table VIII).

That part of  $\delta_s \log k^S/k^0$  which depends on reactant solvation, whether the reactants be anions, cations, or uncharged species, is readily understandable in terms of the discussion following Tables II-VII and Figure 1. We have seen in Table

VIII that solvation of reactant anions is the dominant factor in determining rates of substitution reactions (eq 1) in protic and in dipolar aprotic solvents; however, we must now consider the smaller more subtle differences in solvation of transition state anions. This depends on the mechanism of substitution reactions. In the following discussion, the changes in  $\log {}^0\gamma_{\text{YRX}}^{\ddagger}$  are assigned to the effect of one or sometimes two variables, such as entering group, leaving group, substituents, etc. Sometimes only one interaction mechanism involving that variable (*e.g.*, steric effects of substituents) is considered. Lefler and Grunwald<sup>38</sup> have pointed out the hazards in this approach. It is usually impossible to rigorously isolate any one factor and call it an "effect." Despite these weaknesses, the following discussion may lead to an improved understanding and an ability to predict protic-dipolar aprotic effects on rate.

#### 1. Tight and Loose SN2 Transition States

Bimolecular nucleophilic substitution at a saturated carbon atom<sup>13,25,85</sup> can be represented by eq 14. The nucleophile Y is commonly an anion or uncharged species and the substrate



R<sub>3</sub>CX is a cation, anion, or uncharged species, so that reactions and transition states of various charge types<sup>26</sup> are possible. The transition state for these reactions has received an enormous amount of attention.<sup>85</sup> A current point of view<sup>21,22,86,87</sup> is that SN2 transition states 4 cover a spectrum between structures 3 and 5. In 3, bond forming (C-Y) and bond breaking (C-X) are synchronous, and the structure is described as "tight." In 5, the bonding is not synchronous: bond breaking is way ahead of bond forming and 5 is said to be "loose." An actual SN2 transition state 4 is said to be tighter or looser than another one, according to their relative positions in the SN2 spectrum. Apart from the degree of bonding, there is much more positive charge at C<sub>α</sub> and X and Y are much more negative in 5 than in 3, irrespective of the charge type of the reaction.

(85) C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier Publishing Co., New York, N. Y., 1963.

(86) E. R. Thornton, *J. Am. Chem. Soc.*, **89**, 2915 (1967).

(87) G. J. Frisone and E. R. Thornton, *ibid.*, **90**, 1211 (1968).

Table VIII

Bimolecular Substitution Reactions between Anions and Polar Molecules at 25° in Protic and Dipolar Aprotic Solvents (Reference Solvent: Methanol)<sup>a</sup>

No.	Reactants <i>RX + Y<sup>-</sup></i>	Log <i>k<sup>M</sup></i> <sup>b</sup>	Solvent	Log <i>k<sup>S</sup>/k<sup>M</sup></i> <sup>b</sup>	Log <i>Mγ<sup>S</sup><sub>RX</sub></i>	Log <i>Mγ<sup>S</sup><sub>Y<sup>-</sup></sub></i>	Log <i>Mγ<sup>S</sup><sub>±<sup>e,h</sup></sub></i>	Log <i>Mγ<sup>S</sup><sub>RX</sub>/Mγ<sup>S</sup><sub>±<sup>e,h</sup></sub></i>
A. S <sub>N</sub> 2 Reactions								
1a	CH <sub>3</sub> Cl + N <sub>3</sub> <sup>-</sup>	-6.1	HCONH <sub>2</sub>	1.3	0.1	0.2	-1.0	1.1
1b		-6.1	DMF	3.3	-0.4	4.9	1.2	-1.6
2	CH <sub>3</sub> Cl + SCN <sup>-</sup>	-5.8	DMF	1.4	-0.4	2.7	0.9	-1.3
3a	CH <sub>3</sub> Br + Cl <sup>-</sup>	-5.2	H <sub>2</sub> O	0.1 <sup>d</sup>	1.2	-2.5	-1.4	2.6
3b		-5.2	DMF	4.8	-0.3	6.5	1.4	-1.7
3c		-5.2	Me <sub>2</sub> CO	5.7	...	...	...	...
4a	CH <sub>3</sub> Br + N <sub>3</sub> <sup>-</sup>	-4.3	HCONH <sub>2</sub>	1.1	0.2	0.2	-0.7	0.9
4b		-4.3	DMF	3.9	-0.3	4.9	0.7	-1.0
5	CH <sub>3</sub> Br + SCN <sup>-</sup>	-3.6	DMF	1.7	-0.3	2.7	0.7	-1.0
6a	CH <sub>3</sub> Br + I <sup>-</sup>	-3.0 <sup>e</sup>	H <sub>2</sub> O	-0.2 <sup>d</sup>	1.2	-1.5	-0.1	+1.3
6b		-3.0	Me <sub>2</sub> CO	2.6	...	...	...	...
7a	CH <sub>3</sub> I + Cl <sup>-</sup>	-5.5	H <sub>2</sub> O	0.05 <sup>f</sup>	1.4	-2.5	-1.1	2.5
7b		-5.5	HCONH <sub>2</sub>	1.2	0.5	0.0	-0.7	1.2
7c		-5.5	DMF	5.9	-0.5	6.5	0.1	-0.6
7d		-5.5	DMAC	6.4	-0.6	7.8	0.8	-1.4
7e		-5.5	CH <sub>3</sub> CN	4.6	-0.4	6.3	1.3	-1.7
7f		-5.5	NMePy	6.9 <sup>g</sup>	-0.7	8.1	0.5	-1.2
7g		-5.5	Me <sub>2</sub> CO	6.2	-0.4	...	...	...
7h		-5.5	CH <sub>3</sub> NO <sub>2</sub>	4.2	-0.2	4.9	0.5	-0.7
8a	CH <sub>3</sub> I + N <sub>3</sub> <sup>-</sup>	-4.1	HCONH <sub>2</sub>	1.0	0.5	0.2	-0.3	+0.8
8b		-4.1	DMF	4.6	-0.5	4.9	-0.2	-0.3
9a	CH <sub>3</sub> I + SCN <sup>-</sup>	-3.3	H <sub>2</sub> O	-0.2 <sup>f</sup>	1.4	-1.2	0.4	+1.0
9b		-3.3	HCONH <sub>2</sub>	0.5	0.5	-0.3	-0.3	+0.8
9c		-3.3	DMF	2.2	-0.5	2.7	0.0	-0.5
9d		-3.3	DMAC	2.5	-0.6	3.2	0.1	-0.7
9e		-3.3	CH <sub>3</sub> CN	1.4	-0.4	2.6	0.8	-1.2
9f		-3.3	NMePy	3.5 <sup>g</sup>	-0.7	2.9	-1.3	+0.6
9g		-3.3	Me <sub>2</sub> CO	2.5	-0.4	...	...	...
9h		-3.3	CH <sub>3</sub> NO <sub>2</sub>	1.3	-0.2	2.4	+0.9	-1.1
9i		-3.3	HCONHNe	0.9	...	...	...	...
10a	CH <sub>3</sub> I + Br <sup>-</sup>	-4.1	H <sub>2</sub> O	-0.3 <sup>f</sup>	1.4	-2.1	-0.4	1.8
10b		-4.1	HCONH <sub>2</sub>	0.7	0.5	-0.1	-0.3	0.8
10c		-4.1	DMF	4.2	-0.5	4.9	0.2	-0.7
10d		-4.1	NMePy	5.4 <sup>g</sup>	-0.7	(6.1)	(0.0)	(-0.7)
10e		-4.1	Me <sub>2</sub> CO	5.1	-0.4	...	...	...
11a	CH <sub>3</sub> I + OAc <sup>-</sup>	-5.6	HCONH <sub>2</sub>	1.4	0.5	(0.6)	(-0.3) <sup>h</sup>	(0.8)
11b		-5.6	DMF	6.9	-0.5	9.2	1.8	-2.3
12	CH <sub>3</sub> I + ArO <sup>-i</sup>	-5.6	DMF	3.6	-0.5	(4.1)	(0.0)	(-0.5)
13	CH <sub>3</sub> I + Ar'O <sup>-i</sup>	-7.0	DMF	3.4	-0.5	(3.9)	(0.0)	(-0.5)
14	CH <sub>3</sub> I + ArS <sup>-i</sup>	-1.2	DMF	2.4	-0.5	(2.9)	(0.0)	(-0.5)
15a	CH <sub>3</sub> I + SeCN <sup>-</sup>	-2.4	DMF	2.0	-0.5	(2.5)	(0.0)	(-0.5)
15b		-2.1	NMePy	2.6 <sup>g</sup>	-0.7	(3.3)	(0.0)	(-0.7)
16a	CH <sub>3</sub> I + CN <sup>-</sup>	-3.2	H <sub>2</sub> O	0.0 <sup>f</sup>	1.4	(-1.5)	(-0.1)	(1.5)
16b		-3.2	HCONH <sub>2</sub>	1.2	0.5	(0.4)	(-0.4)	(0.9)
16c		-3.2	DMF	5.7	-0.5	(6.2)	(0.0)	(-0.5)
17a	CH <sub>3</sub> I + I <sup>-</sup>	-2.5 <sup>i</sup>	H <sub>2</sub> O	-0.8 <sup>f</sup>	1.4	-1.5	0.7	0.7
17b		-2.5	EtOH	+0.5 <sup>j</sup>	...	...	...	...
17c		-2.5	Me <sub>2</sub> CO	3.4	-0.4	...	...	...
18	CH <sub>3</sub> I + OMe <sup>-</sup>	-3.6 <sup>k</sup>	DMSO	5.4 <sup>k</sup>	-0.5	(5.3)	(-0.6)	(+0.1)
19a	CH <sub>3</sub> OTs + N <sub>3</sub> <sup>-</sup>	-3.3	H <sub>2</sub> O	-0.4 <sup>l</sup>	...	-1.8	...	1.4
19b		-3.3	DMF	2.0	-0.6	4.9	2.3	-2.9
20a	CH <sub>3</sub> OTs + SCN <sup>-</sup>	-3.9	H <sub>2</sub> O	-0.2 <sup>l</sup>	...	-1.2	...	1.0
20b		-3.9	DMF	0.8	-0.6	2.7	1.3	-1.9
21	CH <sub>3</sub> OTs + Br <sup>-</sup>	-4.6	DMF	3.1	-0.6	4.9	1.2	-1.8
22	CH <sub>3</sub> OTs + I <sup>-</sup>	-3.4	DMF	1.4	-0.6	2.6	0.6	-1.2
23a	CH <sub>3</sub> OTs + ArS <sup>-i</sup>	-1.8	DMF	1.6	-0.6	(2.9)	(+0.7)	(-1.3)
23b		-1.8	Me <sub>2</sub> CO	1.7	...	...	...	...
24	CH <sub>3</sub> OTs + Cl <sup>-</sup>	-5.1 <sup>m</sup>	DMF	3.8	-0.6	6.5	+2.1	-2.7
25	<i>n</i> -BuBr + ArS <sup>-i</sup>	-3.1	Me <sub>2</sub> CO	2.2	...	...	...	...
26	CH <sub>3</sub> OPO(OMe) <sub>2</sub> + N <sub>3</sub> <sup>-</sup>	-6.6	DMF	1.8	-0.4	4.9	2.7	-3.1

(Continued)

Table VIII (Continued)

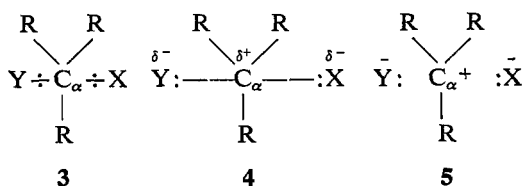
No.	Reactants $RX + Y^-$	Log $k^M$ <sup>b</sup>	Solvent	Log $k^S/k^M$ <sup>b</sup>	Log $M_{\gamma^S_{RX}}$	Log $M_{\gamma^S_{Y^-}}$	Log $M_{\gamma^S_{\pm}}$ <sup>c,h</sup>	Log $M_{\gamma^S_{RX}}/M_{\gamma^S_{\pm}}$
27a	<i>n</i> -BuBr + $N_3^-$	-5.1 <sup>n</sup>	H <sub>2</sub> O	0.8 <sup>n</sup>	...	-1.8	...	...
27b		-5.1	HCONH <sub>2</sub>	1.1 <sup>n</sup>	0.3	0.2	-0.6	+0.9
27c		-5.1	DMF	3.4 <sup>n</sup>	0.0	4.9	1.5	-1.5
27d		-5.1	TMS <sup>i</sup>	2.6 <sup>n</sup>	...	5.4	...	-2.8
27e		-5.1	DMAC	3.9	-0.1	6.2	2.2	-2.3
27f		-5.1	DMSO	3.1 <sup>n</sup>	+0.1	3.5	0.5	-0.4
27g		-5.1	CH <sub>3</sub> CN	3.7 <sup>n</sup>	-0.2	4.7	0.8	-1.0
27h		-5.1	HMPT	4.3 <sup>n</sup>	-0.4	7.2	2.5	-2.9
27i		-5.1	Me <sub>2</sub> CO	3.6	-0.1	...	...	...
28a	<i>n</i> -BuI + Cl <sup>-</sup>	-6.4	DMF	5.2	-0.3	6.5	1.0	-1.3
28b		-6.4	DMSO	4.6	0.0	5.5	0.9	-0.9
29	<i>n</i> -BuI + Br <sup>-</sup>	-5.5	DMSO	3.6	0.0	3.6	0.0	0.0
30a	<i>n</i> -BuI + I <sup>-</sup>	-4.2 <sup>o</sup>	CH <sub>3</sub> CN	1.8 <sup>o</sup>	-0.3	2.4	0.3	-0.6
30b		-4.2	Me <sub>2</sub> CO	3.1 <sup>p</sup>	...	...	...	...
31a	<i>n</i> -BuI + SCN <sup>-</sup>	-4.5	DMF	1.9	-0.3	2.7	0.5	-0.8
31b		-4.5	DMSO	1.7	0.0	1.4	-0.3	+0.3
31c		-4.5	HMPT	3.3	...	3.4	...	-0.1
32a	<i>n</i> -BuI + $N_3^-$	-4.6	DMF	4.0	-0.3	4.9	0.6	-0.9
32b		-4.6	DMSO	3.5	0.0	3.5	0.0	0.0
32c		-4.6	CH <sub>3</sub> CN	3.1	-0.3	4.7	1.3	-1.6
33a	<i>n</i> -BuI + NO <sub>2</sub> <sup>-</sup>	-5.2	DMSO	3.8	0.0	(3.7)	(-0.1)	(+0.1)
34	<i>i</i> -BuBr + $N_3^-$	-6.3	DMF	3.3	...	4.9	...	-1.6
35	<i>n</i> -BuBr + C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	-2.3	DMF	4.0	-0	(4.9)	(0.9)	(-0.9)
36	<i>i</i> -PrBr + C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	-3.8	DMF	3.1	-0.1	(4.9)	(1.7)	(-1.8)
37	<i>i</i> -PrBr + $N_3^-$	-5.1	DMF	2.7	-0.1	4.9	2.1	-2.2
38	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Cl + $N_3^-$	-4.2 <sup>q</sup>	Me <sub>2</sub> CO	3.5 <sup>q</sup>	...	...	...	...
39a	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br + $N_3^-$	-2.4	DMF	3.9	-1.2	4.9	-0.2	-1.0
39b		-2.4	Me <sub>2</sub> CO	4.2 <sup>q</sup>	...	...	...	...
40	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl + $N_3^-$	-4.3	DMF	2.4	0.2	4.9	2.7	-2.5
B. Substitution by Addition-Elimination								
41	<i>trans</i> -TsCH=CHCl <sup>r</sup> + $N_3^-$	-2.8	DMF	3.2	-1.1	4.9	0.6	-1.7
42a	CH <sub>3</sub> CO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> -4 + $N_3^-$	-1.6	H <sub>2</sub> O	0.2 <sup>s</sup>	...	-1.5	...	1.8
42b		-1.6	DMF	1.4	-0.9	5.9	2.6	-3.5
43	( <i>i</i> -Pr) <sub>2</sub> POCl + OAr <sup>-</sup>	-1.6	DMF	2.3	-0.3	(4.1)	(1.5)	(-1.8)
44a	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> F + $N_3^-$	-7.2	HCONH <sub>2</sub>	0.8	...	0.2	...	0.6
44b		-7.2	DMF	4.5	...	4.9	...	-0.4
44c		-7.2	DMAC	5.0	...	6.2	...	-1.2
44d		-7.2	DMSO	3.9	...	3.5	...	+0.4
44e		-7.2	CH <sub>3</sub> CN	3.9	...	4.7	...	-0.8
44f		-7.2	CH <sub>3</sub> NO <sub>2</sub>	3.5	...	4.6	...	-1.1
44g		-7.2	TMS <sup>i</sup>	4.5	...	5.4	...	-0.9
44h		-7.2	NMePy	5.3	...	6.3	...	-1.0
44i		-7.2	HMPT	7.3	...	7.2	...	0.1
44j		-7.2	Me <sub>2</sub> CO	4.9	...	...	...	...
45	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> F + C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	-3.8 <sup>t</sup>	DMF	4.4	...	(4.9)	...	(-0.5)
46a	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> I + $N_3^-$	-9.5	DMF	4.2	-1.2	4.9	-0.5	-0.7
46b		-9.5	CH <sub>3</sub> CN	3.8	-0.4	4.7	+0.5	-0.9
46c		-9.5	NMePy	4.7	-1.4	6.3	0.2	-1.6
46d		-9.5	HMPT	6.3	-1.5	7.2	-0.6	-0.9
47	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> I + C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	-4.2	DMF	3.6	-1.2	(4.9)	(+0.1)	(-1.3)
48	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> I + C <sub>6</sub> H <sub>5</sub> O <sup>-</sup>	-8.7	DMF	7.0 <sup>u</sup>	-1.2	(7.7)	(-0.5)	(-0.7)
49	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> Cl + $N_3^-$	-3.3	DMF	4.1	<-1 <sup>v</sup>	4.9	<-0.2 <sup>v</sup>	-0.8
50	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> Cl + SCN <sup>-</sup>	-6.5	DMF	2.5	<-1	2.7	<-0.8 <sup>v</sup>	-0.2
51	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> Br + SCN <sup>-</sup>	-5.5	DMF	2.0	...	2.7	...	-0.7
52	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> Br + I <sup>-</sup>	-8.5	DMF	2.6	...	2.6	...	-0.0
53a	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> I + SCN <sup>-</sup>	-5.4	NMePy	2.0	...	2.9	...	-0.9
53b		-5.4	DMF	1.7	...	2.7	...	-1.0
53c		-5.4	Me <sub>2</sub> CO	2.8	...	...	...	...
53d		-5.4	HCONH <sub>2</sub>	-0.3	...	-0.3	...	0.0
53e	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> I + SCN <sup>-</sup>	-5.4	DMAC	2.1	...	3.2	...	-1.1
53f		-5.4	CH <sub>3</sub> CN	1.6	...	2.6	...	-1.0
53g		-5.4	DMSO	1.2	...	1.4	...	-0.2
53h		-5.4	CH <sub>3</sub> NO <sub>2</sub>	1.3	...	2.4	...	-1.1
53i		-5.4	TMS <sup>i</sup>	1.7	...	2.6	...	-0.9

(Continued)

Table VIII (Continued)

No.	Reactants RX + Y <sup>-</sup>	Log k <sup>M</sup> <sup>b</sup>	Solvent	Log k <sup>S</sup> /k <sup>M</sup> <sup>b</sup>	Log M <sub>γ<sup>S</sup>RX</sub>	Log M <sub>γ<sup>S</sup>Y<sup>-</sup></sub>	Log M <sub>γ<sup>S</sup>±<sup>-e,h</sup></sub>	Log M <sub>γ<sup>S</sup>RX</sub> /M <sub>γ<sup>S</sup>±<sup>-</sup></sub>
54a	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> I + Cl <sup>-</sup>	-10.2	DMF	6.5	...	6.5	...	0.0
54b		-10.2	HMPT	8.8	...	8.8	...	0.0
55	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> I + Br <sup>-</sup>	-9.0	DMF	4.9	...	4.9	...	0.0
56	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> OAr + N <sub>3</sub>	-2.7	DMF	3.4	-2.0	4.9	-0.5	-1.5

<sup>a</sup> Data from ref 21 unless stated otherwise. <sup>b</sup> The second-order rate constants for reaction in methanol, k<sup>M</sup>, and for reaction in solvent S, k<sup>S</sup>, are in l. mole<sup>-1</sup> sec<sup>-1</sup>. <sup>c</sup> Calculated from eq 6; ± denotes transition state. <sup>d</sup> R. H. Bathgate and E. A. Moelwyn-Hughes, *J. Chem. Soc.*, 2642 (1959). <sup>e</sup> E. A. Moelwyn-Hughes and J. S. McKinley-McKee, *ibid.*, 838 (1952). <sup>f</sup> G. C. Lalor and E. A. Moelwyn-Hughes, *ibid.*, 2201 (1965). <sup>g</sup> Reference 158. <sup>h</sup> Some values are in parentheses because they are derived from a linear free-energy relationship (eq 7), which assumes that log <sup>0</sup>γ<sup>S</sup>RX/<sup>0</sup>γ<sup>S</sup>Y<sup>-</sup> ± is constant for this and related reactions. These values cannot of course be used in the later discussion, which attempts to justify the relationship. <sup>i</sup> Ar is 4-nitrophenyl; Ar' is 2,4-dinitrophenyl; TMS is tetramethylene sulfone. <sup>j</sup> P. Beronius, *Acta Chem. Scand.*, 15, 1151 (1961). <sup>k</sup> Reference 147. <sup>l</sup> R. E. Davis, *J. Am. Chem. Soc.*, 87, 3010 (1965). <sup>m</sup> Reference 171. <sup>n</sup> Reference 179. <sup>o</sup> Reference 152. <sup>p</sup> E. A. S. Cavell and J. A. Speed, *J. Chem. Soc.*, 1453 (1960). <sup>q</sup> U. Miotti, *Gazz. Chim. Ital.*, 254 (1967). <sup>r</sup> *trans*-1-Chloro-2-(*p*-toluenesulfonyl)ethene. <sup>s</sup> W. P. Jencks and J. Carrulio, *J. Am. Chem. Soc.*, 82, 1778 (1960). <sup>t</sup> C. W. Bevan and J. Hirst, *J. Chem. Soc.*, 254 (1956). <sup>u</sup> A. Berge and J. Ugelstad, *Acta Chem. Scand.*, 19, 742 (1965). <sup>v</sup> *I.e.*, more negative than this value.



The S<sub>N</sub>1 transition state is a logical extension of 4 very like 5, but 5 is not meant to represent the pure S<sub>N</sub>1 transition state. The structure is an extreme of the S<sub>N</sub>2 spectrum and could represent attack by the nucleophile on a preformed ion pair.<sup>88</sup> This picture of a S<sub>N</sub>2 spectrum receives support from theoretical studies,<sup>86</sup> from the substituent effects on the rates of S<sub>N</sub>2 reactions of substituted benzyl compounds,<sup>22</sup> from bromide tosylate leaving-group tendencies,<sup>89</sup> and from nucleophilic tendencies toward methyl and primary and secondary carbon atoms.<sup>22</sup> The most compelling evidence, however, comes from protic-dipolar aprotic solvent effects on rate.<sup>22</sup>

It is only when Y and X are the same (*e.g.*, radiochloride exchange) that C-Y and C-X need be at the same degree of tightness or looseness in the transition state. Such have not been studied extensively. In the following discussion, the effects of variables on tightness and looseness of S<sub>N</sub>2 transition states are considered for reactions where Y (*e.g.*, N<sub>3</sub>) and X (*e.g.*, Br) are different, but only slightly so. The discussion is as though Y and X were equally bound to C<sub>α</sub> in the transition state, but this is only approximately true. A thorough study of symmetrical exchange reactions in methanol, in conjunction with data available for acetone as solvent,<sup>90,91</sup> might modify the conclusions, but it would be surprising if the principles were changed.

The solvent activity coefficients for four sets of S<sub>N</sub>2 transition state anions, which are becoming progressively "looser" as one variable is changed, are shown in Table IX. Some of the "loosening factors" to be considered<sup>22,67</sup> are steric interactions of Y and X with increasingly bulky R groups at C<sub>α</sub>, increasing stabilization of positive charge at C<sub>α</sub> by electron-donating R groups, increasing size of X and Y, increasing negative charge dispersal in X and Y, as in phosphates, acetates, and tosylates, relative to halides, and change from dipolar aprotic to protic solvents which strongly solvate anions. A

"tightening" factor is the need, in 4, for the loss of C-X bond energy to be compensated somewhat by the gain in C-Y bond energy.

Three loosening factors are demonstrated in Table IX by  $\delta \log M_{\gamma}^{\text{DMF}} \pm$  values, *i.e.*, by the effect of one variable on the solvent activity coefficient of a transition state, transferred from methanol to DMF at 25°. As far as possible, other variables are held constant or are thought to be of negligible importance relative to the variable under consideration. Of course this is not always possible, especially where steric and electronic effects are concerned.<sup>88</sup>

The guiding principle used<sup>22</sup> to determine looseness is that increasingly positive values of  $\delta \log M_{\gamma}^{\text{DMF}} \pm$  indicate increasing localization of negative charge on X and Y in the transition state, *i.e.*, a transition state 4 which is becoming increasingly loose and like 5. In other words, transition state anions, which become increasingly more solvated by a protic solvent than by a dipolar aprotic solvent, have an increasing localization of negative charge, as already discussed for data in Tables V and VI. If we accept that increasing looseness is indicated by more positive values of  $\delta \log M_{\gamma}^{\text{DMF}} \pm$ , then the data in Table IX are interpreted as follows.

The set a, labeled electronic effects, shows that as an aryl substituent at C<sub>α</sub> is more able to stabilize positive charge at C<sub>α</sub>, *i.e.*, from *p*-NO<sub>2</sub> through H to *p*-OMe, so the transition state 4 becomes looser, *i.e.*, more like 5. The change is made at a *para* position, removed from the reaction center, so that steric effects are more or less constant within the set. The entering and leaving groups are constant in the set. A complication is that, apart from effects at the reaction center, a *p*-nitrobenzyl group, being very polarizable, is more solvated by DMF than by ethanol (*cf.* Table II) so that the transition state for reaction of *p*-nitrobenzyl bromide has a solvent activity coefficient, suggesting that it is tighter than it actually is. Nevertheless, as shown in Table IX, the effect of the *p*-nitrobenzyl solvation, as indicated by the solvation of *p*-nitrobenzyl bromide, is not sufficient to invalidate the interpretation given above.

The effect of methyl substituents at C<sub>α</sub><sup>90</sup> is a combination of steric and electronic effects, leading to a looser transition state. Methyl groups stabilize positive charge and are bulkier than hydrogen. Both factors favor transition states more like 5 as methyl is substituted for hydrogen.

Leaving or entering groups bound to C<sub>α</sub> through oxygen, as in tosylates, phosphates, or acetates, seem to lead to transition states with  $\log M_{\gamma}^{\text{DMF}} \pm$  more positive than when Y and

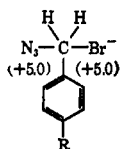
(88) H. Weiner and R. A. Snee, *J. Am. Chem. Soc.*, 87, 287 (1965).

(89) H. M. R. Hoffmann, *J. Chem. Soc.*, 6762 (1965).

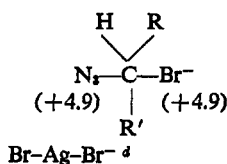
(90) C. K. Ingold, *Quart. Rev. (London)*, 11, 1 (1957).

(91) D. Cook and A. J. Parker, *J. Chem. Soc., B*, 142 (1968).

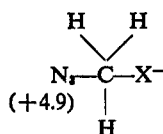
Table IX

Solvation of SN2 Transition State Anions at 25°. Loosening Factors<sup>a</sup>Transition state  $YCR_3X^-$        $R$        $\delta_R \log E_{\gamma}^{DMF} \pm$        $\delta_R \log E_{\gamma}^{DMF}_{R_1CB_r}$        $\delta_R \log k^{DMF}/k^E$ (a) Electronic Effects<sup>a</sup>

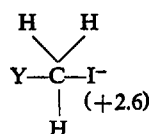
$NO_2$	+0.2	-1.2	3.6
H	+2.2	-0.2	2.6
OMe	+3.0	0.0	2.0

(b) Steric and Electronic<sup>b</sup>

$R$	$R'$	$\delta_R \log M_{\gamma}^{DMF} \pm$	$\delta_R \log M_{\gamma}^{DMF}_{RR'CHBr}$	$\delta_R \log k^{DMF}/k^M$
H	H	+0.7	-0.3	3.9
H	<i>n</i> -Pr	+1.5	0.0	3.4
H	<i>i</i> -Pr	+1.6	0.0	3.3
Me	Me	+2.1	-0.1	2.7
...	...	-1.2	...	...

(c) Leaving Group<sup>b</sup>

$X$	$\delta_X \log M_{\gamma}^{DMF} \pm$	$\delta_X \log M_{\gamma}^{DMF}_{CH_3X}$	$\delta_X \log M_{\gamma}^{DMF}_{X^-}$	$\delta_X \log k^{DMF}/k^M$
I	-0.2	-0.5	+2.6	4.6
Br	+0.7	-0.3	+4.9	3.9
OTS	+2.3	-0.6	+3.5	2.0
OPO(OMe) <sub>2</sub>	+2.7	-0.4	...	1.8

(d) Entering Group<sup>b</sup>

$Y$	$\delta_Y \log M_{\gamma}^{DMF} \pm$	$\delta_Y \log M_{\gamma}^{DMF}_{Y^-}$
SCN	0.0	2.7
Cl	+0.1	6.5
OCOCH <sub>3</sub>	+1.8	9.2

<sup>a</sup> Reference solvent ethanol; data from ref 22. <sup>b</sup> Reference solvent methanol; data from ref 21. <sup>c</sup> The numbers in parentheses below the transition state structures are  $\log {}^0\gamma^{DMF}_{Y^-}$  and  $\log {}^0\gamma^{DMF}_{X^-}$ , respectively, from Table V. <sup>d</sup> This is a "real" anion, not a transition state.

$X$  are halogen or halogenoid. The effect, in the case of the tosylate at least, must be due to a looser transition state,<sup>89</sup> because tosylate anion itself has a *less* positive  $\log M_{\gamma}^{DMF}$  than does bromide ion, yet the transition state containing tosylate has  $\log M_{\gamma}^{DMF} \pm$  more positive than is the case for the comparable transition state containing bromide. Thus the tosylate probably carries more negative charge than the bromide, in equivalent (same  $R_3C$ , same  $Y$ ) SN2 transition states. It is likely that phosphate and acetate are also more loosely bound than halide, whether entering or leaving group, in SN2 transition states. Steric factors due to the bulk of  $X$  are difficult to estimate, so the above discussion is purely qualitative.

Solvent activity coefficients for some of the entering or leaving anions are shown, as logarithmic values, in parentheses below the transition state structures in Table IX. It is interesting to calculate the most positive value which we could expect for  $\log M_{\gamma}^{DMF} \pm$ . As an extreme example, assume that the completely "loose" structure **5** is simply two solvated anions and a cation. For azide and bromide as  $X$  and  $Y$ , and assuming that  $\log M_{\gamma}^{DMF}_{R_3C^+}$  is 3.5, *i.e.*, like that for related cations in Table VII, eq 15 leads to  $\log M_{\gamma}^{DMF} \pm$  of roughly +6. None of the values in Table IX for transition states approach this value. A better model for **5** would be an ion triplet, like  $Me_3SBr_2^-$ , but dissociation constants for this species are not yet available.

$$\log M_{\gamma}^{DMF} \pm = \log M_{\gamma}^{DMF}_{N_3^-} + \log M_{\gamma}^{DMF}_{Br^-} + \log M_{\gamma}^{DMF}_{R_3C^+} \approx 6 \quad (15)$$

The silver dibromide anion is included in Table IX because this is a model for a very tight transition state. The anion is stable, linear, and has "entering" and "leaving" bromide very like entering azide and leaving bromide in the transition states of Table IX. The value for  $\log M_{\gamma}^{DMF}_{AgBr_2^-}$  of -1.2 is considerably more negative than are any other  $\log M_{\gamma}^{DMF} \pm$  values in Table IX, so that the  $C_{\alpha}-N_3$  and  $C_{\alpha}-Br$  bonds in the transition states may be looser than the  $Ag-Br$  bonds in  $BrAgBr^-$ . The model is far from ideal, because, of course, a linear anion, with silver as central atom, may respond differently on solvent transfer to a "linear" anion, with  $CR_3$  at the center.

It is possible to concentrate on charge distribution at the reaction center in the transition states of Table IX, because, with the exception of *p*-nitrobenzyl, effects due to solvation of  $R_3C$  are expected to be small. This is shown by the small values of  $\log M_{\gamma}^{DMF}_{R_3CX}$  in Tables II and IX.

The preceding discussion leads to the following conclusions about SN2 reactions of various substrates,  $R_3CX$ , which are of practical value and are illustrated by the rate ratios in the final column of Table IX. SN2 displacements of halide ion are much more susceptible to protic-dipolar aprotic solvent rate enhancement than are displacements of tosylates or phos-



phates. Displacements at methyl carbon are more susceptible than at primary carbon than at secondary carbon to protic-dipolar aprotic rate enhancement. Reactions of substituted benzyl compounds respond to protic-dipolar aprotic solvent transfer in different ways, depending upon the electron-withdrawing or electron-donating properties of the substituent.

## 2. Variation of Entering and Leaving Group

Some effects on the solvation of SN2 transition state anions<sup>4</sup> of changing Y or X are shown in Table X.<sup>21</sup> We need not dis-

Table X

Solvation of SN2 Transition State Anions. Effect of Entering and Leaving Group (Reference Solvent: Methanol at 25°)<sup>a</sup>

YCR <sub>3</sub> X <sup>±</sup>	$\delta_X \log k^{DMF}/k^M$	$\delta_X(\log M\gamma^{DMF \pm})_{Y,CR_3}$
Transition State Anion		
N <sub>3</sub> CH <sub>3</sub> Cl <sup>-</sup>	3.3	1.2
N <sub>3</sub> CH <sub>3</sub> Br <sup>-</sup>	3.9	0.7
N <sub>3</sub> CH <sub>3</sub> I <sup>-</sup>	4.6	-0.2
NCSCH <sub>3</sub> Cl <sup>-</sup>	1.4	0.9
NCSCH <sub>3</sub> Br <sup>-</sup>	1.7	0.7
NCSCH <sub>3</sub> I <sup>-</sup>	2.2	0.0
$\delta_Y(\log M\gamma^{DMF \pm})_{X,CR_3}$		
ClCH <sub>3</sub> Br <sup>-</sup>	...	1.4
N <sub>3</sub> CH <sub>3</sub> Br <sup>-</sup>	...	0.7
NCSCH <sub>3</sub> Br <sup>-</sup>	...	0.7
ICH <sub>3</sub> Br <sup>-</sup>	...	0.2
$\delta_Y(\log M\gamma^{DMSO \pm})_{X,CR_3}$		
ClBuI <sup>-</sup>	...	1.4
BrBuI <sup>-</sup>	...	0.7
N <sub>3</sub> BuI	...	0.7
NCSBuI <sup>-</sup>	...	0.2
Model Anion, XAgX <sup>-</sup>		
ClAgCl <sup>-</sup>	...	-0.2
BrAgBr <sup>-</sup>	...	-1.2
IaGI <sup>-</sup>	...	-2.7

<sup>a</sup> Reference 21 and Table VIII.

tinguish between entering and leaving group in the transition state, because all SN2 reactions are reversible, in principle. The results are presented in sets, as  $\delta_X(\log M\gamma^{DMF \pm})_{Y,CR_3}$  or  $\delta_Y(\log M\gamma^{DMF \pm})_{X,CR_3}$ , for transition state anions YCR<sub>3</sub>X<sup>±</sup>, where X or Y is the only variable. It can be seen that  $\delta_X(\log M\gamma^{DMF \pm})_{Y,CR_3}$  and  $\delta_Y(\log M\gamma^{DMF \pm})_{X,CR_3}$  become more negative as X or Y, respectively, become larger, more polarizable, and less able to accept hydrogen bonds from the reference solvent, methanol. This is expected (Table V) because the transition state anions, as a whole, become larger, more polarizable, and weaker hydrogen-bond acceptors with such a change. We assume that they behave like other real anions (cf. Table V). It is necessary to assume that the transition state anions in each set occupy the same position in the SN2 spectrum 3-5. Changes in "tightness" introduce another variable. This assumption may be approximately true, when X and Y are halogens or halogenoids and are attached to relatively unhindered methyl groups.

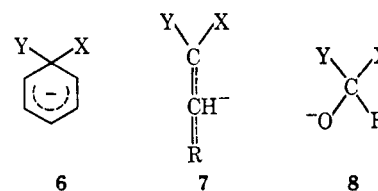
Some real anions, XAgX<sup>-</sup>, have increasingly negative value of  $\delta_X \log M\gamma^{DMF}_{XAgX^-}$  as X becomes larger, more polarizable, and a weaker hydrogen-bond acceptor (Table X). These real anions, although tighter than transition states, act as models,

which illustrate the effect that we are postulating for the hypothetical transition state solvation.

The practical significance of  $\delta_X$  and  $\delta_Y$  effects is shown in the protic-dipolar aprotic solvent effect on rate. Rates of SN2 reactions (eq 1) of alkyl chlorides are less susceptible to dipolar aprotic solvent acceleration than are the same reactions of the corresponding iodides. In everyday terms, protic solvents assist chloride ion to leave more than they assist iodide in SN2 reactions.

## 3. Substitution by Addition-Elimination

Substitutions at aryl, vinyl, and carbonyl carbon are reactions in which bond forming is completely ahead of bond breaking.<sup>24,25</sup> They are, in fact, two-step reactions, an addition to give high-energy adducts, which then eliminate the leaving group. Like Hammond,<sup>22</sup> we would expect the structure and charge distribution in the transition states for formation or decomposition of these high-energy intermediates to be very like that in the intermediates 6-8. These transition states would be tight structures, with little negative charge localized on X or Y. The solvation of such transition state anions is shown as



$\delta_{R,C}(\log M\gamma^{DMF \pm})_{Y,X}$  for two sets in Table XI. A synchronous tight SN2 transition state anion, 4 like 3, with the same X and Y groups, but which has more C-X bond breaking than has 6-8, is included, but, because the mechanism of this SN2 reaction is different, it does not rightly belong to set B.

The solvent activity coefficients are much as expected for anions 4, 6, 7, and 8, after reference to Figure 1 and Tables V and VI. The smaller transition state anions, especially those with negative charge localized on oxygen (cf. Table VI), have much more positive values of  $\delta_{R,C}(\log M\gamma^{DMF \pm})_{Y,X}$  than do the larger more polarizable transition state anions, whose charge is well dispersed. Solvation of the picrate anion is shown in Table XI, because it is regarded as a model for SNAr transition state anions.<sup>1</sup>

The important practical result to be remembered from Table XI is that rates of SN2 displacements (eq 1) at carbonyl carbon (e.g., ester hydrolysis) are very much less sensitive to dipolar aprotic solvent acceleration than are the corresponding SNAr reactions. This is because negative charge is localized on oxygen in the transition state for displacement at carbonyl carbon, making this transition state a good hydrogen-bond acceptor. Note that some of the advantage for rate enhancement, which solvation of the SNAr transition state has over the transition state for SN2 substitution at a methyl carbon, is lost (eq 6) because solvation of reactant nitrohalobenzenes tends to slow SNAr reactions in dipolar aprotic solvents more than solvation of reactant methyl chloride slows SN2 reactions.

## 4. SNAr Transition States

The solvent activity coefficients for some SNAr transition state anions throw some light on two questions.<sup>23</sup> Is bond breaking

(92) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(93) B. O. Coniglio, D. E. Giles, W. R. McDonald, and A. J. Parker, *J. Chem. Soc.*, **B**, 152 (1966).

Table XI

Solvation of Transition State Anions for SN2 Reactions at Aryl, Vinyl, Carbonyl, and a Methyl Carbon Atom. Transfer from Methanol to DMF at 25°C

Transition state $\ddagger$ <sup>b</sup>	$\frac{\delta_{R_1O}}{\log k_{DMF}/k^M}$	$\frac{\delta_{R_1C}(\log M_{\gamma}^{DMF \ddagger})_{Y,X}}{M_{\gamma}^{DMF \ddagger}}$	$\frac{\log M_{\gamma}^{DMF}}{R_1CX}$
Set A			
	3.4	-0.5	-2.0
	2.3	+1.5	...
	1.4	+2.6	-0.9
Set B			
	4.1	<-0.2	<-1
	3.2	+0.6	-1.1
	3.3	+1.2	-0.4
	...	-0.4	...

<sup>a</sup> Data from ref 21. <sup>b</sup> The intermediates are drawn, rather than transition states, but the structures of the transition states are close to this (see text). Ar is 4-nitrophenyl, R is *p*-tolyl. <sup>c</sup> The picrate anion is a real anion, not a transition state.

rate determining in SNAr reactions of thiophenoxide with aryl fluorides<sup>94-97</sup> and are SNAr reactions two-step addition-eliminations<sup>94-96</sup> or synchronous SN2-like reactions?<sup>98</sup> The generally accepted<sup>95</sup> concept of a "tight" SNAr transition state anion, in which the leaving group carries very little negative charge and bond breaking has made very little progress, is supported by the data in Table XII.

If SNAr reactions were synchronous, like SN2 reactions at saturated carbon, or if bond breaking were rate determining,<sup>97</sup> we would expect to have some negative charge localized on the leaving halogens for the SNAr transition states shown in Table XII. If this were the case, a negative charge on small fluorine would give a transition state anion which was a much better hydrogen-bond acceptor than a transition state anion with the same or less charge on iodine. Thus, for a "synchronous" or a "bond-breaking" SNAr reaction,  $\delta_{hal}(\log$

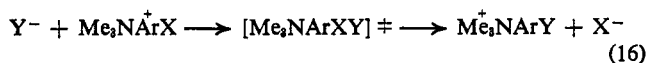
$M_{\gamma}^{DMF \ddagger})_{Ar,N_3}$  and  $\delta_{hal}(\log M_{\gamma}^{DMF \ddagger})_{Ar,SPH}$  in Table XII should be much more positive when hal is fluorine rather than iodine. The greater polarizability of iodine *vs.* fluorine merely reinforces this expected  $\delta_{hal}$  effect. The observed  $\delta_{hal}$  effect, however, is in the opposite direction to this expectation for SNAr reactions and cannot be reconciled with a synchronous process,<sup>98</sup> or with a process in which bond breaking is rate determining.<sup>95,97</sup> The two-step SNAr reaction, with bond forming as the rate-determining step, fits the observed  $\delta_{hal}(\log M_{\gamma}^{DMF \ddagger})$  values.

The values of  $\delta_{hal}(\log M_{\gamma}^{DMF \ddagger})$  for SN2 reactions at saturated carbon, which are included in Table XII, show the difference in solvent behavior of transition states for synchronous SN2 substitution *vs.* SNAr addition-elimination and highlights the mechanistic difference between the two types of reaction. If data were available for SN2 reactions of azide ion with methyl fluoride, no doubt the figures in Table XII would be even more compelling.

## B. UNCHARGED TRANSITION STATES FOR SUBSTITUTION

### 1. Anion-Cation Reactions

Protic-dipolar aprotic solvent effects on  $\delta_S \log k$  for some SN2 reactions, eq 16 and 17, of anionic nucleophiles with cations are analyzed in terms of eq 6 in Table XIII. Both reactions involve charge destruction from reactants to transition state, but the over-all charge type to products is different. The reactions of stabilized carbonium ions with anions in water, meth-



anol, DMSO, and DMF, which were studied by Ritchie, Skinner, and Badding<sup>46</sup> are addition reactions, but, from reactants to transition state, resemble eq 17. Their observations are in agreement with the following discussion.<sup>2</sup> The SNAr reaction of azide with 4-chloro-3-nitrophenyltrimethylammonium cation is faster in DMF than in methanol,<sup>21</sup> almost entirely because of transition state solvation. The large, uncharged, but highly polar and polarizable transition state is much more solvated by DMF than by methanol, as expected for such species (Table II). The reactant azide ion is much more solvated by methanol than by DMF, but this is counterbalanced by the fact that the reactant cation is much more solvated by DMF, as expected (*cf.* Table VII).

The SN2 decompositions of the trimethylsulfonium cation<sup>99,100</sup> (eq 17) are also considerably faster in dipolar aprotic than in protic solvents (Table XIII). This is largely a function of reactant anion solvation, but the rate is also enhanced by stronger solvation of the polar transition state by dipolar aprotic than by protic solvent.<sup>101</sup> The transition state for reaction (eq 17) is less polarizable than that for reaction (eq 16), hence the less negative value of  $\log M_{\gamma}^S$  in Table XIII. The  $Me_3S^+$  cation is more solvated by the dipolar aprotic solvents in Table XIII than by methanol, and this dampens the rate-enhancing effect of the former solvents.

(94) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

(95) A. J. Parker in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Oxford, England, 1961.

(96) J. F. Bunnett, *Quart. Rev.* (London), **12**, 1 (1958).

(97) J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, *J. Am. Chem. Soc.*, **79**, 385 (1957).

(98) R. E. Parker and T. O. Read, *J. Chem. Soc.*, 9 (1962).

(99) Y. Pocker and A. J. Parker, *J. Org. Chem.*, **31**, 1526 (1966).

(100) Y. C. Mac, W. A. Millen, A. J. Parker, and D. W. Watts, *Chem. Soc., B*, 525 (1967).

(101) I. P. Evans and A. J. Parker, *Tetrahedron Letters*, 163 (1966).

Table XII  
Solvation of S<sub>N</sub>Ar and S<sub>N</sub>2 Transition State Anions (Reference Solvent: Methanol at 25°)<sup>a</sup>

Transition state $\ddagger$	$\text{Log } k^{\text{DMF}}/k^{\text{M}}$	$\delta_{\text{hal}}(\text{log } M\gamma^{\text{DMF}} \ddagger)_{\text{Ar}, \text{N}_3, \text{SNAr}}^b$	$\text{Log } k^{\text{HMFT}}/k^{\text{M}}$	$\delta_{\text{hal}}(\text{log } M\gamma^{\text{HMFT}} \ddagger)_{\text{Ar}, \text{N}_3, \text{SNAr}}^b$
S <sub>N</sub> Ar Reactions				
	4.5	~-0.6	7.3	~-1
	4.2	-0.5	6.3	-0.6
$\delta_{\text{hal}}(\text{log } M\gamma^{\text{DMF}} \ddagger)_{\text{Ar}, \text{SPh}, \text{SNAr}}$				
	4.4	~-0.5	...	...
	3.6	+0.1	...	...
S <sub>N</sub> 2 Reactions				
$\text{N}_3\text{CH}_2\text{Cl}^-$	3.3	+1.2	...	...
$\text{N}_3\text{CH}_2\text{I}^-$	4.6	-0.2	...	...

<sup>a</sup> Reference 21. <sup>b</sup> Ar is 4-nitrophenyl.

Table XIII  
Solvent Effects on Anion-Cation Reactions (Eq 16 and 17) at 25°<sup>a</sup>

Reactants $\text{RX}^+ + \text{Y}^-$	$\text{Log } k^{\text{M}}$ (MeOH ref)	Solvent	$\text{Log } k^{\text{S}}/k^{\text{M}}$	$\text{Log } M\gamma^{\text{S}}_{\text{Y}^-}$	$\text{Log } M\gamma^{\text{S}}_{\text{RX}^+}$	$\text{Log } M\gamma^{\text{S}}_{\ddagger}$	$\text{Log } M\gamma^{\text{S}}_{\text{RX}^+}/M\gamma^{\text{S}}_{\ddagger}$
$4\text{-Cl-3-NO}_2\text{C}_6\text{H}_4\text{N}^+\text{Me}_3 + \text{N}_3^-$ <sup>d</sup>	-4.7°	DMF <sup>c</sup>	3.3	4.9	-4.6	-3.0	-1.6
$\text{CH}_3\text{S}^+\text{Me}_2 + \text{SCN}^-$ <sup>b,e</sup>	-7.2°	DMF <sup>c</sup>	1.2	2.7	-3.1	-1.6	-1.5
$\text{CH}_3\text{S}^+\text{Me}_2 + \text{N}_3^-$	-7.4°	DMF <sup>b</sup>	3.1	4.9	-3.1	-1.3	-1.8
		$\text{CH}_3\text{CN}^{\text{b}}$	3.7	4.7	-1.6	-0.6	-1.0
		$\text{Me}_2\text{CO}^{\text{c}}$	4.9	...	-1	...	...
		$\text{EtOH}^{\text{c}}$	1.0	Ca. 0	+1.5	+0.5	+1.0
Transition state models				$\text{Log } M\gamma^{\text{DMF}}_{\text{model}}$		$\text{Log } M\gamma^{\text{DMF}}_{\text{N}_3\text{CH}_2\text{SMe}_2 \ddagger}$	
$\text{NEt}_4^+\text{Br}^-$ <sup>f</sup>		DMF		+3.4 <sup>f</sup>		-1.3	
$\text{Me}_2\text{S} + \text{MeBr}^{\text{g}}$		DMF		-0.7 <sup>g</sup>			
$\text{Me}_2\text{C}^+\text{Br}^-$ <sup>h</sup>		DMF		+0.8			
$\text{Me}_2\text{S}^+ + \text{Br}^-$ <sup>i</sup>		DMF		+1.8			
Reactants							
$\text{CH}_3\text{S}^+\text{Me}_2 + \text{Br}^-$	$\text{Log } k^{\text{E}}$ (EtOH ref) -6.1°	Solvent	$\text{Log } k^{\text{S}}/k^{\text{E}}$	$\text{Log } E\gamma^{\text{S}}_{\text{Y}^-}$	$\text{Log } E\gamma^{\text{S}}_{\text{RX}^+}$	$\text{Log } E\gamma^{\text{S}}_{\ddagger}$	
		DMSO	0.4°	3.6	...	...	
		DMAC <sup>c</sup>	2.3°	5.9	-5.0	-1.4	
		DMF	1.8 <sup>b</sup>	4.9	-4.6	-1.5	
		$\text{CH}_2\text{NO}_2$	2.6°	4.6	-3.5	-1.5	
Transition state models							
$\text{Me}_2\text{S}^+\text{Br}^-$ <sup>f</sup>		Solvent		$\text{Log } E\gamma^{\text{DMAC}}_{\text{model}}$		$\text{Log } M\gamma^{\text{DMAC}}_{\text{BrCH}_2\text{SMe}_2 \ddagger}$	
$\text{Me}_2\text{S} + \text{MeBr}^{\text{g}}$		DMAC		+0.9		-1.4	
$\text{Me}_2\text{S}^+ + \text{Br}^-$ <sup>i</sup>		DMAC		-0.5			
$\text{Me}_2\text{CBr}^{\ddagger}$ <sup>h</sup>		DMAC		+0.9			
		DMAC		+0.2			

<sup>a</sup> Unpublished work by I. P. Evans, H. Hughes, and A. J. Parker unless stated otherwise. <sup>b</sup> Rates measured at ionic strength 0.001–0.008 M. <sup>c</sup> Rates extrapolated to infinite dilution. <sup>d</sup> Reference 21. <sup>e</sup> Reference 100. <sup>f</sup> The model is an ion pair, whose solvent activity coefficient is calculated from ion-pair association constants and  $\log \nu_{\gamma^{\text{S}}}$  for anion and cation. <sup>g</sup> The model is the product, i.e., a pair of polar molecules whose solvent activity coefficients are calculated from Henry's law constants in the two solvents. <sup>h</sup> The model is the transition state for the S<sub>N</sub>1 + E1 solvolysis of *t*-butyl bromide in DMF, DMAC, and methanol; cf. ref 102. <sup>i</sup> The model is the reactants.

Table XIV

Protic-Dipolar Aprotic Solvent Effects on Molecule-Molecule Reactions (Eq 19) (Reference Solvent: Methanol at 25°)<sup>a</sup>

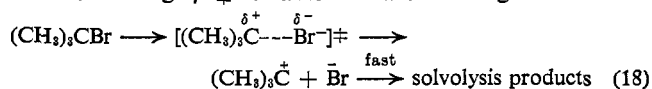
Reactants <sup>a</sup> RX + Y	Log $k^M$	Solvent <sup>a</sup>	Log $k^S/k^M$	Log $^M\gamma^S_{RX}$	Log $^M\gamma^S_Y$	Log $^M\gamma^S_{\pm}$
CH <sub>3</sub> Br + (CH <sub>3</sub> ) <sub>2</sub> S	-4.6 <sup>b</sup>	DMAC	0.5 <sup>b</sup>	-0.3 <sup>c</sup>	-0.4 <sup>d</sup>	-1.5
<i>n</i> -BuI + C <sub>6</sub> H <sub>5</sub> N <sup>e</sup>	-7.4	DMF	1.5	-0.3 <sup>e</sup>	<i>C</i> '	-1.8 + <i>C</i> '
<i>n</i> -BuBr + C <sub>6</sub> H <sub>5</sub> N	-7.4 <sup>e</sup>	DMF	0.8 <sup>e</sup>	-0.1 <sup>e</sup>	<i>C</i> '	-0.9 + <i>C</i> '
	-4.7 <sup>b</sup>	DMF	0.2 <sup>b</sup>	...	...	...
		TMS	0.5 <sup>b</sup>	...	...	...
		PC	0.3 <sup>b</sup>	...	...	...
<i>n</i> -BuCl + C <sub>6</sub> H <sub>5</sub> N <sup>e</sup>	-9.1	DMF	-0.2	-0.6 <sup>e</sup>	<i>C</i> '	-0.4 + <i>C</i> '
ArCl + C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub> <sup>h</sup>	-3.4	80DMSO-M	1.7	<-1 <sup>e,g</sup>	<0 <sup>g</sup>	<-2.8 <sup>g</sup>
Ar'F + C <sub>6</sub> H <sub>10</sub> NH <sup>i</sup>	-3.8 <sup>j</sup>	DMF	1.7 <sup>i</sup>	<-1 <sup>e,g</sup>	<0 <sup>g</sup>	<-2.7 <sup>i,g</sup>
		DMSO	2.2 <sup>i</sup>	<-1 <sup>e,g</sup>	<0 <sup>g</sup>	<-3.2 <sup>i,g</sup>

<sup>a</sup> Unless stated otherwise. <sup>b</sup> Reference 100. <sup>c</sup> Cf. Table I. <sup>d</sup> H. Hughes, unpublished work. <sup>e</sup> Rate data from ref 93, measured at 0° with reference solvent 92% v:v water-methanol. <sup>f</sup> *C* represents the unknown value of  $\log ^M\gamma^{MDF}_{C_6H_5N}$  which is probably negative. <sup>g</sup> Abbreviations: Ar is 2,4-dinitrophenyl, Ar' is 4-nitrophenyl, 80DMSO-M is 80% v:v DMSO-methanol, < means more negative than, PC is propylene carbonate, TMS is sulfolane. <sup>h</sup> Reference 111. <sup>i</sup> Reference 112. Rates measured at 50°. <sup>j</sup> Reference solvent is ethanol. <sup>k</sup> Rate data from ref 109, measured at 50° with reference solvent methanol.

The behavior of some model solutes is compared with that of the transition state for reaction (eq 17) in Table XIII. The ion pairs, <sup>+</sup>NEt<sub>4</sub>Br<sup>-</sup> and Me<sub>3</sub>S<sup>+</sup>Br<sup>-</sup>, are one model for a reactant-like transition state in which bond forming and bond making have made little progress. The  $\log ^M\gamma^{DMF}$  and  $\log ^E\gamma^{DMAC}$  values for this model are quite different from those for the transition states. The much more negative values of  $\log ^M\gamma^S_{\pm}$  and  $\log ^E\gamma^S_{\pm}$ , where S is dipolar aprotic, suggest that Y has much less negative charge localized on it in the transition state than exists in the free anion or in the ion pair. Another model is for a transition state very like products, *i.e.*, like two loosely combined polar molecules. The sum of  $\log ^0\gamma^S_{Me_3S} + \log ^0\gamma^S_{Me_3Br}$  is less negative than  $\log ^0\gamma^S_{\pm}$  for reaction (eq 17), but this model behaves more like the transition state than do any of the others. It may be that bond forming and bond breaking have made significant progress to give a polar transition state, which is more like products than reactants, for eq 17.<sup>21, 100, 101</sup>

The final model is the transition state for an assumed SN1 ionization (eq 18) of *t*-butyl bromide.<sup>14, 102, 103</sup> If the solvolyses of *t*-butyl bromide proceed through an SN1 transition state, as shown in eq 18, then the rate constants, together with  $\log ^0\gamma^S_{t-BuBr}$ , give  $\log ^0\gamma^S_{\pm}$  for this model. However, it is by no means certain that solvolyses of *t*-butyl bromide in dipolar aprotic solvents proceed as shown in eq 18; they may have an SN2 + E2 component.<sup>22, 91, 102, 103</sup>

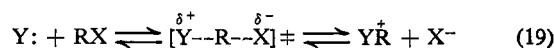
The values of  $\log ^0\gamma^S_{\pm}$  calculated for *t*-butyl bromide (SN1?) solvolysis are much more positive than those for the SN2 decomposition of trimethylsulfonium bromide and azide. Thus, if they are SN1, more negative charge is on bromine in the *t*-butyl bromide solvolysis transition state than in the SN2 transition state for decomposition of Me<sub>3</sub>SX. The solvolysis transition state responds to solvent rather differently from an ion pair or from separated ions: indeed its behavior is intermediate between that of a highly polar molecule and an ion pair. It must be remembered that if the solvolysis of *t*-butyl bromide in any of the solvents is bimolecular, then the numbers recorded for  $\log ^0\gamma^S_{\pm}$  in Table XIII are meaningless.

(102) P. O. I. Virtanen, *Suomen Kemistilehti*, **B40**, 178 (1967).

(103) A. J. Parker, unpublished work.

## 2. Molecule-Molecule Reactions

Protic-dipolar aprotic solvent effects on  $\delta_S \log k$  for SN2 reactions between polar molecules (eq 19)<sup>2</sup> are analyzed in Table XIV. The Menshutkin reaction is the most thoroughly studied reaction<sup>104-107</sup> of this type, as far as solvent effects are concerned, but the SN2 reactions<sup>99</sup> of dimethyl sulfide with



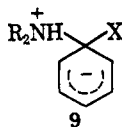
methyl bromide (back-reaction 17) are even better suited to a study of solvent and salt effects on the forward and reverse reaction (eq 19).<sup>100</sup> The forward and reverse reactions (eq 17) of course pass through the same polar uncharged transition state, which is more solvated by dipolar aprotic solvents than by protic solvent<sup>101</sup> (*cf.* Table XIII). As deduced from Table XIII solvation of this transition state, by solvents of much the same dielectric constant, is quite like solvation of reactant Me<sub>2</sub>S and CH<sub>3</sub>X in the back-reaction (eq 17), so that in general these reactions are rather insensitive to protic-dipolar aprotic solvent transfer. Effects due to reactant and transition state solvation roughly cancel for reaction (eq 19) when Y is a tertiary amine such as pyridine,<sup>108, 109</sup> triethylamine,<sup>104</sup> or a dialkyl sulfide,<sup>100</sup> as shown in Table XIV.

The  $\delta_X(\log ^M\gamma^{DMF}_{\pm})_{Y, Bu}$  values for reactions of butyl halides with pyridine, in methanol and DMF, become less negative as the leaving halide (X) changes from iodide to chloride.<sup>93</sup> The same effect was observed for reactions of azide ion with methyl halides<sup>21, 93</sup> (Table X). The explanation already given for the latter reactions applies to the former: a transition state, in which there is some bond breaking with negative charge localized on large, polarizable iodine, will have a more negative  $\log ^M\gamma^{DMF}_{\pm}$  than will a transition state with the same negative charge localized on the much smaller chlorine atom. It is assumed that  $\delta_X$  does not change the tightness of the pyridine-butyl halide SN2 transition state.

The SNAr reactions of primary and secondary amines with aryl halides have transition states which are much more sol-

(104) S. R. Palit, *J. Org. Chem.*, **12**, 752 (1947).(105) S. Popovici and M. Pop, *Compt. Rend.*, **245**, 846 (1957).(106) E. Tommila, *Acta Chem. Scand.*, **13**, 622 (1959).(107) E. F. Caldin and J. Peacock, *Trans. Faraday Soc.*, **51**, 1217 (1955).(108) N. J. T. Pickles and C. N. Hinshelwood, *J. Chem. Soc.*, 1353 (1936).(109) A. J. Parker, *ibid.*, 4398 (1961).

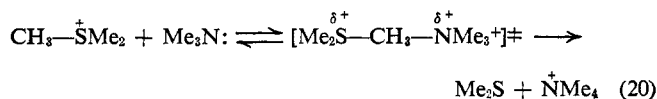
vated by DMF, DMSO, and DMSO-methanol mixtures than by ethanol or methanol (Table XIV), so they are quite susceptible to protic-dipolar aprotic rate enhancement.<sup>110-112</sup> The transition states, with these amines as reactants, as distinct from those for reactions of tertiary amines and dialkyl sulfides, are now strong hydrogen-bond donors,<sup>110,113</sup> *via* hydrogen attached to positive nitrogen, so that structures **9** are solvated



more strongly by strongly basic solvents, like DMF and DMSO (*cf.* Table I), than by methanol or ethanol. The enhanced rate of molecule-molecule reactions of this special category led Kingsbury<sup>111</sup> to the completely erroneous conclusion<sup>2</sup> that "catalysis" by DMSO and related solvents is independent of the charge that the nucleophile bears. The suggestion<sup>111</sup> that "DMSO catalysis"<sup>114</sup> involves polarization of the substrate by a random DMSO molecule, followed by rapid nucleophilic attack on this species, cannot be accepted. This type of "explanation" may be meaningful in terms of the collision theory of reaction rates but is not an explanation in terms of the thermodynamics of the absolute rate theory.<sup>2</sup>

### C. CATIONIC TRANSITION STATES FOR SUBSTITUTION

Reactions which proceed through a cationic transition state<sup>2</sup> in which positive charge is dispersed (eq 20) were first studied by Hughes and Whittingham.<sup>115</sup> The  $\delta_s \log k$  effect is a re-



atively small increase in rate from protic to dipolar aprotic solvent, as shown in Table XV, but the solvent activity coefficients for reactant cation and transition state cation are quite large and these oppose each other in rate eq 6. Precise values are not available at 60.7°, the temperature at which rates were measured,<sup>115,116</sup> but it is clear from solvent activity coefficients at 25° (Table VII) that the reactant cation is considerably more solvated by DMSO, DMAC, and nitromethane than by ethanol or methanol at 60.7°. Trimethylamine would also be more solvated by the dipolar aprotic solvents than by these protic solvents (*cf.* discussion of Table II) so that the transition state cation for reaction, eq 20, must be (eq 6) very much more solvated by the dipolar aprotic solvents than by methanol or ethanol. The value of  $\log {}^M\gamma_{\ddagger}^{\text{S}}$  (where S is dipolar aprotic) for reaction 20 is much more negative than for related cations, like  $\text{Me}_3\text{S}^+$  (Tables VII and XV). This suggests that the transition state cation is larger and much more polarizable than the trimethylsulfonium cation, as expected.

(110) S. D. Ross, *J. Am. Chem. Soc.*, **81**, 2113 (1959).

(111) C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964).

(112) H. Suhr, *Chem. Ber.*, **97**, 3277 (1964).

(113) J. F. Bunnett and J. J. Randell, *J. Am. Chem. Soc.*, **80**, 6020 (1958).

(114) E. Tommila and M. Savolainen, *Acta Chem. Scand.*, **20**, 946 (1966).

(115) E. D. Hughes and D. J. Whittingham, *J. Chem. Soc.*, 806 (1960).

(116) I. P. Evans and A. J. Parker, unpublished work.

Table XV

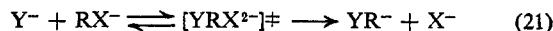
SN2 Cation-Molecule Reactions (Reference Solvent: Methanol)<sup>a,c</sup>

$\log k^{\text{M}}$ <sup>b</sup>	Solvent	$\log k^{\text{S}}/k^{\text{M}}$	$\log {}^M\gamma_{\text{Me}_3\text{S}^+}^{\text{S}}$	$\log {}^M\gamma_{\text{Me}_3\text{N}}^{\text{S}}$	$\log {}^M\gamma_{\ddagger}^{\text{S}}$
-3.67 <sup>b</sup>	H <sub>2</sub> O	-0.8 <sup>b</sup>	~-1.5	...	...
	EtOH	0.2 <sup>b</sup>	+1.5 <sup>a</sup>	~0	~-1.3
<i>Reactants</i>					
$\text{CH}_3\text{S}^+\text{Me}_2 + \text{CH}_3\text{NO}_2$		1.2 <sup>b</sup>	-2.0	<0	<-3.2
$\text{Me}_3\text{N}$	DMSO	0.8	<-3.6	<0	<-4.4
	DMAC	0.8	-3.6	<0	<-4.4

<sup>a</sup> Reference 116. Rate data at 60.7°, solvent activity coefficients at 25°. <sup>b</sup> Reference 115. <sup>c</sup> < means more negative than.

### D. TRANSITION STATE DIANIONS FOR SUBSTITUTION

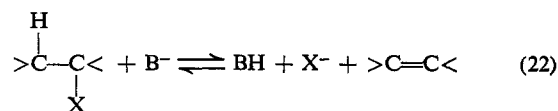
Reactions of this type are represented by eq 21. A transition state which is a dianion is a better hydrogen-bond acceptor than a comparable singly charged anion and so is much more solvated by protic than by dipolar aprotic solvents.



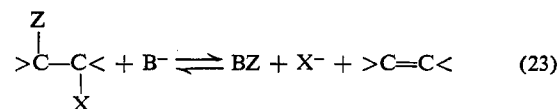
Polar-dipolar aprotic effects,  $\delta_s \log k$ , on reactions 1 and 21 are illustrated in Table XVI. The reactions (eq 21) are faster in dipolar aprotic than in protic solvents but are not as susceptible to rate enhancement as are the corresponding reactions (eq 1) of anions with polar molecules. Although  $\log {}^0\gamma_{\text{RX}^-}^{\text{S}}$  of eq 21 is more positive than  $\log {}^0\gamma_{\text{RX}^-}$  of eq 1, where 0 is protic and S is dipolar aprotic, this solvent effect on reactants is more than compensated for, in the effect on rate, by  $\log {}^0\gamma_{\ddagger}^{\text{S}}$ , which is much more positive than  $\log {}^0\gamma_{\ddagger}^{\text{S}}$ . The value of  $\delta_s \log k$ , for reactions of sodium methoxide with various carboxylate anions,<sup>21,116</sup> is rather insensitive to the position of the carboxylate group, relative to the reaction center, being much the same for *o*- and *p*-carboxylate in nitrohalobenzenes and for  $\alpha$ -carboxylate in the bromoacetate ion.

### E. ANIONIC TRANSITION STATES FOR ELIMINATION

It has been suggested that E2 reactions (eq 22) have transition states whose structures, **11**, cover a spectrum between an E2H transition state **10** and an E2C transition state **12**.<sup>117</sup> Transition states for other types of E2 reaction (eq 23), such as debromination,<sup>118</sup> may cover a similar spectrum. One E2 transi-



X = hal, OTs,  $\overset{\delta+}{\text{S}}\text{Me}_2$ , etc.



X = hal, OTs,  $\overset{\delta+}{\text{S}}\text{Me}_2$ , etc.

Z = hal

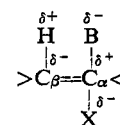
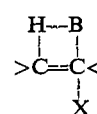
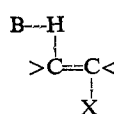
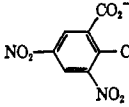
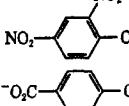
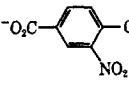
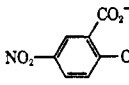


Table XVI  
Solvent Effects on Rates of Substitution Reactions between Anions (Eq 21) and between Anions and Polar Molecules (Eq 1)  
(Reference Solvent: Methanol at 25°)<sup>a</sup>

Reactants	Log $k^M$	Solvent	Log $k^S/k^M$	Log ${}^M\gamma^S_{RX}$	Log ${}^M\gamma^S_{Y^-}$	Log ${}^M\gamma^S_{\ddagger}$	Log ${}^M\gamma^S_{RX}/{}^M\gamma^S_{\ddagger}$
 + $N_3^-$	-4.6	DMF	3.3	1.2	4.9	2.8 (2-)	-1.6
 + $N_3^-$	-3.3	DMF	4.1	<-1	4.9	<-0.2 (-)	-0.8
 + $OMe^-$	-5.4	80DMSO-M	2.4	>1.5	4.0	>3.1 (2-)	-1.6
 + $OMe^-$	-6.2	80DMSO-M <sup>d</sup>	2.7	>1.5	4.0	>2.8 (2-)	-1.3
4-Cl-C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> + $OMe^-$	-6.4	80DMSO-M	3.6	-0.2	4.0	0.2 (-)	-0.4
BrCH <sub>2</sub> CO <sub>2</sub> <sup>-</sup> + $OMe^-$ <sup>b</sup>	-4.5	80DMSO-M	2.2	>3	4.0	>4.8 (2-)	-1.8
CH <sub>3</sub> I + $OMe^-$	-3.6	80DMSO-M	3.5	-0.3	4.0	+0.2 (-)	-0.5

<sup>a</sup> Reference 21, unless stated otherwise. <sup>b</sup> Reference 116. <sup>c</sup> Transition state charge is in parentheses. <sup>d</sup> 80% v:v DMSO-methanol.

Table XVII  
Solvent Effects on Rates of E2 and SN2 Reactions at 25°<sup>a</sup>

Reactants <sup>b</sup> RX + Y <sup>-</sup>	Log $k^0$		Solvent	Log $k^S/k^0$		Log ${}^0\gamma^S_{Y^-}$	Log ${}^0\gamma^S_{RX}$	Log ${}^0\gamma^S_{\ddagger}$		Log ${}^0\gamma^S_{RX}/{}^0\gamma^S_{\ddagger}$	
	E <sub>2</sub>	SN <sub>2</sub>		E <sub>2</sub>	SN <sub>2</sub>			E <sub>2</sub>	SN <sub>2</sub>	E <sub>2</sub>	SN <sub>2</sub>
(a) SN <sub>2</sub> - and E2C-Like Reactions (Reference Solvent: Methanol)											
cyclohex Br + $N_3^-$	-7.7	-6.8	DMF	2.9	2.8	4.9	0.1	2.1	2.2	-2.0	-2.1
cyclohex I + $N_3^-$	-6.7	-6.5	DMF	3.4	3.9	4.9	0.0	1.5	1.0	-1.5	-1.0
cyclohex OTs + ArS <sup>-</sup>	-2.5	-2.7	Me <sub>2</sub> CO	-0.4	-0.3	~3.0	~0	~3.4	~3.3	~-3.4	~-3.3
(b) SN <sub>2</sub> - and E2H-Like Reactions (Reference Solvent: Methanol)											
CH <sub>3</sub> Br + $OMe^-$	...	-3.8	80DMSO-M	...	3.5	4.0	0.0	...	0.5	...	-0.5
<i>i</i> -PrBr + $OMe^-$	-5.7	...	80DMSO-M	3.3	...	4.0	0.1	0.6	...	-0.5	...
(c) SN <sub>2</sub> and E2-Like Reactions (Reference Solvent: Ethanol)											
<i>n</i> -BuBr + C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	...	-2.0	DMF	...	3.7	C <sup>c</sup>	-0.2	...	-3.9 + C	...	...
cyclohex Br + C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	-4.9	-5.1	DMF	2.7	2.7	C <sup>c</sup>	-0.2	-2.9 + C	-2.9 + C	...	...
<i>t</i> -BuBr + C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	-3.6	...	DMF	1.8	...	C <sup>c</sup>	-0.4	-2.2 + C	...	...	...
(d) E2-Hal Reaction (Reference Solvent: Ethanol)											
<i>trans</i> -1,2-cyclohex Br <sub>2</sub> + C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	-4.4	...	DMF	4.4	...	C <sup>c</sup>	-0.4	-4.8 + C	...	...	...

<sup>a</sup> Data from ref 21 and 22. <sup>b</sup> Abbreviations: OTs is *p*-toluenesulfonyl, Ar is 4-nitrophenyl, cyclohex is cyclohexyl. <sup>c</sup> The constant C represents the unknown value of log  ${}^E\gamma^{DMF}_{C_6H_5S^-}$ , which is expected to be ca. + 5.

tion state is said to be more E2C-like or more E2H-like than another, according to their relative positions between **10** and **12**. The E2C transition state <sup>117-122</sup> **12** is seen as a very "loose" structure,<sup>22</sup> with charge localized on B, X, and H and a well-developed double bond between C<sub>α</sub> and C<sub>β</sub>. The E2H transition state **10** is a "tighter" structure,<sup>21,22</sup> with the double bond

less developed and with negative charge dispersed over the whole transition state anion. It is utilized by strong hydrogen bases (RO<sup>-</sup>) reacting with rather acidic compounds having relatively poor leaving groups. E2C-like reactions take place between strong carbon, but weak hydrogen bases (e.g., RS<sup>-</sup>, Cl<sup>-</sup>) and very weakly acidic compounds. The reactions are accompanied by SN<sub>2</sub> reactions, which also proceed through rather "loose" transition states, **4** like **5**. Compounds like the cycloalkyl halides and especially cycloalkyl tosylates, as well as tertiary alkyl halides, are particularly susceptible to an E2C-like mechanism in the presence of bases like chloride, acetate, and mercaptide ions. Electron-withdrawing substituents at C<sub>β</sub> increase the acidity of the substrate: this shifts the transition state to a more E2H-like structure. Many of the factors already discussed, which account for "looseness" in the SN<sub>2</sub> transition state,<sup>22,87</sup> tend to favor reaction *via* the E2C-like

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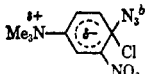
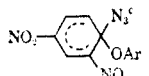
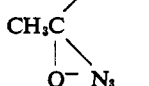
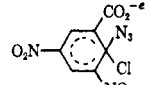
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Table XVIII  
Solvent Activity Coefficients for SN2 Transition States (Reference Solvent: Methanol at 25°)

Transition state <sup>f</sup>	Log $^M\gamma^{\text{DMF}}_{\ddagger}$	Transition state <sup>f</sup>	Log $^M\gamma^{\text{DMF}}_{\ddagger}$
$\text{Me}_2\text{SCH}_2\text{NMe}_2^{\text{a}}$ (+1)	< -4.4	$\text{N}_3\text{CH}_2\text{I}^{\text{d}}$ (-1)	-0.2
 (0)	-3.0	$\text{N}_3\text{CH}_2\text{OTs}^{\text{d}}$ (-1)	+2.3
 (-1)	-2.0	 (-1)	+2.6
$\text{N}_3\text{CH}_2\text{SMe}_2^{\text{b}}$ (0)	-1.3	 (2-)	+2.8

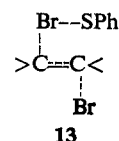
<sup>a</sup> Table XV. <sup>b</sup> Table XIII. <sup>c</sup> Table XI. Ar is 4-nitrophenyl. <sup>d</sup> Table IX. <sup>e</sup> Table XVI. <sup>f</sup> Charge on transition state is in parentheses.

mechanism. Development of positive charge and  $sp^2$  hybridization at  $C_{\alpha}$ , as in structure 5, could be matched by double bond formation to  $C_{\beta}$  and easy removal of a  $\beta$  proton, as in 12.

It must be emphasized that SN2 and E2C reactions do not<sup>121,122</sup> have a common or merged mechanism,<sup>123</sup> *i.e.*, they do not have the same transition state. Nevertheless, as shown in Table XVII,  $\log ^0\gamma^{\text{S}}_{\ddagger}$  for E2C-like reactions is much the same as  $\log ^0\gamma^{\text{S}}_{\ddagger}$  for the corresponding (*i.e.*, same reactants) SN2 reactions. The same factors which determine  $\log ^0\gamma^{\text{S}}_{\ddagger}$  for SN2 transition state anions can be considered for E2C-like transition state anions. The "loosening" effect, observed in the more positive values of  $\log ^E\gamma^{\text{DMF}}_{\ddagger}$  for elimination from *t*-butyl bromide than from cyclohexyl bromide, is consistent with a greater localization of negative charge on bromine and thiophenoxide in the reaction of the tertiary compound.<sup>22</sup> This results at least partly from steric resistance to a "tight" transition state in the tertiary compound. The leaving-group effects,  $\delta_X(\log ^M\gamma^{\text{DMF}}_{\ddagger})_{\text{Y,R,C}}$ , shown in Table XVII for E2C-like reactions could be interpreted in exactly the same way as are the values in Table X for SN2 reactions. It is worth noting that both the E2 and SN2 reactions of cyclohexyl tosylate with 4-nitrothiophenoxide<sup>21</sup> are actually *slower* in acetone than in methanol, even after allowance for greater ion association in acetone. These reactions of secondary tosylates, which proceed through extremely loose transition states, are among the few anion-molecule bimolecular reactions (eq 1) which are *not* accelerated by transfer from protic to a dipolar aprotic solvent.

The transition state anion for the E2H-like reaction of isopropyl bromide with methoxide ion<sup>21</sup> has a similar solvent activity coefficient and is thus a comparable hydrogen-bond acceptor to the very tight SN2 transition state anion,  $\text{CH}_3\text{OCH}_2\text{Br}^{\ddagger}$ . This suggests that E2H-like transition states are tighter than E2C-like transition states, for reactions of secondary alkyl halides: that is, E2H-like transition states have negative charge dispersed over several atoms. In the same way,  $\log ^E\gamma^{\text{DMF}}_{\ddagger}$  for debromination of *trans*-1,2-cyclohexyl dibromide, *via* transition state 13,<sup>22</sup> is very much more negative than the values for corresponding E2C-like dehydrobromination, or the SN2 displacement reactions of cyclohexyl bromide, which

are both loose reactions. This would suggest that this debromination proceeds through a tighter transition state, 13, with negative charge more dispersed, than do dehydrobromination (11 like 12) or substitution (4 like 5) reactions of cyclohexyl bromide. If there is a spectrum for dehalogenations, corre-



sponding to 10-12, then the debromination of *trans*-1,2-cyclohexyl dibromide with thiophenoxide ion may be a rather synchronous process, with thiophenoxide tightly bound to bromine, rather than loosely bound to carbon, in the transition state. In other words, this debromination has a transition state to the "E2Br" side of the hypothetical spectrum.

In practical terms, rates of E2hal and E2H reactions of a given substrate are very much more susceptible to dipolar aprotic solvent rate acceleration than are rates of E2C or SN2 reactions of that or closely related substrates.

## F. CONCLUSIONS

Some solvent activity coefficients for transition states of various charge types for substitution reactions of azide ion are in Table XVIII. The values were scattered through the previous tables but are gathered here to emphasize the fact that solvation of transition states could bring about a change in rate constants of more than  $10^7$  with solvent transfer. These  $\log ^0\gamma^{\text{S}}_{\ddagger}$  values, calculated from eq 6, are reasonable when compared with those for "real" solutes (Tables II and V-VII) which might be models for expected transition states. They provide an excellent means of interpreting rates and mechanism in various solvents and give confidence to those who advocate the transition state theory of reaction rates, with a transition state in equilibrium with its environment.

## IV. Displacements at Platinum

Substitution reactions at platinum (SN2Pt) are thought to be two-step addition-elimination reactions, passing through a five-coordinate unstable intermediate complex and having

bond forming as the rate-determining process.<sup>124-129</sup> As such, they are not unlike S<sub>N</sub>Ar reactions of aryl halides, but they behave very differently upon transfer from protic to dipolar aprotic solvent,<sup>2,129-134</sup> as shown in Table XIX. Four charge types of substitution at carbon and at platinum are shown in Table XIX. The S<sub>N</sub>2Pt reactions are much less sensitive to sol-

Table XIX

Solvent Effects on S<sub>N</sub>2 Displacements at Carbon and at Platinum

Reactants <sup>d</sup>	Temp. °C	—Log <i>k</i> , M <sup>-1</sup> sec <sup>-1</sup> —			
		H <sub>2</sub> O	CH <sub>3</sub> OH	DMSO	DMF
(a) Cation-Molecule					
CH <sub>3</sub> SMe <sub>2</sub> + (CH <sub>3</sub> ) <sub>3</sub> N <sup>o</sup>	60.5	-4.5	-3.7	-2.9	...
[Pt(dien)Cl] <sup>+</sup> + Tu <sup>e</sup>	30	-0.24	...	-2.7	...
(b) Cation-Anion					
CH <sub>3</sub> SMe <sub>2</sub> + N <sub>3</sub> <sup>-o</sup>	25	...	-7.4	...	-4.3
[Pt(dien)Cl] <sup>+</sup> + N <sub>3</sub> <sup>-o</sup>	30	-2.3	...	-3.0	...
(c) Molecule-Molecule					
<i>n</i> -BuBr + C <sub>6</sub> H <sub>5</sub> N <sup>f</sup>	50	...	-4.8	...	-4.6
<i>trans</i> -[Pt(pip) <sub>2</sub> Cl <sub>2</sub> ] + Tu <sup>b</sup>	25	...	+0.1	-0.3	-0.1
(d) Anion-Molecule					
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> F + N <sub>3</sub> <sup>-o</sup>	25	...	-7.2	-3.3	-2.7
CH <sub>3</sub> I + Cl <sup>-o</sup>	25	-5.5	-5.5	...	+0.4
<i>trans</i> -[Pt(pip) <sub>2</sub> Cl <sub>2</sub> ] <sup>b</sup>	25	...	-3.3	-3.0	-3.2

<sup>o</sup> Table XV. <sup>b</sup> Reference 132. <sup>e</sup> U. Belluco, R. Ettore, M. Graziani, and P. Rigo, unpublished data communicated by Dr. U. Belluco. <sup>d</sup> Abbreviations; Tu is thiourea, pip is piperidine, dien is diethylenetriamine. <sup>f</sup> Table XIII. <sup>g</sup> Table XIV. <sup>o</sup> Table VIII.

vent transfer:<sup>130-134</sup> indeed they are often slower in dipolar aprotic than in protic solvents. Until these solvent effects on rate have been split into reactant and transition state solvent activity coefficients,<sup>130</sup> discussion is premature. However, one possibility,<sup>135-137</sup> which is worth further investigation is that the S<sub>N</sub>2Pt transition state is a much stronger base than the reactant complex. It would therefore interact strongly with protic solvents, with acids, cations like lithium, or nucleophiles with acidic hydrogens, like thiourea. Such a transition state might be much more solvated by protic solvents and thus the "usual" (in carbon chemistry) rate-retarding effect of protic solvents due to strong reactant anion solvation is counteracted. It is relevant that thiourea is a very powerful nucleophile toward platinum and that in acetone HBr and LiBr, al-

though very weak electrolytes, displace chloride from *trans*-[Pt(PEt<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>] faster than does the stronger electrolyte NBu<sub>4</sub>Br at the same formal concentration.<sup>137</sup>

Table XIX warns that ideas gained from carbon chemistry cannot always be extended without modification to platinum chemistry.

## V. Reactions in Mixtures of Protic and Dipolar Aprotic Solvents

Protic-dipolar aprotic mixtures are very useful as reaction media. This is especially true when the anion (*e.g.*, OH<sup>-</sup>, F<sup>-</sup>, CN<sup>-</sup>) is so poorly solvated by the pure dipolar aprotic solvent that it is difficult to find a soluble electrolyte to act as a source of the anion. Mixtures of DMSO with water or alcohols have been particularly popular because salts like KOH, NaOMe, KHCO<sub>2</sub>, KCN, KF, and NaOAc are reasonably soluble, but their anions have high activities, relative to their activity in water, in solvents like 90% v:v DMSO-H<sub>2</sub>O or 90% v:v DMSO-MeOH. These electrolytes are only very slightly soluble in dry DMSO. Hydroxides and alkoxides in such mixtures form powerful kinetic<sup>138</sup> and thermodynamic<sup>139</sup> base systems, which have been used for proton abstraction<sup>138,140</sup> and elimination reactions.<sup>8,7,20,141</sup> Ester hydrolyses,<sup>17,48,142-144</sup> substitutions,<sup>114,145-149</sup> and oxidation of iodine by formate<sup>150</sup> have also been studied kinetically in these mixtures.<sup>7</sup> Some representative reactions are in Tables XX and XXI.

All the features already discussed, for protic to dipolar aprotic solvent transfer, are observed in slightly dampened form for transfer from protic to dipolar aprotic-protic mixture. Thus all reactions (eq 1) are faster in the mixtures than in protic solvents. Hydrolysis of esters (B<sub>A</sub>C<sub>2</sub> mechanism, *cf.* Table XI) through transition state **8**, with negative charge localized on oxygen, and of benzyl chloride (S<sub>N</sub>2 mechanism) through a very loose transition state, **4** like **5** (*cf.* Table IX), are considerably less sensitive to solvent transfer than is the S<sub>N</sub>2 hydrolysis of methyl iodide, which proceeds through a tight transition state anion, **4** like **3**. The "loosening" of S<sub>N</sub>2 transition states for reaction of substituted benzyl halides (*cf.* Table IX) with increasing electron donation by the substituted benzyl group is observed at all compositions of DMSO-methanol mixtures, as strikingly shown in Figure 2.<sup>114</sup> The "tight" and polarizable *p*-nitrobenzyl system is much more susceptible to DMSO content than is the looser *p*-methylbenzyl system. The value of δ<sub>8</sub> log *k* for oxidation of formate ion by iodine<sup>150</sup> is almost identical with that for the S<sub>N</sub>2 reaction of acetate ion with methyl iodide (*cf.* Table XX). This would be expected

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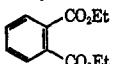
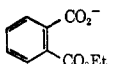
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Table XX

Solvent Effects on Rate in DMSO-Water Mixtures  
(Reference Solvent: Water at 25°)<sup>a</sup>

Reactants	Reaction	Log $k^0$	Log $k^s/k^0$
(a) Transfer to 0.698 Mole Fraction (90% v:v) of DMSO-H <sub>2</sub> O			
CH <sub>3</sub> I + OH <sup>-</sup>	SN2	-4.2 <sup>a</sup>	4.6 <sup>f</sup>
CH <sub>3</sub> I + CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	SN2	-5.6 <sup>b</sup>	3.9 <sup>b</sup>
CH <sub>3</sub> I + F <sup>-</sup>	SN2	-6 <sup>c</sup>	3.4 <sup>f</sup>
CH <sub>3</sub> I + SCN <sup>-</sup>	SN2	-3.3 <sup>b</sup>	1.1 <sup>f</sup>
<i>n</i> -BuBr + CN <sup>-</sup>	SN2	-5.3 <sup>b,f</sup>	2.6 <sup>b,f</sup>
I <sub>2</sub> + HCO <sub>2</sub> <sup>-</sup>	Oxi	-1.7 <sup>i</sup>	4.0 <sup>i</sup>
PhCH <sub>2</sub> CH <sub>2</sub> S <sup>+</sup> Me <sub>2</sub> + OH <sup>-</sup>	E2H	...	6 <sup>i</sup>
CH <sub>3</sub> CO <sub>2</sub> Et + OH <sup>-</sup>	BAC2	-2.1 <sup>c,h</sup>	2.4 <sup>c,h</sup>
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl + OH <sup>-</sup>	SN2	-3.8 <sup>i</sup>	1.9 <sup>i</sup>
(b) Transfer to 0.510 Mole Fraction (80% v:v) of DMSO-H <sub>2</sub> O			
CH <sub>3</sub> I + OH <sup>-</sup>	SN2	-4.2 <sup>a</sup>	4.0 <sup>f</sup>
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl + OH <sup>-</sup>	SN2	-3.8 <sup>i</sup>	1.2 <sup>i</sup>
CH <sub>3</sub> CO <sub>2</sub> Et + OH <sup>-</sup>	BAC2	-2.1 <sup>c,h</sup>	1.7 <sup>c,h</sup>
 + OH <sup>-</sup>	BAC2	-2.5 <sup>d,m</sup>	2.1 <sup>d,m</sup>
 + OH <sup>-</sup>	BAC2	-3.1 <sup>d,m</sup>	1.7 <sup>d,m</sup>

<sup>a</sup> Reference solvent water unless stated otherwise. <sup>b</sup> Reference solvent methanol. <sup>c</sup> Reference solvent 85% v:v ethanol-water. <sup>d</sup> Reference solvent 80% v:v ethanol-water. <sup>e</sup> Reference 147. <sup>f</sup> A. J. Parker and S. H. Tay, unpublished work. <sup>g</sup> R. H. Bathgate and E. A. Moelwyn-Hughes, *J. Chem. Soc.*, 2642 (1959). <sup>h</sup> G. C. Lalor and E. A. Moelwyn-Hughes, *ibid.*, 2201 (1965). <sup>i</sup> An oxidation of formate ion, ref 150. <sup>j</sup> Reference 20. <sup>k</sup> Reference 17. <sup>l</sup> Reference 146. <sup>m</sup> Reference 144.

if  $\delta_s \log k$  were due almost entirely to solvation of these similar reactant anions. The values in Table XX of  $\delta_s \log k$  for the anion-anion (*cf.* Table XI) BAC2 ester hydrolysis<sup>144</sup> and for the anion-cation (*cf.* Table XVII) E2H elimination<sup>20,141</sup> in mixed solvents are typical and as expected from the  $\delta_s \log k$  values already discussed for transfer of such reactions from protic to dry dipolar aprotic solvents.

The Finnish group have given some sophisticated treatments of the influence of solvent mixtures on reaction velocity.

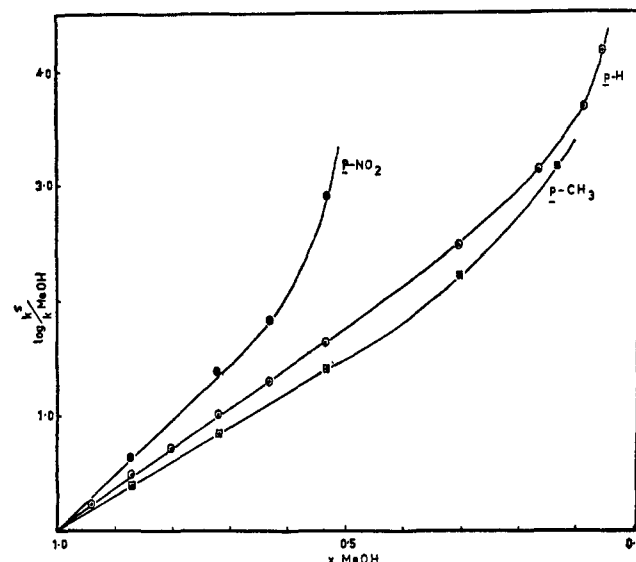


Figure 2. SN2 reactions of *para*-substituted benzyl chlorides with methoxide ion in mixtures of mole fraction,  $X$ , of methanol in DMSO at 25°. Solvent effect on rate of reactions proceeding through tight and loose transition states: data from Tommila and Savolainen.<sup>114</sup>

Papers by Murto,<sup>147</sup> Tommila and Savolainen,<sup>114</sup> Virtanen,<sup>16</sup> and Tommila and Pitkanen<sup>146</sup> are particularly relevant. They recognize that solvation of both reactants and of transition states must be considered and conclude that in DMSO-protic mixtures, of high protic content, the rate enhancement is due mainly to favorable solvation of transition states by the mixture, relative to pure protic solvent. A "catalytic" effect of DMSO, first suggested by Kingsbury<sup>111</sup> and rejected by the writer,<sup>2</sup> is also considered to be important. Tommila and Savolainen<sup>114</sup> have noted that, up to rather high DMSO concentrations, there is sufficient water or alcohol present to form adducts with DMSO and also to completely solvate the hydroxide or methoxide ions. The "rapid" increase in rate of bimolecular anion-molecule reactions when the mole fraction of DMSO in DMSO-H<sub>2</sub>O mixtures exceeds about 0.30 is seen as a result of this. Water forms 2:1 adducts and methanol

Table XXI

Analysis of  $\delta_s \log k$  in Protic-Dipolar Aprotic Mixtures at 25°

Reactants, RX + Y <sup>-</sup>	Reaction	Log $k^0$	Log $k^s/k^0$	Log ${}^0\gamma^s_{RX}$	Log ${}^0\gamma^s_{Y^-}$	Log ${}^0\gamma^s_{\ddagger}$
(a) Transfer from Methanol to 0.697 Mole Fraction of DMSO-MeOH (80% v:v) <sup>a</sup>						
CH <sub>3</sub> I + OMe <sup>-</sup>	SN2	-3.6	3.5	-0.3	4.0	0.2
CH <sub>3</sub> I + Cl <sup>-</sup>	SN2	-5.5	3.7	-0.3	4.2	0.2
CH <sub>3</sub> I + SCN <sup>-</sup>	SN2	-3.3	1.6	-0.3	1.6	-0.3
CH <sub>3</sub> Br + OMe <sup>-</sup>	SN2	-3.8	3.5	0.0	4.0	0.5
<i>i</i> -PrBr + OMe <sup>-</sup>	E2H	-5.7	3.3	0.1	4.0	0.6
4-Cl-3-NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CF <sub>3</sub> + OMe <sup>-</sup>	SNAr	-3.8	3.4	0.0	4.0	0.6
2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> Cl + OMe <sup>-</sup>	SNAr	-6.9	3.3	-0.2	4.0	0.5
4-Cl-3-NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub> SO <sub>2</sub> Me + OMe <sup>-</sup>	SNAr	-2.5	2.8	-1.4	4.0	-0.2
4-FC <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> + OMe <sup>-</sup>	SNAr	-3.7	3.3	...	4.0	...
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl + OMe <sup>-</sup> <sup>b</sup>	SN2	-4.6 <sup>b</sup>	2.5 <sup>b</sup>	0.1 <sup>a</sup>	4.0 <sup>a</sup>	1.4 <sup>a</sup>
(+)-C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> C(H)(CN)CH <sub>3</sub> + OMe <sup>c</sup>	Rac	...	4.2	...	4.0 <sup>a</sup>	<-0.2
(b) Transfer from Water to 0.321 Mole Fraction of DMSO-Water (65% v:v) <sup>d</sup>						
CH <sub>3</sub> I + N <sub>3</sub> <sup>-</sup>	SN2	-4.1	1.4	-0.7	3.7	1.6
CH <sub>3</sub> I + SCN <sup>-</sup>	SN2	-3.5	1.0	-0.7	2.4	0.7
CH <sub>3</sub> I + CN <sup>-</sup>	SN2	-3.2	1.6	-0.7	...	...

<sup>a</sup> Data from ref 21 unless stated otherwise. <sup>b</sup> Reference 114. <sup>c</sup> Reference 138; rates are for racemization *via* a carbanion. <sup>d</sup> A. J. Parker and S. H. Tay, unpublished work.

1:1 adducts with DMSO. Roberts<sup>142</sup> comes to much the same conclusion, that reactant anion desolvation does not explain the "catalytic" effect of DMSO on ester hydrolysis in aqueous DMSO: rather the effect is due to the ability of the DMSO-containing solvation shell to stabilize the transition state. Virtanen<sup>16</sup> has shown that increasing transition state solvation with increasing mole fraction of DMSO is an important factor in determining the rate of the neutral SN2 hydrolysis of methyl iodide in DMSO-water mixtures.

If we are to decide between reactant anion, reactant molecule, or transition state anion solvation or "catalysis"<sup>111</sup> as the major factor in DMSO rate enhancement, it is essential that solvent activity coefficients for all species be considered. This is done in Table XXI for some representative SN2, E2, and SNAr reactions. It is clear that reactant anion solvation is very much the major factor in determining the rate increase on transfer of reactions (eq 1) from methanol to 80% v:v DMSO-methanol (*i.e.*, 0.697 mole fraction of DMSO). The solvent activity coefficient for the benzyl chloride transition state is typical of a "loose" SN2 transition state: it is considerably more solvated by methanol than by the mixture.

Wolford<sup>48</sup> has devoted considerable attention to the "structure" of pure water, of pure DMSO, and of the mixture at mole fraction 0.33 in DMSO in his discussion of rates of acid-catalyzed acetal hydrolysis in DMSO-water mixtures. However, there does not seem to be any unique feature about the 1:2 mixture as far as  $\delta_s \log k$  is concerned.

The solvation of the reactant anion is the *only* factor which accounts for a rate increase in SN2 reactions of methyl iodide from water to the highly structured<sup>46</sup> 65% v:v DMSO-water (0.32 mole fraction of DMSO). The transition state is more solvated by water and reactant methyl iodide is less solvated by water, both of which would tend to give a slower reaction in the mixture. However, the relatively poor solvation of the reactant  $\text{N}_3^-$ ,  $\text{SCN}^-$ , or  $\text{CN}^-$  anions in the mixture is the dominant factor, so that reactions are faster than in water.

Can one assign specific numbers of molecules of the more "active" solvent component in a ternary mixture to the solvation shells of reactants and of transition states? This question, as well as that of a specific rather than a general interaction,<sup>81, 151</sup> has attracted some attention,<sup>17, 18, 81, 111, 114, 138, 152-157</sup> but there is little agreement. Rates of anion-molecule reactions (eq 1) increase continuously with increasing dipolar aprotic component of a protic-dipolar aprotic mixture.<sup>2, 138, 147, 153</sup> The behavior shown in Figure 3 is typical. A significant feature is that reactions are still accelerated markedly by small amounts of dipolar aprotic component.<sup>114, 138, 147, 152</sup>

An anion in a DMSO-water mixture must compete with DMSO and water for the hydrogen bonds donated by water.<sup>48, 153</sup> The DMSO-H<sub>2</sub>O and H<sub>2</sub>O-H<sub>2</sub>O H-bonding interactions are specific, whereas hydrogen bonding between protic solvents and anions seems to be a general interaction, involv-

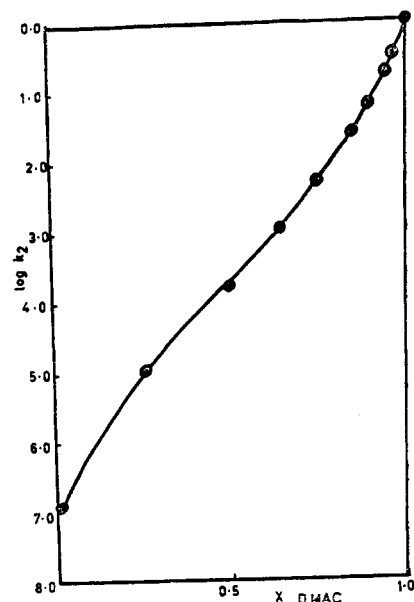
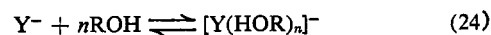


Figure 3. Relation between  $\log k$  for SN<sup>2</sup> reaction of methyl iodide with chloride ion and mole fraction,  $X$ , of DMAC in methanol at 0°. <sup>153</sup>

ing all protic molecules to varying extents. Kinetic<sup>153</sup> and spectroscopic<sup>81</sup> studies support this observation, but investigations by Kolthoff and Chantooni,<sup>155</sup> on the hydration of ions in acetonitrile, suggest on the other hand that specific 1:1 and 1:2 interactions between ions and water take place. Whatever the true situation, it seems that the effect of increasing concentration of protic component on rates in protic-dipolar aprotic mixtures cannot be simply explained<sup>114, 152, 153, 154</sup> in terms of the equilibrium (eq 24). In eq 24  $Y^-$  is an "active" reactant and  $[Y(\text{HOR})_n]^-$  is an "inactive" solvated anion, the latter containing a specific number,  $n$ , of molecules of the protic component in its solvent shell.



Different protic components at the same concentration exert a variety of rate-retarding effects, relative to the pure dipolar aprotic solvent, as shown in Table XXII for a reaction in dimethylacetamide.<sup>153</sup> Virtanen<sup>158</sup> has reported similar observations for reaction in N-methyl-2-pyrrolidone. A variety of competing interactions account for the variations in rate constant.

Table XXII

Effect of 1.0 M Protic Additives on Rates of the Reaction  $\text{Cl}^- + \text{MeI} \rightarrow \text{MeCl} + \text{I}^-$  in DMAC at 0°<sup>a</sup>

Additive	$k^s/k^0$ <sup>b</sup>	Additive	$k^s/k^0$ <sup>b</sup>
$\text{C}_6\text{H}_6$	1	$\text{C}_6\text{H}_5\text{CO}_2\text{H}$	0.051
$\text{D}_2\text{O}$	0.36	$\text{C}_6\text{H}_5\text{SH}$	0.025
$\text{H}_2\text{O}$	0.32	$\text{C}_6\text{H}_5\text{OH}$	0.011
$\text{C}_6\text{H}_5\text{NH}_2$	0.1	$4\text{-NO}_2\text{C}_6\text{H}_4\text{OH}$	0.0023
MeOH	0.052		

<sup>a</sup> Reference 153. <sup>b</sup>  $k^s$  is the rate constant in DMAC containing 1.0 M additive;  $k^0$  is the rate constant ( $9.5 \times 10^{-1} \text{ M}^{-1} \text{ sec}^{-1}$ ) in pure DMAC at 0°.

(151) N. S. Bayliss and C. J. Brackenridge, *J. Am. Chem. Soc.*, **77**, 3959 (1955).

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## VI. Reactivity in SN2 Reactions

Much useful chemistry has resulted from the application of empirical ideas about reactivity in organic reactions.<sup>13,25</sup> For example, most organic chemists can make generalizations about  $\delta \log k$  for the SN2 reaction, where the change ( $\delta$ ) is in the solvent, S, the nucleophile, Y; the leaving group, X, or substituents, R.<sup>25</sup> These generalizations are often expressed as linear free-energy relationships.<sup>88</sup> However, the variables mentioned depend on each other in such a way that generalizations about one variable sometimes have very limited application. Protic-dipolar aprotic solvent effects on rates ( $\delta_S \log k$ ), in particular, play havoc with empirical ideas about reactivity.<sup>2,93</sup> It is often impossible to find any simple relationship between behavior in dipolar aprotic solvents and in the classical solvents, such as water, alcohols, and their mixtures with "inert" solvents.

One should never attempt to allot to an observed  $\delta \log k$  effect an intrinsic (gas phase) property (*e.g.*, bond strength,  $\alpha$  effect, polarizability, size, molecular orbitals, electronegativity, hardness) of the reactants and/or transition state, until it is firmly established that the effect observed is at least qualitatively solvent independent. A convincing example is provided by the halide ions;<sup>31</sup> their nucleophilic tendencies toward saturated carbon are  $I^- > Br^- > Cl^-$  in protic solvents and  $Cl^- > Br^- > I^-$  in dipolar aprotic solvents.<sup>2,159</sup> One cannot sensibly claim that saturated carbon is "soft" in protic solvents and "hard" in dipolar aprotic solvents, and yet this is required if the hard acids-soft bases theory<sup>160-162</sup> is to be applied to this observation.

It is convenient to use the principles clearly set out by Leffler and Grunwald<sup>88</sup> when discussing the effects of variables on reactivity. Thus  $\delta_Y(\log k)_{R,C,X,S} \dots$  are the differences between some reference rate constant and the rate constants for reactions (eq 14) when all variables, other than Y, are held constant. The values are a measure of the nucleophilic tendencies of Y. Equivalent expressions can be written for changes in any other single variable. Linear free-energy relationships between rate constants arise if  $\delta(\log k)$  terms are proportional, for a change in two or more variables.

In this section we are concerned with  $\delta_S \delta_Y(\log k)_{R,C,X} \dots$ ,  $\delta_S \delta_X(\log k)_{R,C,Y} \dots$ , and  $\delta_S \delta_{R,C}(\log k)_{Y,X} \dots$  (*i.e.*, with protic-dipolar aprotic solvent effects on nucleophilic tendencies, on leaving group tendencies, and on substituent effects) for SN2 reactions (eq 14).<sup>25</sup>

### A. NUCLEOPHILIC TENDENCIES

The topic<sup>25</sup> has been reviewed in well-balanced articles by Bunnett,<sup>163</sup> Hudson,<sup>164</sup> and Pearson, Sobel, and Songstad.<sup>165</sup> Qualitative discussions of nucleophilic tendencies in the SN2 reaction abound in the literature but are confined mainly to rates measured in hydroxylic solvents and deal with intrinsic properties like polarizability, C-Y bond strength, size of Y,  $\alpha$

effects, softness of Y, and so on.<sup>163,165,166</sup> However, nucleophilic tendencies of anions and uncharged bases are very sensitive to the change from protic to dipolar aprotic solvent. Some nucleophilic tendencies are leveled, some are reversed, and some are differentiated with solvent transfer, as shown in Table XXIII. A particularly striking example is the increase of  $10^6$  in the nucleophilic tendency toward saturated carbon of acetate ion relative to thiocyanate ion, on transfer from methanol to DMF. The nucleophilic tendency toward methyl iodide of  $I^- > SCN^- \approx CN^- > N_3^- \approx Br^- > Cl^- > OAc^-$  in protic solvents<sup>165</sup> becomes  $CN^- > OAc^- > Cl^- \approx Br^- \approx N_3^- > I^- > SCN^-$  in dipolar aprotic solvents.

Nucleophilic tendencies toward methyl iodide, with thiocyanate ion as reference nucleophile, in methanol and in DMF at 25° are shown as  $\delta_Y(\log k_Y - \log k_{SCN^-})_{CH_3I} \dots$  in Table XXIII. We cannot use the Swain-Scott<sup>167</sup> equation, (25), for

Table XXIII  
Nucleophilic Tendencies for  $CH_3I + Y^- \rightarrow CH_3Y + I^-$  in Methanol and in DMF at 25°

Nucleophile, Y	$n_Y - n_{SCN^-}$ (H <sub>2</sub> O)	$\delta_Y - \log$ $k_{M_Y^-}^M / k_{M_{SCN^-}}^M$	$\delta_Y \log$ $k_{DMF}^D / k_{SCN^-}^D$
CH <sub>3</sub> OH	-5.8	-6.70	...
HCONMe <sub>2</sub>	...	...	-6.8 <sup>d</sup>
ClCH <sub>2</sub> CO <sub>2</sub> <sup>-</sup>	...	-3.4 <sup>e</sup>	+0.5 <sup>e</sup>
CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup>	-2.05	-2.4	+2.4
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> O <sup>-</sup>	...	-2.2	-0.8
Cl <sup>-</sup>	-1.73	-2.33	+1.5
Br <sup>-</sup>	-0.88	-0.91	+1.2
N <sub>3</sub> <sup>-</sup>	-0.77	-0.92	+1.6
SCN <sup>-</sup>	0.00	0.00	0.0
CN <sup>-</sup>	+0.33	0.00	+3.6
I <sup>-</sup>	+0.27	+0.7	+0.7 <sup>f</sup>
SeCN <sup>-</sup>	...	+1.15	+1.1
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> S <sup>-</sup>	...	+2.1 <sup>e</sup>	+2.3
C <sub>6</sub> H <sub>5</sub> S <sup>-</sup>	...	+3.2	+5.0 <sup>g</sup>

<sup>a</sup> Swain-Scott nucleophilic constants in water from ref 25.  
<sup>b</sup> From ref 165 unless stated otherwise. Rate data are in Table VIII.  
<sup>c</sup> From rate constants in Table VIII, unless stated otherwise.  
<sup>d</sup> Reference 31. <sup>e</sup> D. Cook, I. P. Evans, E. C. F. Ko, and A. J. Parker, *J. Chem. Soc., B*, 404 (1966). <sup>f</sup> Estimated value from a linear free-energy relationship (eq 28) using a *P* value for iodide ion of 0.  
<sup>g</sup> Value estimated from nucleophilicity toward *n*-butyl bromide in DMF (*cf.* Table VIII).

nucleophilic tendencies in the form originally intended, because it is clear that quite different nucleophilic constants, *n*, must be used for any one anion in the two solvents; *i.e.*, the solvent effect cannot be accommodated by different substrate constants, *S*. Inclusion of solvent activity coefficients for Y<sup>-</sup>

$$\log \frac{k_{Y^-}}{k_{SCN^-}} = S_n \quad (25)$$

and for thiocyanate ion, as *P* values,<sup>83</sup> does give a better, but still only approximate, linear free-energy relationship (eq 26, *cf.* Figure 4) which holds for a variety of solvent systems. In eq 26, the superscripts 0 and S denote reference and other solvent, respectively, and *S*<sup>0</sup> and *n*<sup>0</sup> are the usual Swain-Scott values<sup>167</sup> for reactions in the reference solvent (*e.g.*, methanol or water), but with thiocyanate, rather than water, as refer-

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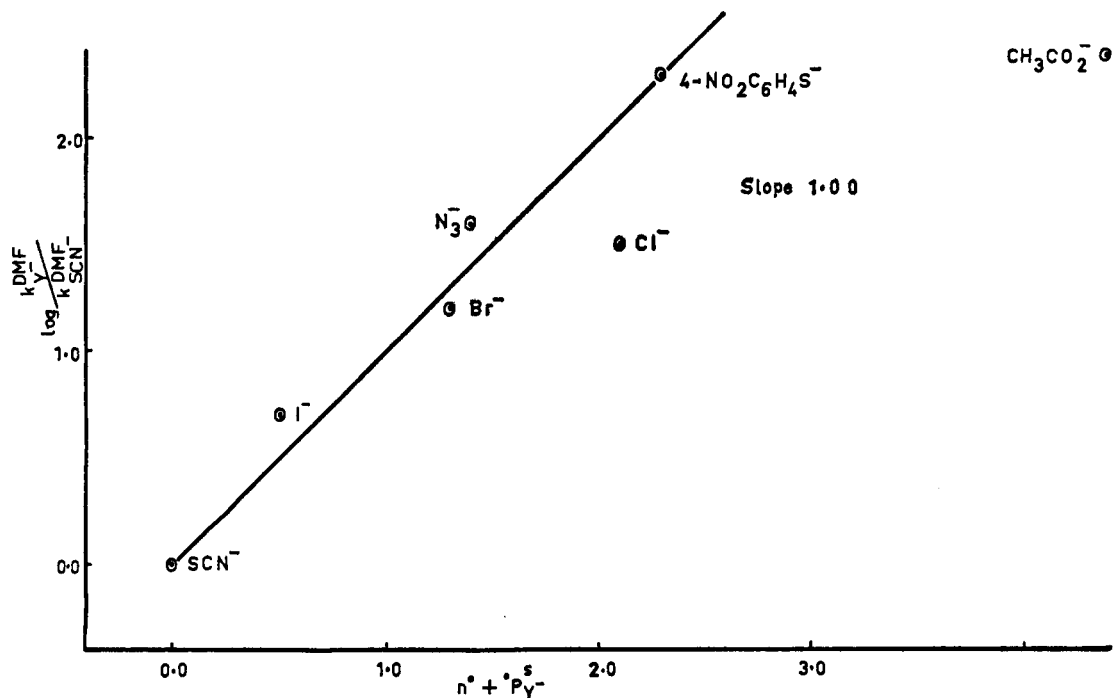
(163) J. F. Bunnett, *Ann. Rev. Phys. Chem.*, **14**, 271 (1963).

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(166) J. O. Edwards and R. G. Pearson, *ibid.*, **84**, 16 (1962).

(167) C. G. Swain and C. B. Scott, *ibid.*, **75**, 141 (1953).



**Figure 4.** Test of eq 26 for SN2 reactions of methyl iodide with anions  $Y^-$  and  $SCN^-$  in DMF at 25°. Rate constants are from Table VIII, nucleophilic constants  $n^0$  are for water and methanol as solvents from Leffler and Grunwald,<sup>38</sup> and  $^0P^S_{Y^-}$  are  $P$  values,<sup>38</sup> with thiocyanate as reference anion, for transfer of anions from methanol to DMF, calculated from data in Table V. Methyl iodide is given a substrate constant  $S^0$  of 1.00.

ence nucleophile. Equation 26 is usually valid because  $\delta_S\delta_{Y^-}$ .  $\log k$  is often due mainly to changes in  $\delta_{Y^-}(\log ^0\gamma^S_{Y^-})_{0,S^2}$ ,

$$\log \frac{k^S_{Y^-}}{k^S_{SCN^-}} = S^0 n^0 + \log \frac{{}^0\gamma^S_{Y^-}}{{}^0\gamma^S_{SCN^-}} = S^0 n^0 + {}^0P^S_{Y^-} \quad (26)$$

with only a small contribution from the solvation of transition states containing different  $Y$  groups, as already discussed (Table X). Equation 26 applies to those reactions which obey the more fundamental free-energy relationship (eq 7), which is discussed later.

## B. LEAVING GROUP TENDENCIES

The solvation of substrates,  $R_3CX$ , and of SN2 transition states,  $YCR_3X^\ddagger$ , varies according to the nature of  $X$ , as already discussed. Thus leaving group tendencies,<sup>25, 168, 169</sup>  $\delta_X$  ( $\log k$ )<sub>R,C,Y</sub> . . . , change with protic to dipolar aprotic solvent transfer.<sup>93</sup> The leaving group tendencies of the halogens, for SN2 reactions at saturated carbon, are "leveled" by methanol relative to DMF, as shown in Table XXIV. Methanol is a leveling solvent because it favors departure of the smaller more strongly bound halide ions and thus dampens their intrinsic leaving group tendencies. With esters, *e.g.*, tosylate, phosphate, as leaving group from saturated carbon, the SN2 transition states are much "looser" than those containing halide as leaving group, so that, relative to iodide ion, ester groups are encouraged to leave by methanol more than they are by DMF (*cf.* Table XXIV). Leaving group tendencies from loose transition states are very sensitive to solvent.

Leaving group tendencies for attack by different nucleophiles are very much more regular when DMF, rather than

methanol, is the solvent. Values of  $\delta_Y\delta_X(\log k)_{R,C,S}$  . . . in Table XXIV are roughly the same for each nucleophile  $Y$  in DMF. Perhaps behavior in dipolar aprotic solvents gives a better picture of intrinsic leaving group tendencies for SN2 reactions at saturated carbon, *i.e.*,  $I > Br > OTs > Cl > S^+Me_2 > OP(OMe)_2$  in DMF.

The hard acids-soft bases principle,<sup>161, 162</sup> although of some value, should not be taken too seriously when considering chemical reactivity.<sup>170</sup> Pearson and Songstad,<sup>171</sup> for instance, claim that symbiotic effects dominate leaving group tendencies in SN2 reactions of "hard" methyl tosylate and of "soft" methyl iodide with a variety of hard and soft nucleophiles. They expected that a grouping of hard nucleophile and hard leaving group, or of soft nucleophile and soft leaving group, would stabilize the SN2 transition state. Thus  $k_{OTs}/k_I$  rate ratios would be high for hard nucleophiles (*e.g.*,  $N_3^-$ ,  $OMe^-$ ,  $Cl^-$ ) and low for soft nucleophiles (*e.g.*,  $I^-$ ,  $SCN^-$ , 4-nitrothiophenoxide). This expectation was realized for the reactions which they studied in methanol as solvent. However, the "symbiotic effect," which, as an intrinsic property of the reactants, must be solvent independent, disappears when DMF is the solvent. Values of  $\log k_{OTs}/k_I$  in Table XXIV are virtually constant at  $-1.6$  for reactions of both hard and soft bases in solvent DMF.<sup>21</sup> It is necessary to probe more deeply into the data of Table XXIV, perhaps by considering tight and loose transition states as well as symbiosis.

Important clues as to the mechanism of aromatic nucleophilic substitution reactions are provided by the leaving group tendencies of the halogens in  $SNAr$  reactions (Table XXV).<sup>93</sup> Leaving group tendencies,  $\delta_Y\delta_X(\log k)_{Ar,S}$  . . . , change for different nucleophiles,  $Y$ , in the one solvent. Part of the effect

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(169) H. M. R. Hoffman, *J. Chem. Soc.*, 6753 (1965).

(170) G. Klopman, *J. Am. Chem. Soc.*, **90**, 223 (1968).

(171) R. G. Pearson and J. Songstad, *J. Org. Chem.*, **32**, 2899 (1967).

Table XXIV

Leaving Group Tendencies for  $Y + CH_3X \rightarrow CH_3Y + X$  in Methanol and DMF at 25°. <sup>a</sup> Effect of Changing Solvents,  $\delta_S \delta_X(\log k)_Y$ , and Nucleophile,  $\delta_Y \delta_X(\log k)_S$ 

Y	Solvent	$-\log k(CH_3X) - \log k(CH_3I)$ for X =					
		Cl	Br	I	OTs	S <sup>+</sup> Me <sub>2</sub>	OP(OMe) <sub>2</sub>
OMe <sup>-</sup>	MeOH	...	-0.2	0.0	+0.6 <sup>b</sup>	...	...
N <sub>3</sub> <sup>-</sup>	MeOH	-2.0	-0.2	0.0	+0.8	-3.3 <sup>c</sup>	-2.5
	DMF	-3.3	-0.9	0.0	-1.8	-4.8 <sup>c</sup>	-5.3
Cl <sup>-</sup>	MeOH	...	+0.3	0.0	+0.4	...	...
	DMF	...	-0.8	0.0	-1.7	...	...
Br <sup>-</sup>	MeOH	...	...	0.0	-0.5	-3.0 <sup>c</sup>	...
	DMF	...	...	0.0 <sup>d</sup>	-1.6	-4.4 <sup>c</sup>	...
I <sup>-</sup>	MeOH	...	-0.5	0.0	-0.9	...	...
	DMF	...	...	0.0	-1.6	...	...
SCN <sup>-</sup>	MeOH	-2.5	-0.3	0.0	-0.6	-3.9 <sup>c</sup>	...
	DMF	-3.3	-0.8	0.0	-2.0	-4.9 <sup>c</sup>	...
ArS <sup>-e</sup>	MeOH	...	...	0.0	-0.6	...	...
	DMF	...	...	0.0	-1.4	...	...
C <sub>6</sub> H <sub>5</sub> N <sup>g</sup>	MeOH	-1.6	-0.1	0.0	...	...	...
	DMF	-3.4	-0.7	0.0	...	...	...

<sup>a</sup> Data from Table VIII unless stated otherwise. <sup>b</sup> Reference 171. <sup>c</sup> Table XIII. <sup>d</sup> Log *k* for iodide exchange in DMF estimated at -0.4 from a linear free-energy relationship (eq 7). <sup>e</sup> Reaction of pyridine with *n*-butyl halides at 0° from ref 93. <sup>f</sup> *I.e.*, log *k* for reaction of Y<sup>-</sup> with CH<sub>3</sub>X - log *k* for reaction of CH<sub>3</sub>I with Y<sup>-</sup>. <sup>g</sup> Ar is 4-nitrophenyl.

Table XXV

Leaving Group Tendencies of Halogens in S<sub>N</sub>Ar Reactions in Methanol and DMF at 0°. <sup>a</sup> Effect of Changing Solvent,  $\delta_S \delta_X(\log k)_{Y,Ar,\dots}$ , and Nucleophile,  $\delta_Y \delta_X(\log k)_{S,Ar,\dots}$ 

Reactants Arhal + Y	Solvent	$-\delta_X \log k$			
		$\log k(Arhal)$ F	$\log k(ArI)$ Cl	$\log k(ArI)$ Br	$\log k(ArI)$ I
2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> hal + N <sub>3</sub> <sup>-</sup>	MeOH	...	0.3	...	0.0
	DMF	...	0.6	...	0.0
2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> hal + SCN <sup>-</sup>	MeOH	...	-1.14	0.0	0.0
	DMF	...	-0.26	0.11	0.0
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> hal + N <sub>3</sub> <sup>-</sup>	MeOH	1.83	...	...	0.0
	DMF	2.59	...	...	0.0
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> hal + PhS <sup>-</sup>	MeOH	0.35	...	...	0.0
	DMF	1.09	...	...	0.0
2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> hal + OMe <sup>-c</sup>	MeOH	3.76	0.81	0.65	0.0
2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> hal + PhS <sup>-d</sup>	MeOH	1.30	-0.12	0.11	0.0

<sup>a</sup> Reference 93. <sup>b</sup> *I.e.*, log *k* for reaction of the aryl halide - log *k* for corresponding reaction of the aryl iodide. <sup>c</sup> At 50°: A. Beckwith, J. Miller, and G. D. Leahy, *J. Chem. Soc.*, 3552 (1952), <sup>d</sup> J. F. Bunnett and W. Merritt, *J. Am. Chem. Soc.*, **79**, 5967 (1957).

observed for the "hard" methoxide and azide ions *vs.* the soft thiocyanate and thiophenoxide ions on the leaving group tendencies of fluoride or chloride, relative to iodide, could be due to symbiosis. Thus  $k_F/k_I$  or  $k_{Cl}/k_I$  is much greater for reaction of the harder nucleophiles. S<sub>N</sub>Ar transition states for halide displacement are all tight. Such an explanation was expressed earlier and in a more sophisticated way by Bunnett.<sup>96,172</sup>

Leaving group tendencies change on transfer from methanol to DMF, *i.e.*,  $\delta_S \delta_X(\log k)_{Ar,Y,\dots}$  is not zero.<sup>93</sup> There is no evidence in this solvent effect for a kinetically significant bond-breaking step in the S<sub>N</sub>Ar reactions of azide, thiocyanate, or thiophenoxide ions with aryl halides.<sup>1,95,96,97,173</sup> Indeed, S<sub>N</sub>Ar displacement of fluoride or chloride, relative to iodide, is favored by transfer from methanol to dipolar aprotic solvent. If

there were any negative change on these halides in the transition state, *i.e.*, if there were any bond breaking, methanol would be expected to solvate the smaller F<sup>-</sup> and Cl<sup>-</sup> more than I<sup>-</sup>, so that the leaving group tendency, F > I, would be greater in methanol than in DMF.<sup>93</sup> Exactly the reverse of this expectation is shown in Table XXV, so it was concluded<sup>98</sup> that there is virtually no negative charge on the leaving halogen in the S<sub>N</sub>Ar reactions shown there. The effect of solvent transfer on  $k_F/k_I$  or  $k_{Cl}/k_I$  ratios in bond-forming S<sub>N</sub>Ar reactions (Table XXV) is quite the opposite from the effect on these ratios observed for synchronous S<sub>N</sub>2 reactions at saturated carbon (Table XXIV). In the latter reactions there is of course some bond breaking in the transition state, with negative charge on the leaving halogen.

The reaction of sodium azide with 4-fluoronitrobenzene in DMF does not precipitate sodium fluoride, despite the low solubility of sodium fluoride.<sup>1</sup> This, together with some careless spectroscopic work, lead Bolton, Miller, and Parker<sup>174</sup> to a quite plausible but incorrect,<sup>103,175</sup> interpretation, *i.e.*, that this S<sub>N</sub>Ar intermediate complex was stable in dipolar aprotic solvents, because<sup>1</sup> the poorly solvated fluoride ion could not leave the well-solvated complex anion. Despite a retraction,<sup>175</sup> this work has appeared in two otherwise excellent text books.<sup>24,25</sup>

### C. SUBSTITUENT EFFECTS

The effect of substituents on rate,  $\delta_R(\log k)_{Y,X,OR_2,\dots}$ , in protic solvents should sometimes be different in dipolar aprotic solvents.<sup>21,176,177</sup> As discussed in an earlier section, transition states for S<sub>N</sub>2 reactions at saturated carbon are tighter or looser, according to the steric and electronic properties of the substituent.<sup>22</sup> Thus a 4-nitrophenyl substituent leads to a

(174) R. Bolton, J. Miller, and A. J. Parker, *Chem. Ind. (London)*, 1026 (1960).

(175) R. Bolton, J. Miller, and A. J. Parker, *ibid.*, 492 (1963).

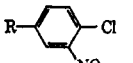
(176) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 3146 (1963).

(177) C. D. Ritchie and E. S. Lewis, *ibid.*, **84**, 591 (1962).

(172) J. F. Bunnett, *J. Am. Chem. Soc.*, **79**, 5969 (1957).

(173) A. J. Parker, Ph.D. Thesis, University of Western Australia, Nedlands, Western Australia, 1957.

Table XXVI  
Substituent Effects on SN2 and SNAr Reactions in Protic and Dipolar Aprotic Solvents at 25°<sup>a</sup>

Reactants	Solvent	$\delta_R(\log k)_{Y,X} \dots^b$					
		SN2 Reactions, $\alpha$ Substituents			$C_6H_{11}$	$t\text{-Bu}$	
		$R = n\text{-Bu}$	$i\text{-Pr}$				
RBr + PhS <sup>-</sup>	EtOH	0.0	-1.5	-3.1	-2.6 - x <sup>c</sup>		
	DMF	0.0	-2.4	-4.1	-4.5 - x		
		SN2 Reactions, $\beta$ Substituents					
		$RCH_2 = H\text{-}CH_2$	$n\text{-Pr}CH_2$	$i\text{-Pr}CH_2$	$4\text{-NO}_2C_6H_4CH_2$	$C_6H_5CH_2$	$4\text{-MeOC}_6H_4CH_2$
RCH <sub>2</sub> Br + N <sub>3</sub> <sup>-</sup>	MeOH <sup>d</sup>	-1.9	-2.7	-3.9	0.0	...	...
	EtOH <sup>a</sup>	...	...	...	0.0	-0.1	+0.9
	DMF	-1.9 <sup>d</sup>	-3.2 <sup>d</sup>	-4.5 <sup>d</sup>	0.0 <sup>a</sup>	-1.1 <sup>a</sup>	-0.7 <sup>a</sup>
		SNAr Reactions, <i>para</i> Substituents					
		$R = H$	$CO_2^-$	$CF_3$	$SO_2Me$	$+NMe_3$	
 R- <chem>c1ccc(Cl)cc1[N+](=O)[O-]</chem> + OMe <sup>-</sup>	MeOH <sup>d</sup>	0.0	1.5	3.1	4.4	4.4	
	80DMSO-M <sup>d</sup>	0.0	0.6	3.2	3.9	3.5	

<sup>a</sup> Data from ref 22 unless stated otherwise. <sup>b</sup> Rate constants recorded as  $\log k$  relative to  $\log k$  for reaction of the reference compound whose value is recorded as 0.0. <sup>c</sup> Value estimated from the E2 elimination rate and the observation that the reactions of *t*-butyl bromide in both solvents are less than 10% SN2. The fraction of SN2 reaction in SN2 + E2 processes is not significantly influenced by solvent transfer (*cf.* ref 22) so that  $x$  is the same in both solvents. <sup>d</sup> Reference 21.

much tighter transition state than does a 4-methoxyphenyl substituent for SN2 reactions of RCH<sub>2</sub>X. Rates of reactions through tight transition states respond differently from those through loose transition states, on transfer from protic to dipolar aprotic solvent (Table IX) so that a 4-nitrophenyl substituent is less activating than 4-methoxyphenyl in ethanol, but is more activating in DMF, as shown in Table XXVI. Related solvent-dependent substituent effects on rate would be expected<sup>21,22</sup> for most  $\alpha$  substituents, R, in SN2 reactions of RCH<sub>2</sub>X with anionic nucleophiles. The theoretical calculations of  $\delta_R(\log k)_{Y,X} \dots$  made by Ingold<sup>90</sup> for the effect of  $\alpha$ - and  $\beta$ -alkyl substitution in R<sub>3</sub>CBr and R<sub>3</sub>CCH<sub>2</sub>Br on the rates of SN2 bromide exchange were made on the assumption that  $\delta_R(\log k)_{Y,X}$  was solvent independent.<sup>2</sup> The calculations work remarkably well for reactions in acetone and DMF,<sup>2,90,91</sup> but Table XXVI warns that they might be less successful when compared with rates measured in protic solvents.

The solvent dependence of the effect on rate of a *para* substituent, R, in SNAr reactions of methoxide ion with 1-chloro-2-nitro-4-R-benzenes<sup>21</sup> is also shown in Table XXVI. Considering the variety of charge types chosen, the deviations from a Hammett  $\rho$   $\sigma$  relationship<sup>88</sup> are surprisingly mild. Nevertheless, the differences of  $\delta_R(\log k)_{Y,X,Ar} \dots$  on solvent transfer cannot be accommodated by changes in  $\rho$  alone. New substituent constants,  $\sigma$ , as well as a new reaction constant,  $\rho$ , are needed for reactions in the dipolar aprotic solvent, and this invalidates the Hammett linear free-energy relationship, as originally formulated.<sup>178</sup>

## VII. Entropy and Enthalpy of Activation

A decrease in enthalpy of activation, rather than an increase in entropy of activation, is the major factor for increased rates of reaction between anions and polar molecules, between anions and cations, and between two anions, on transfer from protic to dipolar aprotic solvents.<sup>2,20,21,114,146-148,150,179,180</sup>

Reactions between polar molecules show large changes in  $\delta_S\Delta H^\ddagger$  and  $\delta_S\Delta S^\ddagger$ , but the two factors compensate,<sup>2,28,109</sup> so that the effect of protic to dipolar aprotic solvent transfer on  $\delta_S\Delta G^\ddagger$  is small. The effects shown in Table XXVII seem to be characteristic. The  $\delta_S\Delta H^\ddagger$  and  $\delta_S\Delta S^\ddagger$  values are presented as dimensionless units, corresponding to  $\delta_S \log k$  for the appropriate reaction and are compared with the change in chemical potential of the reactant anion on solvent transfer. Two points emerge;  $\delta_S \log k$  is due mainly to  $\delta_S\Delta H^\ddagger$ , and  $\delta_S\Delta H^\ddagger$  corresponds roughly to  $2.303RT \log {}^0\gamma_{Y^-}$ ; *i.e.*, most of the effect of solvent on reaction rate (eq 1) is due to changes in the enthalpy of solvation of the reactant anion.<sup>21</sup> Thus values of  $\delta_S \log k$  are greater at lower temperatures, as expected for an effect associated with solvent structure and hydrogen-bonding interactions.

There has been some work on enthalpies of solvation of anions with transfer from protic to dipolar solvents.<sup>29,68,181,182</sup> In agreement with the expectation that protic-dipolar aprotic solvent effects on the solvation of anions is mainly an enthalpy effect, it has been observed<sup>21</sup> that  $\delta_S[\Delta\bar{H}(\text{NEt}_4\text{hal}) - \Delta\bar{H}(\text{NEt}_4\text{-I})]$  for transfer of the tetraethylammonium halides<sup>68</sup> is almost identical with  $\delta_S[\Delta\bar{G}(\text{Aghal}) - \Delta\bar{G}(\text{AgI})]$  for transfer of the silver halides<sup>68</sup> from water to DMSO at 25°.

Arnett and McKelvey<sup>68</sup> and Wu and Friedman<sup>29</sup> have obtained values for single ion enthalpies of transfer from water to dipolar aprotic solvents using the tetraphenylarsonium tetraphenylboride assumption. Their values seem reasonable, when compared with changes in chemical potential on solvent transfer, but it would be surprising if the methods used to split  $\log ({}^0\gamma_{S^+})$  ( ${}^0\gamma_{S^-}$ ) were generally successful when used to split  $\delta_S\Delta\bar{H}$  for solvation of electrolytes. Some of the success of the assumptions, used to split changes in chemical potential of electrolytes into individual ionic contributions, is thought to be due to the frequently observed<sup>88</sup> compensation of enthalpy and entropy effects.

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(179) J. J. Delpuech, *Tetrahedron Letters*, 2111 (1965).

(180) E. Tommila, *Acta Chem. Scand.*, 20, 923 (1966).

(181) R. P. Held and C. M. Criss, *J. Phys. Chem.*, 71, 2487 (1967).

(182) A. Finch, P. J. Gardner, and C. J. Steadman, *ibid.*, 71, 2996 (1967).

Table XXVII

Protic-Dipolar Aprotic Solvent Effects on Enthalpy and Entropy of Activation for Bimolecular Reactions at 25° (Reference Solvent: Methanol)

Reactants RX + Y	Reaction type	$\Delta H_0^\ddagger - \Delta H_8^\ddagger$ $\Delta S_0^\ddagger - \Delta S_8^\ddagger$ $\Delta G_8 - \Delta G_0^\ddagger$ (Y <sup>-</sup> )		
		$\frac{\Delta H_0^\ddagger - \Delta H_8^\ddagger}{2.303R298}$	$\frac{\Delta S_0^\ddagger - \Delta S_8^\ddagger}{2.303R}$	$\frac{\Delta G_8 - \Delta G_0^\ddagger}{2.303R298}$
To DMF = S				
CH <sub>3</sub> Cl + N <sub>3</sub> <sup>-</sup>	SN2	4.3	1.0	4.9
CH <sub>3</sub> Cl + SCN <sup>-</sup>	SN2	2.8	1.4	2.7
CH <sub>3</sub> I + SCN <sup>-</sup>	SN2	3.2	1.0	2.7
<i>n</i> -BuBr + N <sub>3</sub> <sup>-</sup> <sup>c</sup>	SN2	3.5	0.5	4.9
<i>i</i> -BuBr + N <sub>3</sub> <sup>-</sup>	SN2	3.3	0.1	4.9
<i>n</i> -BuBr + C <sub>6</sub> H <sub>5</sub> N	SN2	2.6	1.8	...
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Cl + C <sub>6</sub> H <sub>5</sub> N <sup>d</sup>	SN2	5.0	4.8	...
(CH <sub>3</sub> ) <sub>3</sub> S <sup>+</sup> + N <sub>3</sub> <sup>-</sup>	SN2	4.3	1.1	4.9
C <sub>6</sub> H <sub>11</sub> Br + N <sub>3</sub> <sup>-</sup>	SN2	3.7	0.8	4.9
C <sub>6</sub> H <sub>11</sub> Br + N <sub>3</sub> <sup>-</sup>	E2	2.8	-0.1	4.9
<i>trans</i> -TsCH=CHCl + N <sub>3</sub> <sup>-</sup> <sup>e</sup>	SN <sup>g</sup>	2.9	0.0	4.9
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> F + N <sub>3</sub> <sup>-</sup>	SNAr	3.5	-0.9	4.9
2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> I + Cl <sup>-</sup>	SNAr	6.2	-0.3	6.5
2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> Cl + SCN <sup>-</sup>	SNAr	2.2	+0.2	2.7
2-Cl-3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CO <sub>2</sub> <sup>-</sup> + N <sub>3</sub> <sup>-</sup>	SNAr	3.1	-0.2	4.9
To 80DMSO-M = S'				
2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Cl + OMe <sup>-</sup>	SNAr	2.9	-0.3	4.0
4-Cl-3-NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CO <sub>2</sub> <sup>-</sup> + OMe <sup>-</sup>	SNAr	3.3	+0.5	4.0
4-Cl-3-NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub> N <sup>+</sup> Me <sub>3</sub> + OMe <sup>-</sup>	SNAr	3.7	+1.7	4.0
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl + OMe <sup>-</sup>	SN2	3.7	+1.3	4.0
I <sub>3</sub> <sup>-</sup> + HCO <sub>2</sub> <sup>-</sup> <sup>f</sup>	...	2.9	+1.5	...

<sup>a</sup> Data from ref 21 unless stated otherwise. <sup>b</sup> This is  $\log {}^0\gamma_{S_Y}^\ddagger$  for the reaction anion, from Table V. <sup>c</sup> Reference 179. <sup>d</sup> Reference 23. <sup>e</sup> *trans*-2-(*p*-Toluenesulfonyl)-1-chloroethane; reaction is a vinyl substitution. <sup>f</sup> Solvent is 80% v:v DMSO-methanol. <sup>g</sup> Reference 150; reaction is an oxidation. Transfer is from 0.409 mole fraction to 0.800 mole fraction of DMSO-water.

### VIII. A Linear Free-Energy Relationship

Protic-dipolar aprotic solvent effects on rates of bimolecular reactions of anions can often be predicted to within  $\pm 200\%$  by a simple linear free-energy relationship<sup>21</sup> (eq 7). Only a small number of constants,  $C$ , are needed. Values of  $C$  range from  $-0.6$  to  $-3.3$ , for transfer from methanol to DMF, but do so in a manner which can be predicted from the preceding discussion of solvation of various types of transition states. When it is remembered that  $\delta_B k$  can vary by over  $10^8$ , for transfer from protic to dipolar aprotic solvent, the correlation of  $\pm 200\%$  is a satisfactory one. Equation 7 follows from eq 6 and requires that  $\log {}^0\gamma_{RX}^\ddagger / {}^0\gamma_{YRX}^\ddagger$  be roughly constant for reactions of related compounds, RX, with anions, Y<sup>-</sup>.<sup>2</sup> Variations in  $\log {}^0\gamma_{RX}^\ddagger$  and  $\log {}^0\gamma_{YRX}^\ddagger$  have been described in this review, but most of the protic-dipolar aprotic solvent effect on rate (eq 1) is due to  $\log {}^0\gamma_{Y^-}$ , so that this term dominates the right-hand side of eq 6. Suggested values of  $C$ , for transfer from methanol to DMF, are in Table XXVIII. They are estimated from values of  $\log {}^0\gamma_{RX}^\ddagger / {}^0\gamma_{YRX}^\ddagger$  recorded in Tables VIII, XIII, XVI, and XVII. They do vary, being more negative the looser the transition state, more negative for acyl substitution *vs.* alkyl substitution, and more negative for leaving groups (*e.g.*, Cl<sup>-</sup>) which are stronger hydrogen-bond acceptors, but, as stated, these variations are predictable. In fact, with experience, reasonable values of  $\log k^{\text{DMF}}$  can be estimated from  $\log k^{\text{MeOH}}$  and  $\log M_{Y^-}^{\text{DMF}}$ , using a basic  $C$  value  $-1.5$ , with minor ( $\pm 1$ ) modifications of this value, according to the type of transition state.

This linear free-energy relationship can be used to estimate rate constants in new circumstances, or to estimate values of  $\log {}^0\gamma_{Y^-}$  for use in interpreting protic-dipolar aprotic sol-

Table XXVIII

Values of  $C$  in the Linear Free-Energy Relationship  $\log k^{\text{DMF}}/k^{\text{MeOH}} = \log {}^0\gamma_{Y^-}^\ddagger + C$  for Transfer from Methanol to DMF at 25° (Eq 1)

Reactants RX	$C^a$	No. of observations <sup>b</sup>
1. Mono- and dinitrohalobenzenes, methyl iodide	$-0.4 \pm 0.4$	15 <sup>c</sup>
2. Primary RI	$-0.9 \pm 0.4$	3
3. CH <sub>3</sub> Br, primary RBr, secondary RI, <i>p</i> -nitrobenzyl bromide, Me <sub>3</sub> S <sup>+</sup> , aryl anions, aryl cations, aryl ethers, methyl chloride, and vinyl chlorides	$-1.3 \pm 0.4$	17
4a. Methyl tosylate	$-2.0 \pm 0.8$	5
4b. Secondary alkyl bromides	$-2.0 \pm 0.2$	4
5. Benzyl halides <sup>d</sup>	$-2.5$	1
6. Esters	$-3.3 \pm 0.2$	2

<sup>a</sup> Values of  $C$  are  $\log M_{Y^-}^{\text{DMF}}/M_{Y^-}^{\text{MeOH}}$  from Tables VIII, XIII, XVI, and XVII. <sup>b</sup> Total number of reactions of this type in Tables VIII, XIII, XVI, and XVII. <sup>c</sup> Reaction IIb, Table VIII, deviates considerably from  $C$ . <sup>d</sup> Those with weakly electron-withdrawing or electron-donating substituents, *i.e.*, those with loose transition states.

vent effects on acid-base equilibria,<sup>18g</sup> solubilities,<sup>6g</sup> instability constants,<sup>6g</sup> ion-pair association constants, and redox potentials.<sup>4</sup> Perhaps most usefully, comparison of  $C$  values indicates similarities or differences between transition state structures for model reactions and for reactions whose mech-

Table XXIX

Values of  $C$  in the Linear Free-Energy Relationship,  $\log k^S/k^0 = \log {}^0\gamma_{Y^-}^S + C$ , for Transfer of Representative Reactions from Methanol to Other Solvents at 25°

Reactants	$C^a$ for solvent <sup>d</sup>								
	H <sub>2</sub> O	HCONH <sub>2</sub>	DMF	DMAC	CH <sub>3</sub> CN	NMePy	CH <sub>3</sub> NO <sub>2</sub>	DMSO	TMS
	Group 1 <sup>b</sup>								
CH <sub>3</sub> I + Cl <sup>-</sup>	2.5	1.2	-0.6	-1.4	-1.7	-1.2	-0.7	...	...
CH <sub>3</sub> I + SCN <sup>-</sup>	1.0	0.8	-0.5	-0.7	-1.2	-1.2	-1.1	...	...
4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> F + N <sub>3</sub> <sup>-</sup>	...	0.6	-0.4	-1.2	-0.8	-1.0	-1.1	+0.4	-0.9
2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> I + SCN <sup>-</sup>	...	...	-1.0	-1.1	-1.0	...	-1.1	-0.2	-0.9
Mean value <sup>c</sup>	...	0.8	-0.6	-1.2	-1.1	-1.1	-1.1	0.0	-0.9
	Group 2 <sup>b</sup>								
<i>n</i> -BuBr + N <sub>3</sub> <sup>-</sup>	...	0.9	-1.5	-2.3	-1.0	...	...	-0.4	...

<sup>a</sup> Values of  $\log {}^0\gamma_{RX}^S/{}^0\gamma_{YRX}^S$  from Table VIII. <sup>b</sup> Grouping reactions of substrates as in Table XXVIII. <sup>c</sup> Mean value is that of all reactions of this group shown in Table VIII. <sup>d</sup> Abbreviations: NMePy is N-methyl-2-pyrrolidone, TMS is tetramethylene sulfone.

anism is under investigation.<sup>22,24</sup> Thus highly negative values of  $C$ , for transfer from protic to dipolar aprotic solvent, indicate that the transition state may be strong hydrogen-bond acceptor and might suggest looseness<sup>22</sup> or localization of negative charge on, for example, oxygen.<sup>21</sup> A negative value of  $C$ , which is comparable with a positive value of  $\log {}^0\gamma_{Y^-}^S$  or is more negative than  $\log {}^0\gamma_{Y^-}^S$  is positive, may indicate that the mechanism is not associative,<sup>44</sup> or that the transition state is very susceptible to electrophilic catalysis, as in displacements at platinum.<sup>2,137</sup>

The boundary between protic and dipolar aprotic solvents, in so far as they influence rates, is a sharp one. For this reason, an even more approximate linear free-energy relationship (eq 27) which correlates rate constants for S<sub>N</sub>2 and S<sub>N</sub>Ar reactions of methyl and primary alkyl iodides and of nitroaryl

$$\log k^S/k_{MeOH}^S = \log {}^M\gamma_{Y^-}^S - 0.8 \pm 0.5 \quad (27)$$

halides in methanol, DMF, DMAC, acetonitrile, N-methylpyrrolidone, nitromethane, and sulfolane is proposed. Supporting data for eq 27 come from values of  $\log {}^0\gamma_{RX}^S/{}^0\gamma_{YRX}^S$  in Table VIII. Some values of the constant for representative reactions, in a variety of solvents, are in Table XXIX. More negative values of the constant should be used for reactions of secondary alkyl halides, primary alkyl bromides, and primary alkyl chlorides, following the trends shown in Table XXVIII for transfer of reactions from methanol to DMF. Reactions in DMSO and HMPT have a constant close to zero, but the data are limited and there are anomalies. These latter solvents solvate transition states quite strongly. Reactions in

formamide have a constant of +0.8 in eq 27. A much larger sample of protic-dipolar aprotic solvent effects on rates of reaction (eq 1) than is provided by Table VIII is needed before the free-energy relationships shown in eq 7 and 27 can gain wide acceptance. However, it is an appropriate time to note that they do correlate existing information in a quite satisfactory way. The correlation is less satisfactory when the protic solvent is water, rather than formamide or the alcohols, because some nonelectrolytes show unusual behavior in water.

Another linear free-energy relationship,<sup>2</sup> which is also based on eq 6, is expressed by eq 28, in which  $\log (k^S/k^0)(Y^-)$  is the

$$\log (k^S/k^0)(Y^-) = {}^0P_{Y^-}^S + {}^1\log (k^S/k^0)(B^-) \quad (28)$$

ratio of rate constants for reaction 1 of any substrate with an anion Y<sup>-</sup> in two solvents,  $\log (k^S/k^0)(B^-)$  is for reaction of the same substrate with any reference anion B<sup>-</sup> (e.g., SCN<sup>-</sup>), and  ${}^0P_{Y^-}^S$  is given by  $\log {}^0\gamma_{Y^-}^S - \log {}^0\gamma_{B^-}^S$ . Equation 28 should be compared with the relationship<sup>2</sup> (eq 29) for transfer of acid-base equilibria<sup>183</sup> (eq 30) or of slightly soluble electrolytes<sup>63</sup> (eq 31) from protic to dipolar aprotic solvent. The equilibrium constants for eq 30 and 31 are concentration quotients.

$$\log K^0/K^S = {}^0P_{Y^-}^S \quad (29)$$

