Solvent Effects of Dipolar Substituents in Close Proximity to a Charged Reaction Centre

Allan D. Headley*
Department of Chemistry, University of the West Indies, Kingston 7, Jamaica

Regarding the unusually good solvating properties and high dielectric constant of bulk water, an exceptional case is observed in the solvation of non-specifically solvated dipolar substituents, which are in close proximity to a charged reaction centre. The basicity of dipolar substituted trimethylamines was studied in water, acetonitrile (AN), and dimethyl sulphoxide (DMSO). The lines of force between the dipole and the charged reaction centre are evidently not transmitted significantly through the high dielectric constants of bulk water, but instead a medium more like a single water molecule. The results are consistent both on steric grounds as well as the correlation of the solvent attenuation factor (SAF) with the molecular dipole moment of water.

The basicities and acidities of substituted compounds in various solvents are strongly dependent on four factors: (a) substituents;[1] (b) type and extent of substituent solvation;[2] (c) type and extent of solvation of reaction centre;[3] and (d) the molecular composition of the medium through which transverse the lines of force between dipolar substituents and the centre of charge. The importance of factor (d) is made apparent in this paper for the first time.

Consider equilibrium (1), which represents a proton-transfer

$$\text{X-Y-B} + \text{H-Y-BH}^+ \underset{K}{\rightleftharpoons} \text{X-Y-BH}^+ + \text{H-Y-B} \qquad (1)$$

reaction: X represents any substituent for which considerable solvation is possible, Y is any rigid framework, and B is the reaction centre. Any change in equilibrium (1), due solely to different substituents, X, compared with hydrogen, can be predicted from relationship (2)[4] where ρ represents the reaction

$$\delta\Delta G^\circ = \rho_R\sigma_R + \rho_F\sigma_F + \rho_\alpha\sigma_\alpha + c \qquad (2)$$

constant for resonance, field-inductive, and polarizability effects and σ is the substituent constant. In solution, depending on the solvent, solvation of a reaction centre plays a dominant role in altering the equilibrium position, compared with that in the gas phase, due to the extra stability of reacting species gained from specific and/or non-specific solvation.[5] Any change in equilibrium (1), due to solvation, can usually be predicted fairly accurately from the relationship (3)[2] where π^* is a measure of

$$\delta\Delta G^\circ = s\pi^* + a\alpha + b\beta + c \qquad (3)$$

solvent dipolarity–polarizability, which describes the ability of the solvent to stabilize a charge or a dipole by virtue of its dielectric effect, α is the hydrogen-bond donating ability (HBD) of the solvent, and β is the hydrogen bond accepting ability. The changes in equilibrium (1) brought about by the combination of substituent effect and all aspects of solvent effects become very difficult to predict.

The approach used here to help understand this complex situation is to analyse substituent effects on the basicity of substituted trimethylamines in the gas phase. A comparison of these results with those in various solvent systems will reveal any solvent effects.

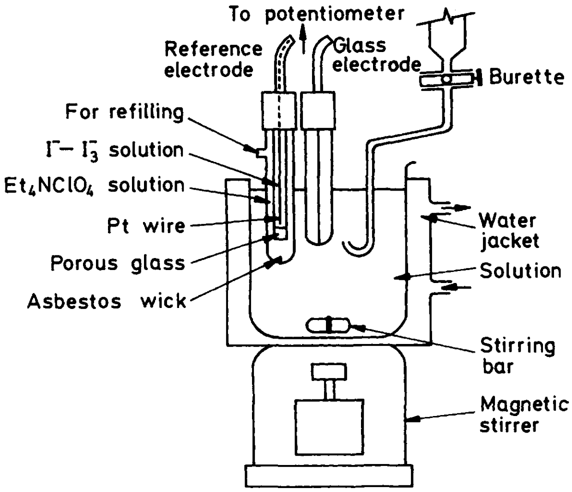


Figure 1. Equipment for potentiometric titrations.

Experimental

Acetonitrile (AN)[6] and dimethyl sulphoxide (DMSO)[7] were purified as described elsewhere.

Potentiometry.—Potentiometric titrations of acetonitrile and dimethyl sulphoxide solutions of substituted trimethylamines (*ca.* 10^{-2} mol dm^{-3}) were carried out at 25 °C in a glove box under dry nitrogen using standardized trifluoromethanesulphonic acid, which was also in acetonitrile or dimethyl sulphoxide. Constant ionic strength was maintained with (0.100 mol dm^{-3})Et_4NI in both solutions. The electrode system is shown in Figure 1. Stable readings were obtained within 1 min on a Beckman 404 pH meter.

Results

Free Energy.—The Gibbs free energies, relative to trimethylamine, were determined for reaction (4) where X represents any dipolar substituent not specifically solvated, in acetonitrile and dimethyl sulphoxide. From the neutralization of each amine by triflouromethanesulphonic acid, potentiometric curves were plotted and equilibrium constants calculated.

---

* *Present address:* Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79 409, USA.

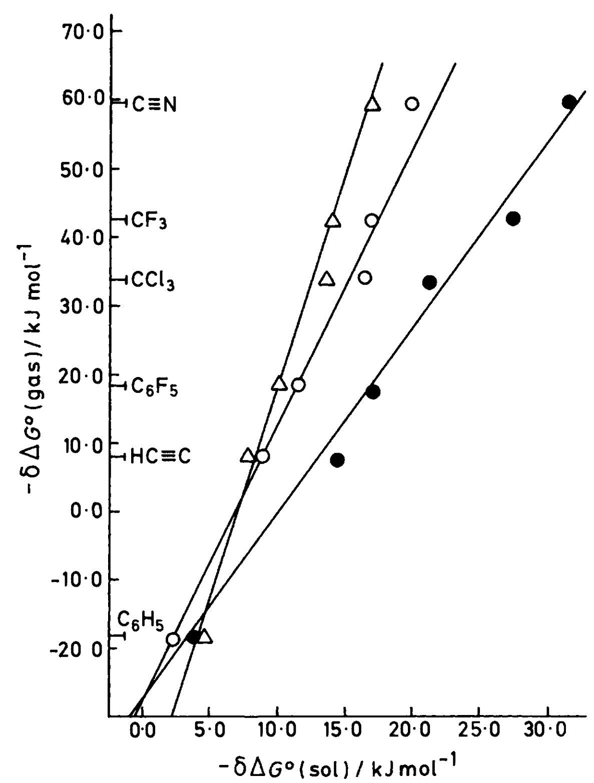


Figure 2. Relative basicities of dipolar, substituted trimethylamines: gas phase *versus* various solvents; Δ, DMSO, slope 5.8; ○, AN, slope 4.3; ●, H_2O, slope 2.7.

$$\mathrm{X\text{-}CH_2N(CH_3)_2 + (CH_3)_3NH^+ \overset{K}{\rightleftharpoons} X\text{-}CH_2N(CH_3)_2H^+ + (CH_3)_3N} \quad (4)$$

The slopes of the least square plots of the e.m.f. of the glass electrode against log (activity of BH^+/B) (where BH^+ and B represent the protonated and free amine, respectively) varied between 59.0 and 60.0 mV depending on the amine. The equilibrium constants for $B + H^+ \rightleftharpoons BH^+$ were determined from relationship (5).

$$K = [BH^+]\gamma_{BH^+}/[B]a_{H^+} \quad (5)$$

The activity of the proton was determined directly from the glass-electrode calibration curve and the activity coefficients were determined for the relationships: $-\log\gamma_i = 1.64\mu^{\frac{1}{2}}/(1 + 0.48 \times 10^{-7}a\mu^{\frac{1}{2}})$[8] for AN and $-\log\gamma_i = 1.12\mu^{\frac{1}{2}}/(1 + 3.9 \times 10^{-7}a\mu^{\frac{1}{2}})$[9] for DMSO, where μ is the ionic strength in mol dm^{-3} and a = 6 Å. It was assumed that each solution was sufficiently dilute and no substantial ion–molecule interactions occurred, thus a fairly accurate thermodynamic equilibrium constant could be determined. The changes in standard relative Gibbs free energies, shown in Table 1, were determined from the relationship: $\Delta G = -RT(\ln K)$, where all values are relative to trimethylamine. The Gibbs free energies in the gas and aqueous phases are included and the actual methods of determination are reported elsewhere.[10]

Figure 2 shows a plot of $-\delta\Delta G$(gas) *versus* $-\delta\Delta G$(sol) for water, dimethyl sulphoxide, and acetonitrile [reaction (4)]. Good correlations are observed, suggesting consistent solvation patterns in all phases. The correlations do not pass through the origin, *i.e.*, the hydrogen substituent, since various forms of solvation, available for dipolar substituents, are not possible for the hydrogen substituent. The substituent effects for reaction (4) in each phase were analysed by dual- and single-parameter $\rho\sigma$ correlations* (6)–(13).

$$\delta\Delta G(\text{gas}) = (120 \pm 2)\sigma_F + (28 \pm 1)\sigma_\alpha - 0 \pm 1 \quad (6)$$
$$n = 14, r = 0.999, \text{s.d.} = 1$$

$$\delta\Delta G(\text{aq}) = (60 \pm 3)\sigma_F + (4 \pm 3)\sigma_\alpha - 0 \pm 2 \quad (7)$$
$$n = 10, r = 0.994, \text{s.d.} = 2$$

$$\delta\Delta G(\text{AN}) = (40 \pm 3)\sigma_F - (2 \pm 3)\sigma_\alpha - 1 \pm 1 \quad (8)$$
$$n = 10, r = 0.984, \text{s.d.} = 2$$

$$\delta\Delta G(\text{DMSO}) = (30 \pm 2)\sigma_F + (1 \pm 2)\sigma_\alpha - 1 \pm 1 \quad (9)$$
$$n = 10, r = 0.985, \text{s.d.} = 2$$

$$\delta\Delta G(\text{gas}) = (119 \pm 10)\sigma_F - 16 \pm 3 \quad (10)$$
$$n = 14, r = 0.957, \text{s.d.} = 1$$

$$\delta\Delta G(\text{aq}) = (55 \pm 3)\sigma_F - 2 \pm 1 \quad (11)$$
$$n = 12, r = 0.990, \text{s.d.} = 2$$

$$\delta\Delta G(\text{AN}) = (40 \pm 3)\sigma_F - 2 \pm 1 \quad (12)$$
$$n = 10, r = 0.982, \text{s.d.} = 2$$

$$\delta\Delta G(\text{DMSO}) = (32 \pm 2)\sigma_F - 1 \pm 1 \quad (13)$$
$$n = 10, r = 0.985, \text{s.d.} = 1$$

The substituent polarizability effect is recognized as a very important contribution for many gas-phase reactions.[10] This importance is demonstrated by the fact that the excellent correlation obtained for equation (6) is totally destroyed if substituent polarizability (σ_α) is neglected as shown in equation (10). In solution this effect is very small as shown from equations (7)–(9). The single-parameter equations, considering only field-inductive effects, are still good as shown from equations (11) and (12). In this study, calculations of field-inductive attenuation factors were calculated using equations (6) and (11)–(13).

Figure 3 shows a plot of $-\delta\Delta G°$(aq) *versus* $-\delta\Delta G°$(AN) for various substituted dimethylamines; both alkyl and dipolar substituents are considered. Alkyl substituents need not necessarily be isolated from the reaction centre by a methylene unit, since the only substituent effect offered is charge-induced stabilization.[11] Good correlations are observed for both types of substituent.

Discussion

Substituent Effect.—A close examination of equations (7)–(9) shows a minor substituent polarizability effect for reaction (4) in condensed phases, where each substituent is removed from the reaction centre by a methylene unit. This observation can be justified by using equation (14) which describes the

$$\alpha = q^2/Dr^4 \quad (14)$$

interaction of a polarizable centre, α separated from a charge q by a distance r in a medium of dielectric constant D. Charge-induced stabilization is inversely related to the fourth root of the intervening distance separating a polarizable centre and a charge. In solution the charge on the ammonium ion is much less reduced, compared with the gas phase, due to specific

---

* (a) In order to minimize substituent resonance effects, the intervening methylene unit between each substituent and reaction centre is necessary. (b) Values for σ_α and σ_F are taken from ref. 10; for the C_6F_5 substituent, values used for σ_α and σ_F are −0.70 and 0.35, respectively.

Table 1. Free energies for the basicities of substituted dimethylamines in the gas phase, water, acetonitrile, and dimethyl sulphoxide (values are relative to trimethylamine).

X	$\delta\Delta G°$(gas)/kJ mol^{-1}	$\delta\Delta G°$(aq)/kJ mol^{-1}	$\delta\Delta G°$(AN)/kJ mol^{-1}	$\delta\Delta G°$(DMSO)/kJ mol^{-1}
CH_3	0.0	0.0	0.0	0.0
C_2H_5	−9.6	−2.5	−2.5	−1.3
n-C_3H_7	−12.5	−2.5	−2.9	−1.7
i-C_3H_7	−19.7	−4.2	−5.0	−2.5
t-C_4H_9	−27.2	−6.3	−6.3	−3.3
c-C_6H_{11}	−30.5	−6.7	−7.5	−3.8
t-C_5H_{11}	−33.0	−7.5	−7.9	−3.8
N≡C-CH_2	59.8	31.4	19.7	16.7
CF_3-CH_2	43.1	27.6	17.1	14.6
CCl_3-CH_2	33.9	22.6	16.3	14.2
C_6F_5-CH_2	18.4	16.7	11.3	10.0
HC≡C-CH_2	8.8	14.2	9.6	8.4
$C_6H_5CH_2$	−18.4	3.8	2.1	4.2

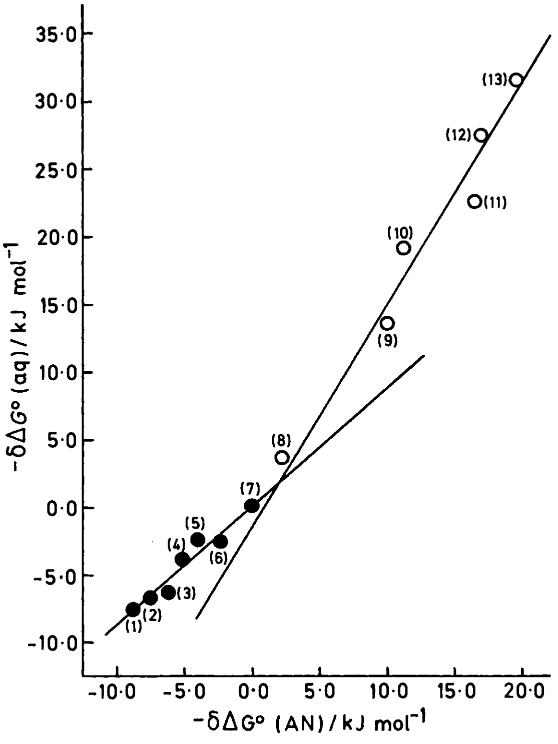


Figure 3. Relative basicities of substituted dimethylamines in the aqueous phase *versus* acetonitrile: (1) t-C_5H_{11}, (2) C_6H_{11}, (3) t-C_4H_9, (4) i-C_3H_7, (4) n-C_3H_7, (5) C_2H_5, (7) CH_3, (8) $C_6H_5CH_2$, (9) HC≡C-CH_2, (10) $C_6F_5CH_2$, (11) CCl_3CH_2, (12) CF_3CH_2, (13) N≡C-CH_2; ○, dipolar substituent, slope 1.9; ●, alkyl substituent, slope 0.9.

solvation, primarily by the hydrogen-bond accepting ability of the solvent.[12] Field-inductive substituent effects play a significant role in the equilibrium position of reaction (4) in different solvents, which is manifested by different values of σ_F. Thus, the field-inductive effect is solvent dependent.

Field-inductive attenuation factors, σ_F(gas)//σ_F(sol), are often used to measure the relative dependence of this effect on a particular reaction in various solvents relative to that in the gas phase. A value of unity suggests no alteration of this effect by the solvent. For reaction (4), attenuation factors are 4, 3, and 2 for dimethyl sulphoxide, acetonitrile, and water, respectively. The interactions of solvents with dipoles may be described in two ways: (a) solvent molecule–dipole or (b) bulk solvent–dipole interactions. These attenuation factors are directly proportional to the dipole moment of the solvent, a molecular property. The solvatochromic parameter π^* and the dielectric constant, both bulk properties, show direct relationships with these factors only for AN and DMSO, not water (Table 2).

Table 2. Various solvent parameters used in the analysis of the basicity of dipolar-substituted trimethylamines.

Solvent	FAF	SAF	ε†	μ(D)†	π^{*2}	$\beta_{(1)}$
(Gas phase)	1.0	1.0				
H_2O	2.0	2.7	78.5	1.84	1.09	0.45
AN	3.0	4.3	37.5	3.56	0.85	0.37
DMSO	4.0	5.8	46.7	3.90	1.00	0.78

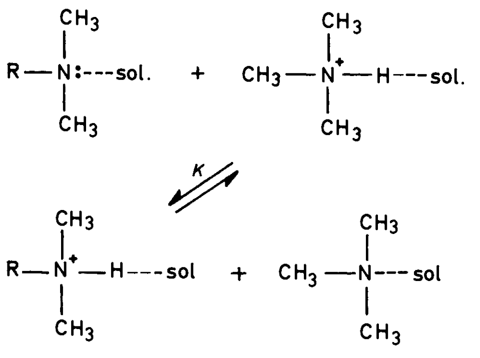
$\beta_{(1)}$ refers to solvent hydrogen-bond acceptor value. For bulk water the current accepted value is from S. G. Mills and P. Beak, *J. Org. Chem.* 1985, **50**, 1216 and personal communication from Professor R. W. Taft. † J. A. Riddisk and W. B. Binger, 'Organic Solvents,' in A. Weissberger, 'Techniques of Chemistry,' Wiley-Interscience, New York, 1970, 3rd edn., vol. III.

Field-inductive attenuation factors for the basicity of 2- and 4-substituted dipolar substituted pyridines in water are 1.8 and 2.5, respectively.[13] For dipolar substituents in the 2-position, the lines of charge–dipole interactions pass through a region of lower effective dielectric constants of the solvent. The distance separating dipolar substituents and a charged centre is directly related to the attenuation factors. This observation is consistent with the Kirkwood–Westheimer theory, which considers the effective dielectric constant of the medium between a polar substituent and a charged centre.[14] A short distance between dipolar substituents and a charged centre will result in the lowering of the effective dielectric constant of the solvent in the vicinity of the of the charge–dipole. The distance between substituents and charged centre for reaction (4) is constant in all solvents studied, therefore, changes in attenuation factors can be argued in terms of the interactions of each solvent with the substituents; for water, this interaction seems to be less intimate compared with AN and DMSO resulting in a smaller attenuation factor.

Solvent Effect.—Solvent attenuation factors (SAF), which reflect the overall solvation of reactions relative to that in the gas phase, $-\delta\Delta G$(gas)/$-\delta\Delta G$(sol), are often used to analyse solvent effects. A factor of unity suggests minimal solvation. To understand the effect of solvents on the reaction centre of reaction (4) in the absence of solvent-assisted effects, a comparison can be made with reaction (15) where R represents

$$R\text{-}N(CH_3)_2 + (CH_3)_3NH^+ \rightleftharpoons R\text{-}N(CH_3)_2H^+ + (CH_3)_3N \quad (15)$$

any alkyl substituent. Alkyl substituents are solvated only minimally.[15] Scheme 1 shows the primary mode of solvation, mainly by hydrogen bonds to the solvent.[12] Solvent attenuation factors for reaction (15) are 4.2, 4.3, and 8.5 for acetonitrile, water, and dimethyl sulphoxide, respectively. SAF for reaction (4), as seen in Figure 2, are 2.7, 4.3, and 5.8 for water, acetonitrile, and dimethyl sulphoxide, respectively. Any difference in this trend must be due to solvent effects caused by the introduction of dipolar substituents.

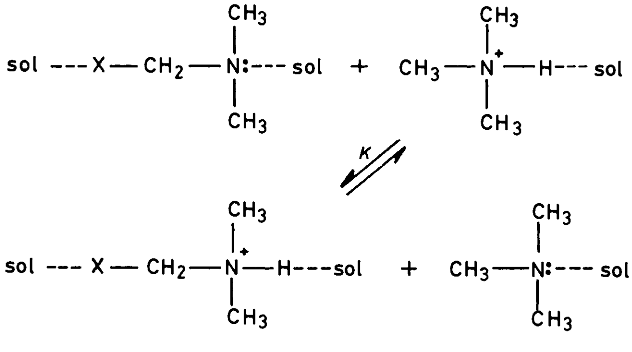


R = alkyl substituent

sol = solvent

Scheme 1.

For dipolar substituents, solvents play a dominant role, not only in controlling the reactivity at the reaction centre, but in modifying the effects of substituents.[16] Solvation of dipolar substituents may take different forms, *i.e.*, specific and/or non-specific solvation. For the acidities of dipolar substituted pyridinium ions, important contributions arise from both specific and non-specific solvation.[17] Scheme 2 shows the solvation pattern of reaction 4. Type E solvation,[18] which involves negligible specific substituent solvation but appreciable specific functional-group and differential-substituent dipole solvation best describes the observed solvation pattern.



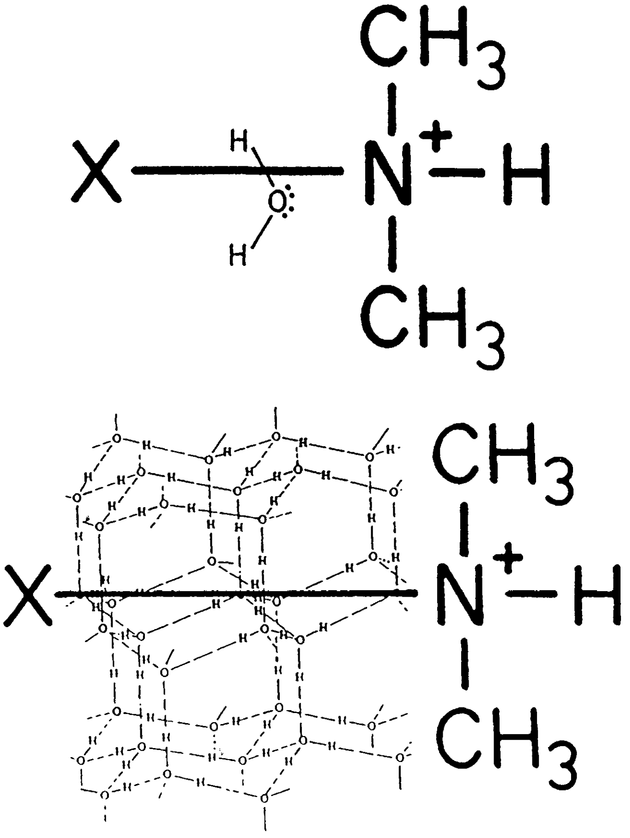
X = dipolar substituent

sol = solvent

Scheme 2.

Figure 3 shows the different solvation trends for reactions (4) and (15). Water solvates the alkylammonium ion better than acetonitrile, *i.e.*, slope less than unity, whereas, for the dipolar substituted dimethylammonium ion (where substituents are X–CH_2) solvation by water is less, *i.e.*, slope greater than unity. This observation is not surprising since aromatic ammonium ions are considerably stronger acids in acetonitrile than would be predicted from the acidities of aliphatic ammonium ions. The explanation offered is that there is an increased solvation of aromatic ammonium ions in acetonitrile.[19]

Solvent attenuation factors, like field-inductive attenuation factors, are related to the distance between dipolar substituents and a charged reaction centre. Aqueous SAF for the basicity of $CF_3(CH_2)_nNH_2$ are 1.91, 2.4, and 2.78 for n = 1, 2, and 3, respectively.[20] The implication is that as the distance between dipolar substituents and the charged reaction centre increases, solvation by water also increases. Thus, the prediction that water is a good solvating solvent, as indicated by its bulk properties such as dielectric constant and π^*, seems to apply to situations where dipolar substituents and a charged reaction centre are separated by long distances. At short distances bulk water cannot gain adequate access between the lines of force of the dipoles and the charge centre for effective solvation (Scheme 3).



Scheme 3. Aqueous solvation of a dipolar substituted dimethylammonium ion with substituent at different distances from the charged centre.

Evaluation of the solvation properties of water is best performed, in this case, at the molecular level. The dipole moment, which measures the internal charge separation of molecules, is important in evaluating how the solvent molecule clusters around a solute particle that itself has a dipole.[21] Solvents with large dipole moments play a significant role in the acidities of alcohols.[22] In water, even though it seems to cluster closer to ions than other solvents, the non-specific interactions really depend on the dipole moment.[23] Aqueous solvation of dipolar substituents in close proximity to a charged reaction centre occurs primarily by individual water molecules. Compared with bulk water, individual water molecules can be better accommodated between the lines of force created by dipoles and a charged centre.

References

1 L. P. Hammett, 'Physical Organic Chemistry,' McGraw–Hill, New York, 1940.

2 M. Mishima, R. T. McIver, Jr., and R. W. Taft, *J. Am. Chem. Soc.*, 1984, **106**, 2717.

3 R. W. Taft, J. L. M. Abboud, M. J. Kamlet, and M. H. Abrahams, *J. Solution. Chem.*, 1985, **14**, 153.

4 R. W. Taft, J. L. M. Abboud, F. Anvia, M. Berthelot, M. Fujio, J-F. Gal, A. D. Headley, W. G. Henderson, I. Koppel, J. H. Qian, M. Mishima, M. Taagepera, and S. Ueji, *J. Am. Chem. Soc.*, 1988, **110**, 1797.

5 R. W. Taft, *Prog. Org. Chem.*, 1983, **14**, 247.

6 I. M. Kolthoff, S. Bruckenstein, and M. K. Chartooni, *J. Am. Chem. Soc.*, 1961, **83**, 3927.

7 F. G. Bordwell, *J. Am. Chem. Soc.*, 1973, **97**, 7006.

8 J. F. Coetzee, *Prog. Phys. Org. Chem.*, 1967, **4**, 45.

9 I. M. Kolthoff, M. K. Chantooni, Jr., and S. Bhowmik, *J. Am. Chem. Soc.*, 1968, **90**, 23.

10 A. D. Headley, *J. Am. Chem. Soc.*, 1987, **109**, 2347.

11 (*a*) N. C. Stutchbury and D. L. Cooper, *J. Chem. Phys.*, 1983, **79**, 4967; (*b*) F. G. Bordwell, G. E. Drucker, and G. J. McCollum, *J. Org. Chem.*, 1976, **41**, 2786.

12 A. D. Headley, *J. Org. Chem.*, 1988, **53**, 312.

13 R. W. Taft and R. D. Topsom, *Prog. Phys. Org. Chem.*, 1987, **16**, 1.

14 (*a*) F. H. Kirkwood and J. G. Westheimer, *J. Chem. Phys.*, 1938, **6**, 506; (*b*) J. G. Westheimer and F. H. Kirkwood, *ibid.*, p. 513.

15 R. W. Taft, D. Gurka, L. Joris, P. v. R. Schlajer, and J. W. Rakshys, *J. Am. Chem. Soc.*, 1969, **91**, 4801.

16 M. Mishima, R. T. McIver, Jr., R. W. Taft, F. G. Bordwell, and W. N. Olmstead, *J. Am. Chem. Soc.*, 1984, **106**, 2717.

17 (*a*) E. M. Arnett, B. Chawla, L. Bell, M. Taagepera, W. J. Hehre, and R. W. Taft, *J. Am. Chem. Soc.*, 1977, **99**, 5729; (*b*) W. R. Davidson, J. Sunner, and P. Kebarle, *ibid.*, 1979, **101**, 1675.

18 R. W. Taft, *Prog. Phys. Org. Chem.*, 1983, **14**, 247.

19 J. F. Coetzee and G. R. Padmanabhan, *J. Am. Chem. Soc.*, 1965, **87**, 5005.

20 R. W. Taft, 'Proton Transfer Reactions,' eds. E. Caldi and V. Gold, Chapman and Hall, London, 1975, p. 31.

21 T. H. Lowry and K. S. Richardson, 'Mechanism and Theory in Organic Chemistry,' Harper and Row, New York, 1981, 2nd edn.

22 J. F. Coetzee and C. D. Ritchie, 'Solute Solvent Internactions,' Marcel Dekker, New York, 1976, vol. 2, p. 240.

23 R. Yamdagni and P. Kebarle, *J. Am. Chem. Soc.*, 1972, **94**, 2940.

Received 7*th March* 1988; *Paper* 8/00920A