

THE INFLUENCE OF SOLVENTS ON THE BASICITY OF DIPOLAR AMINES

ALLAN D. HEADLEY* AND MIKE E. McMURRY

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, U.S.A.

The relative basicities of six monosubstituted dipolar trimethylamines (XCH_2NMe_2) were determined in nine different solvents from potentiometric titration. Solvation effects on basicity variations were analyzed by the solvatochromic parameters (π^* , α and β). Non-specific solvation of the substituted dimethylammonium ions is not reflected adequately by the solvent's dipolarity-polarizability constant, π^* . A better representation of non-specific interaction between solvents and the monosubstituted dipolar trimethylammonium ions is gained from the product of π^* and the solvent dipole moment (μ). For these ions where the dipolar substituents are separated from the reaction center by one methylene unit, there is an interaction between the charge of the ammonium ion and the dipolar substituent. As a result, solvent molecules must not only solvate the dipolar substituents, but must also gain access between the lines of force of the dipolar substituent and the charge. Bulky solvents, such as nitrobenzene, cannot access adequately the region between the dipolar substituents and the reaction center to accomplish similar solvation as less bulky solvents.

INTRODUCTION

For over a century, the effects that solvents have on reaction rates and equilibria have concerned chemists.¹ A large percentage of organic reactions are performed in non-aqueous media, and the prediction of the reactivities in such media requires a knowledge of possible interactions between solvents and solutes. Unfortunately, most analyses of the reactivity of compounds in different solvents are based on our knowledge of the effects that water, which itself is poorly understood, has on the reactivities of a limited range of organic compounds. Solvents play a dominant role, not only in controlling the reactivity of compounds, but also in modifying the effects that substituents have on their reactivity.² For example, the acidities of dipolar pyridinium ions depend on important contributions from specific and non-specific solvation of both reaction center and substituents.³ Solvents affect reactions by any combination of (a) solvation of substituents and (b) solvation of reaction center.⁴ For any species involved in a reaction, there is the possibility of specific solvation, which involves the formation of hydrogen bonds between solvent and solute molecules, and/or non-specific solvation, which involves electrostatic interaction between a charged (or dipolar) solute and solvent molecules. For the acidities of phenols in an aqueous medium, the interaction of strong hydrogen bond

acceptor substituents with solvents increases the strength of the acids, whereas interactions of strong hydrogen bond donor substituents with solvent molecules decrease the strengths of the acids.⁵ The difference in acid strengths is caused by the modifications of substituent field-inductive and resonance effects which are brought about by solvation of the substituents.⁶ Similar observations have been made in dimethyl sulfoxide.²

Over the years, different parameters have been developed to quantify the interactions between solutes and solvents. Recently, the focus has been on the determination of parameters which describe non-specific interactions.⁷ However, most of these parameters are for molecules that have one functionality and only a few parameters exist for difunctional molecules. α -Amino acids are very important difunctional molecules that have both functionalities in close proximity to each other and the extent of zwitterion formation and factors that influence its formation are of extreme importance to biological chemistry. Knowledge of the factors that affect the ionization of such compounds is necessary in order to interpret correctly structure-activity relationships such as dissolution rates of absorption.⁸ The tautomeric equilibrium that governs the formation of zwitterions of amino acids is dependent on the medium.⁹ In the gas phase, amino acids are known to exist as neutral molecules,¹⁰ whereas glycine

* Author for correspondence.

and other soluble amino acids exist as zwitterions in aqueous solution and in the solid crystalline state.¹¹ For glycine, different solvents are known to alter the magnitude of the tautomeric equilibrium.¹² An increase in the mole fraction of methanol in water favors the neutral form of glycine. For other amino acids, similar observations have been made for alcohol-water mixtures.¹³ Compared with amino acids, the effects that solvents have on the magnitude of the tautomeric equilibrium of α -(*N,N*-diethylamino)acetic acid are more pronounced.¹⁴ In dimethyl sulfoxide, a substantial amount of the neutral α -(*N,N*-dimethylamino)acetic acid exists; the neutral to zwitterionic ratio is 31 : 69.¹⁵ Hence the ability to predict quantitatively the solvation effects on such compounds that have dipolar groups in close proximity to each other is of extreme importance to chemistry.

We shall demonstrate in this paper that a unique non-specific solvation mode of $XCH_2NMe_2H^+$ ions exists, and for the basicity of the conjugate base, a significant role is played by this solvation mode. Owing to the interaction of dipolar substituents with the charge of the ammonium ion, the solvatochromic parameter, π^* , which is used to describe similar effects of alkylammonium ions,¹⁶ does not represent adequately the non-specific solvation of these ions.

EXPERIMENTAL

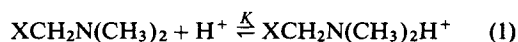
Spectrophotometric-grade solvents were purchased from Aldrich Chemical and were stored over Molecular Sieves (4A) before being used. The procedure for the potentiometric titration for the determination of equilibrium constants for the basicity of amines can be found elsewhere.¹⁷

RESULTS AND DISCUSSION

Basicity of dipolar amines

Table 1 shows the relative free energy changes for the

basicity of various monosubstituted dipolar trimethylamines [reaction (1)] in different solvents and the gas phase.



For each solvent, the values differ and to account for the relative basicity variations of these, and similar dipolar amines, it is necessary to know why the equilibrium position differs in different solvents. Solvent attenuation factors (*SAF*) are often used to analyze solvation effects on reactions.¹⁸ *SAF* for the basicity of amines in this study are determined from the slopes for plots of the relative gas-phase basicities, $\delta \Delta G(\text{gas})$, and solution-phase basicities, $\delta \Delta G(\text{sol})$. Since the concentrations of solutions for the basicity determinations were the same and the titrations were carried out with the same acid, trifluoromethanesulfonic acid, basicity variations should arise primarily from structural differences of the bases, and the difference in the relative basicity in the gas phase compared with that in solution should be caused mainly by solvation effects. Even though ion pairing is possible for the conjugate acid of these amines, this effect on basicity variations should be small since the solvents used (Table 1) are polar.¹⁹ As a result, *SAF* should reflect fairly well the solvation effects on the relative basicity of these amines compared with that in the gas phase. For the basicity of the amines shown in Table 1, *SAF* are shown in Table 2 along with the standard deviations and the correlation coefficients (*r*) for their determinations. Large slopes are observed when there is effective solvation of solutes, whereas slopes close to unity are obtained when there is minimal solvation of the equilibrium species. The correlation coefficients of *SAF* are close to unity for equilibria in which the solvation modes of the equilibrium species are similar. Hence the types of specific and non-specific solvation modes are similar. However, for a particular series of solutes, the demand of solvation may vary depending on the solvating ability of the solvent and different magnitudes of *SAF*. On the other hand, as the relationship breaks down, i.e. poor stan-

Table 1. Relative free energy changes (kcal mol⁻¹) for the basicity of various monosubstituted dipolar trimethylamines [XCH₂N(CH₃)₂] in various solvents measured at 298 K^a

X	Gas ^b	Aq	MeOH	EtOH	2-PrOH	EG	DMSO	TEP	AN	NB
NC	14.3	7.5	9.0	9.2	10.5	7.0	4.0	5.4	4.7	10.0
CCl ₃	8.1	5.5	5.5	6.5	7.3	4.9	3.4	3.9	3.9	9.8
C ₆ F ₅	4.4	4.0	4.7	4.9	5.8	3.6	2.4	3.2	2.7	4.8
HC≡C	2.1	3.4	2.8	3.8	5.1	2.5	2.0	3.1	2.3	4.2
H ₂ C=CH	-1.9	1.3	2.1	1.1	1.9	1.0	1.4	1.1	1.2	1.0
C ₆ H ₅	-4.4	0.8	1.0	1.2	0.6	0.6	1.0	1.1	0.5	2.2

^a Values are relative to (CH₃)₃N and are within ± 0.1 kcal mol⁻¹. Aq, water; MeOH, methanol; EtOH, ethanol; 2-PrOH, propan-2-ol; EG, ethylene glycol; DMSO, dimethyl sulfoxide; TEP, triethyl phosphate; AN, acetonitrile; NB, nitrobenzene.

^b Ref. 18.

Table 2. Various solvatochromic parameters,⁴ dipole moments²⁰ and solvent attenuation factors (*SAF*) for the basicity of dipolar substituted amines shown in Table 1

Solvent ^a	μ	π^*	$\mu\pi^*$	α	β	<i>SAF</i>	<i>r</i>
Gas	—	-1.10	—	0.00	0.00	1.0	—
Aq	1.84	1.09	2.01	1.10	0.47	2.7 ± 0.2	0.996
MeOH	2.87	0.60	1.72	0.93	0.66	2.3 ± 0.1	0.987
EtOH	1.66	0.54	0.90	0.83	0.75	2.2 ± 0.1	0.991
2-PrOH	1.68	0.46	0.77	0.78	0.90	1.9 ± 0.2	0.980
EG	2.28	0.92	2.10	0.92	0.52	2.8 ± 0.2	0.997
DMSO	3.90	1.00	3.90	0.00	0.76	5.8 ± 0.4	0.991
TEP	3.12	0.72	2.25	0.00	0.77	4.0 ± 0.4	0.980
AN	3.56	0.75	2.67	0.19	0.40	4.3 ± 0.3	0.990
NB	3.99	1.01	4.03	0.00	0.39	—	0.931

^a Aq, water; MeOH, methanol; EtOH, ethanol; 2-PrOH, propan-2-ol; EG, ethylene glycol; DMSO, dimethyl sulfoxide; TEP, triethyl phosphate; AN, acetonitrile; NB, nitrobenzene.

standard deviations and low correlation coefficients, there is the possibility of different or additional solvation modes. Note that the standard deviations are small and the correlation coefficients are close to unity for the determination of *SAF* (except for nitrobenzene, which will be discussed later). Hence similar modes of solvation exist for the equilibrium species shown in reaction (1).

The substituents used in this study (see Table 1) have no acidic or basic sites and the possibility of specific substituent solvation is unlikely. However, owing to the polar nature of these substituents, non-specific substituent solvation will occur. The dimethylamino and the dimethylammonium ion functionalities [reaction (1)] have basic and acidic sites, respectively, and substantial specific and non-specific solvations exist in this region of these molecules. Solvation of species of this type is best described by type E solvation,⁶ which involves negligible specific substituent solvation but appreciable specific functional group and differential-substituent dipole solvation.

To gain a better insight into the extent and effects that solvents have on reaction rates and equilibria, the solvatochromic parameters are often used.²¹ Equation (2) shows the multi-linear regression (MLR) equation of the *SAF* shown in Table 2 and the solvent's dipolarity-polarizability (π^*), hydrogen bond acidity (α) and hydrogen bond basicity (β) constants. Nitrobenzene was not used for this MLR correlation equation.

$$SAF = (2.3 \pm 0.3)\pi^* - (2.5 \pm 0.3)\alpha - (0.6 \pm 0.7)\beta + 3.4 \pm 0.4 \quad (2)$$

$$n = 9; r = 0.976; \text{s.d.} = 0.4$$

The importance of particular solvent properties is reflected by the magnitude and sign of the coefficients of the equation; a large negative value suggests that there is solvation of reactant(s) whereas a small positive value implies minimal solvation of the product(s). From equation (2), the solvent's dipolarity-polarizability and acidity properties have the largest coefficients and hence play the most important roles in the equilibrium position of reaction (1). To rationalize the magnitudes of the coefficients, the solvation of each species involved in reaction (1) must be considered. Solvation of the proton can be neglected²² since its solvation is common to all reactions studied. Therefore, the influence of the solvents on the neutral dipolar amine and the charged dipolar dimethylammonium ion must be analyzed. The conjugate acid of each dipolar amine is charged and a strong electrostatic interaction between a polar solvent and the ion will exist. On the other hand, owing to the unshared pair of electrons on the neutral amine, the solvent will interact with the neutral amine via specific solvation. The contribution of basic solvents to basicity variations is of no statistical significance; the MLR correlation equation in which this parameter was omitted showed no improvement. Interestingly, basic solvents play a very important role in the prediction of the relative basicity of alkyl-substituted dimethylamines.¹⁷ The presence of alkyl substituents of dimethylamines provides an additional driving force for the formation of the dimethylammonium ion, and its solvation is favored by basic solvents. However, dipolar substituents have the opposite effect on the basicity of the amines in this study. Owing to the electronegative nature of the dipolar substituents, the formation of the conjugate acids is not favored and this concentration will be relatively small in all solvents.

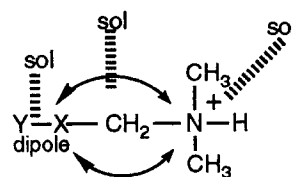
Proximity effect

Our first indication that the distance between a polar substituent and a charged center of solutes plays a role in the type of solvation experienced by solutes comes from the ratio of $\delta \Delta G(\text{gas})/\delta \Delta G(\text{water})$ for the basicity of $\text{CF}_3(\text{CH}_2)_n\text{NH}_2$.²³ The magnitude of this ratio is 1.91 for $n = 1$ compared with 2.78 for $n = 3$. These results indicate that the distance between the dipolar substituent and the charged ammonium ion end of the ion plays an important role in the solvation of the ammonium ion. As the distance decreases, so does the solvation of the ammonium ion. One consequence of dipolar group being close to a charged center is that there will be a mutual interaction between them and this interaction will influence the type and extent of solute solvation. The possibility of such an interaction was recently demonstrated:²⁴ for the basicity of alkanolamines in water there is an interaction, by delocalization, between the nitrogen and oxygen atoms across one methylene unit. For the basicity of the substituted dipolar trimethylamines in this study, where the polar substituents are separated from the dimethylammonium ion by one methylene unit, a similar interaction is expected.

In a previous paper,¹⁴ importance of the molecular composition of the medium in the region of a solute which has a charge and a dipolar substituent separated by one methylene unit was made apparent. It was shown that bulk solvent properties, such as dielectric constant (ϵ) or solvatochromic dipolarity–polarizability parameter (π^*), do not reflect adequately the non-specific solute–solvent interactions of such solutes. For the basicity of the substituted dipolar trimethylamines in this study, note that the relationship between $\delta \Delta G(\text{gas})$ and $\delta \Delta G(\text{sol})$ in nitrobenzene is poor (see Table 1). One major difference between nitrobenzene and the other solvents in this study is that nitrobenzene is a very bulky solvent. As a result, nitrobenzene cannot access adequately the region between the dipolar substituent and the charged end of the ion to accomplish a similar solvation as the other solvents. Scheme 1 shows our proposed model for the non-specific solvation of monosubstituted dipolar trimethylammonium ions where the dipolar substituents are close to the ammonium ion.

One major observation that can be made from equation (2) is that the correlation coefficient has room for improvement.²⁵ A lack of an excellent correlation for such MLR correlation equations usually means that the independent variables used, here the solvatochromic parameters, do not describe adequately all solute–solvent interactions. The solvatochromic parameter, π^* which is used to describe the non-specific solvation in equation (2), does not describe adequately the solute–solvent interactions of some very complex molecular solvent–solute interactions.²⁶ Since the correla-

tion coefficient for a similar MLR equation for the basicity of alkyl-substituted dimethylamines, in which the conjugate acids have only one charged region on the ion, is excellent,⁸ π^* may not reflect the non-specific solvation of systems where charges are very close to each other. From Scheme 1, one mode of solvation involves an intimate interaction of solvent molecules around the dipolar end, X–Y, of the ion. A solvent's dipole moment (μ) reflects how well solvent molecules are oriented around a dipole, hence the dipole moment of the solvent should play an important role in the description of the solvation of the dipolar dimethylammonium ions. However, the correlation coefficient of equation (2) is not improved if μ substituted for π^* . Based on the model in Scheme 1, the ideal description



Scheme 1. Non-specific solvation of a dipole, X–Y, and a charged ammonium ion separated by a methylene unit

of non-specific solvation should involve a combination of both solvation properties. As a result, the product of the dipole moment and dipolarity–polarizability was used to describe the non-specific solvation effect on this system. The evaluation of solvent properties by such an electrostatic factor is not uncommon, an electrostatic factor (EF),²⁷ the product of the dipole moment and dielectric constant, has been used to categorize solvents in terms of the various types of non-specific interactions. Equation (3) shows the correlation equation in which this non-specific solvation property ($\mu\pi^*$), along with the other solvatochromic parameters, α and β , is used. This equation shows improvements of the correlation coefficient and the standard deviation over equation (2).

$$SAF = (1.1 \pm 0.1)\mu\pi^* - (0.9 \pm 0.2)\alpha - (0.7 \pm 0.3)\beta + 1.1 \pm 0.2 \quad (3)$$

$$n = 9; r = 0.992; \text{s.d.} = 0.2$$

Unfortunately, no quantitative information regarding the various requirements from the solvents for reaction (1) can be gained from this improved equation, since the $\mu\pi^*$ parameter used in equation (3) is not on the same scale as the other solvatochromic parameters. However, compared with equation (2), equation (3) describes much better the solvation effects of systems where a charged center and a dipolar substituent are in close proximity to each other and thus the prediction of

the basicity of such system in different media with a higher degree of accuracy is possible.

ACKNOWLEDGMENT

We are pleased to acknowledge support from grant from the National Science Foundation (RII-9019759).

REFERENCES

1. J. Shorter, *Correlation Analysis of Organic Reactivity*, Research Studies Press, New York (1982).
2. M. Mishima, R. T. McIver, Jr, R. W. Taft, F. G. Bordwell and W. N. Olmstead, *J. Am. Chem. Soc.* **106**, 2717 (1984).
3. (a) E. M. Arnett, B. Chawla, L. Bell, M. Taagepera, W. J. Hehre and R. W. Taft, *J. Am. Chem. Soc.* **99**, 5729 (1977); (b) W. R. Davidson, J. Sunner, P. Kebarle, *J. Am. Chem. Soc.* **101**, 1675 (1979).
4. R. W. Taft, J.-M. L. Abboud, M. J. Kamlet and M. H. Abraham, *J. Solut. Chem.* **14**, 153 (1985).
5. M. Fujio, R. T. McIver, Jr, and R. W. Taft, *J. Am. Chem. Soc.* **103**, 4017 (1981).
6. R. W. Taft, *Prog. Phys. Org. Chem.* **14**, 305 (1983).
7. (a) J. Li, Y. Zhang, A. J. Dallas and P. W. Carr, *J. Chromatogr.* **550**, 101 (1991); (b) M. H. Abraham, G. S. Whiting, R. M. Doherty and W. J. Shuely, *J. Chromatogr.* **587**, 213 (1991).
8. A. Albert, *Selective Toxicity. The Physico-Chemical Basis of Therapy*, 7th ed. Chapman and Hall London (1985).
9. G. M. Borrow, *J. Am. Chem. Soc.* **80**, 86 (1958).
10. G. Gorman, J. P. Speir, C. A. Turner and I. J. Amster, *J. Am. Chem. Soc.* **114**, 3986 (1992).
11. (a) I. M. Klotz and D. M. Green, *J. Phys. Chem.* **52**, 961 (1948); (b) P. Haberfield, *J. Chem. Educ.* **57**, 346 (1980).
12. G. Wada, E. Tamura, M. Okina and M. Nakamura, *Bull. Chem. Soc. Jpn.* **55**, 3064 (1982).
13. J. T. Edsall and M. H. Blanchard, *J. Am. Chem. Soc.* **55**, 2337 (1933).
14. A. D. Headley, *J. Chem. Soc., Perkin Trans. 2* 457 (1989).
15. D. L. Hughes, J. J. Bergan and J. J. Grabowski, *J. Org. Chem.* **51**, 2579 (1986).
16. A. D. Headley, *J. Org. Chem.* **56**, 3688 (1991).
17. A. D. Headley, *J. Org. Chem.* **53**, 312 (1988).
18. A. D. Headley, *J. Am. Chem. Soc.* **109**, 2347 (1987).
19. T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*. Harper and Row, New York (1987).
20. J. A. Riddick and N. B. Bunger, *Organic Solvents (Techniques of Chemistry)*, edited by A. Weissberger, Vol. 11). Wiley-Interscience, New York (1985).
21. M. J. Kamlet, J.-L. M. Abboud and R. W. Taft, *Prog. Phys. Org. Chem.* **13**, 485 (1981).
22. F. G. Bordwell, *Acc. Chem. Res.* **21**, 456 (1988).
23. R. W. Taft, in *Proton Transfer Reactions*, edited by E. Caldin and V. Gold, p. 58. Chapman and Hall, London (1975).
24. G. Stevens, S. Chen, P. Huyskens and S. De Jaegere, *Bull. Soc. Chim. Belg.* **100**, 493 (1991).
25. H. H. Jaffé, *Chem. Rev.* **53**, 191 (1953).
26. J.-L. M. Abboud, G. Guiheneuf, M. Essfar and R. W. Taft, *J. Phys. Chem.* **88**, 4414 (1984).
27. M. R. J. Dack. *Solutions and Solubilities, Part 11 (Techniques of Chemistry)*, edited by M. R. J. Dack, Vol. 8). Wiley, New York (1976).