Quantitative Analysis of Solvation Effects and the Influence of Alkyl Substituents on the Basicity of Amines

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From potentiometric titrations, the relative free energy changes for the basicities of selected alkyl-substituted dimethylamines have been determined in 11 different solvents. Solvation effects on basicity variation have been analyzed by solvent attenuation factors (SAF). Multilinear regression analyses of SAF and various solvent parameters show the best correlation equation with the solvatochromic parameters. From this equation, analysis of the sign and magnitude of the coefficients indicates that hydrogen bonds formed from the acidic hydrogen on the nitrogen of the ion to basic sites of solvents play a dominant role in basicity determinations and that solvation of the neutral amine is minimal compared to the ammonium ion. For all the solvents used, the size of alkyl substituents on dimethylamines plays a significant role in basicity. For each solvent, increased basicities are dictated primarily by substituent polarizability effect. The sensitivity of the basicity to a change of substituent depends largely on dipolarity/polarizability and basicity properties of solvents.

Introduction

Surprisingly, most of the basic knowledge regarding the effects of nonaqueous solvents on various reactions is gained indirectly from studies in aqueous medium (or a mixture of water and other solvents). Solvation properties of mixed solvents are very difficult to identify, much less describe. The effects that solvents have on the reactivity and solubility of molecules have been an area of active research.[1] The irregular trend observed for the basicity of alkylamines and ammonia in aqueous solution, which is $NH_3 < NMeH_2 < NMe_2H > NMe_3$,[2] has been a concern to chemists.[3] Various explanations have been proposed to justify this trend, of which the B strain, when proposed, gained widespread popularity.[4] Another explanation includes a stability competition between alkyl stabilization and solvation effects of the ammonium ions. The exact trend in other solvents is still not clear and is under investigation in our laboratories.

With the advent of ion cyclotron resonance (ICR) spectrometry[5] came the possibility of studying reactions in the absence of solvents. One important observation made for the basicity of amines is the surprisingly different trend in the gas phase, which is $NMe_3 > NMe_2H > NMeH_2 > NH_3$.[6] It appears that the general basicity trend is dictated by the size of the alkyl group. Since alkyl groups are polarizable,[7] larger alkyl groups favor increased reactivity. Similar effects have been observed for the acidity of mercaptans[8] and phenols.[9] The charge that results from the deprotonation or protonation of a neutral acid or base causes a redistribution of the alkyl substituent electrons—induced dipole—which serves to stabilize the conjugate base or acid, in this case the ammonium ion.[10] Thus, for the basicity of amines, the charged conjugate ammonium ion is stabilized to varying degree by polarizability effect depending of the size of the alkyl substituent.

The difference in trends for the basicity in the gas and aqueous phases must be attributed to solvation effects, since the same reactions occur in both phases.[11] Solvents are known to have numerous different effects on the reactivity of molecules.[12] The general ways in which solvents alter reactivity, when compared to that in the gase phase, are (a) type and extent of substituent solvation[13] and (b) type and extent of solvation of the reaction center.[14] In order to analyze solvation effects, identification, and most importantly, quantification of solvent–solute interactions must be accomplished. These are extremely difficult tasks due to the complexity of solvent structure. For example, even though, ethanol and dimethyl ether are isomers, the mere positioning of the atoms makes a drastic difference in the solvation properties of these two solvents. A very simplified approach is to classify solvents as protic or aprotic; however, by this method, important interactions between solvents and solutes are not adequately described.

Over the years, various parameters and equations have been developed to describe solvation properties and their effects on reactions.[15] In this study, analysis of the solvation effects on the basicity of alkyl-substituted dimethylamines is performed by analyzing the basicity variation of a select series of amines in several solvents with known solvent parameters. As a result, predictions of the relative basicities of other alkyl-substituted dimethyl-

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Table I. Relative Free Energy Change for the Basicity of Alkyl-Substituted Dimethylamines in Various Solvents (Measured at 298 K).[a] Values Relative to $(CH_3)_3N$ in kcal/mol

X	(gas)	DMF	MeOH	EtOH	DMA	AQ
CH_3	0.0	0.0	0.0	0.0	0.0	0.0
C_2H_5	−2.3	−0.1	−0.4	−0.2	−0.3	−0.6
n-C_3H_7	−3.0	−0.1	−0.6	−0.1	−0.3	−0.6
n-C_4H_9	−4.4	−0.3	−0.4	−0.4	−0.3	−0.6
i-C_3H_7	−4.7	−0.6	−0.8	−0.8	−0.7	−1.0
sec-C_4H_9	−5.9	−0.7	−1.0	−0.8	−0.7	−1.1
t-C_4H_9	−6.5	−0.8	−1.2	−0.8	−0.8	−1.4
c-C_6H_{11}	−7.3	−0.8	−1.0	−1.0	−0.8	−1.6
t-C_5H_{11}	−7.9	−0.8	−1.5	−1.1	−0.8	−1.8

X	DMSO	AN	NM	EG	NB	TEP
CH_3	0.0	0.0	0.0	0.0	0.0	0.0
C_2H_5	−0.3	−0.6	−0.3	−0.2	−0.3	−0.1
n-C_3H_7	−0.4	−0.7	−0.3	−0.3	−0.4	−0.1
n-C_4H_9	−0.5	−1.1	−0.4	−0.3	−0.4	−0.3
i-C_3H_7	−0.6	−1.2	−1.0	−0.7	−0.8	−0.3
sec-C_4H_9	−0.6	−1.4	−1.1	−0.7	−0.6	−0.4
t-C_4H_9	−0.8	−1.5	−1.2	−1.0	−1.1	−0.7
c-C_6H_{11}	−0.9	−1.8	−1.2	−0.8	−1.0	−0.7
t-C_5H_{11}	−0.9	−1.9	−1.3	−1.4	−1.1	−0.8

[a] Key: (gas), gas phase; DMF, *N,N*-dimethylformamide; MeOH, methanol; EtOH, ethanol; DMA, *N,N*-dimethylacetamide; AQ, water; DMSO, dimethyl sulfoxide; AN, acetonitrile; NM, nitromethane; EG, ethylene glycol; NB, nitrobenzene; TEP, triethyl phosphate.

amines in other solvents are possible once solvent parameters are ascertained.

Experimental Section

Anhydrous solvents and amines were used in purest commercial form without further purification and were stored over molecular sieves until time of use. The method for potentiometric determinations is described elsewhere.[16]

Results and Discussion

Solvation Effects. Due to no pK_b variations for primary alkylamines in solution, solvation effects analysis on these molecules is impossible. Solvation effects seem to overwhelm any observable inherent effects. However, for alkyl-substituted dimethylamines, pK_b variations are observed in aqueous solution,[17] suggesting that solvation effects are drastically reduced. For this reason, substituted dimethylamines were chosen to understand solvation effects on alkylamine basicities. Since the interaction of solvents with both substituent and reaction site alter basicity, analysis, considering both solvation possibilities, must be taken into account. However, alkyl substituent solvation is minimal;[8] thus, meaningful analysis can be accomplished by considering solvation effects at only the reaction site.

For reaction 1, where X represents selected alkyl substituents, Table I shows the relative free energy changes for the basicity of nine alkyl-substituted dimethylamines in various solvents (and the gas phase).[18] It is obvious that

$$X\text{-}N(CH_3)_2 + H^+ = X\text{-}N(CH_3)_2H^+ \qquad (1)$$

the relative basicity differs as a function of solvent. That is, for any two amines, the basicity difference in all solvents is not the same. Since solvation of alkyl substituents is minimal, the type(s) of solvation of the reaction site will be the same for all, but not necessarily to the same extent. Therefore, instead of individual examinations, the entire series can be examined by solvent attenuation factors (SAF), which are the slopes of plots of $\delta\Delta G$(gas) vs $\delta\Delta G$(sol); values are shown in Table II. A value of unity suggests no solvation effects, while a large value implies considerable solvation. A value of unity has been observed for very stable species in which inherent stabilization overwhelms solvation effects.[19] On the other hand, for primary amines, factors approach infinity—indicative of considerable solvation.[20] The correlation coefficients for SAF determinations are fairly good (correlation coefficients were at least 0.9); however, if nonalkyl substituents are included, the linearity is destroyed,[21] demonstrating that solvation of only the reaction site exists for the entire series of alkyl-substituted dimethylamines.

SAF analysis involves the use of multilinear regression analysis equations as shown below[22]

$$\text{SAF} = a_1X_1 + a_2X_2 + \dots + a_nX_n \qquad (2)$$

where X_1, X_2, ..., X_n are constants for various solvent properties, and a_1, a_2, ..., a_n are the slopes for each property. The magnitude and sign of the slopes for each term give quantitative information regarding solvation property and the species involved, respectively. For example, a negative sign of a slope refers to the solvation of the reactant molecule(s), which means that its solvation is larger than the product molecule(s)—in this case, the neutral-substituted dimethylamine and the proton. Likewise, if solvation of the product molecule(s) is greater than the reactant molecule(s), the slope reflecting this particular property will be positive. The solvation of the proton can be neglected since its solvation is fairly constant for solvents used.[23] Therefore, analysis can be accomplished by considering solvation of the neutral amine and the charged ammonium ion.

In a previous paper,[16] it was shown (qualitatively) that the solvation effects on the basicity of alkyl-substituted dimethylamines show a dependence on the solvent's basicity. Various scales have been developed to measure this property.[24] Single parameter correlation equations[25] with the solvatochromic parameter β, which is the solvent's hydrogen bond acceptor ability (HBA),[26] and Lewis basicity (B)[27] are shown below:

$$\text{SAF} = (7.7 \pm 1.3)\beta + 1.6 \pm 0.7 \qquad (3)$$

$$n = 12,\ r = 0.8768$$

$$\text{SAF} = (0.03 \pm 0.01)B + 1.9 \pm 0.9 \qquad (4)$$

$$n = 8,\ r = 0.871$$

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Table II. Solvent Attenuation Factors for the Basicity of Alkyl-Substituted Dimethylamines and Solvent Parameters Used for Multiple Regression Correlations

solvent	SAF	π^{*a}	α^a	β^a	B^b	E^b	ϵ^c	μ^c
(gas)	1.0	−1.1			0	0.0	1.0	
water	4.3	1.09	1.17	0.45	90	21.8	78.5	1.84
methanol	5.2	0.60	0.98	0.62	114	14.9	32.7	2.87
ethanol	5.9	0.54	0.86	0.77	117	11.6	24.3	1.66
ethylene glycol	5.3	0.92	0.92	0.52			37.7	2.28
dimethyl sulfoxide	8.5	1.0	0.0	0.76	192	3.2	46.6	3.90
acetonitrile	4.4	0.76	0.15	0.31	103	5.2	37.5	3.56
N,N-dimethylformamide	7.1	0.88	0.0	0.69	166	2.6	36.7	3.86
nitromethane	4.9	0.85	0.23	0.37		5.15	35.9	3.56
nitrobenzene	6.1	1.01	0.0	0.39	53	0	34.8	3.99
N,N-dimethylacetamide	8.1	0.88	0.0	0.76		2.13	37.8	3.79
triethyl phosphate	8.2	0.72	0.0	0.77			10.8	3.12[d]

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Both equations have positive slopes, which indicate that solvation of the charged ammonium ion plays a major role on basicity. Both equations, however, show poor correlation coefficients;[28] thus, they cannot be used to quantitatively analyze solvation effects. By including, as an extension of eq 3, other solvatochromic parameters (π^*, which measures the solvent's dipolarity/polarizability and describes the solvent's ability to stabilize a dipole by virtue of its dielectric effects—a nonspecific solvation interaction, and α, which is the solvent's hydrogen bond donor ability (HBD),[29] the correlation coefficient improves tremendously as shown below:

$$\mathrm{SAF} = (1.2 \pm 0.2)\pi^* - (1.7 \pm 0.3)\alpha + (6.4 \pm 0.5)\beta + (2.2 \pm 0.3) \quad (5)$$

$$n = 12,\ r = 0.9908,\ \mathrm{SD} = 0.3$$

Similarly, the inclusion of corresponding solvation properties such as Lewis acidity, E, and dielectric constant, ϵ, or dipole moment, μ, improve the correlation coefficient of eq 4 as shown in eqs 6 and 7, respectively:

$$\mathrm{SAF} = (0.03 \pm 0.01)B - (0.09 \pm 0.08)E + (0.03 \pm 0.03)\epsilon + 1.9 \pm 1.1 \quad (6)$$

$$n = 8,\ r = 0.9047,\ \mathrm{SD} = 1.3$$

$$\mathrm{SAF} = (0.02 \pm 0.01)B - (0.01 \pm 0.05)E + (0.6 \pm 0.4)\mu + 1.3 \pm 1.1 \quad (7)$$

$$n = 8,\ r = 0.929,\ \mathrm{SD} = 1.1$$

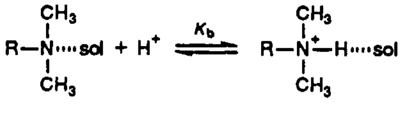
Due to the different scales for Lewis acidity, Lewis basicity, dielectric constant, and dipole moment, eqs 6 and 7 can only be used to demonstrate that both nonspecific and specific solvation effects are operational, as demonstrated by the improved correlation equation, but no real quantitative information can be gained for the slopes. However, for eq 5, since the solvatochromic parameters are all approximately on the same scale, quantitative solvation effects analysis can be accomplished for reaction 1.

Nonspecific Solvation. The positive slope of the dipolarity/polarizability effect implies that solvation of the charged ammonium ion is greater than the amine. The amine is neutral, but is also dipolar due to the difference in electronegativities of the carbon and the nitrogen atoms; hence, electrostatic stabilization from the solvent is expected, but minimal. On the other hand, since the product ammonium ion is charged, stabilization from the solvent molecules is needed to a greater extent. Dipolar solvent molecules will orient themselves around the charged ion to create intimate interactions that serve to disperse the charge into solvent molecules.

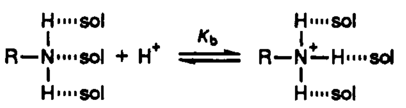
In order to gain a quantitative description of the dipolarity/polarizability effect, the value of the slope for this property must be looked at relative to the other values in that equation. Since the value for the solvent basicity, β, is the largest, a comparison is made to that value. The ratio (5.3) means that dipolarity/polarizability stabilization is about five times less effective than the most dominant form—which will be discussed later.

Specific Solvation. For solvent acidity, α, its negative slope suggests that solvation of the reactant molecule is greater than the ammonium ion. The neutral amine has an unshared pair of electrons capable of participating in hydrogen bonds to acidic solvents, whereas the ammonium ion has no basic sites. A similar treatment of slopes to analyze the relative quantitative contribution of this interaction yields a ratio of 3.8, which implies that solvation effects by this mode are slightly larger than dipolarity/polarizability solvation, but smaller than solvent's basicity.

For solvent basicity parameter, β, its positive slope indicates that the product ammonium ion is solvated more than the amine. The positively charged alkyl-substituted dimethylammonium ion has one relatively acidic hydrogen by which bonding to basic sites of solvents relieves it of some of the charge. Since this property is used for comparison to the other solvation properties, the ratio is unity and reflects the dominant form of solvation. That is, stabilization of the ammonium ion by this mode is considerable and as a result is primarily responsible for shifting the equilibrium shown below to the right, which in effect determines the basicities of the amines.



The explanation for no pK_b variation for primary amines is due to the effective specific solvation of three acidic hydrogens of the primary ammonium ion, thus providing a leveling effect for pK_b values, as shown below: R is any



alkyl substituent and sol represents any solvent. For this reason, the hydrogen substituent was not considered.

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Table III. ρ Values for the Basicity of Substituted Amines in Various Solvents

solvent	ρ_α[a]	r	SD
(gas)	16.5 ± 0.3	0.998	0.2
water	3.7 ± 0.6	0.994	0.3
methanol	2.9 ± 0.4	0.931	0.2
ethanol	2.5 ± 0.5	0.896	0.2
ethylene glycol	2.7 ± 0.5	0.907	0.2
dimethyl sulfoxide	1.9 ± 0.1	0.992	0.1
acetonitrile	3.9 ± 0.7	0.989	0.1
N,N-dimethylformamide	2.1 ± 0.3	0.905	0.2
nitromethane	3.0 ± 0.5	0.902	0.2
nitrobenzene	2.4 ± 0.4	0.916	0.1
N,N-dimethylacetamide	1.8 ± 0.2	0.894	0.1
triethyl phosphate	1.9 ± 0.2	0.956	0.1

[a] Values determined from the correlation equation SAF = $\rho_\alpha \sigma_\alpha + c$; substituent parameters taken from ref 32.

These results contradict the observation that solvation effects on the basicities of amines and pyridines in water are accomplished primarily by nonspecific solvation,[30] but substantiate the findings that solvation effects are dominated by specific solvation in which hydrogen bonds are formed from solvents to the acidic hydrogen on the ammonium and pyridinium ions.[31]

Substituent Effect. From Table I, the effects—even though small—that alkyl substituents have on the basicity of dimethylamines vary as a function of the solvent. Table III shows the results of single-parameter correlation analyses considering substituent polarizability and SAF, utilizing the format of eq 2. For alkyl substituents, stabilization by field/inductive and resonance effects are minimal[32] and charge-induced stabilization is predominant. The sensitivity of reaction 1 to changes of substituents is reflected in the slope, ρ_α. Large values signify that the reaction is very sensitive to changes of substituents and not necessarily to changes of solvents, whereas small values signify the opposite. Due to the wide range covered by ρ_α, reaction 1 is sensitive to changes of both substituents and solvents. The most polar solvent, dimethyl sulfoxide, reflects the smallest ρ_α value, and the least polar solvent, acetonitrile, has the largest (of course, the gas phase reflects no solvation effects and has the largest value of 16.5). Thus, the difference in basicity between any two amines is the largest in acetonitrile. In order to understand the solvation effects on ρ_α, a regression analysis was carried out. Due to a lack of colinearity of ρ_α and solvent's dielectric constant or dipole moment for single parameter equations, other solvent properties were considered as shown in eq 8. The solvatochromic parameters were chosen since, as shown earlier, they describe the solvation of this system very effectively.

$$\rho_\alpha = (5.2 \pm 0.6)\pi^* - (0.1 \pm 0.6)\alpha + (5.6 \pm 1.4)\beta - 10.2 \pm 0.7 \quad (8)$$

$$r = 0.9816,\ n = 12,\ \mathrm{SD} = 0.9$$

Due to the fairly large positive value of the slope for solvent dipolarity/polarizability, the substituents are very sensitive to the reduction of the charge on the ammonium ion by nonspecific solvation—a reasonable observation since substituent polarizability effect is proportional to the square of the charge being stabilized. That is, a small charge can result in a relatively large substituent effect. From eq 8, the sensitivity of substituents to solvent's acidity is practically zero. Solvent's acidity property plays a major role only in the solvation of the neutral amine and not as much of the charged ammonium ion. Furthermore, since substituent polarizability results from the stabilization of a charge by means of that charge inducing a dipole in the alkyl substituent, which in turn stabilizes the charged center, solvent acidity should not affect substituent effect. Equation 8 also reveals that substituents are sensitive to the solvent's basicity; from the positive sign, the ammonium ion is affected the most. This observation is reasonable since basic solvent can disperse the positive charge from the ion by the formation of hydrogen bonds to the solvent. The molecular composition of the solvent between the charged reaction center and substituent also plays a role on the magnitude of ρ_α.[33] The effective dielectric constant varies in the region between a charged center and an induced charged dipolar substituent. Therefore, the lines of force communicating the effect of the substituent to the charged center and vice versa are dependent on the molecular composition of the solvent in this region. However, this property is expected to be minimal since the charge difference between each substituent and reaction center is small and can be neglected as shown by the fairly good correlation coefficient of eq 8. Methods to quantify this property are presently being developed in our laboratories.

Very basic solvents cannot effectively discriminate between the basicity of various substituted alkylamines when compared to less basic solvents. From the solvent's basicity parameter, it is possible to approximate the relative basicity of these amines in different solvents, of course, since solvent's acidity and dipolarity/polarizability properties also play roles in the position of the equilibrium, a more accurate prediction can be arrived at when all three solvent properties are considered. Due to the sensitivity of alkyl substituents on the charge of the ammonium ion, the best solvents in which alkyl substituent effects can be observed are in solvents with low dipole moment or dielectric constant and solvents that are not extremely basic.

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