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Analysis of the basicity of substituted dimethylamines in different solvents by theoretical descriptors

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ABSTRACT: By using theoretically determined descriptors in quantitative structure–property relationships, quick and good *a priori* predictions of molecular properties can be accomplished. In this study, theoretical linear solvation energy relationship descriptors are used to analyze structural effects that contribute to the basicity variation of substituted dimethylamines in different solvents. A multilinear regression (MLR) analysis approach is used to generate equations and, owing to the goodness of the 'fit' of the different MLR equations, the descriptors used account very well for the structural effects that determine the relative basicity of dimethylamines. Good agreement is obtained between the basicity values predicted by this method and the experimental basicity values of 14 substituted dimethylamines in eight solvents and the gas phase. The Lewis basicity ε_B and the polarizability/dipolarity π_i are the important factors that contribute to basicity variation. For the basicity of $NCCH_2N(CH_3)_2$, a good prediction was not achieved and a discussion is presented. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: basicity; substituent effects; amines; quantitative structure–property relationships

INTRODUCTION

The basicity of compounds is not determined only by the nature and extent of solute–solvent interactions involving the equilibrium species, but also by structural features of the molecules. The relationships that exist between the chemical properties of molecules and their molecular structural features have been used to correlate the molecular structural properties of compounds with known biological, chemical, and physical properties.[1] Quantitative structure–activity relationships (QSARs) are generally used when biological activities are examined; in cases where a specific property is examined, as in this study, quantitative structure–property relationships (QSPRs) are used. The success of QSARs and QSPRs depends on the assumption that quantitative relationships exist between microscopic features and macroscopic properties of molecules. Such relationships have been used successfully to predict different properties of compounds that have similar molecular features as other compounds in a particular series.[2] The ability of these relationships to make successful predictions of macroscopic properties depends strongly on the accurate quantification of microscopic features of the molecule, which are often referred to as descriptors.

The ability to predict property variations of different molecules in various media requires knowledge of various solute–solvent interactions. Taft and co-workers have examined such interactions and have described the important ones as shown in Eqn. (1).[3]

$$\begin{aligned}\text{Property} = {} & \text{bulk/cavity term} \\ & + \text{dipolarity/polarizability term(s)} \\ & + \text{hydrogen bonding term(s)} + \text{constant}\end{aligned} \quad (1)$$

The bulk/cavity term is a measure of the energy that is needed to overcome the cohesive solvent–solvent interactions to form a cavity for the solute molecule. The dipolarity/polarizability terms are measures of the energies of solute–solvent dipole and induced dipole interactions that contribute to solvation. Hydrogen bonding terms measure specific interactions between solvent and solute. They reflect the ability of the solvent to accept a hydrogen bond(s) from the solute, which is described as the hydrogen bond acceptor basicity (HBAB), and the ability of the solvent to donate a hydrogen bond(s) to the solute, which is described as the hydrogen bond donor acidity (HBDA). The first term in Eqn. (1) is endoergic, whereas the last two terms are exoergic. For Eqn. (1), linear statistical fitting between the variables is used. This approach is not the only form of statistical fitting that can be used, but numerous QSAR

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Table 1. Theoretical descriptors for substituted dimethylamine X—N$(CH_3)_2$

No	X	V_{mc}	π_i	ε_B	q_-	ε_A	q_+
1	CH_3	77.889	0.1008	0.1496	0.4366	0.1486	−0.0033
2	C_2H_5	95.361	0.1019	0.1507	0.4450	0.1500	0.0015
3	*n*-C_3H_7	112.835	0.1029	0.1508	0.4489	0.1501	0.0127
4	*i*-C_3H_7	112.552	0.1031	0.1500	0.4142	0.1514	0.0087
5	*n*-C_4H_9	130.319	0.1036	0.1509	0.4505	0.1504	0.0125
6	*sec*-C_4H_9	130.393	0.1031	0.1515	0.4500	0.1511	0.0103
7	*t*-C_4H_9	129.901	0.1034	0.1510	0.4285	0.1525	0.0079
8	*t*-C_5H_{11}	147.333	0.1040	0.1524	0.4588	0.1528	0.0159
9	*c*-C_6H_{11}	153.514	0.1082	0.1517	0.4489	0.1514	0.0156
10	$CH_2C{\equiv}N$	97.435	0.0988	0.1454	0.4602	0.1622	0.0199
11	CH_2CCl_3	139.435	0.1168	0.1443	0.4416	0.1762	0.0283
12	$CH_2C_6F_5$	179.422	0.1058	0.1443	0.4341	0.1942	0.0225
13	$CH_2C{\equiv}CH$	101.422	0.1026	0.1496	0.4401	0.1603	0.1559
14	$CH_2CH{=}CH_2$	106.944	0.1053	0.1500	0.4309	0.1665	0.0471
15	$CH_2C_6H_5$	152.648	0.1166	0.1527	0.4323	0.1753	0.0632

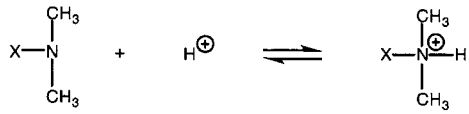
analyses have been carried out successfully by this approach. Descriptors[4] developed from thermodynamic and spectroscopic data for solvents and solutes are used commonly in Eqn. (1), and they have been used successfully to correlate the chemical, physical and biological properties of more than 200 compounds by this approach.[5] For multi-linear relationships (MLRs) where solute–solvent interactions are considered, the term that is often used to describe the relationships is linear solvation energy relationships (LSERs).

One disadvantage in the use of LSERs and other classical approaches for the analysis of solute–solvent interactions is that the descriptors used to analyze property variations are empirically developed; thus, unusual interactions may be misinterpreted. One way to circumvent this problem is to use descriptors in QSARs that are developed from theoretical chemistry. Molecular orbital calculations have been used for the development of molecular descriptors,[6] and descriptors that are obtained by computational methods are often reliable and are obtained quickly.[7] Statistically based interaction indices derived from molecular surface electrostatic potentials have also been used to predict the properties of molecules.[8] A set of six theoretical linear solvation energy relationship (TLSER) descriptors have been developed by Famini and co-workers for a wide variety of compounds and they have been used successfully to correlate the properties of a wide variety of compounds,[9] including: five nonspecific toxins; the activity of some local anesthetics and their molecular transform; opiate activity of some fentanyl-like compounds; and six physicochemical properties: charcoal on absorption, high-performance liquid chromatography retention index, octanol–water partition coefficients, phosphonothiolate hydrolysis rate constants, aqueous equilibrium constants and electronic absorption of some ylides. TLSER descriptors have also been used successfully to describe the effects of structural variations of carboxylic acids, alcohols, silanols, anilines, hydrocarbons, and oximes on their acid–base properties in the gas phase.[10] Since these TLSER parameters are determined solely from computational methods, *a priori* predictions of the properties of compounds are possible. The TLSER descriptors were developed to correlate closely with LSER descriptors to give multilinear regression (MLR) equations with correlation coefficients R, and standard deviations (SDs) close to those for LSERs, and to be as widely applicable to solute–solvent interactions as the LSER set. The TLSER descriptors are developed to represent specific electronic properties of molecules in the gas phase. Since the electronic interactions between molecules depend only on the nature of the molecules, these descriptors also depict solute–solvent interactions.

The generalized TLSER equation for solutes in a given medium is shown in Eqn. (2):

$$\mathrm{SSP} = aV_{mc} + b\pi_i + c\varepsilon_B + dq_- + e\varepsilon_A + fq_+ + \mathrm{SSP}_0 \quad (2)$$

In this study, SSP represents structural features that cause basicity variation for different substituted dimethylamines [Eqn. (3), where X is shown in Table 1].



(3)

V_{mc} ($\mathring{A}^3$) describes the molecular van der Waals volume. π_i describes the dipolarity/polarizability contribution and is obtained from the division of the polarizability volume by the molecular volume to produce a unitless, size-independent quantity that indicates the ease with which the electron cloud of a dimethylamine molecule may be moved or polarized. ε_B is part of the HBAB contribution and is the energy difference between the highest occupied molecular

Table 2. Theoretical descriptors for selected solvents

Solvent	V_{mc}	π_i	ε_B	q_-	ε_A	q_+
H_2O	20.478	0.0549	0.1237	0.3256	0.1237	0.1628
MeOH	38.558	0.0814	0.1314	0.3292	0.1402	0.1803
EtOH	56.073	0.0893	0.1324	0.3234	0.1442	0.1784
EG	65.172	0.0869	0.1372	0.3276	0.1455	0.1875
DMSO	75.295	0.0980	0.1540	0.7146	0.1615	0.0564
TEP	176.407	0.1000	0.1259	0.5581	0.1721	0.0146
AN	49.110	0.0863	0.1176	0.1143	0.1621	0.0208
NB	112.439	0.1182	0.1425	0.3422	0.1903	0.0951

orbital (HOMO) of the dimethylamine molecule and the lowest unoccupied molecular orbital (LUMO) of water. Water is chosen as the reference because it is the most common solvent. The electrostatic basicity term q_- is the largest negative formal charge on an atom of a dimethylamine molecule; the unit is the atomic charge unit (acu). ε_A describes the covalent acidity, which reflects the ability of a dimethylamine molecule to act as a Lewis acid. These descriptors are obtained from the difference between the energies of the LUMO of the dimethylamine molecule and the HOMO of water. q_+ (acu) is the electrostatic acidity term and is the largest positive formal charge on a hydrogen atom of a dimethylamine molecule; SSP_0 is the intercept. The magnitude of the coefficients for the MLR equations, *a, b, c, d, e*, and *f* indicates the relative importance of the different structural features to basicity variation.

A major advantage of using TLSER and other theoretical methods to determine the properties of compounds is the low cost. It is extremely costly to determine and fully understand, through experimentation, the properties of a single molecule.[11] Owing to the relatively low cost of carrying out computations, accurate estimates of the properties of most compounds can be achieved by this method at a fraction of the cost of conventional methods. In this paper, equations of the format shown in Eqn. (2) are developed and used to predict the basicity of dimethylamines in different media. Also, significant structural features that contribute to the basicity variation in each medium are identified and discussed.

EXPERIMENTAL SECTION

Experimental basicities were determined from potentiometric titrations using trifluoromethane sulfonic acid and the procedure is described elsewhere.[12] Basicity values, relative to trimethylamine, are shown in Table 3 and were determined to within ± 0.1 pK unit and converted to ΔG values, relative to trimethylamine. The TLSER descriptors[13] shown in Tables 1 and 2 were computed using the MNDO algorithm contained in MacSpartan.[14] The Minitab multilinear regression analysis computer program was used to obtain the correlation equations.[15]

RESULTS AND DISCUSSION

Substituted dimethylamine and solvent TLSER descriptors used in this study are shown in Tables 1 and 2. Table 3 shows the experimental basicity values (along with predicted basicity values) for substituted dimethylamines in the gas phase[†] and in different solvents. The predicted basicities are obtained from MLR correlation equations of the format shown in Eqn. (2). Table 4 shows the coefficients and the statistics of the TLSER correlation equations used to predict the basicity values. The basicity values used in the correlations are relative free energy terms (kcal mol^{-1}) relative to trimethylamine. For the TLSER equations, good correlation coefficients are obtained ($0.961 < R < 0.988$). Not all terms of the equations are significant–the terms that are retained are at the 0.95 level or higher. Each coefficient is accompanied by its standard error ($\pm$), *t*-statistic (t-stat), and the variance inflation factor (VIF) to indicate the quality of the 'fit' and the degree of cross-correlation of the independent variables. The outliers with studentized residuals greater than 3.0 were removed from the correlations. A total of nine regression equations were developed, one for each medium.

From the results shown in Table 4, the coefficients for the structural features examined are different. Significant contributions that affect basicity variations come from the Lewis basicity term ε_B, and the polarizability/dipolarity term π_i. The electrostatic acidity term q_+ also contributes to basicity variations, but it is not as important as the Lewis basicity and polarizability/dipolarity terms. For each regression $NCCH_2N(CH_3)_2$ (compound **10**) was found to be an outlier and its basicity value was therefore omitted from the entries shown in Table 4. Thus, compared with the other compounds of this data set, $NCCH_2N(CH_3)_2$ has unusual features not

[†]Gas-phase data were obtained from Professor J. Bartmess, Department of Chemistry, University of Tennessee, Knoxville, TN 37996-1600.

Table 3. Experimental and predicted (parentheses) $\delta\Delta G°$ values for the basicity of substituted dimethylamines in various solvents at 298 K

No.	X	Gas	H_2O	MeOH	EtOH	EG	DMSO	TEP	AN	NB
1	CH_3	0.0 (−0.8)	0.0 (−0.5)	0.0 (−0.3)	0.0 (−0.2)	0.0 (−0.2)	0.0 (−0.4)	0.0 (−0.2)	0.0 (−0.8)	0.0 (−0.5)
2	C_2H_5	−2.3 (−3.3)	−0.6 (−1.1)	−0.4 (−0.8)	−0.2 (−0.7)	−0.2 (−0.7)	−0.3 (−0.6)	−0.1 (−0.5)	−0.6 (−1.2)	−0.3 (−1.0)
3	*n*-C_3H_7	−3.0 (−3.9)	−0.6 (−0.8)	−0.6 (−0.5)	−0.1 (−0.4)	−0.3 (−0.5)	−0.4 (−0.4)	−0.1 (−0.2)	−0.7 (−0.9)	−0.4 (−0.6)
4	*i*-C_3H_7	−4.7 (−2.7)	−1.0 (−0.3)	−0.8 (0.0)	−0.8 (0.1)	−0.7 (−0.1)	−0.6 (−0.1)	−0.3 (0.1)	−1.2 (−0.6)	−0.8 (0.0)
5	*n*-C_4H_9	−4.4 (−4.9)	−0.6 (−0.8)	−0.4 (−0.5)	−0.4 (−0.4)	−0.3 (−0.5)	−0.5 (−0.4)	−0.3 (−0.2)	−1.1 (−0.9)	−0.4 (−0.5)
6	*sec*-C_4H_9	−5.9 (−6.1)	−1.1 (−1.3)	−1.0 (−1.0)	−0.8 (−1.0)	−0.7 (−0.9)	−0.6 (−0.7)	−0.4 (−0.6)	−1.4 (−1.3)	−0.6 (−1.2)
7	*t*-C_4H_9	−6.5 (−5.2)	−1.4 (−1.0)	−1.2 (−0.7)	−0.8 (−0.6)	−1.0 (−0.6)	−0.8 (−0.5)	−0.7 (−0.4)	−1.5 (−1.1)	−1.1 (−0.8)
8	*t*-C_5H_{11}	−7.9 (−8.2)	−1.8 (−1.7)	−1.5 (−1.4)	−1.1 (−1.4)	−1.4 (−1.2)	−0.9 (−0.9)	−0.8 (−0.8)	−1.9 (−1.6)	−1.1 (−1.6)
9	*c*-C_6H_{11}	−7.3 (−6.5)	−1.6 (−0.8)	−1.0 (−0.5)	−1.0 (−0.4)	−0.8 (−0.5)	−0.9 (−0.3)	−0.7 (−0.2)	−1.8 (−1.0)	−1.0 (0.0)
10	$CH_2C{\equiv}N$	14.3	7.5	9.0	9.2	7.0	4.0	5.4	4.7	10.0
11	CH_2CCl_3	8.1 (8.4)	5.5 (5.4)	5.5 (5.8)	6.5 (6.4)	4.9 (4.8)	3.4 (3.4)	3.9 (4.0)	3.9 (3.9)	9.8 (8.7)
12	$CH_2C_6F_5$	4.4 (3.7)	4.0 (4.2)	4.7 (4.5)	4.9 (4.9)	3.6 (3.7)	2.4 (2.5)	3.2 (3.1)	2.7 (2.9)	4.8 (5.9)
13	$CH_2C{=}CH$	2.1 (2.1)	3.4 (3.5)	2.8 (3.1)	3.8 (3.8)	2.5 (2.5)	2.0 (2.2)	3.1 (3.2)	2.3 (2.5)	4.2 (3.9)
14	$CH_2CH{=}CH_2$	−1.9 (−1.0)	1.3 (0.9)	2.1 (1.0)	1.1 (1.3)	1.0 (0.8)	1.4 (0.6)	1.1 (1.0)	1.2 (0.4)	1.0 (1.5)
15	$CH_2C_6H_5$	−4.4 (−5.2)	0.8 (0.5)	1.0 (0.7)	1.2 (1.0)	0.6 (0.5)	1.0 (0.7)	1.1 (0.8)	0.5 (0.1)	2.2 (2.4)

Table 4. Coefficients and statistics for the MLR for the individual sets. $\delta\Delta G = aV_{mc} + b\pi_i + c\varepsilon_B + dq_- + e\varepsilon_A + fq_+ + g$

							Coeff. ± *t*-stat. VIF					
		a	*b*	*c*	*d*	*e*	*f*	*g*	*N*	*R*	*F*	*s*
1	gas	−5.64	205.54	−1628.2	n/s	n/s	24.45	226.49	14	0.980	54	1.120
		1.39	76.3	125.4			7.87	21.51				
		−4.06	2.69	−12.99			3.11	10.53				
		1.5	1.5	1.1			1.1					
2	H_2O	n/s	96.38	−683.41	n/s	n/s	24.46	92.07	14	0.983	96	0.479
			27.67	53.37			3.31	9.2				
			3.48	−12.8			7.39	10.01				
			1.1	1.1			1.0					
3	MeOH	n/s	110.01	−687.33	n/s	n/s	20.05	91.55	14	0.978	72	0.541
			31.27	60.33			3.74	10.4				
			3.52	−11.39			5.36	8.81				
			1.1	1.1			1.0					
4	EtOH	n/s	119.62	−730.92	n/s	n/s	23.64	97.19	14	0.988	137	0.427
			24.65	47.54			2.95	8.19				
			4.85	−15.37			8.02	11.86				
			1.1	1.1			1.0					
5	EG	n/s	89.91	−580.04	n/s	n/s	16.42	77.54	14	0.987	127	0.342
			19.75	38.09			2.36	6.56				
			4.55	−15.23			6.95	11.81				
			1.1	1.1			1.0					
6	DMSO	n/s	80.91	−381.14	n/s	n/s	15.24	48.55	14	0.967	49	0.407
			23.5	45.34			2.81	7.81				
			3.44	−8.41			5.42	6.21				
			1.1	1.1			1.0					
7	TEP	n/s	66.6	−453.6	n/s	n/s	20.19	61.06	14	0.988	141	0.279
			16.09	31.04			1.93	5.35				
			4.14	−14.61			10.49	11.42				
			1.1	1.1			1.0					
8	AN	n/s	74.79	−532.07	n/s	n/s	19.75	71.36	14	0.961	41	0.578
			33.38	64.39			3.99	11.1				
			2.24	−8.26			4.95	6.43				
			1.1	1.1			1.0					
9	NB	n/s	248.03	−848.13	n/s	n/s	25.05	101.45	14	0.976	68	0.775
			44.78	86.38			5.36	14.89				
			5.54	−9.82			4.68	6.82				
			1.1	1.1			1.0					

found in the other dimethylamines. An unusual feature might arise from the protonation of the cyano group to produce a slightly different molecule than that described by the theoretical descriptor for compound **10**. As a result, its inherent factors that contribute to basicity variations are different from those calculated for $NCCH_2N(CH_3)_2$, and its basicity cannot be predicted accurately from the TLSER equations.

Lewis basicity contribution

A large coefficient for a particular feature in Eqn. (2) suggests that the inherent feature examined has an important contribution to basicity variation. On the other hand, structural features that do not have important contributions to basicity variation have relatively small coefficients. The ε_B TLSER descriptor reflects the ability of each dimethylamine molecule to donate its pair of electrons, not only to the proton to form the ammonium ion, but also to the reaction medium. From Table 4, the coefficient *c* varies as a function of the medium, which suggests that the medium also influences basicity variation. The coefficient for this property is the largest in the gas phase, since there are no solvent molecules to compete with the proton for the dimethylamine pair of electrons. Since dimethyl sulfoxide (DMSO), triethyl phosphate (TEP) and acetonitrile (AN) (Class B solvents) do not possess the ability to form effective hydrogen bonds to the basic dimethylamine molecules, it is expected that the coefficients in these solvents should be large; but they are relatively small, as shown in Table 4. Class B solvents, on the other hand, have the exceptional ability to form effective hydrogen bonds

with the acidic hydrogen of the ammonium ion product, as reflected by the relatively large q_- values for these solvents (Table 2). The value for AN is smaller than the other solvents in this class owing to the sp-hybridized nitrogen. Owing to effective solvation of the ammonium ion by Class B solvents, the structural Lewis basicity effect of the dimethylamines on basicity variation is highly attenuated in Class B solvents, and, as a result, the coefficients in these solvents are relatively small. The Lewis basicity term is the only exoergic term in the regression, which implies that better covalent bases will give more negative $\delta\Delta G$ values, thus enhancing basicity.

The coefficients for the inherent effect of Lewis basicity on basicity variation of the dimethylamines in water (H_2O), methanol (MeOH), ethanol (EtOH) and ethylene glycol (EG) (Class A solvents) are larger than those in Class B solvents. Since q_+ values for Class A solvents (Table 2) are larger than those of Class B solvents, and hence form effective hydrogen bonds to the solute, it is expected that the coefficients should be smaller than those of Class B solvents. The coefficients for Class A solvents, however, are greater than those of Class B solvents. Since q_- values for Class A solvents are not as large as those of Class B solvents (with the exception of AN), solvation of the ammonium ion is not as effective as that of Class B solvents. Thus, the coefficients in Class A solvents are larger than those of Class B solvents, but not nearly as large as that in the gas phase. Owing to the relatively large coefficient observed in nitrobenzene (NB), it is placed in a separate category, and the factors that contribute to this exceptionally large coefficient will be discussed later.

Dipolarity/polarizability effect

Another important inherent contributor to basicity variation is the dipolarity/polarizability term, which describes how well the electron cloud of each dimethylamine can be moved and, as a result, influence basicity variation. For polarizable dimethylamines the electron cloud is easily moved, and hence serves to increase the basicity of the dimethylamines. The trend of the gas-phase basicity data shown in Table 3 implies that the basicity of substituted dimethylamines increases as the polarizability effect of the substituents increases, i.e. *tert*-butyl dimethylamine is a stronger base than trimethylamine in all media studied. It has been demonstrated that substituent polarizability influences the basicity of dimethylamines in the condensed phase.[16] From Table 4, the dipolarity/polarizability effect is highly attenuated in Class B solvents; the coefficients in these solvents are relatively small, compared with the gas phase and Class A solvents, with the largest coefficient observed in the gas phase.

With the advent of ion cyclotron resonance spectrometry[17] came the possibility of studying reactions in the gas phase. An important observation made for the basicity of amines is that the trend in the gas phase is different from that in solution, and that the general basicity trend is dictated by the polarizability effect of the alkyl group.[18] Similar observations are made for the basicities of other compounds in the gas phase.[16,19] For non-alkyl dimethylamines, LFERs show that both inductive and polarizability effects dictate basicity variation and that molecules with polarizable alkyl groups favor increased reactivity;[20] similar effects have been observed for the acidity of mercaptans[20a] and phenols.[20b] The charge resulting from the deprotonation or protonation of a neutral acid or base causes a redistribution of the alkyl substituent electrons—induced dipole—that serves to stabilize the conjugate base or acid.[21] The substituent polarizability effect is pronounced for ions that have a localized charge, compared with ions that have delocalized charges, such as the acetate anion.[22] Thus, for the basicity of amines, the charged conjugate ammonium ion is stabilized to varying degrees by the polarizability effect. In Class B solvents, the coefficients are smaller than those in Class A solvents.

Basicity in nitrobenzene (NB)

The inherent solute properties that contribute to basicity variation are very pronounced in NB. From Table 4, the coefficients for ε_B and π_i are much larger in NB than in the other media; these results indicate that, in NB, inherent effects are not attenuated. It has been shown that bulky solvents, such as NB, cannot access adequately the region between the dipolar substituents and the reaction center to accomplish a similar solvation as can the less bulky solvents.[23] For effective solvation of the dimethylamines, especially those that have dipolar substituents, the solvent molecules must gain access between the lines of force of the dipolar substituent and the amine functionality. As a result, inherent effects that contribute to basicity variation are not attenuated in NB, and the magnitude of the coefficients for the solute properties are larger than those of the other solvents, which can better solvate the amines.

CONCLUSIONS

Based on the goodness of the 'fit' of the relationships shown in Table 4, the TLSER descriptors model fairly well the substituent effects on the basicity of dimethylamines. The good agreement that is obtained between experimental and predicted basicities for 14 substituted dimethylamines in nine different media suggests that this model can be very useful for the prediction of the basicity of other substituted dimethylamines in these media, and for the determination of inherent factors that contribute

to basicity variation. In the solution phase, amine basicity variation arises mainly from Lewis basicity and dipolarity/polarizability effects. For the basicity of $NCCH_2N(CH_3)_2$, the model fails to give accurate basicity predictions, since protonation of the nitrile functionality can also occur. Owing to the different solvating abilities of the solvents used in this study, the inherent factors that affect basicity variations are highly attenuated in Class B solvents, whereas in Class A solvents these effects are more pronounced. Since NB is a much bulkier solvent than the other solvents used, it does not solvate dimethylamines as well as the other solvents, and inherent effects that contribute to basicity variations are more pronounced in NB than in the other solvents.

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