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SOLVATION EFFECTS ON THE RELATIVE BASICITY OF PROPYLAMINES

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Slight structural molecular variations are known to affect different properties of compounds. In solution, different solute–solvent interactions are known also to alter the properties of numerous compounds. Quantitative structure–activity relationships (QSAR) are used regularly to analyze and predict the variations of different properties of compounds that are caused by structural variations and significant solute–solvent interactions. The relative basicities of *n*-propylamine, dipropylamine and tripropylamine were determined in nine different solvents from potentiometric titrations. QSAR that were developed from these experimental basicity values were used to evaluate the type and significance of the solute–solvent interactions. The important interactions that influence basicity variations for the propylamines studied are dipolarity-polarizability interaction between the solute and the solvent and hydrogen bonds from the propylammonium ions to basic solvents. The role of hydrogen bonds from the propylamines to acidic solvents is minor.

INTRODUCTION

The nature and extent of solute–solvent interactions can alter tremendously various properties of some compounds. Another factor that modifies the property of compounds in a particular solvent is structural variations of the solutes. The search for a better understanding of the effects that these factors have on property variations has been an active area of research[1]. Owing to the increased use of different solvents in today's research, knowledge of possible solute–solvent interactions for a wide range of solutes and solvents is needed in order to be able to predict effectively any property variations that are caused by these interactions. Quantitative structure–activity relationships (QSAR) are used regularly to relate property variations of different compounds with significant solute–solvent interactions.[2] For QSAR, the assumption is made that quantitative relationships exist between microscopic features and macroscopic properties of molecules. In cases where a specific property is examined, as in this study, the term that is often used is quantitative structure–property relationships (QSPR).

In order to make effective predictions of the property of compounds, identification and, most important, quantification of solute–solvent interactions must be accomplished. These tasks are extremely difficult. Owing to the complexity of the structure of solvents, numerous interactions between solutes and solvents are possible.[3] Over the years, various solute–solvent interactions have been recognized,[4] but those identified by Kamlet, Taft and co-workers have been used widely for the prediction of the properties of a number of compounds by QSAR technique.[5] The important solute–solvent contributions to property variations of compounds can be expressed by

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

The bulk term is a measure of the energy that is needed to overcome the cohesive solvent–solute 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 which contribute to solvation. Hydrogen bonding terms measure specific interactions between solvent and solute. These terms 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). Descriptors derived from linear solvation energy relationships (LSER) are used usually in equation (1). The chemical, physical and biological properties of more than 200 compounds have been correlated successfully by this method.[6]

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Descriptors derived by different methods are used to generate equations of the format shown in equation (1). Recently, a descriptor was developed to describe a unique solute–solvent interaction that involves dipolar amines.[7] In this paper, the solvatochromic descriptors are used to generate equations of the format shown in equation (2) for the basicity of propylamines. These equations are used to analyze the different solute–solvent interactions that affect the relative basicity ($\delta\Delta G$) of propylamine, dipropylamine and tripropylamine in different solvents.

$$\delta\Delta G = s\pi^* + a\alpha + b\beta + \delta\Delta G_0 \qquad (2)$$

where π^*, α and β represent the solvent's dipolarity–polarizability, hydrogen bond donor ability and hydrogen bond acceptor ability, respectively, and $\delta\Delta G_0$ represents the intercept, i.e. the relative basicity in the absence of solvents. The extent and importance of the different solute–solvent interactions are gained from the sign and magnitude of the coefficients s, a and b. For a particular solute–solvent interaction that results in increased basicity, the coefficient is negative, whereas, a large magnitude for a coefficient means that a particuar solute–solvent interaction increases the basicity when compared with another which has a smaller and less significant coefficient. The irregular basicity trend observed for alkylamines and ammonia in aqueous solution has been known for a long time.[8] $NH_3 < NMeH_2 < NMe_2H > NMe_3$ is the basicity trend in water,[9] whereas in the gas phase the trend is $NMe_3 > NMe_2H > NMeH_2 > NH_3$.[10] With the advent of different techniques that are capable of studying reactions in the gas phase, such as ion cyclotron resonance (ICR) spectrometry,[11] came the possibility of analyzing the factors that affect reactions in the absence of solvents. Based on the results of the study of different gas-phase reactions, it became clear that important solute–solvent interactions affect different properties of compounds.

Amino acids form a very important category of compounds which have an amino functionality and the effects that *N*-alkylation have on the overall properties of amino acids are not known fully. *N*-Alkylated and *N*,*N*-dialkylated amino acids are very important compounds in biological chemistry,[12] and different solute–solvent interactions play important roles in their ionization.[13] Thus, knowledge of the solute–solvent interactions that affect the basicity of the propylamines in this study will lead to a better understanding of the solute–solvent interactions that affect the tautomeric equilibrium of *N*-alkylated amino acids.

EXPERIMENTAL

Anhydrous solvents and propylamines were used in their purest commercial form as received and were stored over molecular sieves (4 Å) until used. The method for potentiometric determinations of the basicity of the propylamines is similar to that described elsewhere.[14] Each basicity measurement was repeated at least three times, and the basicity reproducibility is within ±0·05 p*K* unit. The changes in relative Gibbs free energies, shown in Table 1, were determined from the relationship $\delta\Delta G = -RT(\ln K)$, where all values are relative to diethylamine. Regression analyses were accomplished by the use of a computer program developed by Dr R. M. Doherty based on Ref. 15.

RESULTS AND DISCUSSION

Table 1 shows the basicity variations of propylamines in the gas phase[16] and in different solvents. The basicity values shown in Table 1 are relative to diethylamine; the equilibrium is

$$Pr_nNH^+_{(4-n)} + Et_2NH \rightleftharpoons Pr_nN + Et_2NH_2^+ \qquad (3)$$

where $n = 1$, 2 or 3.

Propylamines with positive basicity values are less basic than diethylamine and propylamines with negative basicity values are more basic than diethylamine. The basicity trend shown in Table 1 indicates that dipropylamine is the most basic amine in all the solvents used, except in DMSO, where propylamine is the most basic amine. Since the trend for the solution basicity is different from that for the gas-phase basicity, the nature and significance of solute–solvent interactions may be important, especially in DMSO. In this paper, dipolarity–polarizability and hydrogen bonding contributions that affect the basicity variations of propylamine, dipropylamine and tripropylamine are analyzed by QSAR. The correlation, coefficients and statistics for each relationship are given in Table 2.

Table 1. Solvent solvatochromic parameters[a] and the relative basicities ($\delta\Delta G$) of propylamines in the gas phase and various solvents, (values are in kcal mol^{-1} at 298 K and relative to diethylamine)

Solvent[b]	π^*	α	β	$PrNH_2$	Pr_2NH	Pr_3N
(Gas)[c]	−1·1	—	—	6·8	−2·3	−8·7
AQ	1·09	1·17	0·18	0·61	−0·03	0·44
MeOH	0·60	0·98	0·62	0·47	0·29	1·39
EtOH	0·54	0·86	0·77	0·38	0·23	1·56
2-PrOH	0·46	0·78	0·90	0·56	0·31	1·11
EG	0·92	0·92	0·52	0·48	0·40	2·11
DMSO	1·00	0·00	0·76	0·30	1·02	2·61
AN	0·76	0·15	0·31	1·24	0·00	0·83
NB	1·01	0·00	0·39	0·75	0·29	1·11
NM	0·85	0·23	0·37	1·00	0·00	0·88

[a] From ref. 23.

[b] (Gas), gas phase; AQ, water; MeOH, methanol; EtOH, ethanol; 2-PrOH, propan-2-ol; EG, ethylene glycol; DMSO, dimethyl sulfoxide; AN, acetonitrile; NB, nitrobenzene; NM, nitromethane.

[c] Gas-phase basicity values are taken from Ref. 16.

Table 2. Coefficients for the correlation equations for the basicity of propylamines: $\delta\Delta G = \pi\& + a\alpha + b\beta + \delta\Delta G_0$

Amine	*s*	*a*	*b*	$\delta\Delta G_0$	*N*	*R*	*F*	s.d.
$PrNH_2$	$-2{\cdot}4 \pm 0{\cdot}2$	$-0{\cdot}6 \pm 0{\cdot}2$	$-2{\cdot}3 \pm 0{\cdot}3$	$4{\cdot}1 \pm 0{\cdot}2$	10	0·995	179	0·3
Pr_2NH	$1{\cdot}0 \pm 0{\cdot}1$	$-0{\cdot}1 \pm 0{\cdot}1$	$1{\cdot}4 \pm 0{\cdot}2$	$-1{\cdot}2 \pm 0{\cdot}1$	10	0·993	144	0·1
Pr_3N	$3{\cdot}9 \pm 0{\cdot}3$	$0{\cdot}2 \pm 0{\cdot}5$	$4{\cdot}3 \pm 0{\cdot}7$	$-4{\cdot}2 \pm 0{\cdot}4$	10	0·991	111	0·5

Each coefficient is accompanied by its standard error (±); the correlation coefficient (*R*), *F* statistic (*F*) and standard deviation (s.d.) of the equations are given. All nine solution-phase basicities and the gas-phase basicity were used for the determination of the coefficients in Table 2. The solvent solvatochromic parameters, which are given in Table 1, were used to generate the MLR equations.

Dipolarity–polarizability

The dipolarity–polarizability term is a measure of the energies of the solute–solvent interactions that are caused by the dipolar interactions or by induced dipolar interactions which contribute to solvation. These interactions are sometimes referred to as non-specific interactions. Since the basicity is dictated by the nature of the equilibrium species, the solute–solvent interactions of all equilibrium species shown in equation (3) must be examined. Non-specific solutet–solvent interactions that involve Pr_nN and Et_2NH are expected to be minimal owing to the neutrality of the solutes. On the other hand, non-specific solute–solvent interactions of $Pr_nNH^+_{(4-n)}$ and $Et_2H_2^+$ are expected to be substantial owing to the charge of these ions.

For $Pr_nNH^+_{(4-n)}$ ions, the magnitude of the charge that resides on the ion is dictated by the value of *n*. When $n = 1$, the charge on the propylammonium ion is less than the charge on the ion when $n = 2$ or 3. The reduction of the charge is caused by another form of solute–solvent interaction, which will be discussed in the following sections. It is evident from the MLR equations (Table 2) that the strongest interaction is between the solvent and the tripropylammonium ion. The largest coefficient of the dipolarity–dipolarizability interaction is for the basicity of tripropylamine. For these propylamines, ion–pairing apparently does not contribute to basicity variations. The goodness of the fit for the MLR with DMSO excluded is essentially the same as that with its inclusion. DMSO is a polar solvent and ion–pairing is expected to be minimal in such solvents.[17]

From the correlation equations shown in Table 2, the sign of the dipolarity–polarizability coefficient is negative for propylamine, but changes to a positive value for the basicity of dipropylamine and tripropylamine. For the basicity of propylamine, non-specific interactions that involve the propylammonium ion, and diethylammonium ion must be examined. Compared with the propylammonium ion, the diethylammonium ion is expected to have a slightly larger residual charge, owing to fewer modes of specific solvation (see the next section). As a result, non-specific solvation of the diethylammonium ion is more important than that of the propylammomum ion. As a result, a negative coefficient for this property is obtained. For the basicity of dipropylamine, the coefficient for the polarity–polarizability effect is positive and slightly greater than zero. The magnitude and sign of this coefficient imply that the reverse of equilibrium (3) is favored by this effect. Owing to the slightly larger size of a propyl group compared with that of an ethyl group, inherent stabilization of the dipropylammonium ion by the propyl groups is slightly greater than the inherent stabilization of the diethylammonium ion by its alkyl groups. It has been shown that alkyl substituents, which are polarizable,[18] do contribute to the reduction of positive character of ammonium ions.[19] However, this contribution is highly attenuated in solution.[20] For the basicity of tripropylamine, a similar argument holds for the large positive coefficient. Since there are fewer modes of specific solvation for the tripropylammonium ion compared with the diethylammonium ion, non-specific solute–solvent interaction is important for the solvations of the tripropylammonium ion. As a result, a relatively large positive coefficient is obtained from the MLR (Table 2).

Solvent acidity

Protic solvents interact with solutes that have basic sites. This type specific interaction that is created by the formation of hydrogen bonds between a solvent molecule and a solute molecule is one form of solvation that is often referred to as specific solvation. All propylamines are similar to diethylamine in that they have only one pair of electrons with which to form hydrogen bonds to the solvent. As a result, the coefficient for this property is (*a* in Table 2) close to zero for the basicity of propylamines. The effectiveness of such hydrogen bonds depends on the ability of both solvent and solute molecules to approach close enough to allow the formation of the hydrogen bond. This aspect is significant particularly for tripropylamine owing to its bulkiness. As the steric congestion around the nitrogen atom increases in the order $PrNH_2 < Pr_2NH < Pr_3N$, the existence of significant hydrogen bonding in the case of $PrNH_2$, but not the other amines, may well be due to a steric effect. As a result, the large standard error for the coefficient for the basicity of tripropylamine may indicate the steric inhibition to its solvation compared to the other propylamines.

Solvent basicity

Basic solvents form hydrogen bonds to acidic sites of solutes. This form of solvation is the other mode of specific solvation. The number of acidic sites differs for the different type ammonium ions. Propylammonium ion has three acidic hydrogens to which individual specific solute–solvent interactions take place. On the other hand, tripropylammonium ion, which has only one acidic hydrogen, depends strongly on this type specific solute–solvent interaction for the dispersal of the charge into the solvent. For the basicity of propylamine, the coefficient is negative. Since there are two acidic hydrogens on the diethylammonium ion (compared with three in the reactant) by which the charge can be dispersed into the solvent, the hydrogen bonds to the diethylammonium ion are more important for charge dispersal than those of the propylammonium ion. For the basicity of dipropylamine, solvation of the dipropylammonium ion and the diethylammonium ion are very similar and, as a result, the coefficient is relatively small.

The specific solute–solvent interaction is most pronounced for the basicity of tripropylamine. The sign is positive, which means that the solvation of the tripropylammonium ion is very important compared with the diethylammonium ion. There is only one acidic hydrogen on the tripropylammonium ion compared with the diethylammonium ion, so that the effectiveness by which the charge of the tripropylammonium ion is dispersed into the solvent depends strongly on the interaction of the single hydrogen with basic solvents. Owing to the dominance of solute–solvent interaction by this mode, the basicity trend is the reverse in DMSO compared with the gas phase. Since DMSO is a very basic solvent, effective solvation of the primary ammonium ion by this mode overshadows any substituent polarizability effect. A similar trend is observed also for these amines in ethyl acetate,[21] which is an aprotic dipolar solvent.

CONCLUSIONS

For the basicity of propylamines in solution, solute–solvent interactions of the ammonium ions with dipolar basic solvents play the greatest role in the determination of the relative basicities. This observation is consistent with that made for the basicity of substituted ethylamines, in which it was shown that their basicities are very sensitive to the polar, acidic and basic nature of the medium.[22] Based on the quality of the 'fit' of the MLR equations, the solvatochromic parameters describe very well the solute–solvent interactions that contribute to the basicity variations of propylamines. The intercepts of these equations are different and represent the basicity of the amines in a solvent-free atmosphere. Since the gas phase is not simply a medium-free atmosphere, no conclusions regarding the relationship between the intercept of the regression equation and the gas-phase basicities can be drawn. However, the trend shown for the basicity of propylamines from the intercept is the same as the experimental gas-phase basicity, which suggests that the intercepts do reflect, to some extent, gase-phase basicity.

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