

Significance of Nucleophilic Solvation of Ammonium Bond ($\equiv\text{N}^+\text{-H}$) in Protonated Amines: A Thought Provoking Physical-Organic Chemistry Lecture to Graduate Students

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Received August 13, 2013; Revised August 27, 2013; Accepted August 28, 2013

Abstract Our mission has perceived and still continuing exceptional achievement on ‘Transforming chemistry research in to chemistry teaching’. In this course of events we have been able to publish several articles in the area of chemical education. In continuation of this, the present article using a total of 38 amines is one of our successful aftermaths of the importance of nucleophilic solvation of ammonium bond ($\equiv\text{N}^+\text{-H}$) in protonated amines. We have explained the significance of nucleophilic solvation of ammonium bond in protonated amines in a simple and lucid way using Taft linear polar free energy correlations of pK_a ’s in aqueous solution and dipole moments in gas phase, in benzene, in cyclohexane and of pure liquids of several primary, secondary and tertiary amines as a function of Taft polar substituent constants. Our performed Taft correlations showed that the solvation of ammonium bond in protonated amines through $\equiv\text{N}^+\text{-H}$ bond is worth understanding in terms of steric hindrance which is absent in gas phase, in benzene and in cyclohexane as it imparts its substance in biology.

Keywords: nucleophilic solvation, ammonium bond, Taft correlations

Cite This Article: R. Sanjeev, V. Jagannadham, and R. Veda Vrath, “Significance of Nucleophilic Solvation of Ammonium Bond ($\equiv\text{N}^+\text{-H}$) in Protonated Amines: A Thought Provoking Physical-Organic Chemistry Lecture to Graduate Students.” *World Journal of Chemical Education* 1, no. 1 (2013): 1-5. doi: 10.12691/wjce-1-1-1.

1. Introduction

Rotation, solvation, and hydrogen bonding of aqueous ammonium ions are well studied [1]. Amines are abundant in biology. Amino acids release amines when they breakdown, in the case of decaying fish which smell of trimethylamine. The amines like epinephrine, norepinephrine, dopamine, serotonin, and histamine are known as better neurotransmitters. Protonated amino groups ($-\text{NH}_3^+$) are the most common positively charged moieties in proteins, specifically in the amino acid lysine [2]. The negatively charged polymer DNA is typically bound to various amine-rich proteins [3]. Additionally, the terminal charged primary ammonium ion of lysine forms salt bridges with carboxylate groups of other amino acids in polypeptides, which is one of the bases of the three-dimensional structures of proteins [4]. Hence amines play an important role in physiological activity. Hydrogen bonding significantly influences the properties of primary, secondary and tertiary amines as well as the protonated derivative so called amines. Especially the solvation of amines and ammonium ions are subject of interest in terms of steric hindrance [5,6,7]. Therefore as the

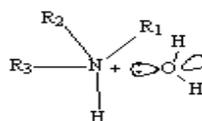
operating system of human body is water, in the present article we have performed a systematic study on the significance of nucleophilic aqueous solvation of ammonium ions.

2. Discussion

The solvation of protonated amines changes upon their conversion to ammonium compounds [8]. Typically salts of ammonium compounds exhibit the following order of solubility in water: primary ammonium (RNH_3^+) > secondary ammonium (R_2NH_2^+) > tertiary ammonium (R_3NH^+). Quaternary ammonium salts usually exhibit the lowest solubility of the series. In sterically hindered amines, as in the case of trimethylamine, the protonated form is not well-solvated. Briegleb [9] and others [10] have calculated the heats of hydration of amines and the corresponding ammonium ions. The heat of hydration of amines ranges between 10-12 kcal/mole and that of ammonium ions ranges between 83-85 kcal/mole. Hence it is important to understand the solvation pattern of ammonium ions through $\equiv\text{N}^+\text{-H}$ bond as most of the polypeptides and proteins exist as protonated amines under physiological conditions. Trotman-Dickenson [11]

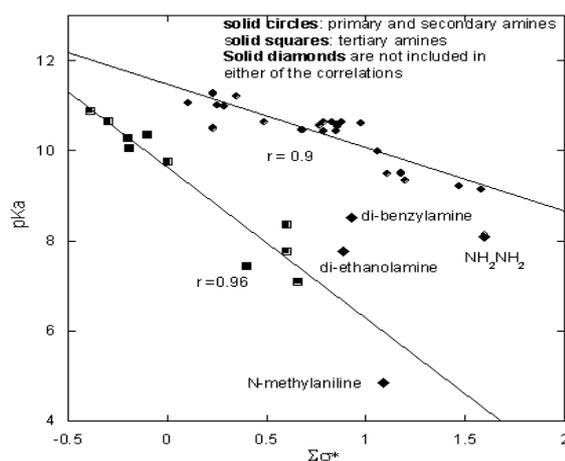
has shown that the hydrogen bonding between ammonium ions and water molecules was through the ammonium bond $\equiv\text{N}^+\text{-H}$. He observed that the more are the $\equiv\text{N}^+\text{-H}$ bonds the greater are the hydrogen bonds. Further it is observed that the pK_a 's of primary, secondary and tertiary amines are well correlated [6,11] as a function of Taft $\Sigma\sigma^*$ values separately in their own pattern. Different correlations for primary, secondary and tertiary amines were explained due to degree of differences in steric hindrance of substituents in amines [5].

We have used the data of some of the amines from the reference 5 with some additional amines whose dipole moments are available in literature [12]. First we made the correlations with pK_a values as the function of $\Sigma\sigma^*$. The points of primary and secondary amines fall on one straight line and that of tertiary amines on a different line of correlation. Though the correlation coefficients are bit poor the trends are unmistakable (Figure 1). The difference in correlation of pK_a 's with $\Sigma\sigma^*$ of primary and secondary amines and tertiary amines was due to degree of differences in the steric hindrance of substituents in the amines towards their degree of solvation [6]. The degree of solvation of amines is again due to the number of water molecules involved in solvation. Evidently tertiary amines would be solvated by only one water molecule because they have only one ammonium bond $\equiv\text{N}^+\text{-H}$ (Scheme 1).



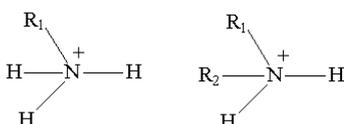
Scheme 1

The other three bonds of nitrogen are involved with the three substituents which make much steric hindrance towards solvation. And they correlated on one line (Figure 1: solid squares)

Figure 1. Plot of pK_a vs $\Sigma\sigma^*$

Primary and secondary amines have more than one ammonium bond (Scheme 2). This makes more degree of solvation hence their pK_a values are correlated with a different straight line (Figure 1: solid circles).

Scheme 2



Though Hall et. al. did not make any correlation of nucleophilicities of different amines as a function of $\Sigma\sigma^*$ in his communication [5] we went ahead further a little to it. The nucleophilicities of some primary, secondary and tertiary amines were correlated as a function of $\Sigma\sigma^*$ (Figure 2). Interestingly the points for all three types of amines fell on three different lines. Though the correlations for primary and secondary amines are poor but they fell in to two distinct groups of their own pattern, the correlation with tertiary amines was excellent ($r = 0.99$).

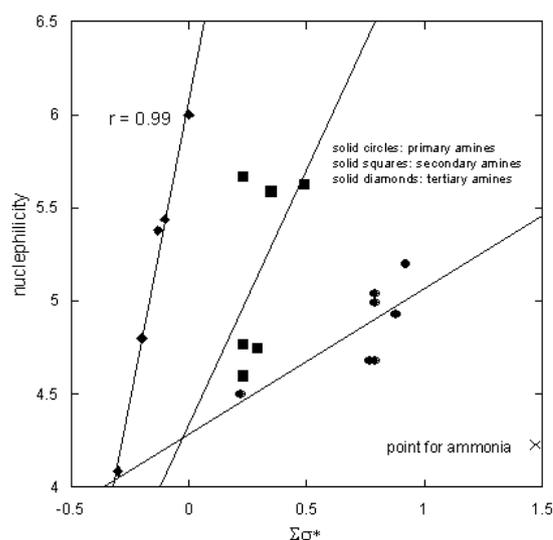
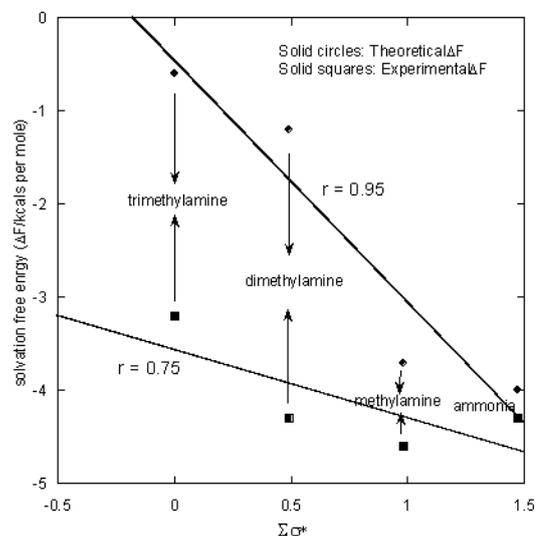


Figure 2. Plot of nucleophilicities versus

Again either theoretical (correlation coefficient = 0.95) or experimental (correlation coefficient = 0.75) solvation free energies of ammonia, methylamine, dimethylamine and trimethylamine did not correlate well as a function of $\Sigma\sigma^*$ (Figure 3) because each amine belongs to different category with respect to branching. The solvation free energies are from reference [7]. This once again clearly shows that the non-correlation of solvation free energies with $\Sigma\sigma^*$ is due primarily to the increase in excessive steric hindrance of near increasing number of proximate substituents on amine nitrogen [5,7] and also the solvation is a function of number of amine/ammonium bonds [6].

Figure 3. Plot of solvation free energies of ammonia, methylamine, dimethylamine and trimethylamine versus $\Sigma\sigma^*$

Hall in his communication [6] mentioned on the basis of Taft's work [13] on the good correlation of dipole moments in benzene of all the three types of amines as a function of $\Sigma\sigma^*$ fell on the same single straight line. This gave us a scope to see the Taft plot (Figure 4) of dipole moments in benzene versus $\Sigma\sigma^*$ for some of the amines whose dipole moments in benzene are available in literature used in Figure 1.

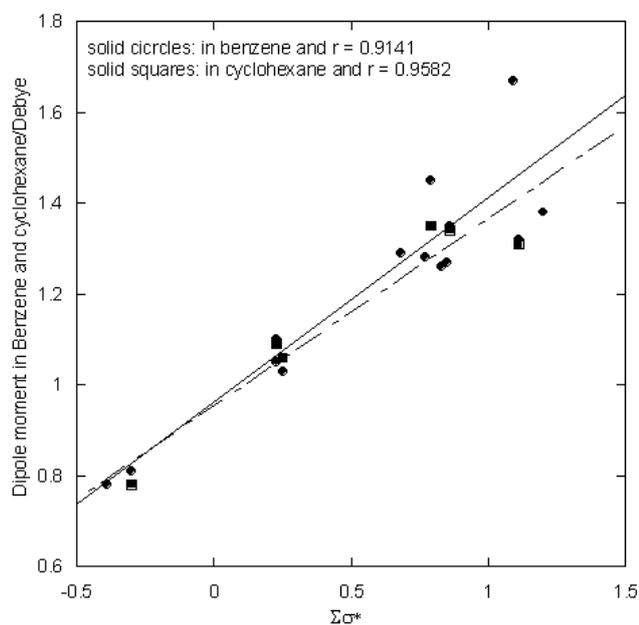


Figure 4. Plot of dipole moments in benzene and cyclohexane versus $\Sigma\sigma^*$

In this context we have further stretched our discussion to see any correlation of dipole moments of amines in gas phase versus $\Sigma\sigma^*$. In fact we got a good correlation (Figure 5) irrespective of whether the amine is primary or secondary or tertiary.

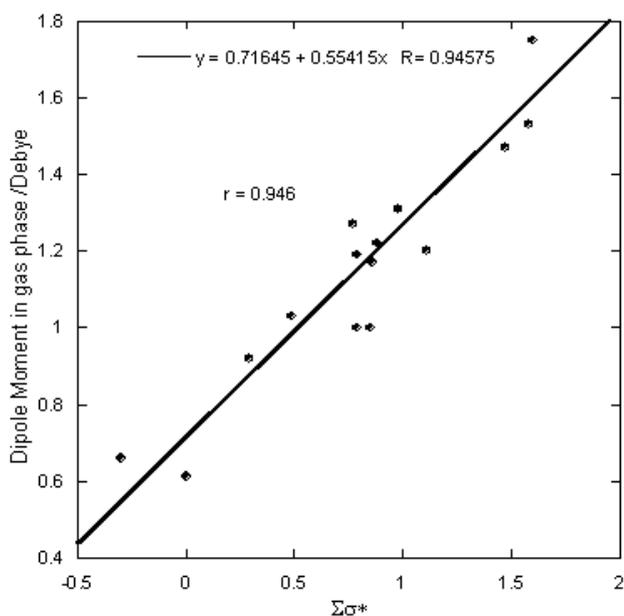


Figure 5. Plot of dipole moments in gas phase versus $\Sigma\sigma^*$

Similarly a plot of dipole moments in gas phase of ammonia, methylamine, di-methylamine and tri-methylamine vs $\Sigma\sigma^*$ was found to be very satisfactory (Figure 6).

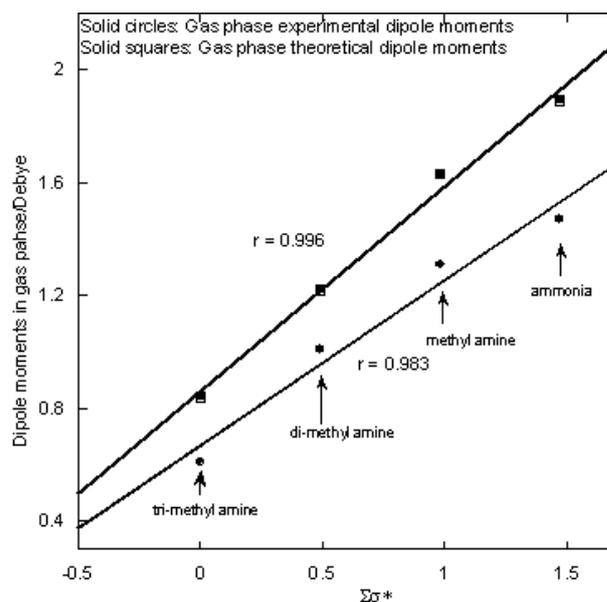


Figure 6. Plot of dipole moments in gas phase versus $\Sigma\sigma^*$

The gas phase experimental and theoretical dipole moments used in Figure 6 are from reference 7.

The reasonably good correlations of dipole moments in benzene and in gas phase vs $\Sigma\sigma^*$ shown in Figure 4, Figure 5 and Figure 6 are due to absence of solvation of amines or ammonium ions and the absence of solute-solute, solute-solvent and solvent-solvent interactions. This type of correlations of two or three types of straight lines shown above (Figure 1, Figure 2 and Figure 3) indicate that the amine or ammonium bonds are solvated in water and the solvation is absent either in benzene which is a non-polar solvent and in gas phase in which the system behaves like an ideal non-interacting system of particles as evidenced in statistical thermodynamics.

Finally we have made an attempt to correlate the dipole moments of pure liquids for 6 amines whose dipole moments are available in literature [12] as a function of $\Sigma\sigma^*$ (Figure 7).

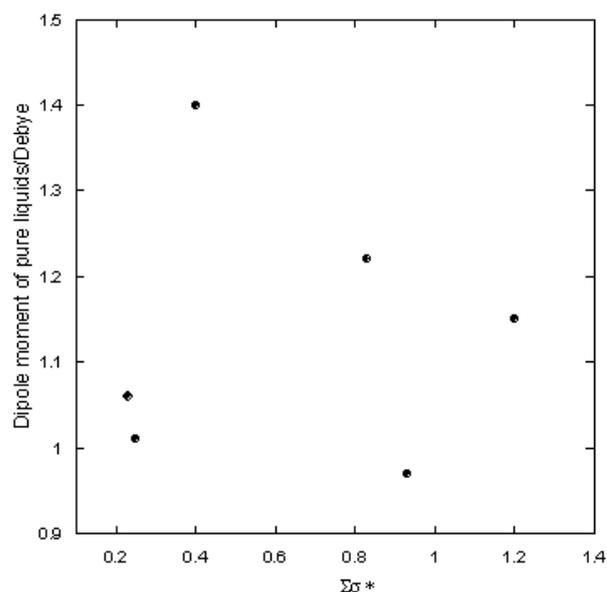


Figure 7. Plot of Dipole moment of pure liquids vs $\Sigma\sigma^*$

But no good correlation was observed for pure liquids (Figure 7). This is explained as follows [14]: The liquid is

a collapsed solid. Among the three states of matter the liquid state is tricky to be understood. The gas in an ideal approximation obeys the Maxwell-Boltzmann distribution. The solid if it is an ideal crystal follows the model of Einstein's theory of heat capacity of solids. The properties of liquid lie in between those of gases and solids. Because the two states of matter i.e. perfect chaos (gas) and perfect order (solid) are relatively simple to treat mathematically and it is possible to evaluate partition functions and hence several thermodynamic properties in both the cases. The cohesive forces are strong enough to lead to a condensed state from gaseous state, but not strong enough to prevent a considerable translational energy of the individual molecules in liquid to become an ordered solid. Thermal motions introduce a disorder in to the liquid without

completely destroying the regularity of its structure, it is therefore difficult to evaluate a partition function for a liquid and hence the thermodynamic properties. As the solvation free energies or solvation enthalpies are thermodynamic properties of liquids which are difficult to be evaluated using statistical thermodynamic principles, the same difficulty arises in understanding the non-correlation of dipole moments of pure liquid amines with Taft $\Sigma\sigma^*$ values. Here one must understand two points of interest i.e. the solid is perfect static crystal and the gas is a very dilute system and it is a perfect example of system containing non-interacting particles. But the case with liquid is different to be understood.

Table 1. Taft $\Sigma\sigma^*$, pK_a , nucleophilicities (n) and dipole moments of different amines. All the physical quantities are from references [5,6,12,15]

Sl.No.	Amine	$\Sigma\sigma^*$	pK_a (aq.sol.)	n	Dipole moments in			
					Benzene	Cyclohexane	Gas phase	Pure liquids
1	NH ₃	1.47	9.21	4.23			1.47	
2	H ₂ NNH ₂	1.60	8.10				1.75	
3	CH ₃ NH ₂	0.98	10.62	5.20			1.31	
4	C ₂ H ₅ NH ₂	0.88	10.63	4.93			1.22	
5	n-PrNH ₂	0.86	10.53		1.35	1.34	1.17	
6	n-BuNH ₂	0.79	10.43	5.04	1.45	1.35	1.00	
7	i-PrNH ₂	0.79	10.63	4.68	1.45		1.19	
8	sec-BuNH ₂	0.77	10.56	4.68	1.28			
9	t-BuNH ₂	0.68	10.45		1.29			
10	i-BuNH ₂	0.85	10.59	4.99	1.27		1.27	
11	CH ₂ =CHCH ₂ NH ₂	1.11	9.49		1.32	1.31	1.2	
12	HOCH ₂ CH ₂ NH ₂	1.18	9.50					
13	NH ₂ CH ₂ CH ₂ NH ₂	1.06	9.98					
14	C ₆ H ₅ CH ₂ NH ₂	1.20	9.34		1.38			1.15
15	C ₆ H ₅ NH ₂	1.58	9.13				1.53	
16	cy-C ₆ H ₁₁ NH ₂	0.83	10.64		1.26			1.22
17	(CH ₃) ₂ NH	0.49	10.64	5.63			1.03	
18	(C ₂ H ₅) ₂ NH	0.29	10.98	4.75			0.92	
19	(n-Pr) ₂ NH	0.25	11.0		1.03	1.06		1.01
20	(i-Pr) ₂ NH	0.11	11.05		1.26			
21	(n-Bu) ₂ NH	0.23	11.25	4.77	1.12	1.09		
22	(i-Bu) ₂ NH	0.23	10.5	4.60	1.10			1.06
23	C ₆ H ₅ CH ₂ (Et)NH	0.61	10.3					
24	(C ₆ H ₅ CH ₂) ₂ NH	0.93	8.52		1.02			0.97
25	C ₆ H ₅ (CH ₃)NH	1.09	4.85		1.67			
26	(CH ₂ CH ₂ OH) ₂ NH	0.89	7.76		2.84			
27	(CH ₃) ₃ N	0.00	9.76	6.00			0.612	
28	(C ₂ H ₅) ₃ N	-0.30	10.65	4.09	0.81	0.78	0.66	
29	(n-Bu) ₃ N	-0.39	10.89		0.78			
30	(CH ₂ CH ₂ OH) ₃ N	0.60	7.77		3.57			
31	(C ₆ H ₅ CH ₂) ₃ N	0.66	7.10		0.65			
32	C ₆ H ₅ (CH ₃) ₂ N	0.60	8.35					
33	C ₆ H ₅ (C ₂ H ₅) ₂ N	0.40	7.44		1.80			1.40
34	pyrrolidine	0.23	11.27	5.67				
35	piperidine	0.35	11.22	5.59				
36	(CH ₃) ₂ N(C ₂ H ₅)	-0.10	10.36	5.44				
37	(CH ₃) ₂ N(n-C ₄ H ₉)	-0.19	10.06	5.38				
38	(CH ₃)N(C ₂ H ₅) ₂	-0.20	10.29	4.80				

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