Protonation of Cubylamine

Stereoelectronic, Strain, and Medium Effects on the Protonation of Cubylamine, a Janus-like Base**

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In 1991 it was concluded on the basis of theoretical studies[1] that the amino group in cubylamine[2] (**1**NH_2, Scheme 1)

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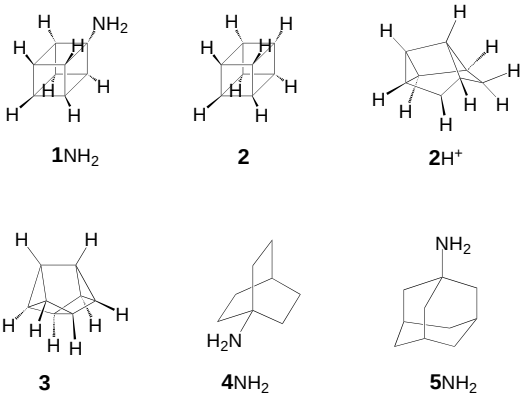


Scheme 1. Structures of cubylamine (**1**NH_2), cubane (**2**), tetracyclo[4.2.0.0^{2,4}.0^{3,8}]oct-7-ylium cation (**2**H^+), cuneane (**3**), bicyclo[2.2.2]oct-1-ylamine (**4**NH_2), and 1-adamantylamine (**5**NH_2).

interacts with the hydrocarbon moiety in a stereoelectronic fashion. To our knowledge, the potential consequences of this interesting feature were never explored. More recently we have shown[3] that the gas-phase protonation of the parent hydrocarbon, cubane (**2**), is irreversible and leads through ring opening to the formation of tetracyclo[4.2.0.0^{2,4}.0^{3,8}]oct-7-ylium cation (**2**H^+) which, on deprotonation, yields cuneane (**3**),[4] a less strained[5] isomer. These facts led us to study the protonation of **1**NH_2 in the gas phase (by using Fourier Transform Ion Cyclotron Resonance Spectroscopy, FT-ICR) and in solution (by means of potentiometric techniques as well as ^{1}H and ^{13}C NMR spectroscopy). The experimental findings were analyzed further by means of density functional theory (DFT) methods.[6]

We obtained the ^{1}H and ^{13}C NMR spectra of **1**NH_2 and its conjugate acid (see Supporting Information) and found that the ^{1}H and ^{13}C NMR shifts for **1**NH_2 are not only consistent with each other, but they are also in agreement with predicted shifts based on literature values for a number of monosubstituted cubanes.[7] Significantly, the data demonstrate that the cubic structure of the hydrocarbon framework of the parent hydrocarbon **2** is preserved in both **1**NH_2 and its conjugate acid. In addition, the ^{13}C chemical shifts of **2**,[8] **1**NH_2, and **1**NH_3^+ (assuming nitrogen protonation) from GIAO calculations[9] nicely correlate ($r^2 > 0.99$) with the experimental values.

The pK_a of **1**NH_3^+ in water at 25 °C (8.66 ± 0.02), which we measured,[10] can be compared to values given in Table 1 for other ammonium ions. There we see, for example, that **1**NH_3^+ is more acidic by two pK_a units than bicyclo[2.2.2]oct-1-ylammonium (**4**NH_3^+), a species having the same carbon content and a caged structure, and even more acidic than ammonium ion itself.

Table 1: Experimental pK_a and GB values for selected bases.

Base	pK_a[a]	GB [kcal mol^{-1}]
NH_3	9.24[b]	195.7[e]
CH_3NH_2	10.64[b]	206.6[e]
n-$C_3H_7NH_2$	10.53[b]	211.3[e]
bicyclo[2.2.2]oct-1-ylamine (**4**NH_2)	10.66[c]	217.8[e]
1-adamantylamine (**5**NH_2)	10.55 ± 0.02[d]	219.0[e]
1NH_2	8.66 ± 0.02[d]	(227.4 ± 2.3)[d,f]

[a] pK_a of the conjugate ion. [b] In kcal mol^{-1}. [b] From ref. [11]. [c] From ref. [12]. [d] This work. [e] From ref. [13]. [f] Apparent value.

To rationalize this result we carried out calculations at the B3LYP6-311 + G(d,p) level[14] (see Supporting Information). We found that the computed C–C bond lengths involving the carbon atom α to the amino group in **1**NH_2 (see Figure 1) fully

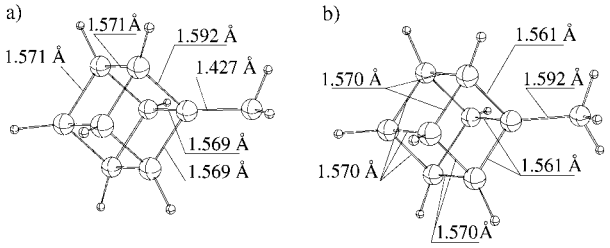


Figure 1. Selected geometry parameters for a) neutral and b) N-protonated cubylamine (B3LYP6-311 + G** data).

support the existence of a stabilizing stereoelectronic interaction, in which electron density is transferred from the amino group to the hydrocarbon moiety.[1] Furthermore, we have applied the NBO (natural bonding orbitals) methodology[15] to **1**NH_2 and found indeed a strong stabilizing interaction (14.2 kcal mol^{-1}) between the nitrogen lone pair and the antiperiplanar antibonding C–C orbital. This interaction, responsible for the elongation of the corresponding C–C bond, obviously disappears upon nitrogen protonation (see Figure 1). At the same level of theory the gas-phase basicity (GB) of **1**NH_2, assuming nitrogen protonation (i.e. the standard Gibbs energy change for Equation (1)), amounts

$$\mathbf{1}NH_3^+(g) \rightarrow \mathbf{1}NH_2(g) + H^+(g) \quad \Delta_r G^o(1) \qquad (1)$$

to 211.7 kcal mol^{-1}, a value close to the experimental value for the much less polarizable propylamine and significantly lower than GB(**4**NH_2) (see Table 1).

The intrinsic (gas-phase) basicity of **1**NH_2 (assuming protonation at nitrogen) is thus lower than expected on the basis of polarizability effects. The aqueous basicity of **1**NH_2 is also significantly lower than that of **4**NH_2 and other alicyclic and aliphatic primary amines. This is a very important fact, because these aqueous basicities are remarkably constant and very insensitive to polarizabilty effects,[16] a situation depicted in Figure 2. This implies the influence of a contribution other than polarizability.

All these results are consistent with **1**NH_2 behaving in solution as a nitrogen base weakened by electronic factors. In addition to the stereoelectronic interactions mentioned above, the most relevant electronic factors are likely hybridization effects originating in the large s character of the orbitals on the carbon bearing the amino group.[2b,17,18]

Our FT-ICR experiments show that under conditions of chemical ionization, **1**NH_2(g) is cleanly protonated to yield a

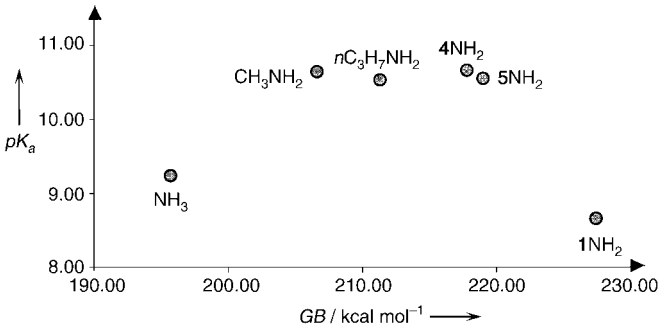


Figure 2. Correlation between gas-phase basicities and aqueous pK_a values for some amines.

cation $C_8H_{10}N^+$ (**6**H$^+$). Ion selection experiments were performed on mixtures of **1**NH_2(g) and a number of bases B of known GB to quantitatively examine the protonation of **1**NH_2(g) [Eq. (2)] and the deprotonation of **6**H$^+$ [Eq. (3)]

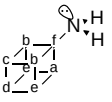
$$\mathbf{1}NH_2(g) + BH^+(g) \rightarrow \mathbf{6}H^+(g) + B(g) \;\; \Delta_r G^o(2) \qquad (2)$$

$$\mathbf{6}H^+(g) + B(g) \rightarrow \mathbf{6}(g) + BH^+(g) \;\; \Delta_r G^o(3) \qquad (3)$$

(details given in the Supporting Information). These experiments led to an "apparent gas-phase basicity" for **1**NH_2 of approximately 224.7 ± 2.3 kcal mol^{-1}. The structure of **6**H$^+$(g) has to be consistent with this finding.

The "apparent GB" of **1**NH_2(g) is appreciably higher than that of 1-adamantylamine (**5**NH_2, Scheme 1, GB = 219.0 kcal mol^{-1}), a primary amine endowed with a more polarizable framework and thus expected to be a stronger base in the gas phase. Cubylamine (**1**NH_2) is also 13 kcal mol^{-1} stronger than expected for nitrogen protonation (see above). These facts rule out the amino group as the basic center in the gas-phase molecule and, by analogy with the behavior of **2**(g), they suggest that **1**NH_2(g) is also undergoing ring opening on protonation.

There are six inequivalent carbon atoms in **1**NH_2 which can supposedly be the protonation centers (see Scheme 2). We summarize in Scheme 3 the structures and standard Gibbs energy changes computed at the B3LYP6-311 + G(d,p) level for the formation of all possible species **6**H$^+$(g) by protonation of **1**NH_2(g) in a one-step process as well as the most stable neutral products following deprotonation. Protonation at carbon f leads (without any barrier) to the N-protonated form **1**NH_3^+. Edge, face, and endohedral protonation of **1**NH_2 did not lead to independent minima, in analogy to **2**.[3]

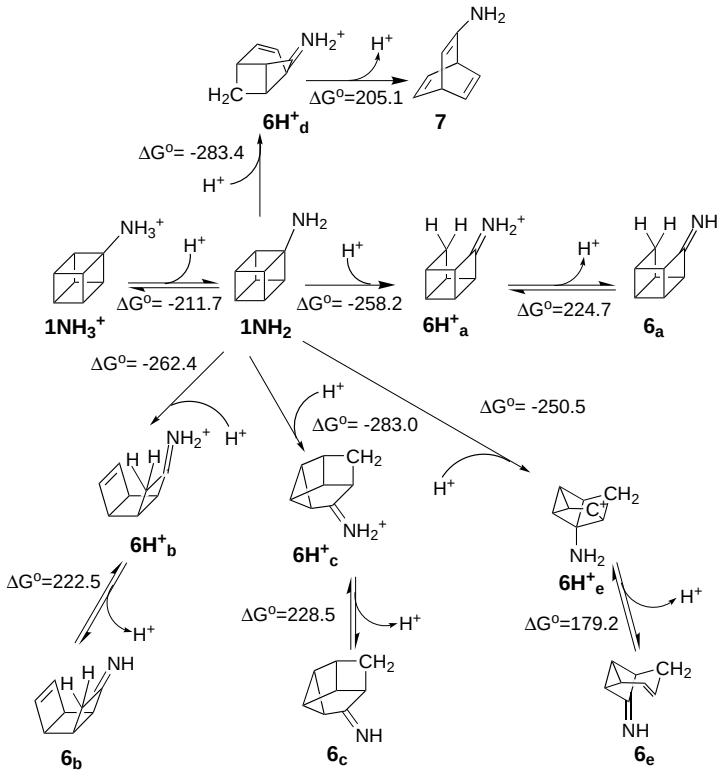


Scheme 2. Nonequivalent carbon atoms in **1**NH_2.

The computed Gibbs free energy changes of reaction (1) for carbon-protonated **1**NH_2(g) are at least 250.5 kcal mol^{-1}. Hence **1**NH_2(g) should be able to deprotonate the conjugate acids of bases with GB values of at least 250.5 kcal mol^{-1}. We maintain that the apparent GB for **1**NH_2(g) is appreciably smaller.

The fact that measurements in both the forward and reverse directions give the same basicity strongly suggests that kinetic factors are unimportant and that we are probing the properties of a single species, namely some (or all) of the ions **6**H^+_a–**6**H^+_e. Thus, when **1**NH_2 reacts in the gas phase with the ammonium ions mentioned above, it ring-opens to give a complex between one of these species and the deprotonated acid (i.e., reference base). The observable outcome is determined by the relative basicities of the ring-opened species and the reference amine, rather than by the difficulty of protonating the relevant carbon atom in **1**NH_2(g). There are important precedents of gas-phase isomerization through protonation[19]

Our computational results summarized in Scheme 3 are fully consistent with this concept, as iminium ions **6**H^+_a to **6**H^+_c can be deprotonated by bases with GB values in the



Scheme 3. Protonation of cubylamine at different sites and the preferred deprotonation of the resulting cations. All reaction free energies are given in kcal mol^{-1}.

range of 224.7 to 228.5 kcal mol^{-1} while the apparent GB of **1**NH_2 is 224.7 ± 2.3 kcal mol^{-1}. On these grounds, structures **6**H^+_d and **6**H^+_e can be excluded as the corresponding neutral bases (bicyclo[2.2.2]octa-2,5,7-trien-2-ylamine (**7**), GB = 204.4, and **6**$_e$, GB = 179.2 kcal mol^{-1}) are much weaker. On the other hand, in the light of the previous discussion, the formation of any of the structures **6**H^+_a to **6**H^+_c is possible and the formation of a mixture of these iminium ions can not be ruled out.

Last we draw attention to the importance of medium effects on the structure of protonated **1**NH_2. Although a number of cases have been reported wherein the structure of

the protonated[20] or deprotonated[21] species is determined by the medium, this seems to be the first case involving a basic carbon center. Our computational results show that in the gas phase protonation followed by ring opening is favored over protonation at the amino group by 46.5–71.7 kcal mol^{-1}, and this large energetic advantage seems to be overrun in aqueous solution. On the other hand, we thought it unlikely that the stabilization of the ammonium ion **1**NH_3^+ through solvation could be so much larger than that of the iminium ions **6**H^+_a to **6**H^+_c. This led us to quantitatively estimate the corresponding changes in the Gibbs energies of solvation for these species, with water as the solvent, by using the the Polarized Continuum Model (PCM)[22] as implemented in the Gaussian 98 package. The corresponding Gibbs energy changes for solvation of the species **1**NH_3^+ and **6**H^+_a–**6**H^+_c are indeed quite close, −62.2, −59.6, −60.2 and −58.6 kcal mol^{-1}, respectively. It thus seems more likely that the release of energy attending the formation of the collision complex in the FT-ICR experiments is sufficient to overcome the activation barrier involved in the ring-opening process (as it is the case for **2**(g)) This energy release is absent in the reaction in solution.

Our results can be summarized as follows:

1) In the gas phase, **1**NH_2 is irreversibly protonated on the carbon atom, leading to the formation of iminium ions through ring opening.
2) In aqueous solution, **1**NH_2 is protonated on the amino nitrogen atom, and the cubic structure of the hydrocarbon moiety is preserved. The aqueous basicity of **1**NH_2 is appreciably lower than expected for a normal alicyclic amine. This effect is quite consistent with the stereoelectronic interaction between the amino group and the hydrocarbon framework as well as with the large *s* character of the orbitals on the carbon bearing the amino group.

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