Protonation of Cubylamine

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

José-Luis M. Abboud,* Ilmar A. Koppel,* Ibon Alkorta, Ernest W. Della, Paul Müller, Juan Z. Dávalos, Peeter Burk,* Ivar Koppel, Viljar Pihl, and Esther Quintanilla

In 1991 it was concluded on the basis of theoretical studies[1] that the amino group in cubylamine[2] (INH₂, Scheme 1)

[1] Prof. Dr. J.-L. M. Abboud, Dr. J. Z. Dávalos, Eng. E. Quintanilla
Instituto de Química Física "Rocasolano", CSIC
C/Serrano, 119, 28006 Madrid (Spain)
Fax: (+34) 91-5855184
E-mail: jlabboud@iqfr.csic.es
Prof. Dr. I. A. Koppel, Prof. Dr. P. Burk, Dr. I. Koppel, Dr. V. Pihl
Institute of Chemical Physics, University of Tartu
2 Jakobi St. 51014 Tartu (Estonia)
Fax: (+372) 7-375-264
E-mail: ilmar@chem.ut.ee
peeter@chem.ut.ee
Dr. I. Alkorta
Instituto de Química Médica, CSIC
C/Juan de la Cierva, 3, 28006, Madrid (Spain)
Prof. Dr. E. W. Della
Department of Chemistry, Flinders University
Bedford Park, South Australia 5042 (Australia)
Prof. Dr. P. Müller
Department of Organic Chemistry, University of Geneva
30, quai Ernest Ansermet, 1211 Geneva 4 (Switzerland)
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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 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\(^1\).0\(^3\).0\(^7\).0\(^9\)]oct-7-yl cation (2H\(^+\)) which, on deprotonation, yields cuneane (3),\(^{[4,5]}\) a less strained isomer. These facts led us to study the protonation of INH\(_2\) 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 INH\(_2\) and its conjugate acid (see Supporting Information) and found that the \(^1\)H and \(^13\)C NMR shifts for INH\(_2\) 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 INH\(_2\) and its conjugate acid. In addition, the \(^13\)C chemical shifts of 2,\(^{[8]}\) INH\(_2\), and INH\(_2^+\) (assuming nitrogen protonation) from GIAO calculations\(^{[9]}\) nicely correlate \((\rho > 0.99)\) with the experimental values.

The pK\(_a\) of INH\(_2^+\) 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 INH\(_2^+\) is more acidic by two pK\(_a\) units than bicyclo[2.2.2]oct-1-ylammonium (4NH\(_3^+\)), a species having the same carbon content and a caged structure, and even more acidic than ammonium ion itself.

To rationalize this result we carried out calculations at the B3LYP-6-311 + G(d,p) level\(^{[11]}\) (see Supporting Information). We found that the computed C–C bond lengths involving the carbon atom α to the amino group in INH\(_2\) (see Figure 1) fully support the existence of a stabilizing stereoelectronic interaction, in which electron density is transferred from the amino group to the hydrocarbon moiety.\(^{[12]}\) Furthermore, we have applied the NBO (natural bonding orbitals) methodology\(^{[13]}\) to INH\(_2\) and found indeed a strong stabilizing interaction (14.2 kcal mol\(^{-1}\)) between the nitrogen lone pair and the 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 INH\(_2\), assuming nitrogen protonation (i.e. the standard Gibbs energy change for Equation (1)), amounts to 211.7 kcal mol\(^{-1}\), a value close to the experimental value for the much less polarizable propylamine and significantly lower than GB(4NH\(_3\)) (see Table 1).

The intrinsic (gas-phase) basicity of INH\(_2\) (assuming protonation at nitrogen) is thus lower than expected on the basis of polarizability effects. The aqueous basicity of INH\(_2\) is also significantly lower than that of 4NH\(_3\) and other aliphatic and aliphatic primary amines. This is a very important fact, because these aqueous basicities are remarkably constant and very insensitive to polarizability effects\(^{[14]}\) a situation depicted in Figure 2. This implies the influence of a contribution other than polarizability.

All these results are consistent with INH\(_2\) 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.\(^{[12,17,18]}\)

Our FT-ICR experiments show that under conditions of chemical ionization, INH\(_2^+(g)\) is cleanly protonated to yield a
cation C\textsubscript{6}H\textsubscript{4}N\textsuperscript{+} (6H\textsuperscript{+}). Ion selection experiments were performed on mixtures of 1NH\textsubscript{2}(g) and a number of bases B of known GB to quantitatively examine the protonation of 1NH\textsubscript{2}(g) [Eq. (2)] and the deprotonation of 6H\textsuperscript{+} [Eq. (3)]

\begin{align}
1\text{NH}_{2}(g) + B\textsuperscript{+}(g) &\rightarrow 6\text{H}^{+}(g) + B(g) \quad \Delta G^\circ(2) \quad (2) \\
6\text{H}^{+}(g) + B(g) &\rightarrow 6\text{H}(g) + B\textsuperscript{+}(g) \quad \Delta G^\circ(3) \quad (3)
\end{align}

(details given in the Supporting Information). These experiments led to an "apparent gas-phase basicity" for 1NH\textsubscript{2} of approximately 224.7 ± 2.3 kcal mol\textsuperscript{-1}. The structure of 6H\textsuperscript{+}(g) has to be consistent with this finding.

The "apparent GB" of 1NH\textsubscript{2}(g) is appreciably higher than that of 1-adamantylamine (SNH\textsubscript{2}, Scheme 1, GB = 219.0 kcal mol\textsuperscript{-1}), a primary amine endowed with a more polarizable framework and thus expected to be a stronger base in the gas phase. Cubylamine (1NH\textsubscript{2}) is also 13 kcal mol\textsuperscript{-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 1NH\textsubscript{2}(g) is also undergoing ring opening on protonation.

There are six inequivalent carbon atoms in 1NH\textsubscript{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 6H\textsuperscript{+}(g) by protonation of 1NH\textsubscript{2}(g) in a one-step process as well as the most stable neutral products following deprotonation. Protonation at carbon \( d \) (without any barrier) to the N-protonated form 1NH\textsubscript{2}\textsuperscript{+} has been found to be the most stable configuration. Edge, face, and endohedral protonation of 1NH\textsubscript{2} did not lead to independent minima, in analogy to 2.\textsuperscript{[23]}

The computed Gibbs free energy changes of reaction (1) for carbon-protonated 1NH\textsubscript{2}(g) are at least 250.5 kcal mol\textsuperscript{-1}. Hence 1NH\textsubscript{2}(g) should be able to deprotonate the conjugate acids of bases with GB values of at least 250.5 kcal mol\textsuperscript{-1}. We maintain that the apparent GB for 1NH\textsubscript{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 6H\textsuperscript{+}\textsubscript{c} - 6H\textsuperscript{+}\textsubscript{c}. Thus, when 1NH\textsubscript{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 1NH\textsubscript{2}(g). There are important precedents of gas-phase isomerization through protonation\textsuperscript{[19]}

Our computational results summarized in Scheme 3 are fully consistent with this concept, as iminium ions 6H\textsuperscript{+}\textsubscript{c} to 6H\textsuperscript{+}\textsubscript{c} can be deprotonated by bases with GB values in the range of 224.7 to 228.5 kcal mol\textsuperscript{-1} while the apparent GB of 1NH\textsubscript{2} is 224.7 ± 2.3 kcal mol\textsuperscript{-1}. On these grounds, structures 6H\textsuperscript{+}\textsubscript{a} and 6H\textsuperscript{+}\textsubscript{b} can be excluded as the corresponding neutral bases (bicyclo[2.2.2]octa-2,5,7-trien-2-yamine (7), GB = 204.4, and 6\textsubscript{a} GB = 179.2 kcal mol\textsuperscript{-1}) are much weaker. On the other hand, in the light of the previous discussion, the formation of any of the structures 6H\textsuperscript{+}\textsubscript{c} to 6H\textsuperscript{+}\textsubscript{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 1NH\textsubscript{2}. Although a number of cases have been reported wherein the structure of
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the protonated or deprotonated 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 NH₄⁺ through solvation could be so much larger than that of the iminium ions H⁺ to H⁺. 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 Polarized Continuum Model (PCM) as implemented in the Gaussian 98 package. The corresponding Gibbs energy changes for solvation of the species NH₃, H⁺, and O⁻, are indeed quite close, −62.2, −59.6, 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 FTIR experiments is sufficient to overcome the activation barrier involved in the ring-opening process (as it is the case for 2g). This energy release is absent in the reaction in solution.

Our results can be summarized as follows:
1) In the gas phase, NH₃ is irreversibly protonated on the carbon atom, leading to the formation of iminium ions ring opening.
2) In aqueous solution, NH₃ is protonated on the amino nitrogen atom, and the cubic structure of the hydrocarbon moiety is preserved. The aqueous basicity of NH₃ is appreciably lower than expected for a normal aliphatic 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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[18] Our own NBO calculations yield a 28.4% s character.