cis-1,5-Diaminocyclooctane: the most basic gaseous primary amine?

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The gas phase basicity of the title compound has been determined to be greater than that of putrescine, making it the most basic primary diamine measured to date.

Enzymic catalysis often includes removal of a proton from a site on the substrate that does not have high acidity. Given that amino acid side chains do not contain functional groups any more basic than primary amines or guanidino groups, it is not obvious what can accomplish this. One hypothesis suggests that two basic groups in the protein can be held so closely together that strong hydrogen bonding stabilizes their conjugate acid. Fig. 1 portrays a model for this sort of behavior. In the neutral base the nitrogens are positioned at a distance $d_{	ext{NN}}$ and ring constraints make 1 the most basic of the linear diamines.

Ab initio and DFT calculations agree with this view of the protonated diamines. The theoretical picture of the neutral diamines is more complicated. Although internally hydrogen bonded geometries (as Fig. 1 depicts) represent energetic minima for linear diamines, entropy does not favor them. Thus, hydrogen-bonded geometries ($D_{	ext{NN}}$ in Table 1) constitute minor species for gaseous, neutral diamines. The entropy change for making an internal hydrogen bond in HO(CH$_2$)$_4$OCH$_3$ in solution has been reported as −16.2 e.u. at 298 K, which does not differ greatly from the reported entropy change for transferring a proton from a monoaamine to 1, −14.3 e.u. Hence it seems likely that the topological change from a chain to a ring accounts for most of the entropy change upon protonation of a linear diamine.

The reasoning implies that more rigid, cyclic diamines might display greater basicity than linear diamines, because of a less unfavorable entropy change (so long as the nitrogens can get close to one another in the conjugate acid). To test this hypothesis, we have synthesized cis-1,5-diaminocyclooctane, 3, and here report its gas phase basicity relative to that of 1. Ab initio (MP2/6-311G**) geometry optimization predicts that the lowest energy conformation of neutral 3 places the amino groups too far apart to hydrogen bond to one another, as eqn. 1 illustrates. By contrast, the conjugate acid, 3H+, changes conformation to form a strong internal hydrogen bond. Our experiments show that the gas phase basicity for 3 (GB, which is defined as $-\Delta G$ for protonation) is greater than that for 1, although its proton affinity (PA, which is defined as $-\Delta H$ for protonation) is slightly lower.

This work.

Compound 3 was synthesized in a straightforward fashion starting with the ditosylate of cis-1,5-cyclooctandiol, as eqn. 2 depicts. The neutral diamine (bp 60–61 °C/0.25 Torr) forms a crystalline hydrobromide salt, which exhibits the expected m/z 143 MH$^+$ ion by electrospray mass spectrometry. The only reference base that was found to form proton-bound dimer ions with 1, 2, and 3, was canavanine, 4, a non-protein amino acid analog of arginine. Collision-induced dissociation of these cluster ions was used to assess the gas phase basicities of the diamines.

The 1H$^+$ cluster ion happens to have the same mass as the proton-bound trimer of 1. To rule out that interference, isotopically labeled 1 was prepared by catalytic deuteration of succinonitrile. Contrary to a previous literature report, this reduction does not give pure $d_1$ product, but a 1 : 8 : 1 mixture of $d_1$ : $d_5$ : $d_5$ isotopomers. Since these are easily resolved in the mass spectrometer, the presence of these impurities presents no obstacle.

Mass spectrometric measurements were performed on a Finnigan LCQ-DECA ion trap instrument using procedures described in detail elsewhere. Proton affinities were obtained using the extended kinetic method. In this approach, cluster ions of various amines with 4H$^+$ are produced by electrospray injection into a quadrupole ion trap, where they are mass selected and then dissociated by collisions with background helium gas at several collision energies. The partner that retains the proton more often is judged to be the more basic. Dissociation of the 1H$^+$4 cluster ion gives more 4H$^+$ than 1H$^+$. As expected, the 2H$^+$4 cluster gives an even greater ratio (≈99% 4H$^+$), which is too large to be of use in quantitative assessments. In contrast to clusters of 4 with monoamines or with linear diamines, collision-induced dissociation of the 3H$^+$4 cluster ion gives less 3H$^+$ than 3H$^+$. This means that 3 is more basic than canavanine (which, in turn, is more basic than...
The variation of fragment ion ratios with collision energy gives a quantitative assessment of relative gas-phase basicities.

The proton affinity of 3 was determined by the single reference variant of the kinetic method that has recently been demonstrated by Wenthold and co-workers. In the present work, canavanine served as the reference base. Proton bound dimers 3•+4 were generated and allowed to undergo collision-induced dissociation at laboratory frame energies of 0.75, 1.25, 1.75 and 2.5 V. The natural logarithms of ratios 4H+/BH+ from a separate study are subtracted from ln[3H+/4H+] at each energy and are plotted versus (PA – PAavg), as shown in Fig. 2 along with best fit lines. PAavg is the mean proton affinity of the reference bases. A second plot (Fig. 3) of the negative of the y-intercepts of the best-fit lines vs. their slopes extracts proton affinities and entropies from the data. The values of ln[3H+/4H+] – ln[1H+/BH+] were also analyzed in the same way. Those graphs (analogous to Fig. 2 and 3) are not shown, but the resulting experimental proton affinity, PA = 240.3 kcal mol⁻¹, is in excellent agreement with previously published determinations.

Determined in this manner, the experimental proton affinity of 3 is APA = 0.8 kcal mol⁻¹ less than that of 1. An alternative way to obtain the PA of 3 relative to 1 would be to incorporate the points corresponding to dissociation of the 1H•4 clusters into the graphs in Fig. 2. Since the 1H•4 points lie far from the least-squares lines for the monomines (as Fig. 2 depicts), the quality of fit becomes worse. Gauged in this fashion, the PA of 3 would become ΔPA = 1.1 kcal mol⁻¹ greater than that of 1.

An estimate for the entropy difference between a neutral and its conjugate acid, ΔSp, is given by the intercept of Fig. 3. The entropy change for 3 → 3H+ is ΔSps = 9.7 e.u. less negative than for 1 → 1H+. By contrast, the difference in entropy changes becomes ΔSps = 4.6 e.u. if the 1H•4 points are included in the least squares fits of Fig. 2. The corresponding differences in gas phase basicities, ΔGB = PA3 – PA1 + TΔSps are ΔGB = 2.1 and 2.5 kcal mol⁻¹, respectively, for the two methods at 300 K. We take the mean of these two values, ΔGB = 2.3 ± 0.2 kcal mol⁻¹, to be the ΔGB between protonation of 1 and protonation of 3.

The proton affinity difference, ΔPA, exhibits a large variation, depending on how the experimental data are analyzed. The gas phase basicity difference ΔGB is relatively independent of the method of data analysis. Computation (MP2/6-311G**) electronic energy differences corrected by counterpoise, with unscaled B3LYP/6-31G** zero point energy corrections) predicts gauche 1 (the most prevalent conforma-

**Notes and references**

13 E. J. Andriole and J. C. Poutsma, to be published.