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

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Received (in Corvallis, OR, USA) 9th May 2003, Accepted 26th June 2003

First published as an Advance Article on the web 4th July 2003

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.

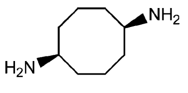
Enzymic catalysis often includes removal of a proton from a site on the substrate that does not have high acidity. Given that amino acid side chains do not contain functional groups any more basic than primary amines or guanidino groups, it is not obvious what can accomplish this. One hypothesis suggests 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_{NN}. Upon protonation they move towards one another to a distance d_{NN}, where strong hydrogen bonding stabilizes the conjugate acid. The two N–H distances, r_{NH} and r_{HN}, remain unequal.

As has long been known,[1] strong hydrogen bonds favor a linear arrangement of the hydrogen bond donor, the bridging proton, and the hydrogen bond acceptor (angle θ = 180°). The increased basicity of linear diamines (such as 1,4-diaminobutane, **1**, and 1,5-diaminopentane, **2**) has been viewed as a result of strong hydrogen bonding.[2] The conjugate acids have cyclic structures. Ring constraints make **1** the most basic of the linear diamines.

$H_2N\text{-}(CH_2)_n\text{-}NH_2$

1, n=4

2, n=5



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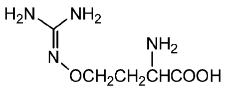

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Ab initio and DFT calculations agree with this view of the protonated diamines. The theoretical picture of the neutral diamines is more complicated. Although internally hydrogen bonded geometries (as Fig. 1 depicts) represent energetic minima for linear diamines, entropy does not favor them. Thus, hydrogen-bonded geometries (D_{NN} in Table 1) constitute minor species for gaseous, neutral diamines. The entropy change for making an internal hydrogen bond in $HO(CH_2)_4OCH_3$ in solution has been reported as −16.2 e.u. at 298 K,[3] which does not differ greatly from the reported entropy change for transferring a proton from a monoamine to **1**, −14.3 e.u.[4] 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.

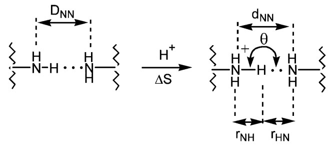


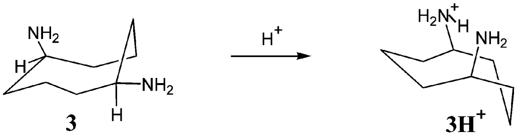
Fig. 1 Geometric features of neutral and protonated diamines.

Table 1 Distances (Å) and angles (°)[a] for diamines (MP2/6-311G**)

	D_{NN}	d_{NN}	r_{NH}	r_{HN}	θ	PA_{expt}[b]
1	2.95	2.63	1.13	1.52	165	240.3[c]
2	3.30	2.64	1.13	1.51	177	238.9[c]
3	3.17	2.65	1.12	1.53	174	239.5[d]

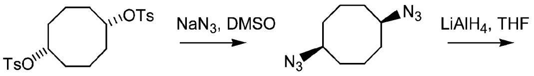
[a] For definitions, see Fig. 1. [b] kcal mol^{-1} [c] Ref 14. [d] This work.

This 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.



3 **3H$^+$** (1)

Compound **3** was synthesized in a straightforward fashion starting with the ditosylate of *cis*-1,5-cyclooctanediol,[5] 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.



3 (2)

The **1·H·4**$^+$ 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,[6] this reduction does not give pure d_4 product, but a 1 : 8 : 1 mixture of d_3 : d_4 : 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.[7] Proton affinities were obtained using the extended kinetic method.[8–11] In this approach, cluster ions of various amines **B** 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 **1·H$^+$·4** cluster ion gives more **4H$^+$** than **1H$^+$**. As expected, the **2·H$^+$·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 **3·H$^+$·4** cluster ion gives less **4H$^+$** than **3H$^+$**. This means that **3** is more basic than canavanine (which, in turn, is more basic than

DOI: 10.1039/b305239g

1 or **2**). 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.[12] In the present work, canavanine served as the reference base. Proton bound dimers $\mathbf{3}\cdot\mathrm{H}^+\cdot\mathbf{4}$ 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 $\mathbf{4H}^+/\mathrm{BH}^+$ from a separate study[13] are subtracted from $\ln[\mathbf{3H}^+/\mathbf{4H}^+]$ at each energy and are plotted *versus* ($\mathrm{PA} - \mathrm{PA}_{\mathrm{avg}}$), as shown in Fig. 2 along with best fit lines. $\mathrm{PA}_{\mathrm{avg}}$ is the mean proton affinity of the reference bases.[14] 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 $\ln[\mathbf{1H}^+/\mathbf{4H}^+] - \ln[\mathrm{BH}^+/\mathbf{4H}^+]$ 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.[14,15]

Determined in this manner, the experimental proton affinity of **3** is ΔPA = 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 $\mathbf{1}\cdot\mathrm{H}^+\cdot\mathbf{4}$ clusters into the graphs in Fig. 2. Since the $\mathbf{1}\cdot\mathrm{H}^+\cdot\mathbf{4}$ points lie far from the least-squares lines for the monoamines (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**.

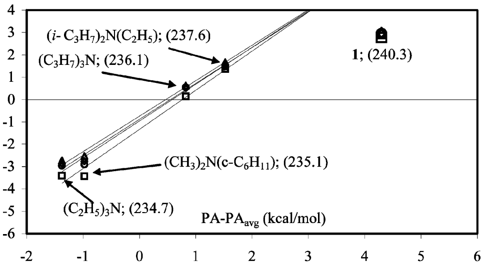


Fig. 2 Plot of $\ln[\mathbf{3H}^+/\mathbf{4H}^+] - \ln[\mathrm{BH}^+/\mathbf{4H}^+]$ *vs.* $[\mathrm{PA} - \mathrm{PA}_{\mathrm{avg}}]$ at laboratory collision energies of 0.75 V (□), 1.25 V (○), 1.75 V (◊), and 2.5 V (Δ). $\mathrm{PA}_{\mathrm{avg}}$ is the mean PA of four bases indicated with arrows. Symbols to the right show $\ln[\mathbf{3}\mathrm{H}^+/\mathbf{1}\mathrm{H}^+]$. PAs (kcal mol^{-1}; in parentheses) from ref. 14.

An estimate for the entropy difference between a neutral and its conjugate acid, ΔS_{p}, is given by the intercept of Fig. 3. The entropy change for $\mathbf{3} \rightarrow \mathbf{3H}^+$ is $\Delta\Delta S_{\mathrm{p}}$ = 9.7 e.u. less negative than for $\mathbf{1} \rightarrow \mathbf{1H}^+$. By contrast, the difference in entropy changes becomes $\Delta\Delta S_{\mathrm{p}}$ = 4.6 e.u. if the $\mathbf{1}\cdot\mathrm{H}^+\cdot\mathbf{4}$ points are included in the least squares fits of Fig. 2. The corresponding differences in gas phase basicities, $\Delta\mathrm{GB} = \mathrm{PA}_{\mathbf{3}} - \mathrm{PA}_{\mathbf{1}} + T\Delta\Delta S_{\mathrm{p}}$ 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 $\Delta\Delta G$ 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 conformation) to have a PA 0.3 kcal mol^{-1} greater than that of **3**. To decide whether **1** or **3** has the greater PA, ΔS_{p} has been assessed independently, using the method of group equivalents for the entropies of the neutrals[16] and DFT calculations (at B3LYP/6-31G**) of the entropies of their conjugate acids.

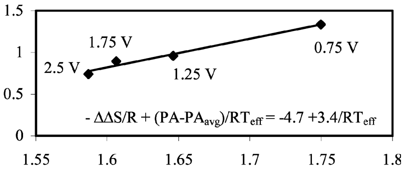


Fig. 3 Plot of $[(\mathrm{PA}_{\mathbf{3}} - \mathrm{PA}_{\mathrm{avg}}) - T_{\mathrm{eff}}\Delta\Delta S]/RT_{\mathrm{eff}}$ *vs.* $1/RT_{\mathrm{eff}}$.

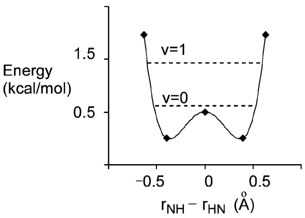


Fig. 4 MP2 electronic energy curve for the bridging proton in $\mathbf{1H}^+$.

The ions have rigid structures, but one internal degree of freedom must be taken as anharmonic: motion of the bridging proton between the two nitrogens. We calculate its vibrational energy levels separately[17] and correct the entropy accordingly. The potential energy curve for this asymmetric stretch corresponds to that of a low-barrier hydrogen bond,[18] as Fig. 4 illustrates, where the height of the central barrier is 0.5 kcal mol^{-1} for both $\mathbf{1H}^+$ and $\mathbf{3H}^+$. The first two vibrational levels are separated by approximately 230 cm^{-1}, as drawn in Fig. 4. If the proton moves with no change in the distance d_{NN}, the appropriate co-ordinate is r_{NH}–r_{HN} in the limit where $\theta = 180°$. As Table 1 summarizes, strongly hydrogen-bonded diamines approach that limit. This anharmonic correction to the vibrational entropy (assuming no coupling between this motion and the other vibrations) gives the same increment, 1.5 e.u., for both $\mathbf{1H}^+$ and $\mathbf{3H}^+$.

Estimated in this fashion, the ΔS_{p} for **1** has a value of −13.8 e.u. (in good agreement with experiment), as compared with −0.4 e.u. for **3**. This estimate of $\Delta\Delta S_{\mathrm{p}}$ = 13.4 e.u. implies that the greater basicity of **3** is due to more favorable entropy, and that the proton affinity of **3** is less than that of **1**. It is clear that constraining a diamine can substantially increase its basicity.

The authors are grateful to Prof M. M. Midland for helpful discussions. This work was supported by The Dreyfus Foundation, the Jeffress Memorial Trust, ACS-PRF and the Research Corporation (JCP) and by NSF grant CHE0316515 (THM).

Notes and references

1 T. H. Morton and J. L. Beauchamp, *J. Am. Chem. Soc.*, 1972, **94**, 3671.
2 D. H. Aue, H. M. Webb and M. T. Bowers, *J. Am. Chem. Soc.*, 1973, **95**, 2699.
3 L. H. Prabhumirasi and C. I. Jose, *J. Chem. Soc., Faraday Trans. 2*, 1978, **74**, 255.
4 M. Meot-Ner (Mautner), P. Hamlet, E. P. Hunter and F. H. Field, *J. Am. Chem. Soc*, 1980, **102**, 6393.
5 E. J. Corey and E. Block, *J. Org. Chem.*, 1966, **31**, 1663.
6 G. A. van den Berg, H. Elzinga, G. T. Nagel, A. W. Kingma and F. A. J. Muskiet, *Biochim. Biophys. Acta*, 1984, **802**, 175.
7 A. F. Kuntz, A. W. Boynton, G. A. David, K. E. Colyer and J. C. Poutsma, *J. Am. Soc. Mass Spectrom.*, 2002, **13**, 72.
8 R. G. Cooks, J. S. Patrick, T. Kotiaho and S. A. McLuckey, *Mass Spectrom. Rev.*, 1994, **18**, 287.
9 B. A. Cerda and C. Wesdemiotis, *J. Am. Chem. Soc.*, 1996, **118**, 11884.
10 Z. Wu and C. Fenselau, *Rapid Commun. Mass Spectrom.*, 1994, **8**, 777.
11 P. B. Armentrout, *J. Am. Soc. Mass Spectrom.*, 2000, **11**, 371.
12 H. A. Lardin, R. R. Squires and P. G. Wenthold, *J. Mass Spectrom.*, 2001, **36**, 607.
13 E. J. Andriole and J. C. Poutsma, to be published.
14 E. P. Hunter and S. G. Lias, *J. Phys. Chem. Ref. Data*, 1998, **27**, 3.
15 Z. Wang, I. K. Chu, C. F. Rodriquez, A. C. Hopkinson and K. W. M. Siu, *J. Phys. Chem. A*, 1999, **103**, 8700.
16 E. S. Domalski and E. D. Hearing, *J. Phys. Chem. Ref. Data.*, 1993, **22**, 805.
17 M. M. Kreevoy and T. M. Liang, *J. Am. Chem. Soc*, 1980, **102**, 3315.
18 D. F. Bocian, G. A. Schick and R. R. Birge, *J. Chem. Phys.*, 1981, **74**, 3660. We are grateful to Professor Bocian for making his FORTRAN code available to us.