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Extended Hydrogen Bond Network Enabled Superbases

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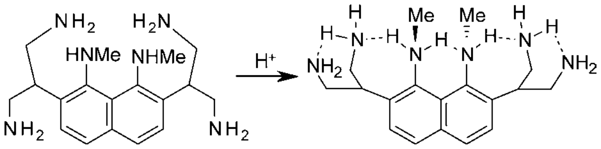
ABSTRACT



New superbases, those organic compounds whose basicities are greater than that of proton sponge, are suggested that involve extended hydrogen-bonding networks. Addition of aminoethyl and related groups to the 1,8-diaminonaphthalene framework provide second- and third-layer hydrogen bonding in the conjugate base. DFT computations predict these compounds to be 10−15 kcal mol^{-1} more basic than the proton sponge.

The concept of superbases began with the discovery of 1,8-bis(dimethylamino)naphthalene **1** (DMAN),[1] later rechristened "proton sponge". Since many strong bases are salts and thereby have limited solubility in organic solvents, the quest for even stronger nonionic bases than **1** has continued, including suggestions originating from computational studies.[2−12] Most of these designs rely on the enhanced basicity coming from two or more nitrogen lone pairs forced to be in proximity, such as in **1** and **2**. Protonation reduces the inherent strain through the formation of at least one intramolecular hydrogen bond.

We proposed a group of superbases built upon the pyridine and quinuclidine scaffold.[13] More distant amine groups could, upon protonation of the central nitrogen, move into a position to form an intramolecular hydrogen bond (including bifurcated and trifurcated hydrogen bonds), thereby stabilizing the conjugate acid. Two of our best candidates are **3** and **4**.

Kass demonstrated that even more remote groups with lone pairs could stabilize the conjugate acids of amine bases by establishing a network of intramolecular hydrogen bonds.[14] In **5H**$^+$, the central ammonium is stabilized by three intramolecular hydrogen bonds, one each to the other three amino groups. In **6H**$^+$, a second layer of intramolecular hydrogen bonds is made with the remote amino groups. This second layer of hydrogen bonding results in substantial stabilization of the conjugate base: the proton affinity of **6** is predicted at B3LYP/aug-cc-pVDZ to be 27 kcal mol^{-1} greater than for **5**. Similar remote, second-layer

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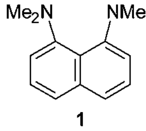
hydrogen bonding leads to dramatic increases in acidity of polyols analogous to the polyamines **5** and **6**.[15,16]



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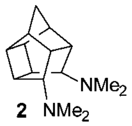

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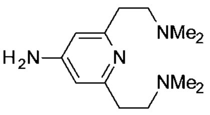

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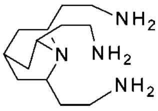

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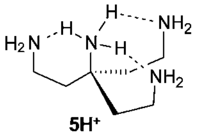
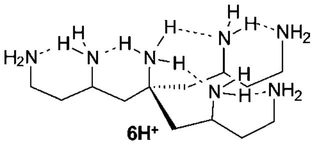
Herein we describe density functional computations on a number of superbases invoking stabilization of the conjugate acid through a network of hydrogen bonding, including amine groups involved in the second and third layer of hydrogen bonding. Many of these polyamines are quite basic and offer an intriguing opportunity for the synthetic chemist.



5H⁺



6H⁺

The geometries of potential superbases **1** and **7**–**19** and their conjugate acids were completely optimized using three different computational methods: M06-2x/6-31+G(d), M062x/6-311+G(2d,p), and ωB97X-D/6-311+G(2d,p).[17,18] All structures were confirmed to be local energy minima via vibrational frequency analysis. The unscaled frequencies were used to compute Δ*H*(298 K) values, which are reported here.

Solvation effects were accounted for by reoptimization of all structures at M06-2x/6-31+G(d) using the polarizable conductor calculation model (CPCM),[19,20] with the standard parameters for cyclohexane and THF. Vibrational frequencies were recomputed and again used without a scaling factor. All computations were performed with the GAUSSIAN-09 suite.[21]

In order to select a computational method, we have compared the gas-phase proton affinity (PA) of 13 nitrogen bases (a subset of the group we previously used[13]) computed with the three methods against the epxperimental values. The best agreement is with ωB97X-D/6-311+G-(2d,p); the mean unsigned error is only 1.2 kcal mol^{-1}. The full list of values can be found in Table S1 (Supporting Information), and the computed and experimental values for **1** and its parent **7** are given in Table 1. Additionally, all three methods predict the relative PAs of these amines with an error of less that 1 kcal mol^{-1}. Overall, the agreement between the ωB97X-D/6-311+G(2d,p) and experimental PAs is quite good, and we will report the enthalpies determined with this method exclusively here for all gas-phase reactions.

Table 1. Computed and Experimental Gas-Phase Proton Affinities (kcal mol^{-1}) of **1** and **7**

compd	M06-2x/6-31+G(d)	M06-2x/6-311+G(2d,p)	ωB97X-D/6-311+G(2d,p)	exptl[a]
1	239.3	241.0	247.7	245.8
7	220.8	221.2	226.1	225.7

[a] Reference 22.

The polycyclic aromatic amines **7**, **8**, and **10** explore the affect of extending out the aromatic framework with amines positioned to create an extended hydrogen-bonding network. The two outside amino groups of **8** act as acceptors of a hydrogen from the central ammonium group, and this second hydrogen bond leads to an increase in the PA of 6.6 kcal mol^{-1} over **7** (see Table 2). An additional arene fusion gives **10**, whereby the last amino group of **10H⁺** creates the second layer of hydrogen bonding. This leads to a further increase of the PA, with the PA of **10** 1.8 kcal mol^{-1} greater than that of **8**.

A much larger effect is seen with incorporating methyl groups on the amines; the PA of the pentamethyl analogue of **8**, compound **9**, has a PA that is predicted to be 20.1 kcal mol^{-1} greater than that of **8**. It is in fact more basic than **1** by 4.1 kcal mol^{-1}. While the methyl groups help to stabilize the positive charge of the conjugate acid, they also destabilize the base through steric interactions that force the amine lone pairs to be near each other; both effects lead toward the enhanced basicity of **9**.

The positioning of the neighboring amino groups in **8**–**10** may not be ideal in terms of forming favorable hydrogen bonds. For example, the N–H···N angles, which ideally should be linear, in **8H⁺** and **9H⁺** are 142.8° and 145.2°, respectively. The three N–H···N angles in **10H⁺** are 142.7, 141.2, and 138.2°. To provide more flexibility we examined the attachment of aminomethyl and (especially) aminoethyl groups to **7**, specifically **11**–**14**. While the N–H···N angles in **11H⁺** and **13H⁺** remain

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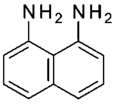
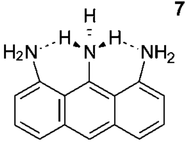
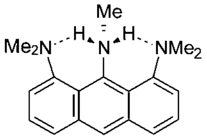


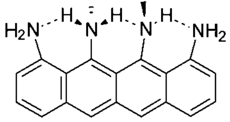
7



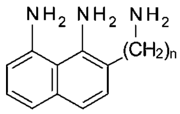
8H⁺



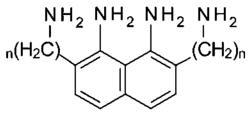
9H⁺



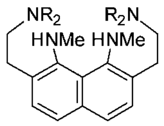
10H⁺



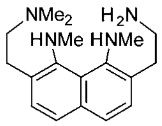
11: n = 1
12: n = 2



13: n = 1
14: n = 2



15: R = H
17: R = Me



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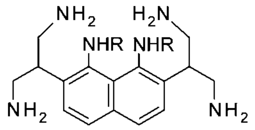

Table 2. Computed Gas-Phase and Solution-Phase Relative Proton Affinities (kcal mol^{-1}) of **1** and **7**–**19**

compd	PA (gas)[a]	PA (cyclohexane)[b]	PA (THF)[b]
1	21.6	16.4	14.2
7	0.0	0.0	0.0
8	6.6	3.1	0.2
9	25.7	17.5	14.0
10	8.4	2.4	−1.2
11	10.3	7.6	5.4
12	14.3	11.0	8.8
13	14.4	10.4	6.9
14	20.3	15.2	11.4
15	31.2	24.3	19.6
16	33.9	26.0	20.6
17	35.0	25.8	20.8
18	21.6	14.9	9.8
19	36.1	27.1	21.0

[a] Computed at ωB97X-D/6-311+G(2d,p). [b] Computed at CPCM/M06-2x/6-31+G(d).

near 140°, the angles are significantly wider in **12H**$^+$ (159.5°) and **14H**$^+$ (158.4, 151.0 and 145.1°). This should manifest in proton affinities that are much higher for **12** and **14**. In fact, **12** is more basic than **11** by 4.0 kcal mol^{-1} and **14** is more basic than **13** by 5.9 kcal mol^{-1}. Compound **14** has a PA that is 20.3 kcal mol^{-1} greater than that of **7** and very close to that of **1**.

Since the addition of methyl groups to the nitrogens of **7**, making **1**, significantly enhances the basicity, addition of a methyl group to each of the aromatic amines of **14**, making **15**, should enhance its basicity as well. The computed PA of **15** is, as expected, greater than that of **14** by 10.9 kcal mol^{-1}. It is also 31.2 kcal mol^{-1} greater than that of **7** and 10 kcal mol^{-1} larger than that of DMAN **1**. This enhanced basicity of **15** over **1** is attributable to the stability of **15H**$^+$ due to (a) an additional hydrogen bond to the protonated amine in the first layer and (b) a second layer hydrogen bond, as seen in in the structure of **15H**$^+$ shown in Figure 1.

Methylation of all of the amines of the first layer characterizes **16**. The additional two methyl groups of **16** compared to **15** leads to a further increase in the PA; the PA of **16** is 2.7 kcal mol^{-1} greater than that of **15**. Methylation of the more distant (second layer of hydrogen bonding) amine group, making **17**, has a smaller effect on the PA. The PA of **17** is only 1.1 kcal mol^{-1} greater than that that of **16**. Methylation of the amine groups in the second or higher layers of the hydrogen bonding network are therefore not critical toward creating organic superbases of the type investigated here. Nonetheless, it is worth noting that the PA of **17** is 13.4 kcal mol^{-1} greater than that of **1**.

Compounds **15**–**17** introduce one second-layer hydrogen bond. To introduce a second-layer hydrogen bond on both sides of the formal protonated (quaternary) amine, we examined compounds **18** and **19**. The structure of **19H**$^+$ shown in Figure 1 has the added aminomethyl groups oriented to form an added hydrogen bond layer on both sides of the compound. Thus, there is a a full first and second layer of hydrogen bonding and one third-layer hydrogen bond. This extended hydrogen bond network does lead to a further increase of the proton affinity. The PA of **18** is 1.3 kcal mol^{-1} greater than that of **14**, the analogous compound lacking the outer two hydrogen bonds. Compound **19** is 4.9 kcal mol^{-1} more basic than **15** and the most basic polyamine of this series. Its PA is nearly 15 kcal mol^{-1} greater than that of DMAN **1**.

To address the question of basicity in organic solution, we computed the structures and energies of all the bases and their conjugate acids using the polarizable conductor model (CPCM) for both cyclohexane and THF solvents. Since the gas-phase M06-2x/6-31+G(d) relative proton affinities of the amine bases examined here (see Table S2 and Figure S1, Supporting Information) are in close agreement with those computed at ωB97X-D/6-311+G-(2d,p), we use this more computationally efficient method for the solution-phase calculations. By computing relative proton affinities, via the reaction **7** + **BH**$^+$ → **7H**$^+$ + **B**, we also avoid having to deal with the difficulties associated with computing the energy of the solvated proton. The computed solution-phase (cyclohexane and THF) proton affinities relative to **7** are listed in Table 2. To assess the computational method, we computed the relative free energy for **7** + **1H**$^+$ → **7H**$^+$ + **1**; the computed value is 11.4 kcal mol^{-1} (8.1 pK_a units) which is in excellent agreement with their experimental[1,23] pK_a difference of 7.73.

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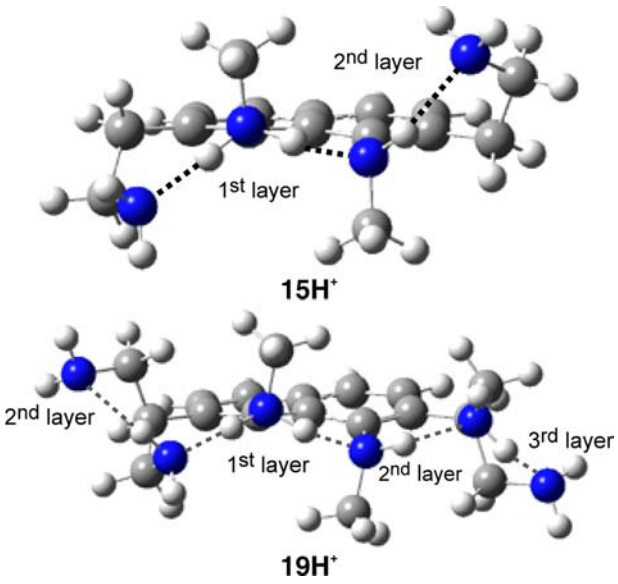

Figure 1. ωB97X-D/67-311+G(2d,p)-optimized geometries of **15H**$^+$ and **19H**$^+$.

The gas-phase structures of the free bases have the remote amino groups involved in long hydrogen bonds to the interior amino groups. We did investigate for a few cases the possibility of base conformations with these long hydrogen bonds being competitive in solution with extended conformations that allow the distant amines to interact with the solvent, such as shown for **12** in Figure 2. In these cases, either the compact conformation was the lowest in energy or is essentially degenerate with an extended structure. We therefore decided to simply reoptimize the gas-phase structure in solution. The myriad of different possible conformations, especially of the free bases, and their likely very similar energies in solution make it difficult to assess the free energies associated with proton affinity, since one would need to take a Boltzmann weighting of all low energy conformations. Therefore, we restrict our analysis to the relative enthalpic proton affinity, recognizing that there may be some entropic disfavorability to the formation of the extended hydrogen bonding networks, particularly in more polar solvents.

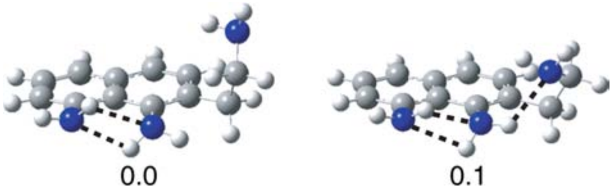

Figure 2. Structures of the extended and hydrogen-bonded conformations of **12** in THF. Relative energies in kcal mol^{-1}.

Inspection of the solvent proton affinities shown in Table 2 identifies a couple of important trends. First, the range of the relative PAs is smaller in cyclohexane than in the gas phase and smaller still in THF. Second, the relative rankings of the basicities of the compounds change very little when moving from the gas to solution phase. Thus, the compounds that can make effective large hydrogen bonded networks in their conjugate acids; namely, **15**, **16**, **17**, and **19** are all predicted to be stronger gas-phase and solution-phase bases than DMAN.

Our computations fully support Kass' proposal[14] for creation of strong bases by incorporation of extended hydrogen bonding networks. The compounds examined here, notably **15**–**17** and **19**, should be synthetically accessible, and we look forward to experimental study of these potential superbases.

Supporting Information Available. Tables S1 and S2, Figure S1, and optimized coordinates and enthalpies for compounds **1** and **7**–**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(23) The pK_a of **1** was measured in DMSO (Benoit, R. L.; Lefebvre, D.; Fréchette, M. *Can. J. Chem.* 1987, *65*, 996–1001) and in acetonitrile (Brzezinski, B.; Schroeder, G.; Grech, E.; Malarski, Z.; Sobzyk, L. *J. Mol. Struct.* 1992, *274*, 75–82) and the ion-pair acidity in THF (Streitwieser, A.; Kim, Y.-J. *J. Am. Chem. Soc.* **2000**, *122*, 11783–11786).