8238 *J. Am. Chem. Soc.* **2000,** *122,* 8238−8244

Relationship between Basicity, Strain, and Intramolecular Hydrogen-Bond Energy in Proton Sponges

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Received March 21, 2000. Revised Manuscript Received May 17, 2000

Abstract: A precisely additive scheme for describing proton sponge basicity is presented as the sum of the proton affinity of an appropriate reference monoamine, the strain released on protonation, and the energy of the intramolecular hydrogen bond formed on protonation. This approach is then tested at the B3-LYP/6-31+G**//HF/6-31G** level on six diamine proton sponges (including two novel compounds) that are polycyclic aromatic hydrocarbon derivatives. A key result is that the loss of destabilizing strain energy on protonation is seldom an important contribution to enhanced basicity, and in some cases an *increase* in strain energy can actually take place which acts to lower the basicity. The scheme is further tested and discussed in the context of other types of proton sponge, including a bridgehead (bicyclic) diamine, a tricyclic tetraamine, and a "resonance-stabilized" vinamidine proton sponge. Linear relationships found between basicity, hydrogen-bond energy, and structural parameters of the free bases and protonated cations offer the possibility of estimating basicity purely from structure.

Introduction

With the advent of new computer architectures and more practicable implementations of electron-correlated quantum chemical methods such as density functional theory, it has become feasible to apply these tools in the design of superbasic compounds (proton sponges).[1−8] The key to the computational design of novel proton sponges, or indeed to understanding the properties of known compounds, undoubtedly lies in a quantitative treatment of the factors responsible for enhanced basicity. Already a number of approaches have been proposed and tested, often on model systems, concerning the estimation of cationic hydrogen-bond energies,[1,4,9] lone pair−lone pair repulsion energies,[7,9] strain energies,[5,7,8] and resonance/aromatic stabilization energies.[2,4] What has been lacking is a unified treatment of these various factors that produce enhanced basicity, enabling the largely structurally based ideas of what makes a proton sponge basic[10−12] to be put on a more sound basis. Here the aim is to develop and test such a treatment, by applying it to the nine proton sponges illustrated in Figure 1.

We begin by recalling the various contributions to (amine) proton sponge basicity: (i) The effective proton affinity (PA) for one of the amine groups (assuming asymmetric protonation at one nitrogen); (ii) the relief of strain (possibly also accompanied by an increase in aromatic stability) caused by loss of destabilizing lone pair−lone pair repulsion on protonation [i.e., strain energy(sponge) − strain energy(sponge·H^+)]; (iii) the formation of an intramolecular cationic hydrogen bond $[N-H\cdots N]^+$, which stabilizes the protonated species; and (iv) the difference in solvation energies of the base and protonated cation, if we are concerned with the situation in solution.

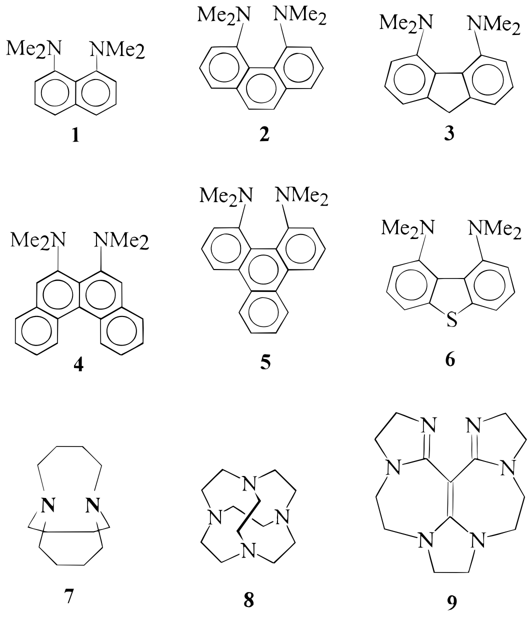

Figure 1. The proton sponges studied in this work.

The calculation of contributions i and ii using quantum chemical techniques would appear to be straightforward. For example, the obvious reference compound for estimating the effective PA of a single amine group in **1** is 1-dimethylami-

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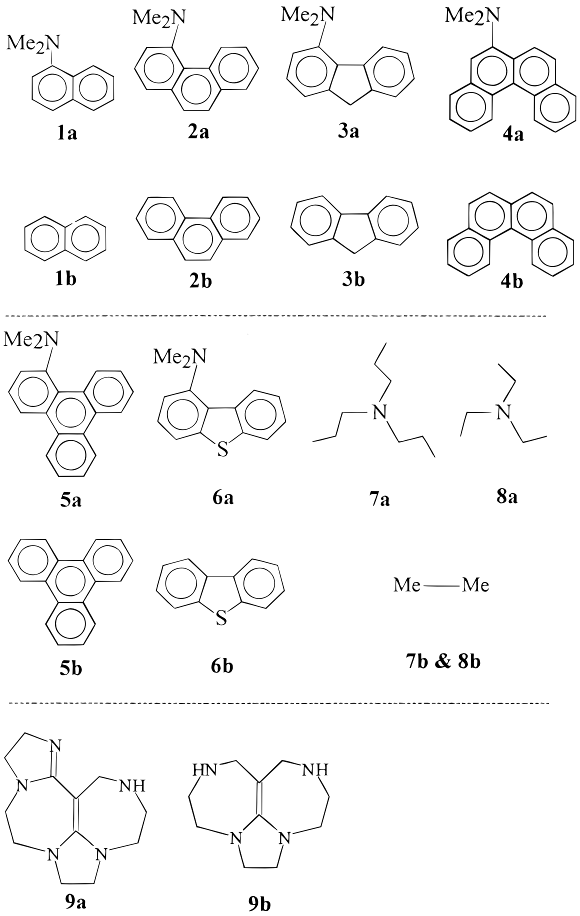
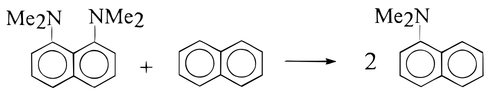
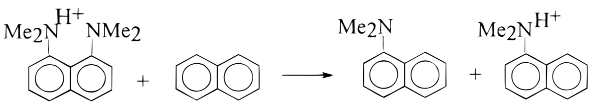


Figure 2. Definition of the "reference monoamines" **1a**−**9a** and other associated compounds **1b**−**9b** needed for the strain and hydrogen-bond energy calculations.

nonaphthalene (**1a** of Figure 2). The strain energy of **1** may be estimated by isodesmic reactions such as

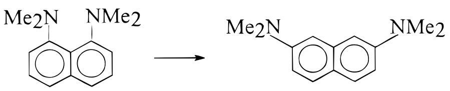

(a)

In this work we will be concerned with gas-phase basicities, so the remaining contribution to proton sponge basicity comes from the intramolecular hydrogen bond formed on protonation. (It will be shown that hydrogen-bond energies for the proton sponges considered here typically range from 50 to 100 kJ/mol.) By analogy with the treatment of strain energy shown above, we can obtain information about the intramolecular hydrogen-bond energy of a protonated cation such as $\mathbf{1}\mathrm{H}^+$ from the isodesmic reaction


(b)

The energy change in the above reaction can be equated with the sum of the cation's hydrogen-bond energy *and* its strain, since both of these have been "lost" in the compounds on the right-hand side. It will be demonstrated that, although the cation strain of some proton sponge cations such as the prototype species $\mathbf{1}\mathrm{H}^+$ is small (<10 kJ/mol), in other cases the cation strain is far from negligible and can actually *exceed* the strain in the unprotonated base.

An alternative to isodesmic reactions is to use the isomer approach,[7] where, for example, the energy change of the reaction


(c)

provides an estimate of the strain energy in the free base. However, the isodesmic reaction method will be preferred here since it guarantees exact additivity of the three contributions to (gas phase) proton sponge PA. This may not be immediately obvious, but it becomes clear if we write the various contributions in terms of their constituent energies using compound **1** as a concrete example. First the PA of **1** is trivially defined as

$$\mathrm{PA}(\mathbf{1}) = E(\mathbf{1}) - E(\mathbf{1}\mathrm{H}^+) \tag{1}$$

(which defines the PA as positive, the usual convention). The energies *E* in the above equation and those that follow are assumed to be the sums of electronic and vibrational energies.

Now the PA of the associated monoamine

$$\mathrm{PA}(\mathbf{1a}) = E(\mathbf{1a}) - E(\mathbf{1a}\mathrm{H}^+) \tag{2}$$

The strain energy (SE) of the unprotonated proton sponge is given by

$$\mathrm{SE}(\mathbf{1}) = E(\mathbf{1}) + E(\mathbf{1b}) - 2E(\mathbf{1a}) \tag{3}$$

and the hydrogen bond energy (HB) + strain energy of its protonated cation by

$$[\mathrm{HB}(\mathbf{1}\mathrm{H}^+) + \mathrm{SE}(\mathbf{1}\mathrm{H}^+)] = E(\mathbf{1}\mathrm{H}^+) + E(\mathbf{1b}) - E(\mathbf{1a}) - E(\mathbf{1a}\mathrm{H}^+) \tag{4}$$

The conventions chosen ensure that the strain energy will be a positive quantity (destabilizing) and the hydrogen-bond energy negative (stabilizing). Our assumed additive scheme for the PA of the proton sponge **1** described earlier is

$$\mathrm{PA}(\mathbf{1}) = \mathrm{PA}(\mathbf{1a}) + [\ \mathrm{SE}(\mathbf{1}) - \mathrm{SE}(\mathbf{1}\mathrm{H}^+)] - \mathrm{HB}(\mathbf{1}\mathrm{H}^+) \tag{5}$$

which equivalently can be written as

$$\mathrm{PA}(\mathbf{1}) = \mathrm{PA}(\mathbf{1a}) + \mathrm{SE}(\mathbf{1}) - [\ \mathrm{HB}(\mathbf{1}\mathrm{H}^+) + \mathrm{SE}(\mathbf{1}\mathrm{H}^+)] \tag{6}$$

Substituting expressions 2−4 into eq 5 or 6 verifies that these equations are satisfied exactly.

It is important at this point to make some observations about the above analysis. First, it should be observed that the additivity scheme makes no assumptions about the nature of the reference monoamine **1a**. Any monoamine for which the appropriate isodesmic reactions can be constructed will guarantee this additivity but in general will lead to different derived strain and hydrogen-bond energies. This is an unavoidable consequence of the methodology. In studying a series of proton sponges, it is therefore desirable to choose the reference monoamines and to construct isodesmic reaction schemes in a consistent way. By focusing on a series of structurally related (diamino benzenoid) sponges such as **1**−**6**, this criteria is satisfied: there is an obvious and consistent choice of reference monoamines viz. compounds **1a**−**6a** and isodesmic reaction schemes a and b. Later we shall also test this methodology on three quite different types of proton sponge, **7**−**9**.

Second, the three additive contributions that we may derive to the proton sponge basicity using isodesmic reactions are those on the right-hand side of eq 6, namely, the PA of a reference

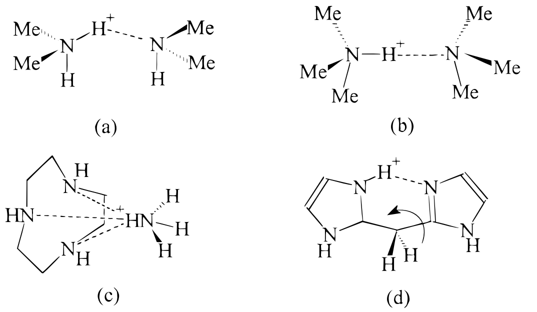


Figure 3. The model systems used to estimate cation hydrogen bond energies of (a) **1**H$^+$−**6**H$^+$, (b) **7**H$^+$, (c) **8**H$^+$, and (d) **9**H$^+$.

monoamine; the strain of the proton sponge; and the hydrogen bond energy + strain energy of the protonated cation, which we shall subsequently denote as (HB+SE)$^+$. To effect a separation of this last term into a "pure" hydrogen-bond energy and a cation strain, some independent information is required. Our proposed scheme is to approximate the cation hydrogen-bond energy as the (vibrationless) binding energy of a model system. For compounds **1**−**6** this will be the proton-bound dimethylamine dimer (Figure 3a) "frozen" in the geometry of the dimethylamine groups of **1a**−**6a**. The chosen reference system (to determine a binding energy) is the same two compounds removed to infinite separation, without permitting geometry relaxation.

In the first part of the Results section, we concentrate on implementing this scheme for diamines which are derivatives of naphthalene, fluorene, and phenanthrene. Various ab initio studies of geometries, basicities, and strain energies have already been reported for compounds **1**−**3**.[5,6,7,9,13,14] Compounds **4**−**6** then each represent a second example for these three structural types (**4** and **5** have not yet been synthesized[15]). Compound **6** and related proton sponges have been prepared and characterized by Staab et al.[16]

Computational Details

Hartree−Fock geometry optimizations employed 3-21G[17] and 6-31G** (6d) basis sets[18] in the program GAMESSUK[19] running on a Silicon Graphics Origin 2000, respectively. The proton sponges **1**−**6** and **9** were assumed to have C_2 symmetry, and their corresponding cations **1**H$^+$−**6**H$^+$ were optimized in both symmetrically protonated (C_2) and asymmetrically protonated (generally C_1) conformations, to obtain proton-transfer barriers. The reference compounds **1a**−**6a** and **9a** and their corresponding protonated cations **1a**H$^+$−**6a**H$^+$ and **9a**H$^+$ were all initially optimized without symmetry constraints at the 3-21G level. In those cases where the compound optimized to a higher symmetry point group, this was the point group applied in the subsequent 6-31G** level optimizations. The calculations on **1b**−**6b** employed the following point groups: naphthalene (D_{2h}), phenanthrene (C_{2v}), fluorene (C_{2v}), benzo[*c*]phenanthrene (C_2), triphenylene (D_{3h}), and dibenzothiophene (C_{2v}). Point group C_2 was applied to **9b**. Calculations on **7a** (tripropylamine) and **8a** (triethylamine) employed C_3 symmetry constraints, with no symmetry used in optimization of **9a**. Harmonic frequency calculations were undertaken for *all* optimized species at the HF/3-21G level, to establish that each was at a potential energy minimum and also to obtain vibrational energy estimates. Intramolecular hydrogen-bond energies (HB) of the cations **1a**−**9a** were estimated from the model compounds illustrated in Figure 3. Full structural details of all compounds may be obtained from the author on request.

B3-LYP/6-31+G** single point calculations were carried out on all optimized structures at the HF/6-31G** geometries using GAUSSIAN98/DFT[20] running on a DEC Alpha RISC Power Challenge at Rutherford-Appleton Laboratories, Chilton, UK. These calculations serve to estimate the effects of electron correlation on PA values, strain, and hydrogen-bond energies. The effects of basis set superposition errors on the proton sponge PA values have been estimated at HF and B3-LYP levels of theory with the usual Boys−Bernardi method.[21]

Results for Compounds 1−6

Structures. Table 1 reports some key details of the optimized structures: the N···N distances in the bases and associated cations; the N···H distance and N−H···N hydrogen-bonding angle in the cations; and the nonplanarity of the unprotonated bases, as measured by the displacement *d* of the nitrogen atoms from the mean plane. All six proton sponges adopt twisted C_2 conformations to varying degrees, with by far the largest nonplanarity observed for **2** and **5**, the sponges based on the phenanthrene structure. The two fluorene derivatives **3** and **6** show similar deviations *d* of the nitrogen atoms from the mean planes (0.31 and 0.41 Å), but the two naphthalene derivatives **1** and **4** do differ appreciably in their nonplanarity, with **4** being markedly more twisted. This is not unexpected, since even the parent hydrocarbon **4b** is twisted (C_2) due to steric interactions, while **1b** is obviously flat. Similar reasoning applies to the N···N nonbonded distances of the proton sponges—these are very similar in the structurally related pairs of compounds {**2**,**5**} and {**3**,**6**}, but differ noticeably between **1** and **4** for the reason just outlined.

Two of the six cations, **1**H$^+$ and **3**H$^+$, are exactly planar (as verified by frequency calculations at the HF/3-21G level). Although nonplanar, the remaining cations all show the expected decrease in nonplanarity relative to the unprotonated bases.

Structures of 1a−6a and Their Protonated Cations. Geometry optimizations on the reference monoamines revealed that **1a** and **2a** prefer no-symmetry structures (methyl groups are asymmetrically placed with respect to the hydrocarbon frame), while their protonated cations **1a**H$^+$ and **2a**H$^+$ possess planes of symmetry (C_s). Thus the "twisting" of the methyl groups in the proton sponges **1** and **2** to produce C_2 symmetry conformers (as opposed to C_{2v}), a feature well-known from both crystallographic structural and ab initio studies of proton sponges, might be an intrinsic property of the associated monoamines and does not derive from lone pair repulsive effects. The same nonplanarity is also found for **4a** and **5a**, although in these cases the protonated cations **4a**H$^+$ and **5a**H$^+$ are also nonplanar. The situation differs yet again with the fluorene derivatives, since the species **3a**, **3a**H$^+$, **6a**, and **6a**H$^+$ all have a plane of symmetry.

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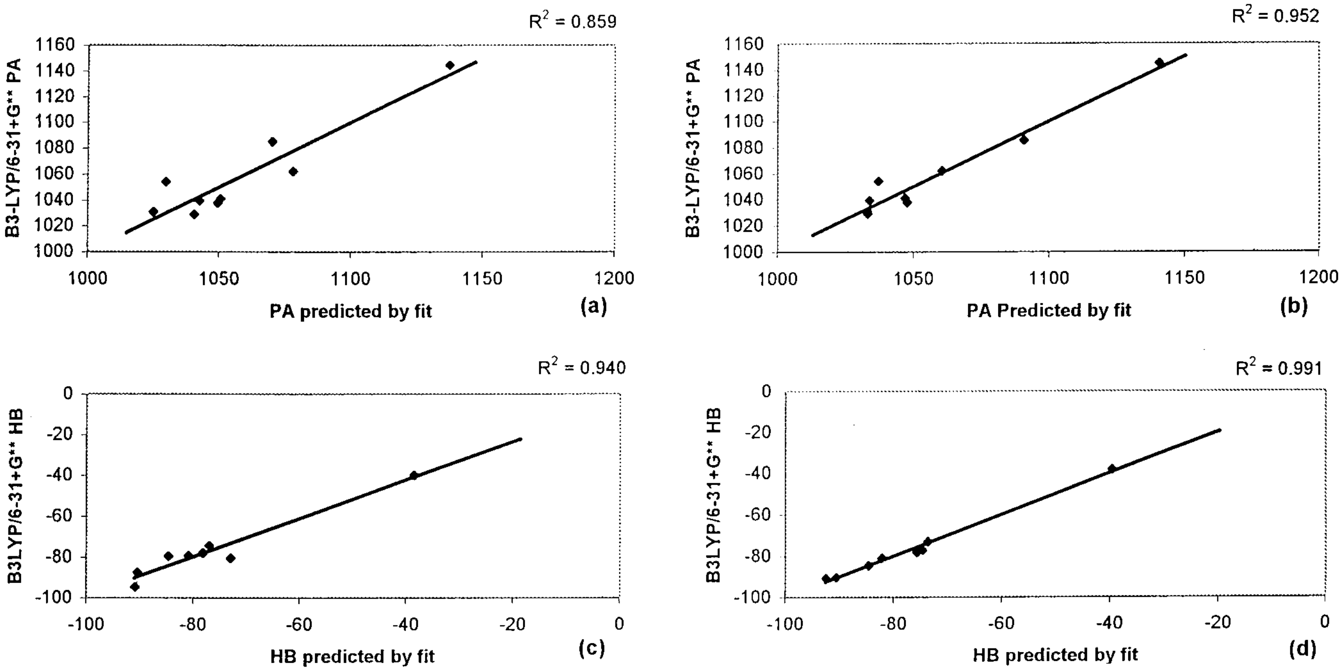


Figure 4. Correlations of structural parameters with proton affinity (PA) and cation intramolecular hydrogen bond energy (HB): (a) one-parameter fit, PA versus PA(Δr(N···N)); (b) two-parameter fit, PA versus PA(Δr(N···N), N−H···N); (c) two-parameter fit, HB versus HB(Δr(N···N), r(N···H)); (d) three-parameter fit, HB versus HB(Δr(N···N)$^+$, r(N···H), N−H···N).

Table 1. HF/6-31G** Optimized Structures, HOMO−LUMO Gaps, and B3-LYP/6-31+G**//HF/6-31G** Dipole Moments[a]

	In The Proton Sponge		In The Cation				
	r(N···N) (Å)	d (Å)	r(N···N)$^+$ (Å)	r(N···H) (Å)	N−H−N (deg)	p (D)	HOMO−LUMO gap (eV)
1	2.791 (2.844) [2.793]	0.140 (0.241) [0.293]	2.684 (2.624) [2.644]	1.706 (1.560)	155.1 (158.4)	1.13 (0.95)	10.24
2	2.829	0.962	2.645	1.616	166.4	0.84	10.09
3	2.913	0.336	2.753	1.712	176.3	0.96	10.39
4	2.778	0.515	2.657	1.680	154.8	0.73	9.60
5	2.840	1.081	2.659	1.645	163.6	1.01	10.07
6	2.845	0.436	2.691	1.646	174.8	2.57	10.21
7	2.871 (2.858) [2.807]		2.628 (2.580) [2.527]	1.575 (1.430)	180.0 (180.0)	0.0 (0.0)	14.24
8	2.948		2.681[b]	1.972	123.1	0.0	14.20
9	3.036	1.017	2.589	1.814	131.2	6.23	11.80

[a] Values in parentheses are from B3-LYP/6-31+G** optimizations of **1**, **1**H$^+$, **7** and **7**H$^+$. Values in brackets are from low-temperature neutron or X-ray diffraction studies.[23,24] [b] There are two unique N···N distances in this (tetraaza) cation. The value given is the distance between the protonated and one of the unprotonated nitrogens.

Table 2. Gas-Phase Proton Affinities of Reference Monoamines (kJ/mol)

	HF/ 6-31G**	B3-LYP/ 6-31+G**// HF/6-31G**		HF/ 6-31G**	B3-LYP/ 6-31+G**// HF/6-31G**
1a	959.8	937.0	**6a**	936.3	925.5
2a	929.7	911.1	**7a**	1014.8	988.6
3a	959.8	944.4	**8a**	1002.2	975.4 (expt 955.6 ± 9)[33]
4a	961.7	942.7	**9a**	1150.7	1107.1
5a	940.0	920.6			

Energetics. Vibrational energies together with HF and B3-LYP total energies for all species are supplied in Tables 1s−3s of the Supporting Information. The PAs, strain, proton-transfer barriers and hydrogen-bond energies derived from these values are found in Tables 2 and 3. The proton affinities of **1**−**6** vary over a range of about 21 kJ/mol, with the prototype proton sponge 1,8-bis(dimethylamino)naphthalene being the least basic. The strain energy range is larger (12−45 kJ/mol), which indicates that energetic effects in the cation (i.e., incomplete release of strain versus variations in hydrogen-bond energy) act in a partly compensating manner. The range of hydrogen-bond energy variation, according to the model systems chosen to represent this stabilization, is in fact fairly small (77−91 kJ/mol). However, evidence that these model systems are not entirely satisfactory for estimating the hydrogen-bond energy comes from comparing the derived values of HB with the (HB+SE)$^+$ values calculated from isodesmic reactions: two hydrogen-bond energies (for **2**H$^+$ and **5**H$^+$) are less negative than the corresponding (HB+SE)$^+$ values, which would imply an (unphysical) negative cation strain. It may be significant that **2**H$^+$ and **5**H$^+$ are the two phenanthrene derivatives, which have by far the most nonplanar cations. Proton-transfer barriers range from 12 to 20 kJ/mol at the HF/6-31G** level but essentially disappear (being all 0 ± 3 kJ/mol) at the B3-LYP/6-31+G**/HF/6-31G** level. This is in line with the MP4 study of the model system [$H_3NH\cdots NH_3$]$^+$ of Ikuta.[1]

It proves useful to define to an "enhanced basicity" of a particular proton sponge as its proton affinity minus that of the

Table 3. Proton Affinities (PA),[a] Strain Energies (SE), and Proton Transfer Barriers (PT) for the Bases and Hydrogen Bond + Strain Energies $(HB+SE)^+$ and Hydrogen-Bond Energies (HB) for the Monoprotonated Cations (all in kJ/mol)

		PA	SE	PT	$(HB+SE)^+$	HB
1	HF	1056.3 (1053.7)	35.7	19.5	−60.8	−70.4
	B3-LYP	1030.7 (1028.0) [1030][b]	26.9	0.0	−66.8	−78.2
2	HF	1055.6 (1053.0)	26.1	12.1	−99.9	−75.2
	B3-LYP	1041.0 (1039.2)	22.6	−2.6	−107.3	−84.6
3	HF	1068.0 (1065.1)	33.2	20.3	−75.0	−83.4
	B3-LYP	1039.3 (1037.5)	11.9	−0.1	−82.9	−90.9
4	HF	1067.8 (1065.6)	45.2	17.0	−60.9	−68.7
	B3-LYP	1054.1 (1052.4)	44.9	−0.5	−66.4	−77.1
5	HF	1051.9 (1049.5)	14.8	13.8	−97.0	−72.1
	B3-LYP	1037.6 (1035.8)	17.0	−1.9	−100.0	−80.9
6	HF	1055.0 (1052.0)	41.9	17.0	−76.7	−81.7
	B3-LYP	1028.9 (1026.8)	17.4	−0.9	−85.9	−90.4
7	HF	1101.7 (1097.4)	58.0	11.0	−28.9	−61.4
	B3-LYP	1085.1 (1081.9)	53.9	−3.1	−42.5	−73.0
8	HF	1091.8 (1088.1)	77.2		−12.3	−83.4
	B3-LYP	1062.1 (1060.0)	80.9		−5.9	−88.1
9	HF	1187.3 (1185.2)	56.0	32.0	+19.3	−36.7
	B3-LYP	1144.6 (1143.7)	53.0	7.0	+15.4	−38.5

[a] The values in parentheses are counterpoise-corrected using the Boys−Bernardi method.[21] [b] Experimental gas-phase PA measured by Kebarle et al.[22]

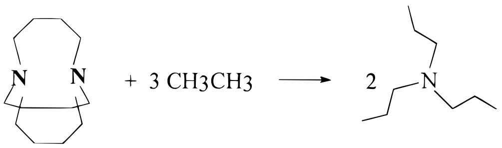
chosen reference monoamine; e.g., PA(**1**)−PA(**1a**). Confining our attention initially to the proton sponges **1**−**6**, which have bis(dimethylamino) substituents, we may then observe that the stabilization due to hydrogen-bond formation (HB) dominates the contribution to enhanced basicity, providing from 67% (in the case of sponges **4** and **5**) up to 96% (in the case of **3**). Structurally related proton sponges (e.g., **1** and **4**, **2** and **5**, etc.) behave similarly with respect to this mechanism of enhanced basicity, e.g. the two sponges in which HB is most dominant in providing enhanced basicity are **3** and **6**, based on the fluorene structure **3b**. This structure appears to be particularly favorable for forming an almost linear and therefore strong cationic hydrogen bond between nitrogens on protonation (N−H···N around 175°; see Table 1). Similarly, HB plays the least important (although still dominant) role for providing enhanced basicity in the two sponges based on the phenanthrene structure, **2** and **5**, contributing 65% and 69%, respectively. However, it must be noted that these are the two cases where the HB energies estimated as the binding energy of the structure in Figure 3a imply negative cation strain energies, as discussed above.

Accuracy of Computed Properties. Very few experimental PA values are available for the proton sponges studied here, but our gas-phase B3-LYP/6-31+G** value for the PA of **1** is in excellent agreement with the experimental value of Lau et al. of 1030 kJ/mol.[22] Peräkyla[5] reported MP2/6-31G*//HF/6-31G* values for the PA values of **1** and **7** that are both ≈12 kJ/mol higher than our values (and experiment).

The influence of using HF- vs B3-LYP-optimized structures has been examined by carrying out full B3-LYP/6-31+G** optimizations for the two smallest proton sponges and their asymmetrically protonated cations, i.e., **1**, **1**H^+ and **7**, **7**H^+. These two proton sponges were also selected for B3-LYP optimization because low-temperature X-ray or neutron diffraction crystal structures are available for the unprotonated and protonated species in both cases.[23,24] The B3-LYP/6-31+G**//B3-LYP/6-31+G** PA values of **1** and **7** (applying scaled HF/3-21G thermal corrections as before), uncorrected for basis set superposition error, are 1031.2 and 1090.1 kJ/mol, respectively, higher by 0.5 and 5.0 kJ/mol than the B3-LYP/6-31+G**//HF/6-31G** values. This indicates that the PA is not too dependent on the fine details of structure and thus provides some support for the use of B3-LYP single points at HF/6-31G**-optimized structures. Yet the actual optimized structures do differ markedly between HF/6-31G** and B3-LYP/6-31+G** (see Table 1). The B3-LYP nonbonded distances $r(N\cdots N)$ or $r(N\cdots N)^+$ are ∼0.04 Å longer than for Hartree−Fock. Comparison with the crystal structure data (also given in Table 1) shows that the HF/6-31G** result for **1** is closer to experiment, whereas B3-LYP shows improved agreement with experiment for **1**H^+ and **8** and **8**H^+. A more detailed comparison of geometry (i.e., comparing HF and B3-LYP structures with experiment for all C−C and C−N bond lengths) confirms the trend that the B3-LYP structures are generally closer to experiment.

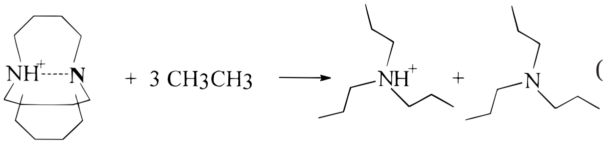
Results for Compounds 7−9

The Bicyclic Diamine 1,6-Diazabicyclo[4.4.4]tetradecane. Compound **7** was synthesized by Alder et al.[23] and was the subject of three previous ab initio studies.[5,25,26] The computational treatment in those studies is extended here to include the determination of strain using the isodesmic reaction



(d)

and hydrogen-bond energy



(e)

The calculated strain energy of ≈54 kJ/mol is rather higher than any of the bis(dimethylamino) sponges **1**−**6**, as might be anticipated for this different case of a bicyclic bridgehead diamine. The hydrogen-bond energy, approximated as the binding energy of the complex in Figure 3b, is unremarkable at −73 kJ/mol, even though the C_3 geometry constrains the hydrogen bond to be precisely linear. Combining this estimate of HB with the value of $(HB+SE) = -42.5$ implies a cation strain of around 31 kJ/mol, which is substantially larger than that found for any of the cations **1a**H^+−**6a**H^+. Nevertheless, it is some 23 kJ/mol lower than the strain of the unprotonated base, so we can deduce that relief of strain on protonation does play a significant (although secondary) role in providing the enhanced basicity of **7**, with the hydrogen bonding providing most (at least 76%) of this stabilization.

The Tricyclic Tetraamine [2^6]Adamanzane. Compound **8** was the subject of a computational study[8] that included a

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[22] Lau, Y. K.; Saluja, P. P. S.; Kebarle, P.; Alder, R. W. *J. Am. Chem. Soc.* **1978**, *100*, 7328.

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[25] Howard, S. T.; Platts, J. A.; Alder, R. W. *J. Org. Chem.* **1995**, *60*, 6085.

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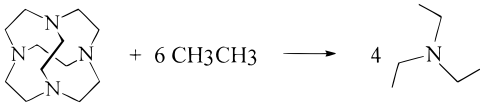
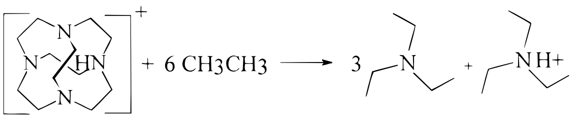
determination of its strain energy using the isodesmic reaction



(f)

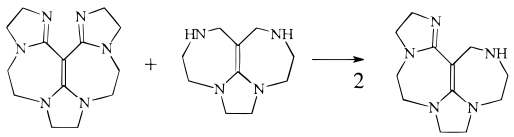
using B-LYP/6-31+G*//HF/6-31+G* methodology and has since been successfully synthesized.[27] We use the nomenclature of Springborg et al.,[28] who synthesized the closely related [3^6]-adamanzane. Because it forms a trifurcated hydrogen bond on protonation, it represents a marked departure from the compounds considered so far and, thus, an interesting test of the methodology. In ref 8 we speculated that the basicity of **8** was perhaps not so high as might be expected because the pseudo-hexacyclic cation might be almost as strained, indeed maybe even more strained, than the unprotonated base. In this case the change in strain on protonation must actually decrease the observed basicity rather than enhance it, an apparently novel concept in proton sponges. The $(HB+SE)^+$ of **8** has been obtained from the associated isodesmic reaction



(g)

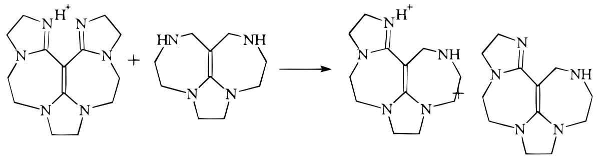
so NEt_3 and ethane are identified as **8a** and **8b**, respectively. **8**H^+ proves problematic when attempting to construct a model for independently estimating its H-bond energy. The obvious system of trimethyltriazacyclononane interacting with, for example, NEt_3 is unworkable in practice, because the methyl groups of the two fragments are too close (even touching) if the model system is to correctly reproduce the same hydrogen-bonding geometry of **8**H^+. This problem is not alleviated by rotating the methyl groups. After some experimentation the best model was $[TACN\cdots NH_4]^+$ (see Figure 3c), which gives a trifurcated hydrogen-bond energy of ≈−88.4 kJ/mol (B3-LYP level). This must be seen as a lower limit to the hydrogen-bond energy, since the NH_4^+ fragment is more acidic than the comparable group in $H[2^6]adz^+$. Taking −88.1 as the lower limit for HB and the B3-LYP value of −5.9 for $(HB+SE)^+$ implies a cation strain of *at least* 82 kJ/mol. So it seems fairly certain that the actual cation strain in this case is significantly larger than the 81 kJ/mol more reliably estimated for **8**. The enhanced basicity of **8** (i.e. its basicity compared to triethylamine) is therefore 100% due to the stabilization of the cationic hydrogen bond formed on protonation, with strain release playing no part.

Schwesinger's Vinamidine Proton Sponge. In the search for the most basic organic compound or class of compounds, the vinamidine proton sponge **9** synthesized by Schwesinger and co-workers[29] is among the most promising candidates to date. This is indicated by their extremely high pK_a's and associated aqueous basicities, as estimated by UV spectrophotometry.[30−33] It represents yet another type of proton sponge in which the enhanced basicity is thought to be at least partly due to resonance stabilization, as in the well-known example of guanidine.[2] The analysis of strain and hydrogen-bond energy for this compound using the isodesmic reactions



(h)

and



(i)

proves to be particularly revealing. The strain energy of the unprotonated base (53.0 kJ/mol) is again higher than in any of the compounds **1**−**6**, but the estimated hydrogen-bond energy of −39 kJ/mol is by far the lowest of the nine compounds reported here. This latter observation is consistent with an unfavorable hydrogen bonding geometry (Table 1); i.e., $N-H\cdots N = 131.2°$. The sum $(HB+SE)^+ \approx 15$ kJ/mol provides the first unquestionable example of a protonated cation with a larger strain energy (≈54 kJ/mol) than the free base. So we have the seemingly paradoxical case of a proton sponge which forms a relatively weak intramolecular hydrogen-bond energy on protonation and is actually *destabilized* by increased strain in the cation and yet is by far the most basic compound here. As postulated by Schwesinger and co-workers, the explanation lies in the very substantial increase in resonance stabilization energy on protonation. This is verified by the huge calculated PA for the reference compound **9a** (Table 2) of 1107 kJ/mol, which shows that it is actually a better proton sponge than any of the polyamine bases **1**−**8**. So although it is true that the enhanced basicity of **9** (compared to **9a**) is 100% due to the hydrogen bond formed, in fact the cooperative effect of the adjacent lone-pair bearing nitrogens is not the underlying mechanism for the "proton sponge effect" in this case.

Structure/Energetics Correlations. Various possible descriptors of the proton sponge basicity, strain, and (cation) hydrogen-bond energy were considered, including those as diverse as the dipole moment and HOMO−LUMO gap of the free bases (reported in Table 1). The best descriptors, and most useful from the standpoint of experimental accessibility, appear to be structural. The one-parameter description of the gas-phase proton affinity in terms of the *change* in the N···N distance on protonation is given by

$$\mathrm{PA} = 980 + 360 \times [r(\mathrm{N}\cdots\mathrm{N}) - r(\mathrm{N}\cdots\mathrm{N})^+] \quad r = 0.96$$

which reproduces the PA values with a mean accuracy of ±10 kJ/mol. Including the hydrogen-bonding angle in a two-parameter fit makes only a marginal improvement,

$$\mathrm{PA} = 925 + 397 \times [r(\mathrm{N}\cdots\mathrm{N}) - r(\mathrm{N}\cdots\mathrm{N})^+] + 0.296 \times (\mathrm{N-H}\cdots\mathrm{N}) \quad r = 0.97$$

reproducing the B3-LYP/6-31+G** PA values with a mean accuracy of ±9 kJ/mol. Turning now to the hydrogen-bond energy, it is found that a three-parameter fit to the structural

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parameters reproduces the B3-LYP/6-31+G** values for the nine compounds with reasonable accuracy (±6 kJ/mol):

$$\mathrm{HB} = 187 + 127 \times [r(\mathrm{N}\cdots\mathrm{N}) - \mathrm{r}(\mathrm{N}\cdots\mathrm{N})^{+}] - 116 \times r(\mathrm{N}\cdots\mathrm{H}) - 0.597 \times (\mathrm{N}-\mathrm{H}\cdots\mathrm{N}) \quad r = 0.92$$

Strain in the unprotonated sponge is not described well by either of the geometrical parameters $r(\mathrm{N}\cdots\mathrm{N})$ and d, or in linear combination. Similarly, the cation strain is not adequately described by the three geometrical parameters listed in Table 1, either individually or in linear combinations (although it should be noted that there is rather greater uncertainty in our estimates of the cation strain, for the reasons discussed earlier). This concurs with our earlier assertion that strain energies cannot be inferred from structure,[7] but only by quantum chemical calculation.

Conclusions

An additive scheme for describing proton sponge basicity in terms of three components (basicity of a reference monoamine + strain release + hydrogen-bond energy) has been described and tested on nine compounds. Analysis of these data reveals that the relief of strain is a minor source of the enhanced basicity of proton sponges—indeed the strain of the cation is shown to be greater than that of the unprotonated base for some compounds. The relative contribution of hydrogen bonding to the “enhanced proton sponge basicity” (defined as the PA of the sponge minus the PA of an appropriately chosen reference monoamine) varies from around 67% for phenanthrene derivatives to 100% in a tricyclic tetraamine and a strongly resonance-stabilized species.

Although the proton sponge structures are more reliably predicted by B3-LYP optimization than with Hartree−Fock, in the two cases where we are able to compare the results in detail this has only a very small effect (ca. a few kilojoules per mole) on the derived basicities. Carrying out full DFT geometry optimizations for larger proton sponges (and especially their no-symmetry protonated forms) is currently too time-consuming, and even HF/6-31G** optimizations on such species are computationally demanding. We judge that HF/6-31G** structures combined with B3-LYP/6-31+G** single point energies provides a sufficiently accurate tool for calculation of basicities, strain, and hydrogen-bond energies in the general context of designing novel sponges.

Regression analyses of the various structural and energetic values derived for nine compounds led to simple formulas for estimating (i) intrinsic basicity of a proton sponge, from a knowledge of its unprotonated and protonated crystal structures, and (less reliably) (ii) the intramolecular hydrogen-bond energy of the protonated cation, from its crystal structure. The latter is less reliable because, in two of the nine cases, our hydrogen-bond energies estimated from model systems imply an unphysical (negative) cation strain. Although we are currently unable to explain this, the fact that the two “anomalous” cases correspond to the two phenanthrene derivatives suggests that this discrepancy might be understood by studying more structurally related examples.

The analysis of the Schwesinger sponge basicity provides a clear example of how useful this computational approach can be in elucidating mechanisms of enhanced basicity. It appears that the enhanced basicity in this case is derived from resonance stabilization in the cation (since **9a** is almost as basic as **9**) and not with the cooperative effects of strain induced by lone pair repulsion or intramolecular hydrogen bonding. Given that **9** is certainly one of the strongest organic aza bases known, this suggests that the design of even more basic sponges may be achieved by concentrating on the “resonance” mechanism exemplified by the guanidine proton sponge,[2] rather than strain relief or hydrogen bonding.

Acknowledgment. The author thanks the EPSRC for access to the Columbus supercomputer at Rutherford-Appleton Laboratories, Oxfordshire. Useful discussions with Dr. James A. Platts are also gratefully acknowledged.

Supporting Information Available: HF/6-31G**-optimized coordinates of **1**−**9** and **1**H^{+}−**9**H^{+} and B3-LYP/6-31G**-optimized coordinates of **1**, **1**H^{+}, **7**, and **7**H^{+} (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0010094