

Density Functional Calculations

DOI: 10.1002/anie.200503254

**Rational Design and First Principles Studies
 Toward the Discovery of a Small and Versatile
 Proton Sponge****

Ernesto Estrada* and Yamil Simón-Manso

More than 30 years ago, Alder et al.^[1] challenged our classical view of acid–base properties with their discovery of a simple organic compound that showed a basicity ten million times higher than typical organic bases. This superbase, 1,8-bis(dimethylamino)naphthalene (DMAN), is known as “proton sponge” because of its high thermodynamic basicity combined with a kinetic inactivity to deprotonation that resembles the affinity of a sponge for water.^[2] Since then, many families of proton sponges have been created and they are finding a growing number of interesting applications.^[2–5] Quantum chemical studies have shed some light on the structural factors influencing the high basicity of proton sponges.^[6–10] Their abnormally high basicity is accepted to be

produced by strong crowding of unshared electron pairs on nitrogen atoms, a strong intramolecular hydrogen bond in the protonated form, and relief of steric strain upon protonation. These characteristics are usually achieved by anchoring two nitrogen atoms sufficiently close in a rigid framework of condensed phenyl rings.^[2–5] Furthermore, hydrophobic substituents on the nitrogen atoms confer kinetic stability.

Herein we report the design of a new molecular framework that differs significantly from the traditional topology of proton sponges. We began with the simplest structure in which two nitrogen atoms are about 250 pm apart and have their lone pairs of electrons facing each other, namely, the boat conformation of piperazine. To enforce the boat conformation, we integrated this unit into the minimal framework provided by the structure of 3,6,7,8-tetraazatricyclo[3.1.1.1^{2,4}]octane (**1**; Scheme 1). This molecule has two



1: R¹ = R² = H; 2: R¹ = CH₃, R² = H
 3: R¹ = H, R² = CH₃; 4: R¹ = R² = CH₃

5: R¹ = H; 6: R¹ = CH₃

Scheme 1. Structures of 3,6,7,8-tetraazatricyclo[3.1.1.1^{2,4}]octane (**1**) and 4,8,9,10-tetraazatricyclo[5.1.1.1^{3,5}]decane (**5**) as well as their methylated derivatives.

pairs of nitrogen atoms fixed in a configuration that should guarantee acid–base properties similar to those of proton sponges. The geometries and proton affinities of **1**, and its 3,6,7,8-tetramethyl (**2**), 1,2,3,4-tetramethyl (**3**), and 1,2,3,4,5,6,7,8-octamethyl (**4**) derivatives, as well as of DMAN and 1,6-diazabicyclo[4.4.4]tetradecane (BDDT), were calculated by using density functional theory (DFT). The last compound has the highest proton affinity (PA) value among all the aliphatic proton sponges studied by Howard.^[11]

Compounds **1–4** have two equivalent protonation sites, one above and another below the plane formed by the carbon atoms. Consequently, we first calculated the PA for the first protonation site with the second site in the deprotonated state and then for the second site keeping the first one protonated. Some of the principal geometrical parameters of the neutral and protonated optimized structures **1–4** are given in Table 1. The N···N distances are about 50 pm lower than the average experimental value of 282.6 pm obtained for 20 proton sponges.^[5] The calculated N···N distances in DMAN and BDDT are 279.2 pm and 292.34 pm, respectively. The former value is in full agreement with the experimental value obtained by X-ray diffraction studies (279.2 pm).^[5] In general, the N···N⁺ distance decreases upon protonation. However, this decrease is almost negligible in **1–4**, particularly for **2** and **3**. An unexpected increase in the N···N⁺ distance is observed in **1** and **2** upon adding a second proton. This increment is not observed in **4**. The N–H···N hydrogen-bonding angles in singly protonated **1–4** range from 103 to 130° and are much

[*] Dr. E. Estrada
 Complex Systems Research Group, X-Ray Unit
 RIAIDT, Edificio CACTUS
 University of Santiago de Compostela
 15782 Santiago de Compostela (Spain)
 Fax: (+34) 981-547-077
 E-mail: estrada66@yahoo.com

Dr. Y. Simón-Manso
 INEST Group, PM-USA and
 Center for Theoretical and Computational Nanosciences
 National Institute of Standards & Technology (NIST)
 100 Bureau Drive, Stop 8380, Gaithersburg, MD 20899-8380 (USA)

[**] We thank Dr. Karl Irikura for his assistance in the preparation of the manuscript. E.E. thanks program “Ramón y Cajal”, Spain, for partial financial support.

Table 1: Ab initio (B3PW91/6-311++g**) gas-phase geometrical parameters of the proton sponges and associated cations.

Sponge	Cation 1				Cation 2		
	$r(\text{N}\cdots\text{N})$ [pm]	$r(\text{N}\cdots\text{N}^+)$ [pm]	$r(\text{N}\cdots\text{H})$ [pm]	$\text{N}-\text{H}\cdots\text{N}$ [°]	$r(\text{N}\cdots\text{N}^+)$ [pm]	$r(\text{N}\cdots\text{H})$ [pm]	$\text{N}-\text{H}\cdots\text{N}$ [°]
1	239.2	233.3	103.7	103.0	237.3	103.2	96.9
2	235.6	233.1	105.7	116.5	236.9	104.4	112.1
3	237.2	232.1	103.5	103.5	231.5	104.0	102.9
4	234.8	226.2	125.0	129.5	226.2	120.4	139.9
5	286.0	254.8	107.4	137.3	269.4	103.7	124.6
6	279.8	257.2	108.0	141.3	269.4	104.6	132.9
DMAN	279.2	260.3	112.0	159.2	–	–	–
BDDT	292.3	257.3	141.8	178.1	–	–	–

lower than those reported for proton sponges. According to the X-ray data compiled by Llamaz-Saiz et al.,^[5] proton sponges generally have angles between 150 and 180°, with the exceptions of tetraamine[2⁶]adamantane and vinamidine proton sponge, which have values of 123.1 and 131.2°, respectively. To summarize, the geometrical parameters for both the bases and the cations of **1–4** are significantly different from those of known proton sponges.

According to our DFT calculations, **1–4** have gas-phase proton affinities that equal or even exceed those of some proton sponges, such as DMAN and BDDT. In particular, the octamethylated compound **4** has a calculated PA that is 20 kJ mol⁻¹ higher than that calculated for BDDT (Table 2). Proton affinities for the second protonation of compounds **1–4** are, in all cases, very small. Howard has expressed gas-phase PA in terms of the changes in the N⋯N distance and the hydrogen-bonding angle on protonation.^[11] Our calculations do not reproduce these correlations for **1–4**. However, the gas-phase proton affinities of **1–4** increase as the N⋯N distance in the base decreases. This is not necessarily a direct cause-and-effect relationship: in particular, methylation of compound **1**, which decreases the N⋯N separation, also tightens and deepens the electrostatic potential in the region between the nitrogen atoms, which makes the proton more stable there. The electrostatic potentials of compounds **1** and **2** are shown in Figure 1 a,b. The two protonation sites (in blue) are more localized in the case where the amine groups are methylated. This kind of region has been described previously as a hydrophobic environment at the nitrogen atoms, to which the “sponge effect” is attributed.^[2]

The most striking geometrical difference between the new proton sponges **1–4** and classical sponges such as DMAN and BDDT is the closeness of the nitrogen atoms in the new sponges. The N⋯N distances in **1–4** are not only atypical compared to other proton sponges, but also compared to intra- and intermolecular N⁺–H⋯N hydrogen bonds in general. In the data of the 150 crystals compiled and analyzed

Table 2: Ab initio (B3PW91/6-311++g**) gas-phase proton affinities at 273 K and estimated pK_a values in water for the protonation of the proton sponges.

	gas phase		PA [kJ mol ⁻¹] aqueous phase		pK _a (Water) ^[a]	
	1 ^[b]	2 ^[b]	1 ^[b]	2 ^[b]	1 ^[b]	2 ^[b]
1	1001.93	554.41	1240.01	1207.97	15.7	10.3
2	1072.96	643.18	1285.93	1224.27	23.4	13.0
3	1044.54	633.94	1241.37	1201.74	15.9	9.2
4	1103.11	697.74	1287.27	1250.15	23.6	17.4
5	1044.66	609.35	1260.35	1222.92	19.1	12.8
6	1073.84	671.86	1268.12	1226.67	20.4	13.4
DMAN	1037.39 ^[c]	–	1218.75	–	12.1 ^[d]	–
BDDT	1082.75	–	1294.33	–	24.8 ^[e]	–

[a] Estimated by the linear regression model: pK_a = 0.1684 PA(aq) – 193.14. [b] First and second protonation are designed as 1 and 2, respectively. [c] Experimental value: 1030.1 kJ mol⁻¹. [d] Experimental value: 12.1 kJ mol⁻¹. [e] Experimental value: 25 kJ mol⁻¹.

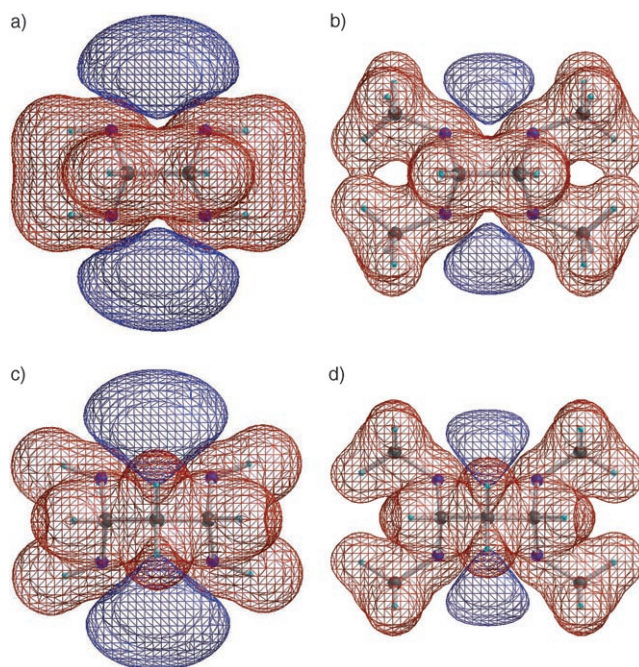


Figure 1. Molecular electrostatic potentials (MEP) of the proton sponges (3D isopotential contours at $|V(\mathbf{r})| = 1.5$ a.u.): a) **1**, b) **2**, c) **5**, and d) **6**.

by Llamas-Saiz et al.^[5] this distance is never below 250 pm, which is in contrast to the values obtained here for **1–4** which are under 240 pm. To investigate the effect of the nitrogen–nitrogen distance we considered separating the nitrogen atoms by four instead of three bonds, thus resulting in 4,8,9,10-tetraazatricyclo[5.1.1.1^{3,5}]decane (**5**) and its methylated derivative **6**, namely 4,8,9,10-tetramethyl-4,8,9,10-tetraazatricyclo[5.1.1.1^{3,5}]decane (Scheme 1). In contrast to **1–4**, the geometrical parameters calculated for **5** and **6** (Table 1) show a close resemblance with those reported for conventional proton sponges. The calculated PA for **5** is 1044.66 kJ mol⁻¹, which is more than 40 kJ mol⁻¹ higher than that of **1**. The electrostatic potentials of **5** and **6** are similar to those observed for **1** and **2** (Figure 1c,d) in that they show a more compact potential between the nitrogen atoms in the methylated compounds. Indeed, **6** has a gas-phase PA very similar to that of **2** despite the different geometrical parameters (Table 2). In fact, **5** and **6** do not follow the same relationship between inter-nitrogen separation in the base and gas-phase PA value which is observed for **1–4**. As shown in Table 2, all these compounds are predicted to behave as strong proton sponges at both sites of protonation in an aqueous phase according to both the PA values and the estimated p*K*_a values (see Methods Section).

In summary, the current findings show that the derivatives of 3,6,7,8-tetraazatricyclo[3.1.1.1^{2,4}]octane can be used as a prototype of a new proton sponge. We hope that this information will stimulate chemists to develop a synthetic method for this new family of proton sponges.

Methods Section

All calculations were performed with the Gaussian98 suite of programs.^[12] Becke's "hybrid" three-parameter exchange and the Perdew-Wang correlation functional (B3PW91) have been used in conjunction with the split-valence, polarized, diffuse functions basis set 6-311++g(d,p).^[13] Harmonic vibrational frequency calculations were used to confirm that the optimized structures were minima, as characterized by positive frequencies. Zero-point vibrational energies were obtained from these calculations without scaling; we take these values to represent an upper limit to the true values. We assume that basis set superposition error (BSSE) is negligible at the present level of calculation for the species considered here, as previously observed for B3PW91.^[14] The optimized geometries were used to evaluate solvation energies, molecular electrostatic potentials (MEP), and other properties at the same level of theory. Solvation energies were calculated by the Self-Consistent Reaction Field (SCRF) using the isodensity model (IPCM) for the cavity.^[15] The p*K*_a values were estimated by a linear regression model of the experimental p*K*_a data reported by Peräkylä^[6] and following an approach reported by Kovačević and Maksić.^[16] The linear regression model obtained here is p*K*_a = 0.1684 PA(aq) – 193.14 with *R* > 0.99.

Received: September 13, 2005

Revised: December 12, 2005

Published online: February 10, 2006

Keywords: basicity · density functional calculations · proton sponges · rational design

- [1] R. W. Alder, P. S. Bowman, W. R. Steele, D. R. Winterman, *Chem. Commun.* **1968**, 723–724.
- [2] A. F. Pozharskii, *Russ. Chem. Rev.* **1998**, 67, 1–24.
- [3] H. A. Staab, T. Saupe, *Angew. Chem.* **1988**, 100, 895–909; *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 865–879.
- [4] R. W. Alder, *Chem. Rev.* **1989**, 89, 1215–1223.
- [5] A. L. Llamas-Saiz, C. Foces-Foces, J. Elguero, *J. Mol. Struct.* **1994**, 328, 297–323.
- [6] M. Peräkylä, *J. Org. Chem.* **1996**, 61, 7420–7425.
- [7] P. R. Mallinson, K. Woźniak, G. T. Smith, K. L. McCormack, *J. Am. Chem. Soc.* **1997**, 119, 11 502–11 509.
- [8] J. A. Platts, S. T. Howard, K. Woźniak, *J. Org. Chem.* **1994**, 59, 4647–4651; S. T. Howard, J. A. Platts, R. W. Alder, *J. Org. Chem.* **1995**, 60, 6085–6090; J. A. Platts, S. T. Howard, *J. Org. Chem.* **1996**, 61, 4480–4482; S. T. Howard, J. A. Platts, *J. Org. Chem.* **1998**, 63, 3568–3571; S. T. Howard, I. A. Fallis, *J. Org. Chem.* **1998**, 63, 7117–7119.
- [9] D. B. DuPré, *J. Phys. Chem. A* **2003**, 107, 10142–10148.
- [10] G. Bucher, *Angew. Chem.* **2003**, 115, 4174–4175; *Angew. Chem. Int. Ed.* **2003**, 42, 4039–4042.
- [11] S. T. Howard, *J. Am. Chem. Soc.* **2000**, 122, 8238–8244.
- [12] Gaussian98 (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.
- [13] A. D. Becke, *J. Chem. Phys.* **1993**, 98, 5648–5652.
- [14] N. X. Wang, K. Venkatesh, A. K. Wilson, *J. Phys. Chem. A* **2006**, 110, 779–784.
- [15] J. B. Foresman, T. A. Keith, K. B. Wiberg, J. Snoonian, M. J. Frisch, *J. Phys. Chem.* **1996**, 100, 16098–16104.
- [16] B. Kovačević, Z. Maksić, *Org. Lett.* **2001**, 3, 1523–1526.