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DFT Studies toward the Design and Discovery of a Versatile Cage-Functionalized Proton Sponge

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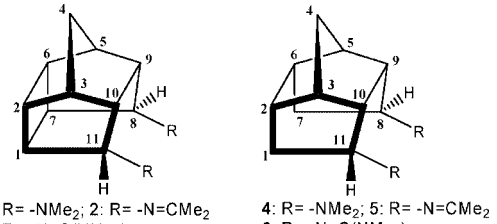
Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (PCU) derivatives were predicted to be superorganic bases by using DFT methods. The new molecular framework (PCU) is versatile in terms of anchoring different functional groups to achieve high basicities in both the gas and solvent phases.

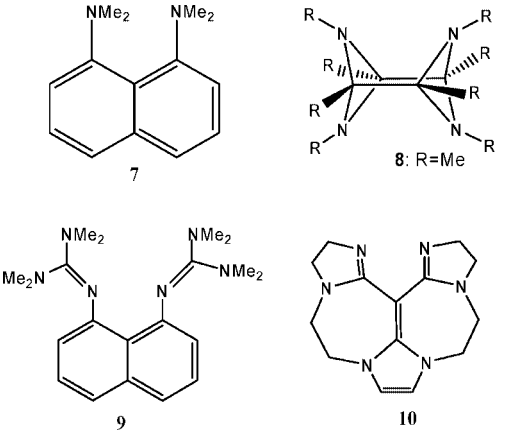
Introduction

The design and synthesis of strong organic bases has long been an active field of research.[1–6] Since the discovery of a simple organic compound, 1,8-bis(dimethylamino)-naphthalene (DMAN), as a superbase, better known as "proton sponge",[7] many proton sponges have been created, and they are finding a growing number of interesting applications.[2–5] With the advent of new computer architectures and more practicable implementations of electron-correlated quantum chemical methods such as density functional theory, it has been feasible to apply these tools in the design of novel proton sponges or to understand the factors responsible for enhanced basicity. Quantum chemical studies have shed light on the structural factors influencing the high basicity of proton sponges.[8–12] Their abnormally high basicity is accepted to be produced by the 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 features are achieved by anchoring two nitrogen atoms close in a rigid framework of condensed phenyl rings.[2–6] This framework of condensed phenyl rings has been anchored with amines, imines, and bisphosphazene to achieve the enhanced basicity.[2–6,13] However, such versatility in terms of different functional groups anchored with other frameworks is limited.

Herein, we report the design of a new molecular framework that differs from other proton sponges, which can be anchored with different functional groups and exhibits very high basicity. The cage polycyclic framework, that is pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane, has been substituted with *endo*,*endo*-8,11-diamines and diimines (Scheme 1) to achieve the properties of a proton sponge. The *endo*,*endo*-8,11-disubstituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes ensure that the nitrogen lone pairs of electrons are in close proximity, and the rigid framework of the polycyclic cage guarantees acid–base properties similar to those of a proton sponge. The geometries and proton affinities of **1**, **2**, and **3** (Scheme 1) as well as of DMAN (**7**), 1,2,3,4,5,6,7,8-octamethyl-3,6,7,8-tetraazatricyclo[3.1.1.1^{2,4}]octane (**8**), bis(tetramethylguanidino)naphthalene (TMGN) (**9**), and vinamidine (**10**) (Scheme 2) were calculated by using density func-



Scheme 1.



Scheme 2.

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tional theory. Compound **8** has the highest proton affinity (PA) value among all the aliphatic proton sponges reported.[14] Further, imine systems such as TMGN **9** and vinamidine **10** are known to have very high proton affinities.[13,15]

Results and Discussion

According to our DFT calculations, **1**–**3** have gas phase proton affinities that exceed or equal some of the proton sponges, such as DMAN (**7**), 1,2,3,4,5,6,7,8-octamethyl-3,6,7,8-tetraazatricyclo[3.1.1.1^{2,4}]octane (**8**), TMGN (**9**), and vinamidine (**10**). In particular, the calculated PA of **1** is 86 kJ/mol higher than that of **7** and 10 kJ/mol higher than that calculated for **8** (Table 1). Tetramethylated guanidino derivative **3** has a proton affinity that is higher by 35.9 kJ/mol than that calculated for **9**, which has the similar guanidino groups anchored to a naphthalene ring. As shown in Table 1, **1**–**3** are predicted to behave as strong proton sponges in acetonitrile and in the aqueous phase. In water and acetonitrile, the proton affinities calculated for **1** have been found to be much higher than that of octamethylated tetraazatricyclooctane **8** (Table 1). Similarly, by comparing the imines, the PA of **3** is higher than that of **9** and **10** in both acetonitrile and the aqueous phase (Table 1). On the basis of the studies performed by Peräkylä and Maksić et al. towards the correlativity of calculated proton affinities in solvents with observed p*K*a values,[8,16] it appears that **1**–**3** would have higher p*K*a values. The p*K*a value calculated for **3** in acetonitrile following the approach reported by Maksić et al. is 35.6 and that is higher than the reported p*K*a values for other imines.[16,17]

Table 1. B3LYP/6-311+G**//B3LYP/6-31G* calculated proton affinities in gas phase, water, and acetonitrile at 278 K in kJ/mol.

	Proton affinity (PA)[a]		
	Gas phase	Aqueous phase	Acetonitrile
1	1110.1	1297.3	1290.1
2	1091.2	1233.1	1235.2
3	1182.8	1300.7	1317.8
4	1112.9	1294.0	1291.3
5	1128.6	1289.8	1281.4
6	1156.7	1297.2	1307.7
7	1025.0[b]	1205.3	1197.6
8	1099.6	1249.2	1252.5
9	1192.0	1223.4	1267.7

[a] Zero point energy corrected. [b] Experimental value: 1030.1 kJ/mol.[7]

Some of the principal geometrical parameters of neutral and protonated optimized structures **1**–**3** are given in Table 2. The calculated N···N distances are around 2.80 to 3.08 Å and are in general agreement with the experimental values obtained for twenty proton sponges.[6] The N···N$^+$ distance decreases upon protonation of **1**–**3**. The computed results suggest that **1**–**3** have asymmetrical hydrogen bonds in the protonated forms with one N···H distance shorter than the other N···H distance (Table 2). The N–H···N hydrogen bonding angles are in the range of 150–170°. X-ray data compiled by Llamaz-Saiz et al.[6] show that proton sponges generally have angles between 150 and 180°, with the exception of vinamidine proton sponge, which has a value of 131.2°. The computed bond angles of **1**–**3** are greater than 150° and are in general agreement with the other reported proton sponges.

Table 2. Calculated geometric parameters of free bases and their conjugate acids at the B3LYP/6-31G* level.

Sponge	*r*(N···N) [Å]	*r*(N···H)$^+$ [Å]	*r*(N···H) [Å]	(N–H···N) [°]
1	2.955			
1H$^+$	2.685	1.098	1.615	163.3
2	2.803			
2H$^+$	2.679	1.073	1.679	152.9
3	3.089			
3H$^+$	2.680	1.057	1.702	151.7
4	3.127			
4H$^+$	2.728	1.097	1.647	167.5
5	2.988			
5H$^+$	2.776	1.076	1.739	160.4
6	3.275			
6H$^+$	2.776	1.048	1.776	158.0
7	2.836			
7H$^+$	2.640	1.110	1.590	157.5
8	2.365			
8H$^+$	2.350	1.052	1.690	116.0
9	2.757			
9H$^+$	2.623	1.046	1.744	138.8
10	3.026			
10H$^+$	2.662	1.025	1.859	132.5

To investigate the strain effect of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane on the proton affinities of **1**, **2**, and **3**, we have performed calculations with **4**–**6**, where the 4-membered ring has been taken out by removing the C_1–C_7 σ-bond in the polycyclic ring (Scheme 1). The B3LYP/6-311+G** computed proton affinities of **4**–**6** are found to be comparable or slightly higher than those of the corresponding PAs of **1**–**3** (Table 1). The calculated geometrical parameters show that the N···N distances in free bases are longer in **4**–**6** than those in **1**–**3** (Table 2). However, the computed N–H···N bond angles are found to be more linear in these cases. These results suggest that the basicities of **1**–**6** appear to be the result of interplay between the overlap of nitrogen lone pairs in the free bases and the formation of a strong intramolecular hydrogen bridge in the monoprotonated compounds.[10]

Conclusions

In summary, the current findings show that the derivatives of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane are highly basic and can be used as prototypes for a new proton sponge. This information will stimulate chemists to synthesize such proton sponges and more importantly, many strategies are already available for the synthesis of derivatives of cage polycyclic compounds.[18]

Experimental Section

All calculations were performed with the Jaguar program package[19] by using Becke's three-parameter exchange function with the correlation function[20] of Lee, Yang, and Parr (B3LYP).[21] All species were fully optimized with the 6-31G* basis set, and harmonic vibrational frequency calculations were used to confirm that the optimized structures were minima, as characterized by positive vibrational frequencies. Single-point calculations were then carried out with the 6-311+G** basis set. Zero point vibrational energies computed at the B3LYP/6-31G* level used in the proton affinity calculations are unscaled. Proton affinities calculated at the B3LYP/6-311+G**//B3LYP/6-31G* level by employing the general equation: PA(B) = (ΔE_{el}) + (ΔZPVE), where (ΔE_{el}) = [E(B) – E(BH^+)] and (ΔZPVE) = [ZPVE(B) – ZPVE(BH^+)] are the electronic and the zero point vibrational energy contributions to the proton affinity, respectively. Here, B and BH^+, denote the base in question and its conjugate acid, respectively. The B3LYP/6-31G* optimized geometries were used to calculate the solvation energies at the B3LYP/6-311+G** level by employing the Poisson–Boltzmann continuum (PB) solvent model[22,23] as implemented in the Jaguar program.[19] In PB-based calculations of solvation energies, the dielectric interface between solvent and solute is taken to be the molecular surface, which is the contact surface between the van der Waals envelope of the solute and a probable solvent molecule (for aqueous solution, a probe radius is 1.4 Å). The internal dielectric constant in the PB calculations is set equal to unity, as molecular polarizability is treated explicitly with quantum chemical calculations. All regions outside of the molecular surface are assigned the experimental solvent dielectric (ε = 78.4 for aqueous solution).

Supporting Information (see footnote on the first page of this article): B3LYP/6-311+G**//B3LYP/6-31G* SCF energies, B3LYP/6-31G* zero point vibrational energies (ZPVE), and cartesian coordinates for **1**–**6** and their monoprotonated ions.

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