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Ab Initio Studies of Proton Sponges (V): 1,4,7,10-Tetraaza-tricyclo[5,5,2,2^{4,10}]hexadecane, a Tricyclic Proton Sponge

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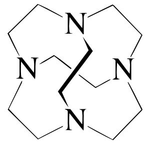
Not long ago, the first bicyclic tetraaza proton sponge based on the cyclen structure was reported,[1] and some related (low-symmetry) cross-bridged tetraaza compounds synthesized by Weisman et al.[2] are also potential proton sponges. However, the great majority of the literature on proton sponges has so far concentrated on diamines. Relatively little is known about the conformational and electronic factors pertinent to designing bicyclic and tricyclic proton sponges with three or more basic centers.

A recent series of papers has demonstrated the usefulness of high-quality quantum chemical calculations in quantifying specific properties for well-known proton sponges, such as basicity, pH, and strain energy.[3−10] However, such an approach clearly has the potential to predict the stability and properties of even unknown proton sponges (as demonstrated by Notario and Elguero[11]). In this note, ab initio calculations are applied to an unknown but intriguing compound, the simplest tetraaza, tricyclic proton sponge 1,4,7,10-tetraaza-tricyclo[5,5,2,2^{4,10}]hexadecane (**1**, hereafter TATH). Such cyclic polyamines usually have several possible structural isomers in which the various nitrogen lone pairs may be *in* (inside the cage) or *out* in various combinations.[12] It is evident that, if a stable (*in*, *in*, *in*, *in*) isomer of TATH exists, then it is potentially a proton sponge of exceptional basicity. The aim here is to establish the (gas phase) stability, proton affinity (PA), and strain energy of this isomer using ab initio quantum chemistry.



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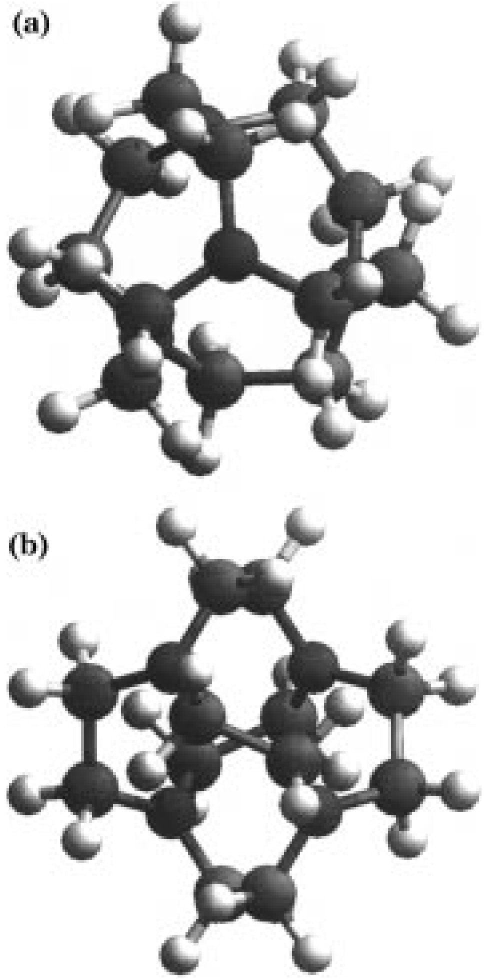

Figure 1. HF/6-31+G(d)-optimized geometry of $N_4(CH_2\text{-}CH_2)_6$: (a) view down a C_3 axis (b) view down a C_2 axis.

The structure of TATH was optimized within the C_3 point group at the Hartree−Fock (HF) level using standard 3-21G[13] and 6-31+G(d) basis sets[14] and the GAMESS program (Figures 1 and 2).[15] At both levels of theory, the optimized structure showed N···N nonbonded contacts all equal within 0.002 Å, implying a higher, tetrahedral symmetry (three perpendicular C_2 axes in addition to the four C_3 axes). This was verified by subsequent re-optimization within the *T* point group. The N···N nonbonded contact distance of 2.950 Å is within the range of N···N distances found in diamine proton sponges at comparable levels of theory.[5] A harmonic frequency calculation at the 3-21G level verifed that this (*in*, *in*, *in*, *in*) form of TATH is stable (since it gave no

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Table 1. Protonation of $N_4(CH_2CH_2)_6$

	$N_4(CH_2CH_2)_6$		$[N_4(CH_2CH_2)_6]H^+$			
theory level	energy (a.u.)	ZPE (kJ/mol)	energy (a.u.)	ZPE (kJ/mol)	CC[a] (kJ/mol)	PA[b] (kJ/mol)
HF/3-21G	−682.27815	1038.5	−682.73486	1082.1	−30.2	1130.1
HF/6-31+G(d)	−686.08876	as above	−686.51094	as above	−3.6	1065.9
BLYP/6-31+G(d)[c]	−690.28029	as above	−690.69248	as above	−1.5	1041.8

[a] Counterpoise correction *a la* Boys and Bernardi. [b] Including 0.89 ΔZPE,[18] and the counterpoise correction. [c] BLYP/6-31+G(d)//HF/6-31+G(d), that is, BLYP single point at the HF-optimized geometry.

imaginary vibrational frequencies), and also provided an estimate of the zero-point energy (ZPE).

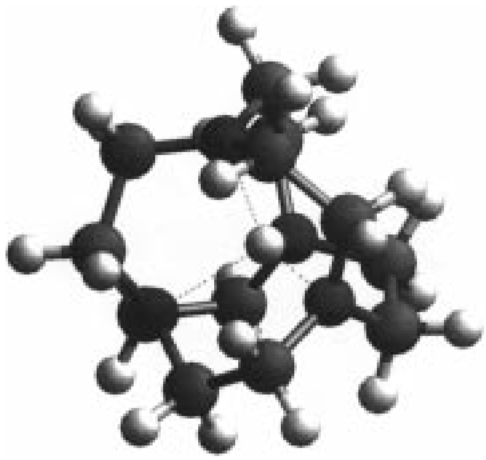


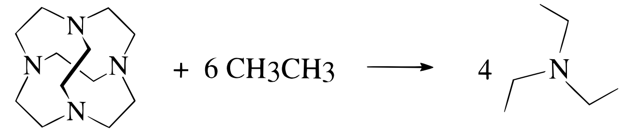
Figure 2. HF/6-31+G(d)-optimized geometry of $[N_4(CH_2CH_2)_6]H^+$. Hydrogen bonds are indicated as broken lines.

The high symmetry of this isomer has the consequence that the first nonzero electric multipole moment is octupolar (the BLYP/6-31+G(d) quadrupole expectation values $<Q_{xx}> = <Q_{yy}> = <Q_{zz}> = -104.4$ D.Å^2, but the quadrupole moment reported in the usual "traceless tensor" definition $= 2<Q_{zz}> - <Q_{xx}> - <Q_{yy}> = 0$.) As a consequence of this, and the (*in*, *in*, *in*, *in*) nature of of TATH, it ought to be highly nonpolar in the liquid phase.

HF/3-21G and HF/6-31+G(d) optimizations followed on $[TATH]H^+$, assuming asymmetric protonation at one nitrogen and with the proton inside the cage. This necessarily lowers the symmetry to C_3, which was the point group applied during optimization. The N···N distances in this species are 2.684 Å (between the protonated nitrogen and unprotonated nitrogens) and 2.864 Å (between unprotonated nitrogens). Destabilizing lone pair−lone pair repulsion between the unprotonated nitrogens presumably increases on protonation, since the N···N distance has fallen by 0.086 Å compared to unprotonated TATH. This partially offsets the stabilization due to the formation of the strong, four-centered intramolecular hydrogen bond. Again, a harmonic frequency calculation at the 3-21G level gave no imaginary frequencies.

BLYP/6-31+G(d) single-point calculations were performed on the HF/6-31+G(d)-optimized conformers of TATH and $[TATH]H^+$ using GAUSSIAN94,[16] enabling an estimate of electron correlation effects to be included in the PA (reported in Table 1). Corrections to the PA due to basis set superposition have also been included at all three levels of theory using the usual counterpoise method of Boys and Bernardi.[17] The BLYP/6-31+G(d) PA of ≈ 1041.1 kJ·mol^{-1} is high, but not exceptional (the bicyclic diamine 1,8-diaza^{4,4,4}tetradecane has a PA of ≈1090 kJ·mol^{-1} [5,7]).

Scheme 1



The relief of strain on protonation is one of the key factors in determining proton sponge basicity.[5] It is possible to estimate the strain energy of TATH as the enthalpy change of an appropriate isodesmic reaction. Unfortunately, the choice of such reference reactions is not unique. The most pertinent choice in this case would seem to be Scheme 1. This reaction not only satisfies the necessary isodesmic criteria of the same number and type of bonds on each side of the equation, but the electronic environment of the nitrogens is identical (i.e., tetriary amines). Optimization, total energy, and frequency calculations were carried out at the appropriate levels of theory on the ancillary species CH_3CH_3 and $N(Et)_3$, with the following results: BLYP/6-31+G(d) electronic energies (a.u.) −79.76640, −292.22940; and HF/3-21G ZPE's (kJ·mol^{-1}) 210.2, 578.9. These data, together with the electronic and zero-point energies of TATH in Table 1, lead to a strain energy of 87.7 kJ·mol^{-1}. This can be seen as an upper limit for the strain which is available to be "relieved" on protonation.

In summary, these calculations indicate that the simplest tetrazaza, tricyclic compound has a stable conformer in which all four (symmetry-equivalent) nitrogen lone pairs are inside the cage. It is the only known example (from either experiment or ab initio calculation) of a proton sponge with tetrahedral symmetry, forming a very strong, four-centered hydrogen bond on "in-protonation". It is therefore a unique proton sponge and a powerful one (its gas-phase PA is larger than most known diamine sponges). There appear to be two reasons why TATH does not have an exceptionally high gas-phase PA: (*i*) the contraction of *all* N···N distances on protonation results in a partial destabilization of the cation by increased lone pair repulsion; and (*ii*) the change from a tricyclic to a *pseudo*-hexacyclic system on protonation implies that the cation may actually be *more* strained than the free base (in contrast to virtually all other known proton sponges). The first of these points indi-

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cates how to design a more basic tetraza compound, that is, introducing some rigidity with an appropriate choice of exo-substituents, in a way which favors contraction *only* in the N$-$H$^+$···N direction.

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