

# Intra-annular cyclophane diamines as proton sponges: a computational study

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**Abstract**—Gas-phase proton affinities of cyclophanes containing intra-annular amino groups were calculated using density functional theory (DFT) at the B3LYP/6-31+G\*\*//B3LYP/6-31G\* level. They are higher in magnitude as those for proton sponges such as 1,8-bisaminonaphthalene, however, they are slightly weaker bases than 1,8-bis(dimethylamino)naphthalene. The high basicity of the cyclophane diamines is attributed mainly to their structural flexibility, which allows them to maximize the hydrogen bond strength in the cations by achieving N–H···N linearity, while strain relief upon protonation is less important. Another contributing factor is the stabilizing interaction of the added proton with adjacent phenyl  $\pi$  systems of the cyclophanes. Barriers for proton transfer between the nitrogen atoms of the diamine cations are also reported.

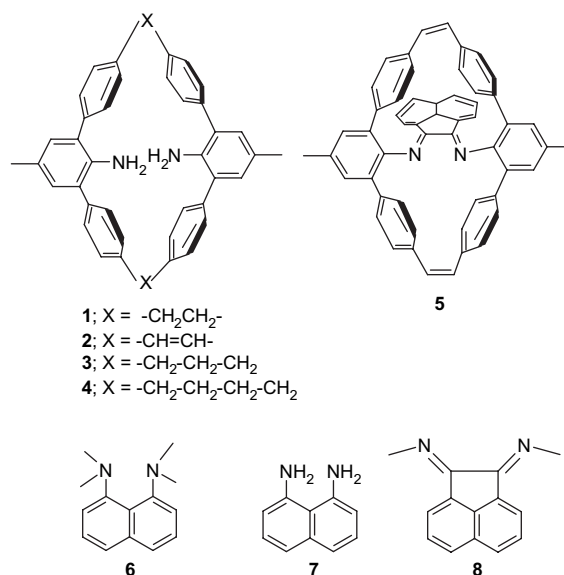
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## 1. Introduction

Aromatic and cyclic diamines, which have exceptionally enhanced basicity are called ‘proton sponges’.<sup>1,2</sup> These compounds have two basic amine sites closely positioned and can accept a proton between the nitrogens. Other types of proton sponges have also been developed, which include Schwesinger’s vinamidine<sup>3</sup> and phosphazene bases,<sup>4</sup> and the proazaphosphatrane bases developed by Verkade.<sup>5</sup> A large number of such compounds have been synthesized and their properties are extensively studied by crystallographic and spectroscopic methods. Several reviews have been published on the ‘proton sponges’.<sup>1–6</sup> Their enhanced basicity has been attributed to a combination of several factors such as repulsion of the nitrogen lone-pairs (LPs) of the neutral molecule, relief of repulsion and strain on protonation, solvation effects, and enforced hydrogen bonding in the protonated ion.<sup>1,2,7–10</sup> In addition to these types of bases, a number of medium ring di- and polyamines have been found to have enhanced basicities.<sup>11</sup>

Besides synthesizing new proton sponges, there is an ongoing effort to characterize efficient proton sponges by high-quality quantum chemical calculations.<sup>8,10a,b,12</sup> Here, we report DFT calculations on some macrocyclic cyclophane diamines (**1–4**) and one such diimine (**5**) (Scheme 1). It will be shown that the special properties of the hydrogen

bonds in their monoprotonated ions are essential for their high basicity, rather than strain relief on protonation. The results of **1–4** are compared with those of the Alder-type proton sponges **6** and **7** (Scheme 1), the experimental proton affinities of which are well reproduced by the chosen DFT approach. In addition, proton-transfer barriers and topological analyses are provided for three of the diamines (**1**, **4**, and **6**). Finally, we report the proton affinity of the simple model compound **8** (Scheme 1) to gauge the influence of the cyclophane environment on the basicity of **5**.



Scheme 1.

**Keywords:** Cyclophane diamines; Proton sponge; H-bonds; DFT calculations.

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## 2. Computational methods

The lowest-energy conformations for **1–4** and their protonated forms were examined using Monte Carlo conformational searches employing the MMFF94 force field (Supplementary data).<sup>13</sup> The lowest-energy conformers obtained were optimized at the RHF/3-21G\* level<sup>14</sup> for **1–4** using Gaussian98.<sup>15</sup> The geometries of **1** and **4–8** were optimized at the B3LYP/6-31G\*<sup>16</sup> level using Gaussian03<sup>17</sup> (starting from RHF/3-21G\* structures in the case of **1** and **4**). Harmonic force constants were computed at the optimized geometries to characterize the stationary points as minima. Zero-point vibrational energies (ZPVE) were determined from the harmonic vibrational frequencies to convert the total energies  $E_c$  to the ground-state energies  $E_0$ . The rigid-rotor harmonic-oscillator approximation was applied for evaluating the thermal and entropic contributions that are needed to derive the enthalpies  $H_{298}$  and Gibbs free enthalpies  $G_{298}$  at 298 K. Further single-point calculations were performed at B3LYP/6-31+G\*\* using B3LYP/6-31G\* optimized geometries. In this case, the ZPVE values were taken from B3LYP/6-31G\* results for the corresponding molecules. To study the weak interactions and characterize the H-bonds, we have used Bader's AIM (atoms-in-molecule) theory as implemented in the MORPHY program.<sup>18</sup>

## 3. Results and discussion

Recently, Guan et al. have reported the synthesis of *m*-terphenyl-based cyclophanes with intra-annular amino groups in the core of the rings (Scheme 1).<sup>19</sup> These cyclic diamines and/or diimines are potential candidates for proton sponges, essentially because this framework provides an ideal geometry for an intramolecular trans-annular hydrogen bond. This structural motif has been realized before in a diazacyclodecane proton sponge.<sup>20</sup> The X-ray single crystal structures determined for **1** and **5** indicate that the two aniline rings lie approximately in the same plane. The N...N intra-annular distance is 3.052 Å in **1** and 2.875 Å in **5**.<sup>19</sup> Such arrangements of diamine/diimine are appropriate for accommodating a proton in the cyclophane core. Furthermore, the phenyl rings around the cyclophane core can provide additional stabilization toward the incoming proton through  $\pi \cdots H^+$  attractions,<sup>21</sup> in addition to  $[N \cdots H \cdots N]^+$  hydrogen bonding in the cyclophane core. In **1–4** the amino groups are non-methylated in the cyclophane core; note that the methylated amines should give rise to stronger proton sponges.<sup>22</sup> In our computations, the chain connecting the phenyl groups in **1–4** was varied to make it more rigid or more flexible, in order to see whether such variations would lead to an even better proton sponge. For computational simplicity, we have not considered the methyl substituents at the central phenyl rings in our calculations.

The lowest-energy MMFF94 conformers for the neutral and protonated forms of **1–4** are shown in Figure S1 (Supplementary data). The most stable protonated conformers **1H<sup>+</sup>–4H<sup>+</sup>** have strong intramolecular (N...H...N)<sup>+</sup> hydrogen bonds. The lowest-energy neutral conformer **1** adopts a geometry similar to the  $C_2$ -symmetric crystal structure.<sup>19</sup> The most stable neutral conformer **2** contains bridging cis double bonds (C=C). The neutral forms of **3** and **4** are quite

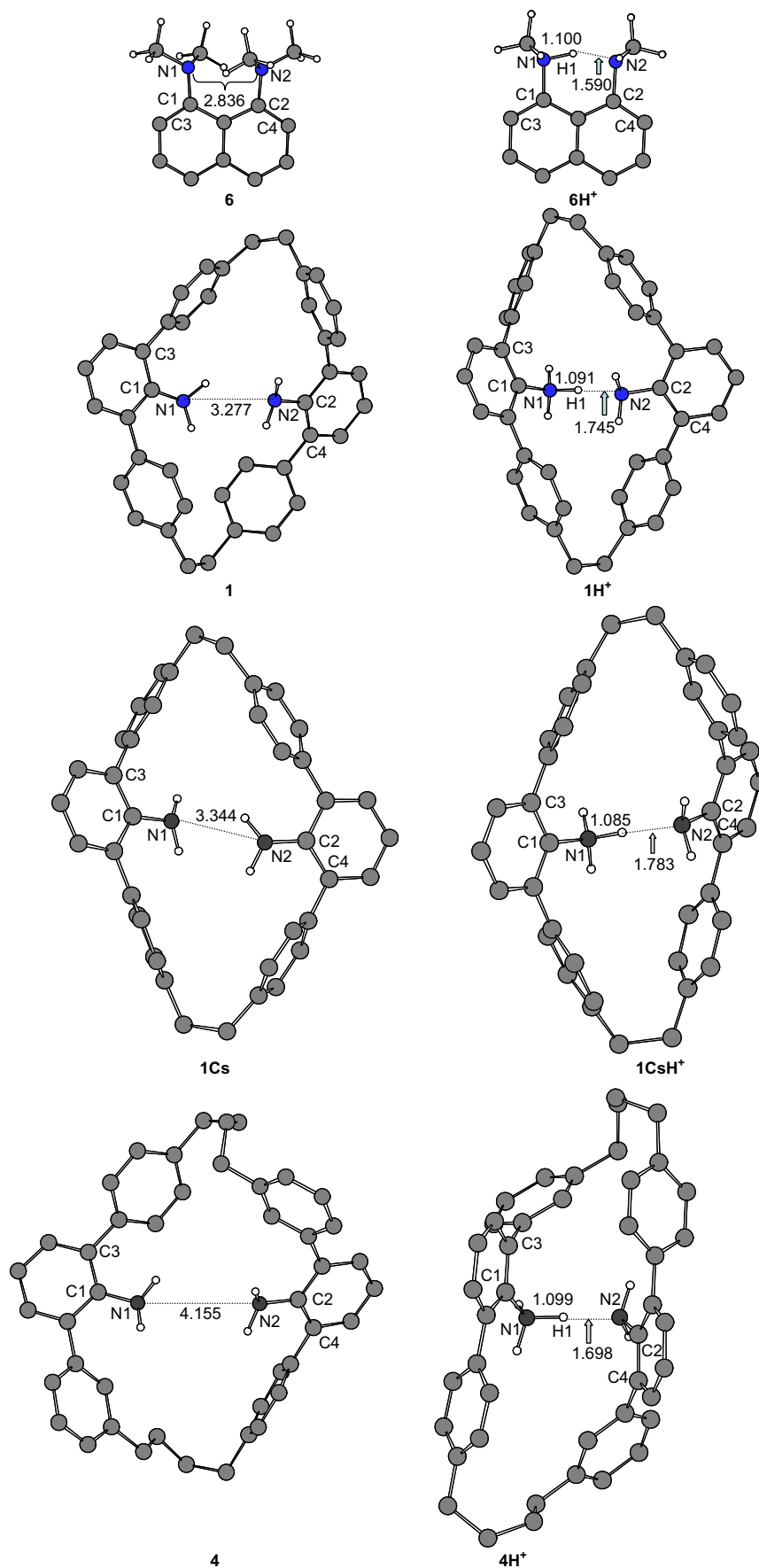
flexible, and a large number of conformers are found in the MMFF94 searches. The N...N distances in the most stable conformers of **3** and **4** are calculated to be 5.03 and 4.67 Å, respectively; higher-energy conformers often show even larger N...N distances (but not always). Comparing the MMFF94 geometries of the neutral and protonated forms, the overall molecular shape is similar in the case of **1** and **2**, whereas in the more flexible systems **3** and **4** the protonated species appear significantly more puckered than their neutral counterparts (Fig. S1).

To examine the proton affinities of **1–4** we initially employed Hartree–Fock calculations at the RHF/3-21G\* level to reoptimize the lowest-energy MMFF94 conformers. This leads to some increase in the non-bonded N...N distances for neutral **1**, **2**, and **3**, and a more pronounced decrease in the case of **4**, which is more flexible (Fig. S2, Supplementary data). The protonated species become generally more compact at the RHF/3-21G\* level, with a shortening of the hydrogen bonds by 0.12–0.26 Å compared with MMFF94. In the protonated form **3H<sup>+</sup>** the central carbon atoms in the propyl bridges are normally on opposite sides (*anti*) of the cyclophane ring (see Figs. S1 and S2), but the MMFF94 searches occasionally also find *syn* conformers with a flipped propyl bridge. RHF/3-21G\* optimization of the lowest such *syn* conformer of **3H<sup>+</sup>** yields an energy of 5.0 kcal/mol higher than that of the lowest-energy *anti* conformer shown in Figure S2.<sup>23</sup>

Table S1 lists the calculated RHF/3-21G\* proton affinities. It is obvious that diamines **1** and **4** are predicted to be significantly more basic than **2** and **3**. The difference between **1** and **2** is reflected in the hydrogen bond lengths, which are shorter and thus stronger in **1H<sup>+</sup>** compared with **2H<sup>+</sup>** (Fig. S2): apparently the ethene bridge in **2H<sup>+</sup>** is too rigid to allow for an optimal geometry of the hydrogen bond. Concerning **3** and **4** one may argue again that the butyl bridge in **4** is more flexible than the propyl bridge in **3**, and may thus allow for better hydrogen bonding in the protonated form. However, one should be cautious with such arguments because of the conformational diversity of **3** and **4**: it may well be that the MMFF94 conformational searches are incomplete, which prevents firm conclusions.

In view of the RHF/3-21G\* results, we performed higher-level B3LYP/6-31G\* optimizations only for **1** and **4**, which were followed by single-point calculations at the B3LYP/6-31+G\*\*//B3LYP/6-31G\* level. In the case of **1**, we also considered an alternative conformation **1Cs** with  $C_s$  symmetry (one of the bridging  $-CH_2-CH_2-$  groups flipped): this conformer is not found in the MMFF94 search, but models suggest that it may easily form an almost linear hydrogen bond upon protonation. To examine the reliability of our approach, the Alder proton sponges **6** and **7** were also calculated at the same level (Scheme 1).

The optimized structures of **1**, **1Cs**, **4**, **6**, and the corresponding protonated species are shown in Figure 1. The B3LYP/6-31G\* geometries obtained for **6** and **6H<sup>+</sup>** are similar to those found at other levels of theory.<sup>10,24</sup> The amine nitrogen planes are twisted and the corresponding angles between the two planes are 19.0°. The naphthalene ring is also twisted and the N...N non-bonded distance for **6** is 2.84 Å. Upon



**Figure 1.** B3LYP/6-31G\* optimized geometries of 6, 6H<sup>+</sup>, 1, 1H<sup>+</sup>, 1Cs, 1CsH<sup>+</sup>, 4, and 4H<sup>+</sup> with selected distances in angstrom (Å). The ring hydrogens are removed for clarity.

protonation, the N···N distance decreases to 2.64 Å and the nitrogen atoms lie in the same plane for an optimum N–H···N hydrogen bond interaction; the N–H···N bond angle is 157.5° and the hydrogen atom sits asymmetrically in between the amine groups in agreement with earlier results.<sup>10</sup> In the neutral cyclophane systems, the intra-annular diamine moieties lie approximately in the same plane with N···N non-bonded distances of 3.28 Å for **1**, 3.34 Å for **1Cs**, and 4.15 Å for **4**, respectively. Upon protonation, the intra-annular diamines come closer to form linear hydrogen bonds with N–H···N bond angles of 173.4°, 177.8°, and 177.0° and with N···N non-bonded distances of 2.832, 2.860, and 2.797 Å, in **1H**<sup>+</sup>, **1CsH**<sup>+</sup>, and **4H**<sup>+</sup>, respectively. The hydrogen atom is again situated asymmetrically between the two nitrogen atoms in all cases (Fig. 1).

The calculated proton affinities (PA) are documented in Table 1. The single-point B3LYP/6-31+G\*\*//B3LYP/6-31G\* value ( $\Delta H=1030$  kJ/mol) equals the experimental PA of **6** ( $\Delta H=1030$  kJ/mol).<sup>10,22</sup> Moving from Alder proton sponge **6** to the non-methylated diamine **7** lowers the computed PA by 80 kJ/mol, in agreement with experiment.<sup>22</sup> The excellent agreement between calculated and experimental proton affinity is somewhat fortuitous, due to cancellation of errors. According to the B3LYP results, **1** and **4** are stronger proton sponges than the parent Alder sponge **7**, but weaker than the methylated Alder sponge **6**. The calculated PA of conformer **1Cs** is slightly higher than that of **1**. The values given in Table 1 for **1** and **1Cs** are derived from the differences **1H**<sup>+</sup>–**1** and **1CsH**<sup>+</sup>–**1Cs**, respectively, for the structures shown in Figure 1. Since the most stable conformers are neutral **1** and protonated **1CsH**<sup>+</sup> (see Table S1, Supplementary data) it is, however, more appropriate to consider the difference **1CsH**<sup>+</sup>–**1**, which leads to an intermediate PA value (entry **1\*** in Table 1). To examine the effect

of methylation on **1**, the methylated analogue **1Me** with two NMe<sub>2</sub> groups was studied at the B3LYP/6-31G\* level. Its PA is indeed significantly higher than that of **1**, as expected, and close to that of **6** (Table 1). To determine the proton transfer barriers in the cations, we computed B3LYP/6-31G\* energy profiles by constraining the difference of the two relevant N–H distances and optimizing the other degrees of freedom. The resulting barriers of proton transfer for **1H**<sup>+</sup>, **4H**<sup>+</sup>, and **6H**<sup>+</sup> are 20.9, 16.7, and 8.8 kJ/mol, respectively.

The proton affinities were also examined in dichloromethane for proton sponges **1** and **4**. Solvent calculations were performed at the B3LYP/6-31+G\*\* level using the CPCM model (conductor like polarized continuum model),<sup>25</sup> with UAKS (united atom Kohn Sham) radii for all atoms.<sup>15,17</sup> Only single-point calculations at gas-phase B3LYP/6-31G\* geometries were done because of the size of these molecules, which makes CPCM optimizations prohibitively expensive. The calculated PAs of **1** and **4** in dichloromethane are 1125.9 and 1120.0 kJ/mol, respectively. They are considerably higher than those in the gas phase (Table 1), by ca. 123 kJ/mol, due to the stronger polarization of the solvent by the cation compared with the neutral diamine.

Topological analyses of  $\rho_b$  and  $\nabla^2\rho_b$  around the N···N region of the bases **1**, **4**, and **6** and their corresponding acids have also been performed (Table 2).<sup>18,26</sup> The asymmetrical H-bonds in the conjugate acids are clearly seen since **6**, **1**, and **4** have typical H-bond density properties (Table 2), with N1–H1 covalent (high  $\rho_b$  and negative  $\nabla^2\rho_b$ ) and N2···H1 ionic (low  $\rho_b$  and positive  $\nabla^2\rho_b$ ). The lone-pair maxima in  $-\nabla^2\rho_b$  at the nitrogen atoms are found to be larger in **6** than in **1** and **4** (Table 2).

There is a continuing debate about whether the enhanced basicity in proton sponges is mainly due to the strain relief on protonation<sup>1,2</sup> or to the special properties of the hydrogen bonds in their protonated forms.<sup>10</sup> The factors that govern the PA of **1** have been investigated with the use of isodesmic reactions. The contributions of the strain energy in the proton sponge **1** and the strain energy+hydrogen bond energy (SE+HBE)<sup>+</sup> in the protonated cation **1H**<sup>+</sup> were estimated from the isodesmic reactions shown in Scheme 2 (reactions a and b). The B3LYP/6-31G\* strain energy for the unprotonated form **1** is 20.5 kJ/mol. The corresponding B3LYP/6-31G\* stabilization energy (SE+HBE)<sup>+</sup> for the protonated form **1H**<sup>+</sup> is –38.2 kJ/mol. Some independent information is required to separate SE and HBE in the cation.<sup>10b</sup> To evaluate the HBE in **1H**<sup>+</sup>, we consider a model system taken from the ‘atomic’ framework of the optimized cation **1H**<sup>+</sup> (Fig. 2). The H-bond stabilization is obtained by performing

**Table 1.** B3LYP/6-31G\* proton affinities in kJ/mol

Entry	$\Delta E_c$	$\Delta E_0$	$\Delta E_t$	$\Delta H_{298}$	$\Delta G_{298}$
<b>1</b>	1044.6(1021.5)	1006.0	1007.0	1007.0(983.9)	1002.1
<b>1Cs</b>	1051.0(1027.0)	1011.8	1012.1	1013.1(987.2)	1007.3
<b>1*</b>	1046.1(1023.1)	1007.5	1008.7	1008.6(984.3)	1002.7
<b>4</b>	1047.2(1021.4)	1006.8	1008.9	1008.9(983.2)	997.2
<b>1Me</b>	1069.6(1058.4)	1026.6	1027.3	1027.3(1016.1)	1026.3
<b>5</b>	1087.0(1074.0)	1050.6	1050.0	1050.0(1037.0)	1052.7
<b>6</b>	1077.4(1066.2)	1041.5	1041.2	1041.2(1030.1)	1042.4
<b>7</b>	994.3(975.5)	960.5	960.8	960.8(941.9)	961.0
<b>8</b>	1082.3(1069.3)	1046.2	1047.2	1047.2(1033.6)	1050.0

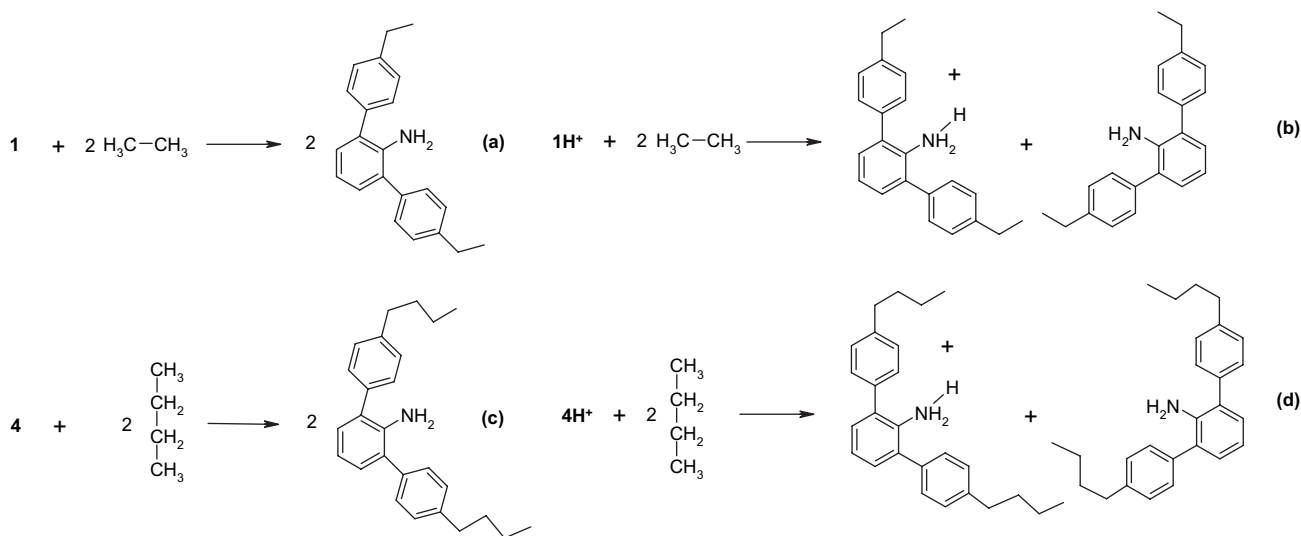
B3LYP/6-31+G\*\*//B3LYP/6-31G\* values are given in parentheses.  $\Delta E_c$ ,  $\Delta E_0$ ,  $\Delta E_t$ ,  $\Delta H_{298}$ , and  $\Delta G_{298}$  represent electronic, zero-point, thermal, enthalpic, and Gibbs free energy differences, respectively. The  $\Delta H$  values at B3LYP/6-31+G\*\* were calculated using ZPVE corrections taken from the B3LYP/6-31G\* level.

**Table 2.** Electron density  $\rho_b$ , Laplacian of the electron density  $\nabla^2\rho_b$ , and ellipticities  $\epsilon$  at bond critical points in compounds **6H**<sup>+</sup>, **1H**<sup>+</sup>, and **4H**<sup>+</sup>

Entry	<b>6H</b> <sup>+</sup>			<b>1H</b> <sup>+</sup>			<b>4H</b> <sup>+</sup>		
	$\rho_b$	$\nabla^2\rho_b$	$\epsilon$	$\rho_b$	$\nabla^2\rho_b$	$\epsilon$	$\rho_b$	$\nabla^2\rho_b$	$\epsilon$
N1–H1	0.277	–1.342	0.002	0.277	–1.404	0.002	0.271	–1.351	0.001
N2···H1	0.079	0.097	0.008	0.052	0.084	0.010	0.059	0.087	0.008
N(lp) <sup>a</sup>	0.589	–3.147		0.554	–2.815		0.559	–2.785	

All values are expressed in au.

<sup>a</sup> In the unprotonated bases.



Scheme 2.

B3LYP/6-31G\* single-point calculations (vibrationless) on this model system and on its components at infinite separation. The calculated HBE obtained for  $1\text{H}^+$  is  $-90.5 \text{ kJ/mol}$ . This computed intramolecular hydrogen bond energy is relatively high.<sup>10b</sup> The resulting strain energy of  $1\text{H}^+$  ( $52.2 \text{ kJ/mol}$ ) is much larger than that of **1** ( $20.5 \text{ kJ/mol}$ ). Further, the strain energy calculated (Scheme 2) for  $4\text{H}^+$  ( $49.3 \text{ kJ/mol}$ ) is again higher compared to the strain energy calculated for unprotonated form **4** ( $9.1 \text{ kJ/mol}$ ). The calculated HBE obtained for  $4\text{H}^+$  is  $-100.7 \text{ kJ/mol}$ . Diamines **1** and **4** are thus among the rare examples, where protonation actually increases the strain energy in a proton sponge.<sup>10b</sup> Therefore, the enhanced basicity of cyclophanes with intra-annular amino groups is due to an exceptionally strong intramolecular hydrogen bond in the cation, and not due to relief of strain on protonation (as in the case of the proton sponge **6**<sup>2,6,10</sup>).

In the cyclophane systems, additional stabilization of the cations is provided by the interaction<sup>21</sup> between the added proton and the phenyl rings that lie at a distance of ca.  $2.9\text{--}3.1 \text{ \AA}$ .<sup>21</sup> To estimate the magnitude of such secondary phenyl  $\pi \cdots \text{H}^+$  interactions, we employ a simple model obtained by cutting out the corresponding phenyl ring with the proton from the optimized geometry of **1** (Fig. 3) and assigning the proton charge to be  $0.45e$  (i.e., the B3LYP/6-31G\* Mulliken charge of the corresponding H atom in  $1\text{H}^+$ ). Using the MESSAGE option in Gaussian98,<sup>15</sup> we computed an interaction energy of  $10.5 \text{ kJ/mol}$ . The

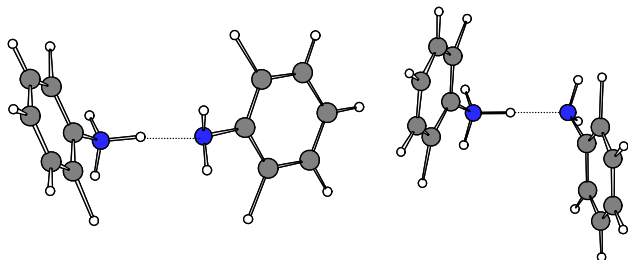


Figure 2. The model system used to estimate HBE in cation of  $1\text{H}^+$  and  $4\text{H}^+$ .

secondary phenyl  $\pi \cdots \text{H}^+$  stabilization thus gives a non-negligible contribution to the basicity of the cyclophane derivatives, but it is less important than the dominant H-bond stabilization (Fig. 3).

We now turn to the  $\alpha$ -diimine ligand **5**, which offers another potential site for protonation having diimine nitrogen atoms at a distance of  $2.87 \text{ \AA}$  in the cyclophane core.<sup>19</sup> The  $\alpha$ -diimine ligand **5** is structurally more rigid than **1** and **4**, however, the initial conformational search was performed with MMFF94 method. The lowest-energy conformation obtained from the molecular mechanics search method was considered for the higher-level calculations. The B3LYP/6-31G\* optimized geometry of the free ligand **5** is in good agreement with the reported X-ray structure.<sup>19</sup> The calculated  $\text{N} \cdots \text{N}$  distance in **5** is  $2.871 \text{ \AA}$  (exp:  $2.875 \text{ \AA}$ ). The protonated form of **5** shows an asymmetric hydrogen bond between the nitrogen atoms with a calculated  $\text{N}-\text{H} \cdots \text{N}$  bond angle of  $105.1^\circ$  (Fig. 4). The proton affinities calculated for **5** at the B3LYP/6-31G\* and B3LYP/6-31+G\*\*//B3LYP/6-31+G\* levels are the highest among all the ligands studied (Table 1). For the rigid central part of **5**, i.e., 1,2-bis(phenylimino)acenaphthylene **8**, we compute a proton affinity of  $1082.3 \text{ kJ/mol}$  at the B3LYP/6-31G\* level, which is only slightly lower than that of **5** ( $1087.0 \text{ kJ/mol}$ ). Hence, the high proton affinity of **5** is

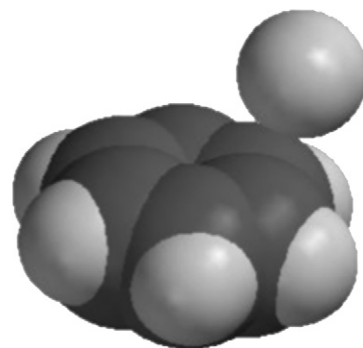
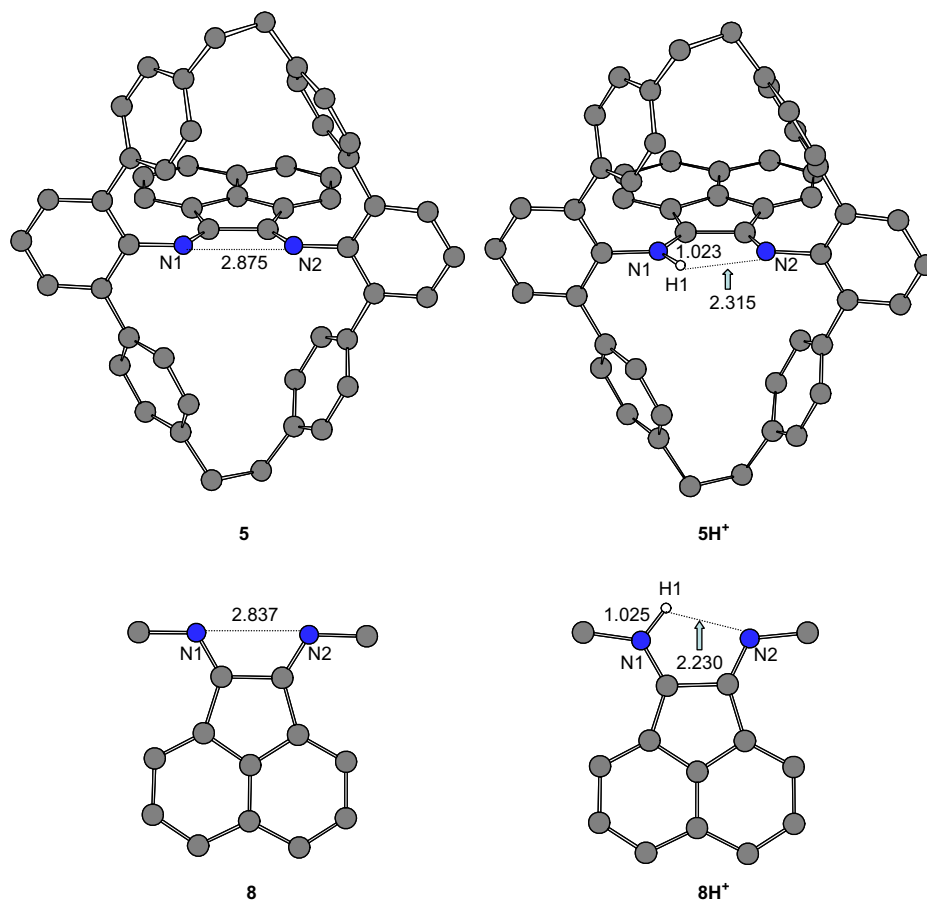


Figure 3. Phenyl ring and proton as obtained from the optimized geometry of  $1\text{H}^+$ .





**Figure 4.** B3LYP/6-31G\* optimized geometries of **5**, **5H<sup>+</sup>**, **8**, and **8H<sup>+</sup>** with selected distances in angstrom (Å). The ring hydrogens are removed for clarity.

essentially due to the intrinsic basicity of **8** and is only slightly affected by the cyclophane environment.

#### 4. Conclusions

In this work, we have performed DFT quantum chemical calculations to study cyclophanes with intra-annular amino groups as proton sponges. The computed large basicities in the diamines arise mostly from strong intramolecular [N–H···N]<sup>+</sup> hydrogen bonding in the protonated cations, which are further stabilized by the interaction of the added proton with adjacent phenyl  $\pi$  planes. The diimine groups present in the cyclophane core of **5** give rise to the highest proton affinity studied in the present study.

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#### Supplementary data

Supplementary data includes energies and Cartesian coordinates of all optimized B3LYP/6-31G\* structures (two tables)

and graphs of optimized MMFF94 and RHF/3-21G\* structures (two figures). This material is available free of charge via the internet at <http://www.sciencedirect.com>. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.05.067.

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