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C_2-Chiral Substituted *cis*-1,3,5,7-Tetraazadecalins as Proton Sponges: A Computational Study

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Dedicated to Professor Benzion Fuchs, Tel-Aviv University, Israel

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Density functional quantum chemical calculations at the B3LYP/6-31+G* and B3LYP/6-31+G** levels have been performed to calculate the proton affinities of chiral *cis*-1,5-diazadecalins **1**,**2** and substituted *cis*-1,3,5,7-tetraazadecalin **3**. The calculated gas-phase proton affinities of *cis*-1,3,5,7-tetraazadecalins are higher than that of 1,8-bis(dimethylamino)naphthalene (**4**). *cis*-1,5-Diazadecalins show lower proton affinities compared with those of substituted 1,3,5,7-tetraazadecalins. Cooperative and anomeric effects seem to be responsible for the additional stabilization of the protonated forms of 1,3,5,7-tetraazadecalins. Intramolecular proton transfer energies have been predicted for these amines and discussed.

Introduction

Aromatic and cyclic diamines that have exceptionally enhanced basicities are called "proton sponges".[1,2] These compounds have two closely positioned basic amine sites that can accept a proton between the two nitrogen atoms. Since the discovery of the remarkable basicity of 1,8-bis(dimethylamino)naphthalene (**4**), the design and synthesis of novel organic bases continues to generate considerable interest,[3,4] and work was carried out on chiral targets.[5] Recently, the calculations performed on C_2-chiral diamines have shown much higher proton affinities (PAs) than those of known diamines; however, these diamines present a certain challenge as synthetic targets.[6a] DFT calculations performed on chiral bis-tetrahydroisoquinoline predicted a slight enhancement of its PA relative to that of **4**.[6b] In general, literature reports on the topic of chiral proton sponges are limited. Therefore, there is a need for a class of chiral proton sponges that can be efficiently synthesized for practical purposes. Herein we report the PAs for chiral nitrogen-substituted *cis*-decalins **1**–**3** calculated at the density functional level (Figure 1).

cis-1,5-Diazadecalin (**1**) is a unique chiral ligand which possesses a well-defined chiral cavity with two lone pairs of electrons from two nitrogen atoms that point (proximal) towards each other (Scheme 1).[7] Another conformation of

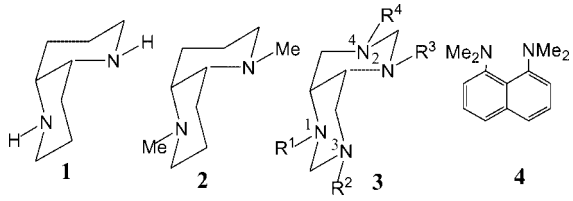
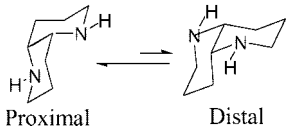


Figure 1. *cis*-1,5-Diazadecalins, *N*-substituted-*cis*-1,3,5,7-tetraazadecalins and 1,8-bis(dimethylamino)naphthalene.

1 is also possible, where the nitrogen atoms do not point in the direction of the cavity (distal). The distal conformation is not the preferred conformation for this compound (Scheme 1).



Scheme 1.

However, in *N*,*N*-dimethyl derivative **2** there is an almost equal participation between these two conformers.[8] Interestingly, protonation of the nitrogen atom shifts the conformational equilibrium of **2** towards the proximal conformation, which leads to a hydrogen-bridged monocation.[7] These observations indicate that *cis*-1,5-diazadecalin systems possess conformational flexibility, and they can also

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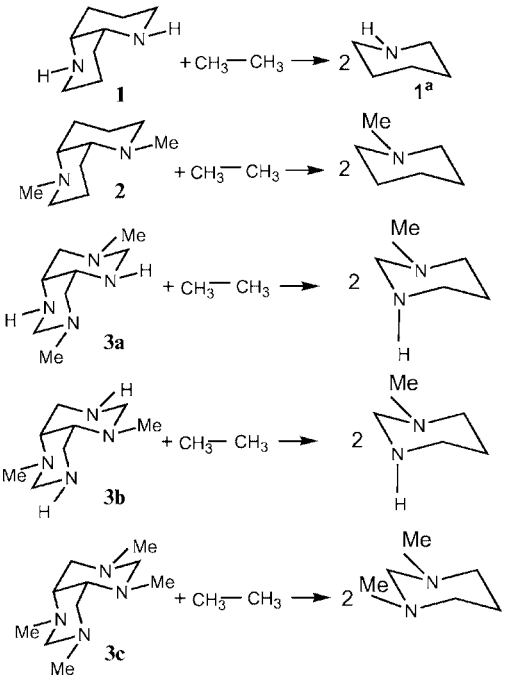
strongly bind the proton with the proximal conformation. However, to the best of our knowledge, the magnitude of the PAs of **1** and **2**, either experimentally or theoretically, has not been reported. Reany et al. have shown that 1,3,5,7-tetraazadecalins and their derivatives can also be synthesized.[9] In particular, the syntheses of di- and tri-*N*-methylated 1,3,5,7-tetraazadecalins reveal that the *N*-methylated nitrogen lone pairs of electrons point towards the chiral cavity (proximal) of the compound. Further, methylation of the nitrogen atom would inhibit the conformational change from the proximal to the distal conformer in these cases. The presence of additional nitrogen atoms that are inherently present in the chiral cavity of the *cis*-1,3,5,7-tetraazadecalin unit compared with that of the *cis*-1,5-diazadecalin unit, renders the tetradecalins attractive candidates for their use as proton sponges. To examine this possibility, we have computed the PAs of C_2-chiral *N*-methyl-substituted-*cis*-1,3,5,7-tetraazadecalins **3a**–**c** and compared the values with those of the known proton sponge 1,8-bis(dimethylamino)naphthalene (**4**), whose experimental PA is reproduced well by the chosen DFT approach. The number of *cis*-1,5-diaza- and *cis*-1,3,5,7-tetraazadecalin derivatives is very large; we have presented representative cases here.[8,9]

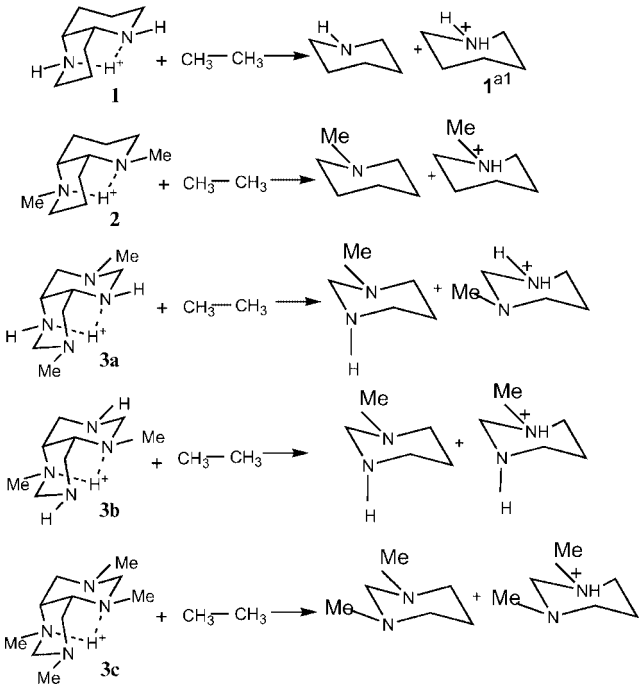


Scheme 2. Isodesmic reactions used to obtain proton sponge strain.

Results and Discussion

Quantum chemistry is a powerful tool for the design of proton sponges.[10] With the employment of DFT methods, we have calculated the PAs of *cis*-1,5-diaza- and *cis*-1,3,5,7-tetraazadecalins (**1**–**3**) at the B3LYP/6-31+G** level of theory. The geometries of **1**–**3** and their corresponding protonated forms were fully optimized at the B3LYP/6-31+G* level and confirmed by frequency calculations. We have calculated the geometries with the *N*-substituents in the equatorial positions. The PAs were calculated at the B3LYP/6-31+G** level as recommended in recent studies.[6a,10e] We have also estimated the relative contributions of hydrogen bonding and strain effect towards the basicity of **1**–**3**. Strain energies (SE) of **1**–**3** have been calculated by isodesmic reactions (Schemes 2 and 3). The monoamines that were considered for the construction of the isodesmic reactions are lowest-energy conformations. These isodesmic reactions provide a qualitative picture of the intramolecular interactions, and therefore, should not be used in a quantitative sense. Proper care should be taken in the selection of the reference monoamines and in the construction of the isodesmic reaction schemes so that they are assembled in a consistent way. Proton transfer (PT) energies have also been estimated from the calculations of cations **1**–**3**. Nonbonded distances *r*(N···N) in both the free base and the cations are reported in Table 1 along with hydrogen-bonded geometries (cation only). PAs and other relevant electronic properties are reported in Table 2.

The calculated results indicate that the *r*(N···N) nonbonded distance is similar (3.0 Å) in all of the three bases. In the hydrogen bonded forms, this distance varies from 2.76 to 2.8 Å (Table 1). The computed results suggest that



Scheme 3. Isodesmic reactions used to obtain the sum of the cation strain and the H-bond energies (SE + HB).

1, **2** and **3** have asymmetrical hydrogen bonds in the protonated forms with one N···H distance shorter than the other N···H distance (Table 1 and Figure 2). Compared with that found in 1,8-bis(dimethylamino)naphthalene (**4**), the $[N\cdots H\cdots N]^+$ angle is smaller in the protonated forms of **1**, **2** and **3a**–**c** (Table 1).

Table 1. B3LYP/6-31+G* calculated structural parameters for **1**–**4**.

	Free base	Monoprotonated cation		
	r(N···N) [Å]	r(N···N) [Å]	r(N···H) [Å]	N···H···N [°]
1	3.036	2.768	1.035(2.235)	110.1
2	3.058	2.813	1.036(2.233)	113.6
3a[a]	3.086	2.768	1.038(2.255)	108.7
3b[a]	3.013	2.811	1.037(2.242)	112.8
3c[a]	3.013	2.779	1.038(2.197)	113.5
4[b]	2.791	2.684	1.772	155.1

[a] N1 to other N distance in the free base. **3a**: $r(N^1\cdots N^3)$ = 2.387 Å, $r(N^1\cdots N^4)$ = 3.086 Å; **3b**: $r(N^1\cdots N^3)$ = 2.419 Å, $r(N^1\cdots N^4)$ = 3.075 Å; **3c**: $r(N^1\cdots N^3)$ = 2.409 Å, $r(N^1\cdots N^4)$ = 2.922 Å (Figure 1). [b] Values are taken from ref.[10e]

Table 2. B3LYP/6-31+G**//B3LYP/6-31+G* proton affinities (PA)[a] of **1**–**3**. The strain energies (SE) for the bases, hydrogen bond + strain energies $(HB+SE)^+$, hydrogen bond energies (HB) and intramolecular proton transfer barriers (PT) for the monoprotonated cations at the B3LYP/6-31+G* level.

	PA [kJ/mol]	SE [kJ/mol]	PT [kJ/mol]	$(HB+SE)^+$ [kJ/mol]	HB [kJ/mol]
1	1034.9 (1032.9)	–5.2	33.9	–48.7	–37.3
2	1049.8 (1048.2)	19.3	12.9	–22.7	–40.0
3a	1057.6 (1055.1)	33.9	13.8	–38.0	–14.5
3a^1	1076.8 (1074.8)	33.8	14.4	–40.8	–13.8
3b	1075.3 (1073.4)	46.9	5.2	–18.5	–16.7
3c	1072.1 (1070.3)	29.1	15.4	–29.4	–18.0
4[b]	1030.7 (1030 ± 2)[c]	26.9	0.0	–66.8	–78.2

[a] The BSSE corrected values for PA in parentheses. [b] Values taken from ref.[10e] [c] Experimental gas phase PA measured by Lau et al.[11]

The PAs predicted at the B3LYP/6-31+G** level for **3a**–**c** show moderately higher values than that of **4**. In the case of **3a**, two PAs were calculated (**3aH$^+$** and **3a^{1}H$^+$**).

In compound **3a**, the proton forms intramolecular hydrogen bonds with the N^1 and N^2 nitrogen atoms (Figure 2). However, in the case of **3a^1**, the proton prefers to form H-bonds with the N^1 and N^4 nitrogen atoms, and interestingly, in this case, one of the N–H bonds flips from the equatorial position to the axial position (Figure 1 and Figure 2). The calculated PA of **3a^1** has been found to be higher than that of **3a** (Table 2).

This result can be attributed to the anomeric effect, which arises in the case of **3a^1** when the N–H bond flips from the equatorial to the axial position during protonation. The anomeric effect imparts an increased nucleophilicity to nitrogen atom N^4, which in turn causes an enhancement in the PA of **3a^1**. The PA calculated for *N*,*N*-dimethyl-substituted tetraazadecalin **3b** has been found to be higher than that of **3a**, and this suggests that methyl substitution at different ring-positions has an effect on the PA of *cis*-1,3,5,7-tetraazadecalins. The additional *N*-methyl substitutions in *cis*-1,3,5,7-tetraazadecalin **3c** do not seem to significantly affect the PA (Table 2).

To examine the influence of methyl substitutions at different positions in the *cis*-1,3,5,7-tetraazadecalin ring, the PA of unsubstituted *cis*-1,3,5,7-tetraazadecalin was calculated. At the B3LYP/6-31+G* level, the PA obtained for unsubstituted *cis*-1,3,5,7-tetraazadecalin is 1056.4 kJ/mol, which is higher than the PA of **3a** (1052.0 kJ/mol) and lower than that of **3b** (1069.6 kJ/mol). These results suggest that substitution at N^3 and N^4 lowers the PA of *cis*-1,3,5,7-tetraazadecalins; however, the substitution enhances the basicity at the N^1 and N^2 nitrogen atoms. Interestingly, the delicate balance of these substitutions can be seen in the PA of **3c**, which lies in between the PAs of **3a** and **3b**. Structural analyses indicate that nitrogen atoms N^3 and N^4 (Figure 1) can work in a cooperative manner with $[N^1\cdots H\cdots N^2]^+$ in these cases; however, the difference between N^3 and N^4 varies and is dependent on the position of the substituents on the ring. The $r(N^3\cdots N^4)$ calculated distance for protonated unsubstituted *cis*-1,3,5,7-tetraazadecalin is 4.47 Å, which is the smallest in the series. For **3a**, **3b** and **3c**, the corresponding $r(N^3\cdots N^4)$ calculated distances are 4.56, 4.52 and 4.62 Å, respectively. These results show that of the PAs obtained, there appears to be an interplay between the position of the methyl substituents and the distance of the $N^3$and N^4 nitrogen atoms from the proton in the *cis*-1,3,5,7-tetraazadecalin rings. Further, a change in the substituent from a methyl to an ethyl group in **3** increases the PA. The PA calculated at the B3LYP/6-31+G* level for ethyl-substituted *cis*-1,3,5,7-tetraazadecalin **3a** was marginally higher (1059 kJ/mol) than that of unsubstituted *cis*-1,3,5,7-tetraazadecalin (1056.4 kJ/mol); however, a large enhancement in the PA was predicted for ethyl-substituted derivative **3b** (1080 kJ/mol). More powerful electron donors can make *cis*-1,3,5,7-tetraazadecalins even stronger proton sponges. DFT results predicted the PA of **2** to be higher than that of 1,8-bis(dimethylamino)naphthalene (**4**) (Table 2).

The predicted, relatively higher PA of **3** over that of **1** and **2** appears to be due to additional stabilization. This stabilization is thought to come from the other two nitrogen atoms (N^3 and N^4) that are present in the molecule at an interactive distance of ≈ 2.50 Å from the proton in the chiral cavity of **3**. The importance of the anomeric effect cannot be excluded as such stereoelectronics enhance the basicity of the nitrogen atoms that interact with the protons present in **3a^1**. Therefore, the enhanced basicity of **3a**–**c** is due to the cooperative effects of the intramolecular H-bonding of adjacent nitrogen atoms that bear lone pairs of electrons and the anomeric effect.

Calculations based on the isodesmic reactions (Scheme 2) show that free bases **2** and **3** are strained (Table 2). The sum of the hydrogen bond energies and the cation strain $(HB+SE)^+$ energies that were calculated for the protonated forms of **1**–**3** (Scheme 3) are shown in Table 2. To obtain the hydrogen bond (HB) energy in the protonated forms, some independent information is required.[10e] For hydrogen bond energy **1H$^+$**, **2H$^+$** and **3H$^+$**, an independent model study was performed (Figure S1, Supporting Information). This model system represents the "atomic" framework of optimized cations **1H$^+$**, **2H$^+$** and **3H$^+$**. The H-bond stabilization energy can be obtained by single-point calculations (vibrationless) performed at the B3LYP/6-31+G* level on the model system and their re-

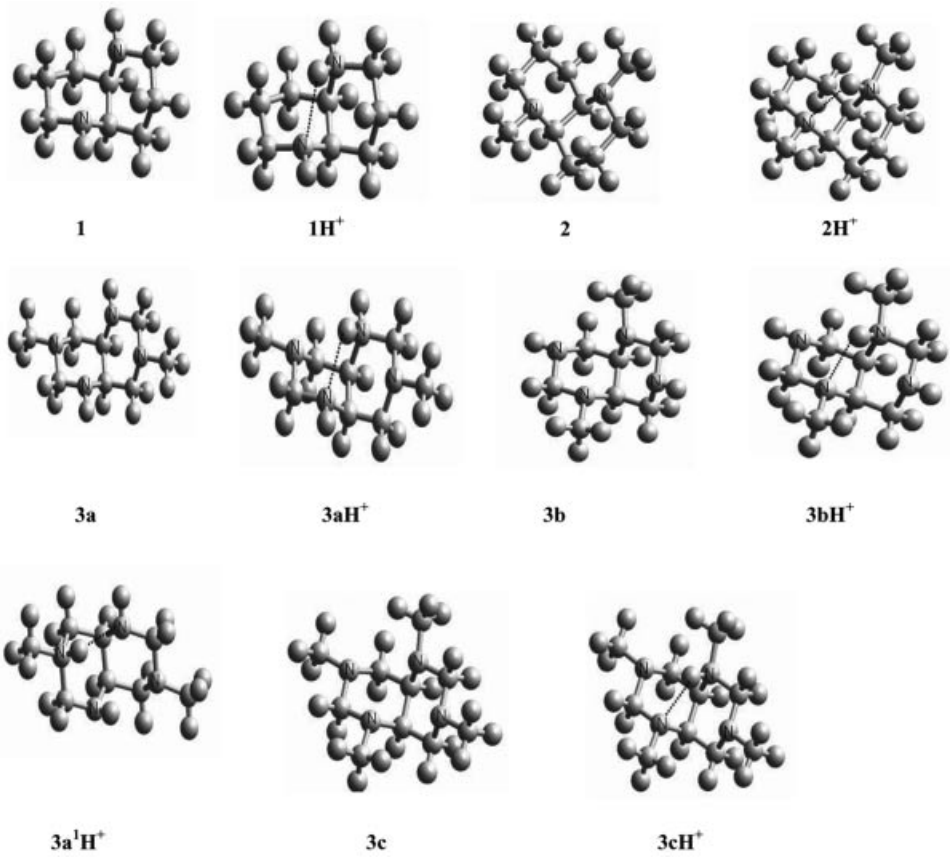


Figure 2. B3LYP/6-31+G* optimized geometries for **1**–**3** and their corresponding protonated forms **1H$^+$**–**3H$^+$**.

spective components at infinite separation. The estimated HB energy for the protonated forms of **1H$^+$**, **2H$^+$** and **3H$^+$** are given in Table 2. The model systems chosen to represent the hydrogen bond stabilization are small. The suggestion that such models are not entirely satisfactory for the estimation of the HB energy is made clear in the comparison of the derived values of HB with the $(HB+SE)^+$ values calculated from the isodesmic reactions. The HB energies are generally less negative than the corresponding $(HB+SE)^+$ values, which implies negative cation strain.[10e] It may be significant that these protonated forms are nonplanar cations (Table 1).

Although it is known that the *cis*-decalin ring provides the chiral environment for the system, it is important to determine whether it has any other influence on the PA of diamines. The PAs of the simplest derivatives of **1** and **2**, 1,2-diaminoethane, *N*,*N*′-dimethylethanediamine and *N*,*N*,*N*′,*N*′-tetramethylethanediamine, have been calculated at the B3LYP/6-31+G* level of theory. The PA calculated for 1,2-diaminoethane is 985.4 kJ/mol and is in good agreement with the reported experimental PA of 982.8 kJ/mol.[12] PAs predicted at the B3LYP/6-31+G* level for *N*,*N*′-dimethylethanediamine and *N*,*N*,*N*′,*N*′-tetramethylethanediamine are 1024.0 and 1029.0 kJ/mol, respectively. The PA calculated for **2** at the B3LYP/6-31+G* level is 1040.8 kJ/mol higher than that of simple derivative *N*,*N*,*N*′,*N*′-tetramethylethanediamine. These results suggest that the decalin moiety not only provides the chiral environment, but it also enhances the basicity of 1,2-diamines. A similar enhancement in the PA of 1,4-diaminobutane was also observed when 1,4-diamine was incorporated in the alicyclic ring systems (such as 1,6-diazacyclodecane and 1,6-diazabicyclo[4.4.4]tetradecane).[10c] The intramolecular proton transfer (PT) typical of diamine proton sponges **1H$^+$**, **2H$^+$** and **3aH$^+$**–**3cH$^+$** have been calculated (Table 2). Generally, low-energy intramolecular proton transfer barriers have been predicted (Table 2), which is particularly relevant to the models for low-barrier hydrogen bonds whose role in enzyme catalysis has been debated. In the case of **1H$^+$**, a larger barrier has been predicted compared to those of the other protonated forms and is due to the flip of one of the decalin rings from the chair to the more strained boat form in the transition state geometry (Table 2).

Conclusions

We have reported the proton affinities for chiral-*cis*-diaza- and *cis*-tetraazadecalins at the DFT B3LYP/6-31+G** level of theory. C_2-substitued-*cis*-1,3,5,7-tetraazadecalins **3** have shown moderate enhancement in their proton affinity over that of 1,8-bis(dimethylamino)naphthalene (**4**). The unsubstituted *cis*-1,3,5,7-tetraazadecalin has been predicted to be a better proton sponge than **4**. The cooperative effect

of ring nitrogen atoms and the anomeric effect that occurs upon protonation is responsible for the relatively higher basicities of *N*-substituted-*cis*-1,3,5,7-tetraazadecalins compared with that of **4**. *cis*-1,5-Diazadecalins **1** and **2** also show comparable and/or higher proton affinities compared with that of **4**. The addition of substituents to all four nitrogen atoms that are present in **3** does not significantly enhance its basicity. The intramolecular proton transfer barrier has been predicted to be generally lower for the protonated systems studied here. These calculated results show that *cis*-1,5-diazadecalins and *N*-substituted-*cis*-1,3,5,7-tetraazadecalins can be used as chiral proton sponges that can have a range of useful applications in asymmetric synthesis.

Computational Methodology

Geometries of compounds **1**–**3** in the neutral and protonated forms were calculated at the B3LYP/6-31+G* level of theory with the Jaguar program package.[13] Geometries were fully optimized without any symmetry constraints. Harmonic force constants were computed at the optimized geometries to characterize the stationary points as minima. Transition states have been located and characterized by their single imaginary frequencies. Basis set superposition error (BSSE) was corrected by the counterpoise method.[14] Further single point calculations were performed at the B3LYP/6-31+G** level with B3LYP/6-31+G*-optimized geometries. The strain energy (SE) of the unprotonated proton sponge is given by:

$$SE(1) = E(1) + E(CH_3–CH_3) – 2E(1^a) \quad (1)$$

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

$$[HB(1H^+) + SE(1H^+)] = E(1H^+) + E(CH_3–CH_3) – E(1^a) – E(1^{a1}) \quad (2)$$

The conventions chosen ensure that the strain energy will be a positive quantity (destabilizing) and the hydrogen-bond energy negative (stabilizing).

Supporting Information (see footnote on the first page of this article): computational data for C_2-chiral substituted-*cis*-1,3,5,7-tetraazadecalins as proton sponges.

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