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Strategic design of small and versatile bicyclic organic superbases: a density functional study†

Ajeet Singh and Bishwajit Ganguly*

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It is shown by a reliable DFT method that bicyclic structures **7–10**, constructed using 1,3-diaminopropane as an essential building block, can act as powerful neutral organic superbases in the gas phase, aqueous solution and in acetonitrile. This new molecular framework is versatile in terms of anchoring different functional groups to achieve higher basicities. The buttressing effect of substituents on the basicity of these organic bases was also observed. The proton affinities calculated at the B3LYP/6-311 + G**//B3LYP/6-31 + G* level for 1,2-diaminoethane and 1,3-diaminopropane were found to be in good agreement with the experimental results. Barriers for proton transfer between the N atoms of the diamine and diimine cations are also reported.

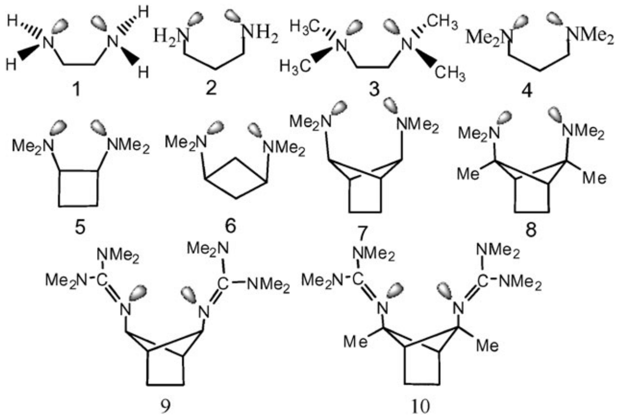
Introduction

Since Alder's pioneering work on the first proton sponge, 1,8-bis(dimethylamino)naphthalene (DMAN), the design and synthesis of neutral organic superbases have received considerable attention.[1–11] This is not surprising as they have distinct advantages over their inorganic counterparts. Organic superbases possess a high solubility in organic solvents, a low sensitivity to moisture and CO_2 and a very good stability at low temperatures, permitting mild reaction conditions.[4,5] The neutral superbases are efficient catalysts, in particular, if immobilized on adequate surfaces they can be useful in green chemistry.[6,7] Since the discovery of a simple organic compound 1,8-bis(dimethylamino)naphthalene (DMAN) as a superbase,[1] many proton sponges have been created and they are finding a growing number of interesting applications.[8–10] 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.[11] Further, quantum chemical studies have shed light on the structural factors influencing the high basicity of proton sponges.[12–14]

In the present work, we report the design of a new molecular framework that differs from other organic superbases, which can be anchored with different functional groups to exhibit high basicity. The discovery of this molecular framework is based on a systematic approach using simple bases like 1,2-diaminoethane and 1,3-diaminopropane (Scheme 1). The experimentally determined proton affinities for simple diamines are less than 1000 kJ mol^{-1} and considered as normal bases.[15] The guiding principles to enhance the basicity of an organic base are the following:[10] (1) the proper structural organization of their molecules which provides sufficient fixation of at least two nitrogen atoms at sufficiently close distance from each other; (2) a destabilizing repulsion effect of unshared electron pairs of nitrogen atoms due to the close proximity in the molecule of a base; (3) the occurrence of a strong hydrogen bond in the cation, which relieves steric and electronic strains characteristic of a base. In this article, we have employed such strategies to turn the simple diamines into organic superbases.

Computational methodology

All calculations were performed with the Jaguar program package[16a] using Becke's three-parameter exchange functional with the correlation functional[17] of Lee, Yang, and Parr (B3LYP).[18] All species were fully optimized with the 6-31 + G* 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.[16] The zero-point vibrational energies computed at the B3LYP/6-31 + G* level used in the proton



Scheme 1

Analytical Division, Central Salt & Marine Chemicals Research Institute, Bhavnagar, 364002 Gujarat, India. E-mail: ganguly@csmcri.org; Fax: +91 278 256 7562; Tel: +91 278 256 7760

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affinity calculations are unscaled. Proton affinities calculated at the B3LYP/6-311 + G**//B3LYP/6-31 + G* level employing the general equation: PA(B) = (ΔEel) + (ΔZPVE), where (ΔEel) = [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/6-31 + G* optimized geometries were used to calculate the solvation energies at the B3LYP/6-311 + G** level employing the Poisson–Boltzmann continuum (PB) solvent model[19,20] as implemented in the Jaguar program.[16] 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 probe solvent molecule (for aqueous solution, the 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 constants (ε = 78.4 for aqueous solution).

Results and discussion

The B3LYP/6-311 + G**//B3LYP/6-31 + G* calculated results show that the proton affinities for 1,2-diaminoethane **1** and 1,3-diamino propane **2** are in excellent agreement with the experimentally observed results (Scheme 1 and Table 1).[15] It is known that the electron-donating groups enhance the basicity of nitrogen atoms, and hence the proton affinities for the methylated 1,2- and 1,3-diamines **3** and **4** were also determined. The calculated results show that the proton affinity for **4** was enhanced upon methylation, however, the PA was found to be lower for **3** than **1** (Table 1). The experimental results are not available for **3** and **4**, and hence the values are predictive in nature. As mentioned earlier, the basicity can be enhanced with proper structural organization which provides sufficient fixation of at least two nitrogen atoms at sufficiently close distance from each other. The large flexibility of acyclic 1,2- and 1,3-diaminoethane[21] can be constrained by employing cyclic rings in the system. Cyclobutane, could be possibly the smallest ring, in which diamino groups can be placed at the 1,2 and 1,3-positions. The proton affinities were calculated for 1,2-diaminocyclobutane **5** and 1,3-diaminocyclobutane **6**. The computed proton affinity was found to be higher for **5** compared to the corresponding acyclic diamine **3** (Table 1). It is noteworthy that the amino nitrogens (N···N) were at a larger distance in the unprotonated **5** than **3**, however, the enhancement in the proton affinity for **5** is presumably due to the strong hydrogen bonding. The computed [N–H···N]$^+$ angle is relatively more linear in the case of **5** than in that of **3** (Table 2). The enhancement of hydrogen bond energy was obtained with the linearity of hydrogen bond angle in agreement with the some of the known proton sponges.[14] The diamino group is further away (4.616 Å) in 1,3-diaminocyclohexane **6** and hence [N–H···N]$^+$ hydrogen bonding is not possible. The gas phase proton affinity calculated for **6** is relatively lower compared to the acyclic 1,3-diamines **2** and **4**, respectively.

At this point, it is required to modify the system in such a way that all the strategies can be employed to enhance the basicity. Such modifications were difficult to conceive for the amino groups placed at the 1,2-positions. However, this can be achieved for 1,3-diamino system. The incorporation of an ethano-bridge to **6** yields a much smaller amino nitrogen (N···N) distance in **7**. The calculated (N···N) distance for bicyclo[2.1.1]hexane **7** is much smaller compared to **4** and **6** (Table 2). Further, such rigidity in the system causes the existence of a destabilizing repulsion effect of the unshared electron pairs of nitrogen atoms at a distance of 3.0 Å, which subsequently destabilizes the base. As a consequence, transition to cation provides additional profit in energy. The PA predicted at B3LYP/6-311 + G**//B3LYP/6-31 + G* for **7** was found to be higher compared to other diamines calculated here (Table 1). Having achieved the higher basicity by employing the strategies in the 1,3-diamine case, one can further expect an enhancement in the basicity. It is to note that the buttressing

Table 1 B3LYP/6-311 + G**//B3LYP/6-31 + G* calculated proton affinities in the gas phase, water and acetonitrile (kJ mol^{-1}). The proton affinity values are corrected by zero-point vibrational energies (ZPVEs)

	Proton affinity (PA)		
Compound	Gas phase[a]	Aqueous	Acetonitrile
1	947.0 [950.0]	1182.7	1184.2
2	975.7 [975.0]	1182.1	1183.3
3	938.1	1207.2	1197.1
4	1016.1	1167.7	1203.2
5	991.4	1165.3	1173.3
6	966.6	1181.8	1183.1
7	1044.4	1157.4	1232.8
8	1068.7	1256.6	1251.2
9	1131.6	1266.2	1276.6
10	1145.7	1289.4	1294.9

[a] The experimental PA is given in [ ].[15]

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

	Bond length/Å			
Compound	r(N···N)	r(N···H)$^+$	r(N···H)	Bond angle (°) (N—H···N)
1	2.871	—	—	—
1H$^+$	2.632	1.632	1.917	121.7
2	3.524	—	—	—
2H$^+$	2.678	1.077	1.730	141.5
3	2.998	—	—	—
3H$^+$	2.702	1.052	1.693	124.6
4	3.577	—	—	—
4H$^+$	2.755	1.077	1.753	152.8
5	3.266	—	—	—
5H$^+$	2.569	1.218	1.519	139.4
6	4.616	—	—	—
6H$^+$	4.652	1.027	4.476	
7	3.020	—	—	—
7H$^+$	2.702	1.069	1.762	144.2
8	2.743	—	—	—
8H$^+$	2.575	1.101	1.548	152.4
9	2.950	—	—	—
9H$^+$	2.704	1.033	1.921	130.1
10	2.706	—	—	—
10H$^+$	2.567	1.040	1.762	131.0

effect of substituents can enhance the proton affinity even further.[22] The methoxy-substituted 1,8-bis(dimethylamino)-naphthalene (DMAN) was found to be a stronger organic superbase than DMAN.[22d] Recently, we have shown that the buttressing effect can be induced through remote substitution.[11] Therefore, it would be interesting to examine the buttressing effect of substituents on bicyclo[2.1.1]hexane **7**. The methyl substituted bicyclo[2.1.1]hexane **8** was examined at the same level of theory. The buttressing effect seems to be operative as the calculated (N···N) distance is much smaller in **8** compared to the corresponding unsubstituted bicyclo[2.1.1]-hexane **7** (Table 2). The computed proton affinity for **8** was found to be much higher than for **7** (Table 1). The computed $[N–H\cdots N]^+$ bond angle is relatively more linear in the case of **8** and hence the hydrogen bonding would be stronger compared to **7** (Table 2). The calculated proton affinities for the bicyclo[2.1.1]hexane derivatives were found to be relatively higher than that of prototype DMAN (1030.0 kJ mol^{-1}).[1,11] It appears that the proton affinity calculated for 1,3-diaminopropane-derived bases (~1070 kJ mol^{-1}) may well be near the limit for such cases.[1c]

The bicyclo[2.1.1]hexane can be versatile in terms of anchoring different functional groups. It has been found that imines show higher proton affinities compared to amines. Therefore, it would be interesting to examine the proton affinity of imine functional groups with the bicyclo[2.1.1]hexane framework. The calculations have been performed with guanidine units anchored to the bicyclo[2.1.1]hexane frameworks **9** and **10**.

The proton affinities calculated for **9** and **10** were found to be much higher than those of the corresponding diamines **7** and **8** (Table 1). The buttressing effect was also seen in this case as the methyl substituents reduced the (N···N) distance in **10** compared to the corresponding unsubstituted derivative **9**.

The discussion so far concentrated on the thermodynamics of protonation of bicyclo[2.1.1]hexane derivatives **7–10**. If these compounds can be prepared, they could prove to be practical bases so long as they are kinetically active. Based on the examination of some calculations and models, it seems likely that this will be the case. Fig. 1 shows space-filling models of **7**, **9** and their complexes with an external acid, HCl. DMAN has been taken as a reference because it worked as a strong base in many experimental studies.[10,23] The complexes minimized with B3LYP/6-31+G* in the gas phase, **7**, **9** and DMAN, are contact ion pairs with N–H distances of 1.069, 1.032, 1.080 Å and H···Cl distances of 2.20, 2.745 and 2.78 Å, respectively. The compound **7** forms a slightly tighter complex compared to **9** and DMAN. It seems unlikely that proton transfer from external acids into these diamines will be prohibitive in these cases.

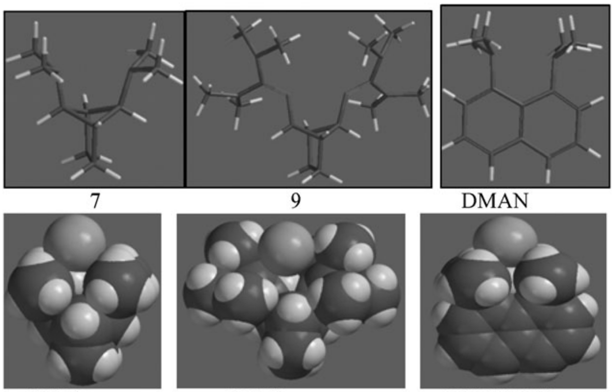
7 9 DMAN
7:HCl 9:HCl DMAN:HCl

Fig. 1 Structures of **7**, **9** and DMAN and their HCl complexes at the B3LYP/6-31+G* level. [White = hydrogen; grey = carbon; light-grey = chlorine].

Further, the intramolecular proton transfer (PT) barriers have been calculated for $\mathbf{7H^+}$ and $\mathbf{9H^+}$. The calculated barriers were found to be −2.50 and −0.1 kJ mol^{-1} for these monoprotonated systems, which is particularly relevant to the models for low-barrier hydrogen bonds whose role in enzyme catalysis has been discussed. As shown in Table 1, the proton affinities predicted for **7–10** is in general higher in acetonitrile and in aqueous phase compared to the normal bases. The studies performed by Peräkylä and by Kovaćević and Maksić[12] towards the correlation of the calculated proton affinities in solvents with observed p*K*a values suggest that **7–10** would have higher p*K*a values.

Conclusion

We have reported the proton affinities for 1,2-, 1,3-diaminoethanes and bicyclo[2.1.1]hexane derivatives at the DFT B3LYP/6-311+G** level of theory. The predicted proton affinities for bicyclo[2.1.1]hexane derivatives were found to be higher than the corresponding prototype 1,8-bis(dimethyl-amino)naphthalene (DMAN). The new bicyclo[2.1.1]hexane molecular framework is also versatile in terms of anchoring different functional groups to achieve high basicities in both the gas and solvent phases. The intramolecular proton transfer barrier has been predicted to be generally very low for the protonated systems studied here. These calculated results show that bicyclo[2.1.1]hexane derivatives can be used as organic superbases that can have a range of useful applications in many synthetic and catalytic processes.

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