DFT studies on a new class of cage functionalized organic superbases†‡

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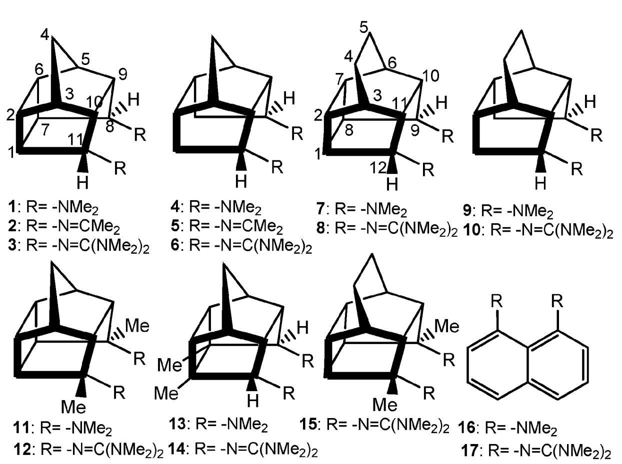
According to DFT calculations, pentacyclo[6.4.0.0^{2,7}.0^{3,11}.0^{6,10}]dodecane (PCD) derivatives have been predicted as organic super bases. The new molecular framework (PCD) is versatile in terms of anchoring different functional groups to achieve high basicities in both gas and solvent phase. Density functional quantum chemical calculations at the B3LYP/6-311+G**//B3LYP/6-31G* level have been performed to calculate the proton affinities of pentacyclo[6.4.0.0^{2,7}.0^{3,11}.0^{6,10}]dodecane (PCD) derivatives and substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (PCU) derivatives. The calculated results suggest that these polycyclic cage units can act as organic superbases when anchored with different functional groups. The flexibility in these polycyclic rings allowed the attainment of better hydrogen bonding compared to the prototype 1,8-bis(dimethyl-amino)naphthalene and 1,8-bis(diguanidino)naphthalene. The predicted higher basicities appeared to be due to the interplay of steric repulsions and the strength of hydrogen bonding in these cases. Intramolecular and intermolecular proton transfer barriers have been calculated for these amines and imines.

Introduction

The design and synthesis of strong organic bases has long been an active field of research.[1–8] Aromatic and cyclic diamines, which have exceptionally enhanced basicity, are called "proton sponges".[2,4,8] Such compounds possess high thermodynamic basicity, however, associated with its low kinetic inactivity for deprotonation. These compounds have two basic amine sites closely positioned and can accept a proton between the nitrogen atoms. Since the discovery of the remarkable basicity of 1,8-bis(dimethylamino)naphthalene, design and synthesis of novel organic bases continues to generate considerable interest.[9–11] Such organic superbases 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 is feasible to apply these tools in the design of novel proton sponges or to understand the factors responsible for enhanced basicity.[12] Further, quantum chemical studies have shed light on the structural factors influencing the high basicity of proton sponges.[13–15]

Recently, we have reported a new molecular framework that differs significantly from the traditional topology of organic superbases.[12c] The pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (PCU) framework anchored with amines and imines has been predicted with higher basicities. In this effort, we have extended our study to pentacyclo[6.4.0.0^{2,7}.0^{3,11}.0^{6,10}]dodecane (PCD) organic superbases **1–6** (Scheme 1).[12c] It has been shown that the PCU framework is versatile in terms of anchoring different functional derivatives **7–10** as organic superbases. Further, we have examined the influence of substitutent effects on the basicities of PCU derivatives **11–14** and PCD **15** (Scheme 1). The calculated basicities with PCD-derivatives were found to be much higher than that of prototype 1,8-bis(dimethylamino)naphthalene (DMAN) **16** and 1,8-bis(tetramethylguanidino)naphthalene (TMGN) **17** (Scheme 1). The higher basicities computed for these derivatives have been rationalized by sets of isodesmic reactions. 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 appeared to be important to control of the basicity in these cases. The intramolecular proton transfer barriers were found to be lower for the systems calculated here. This is in the line of model



Scheme 1 PCU-derivatives, PCD-derivatives, DMAN and TMGN.

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‡ Dedicated to Professor Zvonimir Maksić on the occasion of his 70th birthday.

study system $[H_3NH\cdots NH_3]^+$ of Ikuta.[16] The proton affinity (PA) calculated for these pentacyclo-derivatives with different solvent are also given in this study.

Computational methodology

All calculations were performed with the Jaguar program package[17a] using Becke's three-parameter exchange functional with correlation functional[18] of Lee, Yang, and Parr (B3LYP).[19] All species were fully optimized with 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.[17b–d] Zero-point vibrational energies computed at B3LYP/6-31G* level used in the proton affinity calculations are unscaled. Proton affinities calculated at B3LYP/6-311 + G**//B3LYP/6-31G* 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/6-31G* optimized geometries were used to calculate the solvation energies at B3LYP/6-311 + G** level employing the Poisson–Boltzmann continuum (PB) solvent model[20,21] as implemented in the Jaguar program.[17] 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 van der Waals envelope of the solute and a probe 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 region outside of the molecular surface are assigned the experimental solvent dielectric (ε = 78.4 for aqueous solution). The isodesmic reactions were setup to calculate the strain energy (SE) of the unprotonated organic superbases and hydrogen bond energy plus strain energy $(HB + SE)^+$ for the corresponding protonated bases. The estimation of cationic hydrogen bond energies of such protonated bases was calculated using the approach suggested by Howard.[15f] The details of these calculations are mentioned in the results and discussion part. The conventions chosen ensure that the strain energy will be a positive quantity (destabilizing) and the hydrogen-bond energy negative (stabilizing).

Results and discussion

Quantum chemistry is a powerful tool for the design of organic superbases.[13–15] With the employment of DFT methods, we have calculated the PA of (**7–15**) at the B3LYP/6-311 + G**//B3LYP/6-31G* level of theory (Scheme 1). In previous studies, we have found that use of B3LYP/6-311 + G** was adequate for this purpose.[12,17b–d] The PAs of **1–6** and **16–17** were taken for reference and relative comparisons with the newly calculated systems (Scheme 1).[12c] The relative contributions of electronic properties that control the PAs for these systems were also calculated. The strain energy (SE) of unprotonated bases and hydrogen bonding plus strain effects $(HB + SE)^+$ towards the basicity of **1–17** have been calculated by isodesmic reactions and are shown in (Fig. 1 and 2). 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. To obtain hydrogen bond energy (HB) for $\mathbf{1H^+}$–$\mathbf{17H^+}$, an independent model study was performed (Fig. 3). In this scheme, the cation hydrogen-bond energy was approximated as the (vibrationless) binding energy of a model system. For compounds **1–17**, this will be the proton-bound dimethylamine and imine dimers (Fig. 3) "frozen" in their geometries of **1–17**. The chosen reference system (to determine a binding energy) is the same two compounds removed to infinite separation, without permitting geometry relaxation.

Non-bonded distances $r(N\cdots N)$ in both the free bases and the cations are reported in Table 1. PAs and other relevant

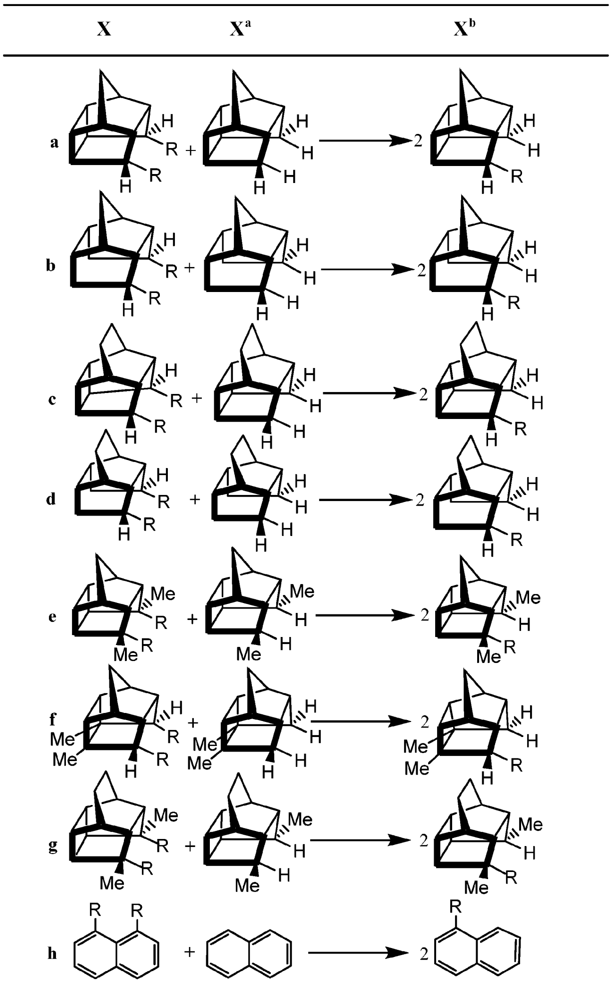

Fig. 1 Isodesmic setups used to obtain strain energies for unprotonated compounds **1–17**, employing the equation $\{\mathbf{SE(X)} = \mathbf{E(X) + E(X^a) - 2E(X^b)}\}$, where **X** = **1–17**. [Isodesmic setup (**a**) applies for compounds **1**, **2** and **3**, (**b**) applies to **4**, **5** and **6**, (**c**) applies to **7**, **8**, (**d**) applies to **9**, **10**, (**e**) applies to **11**, **12**, (**f**) applies to **13**, **14**, (**g**) applies to **15**, **(h)** applies to **16**, **17**].

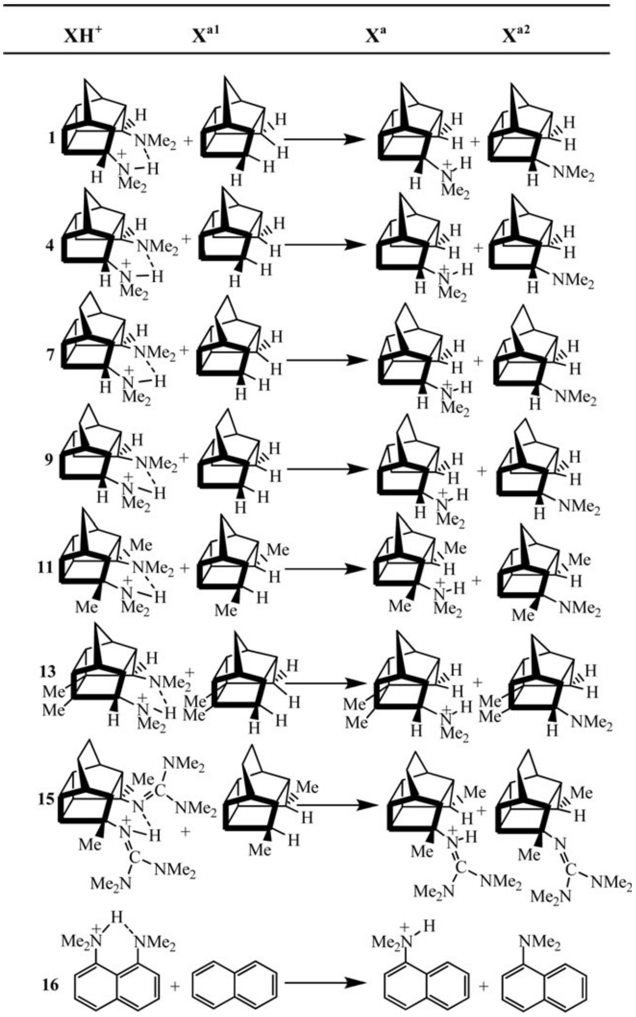

Fig. 2 Isodesmic setups used to obtain the sum of the cation strain and hydrogen-bond energies (SE + HB), for **1–17**, employing the equation: {**[HB(XH$^+$) + SE(XH$^+$)] = E(XH$^+$) + E(X^{a1}) − E(X^a) − E(X^{a2})**} **where X = 1–17**. [Isodesmic setup **1** applies for compounds **2** and **3**, **4** applies to **5** and **6**, **7** applies to **8**, **9** applies to **10**, **11** applies to **12**, **13** applies to **14**, **16** applies to **17**].

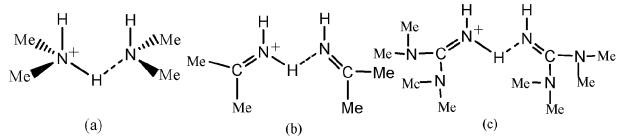

Fig. 3 The model systems used to estimate cationic hydrogen bond energies for (a) **1H$^+$**, **4H$^+$**, **7H$^+$**, **9H$^+$**, **11H$^+$**, **13H$^+$** and **16H$^+$** (b) **2H$^+$**, **5H$^+$** (c) **3H$^+$**, **6H$^+$**, **8H$^+$**, **10H$^+$**, **12H$^+$**, **14H$^+$**, **15H$^+$**, and **17H$^+$**.

Table 1 Calculated geometric parameters of free bases and their conjugate acids at B3LYP/6-31G* level.

Compound	Bond length/Å			Bond angle (°)
	r(N···N)	r(N···H)$^+$	r(N···H)	(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	167.2
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	2.853			
7H$^+$	2.638	1.111	1.555	163.2
8	3.045			
8H$^+$	2.631	1.062	1.647	151.9
9	2.996			
9H$^+$	2.686	1.105	1.597	167.2
10	2.919			
10H$^+$	2.692	1.062	1.672	159.3
11	2.791			
11H$^+$	2.612	1.125	1.497	170.0
12	2.841			
12H$^+$	2.604	1.070	1.586	156.6
13	2.968			
13H$^+$	2.662	1.105	1.584	163.5
14	3.002			
14H$^+$	2.604	1.056	1.699	152.6
15	2.803			
15H$^+$	2.568	1.075	1.540	157.9
16	2.836			
16H$^+$	2.640	1.110	1.590	157.5
17	2.757			
17H$^+$	2.623	1.046	1.744	138.8

Table 2 B3LYP/6-311+G**//B3LYP/6-31G* calculated proton affinities in gas phase, water and acetonitrile

Compound	Proton Affinity (PA)^a in kJ/mol		
	Gas phase	Aqueous	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	1089.1	1261.8	1229.7
8	1190.5	1327.3	1328.4
9	1082.7	1262.6	1297.3
10	1175.2	1314.9	1317.7
11	1111.2	1284.6	1279.0
12	1130.2	1270.0	1268.3
13	1073.5	1259.0	1247.9
14	1184.7	1321.9	1327.2
15	1179.2	1317.9	1311.9
16	1025.0^b	1205.3	1197.6
17	1146.9	1249.2	1252.5

^{a} B3LYP/6-31G* ZPVE values used to correct proton affinities. ^{b} NIST WebBook value: 1028.1 kJ/mol.[7]

electronic properties are reported in Tables 2 and 3. The calculated results indicate that the r(N···N) non-bonded distance of **7–15** is similar (~3.0 Å) to that of calculated for other free bases (**1–6**, **16** and **17**). The protonated forms are unsymmetrical in nature for **7–15** with one N···H distance shorter that the other N···H distance (Table 1). Such unsymmetrical distances were also observed for **1–6** and **16–17** as well (Table 1). In comparison to DMAN (**16**) and TMGN (**17**), the [N···H···N]$^+$ angles are larger in the protonated forms of **7–15** (Table 1).

The PAs predicted at the B3LYP/6-311 + G** level for **7–15** show higher values than the corresponding prototype naphthalene derivatives **16** and **17** (Table 2). Importantly, the proton affinities calculated for PCD derivatives **7–10** showed an interesting trend compared to PCU derivatives **1–6**. The amines ($-NMe_2$) anchored with the PCU units show higher PA values than the PCD units, however, the guanidinio units show the opposite trends (Table 2). Moving to the methyl substituted PCU- and PCD-derivatives **11–14** and **15**, the calculated PAs are either comparable or slightly lower than their corresponding unsubstituted bases **1**, **3** and **8**, respectively (Table 2). The effect of electron-donating substituents is not significant to affect the PAs in these cases.

To understand how the electronic properties control the proton affinities of these superbases, the isodesmic calculations[13c] performed for **1–17** are given in Table 3. Fig. 1 shows the strain involved in the unprotonated bases **1–17** and their sum of hydrogen bond energies and the cation strain $(HB + SE)^+$ energies estimated are shown in Fig. 2. The cationic hydrogen bond energies estimated for the protonated forms of $\mathbf{1H^+}$–$\mathbf{17H^+}$ are also given in Table 3.

The calculated strain energy range is larger (19–72 kJ/mol), which indicates that energetic effects in the cation (*i.e.*, incomplete release of strain *versus* variations in hydrogen bond energy) acts in a partly compensating manner. The range of hydrogen-bond energy variation, according to the model systems chosen to represent this stabilization is relatively higher (94–116 kJ/mol) for $\mathbf{1H^+}$–$\mathbf{17H^+}$ (Fig. 3).[15f] The enhancement of HB bond energy was obtained with the linearity of HB bond angle in agreement with the some of the known proton sponges.[15] Interestingly, the removal of C1–C7 σ-bond in PCU derivatives and C1–C8 σ-bond in PCD derivatives (Scheme 1) allows the $[N\cdots H\cdots N]^+$ angles to attain more linearity compared to their ring counterpart, which is reflected in the HB energies (Tables 1 and 3). However, the HB energies do not directly influence the PAs for **1–15**. Comparing the results obtained from isodesmic reactions suggest that the cation strain is also important to control the basicity for these compounds. The PA calculated for **3** is higher than that of **6**, however, the HB energy is estimated to be higher for **6**. Combining the estimate of HB with the values of (HB + SE) $\mathbf{3H^+}$, it appears that the cation strain is 14.8 kJ/mol lower than the unprotonated base **3**, whereas, the cation strain is 8.3 kJ/mol lower than that of the unprotonated base **6**. The PCD derivatives **8** and **10** also showed that the cation strain is larger in the case of **10** resulting in the lower proton affinity compared to its ring counterpart **8** (Table 2). These results suggest that the basicities appear to be the outcome of interplay between the overlap of nitrogen lone-pairs in the free bases, the relative cation strain in the protonated forms and the formation of a strong intramolecular hydrogen bridge in the monoprotonated compounds. As shown in Table 2, the proton affinities predicted for **7–15** are higher in acetonitrile and in aqueous phase compared to **16** and **17**. Based on the studies performed by Peräkylä and Maksić *et al.* towards the correlativity of the calculated proton affinities in solvents with observed pK_a values, it appears that **7–15** would have higher pK_a values.[13]

Table 3 B3LYP/6-31G* calculated strain energies (SE); hydrogen bond + strain energies $(HB + SE)^+$ and hydrogen bond energies (HB) for the monoprotonated cations in kJ/mol

Compound	SE	$(HB + SE)^+$	HB
1	27.7	−68.4	−112.3
2	26.6	−76.3	−106.7
3	31.9	−81.8	−94.7
4	35.7	−65.5	−114.0
5	30.0	−70.7	−110.1
6	41.6	−67.7	−101.0
7	34.8	−76.4	−114.0
8	63.3	−69.0	−101.2
9	43.3	−63.3	−115.6
10	19.5	−64.8	−104.9
11	50.8	−65.8	−115.9
12	24.3	−36.3	−92.5
13	24.5	−66.7	−113.5
14	65.6	−54.2	−96.0
15	71.7	−31.6	−88.8
16	26.0	−62.0	−88.3
17	38.6	−45.5	−85.8

The results so far discussed are on the thermodynamics of the protonation of PCU- and PCD-derivatives. It is interesting to note that if these compounds can be prepared, they could serve as practical bases. DMAN has been extensively used in many reactions as an organic base.[5,22] It has been found that DMAN works effectively in such reactions. We have calculated the external proton transfer for DMAN **16** and taken **1** as a representative system for the polycyclic compounds **1–15**. Additionally, the intramolecular proton transfer (PT) barriers typical of diamines and diimines $\mathbf{1H^+}$, $\mathbf{4H^+}$, $\mathbf{3H^+}$ and $\mathbf{6H^+}$ have also been calculated. The computed proton transfer free energies (ΔG_{PT}) corrected with ZPVE values for $\mathbf{1H^+}$, $\mathbf{4H^+}$, $\mathbf{3H^+}$ and $\mathbf{6H^+}$ are 7.5 kJ/mol, 11.7 kJ/mol, −22.2 kJ/mol and 23.8 kJ/mol respectively. The energetic values of the proton-transfer barriers cannot be taken in a quantitative sense because the level of calculations do vary the PT values, however, the relative energies are thought to be reliable.[13a] The transition state geometries calculated for the proton transfer from external HCl to **1** and **16** at B3LYP/6-31G* level are shown in Fig. 4. The H–Cl bonds are stretched by 0.18 Å and 0.22 Å in the transition states of **1**:**HCl** and **16**:**HCl**, respectively, which suggests the transfer of proton towards the organic bases. The intrinsic reaction co-ordinate analysis (IRC) calculations suggest that the transition state **1**:**HCl** is connected to the corresponding reactant and product.[23] The

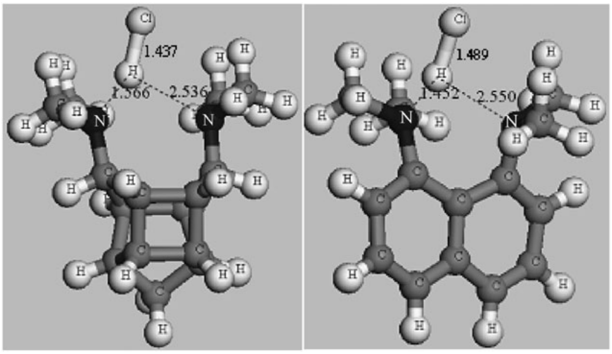

Fig. 4 B3LYP/6-31G* optimized transition states of **1** and **16** with HCl.

formation of contact ion-pair between the protonated organic base and chloride ion seem to exist in the product side. The contact ion pairs for chiral diamines with external acid was also predicted at DFT level of theory.[17d] The free energies of activation calculated with B3LYP/6-31G* for **1** and **16** are ~43.0 kJ/mol (Fig. 4).

Conclusion

We have reported the proton affinities for PCD- and substituted PCU-derivatives at the DFT B3LYP/6-311+G**//B3LYP/6-31G* level of theory. The predicted proton affinities for these polycyclic cage compounds were found to be higher than the corresponding prototype 1,8-bis(dimethylamino)-naphthalene (DMAN) and 1,8-bis(tetramethylguanidino)-naphthalene (TMGN). The new molecular framework (PCD) is versatile in terms of anchoring different functional groups to achieve high basicities in both the gas and solvent phases. The basicities of polycyclic compounds **1–15** appear to be the result of interplay between the overlap of nitrogen lone-pairs in the free bases, the relative cation strain in the protonated forms and the formation of a strong intramolecular hydrogen bridge in the monoprotonated compounds. The intramolecular proton transfer barrier has been predicted to be generally very low for the protonated systems studied here. Further, the computed intermolecular proton transfer barriers were found to be comparable for **1** and DMAN **16**. These calculated results show that polycyclic-derivatives can be used as organic superbases that can have a range of useful applications in synthesis and catalytic processes.

Acknowledgements

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