Computer aided design of organic superbases: the role of intramolecular hydrogen bonding

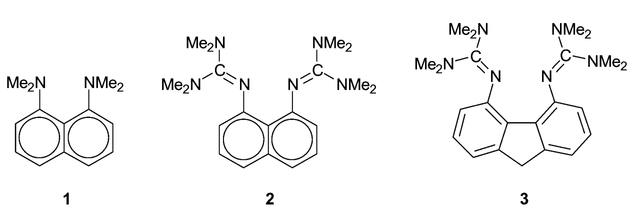
Borislav Kovačević,[a] Zvonimir B. Maksić,*[ab] Robert Vianello[a] and Miljenko Primorac[c]

[a] *Quantum Organic Chemistry Group, Ruđer Bošković Institute, 10000 , Zagreb, Croatia. E-mail: zmaksic@spider.irb.hr; Fax: +385 1 456 1118; Tel: +385–1–4561117*
[b] *Faculty of Science and Mathematics, The University of Zagreb, Marulićev trg 19, 10000 , Zagreb, Croatia*
[c] *Faculty of Forestry and Agriculture, The University of Zagreb, Šimunska c. 25, 10000 , Zagreb, Croatia. E-mail: primorac@hrast.sumfak.hr*

Received (in Montpellier, France) 26th April 2002, Accepted 14th June 2002
First published as an Advance Article on the web 15th August 2002

The role of intramolecular hydrogen bonding (IMHB) in determining the proton affinities and basicities of some bis(tetramethylguanidine)systems was examined. For this purpose a series of molecular backbone moieties serving as carriers of the bis(tetramethylguanidine)crowns were explored. It was found that the best backbones are provided by phenanthrene and 9,10-dihidrophenanthrene, giving rise to proton affinities as large as 268.2 and 266.8 kcal mol^{1-}, respectively. The corresponding $\text{p}K_\text{a}$ values in acetonitrile are 29.0 and 28.8, implying that these two compounds [**6**(bs)and **5**(bs)] are candidates for powerful superbases. Their intramolecular hydrogen bond strengths are $\approx$19 kcal mol^{1-}, which result *inter alia* from the *partial protonation* of the *vis-à-vis* guanidine group.

In the last decade much research interest has been focused on the synthesis, structure and properties of strong neutral organic (super)bases or proton sponges. The subject has been covered lately in several review articles .[1–7] The most studied family of molecules is the archetypal 1,8-bis(dimethylamino)-naphthalene (DMAN, **1** in Scheme 1) and its numerous offsprings.[8–14] Subsequently, acyclic and cyclic guanidines[15–18] and phosphazenes[19–21] have become a subject matter of intensive investigations. It was established that one of the main reasons of the high basicity of these compounds was a strong cationic resonance effect in the resulting conjugate acids. An important new concept was introduced—termed the aromatic domino effect—which emphasized the relevance of the aromatic stabilization triggered by protonation.[22–24] These studies underlined the decisive role of the final state (*i.e.*, the electronic features of the conjugate acids) in determining the pronounced intrinsic basicity of the guanidine group. It was, consequently, a natural extension of the idea of Alder's DMAN to form 1,8-bis(tetramethylguanidino) naphthalene (TMGN, **2**) and 4,5-bis(tetramethylguanidino) fluorene (TMGF, **3**) systems (Scheme 1). The former compound was already synthesized by Raab *et al.*[25] and characterized by X-ray and NMR measurements. The experimental data were supplemented by theoretical calculations,[26] which have conclusively shown that the relatively high proton affinity of TMGN is a consequence of the inherent basicity of the guanidine fragment and a relatively strong intramolecular hydrogen bond (IMHB) in [TMGN]H$^+$. Interestingly, it was found that the proton triggers the resonance stabilization not only in the proton bonded guanidine moiety, but also in the neighboring guanidine fragment, which was more distantly placed from the proton. This feature was termed a *partial protonation*, which substantially contributed to the extent of IMHB stabilization. It was also found that the intramolecular hydrogen bonding was somewhat stronger in TMGF, which together with a higher steric repulsion in the neutral base makes this compound more basic than TMGN.[26] It is important to point out that TMGN has some very favorable properties of a proton sponge,[25] which fits the general picture that strong neutral organic bases have some distinct advantages over their ionic counterparts. They require milder reaction conditions and exhibit increased solubility at the same time.[27,28] We felt it, therefore, worthwhile to extend a series of bis(tetramethyguanidino) compounds started by **2** and **3** by examining backbone molecules other than naphthalene and fluorene. This will reveal the role of the nonbonded repulsions in the initial bases and the intramolecular H bond in the resulting conjugate acids in determining the basicity of these interesting molecular systems. Results of this analysis are described in the present paper.



1 2 3

Scheme 1

Computational method

Absolute proton affinities (APA) in the gas phase are computed in the following standard way:

$$\text{APA}(\text{B}_\alpha) = (\Delta E_\text{el})_\alpha + (\Delta\text{ZPVE})_\alpha \tag{1}$$

$$(\Delta E_\text{el})_\alpha = E(\text{B}) - E(\text{B}_\alpha\text{H})^+ \tag{2}$$

$$(\Delta\text{ZPVE})_\alpha = \text{ZPVE}(\text{B}) - \text{ZPVE}(\text{B}_\alpha\text{H})^+ \tag{3}$$

Here B and BH$^+$ denote the base in question and its conjugate acid, respectively, whereas α signifies the site of proton attack.

DOI: 10.1039/b204072g

Eqns. (2) and (3) give the electronic and zero point vibrational energy (ZPVE) contributions to the proton affinity, respectively. The search of the Born–Oppenheimer energy hypersurfaces has been performed with the efficient Hartree–Fock model employing the 6-31G* basis set. Further, the minima on the potential energy hypersurface that correspond to equilibrium geometric structures were verified by vibrational analyses at the same level. The calculated vibrational frequencies were used in deriving the ZPV energies by the application of a common scale factor, 0.89, as customary. The final single-point calculations take into account the fact that a proper description of the nitrogen lone pair requires the use of the flexible 6-311+G** basis set, and that reliable estimates of the proton affinity require an explicit account of the correlation energy, at least to the level of Møller–Plesset (MP) second order perturbation theory. This gives rise to the MP2(fc)/6-311+G**//HF/6-31G* + ZPVE(HF/6-31G*) model,[29] which offers a good compromise between accuracy and feasibility. It will be abbreviated heretofore as MP2. It should be pointed out that the proton affinity is defined as an enthalpy difference at 298 K between the interacting species (a base and the proton) and the resulting conjugate acid. This includes an additional term of $(5/2)RT$ in eqn. (1), which appears from the translation energy of the proton and the $p\Delta V$ contribution, if we tacitly assume that protonation does not change the heat capacity significantly. This explicit correction is not necessary, however, since our MP2 model is selected in such a way (by a judicious choice of the basis set), that it reproduces the experimental data at room temperature rather well. A somewhat less accurate but more efficient model is provided by the scaled Hartree–Fock scheme ($\mathrm{HF_{sc}}$). It is based on a very good correlation between the MP2 proton affinities and the difference in HF energies of a neutral base and its conjugate acid.[30] The corresponding formula for protonated nitrogens reads:

$$\mathrm{APA(B_N)} = 0.8924\Delta E_{\mathrm{el}}(\mathrm{HF/6\text{-}31G^*})_{\mathrm{N}} + 10.4\ \mathrm{kcal\ mol^{-1}} \tag{4}$$

The reason behind the good performance of eqn. (4) is the fact that the ZPVE contribution to the proton affinity is practically constant in general, being 8.5 ± 0.4 kcal mol^{1-} for nitrogen atoms, which is absorbed in the additive constant in eqn. (4).

The solvent effect calculations in acetonitrile (MeCN) will be described later. All computations are carried out by using Gaussian 98 and GAMESS programs.[31,32]

Results and discussion

The absolute proton affinity

The studied compounds are schematically depicted in Fig. 1, where (mn) and (bs) denote mono(tetramethylguanidino) and bis(tetramethylguanidino) derivatives, respectively. We shall commence discussion with their energetic properties. Total molecular energies and scaled ZPVEs of the examined bases and their conjugate acids are presented in Table 1. Total energies of some molecules entering into homodesmic reactions (*vide infra*) are also given. Perusal of the results shows that $\mathrm{HF_{sc}}$ proton affinities are fairly close to the MP2 values (Table 1). The more approximate $\mathrm{HF_{sc}}$ values are systematically lower than the MP2 estimates, the deviation being sometimes ~3 kcal mol^{1-}. However, this kind of error is not serious, if the $\mathrm{HF_{sc}}$ model is utilized in pilot calculations on large systems in order to check approximately the magnitude of their basicity.

The most basic compound in the gas phase is predicted to be **6**(bs) followed by **5**(bs) and **9**(bs). In order to rationalize the computed APAs, we shall in the first place make use of the concept of homodesmotic *gedanken* reactions.[33] They correspond to the decomposition of a poly/doubly substituted compound into the sum of monosubstituted molecules corrected by the proper number of unsubstituted molecules so that the difference in total energies (or heats of formation of molecules) gives the interaction between substituents. One can write homodesmotic reactions for both bis-substituted neutral bases and for their corresponding conjugate acids:

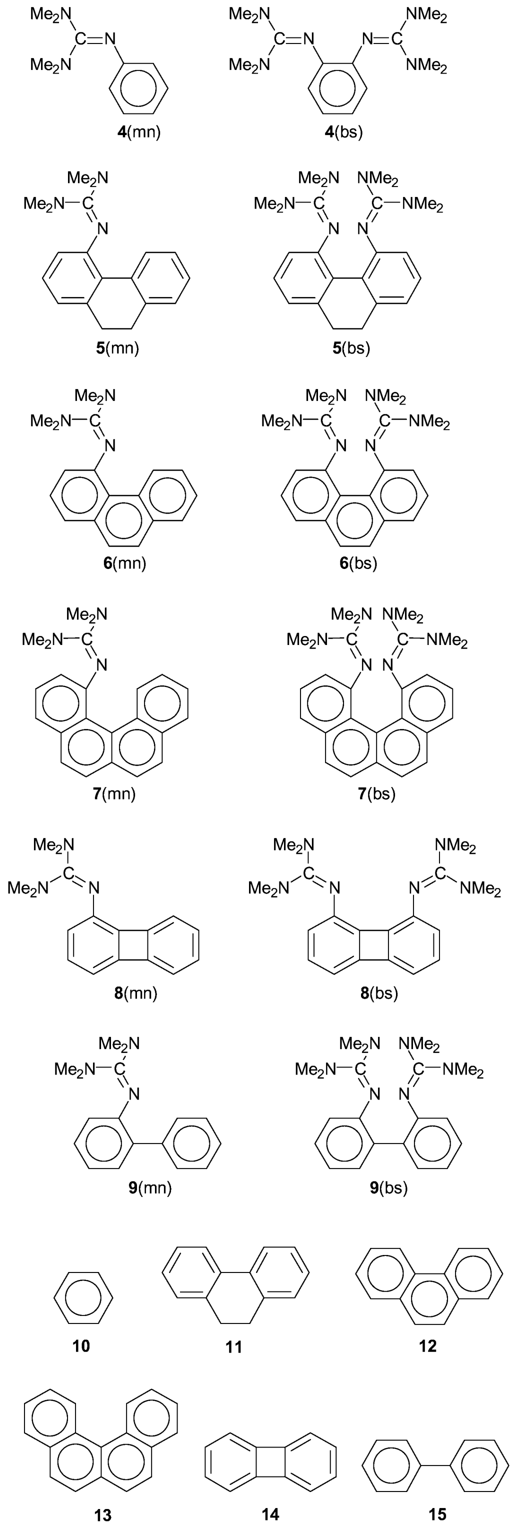


Fig. 1 Schematic representation of the studied organic bases and proton sponges and their unsubstituted molecular backbones.

$$\mathbf{4}(\mathrm{bs}) + \mathbf{10} = 2{\cdot}\mathbf{4}(\mathrm{mn}) + \Delta E(\mathbf{4}) \tag{5a}$$

$$\mathbf{4}(\mathrm{bs})\mathrm{H}^+ + \mathbf{10} = \mathbf{4}(\mathrm{mn}) + \mathbf{4}(\mathrm{mn})\mathrm{H}^+ + \Delta E(\mathbf{4})^+ \tag{5b}$$

$$\mathbf{5}(\mathrm{bs}) + \mathbf{11} = 2{\cdot}\mathbf{5}(\mathrm{mn}) + E(\mathbf{5}) \tag{6a}$$

Table 1 Total molecular energies (in au), ZPVEs (in kcal mol^{1-}), absolute proton affinities obtained by the MP2 (HFsc) models (in kcal mol^{1-}) and pK_a(MeCN) values. The HF$_{SC}$ APAs are given within parentheses

Molecule[a]	E_{el}	ZPVE	APA	pK_a(MeCN)
4(mn)	−592.01674	161.3	–	–
4(mn)H$^+$	−592.42123	170.0	245.1 (244.6)	–
4(bs)	−952.45649	262.5	–	–
4(bs)H	−952.87554	271.2	254.3 (253.3)	24.0
5(mn)	−899.65947	231.4	–	–
5(mn)H$^+$	−900.06470	240.1	245.6 (244.3)	–
5(bs)	−1260.09224	332.2	–	–
5(bs)H$^+$	−1260.53220	341.5	266.8 (264.0)	28.8
6(mn)	−898.46542	217.6	–	–
6(mn)H$^+$	−898.86473	226.4	241.8 (243.6)	–
6(bs)	−1258.88966	318.2	–	–
6(bs)H$^+$	−1259.33186	327.5	268.2 (264.7)	29.0
7(mn)	−1051.68304	245.5	–	–
7(mn)H$^+$	−1052.09503	254.4	249.6 (248.5)	–
7(bs)	−1412.11942	346.1	–	–
7(bs)H$^+$	−1412.54951	355.5	260.5 (260.1)	24.4
8(mn)	−821.17558	196.0	–	–
8(mn)H$^+$	−821.57963	204.7	244.8 (244.6)	–
8(bs)	−1181.61500	296.2	–	–
8(bs)H$^+$	−1182.03189	305.8	252.0 (251.8)	–[b]
9(mn)	−822.43931	209.7	–	–
9(mn)H$^+$	−822.84668	218.3	247.0 (246.3)	–
9(bs)	−1182.87677	310.5	–	–
9(bs)H$^+$	−1183.31212	319.9	263.8 (260.0)	25.9
10	−231.58221	60.1		
11	−539.22240	130.3		
12	−538.02841	116.5		
13	−691.24759	144.8		
14	−460.73818	94.2		
15	−462.00148	108.7		

[a] Molecules **10**, **11**, **12**, **13**, **14** and **15** correspond to benzene, 9,10-dihydrophenanthrene, phenanthrene, 3,4-benzophenanthrene, biphenylene and biphenyl, respectively. [b] We could not achieve convergence of the solvatation calculation for the protonated form of this molecule.

$$\mathbf{5}(\mathrm{bs})\mathrm{H}^+ + \mathbf{11} = \mathbf{5}(\mathrm{mn}) + \mathbf{5}(\mathrm{mn})\mathrm{H}^+ + \Delta E(\mathbf{5})^+ \tag{7a}$$

$$\mathbf{6}(\mathrm{bs}) + \mathbf{12} = 2{\cdot}\mathbf{6}(\mathrm{mn}) + \Delta E(\mathbf{6}) \tag{7a}$$

$$\mathbf{6}(\mathrm{bs})\mathrm{H}^+ + \mathbf{12} = \mathbf{6}(\mathrm{mn}) + \mathbf{6}(\mathrm{mn})\mathrm{H}^+ + \Delta E(\mathbf{6})^+ \tag{7b}$$

$$\mathbf{7}(\mathrm{bs}) + \mathbf{12} = 2{\cdot}\mathbf{7}(\mathrm{mn}) + \Delta E(\mathbf{7}) \tag{8a}$$

$$\mathbf{7}(\mathrm{bs})\mathrm{H}^+ + \mathbf{13} = \mathbf{7}(\mathrm{mn}) + \mathbf{7}(\mathrm{mn})\mathrm{H}^+ + \Delta E(\mathbf{7})^+ \tag{8b}$$

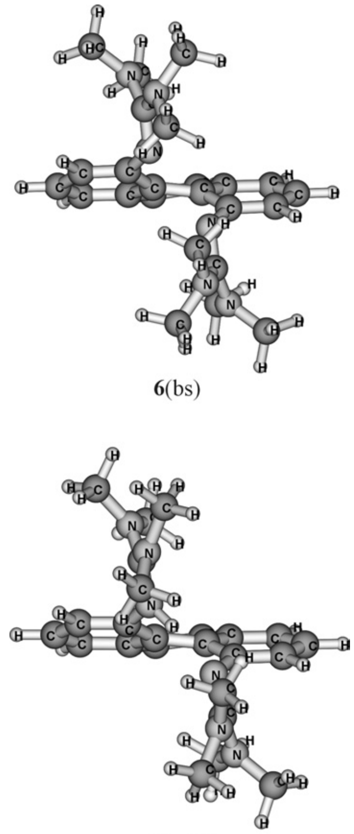
$$\mathbf{8}(\mathrm{bs}) + \mathbf{14} = 2{\cdot}\mathbf{8}(\mathrm{mn}) + \Delta E(\mathbf{8}) \tag{9a}$$

$$\mathbf{8}(\mathrm{bs})\mathrm{H}^+ + \mathbf{14} = \mathbf{8}(\mathrm{mn}) + \mathbf{8}(\mathrm{mn})\mathrm{H}^+ + \Delta E(\mathbf{8})^+ \tag{9b}$$

$$\mathbf{9}(\mathrm{bs}) + \mathbf{15} = 2{\cdot}\mathbf{9}(\mathrm{mn}) + \Delta E(\mathbf{9}) \tag{10a}$$

$$\mathbf{9}(\mathrm{bs})\mathrm{H}^+ + \mathbf{15} = \mathbf{9}(\mathrm{mn}) + \mathbf{9}(\mathrm{mn})\mathrm{H}^+ + \Delta E(\mathbf{9})^+ \tag{10b}$$

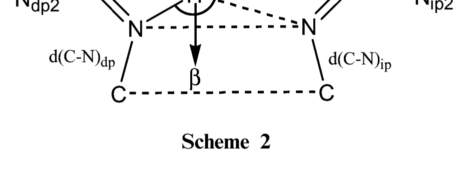
where $\Delta E(\boldsymbol{n})$ and $\Delta E(\boldsymbol{n})^+$ denote the interaction energies of the guanidino groups in the neutral and protonated species, respectively. They are calculated at the MP2 level and $\Delta E(\boldsymbol{n})$ (n = 1–9) is 4.1, 0.7, 3.7, −3.2, 2.4, 7.5, −0.7, −2.9, 0.0 kcal mol^{1-}, respectively, implying that in systems **4**(bs), **7**(bs) and **8**(bs) the interaction between guanidino groups and the molecular frames is slightly stabilizing the system. The corresponding $\Delta(\mathbf{n})^+$ values for the conjugate acids assume the following values: −15.5, −11.8, −13.9, −13.4, −18.8, −18.9, −11.5, −10.0 and −16.7 kcal mol^{1-} for n = 1–9, respectively, meaning that the IMHB energies are largest in **5**(bs)H$^+$, **6**(bs)H$^+$ and **9**(bs)H$^+$. This finding explains the high intrinsic proton affinities of compounds **5**(bs), **6**(bs) and **9**(bs). It should be pointed out that the guanidine fragments assume an *anti* conformation in all systems. This is illustrated by a side view along the C$_2$ symmetry axis in the case of **6**(bs) and its protonated form **6**(bs)H$^+$ presented in Fig. 2. Inspection reveals that the molecular backbone given by phenanthrene is somewhat twisted due to rather strong repulsion between the guanidine groups. This is reflected in the interaction energy $\Delta E(\mathbf{6})$, which is the highest of all the molecules (7.5 kcal mol^{1-}). A certain degree of nonplanarity of the backbone is retained even after protonation (Fig. 2). To be more specific: two phenyl rings flanking the central benzene moiety close up a dihedral angle of 40° across the central CC bond in a neutral base. This dihedral angle ϑ is lessened to 33° upon protonation. On the other hand, nonplanarity is practically nonexistent (ϑ = 1.7°) in **8**(bs), which is reflected in $\Delta E(\mathbf{8})$. The latter is negative (−2.9 kcal mol^{1-}), even implying a small stabilization interaction between two guanidine groups mediated by biphenylene. A similar slightly stabilizing interaction is observed in the **4**(bs) system.


6(bs)

6(bs)H$^+$

Fig. 2 Side view along the C$_2$ symmetry axis of **6**(bs) and **6**(bs)H$^+$.

Let us examine more closely the relevant geometric parameters of the bis(tetramethyl)guanidine portion of molecules **4**(bs)–**9**(bs) and in particular those determining the intramolecular hydrogen bond. They are described in Scheme 2, where d(N···N) and d(C···C) denote nonbonded contacts, whereas d(C=N)$_{dp}$ and d(C=N)$_{ip}$ are bond distances of a directly and



Scheme 2

indirectly protonated C=N bond of a guanidino group. Analogously, amino nitrogens are denoted by indices dp and ip too. Since the hydrogen bond is not linear but bent, we shall characterize its bending by the angle β.

Pyramidalization of amino nitrogens and their planarization upon protonation is of some interest. It is useful to utilize for this purpose an index termed the degree of pyramidalization DP(%), which is defined as:

$$\mathrm{DP}(\%) = \left[360 - \sum_{i=1}^{3} \alpha_i\right] / 0.9 \qquad (11)$$

where the summation extends over three acute bond angles α_i of the apical nitrogen in question.[34] The relevant bond distances and βs, as well as the degrees of pyramidalization, are presented in Table 2. Perusal of the data reveals some interesting and general features of all studied bis(tetramethylguanidino) compounds. The directly and indirectly protonated bonds are lengthened by different amounts, but the changes are practically the same in all systems (0.060 and 0.025 Å, respectively). The initial (unprotonated molecule) distances are surprisingly constant too. The same holds for C–N single bonds, $d(\mathrm{C{-}N})_{\mathrm{dp1}}$ and $d(\mathrm{C{-}N})_{\mathrm{dp2}}$, connecting amino groups with the double bond. They are shortened upon protonation by 0.05 Å in an apparently strong cationic resonance effect. The corresponding shortening of $d(\mathrm{CN})_{\mathrm{ip1}}$ is about 0.025 Å, indicating that partial protonation is operative and that it is a general phenomenon. Interestingly, shortening is somewhat smaller for $d(\mathrm{CN})_{\mathrm{ip2}}$ bond distances (~0.018 Å) since we can distinguish two different distal amino groups. They differ in their degrees of pyramidalization DP(%). Nitrogens $\mathrm{N_{dp1}}$ and $\mathrm{N_{ip1}}$ are pyramidal to an appreciable extent in neutral bases (~12–13%), whereas their counterparts $\mathrm{N_{dp2}}$ and $\mathrm{N_{ip2}}$ are practically planar as evidenced by very low DP(%) values (Table 2). Obviously, the latter already take part in the conjugation interaction in the initial bases (*vide infra*). The cationic resonance interaction in conjugate acids leads to almost complete planarization of $\mathrm{N_{dp1}}$ and $\mathrm{N_{dp2}}$ nitrogens as confirmed by the negligible corresponding DP(%) values. The same occurs for the $\mathrm{N_{ip1}}$ and $\mathrm{N_{ip2}}$ atoms, but with one distinct difference—the former atoms retain some pyramidalization after protonation. The structure of IMHB deserves special scrutiny. The directly bonded proton distance $d(\mathrm{N{-}H^+})_{\mathrm{dp}}$ is practically constant (~1 Å). On the contrary, the distances to the neighboring guanidine group vary to a considerable extent (Table 2). The shortest $d(\mathrm{N\cdots H^+})_{\mathrm{ip}}$ distances are found in systems **6**(bs) and **5**(bs). Not unexpectedly, we found the highest hydrogen bond stabilizations in precisely these two compounds as reflected in the $\Delta(\boldsymbol{n})^+$ interaction energies (n = 6 and 5) being −18.9 and −18.8 kcal mol^{1-}, respectively. These two molecules also have the highest proton affinities (268.2 and 266.8 kcal mol^{1-}, respectively). It seems that this parameter is the most important in determining the IMHB strength. Another structural parameter of interest is the nonbonded contact $d(\mathrm{N\cdots N})$, which is the shortest in **6**(bs) as expected and in its protonated form **6**(bs)H$^+$. However the next shortest $d(\mathrm{N\cdots N})$ contact is found in **7**(bs) and its conjugate acid, and not in **5**(bs). Since APA[**5**(bs)] > APA[**7**(bs)] and $\Delta(\mathbf{5})^+ < \Delta(\mathbf{7})^+$, we conclude that the nonbonded contact N···N is not a good index of the IMHB strength. Finally, the angle β seems to also have some influence on the IMHB interaction. It does not vary much across the series, **4**(bs) system being the exception. The fact of the matter is, however, that β assumes a maximal value (138°) in the two most basic compounds, **6**(bs) and **5**(bs). The next highest β is found for **9**(bs), which also exhibits a high APA [**9**(bs) = 263.8 kcal mol^{1-}] and appreciable IMHB strength [$\Delta(\mathbf{9})$ = −16 kcal mol^{1-}]. However, all attempts to find a direct correlation of the IMHB energies $\Delta(\boldsymbol{n})^+$ with any of the structural parameters failed. We note in passing that $d(\mathrm{C{-}N})_{\mathrm{dp}}$ is increased upon protonation due to rehybridization of the imine nitrogen. This lengthening is fairly constant, being ≈0.03 Å.

Let us now discuss the problem of inequivalent amino groups. For this purpose we consider a series of guanidines pictorially shown in Fig. 3, together with the degree of pyramidalization of their amino groups. Examination of the latter values provides some interesting information on the conjugation interactions involving the amino nitrogen lone pair(s). One observes that the amino group positioned *cis* to the imino N–H bond in guanidine is somewhat less pyramidalized (*i.e.*, it is more "planar") than is its *vis-à-vis* counterpart. This disparity is further enhanced by the CH$_3$ substitution at the imino center (18.8% *vs.* 26.6%). Dimethyl substitution of the amino nitrogen atoms decreases pyramidalization, which is easily rationalized by the fact that a N–C bond requires more s orbital character than an N–H bond. In other words, hybrid orbitals of the nitrogen atom describing N–C bonds possess higher s orbital content compared to N–H bonds, which makes

Table 2 Structural characteristic of IMHBs and the degree of pyramidalization of amino nitrogens.[a] Structural parameters in the protonated species are given within square brackets.

	4(bs)	**5**(bs)	**6**(bs)	**7**(bs)	**8**(bs)	**9**(bs)
$d(\mathrm{C\cdots C})$	1.403 [1.403]	3.234 [3.196]	3.192 [3.174]	3.327 [3.414]	3.790 [3.745]	3.365 [3.236]
$d(\mathrm{N\cdots N})$	2.184 [2.715]	3.004 [2.770]	2.895 [2.704]	2.935 [2.760]	3.855 [3.599]	3.365 [2.909]
$d(\mathrm{N{-}H^+})_{\mathrm{dp}}$	[0.997]	[1.012]	[1.013]	[1.000]	[1.000]	[1.008]
$d(\mathrm{N\cdots H^+})_{\mathrm{ip}}$	[2.559]	[1.937]	[1.865]	[1.989]	[2.837]	[2.095]
β	88.1	137.8	138.0	131.9	133.4	136.4
$d(\mathrm{C{=}N})_{\mathrm{dp}}$	1.264 [1.329]	1.265 [1.326]	1.266 [1.328]	1.266 [1.322]	1.266 [1.330]	1.264 [1.326]
$d(\mathrm{C{=}N})_{\mathrm{ip}}$	1.264 [1.290]	1.265 [1.290]	1.266 [1.293]	1.266 [1.283]	1.266 [1.285]	1.264 [1.287]
$d(\mathrm{C{-}N})_{\mathrm{dp}}$	1.403 [1.431]	1.397 [1.431]	1.397 [1.430]	1.395 [1.433]	1.396 [1.427]	1.396 [1.431]
$d(\mathrm{C{-}N})_{\mathrm{ip}}$	1.403 [1.386]	1.397 [1.410]	1.397 [1.411]	1.395 [1.405]	1.396 [1.392]	1.396 [1.407]
$d(\mathrm{CN})_{\mathrm{dp1}}$	1.390 [1.337]	1.388 [1.337]	1.387 [1.337]	1.386 [1.340]	1.387 [1.334]	1.388 [1.336]
$d(\mathrm{CN})_{\mathrm{dp2}}$	1.387 [1.333]	1.393 [1.337]	1.393 [1.337]	1.389 [1.337]	1.385 [1.333]	1.389 [1.337]
$d(\mathrm{CN})_{\mathrm{ip1}}$	1.390 [1.361]	1.388 [1.363]	1.387 [1.362]	1.386 [1.372]	1.387 [1367]	1.388 [1.367]
$d(\mathrm{CN})_{\mathrm{ip2}}$	1.387 [1.370]	1.393 [1.371]	1.393 [1.369]	1.389 [1.371]	1.385 [1.372]	1.389 [1.372]
DP($\mathrm{N_{dp1}}$)	13.0 [1.0]	12.7 [0.5]	12.3 [0.3]	12.0 [2.0]	12.4 [0.7]	13.4 [0.9]
DP($\mathrm{N_{dp2}}$)	3.7 [0.2]	3.9 [0.3]	4.0 [0.4]	3.6 [0.4]	2.7 [0.1]	2.8 [0.3]
DP($\mathrm{N_{ip1}}$)	13.0 [5.0]	12.7 [2.8]	12.3 [1.8]	12.0 [7.3]	12.4 [4.7]	13.4 [4.8]
DP($\mathrm{N_{ip2}}$)	3.7 [0.6]	3.9 [1.3]	4.0 [1.3]	3.6 [1.1]	2.7 [0.9]	2.8 [0.9]

[a] Distances in Å and β in degrees. DP (degree of pyramidalization) values are given in %. Notice that there is no difference in the quantities indexed by dp and ip for the neutral base since it is not protonated.

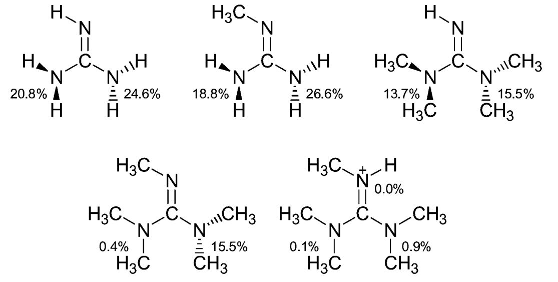


Fig. 3 Degree of pyramidalization (DP%) in some guanidine systems.

dimethyl substituted N atom more "planar". This is corroborated by actual calculations of the NBO (natural bond orbital) hybrids in guanidine and *N*,*N*,*N*′,*N*′-tetramethylguanidine. The s characters of the amino nitrogen atoms in guanidine are N–C (34.9%–29.8%), N–H (25.9%) and N–H' (26.9%). The corresponding s characters in the second compound are (32.8%–30.3%), (30.3%–23.9%) and (29.2%–24.1%), where the nitrogen s characters are given first within the parentheses. The sums of s characters for nitrogen (amino) hybrids in guanidine and *N*,*N*,*N*′,*N*′-tetramethylguanidine are 87.7% and 92.3%, respectively, implying that the substituted nitrogens should be more planar. Still, there is a slight disparity in the degree of pyramidalization between *cis* and *trans* $N(CH_3)_2$ groups (13.7% *vs.* 15.5%). Finally, in pentamethylguanidine the *cis* amino group is planar, but rotated with respect to the plane of the guanidine backbone. This is a result of the interplay between the steric repulsion of the methyl groups, and the conjugation effect between the lone pair on the amino nitrogen in question and the C=N double bond. In contrast, planarization of the *trans* dimethylamine group is not possible, because it would either abolish the conjugation with the C=N double bond or greatly increase the nonbonded steric repulsion with the *cis* dimethylamine group. Consequently, the second $N(CH_3)_2$ fragment remains pyramidalized. This explains the inequivalence of the amino groups in the studied neutral bases. The cationic resonance effect in pentamethylguanidine is so strong that all three nitrogen moieties become practically planar in spite of the increased steric repulsion between the methyl groups.

Basicity in acetonitrile

Recently, we have shown that the basicity of proton sponges in acetonitrile[35] can be conveniently tackled by using the electrostatic model of Miertuš *et al.*[36] for the homogenous solvent. It gives satisfactory results for moderately polar solvents. In determining cavities that surround solvated molecules, we followed suggestions of Wiberg *et al.*,[37] who used isodensity shells with an electronic density of 0.0004 eB^{-3}. This gives rise to the isodensity polarized continuum model (IPCM). Since the calculations of pK_a values in acetonitrile ($\varepsilon = 36.64$) require several expensive iterations, we utilized a more economical B3LYP/6-311+G**//HF/6-31G* model, in which the ZPVEs were taken over from the gas phase calculations evaluated at the HF/6-31G* level. We found an excellent least squares fit between the proton affinities $APA(CH_3CN)$ calculated in acetonitrile and the experimental pK_a values. The corresponding linear relation reads:

$$pK_a(CH_3CN) = 0.4953 \cdot APA(CH_3CN) - 119.7 \qquad (12)$$

A very high regression coefficient $R = 0.997$ and a low average absolute error of 0.4 pK_a testify to a strong correlativity of the theoretical results with experiment.[35] Eqn. (12) will be employed here in a predictive manner to estimate the basicity of the studied systems. We found that the PA in acetonitrile and the accompanying basicity are determined essentially by an interplay of two factors: (a) the intrinsic PA in the gas phase and (b) the size of the base in question. The influence of the latter factor is easily understood by taking into account the simple fact that the positive charge in the corresponding conjugate acid is distributed over all atoms. This is a general feature of the electron density redistribution resulting in the concomitant relaxation energy stabilization, which is characteristic for all cations. Consequently, a bulkier molecule and a larger molecular surface imply a less positive charge residing on the peripheral atoms (which are hydrogens as a rule). This, however, means that the polarization of the solvent continuum is less pronounced. It follows that the solvent effect is inversely proportional to the molecular size.[35] Basicities and pK_a-(MeCN) are presented in Table 1. Very high values of 29.0 and 28.8 are obtained for **6**(bs) and **5**(bs). These two compounds qualify as superbases.

Concluding remarks

It is shown that a judicious choice of the molecular backbone moieties serving as carriers of the bis(tetramethylguanidine) fragments leads to powerful neutral superbases as exemplified by systems **6**(bs) and **5**(bs). Their high basicity is a result of the large intrinsic proton affinity of the methylated guanidine group enhanced by the strong IMHB. The latter stabilizes the protonated species **6**(bs)H^+ and **5**(bs)H^+ by roughly 19 kcal mol^{1-}. It should be mentioned that the former compound derives its basicity also from the nonbonded repulsions in the initial base. It turns out that the basicity of **6**(bs) and **5**(bs) in acetonitrile is very high (29.0 and 28.8, respectively). Hence, synthesis of those compounds is strongly recommended. Other studied systems span the range of proton affinities between 241–264 kcal mol^{1-} with pK_a values between 24.0–26.0. This is of importance too, because reference bases necessary for carrying out the bracketing measurements are badly needed in this range. Finally, we would like to reiterate once again that the IMHB is pivotal in determining high proton affinities and basicities in bis(tetramethylguanidine) systems, since considerable hydrogen bond strengths are achieved *inter alia* by the *partial protonation* of the *vis-à-vis* guanidine fragment.

References

1 (*a*) R. W. Alder, *Chem. Rev.*, 1989, **89**, 1215; (*b*) R. W. Alder, *Tetrahedron*, 1990, **46**, 683.
2 A. L. Llamas-Saiz, C. Foces-Foces and J. Elguero, *J. Mol. Struct.*, 1994, **328**, 297.
3 H. A. Staab and T. Saupe, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 865.
4 E. D. Raczyńska, M. Decouzon, J.-F. Gal, P.-C. Maria, G. Gelbard and J. Vielfaure-Joly, *J. Phys. Org. Chem.*, 2001, **14**, 25.
5 J.-F. Gal, P.-C. Maria and E. D. Raczyńska, *J. Mass. Spectrom.*, 2001, **36**, 699.
6 M. Alcami, O. Mó and M. Yáñez, *Mass. Spectrom. Rev.*, 2001, **20**, 195.
7 M. Alcami, O. Mó and M. Yáñez, *J. Phys. Org. Chem.*, 2002, **15**, 174.
8 R. W. Alder, P. S. Bowman, W. R. S. Steele and D. R. Winterman, *J. Chem. Soc., Chem. Commun.*, 1968, 723.
9 (*a*) J. A. Platts, S. T. Howard and W. Woźniak, *J. Org. Chem.*, 1994, **59**, 4647; (*b*) J. A. Platts and S. T. Howard, *J. Org. Chem.*, 1996, **61**, 4480.
10 A. L. Llamas-Saiz, C. Foces-Foces and J. Elguero, *J. Chem. Soc., Perkin Trans. 2*, 1995, 923.
11 M. Peräkylla, *J. Org. Chem.*, 1996, **61**, 7420.
12 K. Wozniak, H. He, J. Klinowski, W. Jones and T. L. Barr, *J. Phys. Chem.*, 1995, **99**, 14 667.
13 (*a*) C. López, R. M. Claramunt, A. L. Llamas-Saiz, C. Foces-Foces, J. Elguero, I. Sobrados, F. Aguilar-Parrilla and H.-H. Limbach, *New. J. Chem.*, 1996, **20**, 523; (*b*) I. Alkorta and J. Elguero, *Struct. Chem.*, 2000, **11**, 335.

14 A. Szemik-Hojniak, J. M. Zwier, W. J. Buma, R. Bursi and J. H. van der Waals, *J. Am. Chem. Soc.*, 1998, **120**, 4840.

15 E. D. Raczyńska, P.-C. Maria, J.-F. Gal and M. Decouzon, *J. Phys. Org. Chem.*, 1994, **7**, 725.

16 R. Schwesinger, *Angew Chem., Int. Ed. Engl.*, 1987, **26**, 1164.

17 R. Schwesinger, M. Misfeldt, K. Peters and H. G. von Schnering, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1165.

18 Z. B. Maksić and B. Kovačević, *J. Org. Chem.*, 2000, **65**, 3303.

19 R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dimbacher, T. Breuer, C. Ottawa, M. Fletschinger, J. Boele, M. Fritz, D. Putzas, H. W. Rotter, F. G. Bordwell, A. V. Satish, G. Z. Yi, E.-H. Peters and H. G. von Schnering, *Liebigs Ann. Chem.*, 1996, 1055.

20 I. A. Koppel, R. Schwesinger, T. Brener, P. Burk, K. Herodes, I. Koppel, I. Leito and M. Mishima, *J. Phys. Chem. A*, 2001, **105**, 9575.

21 Z. B. Maksić and R. Vianello, *J. Phys. Chem. A*, 2002, **106**, 419.

22 Z. B. Maksić and B. Kovačević, *J. Phys. Chem. A*, 1998, **102**, 7324.

23 Z. B. Maksić and B. Kovačević, *J. Phys. Chem. A*, 1999, **103**, 6678.

24 Z. B. Maksić, Z. Glasovac and I. Petanjek, *J. Phys. Org. Chem.*, 2002, **15**, 499.

25 V. Raab, J. Kipke, R. Gschwind and J. Sundermeyer, *Chem. Eur. J.*, 2002, **8**, 1682.

26 B. Kovačević and Z. B. Maksić, *Chem. Eur. J.*, 2002, **8**, 1694.

27 J. Tang, J. Dopke and J. G. Verkade, *J. Am. Chem. Soc.*, 1993, **115**, 5015 and references cited therein.

28 H. Oediger, F. Möller and K. Eiter, *Synthesis*, 1972, 591.

29 Z. B. Maksić and M. Eckert-Maksić, in *Theoretical and Computational Chemistry*, series eds. P. Politzer and Z. B. Maksić, vol. 5, *Theoretical Organic Chemistry*, ed. C. Parkanyi, Elsevier, Amsterdam, 1998, p. 203 and references cited therein.

30 Z. B. Maksić, B. Kovačević and D. Kovaček, *J. Phys. Chem. A*, 1997, **101**, 7446.

31 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, *Gaussian 98, Rev. A.10,* Gaussian, Inc., Pittsburgh, PA, 1998.

32 GAMESS 1997: M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J. Comput. Chem.*, 1993, **14**, 1347.

33 (*a*) P. George, M. Trachtman, C. W. Bock and A. M. Brett, *Tetrahedron*, 1976, **32**, 317; (*b*) P. George, M. Trachtman, C. W. Bock and A. M. Brett, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1222.

34 Z. B. Maksić and B. Kovačević, *J. Chem. Soc., Perkin Trans. 2*, 1999, 2623.

35 B. Kovačević and Z. B. Maksić, *Org. Lett.*, 2001, **3**, 1523.

36 S. Miertuš, E. Scrocco and J. Tomasi, *J. Chem. Phys.*, 1981, **55**, 117.

37 K. P. Wiberg, P. R. Rablen, D. J. Rush and T. A. Keith, *J. Am. Chem. Soc.*, 1995, **117**, 4261; J. B. Foresman, T. A. Keith, K. B. Wiberg, J. Snoonian and M. J. Frisch, *J. Phys. Chem.*, 1996, **100**, 16098.