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Exceptional Superbasicity of Bis(guanidine) Proton Sponges Imposed by the Bis(secododecahedrane) Molecular Scaffold: A Computational Study

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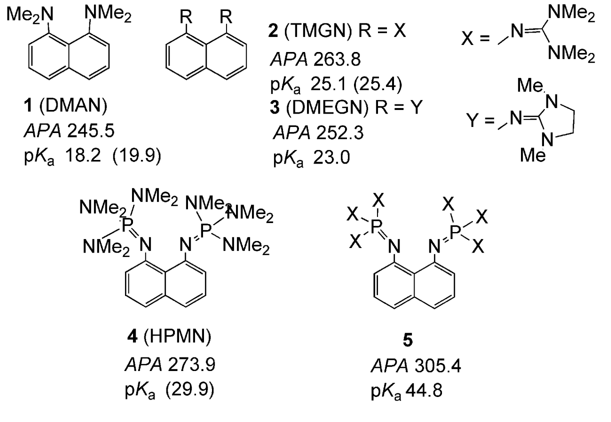
The exceptional superbasicity of a series of bis(guanidines) with a bis(secododecahedrane) molecular scaffold was found in the course of a computational study. The 3-*syn*,13-*syn*-disubstituted bis(secododecahedrane) skeleton ensures that nitrogen lone pairs of electrons are in close proximity, and the rigid framework of the polycyclic cage guarantees acid/base properties similar to those of proton sponges. Amine functionalization with alkyl substituents, imines, and guanidines leads to high basicity. Based on DFT computations, bis(guanidine)–bis(secododecahedrane) proton sponges with a (1,3-dimethylimidazolidin-2-ylidene)amino moiety are predicted to have very high basicities, both in the gas phase and acetonitrile. This skeleton provides the highest proton affinity (*PA*) value among all the aliphatic proton sponges reported (288.7 kcal mol^{-1}, whereas the gas-phase basicity is 284.3 kcal mol^{-1}, at the B3LYP/6-311+G**//B3LYP/6-31G* level). In acetonitrile the calculated *PA* is 319.4 kcal mol^{-1} and the estimated pK_a is 38.5. Substitution of bis(secododecahedrane) with the intrinsically more basic nitrogen functionalities increases the *PA* to 316.3 kcal mol^{-1} and the pK_a to 46.

Introduction

The advantages of neutral organic superbases as catalysts have been recognized as a highly important area of organic chemistry nowadays.[1] The most important advantages are their use as a homogeneous catalysts for organic reactions and their environmentally friendly recyclability. Therefore, design and synthesis of novel organic superbases is a rapidly growing field of research. Amongst the strong organic bases, amidines, guanidines, and phosphazenes are widely used. Variation of their substitution patterns and geometrical arrangements are the standard methods used to enhance their basicity. A further basicity increase could be achieved by bringing two basic centers to close proximity by means of a rigid framework, as in "proton sponges".[2] Similar effects determine the high basicity of vinamidine[3] and polypyridine[4] proton sponges. For an illustration, the archetypal Alder's proton sponge, 1,8-bis(dimethylamino)naphthalene[5] (**1**; DMAN) and its guanidine (**2** and **3**[6,7]) and phosphazene and guanidinophosphazene derivatives (**4** and **5**)[8] are depicted in Scheme 1. It was found that simple *o*-bis(benzoguanidines) are more basic than **1** itself; however, the geometrical constraints limit their basicity to the lower class of the superbasicity scale.[9] The strong lone-pair repulsion in these systems, in conjunction with a strong intramolecular hydrogen bonding (IMHB) upon protonation, with the efficient relief of lone-pair repulsion are the key factors for their extraordinary basicity. Significant efforts have been put into development of basic fragments, which can be put together to enhance the basicity of such systems.[10]



Scheme 1. Naphthalene proton sponges (experimental values are given in parentheses in kcal mol^{-1}).

In this respect, new molecular polycyclic frameworks that significantly differ from the traditional proton-sponge topology of the aromatic skeleton have been developed. These molecular frameworks retain the close proximity of the nitrogen lone pairs of electrons, ensure framework rigidity, and acid/base properties similar to those of proton sponges. Illustrative examples include the work by Ganguly on sim-

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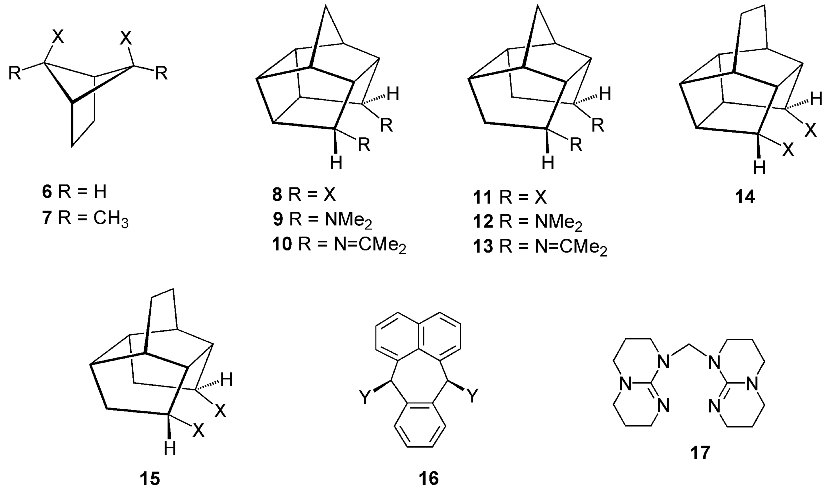
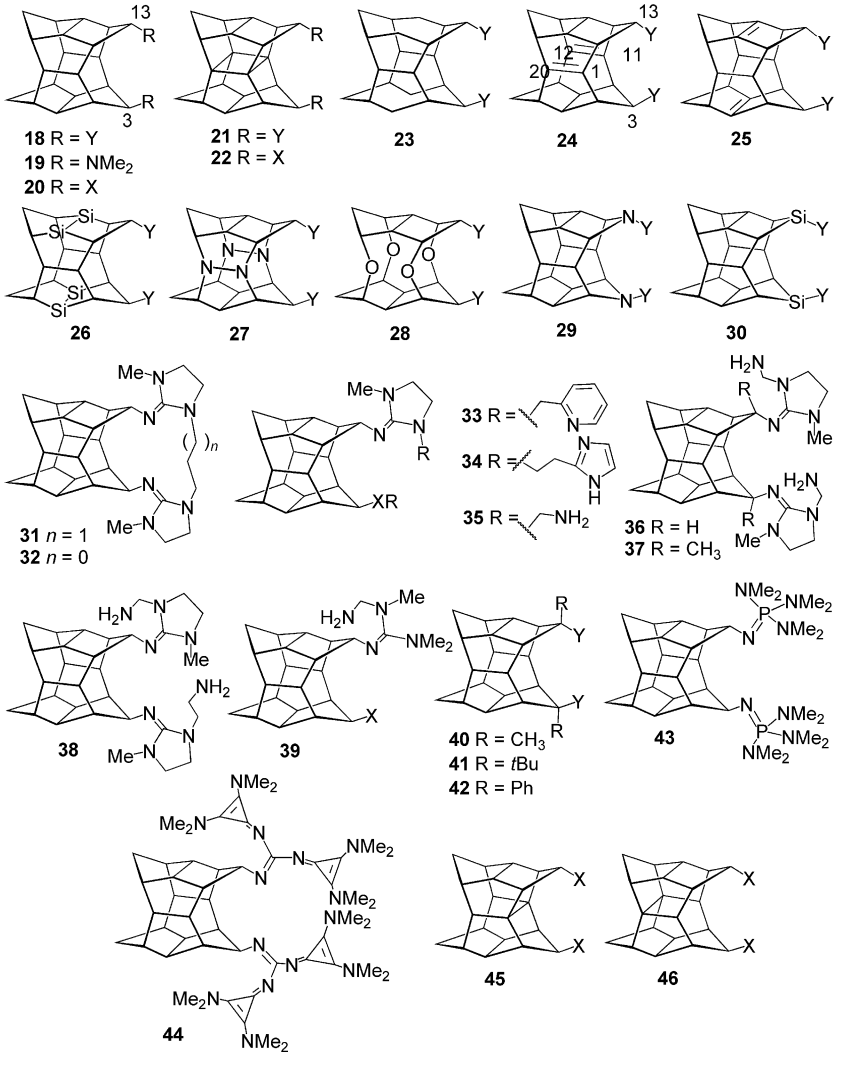


Scheme 2. Polycyclic proton sponges (groups X and Y are refered to in Scheme 1).

ple bicyclic compounds with guanidine units anchored to the bicyclo[2.1.1]hexane frameworks **6** and **7** [proton affinity (*PA*) of **7**: 273.8 kcal mol^{-1}; Scheme 2].[11] Amine, imine, and guanidine functionalization, of the *endo*,*endo*-8,11-disubstituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes **8**–**13** leads to higher basicity.[12] Based on DFT computations,



Scheme 3. Novel polycyclic frameworks for anchoring guanidine sponges (groups X and Y are referred to in Scheme 1).

these bases have gas-phase *PA* values that are higher than that of **1**, and are approaching that of 1,8-bis(tetramethylguanidino)naphthalene [TMGN (**2**)] (**2** is the most basic, $PA = 282.7$ kcal mol^{-1}, at the B3LYP/6-311+G**//B3LYP/6-31G* level and $PA_{\mathrm{MeCN}} = 314.9$ kcal mol^{-1}). A further basicity increase was achieved with the *endo*,*endo*-8,11-disubstituted pentacyclo[6.4.0.0^{2,7}.0^{3,11}.0^{6,10}]dodecane frameworks in **14** and **15**.[13] The highest *PA* value for these bis(guanidine) proton sponges was calculated for **14** (284.5 kcal mol^{-1}, B3LYP/6-311+G**//B3LYP/6-31G* method, $PA_{\mathrm{MeCN}} = 317.5$ kcal mol^{-1}). Polycyclic system **16**,[14] which is based on the 7,12-dihydropleiadene framework, effectively increases the superbasicity of bis(guanidine) proton sponges, the estimated *PA* value of which is 277 kcal mol^{-1} at the B3LYP/6-311+G**//B3LYP/6-31G* level. A less effective proton sponge was found to be bis(triazabicyclo[4.4.0]dec-1-ene) compound **17** ($PA = 270.6$ kcal mol^{-1}, obtained by the B3LYP/6-311+G**//B3LYP/6-31G* model).[15]

The aim of this computational study was to design novel bis(guanidine) superbase systems with enhanced basicity. For this purpose, we examined the basicity properties of a series of bis(guanidines) **18**–**46** possessing a bis(secododecahedrane) molecular framework, substituted at 3-*syn*,13-*syn*-positions with a (1,3-dimethylimidazolin-2-ylidene)amino group (Scheme 3). Since the synthesis of bis(secododecahedranes) is well established,[16] we assume that the synthesis of novel bis(guanidines) could be easily completed by guanylation of the appropriately positioned diamine with 2-chloro-1,3-dimethylimidazolium chloride.[17,18]

Table 1. Absolute proton affinities in the gas phase [$APA_{\mathrm{B3LYP(1)}}$ and $APA_{\mathrm{B3LYP(2)}}$], *GB*, pK_a(MeCN) values, and energies of homodesmotic reactions.[a,b]

	APA B3LYP(1)	*APA* M052X(1)	*APA* B3LYP(2)	*GB*	pK_a (MeCN)	E_1	E_2
18	293.4	287.6	288.7	284.3	38.5	23.5	–14.5
19	269.1	268.0	266.1	260.6	29.2	14.1	–17.7
20	290.2	289.7	287.4	281.2	36.7	16.6	–15.7
21	280.5	278.7	277.0	273.2	31.8	9.5	–14.1
22	264.4	264.5	261.6	255.4	27.7	9.5	–15.8
23	284.4	283.3	281.0	277.4	32.7	12.0	–14.6
24	290.2	287.6	286.6	283.4	35.4	21.1	–14.7
25	284.1	282.4	280.6	277.5	32.5	15.8	–14.5
26	291.4	288.4	293.4	284.6	38.7	22.9	–12.8
27	281.6	280.5	278.1	274.2	31.9	15.1	–14.4
28	282.4	281.1	279.1	274.9	30.5	11.4	–15.3
29	288.2	286.7	285.6	281.7	34.6	29.5	–9.7
30	269.5	264.9	268.0	262.9	27.0	14.3	–11.3
31	284.7	282.5	281.3	277.3	28.2		
32	285.9	285.4	283.0	278.7	31.7		
33	290.8	288.6	287.3	282.8	33.9		
34	286.1	284.8	283.1	278.6	34.1		
35	286.6	283.3	282.5	279.2	34.2		
36	287.2	284.4	283.3	281.6	33.9	20.9	–11.1
37	280.7	275.0	279.2	275.0	34.4	22.3	–10.7
38	286.1	280.1	284.0	278.2	32.4		
39	287.1	285.5	284.8	279.0	35.0		
40	274.6	267.9	272.7	268.6	30.2	14.6	–11.6
41	270.9	268.1	269.1	264.7	28.4	32.1	–18.1
42	277.6	273.5	274.6	269.6	30.3	18.6	–11.6
43	298.9	298.9	296.2	291.2	40.5	24.4	–11.4
44	319.7	316.0	316.3	313.8	46.0	18.7	–12.8
45	266.8	266.8	264.3	258.7	29.3		
46	268.0	268.0	265.2	259.5	28.4		

[a] In kcal mol^{-1}, 1 kcal mol^{-1} = 4.184 kJ mol^{-1}. [b] At 298 K.

Results and Discussion

Bis(guanidine) proton sponges based on 3-*syn*,13-*syn*-bis(secododecahedrane)[19,20] (**18**), 4-*syn*,14-*syn*-diamino-[1.1.1.1]pagodane[21] (**21**), 3-*syn*,13-*syn*-bis(secododecahedra-1,11-diene)[22] (**24**), and 3-*syn*,13-*syn*-bis(secododecahedra-6,15-diene) (**25**) ring systems, which are depicted in Scheme 3 were fully optimized. Total electronic energies of neutral and protonated bases **18**–**46** are given in Table S1 (Supporting Information), selected geometrical parameters are collected in Table S2 (Supporting Information), and basicity parameters are given in Table S3 (Supporting Information). Table 1 contains absolute proton affinities (*APA*) in the gas phase [$APA_{\mathrm{B3LYP(1)}}$ and $APA_{\mathrm{B3LYP(2)}}$], gas-phase basicites (*GB*), and pK_a(MeCN) values.

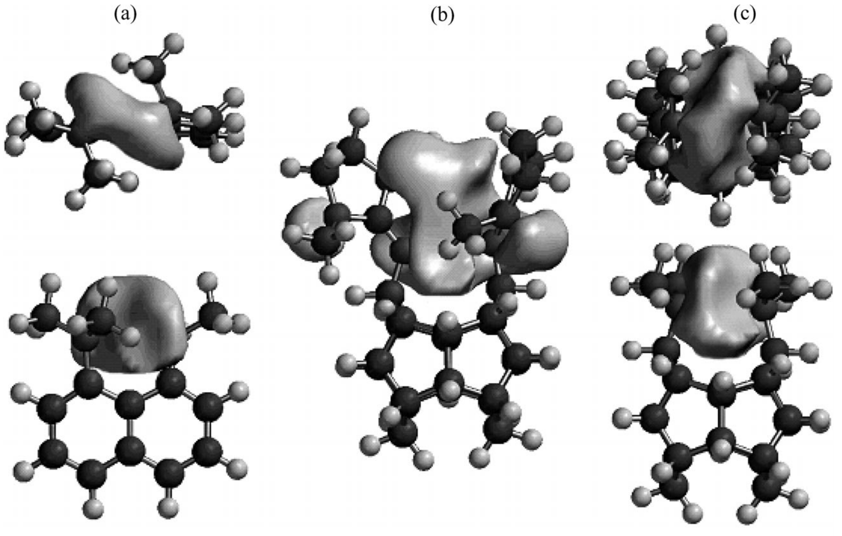
Geometrical Features

The ability of proton sponges to accommodate H$^+$ in the space between two nitrogen atoms is visualized by their electrostatic potential surfaces, and the cases of **1**, **18**, and **19** are illustrated in Figure 1. According to Hehre,[23] the lone pairs of electrons can be depicted by using electrostatic potential surfaces, although it is rarely used in the literature. In our particular system, this way of presentation gives a better picture than the "classical" electrostatic potential (ESP) mapped on the isoelectronic surface. Here, one may observe the position and the protrusion of nitrogen lone pairs in space, which are mainly located in the cavity between two nitrogen atoms, which represents the place where H$^+$ is accommodated upon protonation.

For an illustration, the B3LYP/6-31G*-optimized structures of **26** (**24**) and their respective protonated forms **26H$^+$** (**24H$^+$**) are given in Figure 2. The geometrically important feature upon protonation is the change of the geometry around the protonated imino nitrogen atom (by symmetrization). The geometry around the neutral imino nitrogen atom also changed to a smaller extent. For instance, C_{cage}–N and C=N bonds are lengthened, whereas the C_{guanid}–N bonds are shorter, which indicates partial protonation of the second guanidine moiety.

Geometrical changes induced by protonation are similar to those described in the literature.[24] These are discussed for **18**, and similar observations and conclusions could be derived from the geometrical analysis of other bis(guanidine) superbases studied.

The analysis of key geometrical data for protonated bases collected in Table S2 (see the Supporting Information) reveals that the distance between two imino nitrogen atoms *d*(NN) is within the values of 2.533–2.765 Å (average value 2.647 Å). Within these limits are *d*(NN)



1 (DMAN) **18** **19**

Figure 1. Electrostatic potential surface for (a) **1**, (b) **18**, and (c) **19** (isodensity value: –20 au), top and front views.

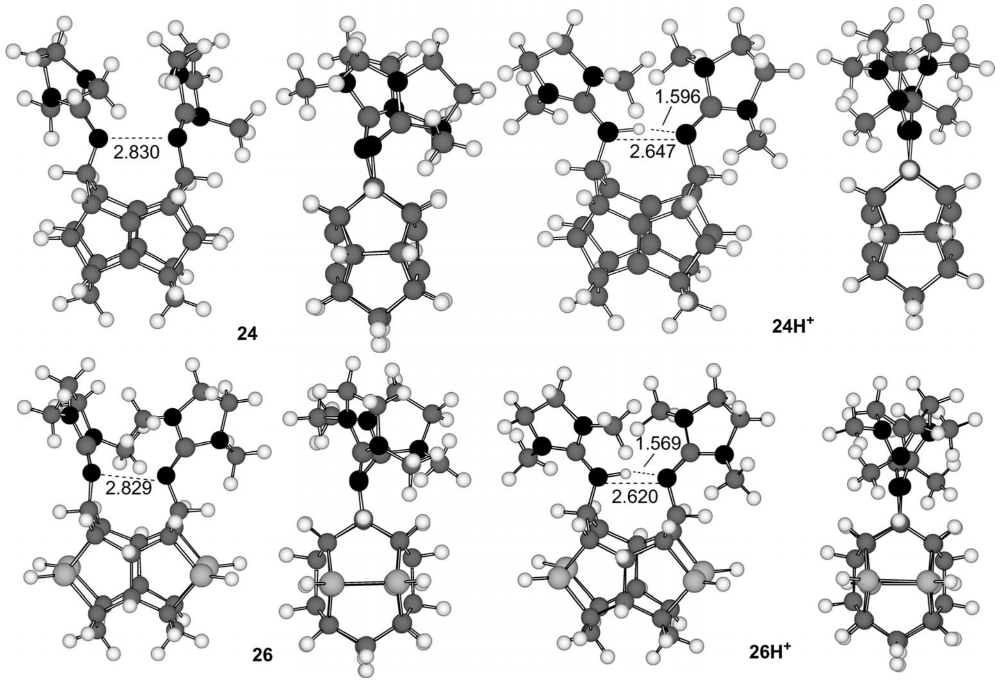


Figure 2. B3LYP/6-31G*-optimized structures of **24** and **26** and their protonated forms **24H$^+$** and **26$^+$** (distances are given in Å, angles in °).

values calculated for classical naphthalene proton sponges **1**–**3** (2.551, 2.620, and 2.613 Å, respectively). It could be noted that the *d*(NN) distances from Table S2 (Supporting Information) are on average longer than that of the classical proton sponge **1**. Literature *d*(NN) values for related polycyclic bis(guanidines) **8** and **17** also feature longer distances (2.680 and 2.713 Å, respectively).

All calculated protonated bases possess an unsymmetrically positioned proton, as shown by the distances between H$^+$ and the neighboring imino nitrogen atom, *d*(N–H$^+$···N). The IMHB distances *d*(N–H$^+$···N) fall within 1.409–1.717 Å (average value 1.591 Å). Similar unsymmetrical IMHB was obtained for guanidine proton sponges **2**, **3**, **8**, and **17** (1.707, 1.725, 1.702, and 1.714 Å, respectively), whereas **1** itself has somehow shorter IMHB [*d*(N–H$^+$···N) = 1.493 Å].

The IMHB angles *α*(N–H$^+$···N) listed in Table S2 (Supporting Information) fall within 157.8–179.4° (average value is 166.5°). Similar values were calculated for **3** (154.7°) and **17** (156.8°), whereas **2** has less linear IMHB [*α*(N–H$^+$···N) = 142.5°]. For comparison, the linearity of the IMHB of the classical proton sponge **1** is 170.5°.

The contraction of the *d*(NN) distance upon protonation for studied molecules is within values of 0.062–0.404 Å.

These values are similar to those calculated for other proton sponges. For comparison, the corresponding value for the proton sponge **1** is 0.285 Å, whereas for **2** and **3** the *d*(NN) contraction is 0.152 and 0.141 Å, respectively. Less pronounced was the concomitant contraction of $d(C^3C^{13})$ (distance of carbon atoms upon which guanidine functionalities are attached) with an average value of 0.048 Å.

There is no obvious trend observed between the basicity and geometrical parameters around IMHB, which indicates that the other stereoelectronic effects are also important in defining the final basicity. For instance, the shortest $d(N\text{–}H^+\cdots N)$ value calculated is 1.409 Å for molecule **36**, which is associated with one of the highest $APA_{B3LYP(2)}$ values of all the bases calculated (283.3 kcal mol^{-1}). Similarly, the largest linearity of IMHB is obtained for bases **45** and **46** [$a(N\text{–}H^+\cdots N)$ = 179.4 and 178.5°, respectively] and is associated with moderate basicity [$APA_{B3LYP(2)}$ = 264.3 and 265.2 kcal mol^{-1}, respectively].

Another point of interest is the degree of pyramidalization (DP) of 2-imidazolidinylidene nitrogen atoms. This was estimated as the deviation of the three bond angles around N atoms from the full angle.[24] It was found that the DP values for N(1) and N(3) atoms on the protonated guanidine moiety in **18H⁺** are very small, at 6.9 and 6.6%, respectively, which indicates that the protonation causes both N atoms to become planar, thus allowing for a strong delocalization effect. This is also obvious from the C–N=, N=C_2 and C–N_1(N_3) bond lengths, which changed upon protonation by roughly 0.01, 0.05 and 0.06 Å, respectively. On the other hand, a higher DP was calculated for the N(1) and N(3) atoms on the neutral guanidine moiety in **18H⁺**, at 15.4 and 9.1%, respectively, which indicates a smaller extent of planarization. The average pyramidalization of the guanidino N(1) and N(3) atoms in the parent neutral compound is higher, 10.8%. Structural analysis indicates that the DP is strongly affected by the imposed ring strain of the imidazolidinylidene moiety, not allowing full planarization upon protonation.

The most important geometrical changes induced by protonation is delocalization and "partial protonation" of the second guanidine moiety. Delocalization is clearly shown by the Δ_{CN} values[25] [measure of delocalization, defined as $d(C\text{–}N_{single}) - d(C\text{–}N_{double})$], for which values generally fall in the range of 0 Å (for a fully delocalized system) to <0.14 Å (for localized bonding). The Δ_{CN} values calculated for the protonated guanidino group of **18H⁺** are smaller than that of the neutral precursor **18** (Δ_{CN} = 0.034, and 0.145 Å, respectively), which is in accord with the increase in delocalization upon protonation. The Δ_{CN} value of the second, formally neutral guanidino group in **18H⁺** is also smaller than that of the fully localized system **18** (Δ_{CN} = 0.091), which is consistent with some degree of delocalization attributed to the partial protonation of this moiety. The Δ'_{CN} value[15] (contribution of the lone pairs of the imidazolidinylidene N^1 and N^3 atoms to the overall bonding) for the protonated guanidine group of **18H⁺** (Δ'_{CN} = 0.015 Å) indicates a relatively low degree of lone-pair delocalization from the tertiary nitrogen atom. The Δ'_{CN} value is reduced for both guanidine moieties, as compared to neutral **18** (0.052 Å). The largest reduction in **18H⁺** is consistent with a greater contribution from the resonance form to offset the positive charge in this moiety. Partial protonation is indicated again in the neutral guanidine moiety of **18H⁺** (Δ'_{CN} = 0.034 Å). Finally, the larger ρ value[15,29] for the protonated guanidine group is consistent with more efficient delocalization (97.6%, i.e. the C=N bond length is equal to 97.6% of the average C–NR_2 bond length; in fully symmetrical guanidinium cations ρ = 1.00).[26] On the other hand, the ρ value for the neutral guanidino group in **18H⁺** is 93.8%, which is another piece of evidence for a lengthened C=N bond relative to that of **18** (ρ = 90.5%), and further structural evidence for the partial protonation of the second guanidino group.

Partial protonation of the second guanidine ring could be visualized by means of electrostatic potentials, which are plotted on the isodensity surface in **18H⁺** (Figure 3). Elec-

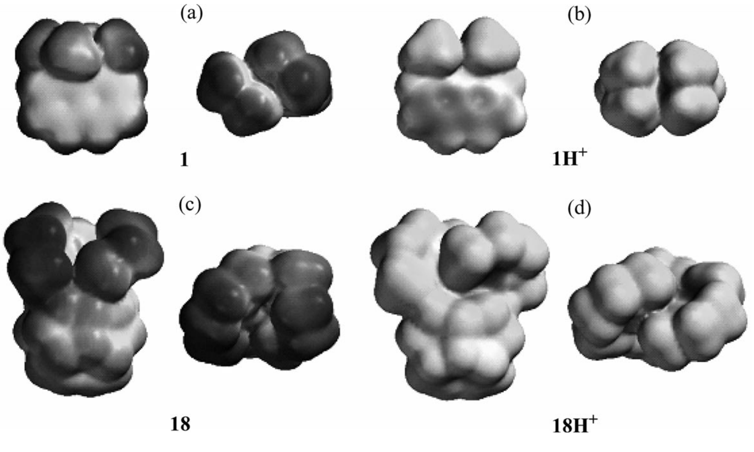


Figure 3. Electrostatic potentials of (a) **1**, (b) **1H⁺**, (c) **18**, and (d) **18H⁺** plotted on the isodensity surface (isodensity value = 0.002), front and back views.

trostatic potentials of **1H**$^+$, on the other hand, due to its more pronounced symmetrical structure features an equal distribution of positive charge over both dimethylamino groups. Similar information could be obtained from the sum of Mulliken atomic charges on neutral and protonated guanidine rings.

Calculated Proton Affinities in the Gas Phase and in Acetonitrile Solution

Proton Affinities in the Gas Phase

The results of calculated proton affinities for neutral organic bases **18**–**46** are given in Table 1. We shall commence the discussion with bis(guanidine) **18**, which possesses a 3-*syn*,13-*syn*-disubstituted bis(secododecahedrane) molecular scaffold to which (1,3-dimethylimidazolidin-2-ylidene)amino groups are attached. This compound that we will use throughout the section as a reference has an extraordinarily high *APA* value of 288.7 [287.6] kcal mol^{-1} as obtained by the B3LYP(2) [B3LYP(1)] methods and gas-phase basicity [*GB*] of [284.3] kcal mol^{-1}. The corresponding $APA_{\mathrm{B3LYP(2)}}$ and [*GB*] values for other studied systems shown in Scheme 3 are lower, with the exception of **26** at 293.4 [284.6] kcal mol^{-1}, which implies that the tetrasila-6,7,16,17-bis(secododecahedrane) skeleton of **26** enhances proton affinity and basicity by 2.3 [0.3] kcal mol^{-1}.

Replacement of the dimethylamino group of **19** with an intrinsically more basic (1,3-dimethylimidazolidin-2-ylidene)amino group causes an incremental increase of $APA_{\mathrm{B3LYP(2)}}$ [*GB*] by 22.6 [23.7] kcal mol^{-1}, whereas the replacement of the 1,8-naphthalene molecular scaffold of **3** by a 3-*syn*,13-*syn*-bis(secododecahedrane) skeleton accounts for an impressive 25.4 [26.6] kcal mol^{-1} increase. The remarkable $APA_{\mathrm{B3LYP(2)}}$ value of 288.7 kcal mol^{-1} for **18** represents the highest proton affinity obtained for any of the aliphatic guanidine proton sponges reported so far, including those of Ganguly[11,12] and Estrada.[27]

The geometrical alterations of the bis(secododecahedrane) molecular scaffold showed a small decrease in proton affinities, while being still very potent superbases. For instance, the [1.1.1.1]pagodane scaffold of **21** (**22**) provides a less basic proton sponge, as well as introduction of the C=C bonds at 1,11- or 5,15-positions in **24** and **25** [bis(secododecahedradienes)]. Similarly, the introduction of single bonds in the bis(secododecahedrane) skeleton (molecular scaffolds **45** and **46**) decreases the *APA* values. In addition, replacement of carbon atoms with nitrogen (molecules **27** and **29**), oxygen (**28**), or silicon (**26** and **30**) atoms decreases their basicity. Contrary to our expectations, the introduction of substituents next to the guanidine moiety did not contribute to increased basicity by a "buttressing effect".[28] Instead, a significant decrease of proton affinities was calculated for **40**, **41**, and **42**, which possess methyl, *tert*-butyl, and phenyl substituents. The inspection of their geometrical features indicates that the steric congestion decreases the overall stabilization of the protonated bases.

When additional functional groups with the ability to form an intramolecular hydrogen bond were added at the N^1 position of guanidines **33**, **34**, **35**, **36**, and **38**, geometrical constraints suppressed their involvement in the stabilization of the positive charge in the centre of two imino nitrogen atoms; therefore, a decrease in the *APA* value was obtained.

Forcing the two guanidine imino nitrogen atoms to a closer position by the alkane tether in proton sponges **31** and **32** effectively reduced the proton affinity, presumably by the introduced additional ring strain and the constrained rotational flexibility of the two guanidine moieties.

An interesting observation was made by the comparison of the *APA* values of **18** and **20**, the latter being less basic. It is an opposite effect relative to the one found when the guanidine moiety of the proton sponge is incorporated in a five-membered ring, such as in bis(dimethylethyleneguanidino)naphthalene **3**. It has been shown for **3** to be less basic than the TMGN (**2**) counterpart by experiment and calculations.[29] The decrease of basicity of **3** is the consequence of constraints imposed by the geometry of the five-membered imidazoline ring. In **2**, dimethylamino groups are conformationally less constrained and thus are in better conjugation with the CN_3 unit. It was found that the proton environment in protonated **18** is sterically less crowded than that of **20**. This trend is in accord with the common view that steric crowding reduces the kinetic activity of proton exchange.[29]

A further increase of basicity could be achieved by the introduction of more basic nitrogen atoms, such as P^1-phospazene and cyclopropyl guanidines. When (1,3-dimethylimidazolidin-2-ylidene)amino guanidine groups were replaced by extended π-electron systems possessing guanidine and cyclopropenimine structural subunits devised by Maksić [cyclopropyl guanidine itself has a $PA(\mathrm{HF_{SC}})$ value of 280.1 kcal mol^{-1}],[30] extraordinarily high $APA_{\mathrm{B3LYP(2)}}$ [*GB*] values were calculated for superbase **44** (316.3 [313.8] kcal mol^{-1}). These $APA_{\mathrm{B3LYP(2)}}$ [*GB*] values are over 10 kcalmol^{-1} higher than those we recently reported for bis(guanidine) proton sponges.[14] For P^1-phosphazene proton sponge **43**, excessively high $APA_{\mathrm{B3LYP(2)}}$ [*GB*] values were obtained, (296.2 [291.2] kcal mol^{-1}), which is comparable to those of **26**. Their B3LYP/6-31G*-optimized structures are depicted in Figure 4. These extraordinary basicity values approaching 300 kcal mol^{-1} are comparable to those calculated by Maksić for azacalix[3](2,6)pyridines {calcd. $APA_{\mathrm{B3LYP(2)}}$ [*GB*] are 296.6 and [291.3] kcal mol^{-1}}[31] or calculated and measured by Koppel and Schwesinger of P^1-triguanidinophosphazenes $\{[(H_2N)_2C{=}N]_2C{=}N\}_3P{=}NH$ (*GB* = 296.2, *PA* = 302.3 kcal mol^{-1}, B3LYP/6-311+G**),[32] and $[(H_2N)_3P{=}N]_2P(NH_2){=}CH_2$ (*GB* = 288.6, *PA* = 295.0 kcal mol^{-1}, B3LYP/6-311+G**).[33]

Calculation of *APA* values by using the M052X/6-31G* method [$APA_{\mathrm{M052X(1)}}$] gives similar basicity trends as obtained with the B3LYP/6-31G* method (Table 1). We came to an identical conclusion for the performance of the M052X/6-31G* method in basicity calculations for our previous paper.[14]

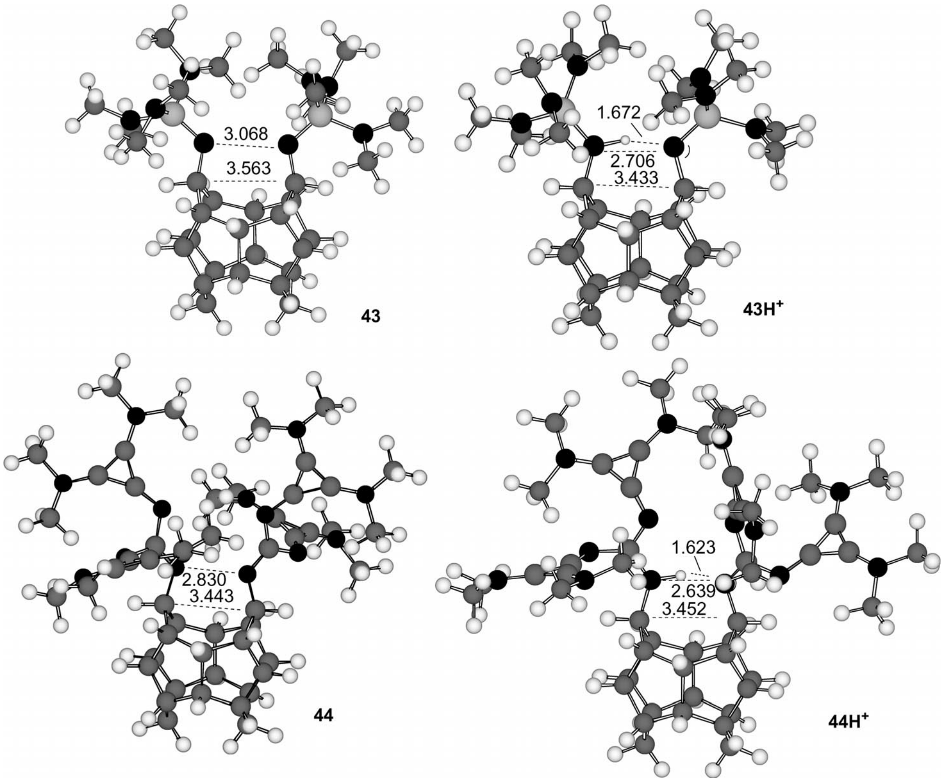


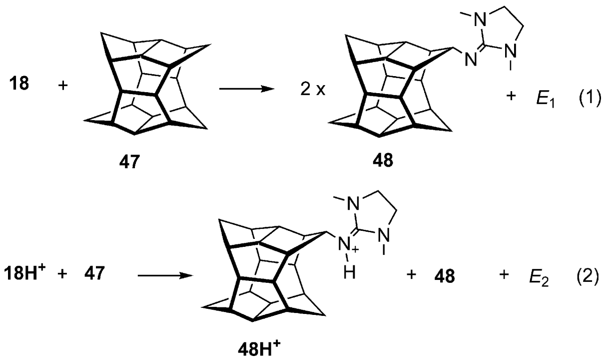
Figure 4. B3LYP/6-31G*-optimized structures of **43** and **44** and their protonated forms **$43H^+$** and **$44H^+$** (distances are given in Å, angles in °).

Calculated Proton Affinities in Acetonitrile Solution

The basicity in solvents, such as MeCN, can be studied by using the isodensity polarized continuum model (IPCM). The calculations of pK_a values in MeCN (ε = 36.64) with the B3LYP/6-311+G**//B3LYP/6-31G* model are listed in Table 1. Estimated pK_a(MeCN) values in acetonitrile obtained by the IPCM/6-311+G**//B3LYP/6-31G* method for the series of molecules in Table 1 are within the range of 27.0–38.7. Value for bis(guanidine) **18** exceeds that of **1** by 20 orders of magnitude. The most remarkable are pK_a(MeCN) values calculated for superbases **43** and **44** (40.5 and 46, respectively) exceeding those of most of the known superbases. Comparable very large solution basicity data include naphthalene guanidinophosphazene sponge **5** [calcd. values: $APA_{\mathrm{B3LYP(2)}}$ = 305.4 kcal mol^{-1}, pK_a(MeCN) = 44.8],[8] P^3-phosphazenes[34,35] [exptl.: pK_a(MeCN) = 38.6], P^4*t*Bu-phosphazene [calcd.: APA_{MeCN} = 322.0 kcal mol^{-1}, pK_a(MeCN) = 43.0 (exptl. 42.7)],[36] and azacalix[3](2,6)pyridines [calcd.: APA_{MeCN} = 304.8 pK_a(MeCN) = 30.9].[37] In addition, absolute proton affinities, which are calculated in MeCN [*APA*(MeCN)], could also be used as an indicator of relative basicity. These values are obtained for the pK_a(MeCN) calculations (at 0 K) and are generally larger by 30 kcal mol^{-1} than gas-phase calculations (exceeding 300 kcal mol^{-1}), whereas the relative basicity order remained almost unchanged (see Table S3 in the Supporting Information).

Contributing Factors to Overall Basicity

The calculations of homodesmotic reactions (shown in Scheme 4) help us to estimate the relative contributions of the factors influencing the high basicity of the studied molecules (Table 1).[29] For this purpose, reaction (a) gives an estimate of the repulsive interactions (lone pair and steric repulsions) present in the neutral form of base, whereas reaction (b) gives an estimate of the IMHB strength. The obtained E_1 and E_2 values for **18** are 23.5 and –14.5 kcal mol^{-1}, respectively, which indicates an important energetic contribution from a decrease in repulsive interactions and stabilization of the system after protonation. In a similar manner, repulsive contributions and the strength of IMHB were estimated for superbases **18**–**46**. Comparison of these results to the values of **2** (E_1 = 0.7, E_2 = 11.8 kcal mol^{-1}) indicates the presence of larger repulsive (steric) interactions in bis(secododecahedrane) systems. The decrease of the steric interactions on going from sterically more demanding **18**, to **20**, to **19** is evidenced by the reduction of the E_1 values (23.5, 16.6, and 14.1 kcalmol^{-1}, respectively). In the bis(secododecahedrane) proton sponges studied, relatively strong IMHB is present (for published diamines, the IMHB contribution to the *APA* is within the values of 10–27 kcal mol^{-1}).[15,13] This fact is corroborated by effective stabilization upon protonation, which is associated with the linearity of their IMHB [i.e. $\alpha(\mathrm{N{-}H^+{\cdots}N})$ angles]. From the analysis of homodesmotic reactions (a) and (b) it may be concluded that a subtle interplay between repulsive interactions and stabilization of the system upon protonation controls the basicity of these compounds.



Scheme 4. Homodesmotic reactions setup to obtain strain energies for unprotonated compounds (a) and to obtain an estimate of IMHB strength (b).

The performance of the M052X/6-31G* method to the calculation of homodesmotic reactions (a) and (b) was also tested. This DFT method was shown by Schreiner to give better energy results.[38] Computation of several homodesmotic reactions indicated that, although the absolute numbers changed, the contributing factors to overall basicity identified by the B3LYP method remained (see Table S3 in the Supporting Information). This finding is in accord with our previous results[14] and could be due the fortuitous cancelation of the B3LYP errors.

Kinetic Activity

Exceptional basicity of organic superbases is associated with their high kinetic activity in proton-exchange reactions. The kinetic activity of bis(guanidine) system **19** is estimated by the calculated low barrier of intramolecular proton transfer (PT) in **19H$^+$**. The gas-phase barrier for proton transfer corrected with a zero-potential vibrational energy value (calculated as the difference in electronic energy between the transition state and the equilibrium ground state at the B3LYP/6-31G* level) for **19H$^+$** is 4.8 kcal mol^{-1}. Furthermore, the transition-state energy calculated for the proton transfer from an external molecule of HCl to **19** at the B3LYP/6-31G* level is 37.1 kJ mol^{-1}, which corroborates well the values obtained for the corresponding proton sponges **1** and **9** (43.0 kJ mol^{-1}), the kinetic activities of which were predicted.[13]

Conclusions

On the basis of B3LYP/6-31G* calculations, it was found that 3,13-disubstituted bis(secododecahedrane) is an ideal molecular scaffold for the construction of highly basic proton sponges. For bis(guanidine) substitution, their basicities in the gas phase and in acetonitrile solution exceed the previously known aliphatic guanidine superbases. Factors responsible for high basicity are the combination of destabilizing steric and electrostatic imino nitrogen lone pair repulsions in the ground state and the repulsion decrease upon protonation by strong intramolecular hydrogen bonding in conjunction with effective cationic stabilization.

Computational Details

All geometrical optimizations were carried out by employing the B3LYP hybrid functional DFT method (Becke's 3-parameter functional with the nonlocal correlation provided by the expression of Lee et al.)[39] with the 6-31G* basis set. Calculations were performed by using the Gaussian 03 suite of programs,[40] implemented on a dual-core Opteron 240 personal computer under a Linux operating system and computer cluster Isabella at the Computing Center of the University of Zagreb, Isabella Computer Cluster (24 dual processor HP ProLiant BLP20p nodes with Intel Xeon 2.8 GHz, 32 dual processor Dell 1850 1 U nodes with Intel Xeon 3.4 GHz and 24 dual processor Pyramid GX28 nodes with AMD Opteron 248). Harmonic vibration frequencies were calculated for all localized stationary structures to verify whether they are minima or transition states. Single-point calculations were conducted by using the B3LYP/6-311+G**//B3LYP//6-31G* method, and the gas-phase basicities (*GB*) were calculated as the Gibbs free energy change of the protonation reaction and corrected to 298 K. The B3LYP/6-311+G**//B3LYP//6-31G* approach was used instead of the computationally more expensive B3LYP/6-311+G**//B3LYP//6-311+G** method; however, it was shown by Maksić that this method gives results of sufficient accuracy.[8] Throughout the manuscript, B3LYP(1)[41] denotes B3LYP/6-31G*+E_{vib}(B3LYP/6-31G*), whereas B3LYP(2)[43] denotes the *APA* obtained at the B3LYP/6-311+G**//B3LYP/6-31G*+E_{vib}(B3LYP/6-31G*) level. The solvent effect in acetonitrile was estimated by employing the polarized continuum model at the IPCM/B3LYP/6-311+G**//B3LYP//6-31G* level.[42] The molecular surface determining a cavity within a solvent is obtained by the isodensity shell of 0.0004 eB^{-3}, thus giving rise to the IPCM[43] utilizing the dielectric constant for acetonitrile $\varepsilon = 36.64$. The absolute proton affinities of guanidines in the gas phase [$APA_{\mathrm{B3LYP(2)}}$] were calculated by using Equations (1), (2), and (3) described by Maksić and Kovačević:[44]

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

$$\Delta E_{\mathrm{el}} = E(\mathrm{B})_{\mathrm{B3LYP(2)}} - E(\mathrm{BH}^+)_{\mathrm{B3LYP(2)}} \tag{2}$$

$$\Delta ZPVE = ZPVE(\mathrm{B})_{\mathrm{B3LYP}} - ZPVE(\mathrm{BH}^+)_{\mathrm{B3LYP}} \tag{3}$$

Here, B3LYP denotes the B3LYP/6-31G* level, whereas B3LYP(2) is the B3LYP/6-311+G**//B3LYP/6-31G* model; *ZPVE* = zero-point vibrational energy. These values are corrected to 298 K. The estimation of *APA* and pK_a values in acetonitrile was achieved by using Equations (4), (5), (6), and (7).[45] Equation (4) was derived from the calculated data (B3LYP/6-311+G**) for a large set of related guanidine bases and shows an excellent correlation with the experimetnal pK_a values.

$$\mathrm{p}K_\mathrm{a} = 0.4953PA(\mathrm{B}_\mathrm{MeCN}) - 119.7 \qquad (4)$$

$$PA(\mathrm{B}_\mathrm{MeCN}) = \Delta E_\mathrm{el\ MeCN} + \Delta ZPVE_\mathrm{B3LYP} \qquad (5)$$

$$\Delta E_\mathrm{el\ MeCN} = E(\mathrm{B})_\mathrm{MeCN} - E(\mathrm{BH}^+)_\mathrm{MeCN} \qquad (6)$$

$$\Delta ZPVE_\mathrm{B3LYP} = ZPVE(\mathrm{B})_\mathrm{B3LYP} - ZPVE(\mathrm{BH}^+)_\mathrm{B3LYP} \qquad (7)$$

In these equations, MeCN denotes the IPCM/B3LYP/6-311+G**//B3LYP/6-31G* model and B3LYP denotes the B3LYP/6-31G* method, hence APA_MeCN = IPCM/6-311+G**//B3LYP/6-31G* + E_vib(B3LYP/6-31G*).[46]

Supporting Information (see footnote on the first page of this article): Cartesian coordinates of all optimized structures.

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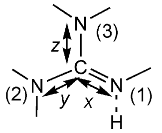

$\rho = 2x/(y + z)$
Δ_CN /Å = $y - x$
Δ'_CN /Å = $z - [(x + y)/2]$

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