Design of New Scaffolds for Increased Superbasicity of Bisguanidine Proton Sponges

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New polycyclic molecular scaffolds for anchoring guanidines were designed and studied by computational methods (DFT). Amongst them, the attachment of guanidine fragments to the 7,12-dihydropleiadene-7,12-diamine framework effectively increases superbasicity of novel bisguanidine proton sponges to the estimated absolute proton affinity of 281 kcal mol^{-1} at the B3LYP/6-31G* level.

Design and synthesis of novel, neutral organic superbases represents a highly important area of organic chemistry nowadays.[1] Many efforts have been put into development of basic fragments, which can be put together to enhance basicity of such systems.[2–4] The systems widely explored are "proton sponges," in which the two basic centers are brought to the close proximity by rigid framework.[5] Strong lone-pair repulsion in these systems, in conjuction with a strong intramolecular hydrogen bonding (IMHB) upon protonation are the key factors for their extraordinary basicity.

The aim of this study was to design novel bisguanidine superbase systems of enhanced basicity. As practical organic chemists, with a view on the synthesis of novel bisguanidine proton sponges, we limited this computational study to a selected, simple molecular framework known in the literature. Synthesis of the appropriate diamino framework could be then effectively completed in one step by guanidination with 2-chloro-1,3-dimethylimidazolium chloride (DMC) reagent[6] to obtain 1,3-dimethyl-2-imidazolidinylidene functionality.

Computational Details

Geometry optimizations of molecules given in Chart 1 were carried out employing B3LYP/6-31G* and M052X/6-31G* methods, followed by single point energy estimations at B3LYP/6-311+G** and M052X/6-311+G** level, using the Gaussian03[7] suite of programs. Absolute proton affinities (APA) and gas phase basicities (GB) were then estimated using standard computational procedures and results compiled in Table 1. For easier comparison with literature data, $APA_{B3LYP(1)}$ will be commented throughout the paper, while the other values are given in Table 1. The $APA_{B3LYP(s)}$, GB_{B3LYP}, and GB_{M052X} values follow the same basicity trend, with absolute numbers differing by 2–5 kcal mol^{-1}. Selected geometric parameters of protonated bases are given in Table 2. Detailed comments on less successful structural variations and substitutions are out of the scope of this communication.

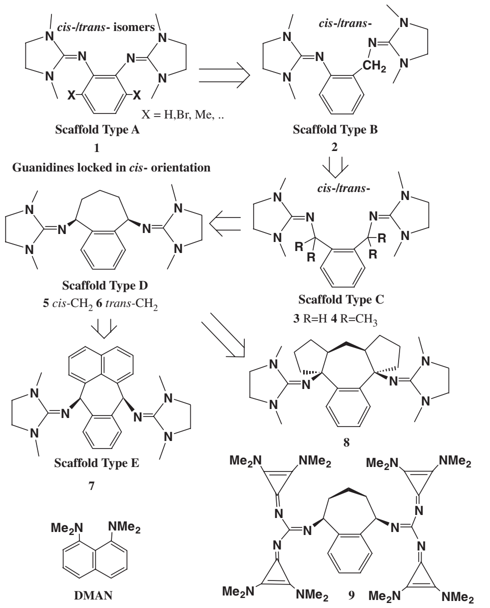

Chart 1. Development of new bisguanidine scaffold systems.

Table 1. Absolute Gas Phase Proton Affinities and Basicities (in kcal mol^{-1})

Molecule	$APA_{B(1)}$$^{a)}$	$APA_{B(2)}$$^{b)}$	$GB_B$$^{c)}$	$APA_{M(2)}$$^{d)}$	$GB_M$$^{e)}$
2	263.9	259.7	257.6	259.0	256.1
3	269.1	262.1	262.4	260.1	259.5
4	267.1	265.1	262.3	262.3	258.7
5	278.7	275.8	273.9	275.4	271.3
6	273.0	268.8	266.7	270.3	268.2
7	280.9	277.0	274.0	276.0	274.6
8	281.1	278.4	275.0	278.5	275.3
9	308.8	303.7	302.7	309.5	306.4

a) $APA_{B3LYP(1)}$: B3LYP/6-31G*+E_{vib}(B3LYP/6-31G*).[8] b) $APA_{B3LYP(2)}$: B3LYP/6-311+G**//B3LYP/6-31G* + E_{vib}(B3LYP/6-31G*).[9] c) B3LYP/6-31G*.[10] d) $APA_{M052\times(2)}$: M052X/6-311+G**//M052X/6-31G* + E_{vib}(M052X/6-31G*) e) M052X/6-31G*.

Results and Discussion

Conceptual development of novel scaffolds for superbasic bisguanidines is given in Chart 1. As starting point, *N*,*N′*-bis(1,3-dimethyl-2-imidazolidinylidene)-*o*-benzenediamine (*o*-bis(diaminomethyleneamino)benzene) **1** was used, which we studied previously (Chart 1, scaffold type **A**).[11,12] The MP2 and RHF/6-31G* quantum-chemical calculations indicated that these compounds belong to the lower part of the superbasicity scale ($APA_{B3LYP(1)} = 254.3–262.8$ kcal mol^{-1}). One of the main reasons for their low basicity is the geometric environment which does not allow effective intramolecular hydrogen

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Table 2. Selected Geometrical Parameters for Protonated Forms of Bases **2**–**9**[a)]

Molecule	*d*(NN)	*d*(N–H)	*d*(N–H$^+$···N)	α(N–H$^+$···N)
2	2.771	1.026	2.019	52.0
3	2.787	1.046	1.810	26.1
4	2.650	1.055	1.653	24.4
5	2.785	1.048	1.794	23.7
6	2.751	1.047	1.786	28.7
7	2.713	1.052	1.714	23.2
8	2.761	1.044	1.810	30.1
9	2.878	1.041	1.915	27.7

a) B3LYP/6-31G*.

bonding (IMHB). The other reason lies in the lower basicity of guanidine imino nitrogen attached to the phenyl substituent than the benzylic one, by approximately 5 kcal mol^{-1}.[13]

Hence, the insertion of one methylene group in scaffold type **B** (molecule **2**) has been beneficial for the increase of the APA to 263.9 kcal mol^{-1}. Further increase of APA was predicted for the second methylene group insertion in scaffold type **C** (with APA$_{\mathrm{B3LYP(1)}}$ values from 265.1 to 269.1 kcal mol^{-1} for **3**). These values are significantly higher than 1,8-bis(dimethylamino)-naphthalene (DMAN). Introduction of steric strain via methyl groups in **4** (butressing effect)[1] reduces APA to 267.1 kcal mol^{-1}. It should be noted at this point that all molecular scaffolds computed so far (**A**–**C**) feature conformational flexibility of *cis*- or *trans*-orientations of two guanidine rings with respect to the central aromatic scaffold. This issue could be resolved by the locking of benzylic positions by the trimethylene bridge in scaffold type **D**.[14] In such a molecular system, the rotational flexibility around the C–N bond required for basicity increase is preserved, while the only existing isomers are *cis*/*trans* of propane group in the respect to the guanidine rings. More important for this study is the fact that propane ring brings closer together two imino nitrogens of guanidines (N–N distance contraction from 3.465 to 2.785 Å), therefore increasing APA. The remarkable APA of 278.7 kcal mol^{-1} was estimated for **5**, exceeding that of the scaffold type **C** by almost 10 kcal mol^{-1}. Results show that replacement of naphthalene in DMAN for scaffold type **C** increases APA by 11 kcal mol^{-1}. The APAs of scaffold type **C** with a CH_2 group in *cis*-position (as in **5**) are higher than for *trans*-isomers (such as molecule **6**, APA = 273.0 kcal mol^{-1}).

When the change to the scaffold type **D** was made, by replacement of the propane bridge by naphthalene, a scaffold type **E** is designed (i.e., 7,12-dihydropleiadene-7,12-diamine framework), molecule **7**. This framework is a synthetically achievable target starting from known 7,12-dihydropleiadene-7,12-dione.[15] DFT calculations of its molecular structure indicated that the 7,12-dihydropleiadene scaffold effectively constrains two imino nitrogens incorporated in 7,12-positions to the distance of 2.982 Å. More remarkable is the calculated APA for **7**. Extraordinary high basicity of 280.9 kcal mol^{-1} is calculated, which is one of the highest for bisguanidine proton sponges[1] and certainly the highest for the synthetically achievable molecule. A comparison of APA with the DMAN indicates an increase by an extraordinary value of 17 kcal mol^{-1} for the replacement of the 1,8-naphthalene scaffold by the 7,12-dihydropleiadene (with NMe_2 functionalities), and the further increase to the total of 26 kcal mol^{-1}, when guanidine groups are attached. As expected, the more basic, 4,5-unsaturated variant of 1,3-dimethyl-2-imidazolidinylidene raises basicity of **7** to 285.4 kcal mol^{-1}.

Further alterations of the scaffold type **E** by introduction of bulky substituents at the 7,12-positions are counterproductive, leading to proton sponges of lower basicity. Amongst the large number of scaffold variants of types **D** and **E** and substitution patterns which were taken into consideration, only the scaffold type **D** with two additional cyclopentane rings (molecule **8**) had APA value which is comparable to that of scaffold type **E** (281.1 kcal mol^{-1}). Results also show that replacement of naphthalene scaffold in DMAN for scaffold type **D** in **8** increases APA by 16 kcal mol^{-1}. However, the synthetic value of this polycyclic scaffold system is diminished by the fact that it is synthetically yet unknown.

Certainly, the theoretical value of newly designed proton sponge scaffold **E** lies in the fact that 1,3-dimethyl-2-imidazolidinylideneimine could be in theory replaced by intrinsically more basic nitrogen atoms such as polyguanidines, phosphazenes, or guanidinophosphazenes.[1] To illustrate this point, we calculated the APA of the molecule **9**, where the more basic 1,3-bis[2,3-bis(dimethylamino)cyclopropenylidene]guanidine[16] moiety was introduced. An extraordinary APA$_{\mathrm{B3LYP(1)}}$ value of 308.8 kcal mol^{-1} is obtained. Calculated GB value of **9** is also extremely high (302.7 kcal mol^{-1}). In addition, estimated APA in solution (acetonitrile, APA$_{\mathrm{MeCN}}$, by IPCM/6-311+G**//B3LYP/6-31G*) also exceeds 300.8 kcal mol^{-1}, while the calculated[17] p$K_{\mathrm{a(MeCN)}}$ is 29.3 units. These values exceed those of most of the known superbases.

Geometric features of protonated forms of proton sponges listed in Chart 1 are given in Table 2, with the most indicative being the N–N distance between two imino nitrogens. The smallest *d*(NN) is calculated for molecule **4** (2.650 Å), which is not directly associated with the largest APA. The reasons for large basicity of novel proton sponges are studied and results for molecule **7** are given in this paper for illustration. Conclusions based on analysis of geometric changes caused by protonation and the consequence to basicity apply to highly basic systems **5**, **7**, and **8**.

All calculated protonated forms of bases possess an unsymmetrically positioned proton, as shown by the distances between H$^+$ and neighboring imino nitrogen, *d*(N–H$^+$···N). For an illustration, the B3LYP/6-31G* optimized structure of **7** and its protonated form **7H**$^+$ is given in Figure 1. The protonated forms, where H$^+$ is positioned in the middle between two imino nitrogens, are calculated to be transition states, with a very low energy barrier of H$^+$ transfer (fast exchange) between two nitrogens (1–2 kcal mol^{-1}).

Very large intrinsic basicity of **7** is associated with the linearity of its IMHB (the N–H$^+$···N angle of 23.2°), indicating effective stabilization upon protonation. This fact is corroborated by the calculations of homodesmotic reactions[2] (Scheme 1), which help to estimate the relative contributions of the factors influencing the high basicity. Here, reaction (1) gives an estimate of the repulsive interactions (lone pair and steric repulsions) present in the neutral form of base, while reaction (2) gives an estimate of IMHB strength. Obtained E_1

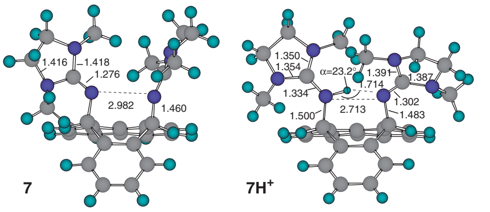
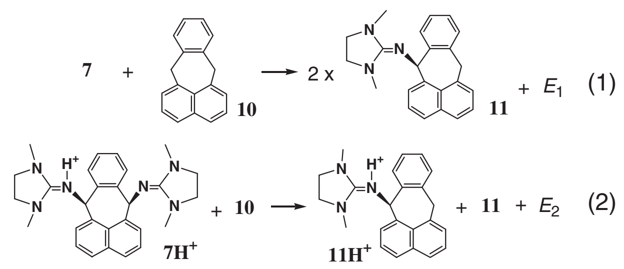


Figure 1. Neutral and protonated structures of **7**.



Scheme 1. Homodesmotic reactions (1) and (2).

and E_2 M052X [and B3LYP] values for **7** are 12.2 [10.3] and 14.7 [11.3] kcal mol^{-1}. In a similar manner repulsive contributions and the strength of IMHB were estimated for superbase **8** ($E_1 = 12.4$ [17.5], $E_2 = 12.2$ [8.3] kcal mol^{-1}). Comparison of the E_1 and E_2 values for **7** and **8** with those of 1,8-bis[bis(dimethylamino)methyleneamino]naphthalene[18] indicates that in the case of **7** and **8** strong IMHB is present, while the neutral systems possess significant repulsive interactions.

The most important geometric changes induced by protonation are as follows. Effective planarization of guanidine moiety upon protonation is indicated by degree of planarity (DP)[19] for imino and tertiary nitrogen atoms in **7H**$^+$. On the protonated guanidino group DPs are very small (2.6 and 8.8°, respectively), while DP of pyramidal tertiary N atom of the neutral guanidino group is much larger (15.2°). In addition, the Δ_{CN} values[2] (measure of delocalization) calculated for the protonated guanidino group of **7H**$^+$ are smaller than that of the neutral precursor **7** ($\Delta_{\mathrm{CN}} = 0.018$, and 0.136 Å, respectively), which is in accord to the increase in delocalization upon protonation. The Δ_{CN} value of the second, formally neutral guanidino group in **7H**$^+$ is also smaller than that of the fully localized system **7**, which is consistent with some degree of delocalization attributed to the "partial protonation" of this moiety. The Δ'_{CN} value[2] (contribution of the lone pair of (amino) N atoms to the overall bonding) for protonated guanidine group of **7H**$^+$ ($\Delta'_{\mathrm{CN}} = 0.012$ Å) indicates a relatively low degree of lone-pair delocalization from the tertiary nitrogen. The Δ'_{CN} value is reduced for both guanidine moieties, as compared to neutral **7** (0.076 Å). The largest reduction in **7H**$^+$ is consistent with 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 **7H**$^+$ ($\Delta'_{\mathrm{CN}} = 0.047$ Å). Finally, the larger ρ value[2] for the protonated group is consistent with more efficient delocalization (98.7%), i.e., C=N bond length is equal to 98.7%, of the average C–NR$_2$ bond distance. On the other hand, the ρ value for the neutral guanidino group is 93.7%, which is another evidence of a lengthened C=N bond compared to **7** ($\rho = 90.3\%$), and further structural evidence for the partial protonation of the second guanidino group.

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