JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2002; **15**: 765–774
DOI: 10.1002/poc.552

The intramolecular hydrogen bond and intrinsic proton affinity of neutral organic molecules: *N,N′,N″*-tris (3-aminopropyl)guanidine and some related systems[†]

Borislav Kovačević,[1] Zoran Glasovac[2] and Zvonimir B. Maksić[1,3]*

[1]Quantum Organic Chemistry Group, Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, P.O. Box 180, 10002 Zagreb, Croatia
[2]Laboratory for Physical Organic Chemistry, Division of Organic Chemistry and Biochemistry, "Ruđer Bošković" Institute, P.O. Box 180, 10002 Zagreb, Croatia
[3]Faculty of Natural Science and Mathematics, University of Zagreb, Marulićev trg 19, 1000 Zagreb, Croatia

Received 9 April 2002; revised 10 July 2002; accepted 13 July 2002

ABSTRACT: Multiple aminopropyl substitutions of the initial *N*,*N′*,*N″*-trimethylguanidine lead to high intrinsic absolute proton affinities (*APA*) and basicities culminating in $APA = 268.4$ kcal mol^{-1} (1 kcal = 4.184 kJ) in *N*,*N′*,*N″*-tris(3-aminopropyl)guanidine (**9**). The reason behind a high proton affinity is identified as a strong cationic resonance in the central guanidine moiety and the strength of the intramolecular hydrogen bonding (IMHB), which is enhanced upon protonation. A cooperative IMHB effect in **9** and **9H**$^+$ realized by three N(sp^3)H···N(sp^3) H-bridges is estimated to be as high as 14.7 and 33.0 kcal mol^{-1}, respectively. It follows that the IMHB effect contributes 18.3 kcal mol^{-1} to the absolute proton affinity of **9**, which is a respectable amount. The basicity of **9** in acetonitrile is estimated to be very high, as evidenced by the corresponding p$K_a = 28.8$. A derivative of **9**, *N*,*N′*,*N″*-tris(3-dimethylaminopropyl)guanidine (**10**), assumes an even higher superbasic proton affinity of 275 kcal mol^{-1} due to an additional relaxation effect caused by the methyl groups. The corresponding pK_a(MeCN) = 29.4. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: basicity; proton affinity; proton sponges; superbases

INTRODUCTION

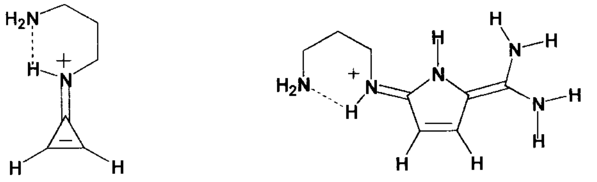
The proton and its reactivity are the central theme in acid–base chemistry and biochemistry.[1–3] It is, therefore, not surprising that a lot of research interest has been devoted to proton affinity, basicity and proton transfer reactions in the last two decades. However, the proton is also a useful probe of the electronic structure of molecules and the simplest model for studying the electrophilic reactivity of aromatic compounds.[4–7] It follows that the proton, despite its very small size, plays major role in a number of chemical phenomena. Recently, considerable emphasis has been laid on the strong organic bases and proton sponges in the gas phase, including acyclic and cyclic guanidines[8–11] and phosphazenes.[12–14] The subject has been covered by several extensive review articles lately.[15–21]

The role of intramolecular hydrogen bonding (IMHB) in determining the basicity of organic compounds was realized rather early. Yamdagni and Kebarle[22] measured the enthalpies of protonation of α,ω-diamines $NH_2(CH_2)_nNH_2$, $n = 2$–7, and found that they were consistent with the internally hydrogen-bonded cyclic structures of the ions. This 'internal (partial) solvation' led to increased basicity in the gas phase, provided that a substantial ring strain was absent. In contrast to the free molecule gas-phase case, the external solvent effect in solution may compete with the intramolecular functional groups and delocalize the positive charge of the protonated atom, thereby weakening its ability to take part in 'internal solvation.' A strong interference of internal and external solvation is expected in highly polar solvents such as H_2O.[23–25] An enhancement of gas-phase basicity by the IMHB cyclization in polyfunctional formamidines has been observed by Raczyńska *et al.*[26,27] It is plausible to expect that IMHB will play an important role in biologically pertinent molecules involving polyfunctional groups. Indeed, it was found that a stable six-membered ring cyclic structure is formed in the protonated histamine[28] and the protonated N^{α},N^{α}-dimethylhistamine.[29] Within this context, it should be mentioned that part of the high basicity of arginine is due to the 'internal solvation' of the guanidinium cation moiety according to a careful *ab initio* study by Maksić and Kovačević,[30] which confirmed earlier conjecture put forward by Raczyńska *et al.*[27] Recently, it was found that

---

*Correspondence to: Z. B. Maksić, Quantum Organic Chemistry Group, Division of Organic Chemistry and Biochemistry, 'Ruđer Bošković' Institute, P.O. Box 180, 10002 Zagreb, Croatia.
E-mail: zmaksic@spider.irb.hr

[†]This paper was presented at the ESOR 8 Conference in Cavtat, Croatia, 1–6 September 2001.



1 **2**

Scheme 1. The intramolecular hydrogen bond corona effect

the aminopropyl chain amplified basicity, if it was linked to the highly basic imine nitrogen, which in turn was a part of the molecular backbone undergoing aromatization upon protonation. As an illustration, we mention cyclopropenimine (**1**) and 2,5-dihydropyrrolimine (**2**) moieties as depicted in Scheme 1.

Protonation at the imine site closes up a pseudo-six-membered ring with the substituted nitrogen atom by formation of a relatively strong hydrogen bond, which stabilizes **1** by ~10 kcal mol^{-1} (Ref. 31) and system **2** by 8 kcal mol^{-1} (Ref. 32). This characteristic closure involving formally sp^3 atoms was termed the corona effect.[31,32] Since the loop starts and ends up with the same atom, it could be named as the *single-center corona effect*. To complete a brief survey of the role of IMHB in determining the high basicity of organic neutral compounds, one should mention the proton sponges, which found a wide range of applications in organic syntheses due to some advantageous features. The paradigmatic proton sponge 1,8-bis(dimethylamino)naphthalene (DMAN) (**3**) was synthesized ~30 years ago followed by its numerous off-spring later on[33–38] (Scheme 2).

The proton in the conjugate acid $\mathbf{3H}^+$ not only remedies the unfavourable electron pair repulsion, but forms in addition a farily strong hydrogen bond. Recently, Raab *et al.*[39] and Kovačević and Maksić[40] have shown that even more favourable IMHB effect can be obtained in 1,8-bis(tetramethylguanidino)naphthalene (TMGN) (**4**) and 4,5-bis(tetramethylguanidino)fluorene (TMGF) (**5**) (Scheme 2). The reason behind the stronger IMHB effect in **4** and **5** compared with DMAN was identified as an interesting additional *partial protonation* phenomenon in the guanidine group, which is not directly attached to the proton. Extension of this work to other compounds possessing different molecular backbones led to proton affinities as high as 268 kcal mol^{-1} and exhibiting basicity in acetonitrile around $\text{p}K_a = 29$.[41]

In this work, we examined the question of whether there are systems with a multiple corona effect unknown as yet, which might lead to compounds possessing very high basicities. Our investigations are related to the gas-phase case and to the liquid-phase case involving moderately polar solvents such as acetonitrile. The answer to the posed question is in the affirmative, as this paper conclusively shows.

COMPUTATIONAL METHOD

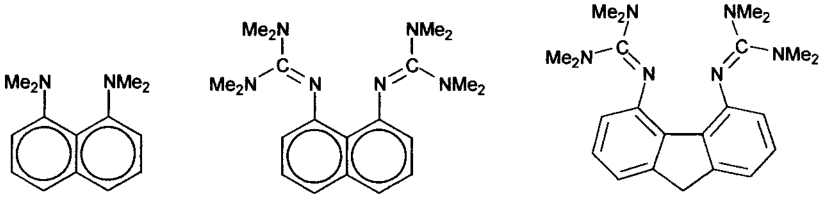
Absolute proton affinities (*APA*) in the gas phase are computed in the following standard way:

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

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

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

where B and BH^+ denote the base in question and its conjugate acid, respectively, and α signifies the site of proton attack. Equations (2) and (3) give the electronic and zero-point vibrational energy contributions to the proton affinity, respectively. A search of the Born–Oppenheimer energy hypersurfaces was 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 is 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 more flexible 6–311 + G** basis set, and that for reliable estimates of the proton affinity an explicit account of the correlation energy is needed at least to the level of Møller–Plesset (MP) perturbation theory of the second order. This gives rise to the MP2(fc)/6–311 + G**//HF/6–31G* + ZPVE(HF/6–31G*) model,[42] which offers a good compromise between accuracy and



3 **4** **5**

Scheme 2. Some proton sponges involving strong IMHB feasibility. It will be abbreviated hereafter as MP2. A somewhat less accurate but more efficient model is provided by the scaled Hartree–Fock scheme (HF_{sc}). It is based on very good correlation between the MP2 proton affinities and the difference in HF energies of a neutral base and its conjugate acid.[42,43] The corresponding equation for protonated nitrogens is

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

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 bases, which in turn is absorbed in the additive constant in Eqn. (4). It should be pointed out that, strictly, the proton affinity is defined as the enthalpy difference at 298 K between the interacting species (a base, proton and the conjugate acid). This includes an additional term [(5/2)*RT*] in Eqn. (1) appearing from the translational energy of the proton and the $p\Delta V$ contribution, if a plausible assumption is adopted that protonation does not change the heat capacity significantly. This additional term is unnecessary in our MP2 model, since the latter is selected in such way (by judicious choice of the basis set) that it reproduces the experimental data at room temperature with reasonable accuracy.

All computations were carried out using the Gaussian 94 program.[44]

RESULTS AND DISCUSSION

Structural features

The target system *N*,*N*′,*N*″-tris(3-aminopropyl)guanidine (**9**) is presented in Fig. 1 together with the parent *N*,*N*′,*N*″-trimethylguanidine (**6**) and its mono- and bisaminopropyl derivatives (**7** and **8**, respectively). The protonated forms are shown in Fig. 2. Systems **7** and **8** can exist in several tautomeric forms, since it is well known that guanidines possessing at least one hydrogen at the *N*-amino atom undergo prototropic tautomerism.[45] Finally, *N*,*N*′,*N*″-tris(3-dimethylaminopropyl)guanidine (**10**) is also considered, since a superbasic gas-phase proton affinity of over 270 kcal mol^{-1} is expected. We shall consider the structural features first. For this purpose it is useful to introduce an index called the degree of pyramidalization of the nitrogen atom [*DP*(%)]. It is defined as[30]

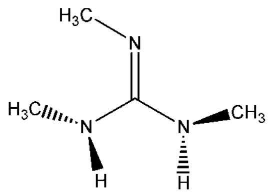
$$DP(\%) = \left[360 - \sum_{i=1}^{3} \alpha_i\right] / 0.9 \quad (5)$$

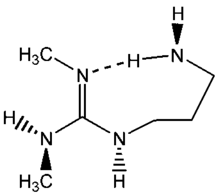
where the summation is extended over three bond angles of the apical nitrogen in question (in degrees).

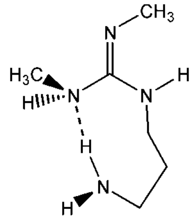
The characteristic bond distances of the parent compound **6** are given in Fig. 3. The central guanidine moiety is essentially planar. One can clearly distinguish between the double bond C=N and single bond C—N distances, the former being shorter by 0.12 Å. Protonation at imine site induces equivalence of all three CN bonds, which assume a distance of 1.326 Å. These bonds resonate strongly, as we have shown in a recent study of the basicity of polyguanides.[11] It appears that a strong cationic resonance is the main reason behind the high intrinsic proton affinity of the guanidine moiety contributing to proton affinity a fairly large energy. More specifically, it lies in the range 24–27 kcal mol^{-1}.[11] Needless to say, the guanidine skeleton remains planar in **6H**$^+$. It is interesting to note a relatively high pyramidalization of the amino groups in **6** (12 and 16%) and their perfect planarization upon protonation. Finally, the single C—N bond distance involving the former imino nitrogens increased to 1.460 Å in **6H**$^+$ due to rehybridization of the protonated nitrogen.

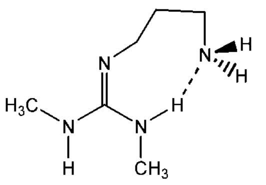
Next, we shall focus on the monoaminopropyl derivative **7** (Fig. 4). One should point out that the nitrogen atom substituted by the aminopropyl group is significantly planarized even in the initial base **7**. In contrast, the NH_2 group at the end of the aminopropyl chain is highly pyramidalized (34.3%). Since the aminopropyl chain is attached to the amino nitrogen and forms the IMHB with the imino nitrogen atom, the corresponding structural and electronic feature could be termed the *two-center corona effect*. Protonation yields an almost perfect planar skeleton of the guanidine fragment in **7H**$^+$. It is important to realize that the IMHB between the aminopropyl chain and imino nitrogen lone pair exists already in the neutral base. In contrast, in conjugate acid **7H**$^+$ the protonated imino nitrogen acts as a proton donor, whereas the side-chain amino group is a proton acceptor. Newly formed IMHB is stronger than in neutral analogue **7**, as evidenced by a decrease in the NH···N distance by ~0.39 Å. This will be discussed in some more detail in the next section. The bis- and tris-substituted systems **8** and **9**, possessing two and three *two-center corona motifs*, respectively, exhibit the same pattern of changes triggered by protonation (Figs 5 and 6).

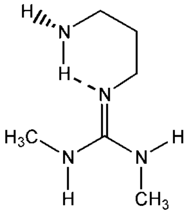
To reiterate: the central guanidine framework becomes planar, the NH···N contacts are shortened and the terminal amino groups in aminopropyl chains are considerably pyramidalized. The bottom line is that the central moiety undergoes substantial cationic resonance interactions in the conjugate acids and that the intramolecular hydrogen bonds are strengthened by protonation. The latter is not surprising, because Coulomb interactions are an essential ingredient of the IMHB. Having said that, it should be mentioned that there are exceptions. For instance, it was found that protonation decreases the strength of the IMHB in tropolone,[46] because the protonated carbonyl oxygen becomes a poorer hydrogen bond acceptor.

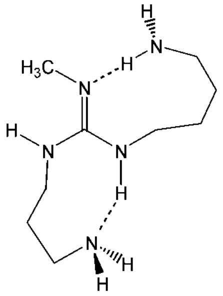

6

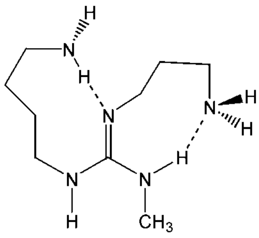

7

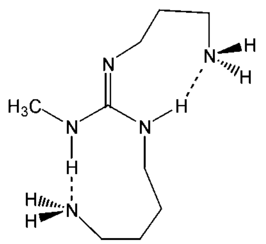

7a

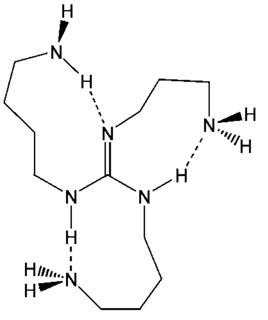

7b


7c


8


8a


8b


9

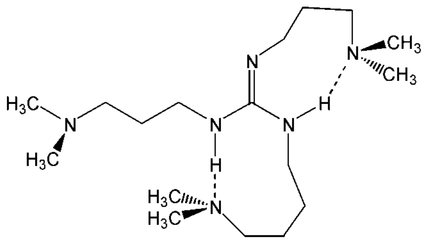

10

Figure 1. Schematic representation of trimethylguanidine **6** and its mono-, bis- and trisaminopropyl-substituted analogones **7, 8** and **9**

Proton affinity in the gas phase

The energetic data are summarized in Table 1. It appears that **6** has an *APA* of 245.7 kcal mol^{-1}, which is comparable to that of archetypal DMAN, where experiment gives 246.2 kcal mol^{-1}.[47] Aminopropyl substitution increases the proton affinity by 8.5 kcal mol^{-1} in **7**. Interestingly, the singly substituted aminopropyl deriva-

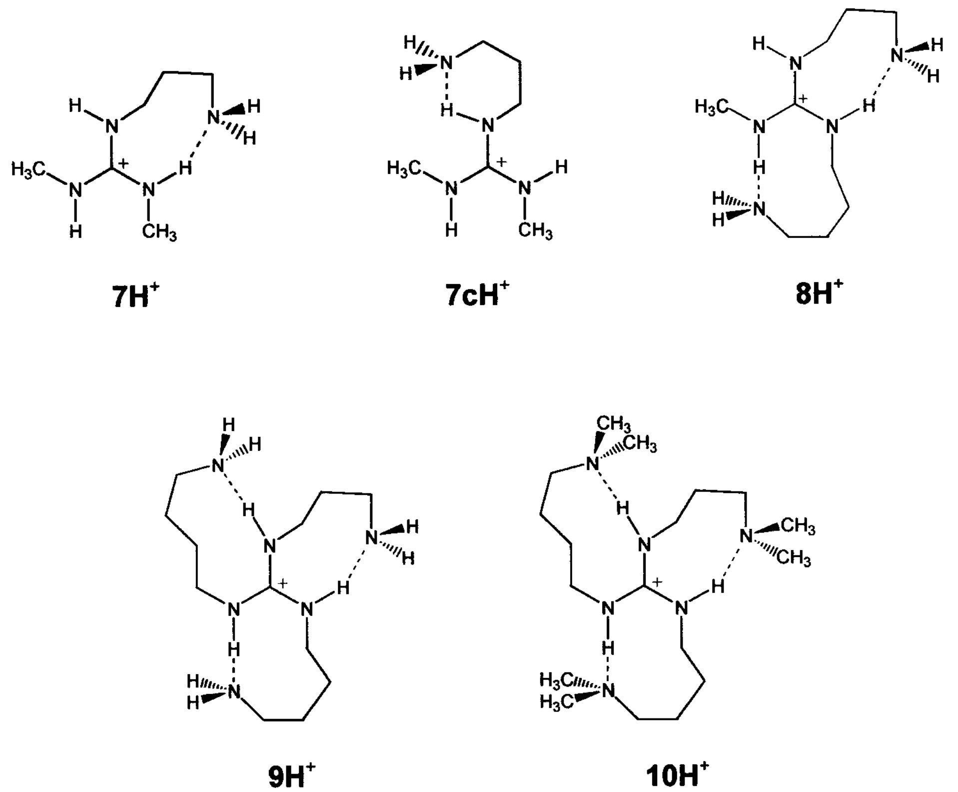
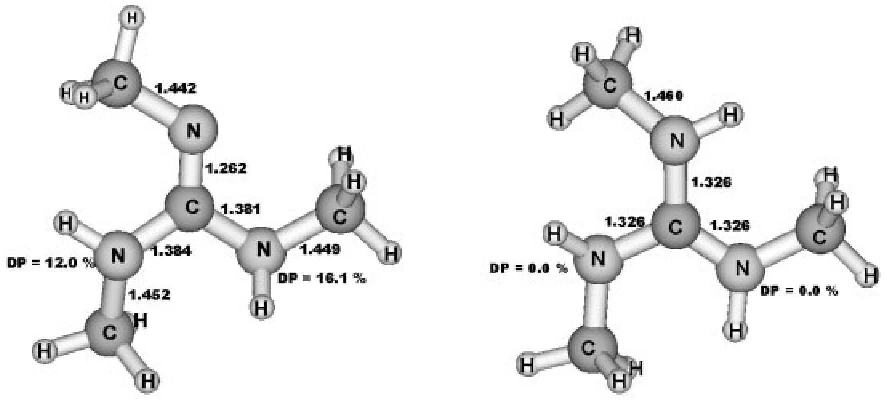

7H⁺ **7cH⁺** **8H⁺** **9H⁺** **10H⁺**

Figure 2. Schematic representation of the protonated forms **7H$^+$, 7cH$^+$, 8H$^+$, 9H$^+$** and **10H$^+$**

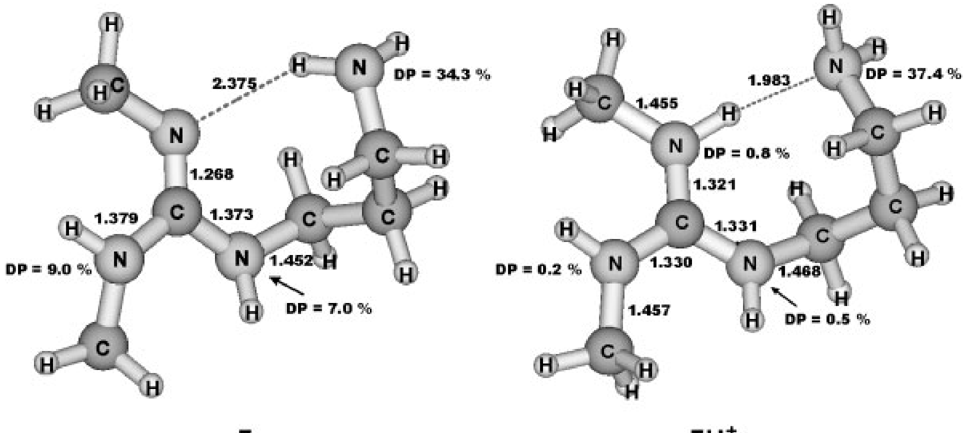
tive **7** has three additional tautomers/conformers, **7a, 7b** and **7c**, lying very close in the total molecular energy. Conformer **7a** is the most and the imino 'self-solvated' compound **7c** is the least stable. Unexpectedly, it appears that the strongest IMHB interaction is between an N(sp^3) hydrogen bond donor (HBD) and an N(sp^3) hydrogen bond acceptor (HBA), which takes place in **7a**. The proton affinities follow the opposite trend. They assume highest and lowest value in **7c** and **7a**, respectively. It should be pointed out that protonation of **7, 7a** and **7b** results in the same conjugate acid **7H$^+$** (Fig. 2), which explains the trend above. It is of interest to estimate the contribution of the IMHB to the *APA* in **7**. For this purpose, the aminopropyl side-chain in **7** and **7H$^+$** is stretched to a zig-zag conformation as shown in Scheme 3.

MP2 model computations reveal that **7**(zig-zag) is less stable than **7** by 5.8 kcal mol^{-1} implying that this is a rough estimate of the IMHB strength in the neutral form **7**. Analogously, it appears that **7H$^+$** is more stable than **7H$^+$**(zig-zag) by 10.1 kcal mol^{-1}. Therefore, the contribution of the IMHB in **7** to its proton affinity is



6 **6H⁺**

Figure 3. Selected geometric parameters of *N,N,N'*-trimethylguanidine (**6**) and its conjugate acid **6H$^+$**



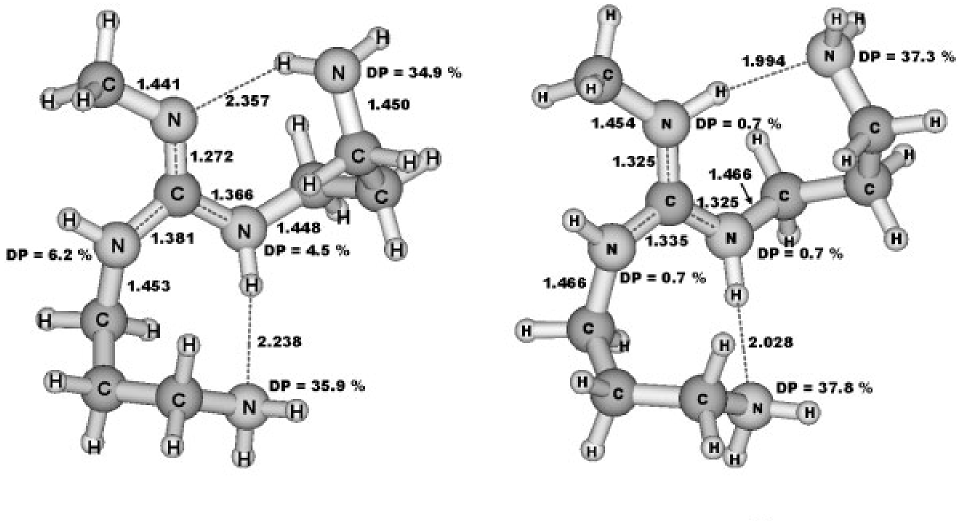
7 **7H⁺**

Figure 4. Selected geometric parameters of the monoaminopropyl derivative of guanidine **7** and its conjugate acid **7H$^+$**

4.3 kcal mol^{-1}. Similarly, **8b** is slightly more stable than **8**, the difference being only 2 kcal mol^{-1}. The reason behind this is simple: the tautomer **8b** has two favourable hydrogen bond donor–acceptor interactions involving four N(sp^3) atoms. All three tautomers have a common conjugate acid **8H$^+$**. Concomitantly, *APA*(**8**) and *APA*(**8b**) are 263.4 and 261.6 kcal mol^{-1}, respectively, the former being higher by ~2 kcal mol^{-1}. Taking into account only the most stable tautomers and conformers of **7** and **8**, one concludes that a double aminopropyl substitution yields an increase in proton affinity of 9.2 kcal mol^{-1}. Triple aminopropyl substitution, which makes a strongly resonating conjugate acid system **9H$^+$**, leads to a remarkable superbasic *APA* = 268.4 kcal mol^{-1} value.

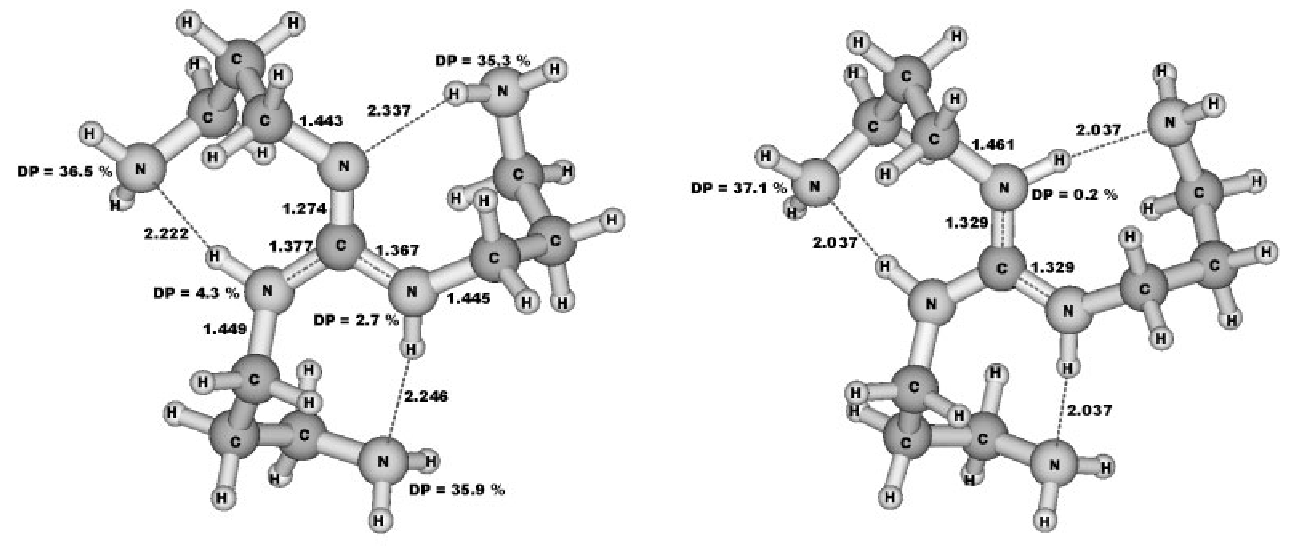
In order to estimate the contribution of the intramolecular hydrogen bonds in **9H$^+$**, we considered unfolded aminopropyl chains conformation **9H$^+$** (zig-zag) depicted in Fig. 7. It is found that the sum of hydrogen bond strengths in **9H$^+$** is 33.0 kcal mol^{-1} as estimated by the MP2 model. On the other hand, the same model yields a sum of the intramolecular hydrogen bonds in neutral **9** of 14.7 kcal mol^{-1}. The difference of 18.3 kcal mol^{-1} represents the IMHB contribution to the absolute proton affinity in **9**. Although this is not exclusively the strength of the intramolecular hydrogen bonds, because the steric interactions in **9** and **9**(zig-zag) are not exactly the same, which also holds for the **9H$^+$** and **9H$^+$**(zig-zag) protonated forms, it can be safely concluded that the total contribution to the proton affinity of the three IMHBs acting in concert in **9** is remarkable.

It is of interest to compare the bond distances of the guanidine moiety in **9** and **9**(zig-zag). One observes also that the C=N bond is longer, whereas both C—N bonds are shorter in **9** compared with the corresponding values in the model system **9**(zig-zag). This is consistent with



8 **8H⁺**

Figure 5. Selected geometric parameters of the bisaminopropyl derivative of guanidine **8** and its conjugate acid **8H$^+$**



9

9H$^+$

Figure 6. The most stable conformation and selected geometric parameters of the trisaminopropyl derivative of guanidine **9** and its conjugate acid **9H$^+$**

the idea of partial protonation[40] of the imino nitrogen via an IMH bond, which occurs in the initial base **9**. It can be expected that the introduction of two additional methyl groups in the aminopropyl substituents would lead to an even more amplified basicity due to the relaxation effect. This supposition is confirmed by actual calculations which gave $APA(\mathbf{10}) = 275.5\ \text{kcal mol}^{-1}$, implying that **10** is a strong superbase in the gas phase.

As a final comment, it should be noted that the efficient HF_{sc} model gives *APA*s that are very close to those given by the more sophisticated MP2 calculations (Table 1).

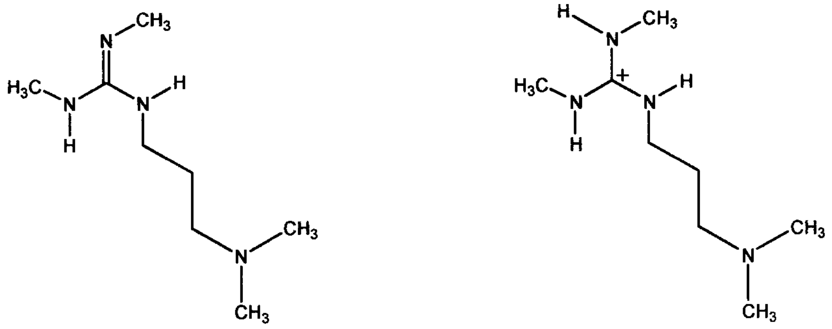
Basicity in acetonitrile

Neutral organic superbases are tailored for applications in moderately polar solvents. One of the widely used solvents of low polarity was acetonitrile[48–50] (for the

Table 1. Electronic energies (au), *ZPVE*s[a] and the proton affinities (kcal mol^{-1}) as obtained by the MP2 and HF_{sc} models[b]

Molecule	HF/6–31G*	MP2	*ZPVE*	*APA*(HF_{sc})	*PA*(MP2)	B3LYP	pK_a
6	−321.19841	−322.42123	96.3	246.4	245.7	−323.39184	24.9
6H$^+$	−321.61986	−322.82557	104.3	–	–	−323.86970	–
7	−454.28983	−456.03871	141.5	254.5	254.2	−457.41048	25.9
7H$^+$	−454.72577	−456.45795	150.4	–	–	−457.89304	–
7a	−454.29406	−456.04243	141.9	252.2	252.2	−457.41316	25.2
7H$^+$	−454.72577	−456.45795	150.4	–	–	−457.89304	–
7b	−454.29017	−456.03914	142.0	254.3	254.4	−457.40891	26.6
7H$^+$	−454.72577	−456.45795	150.4	–	–	−457.89304	–
7c	−454.28082	−456.03062	141.6	256.7	256.5	−457.40242	26.8
7cH$^+$	−454.72071	−456.45338	150.4	–	–	−457.88798	–
8	−587.38630	−589.66139	187.2	262.2	263.4	−591.43191	27.8
8H$^+$	−587.83601	−590.09603	196.5	–	–	−591.92129	–
8a	−587.38649	−589.66311	187.2	262.1	262.4	−591.43177	27.8
8H$^+$	−587.83601	−590.09603	196.5	–	–	−591.92129	–
8b	−587.38896	−589.66463	187.4	260.7	261.6	−591.43308	27.5
8H$^+$	−587.83601	−590.09603	196.5	–	–	−591.92129	–
9	−720.48211	−723.28555	232.8	267.5	268.4	−725.45353	28.8
9H$^+$	−720.94118	−723.72863	242.4	–	–	−725.94653	–
10	−954.64538	−958.40176	333.1	266.9	275.5	−961.33511	29.4
10H$^+$	−955.10345	−958.85529	342.2	–	–	−961.82947	–

[a] *ZPVE*s (in kcal mol^{-1}) are calculated at the HF/6–31G* level of theory and scaled by 0.89.
[b] B3LYP is a shorthand notation for the (IPCM)/B3LYP/6–311 + G**//HF-6–31G* model.



7(zig-zag) **7H$^+$**(zig-zag)

Scheme 3

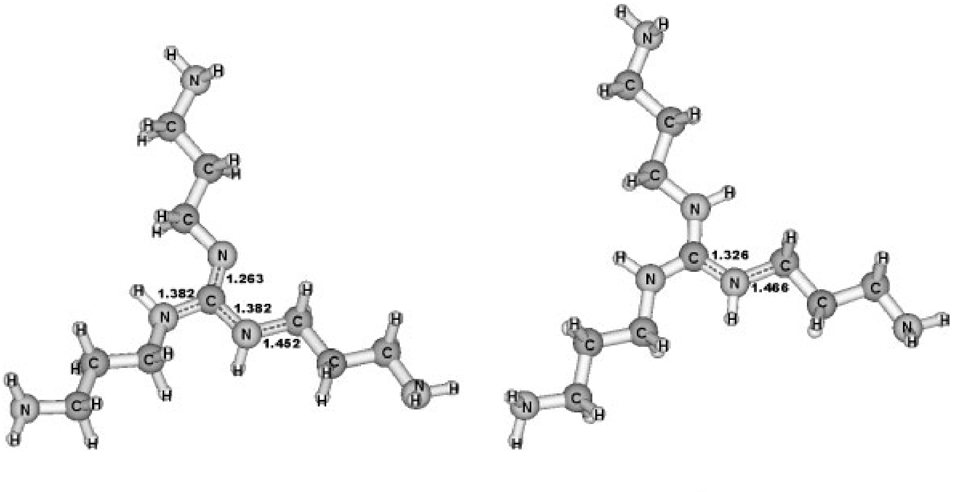
determination of the acidity of strong neutral Brønsted acids in acetonitrile, see Ref. 50). The question therefore arises of whether the highly basic 3-aminopropylguanidines offer compounds exhibiting strong basicities in solutions. Consequently, we consider here their basicity in MeCN, which might prove helpful in the experimental measurements. It was shown recently that the electrostatic model of polarized continuum of Miertuš *et al.*[51] served the purpose of describing the solvent effect very well in moderately and low-polarity solvents such as acetonitrile.[52]

In determining the cavities that surround solvated molecules, we utilize the suggestion of Wiberg and coworkers,[53] which is based on isodensity shells that involve the electron density of 0.0004 eB^{-3}. This approach was termed the isodensity polarized continuum model (IPCM). Since the calculation of pK_a values in MeCN (with permeativity $\epsilon = 36.64$) involves the estimation of the charges on the cavity surfaces in an iterative fashion, a more economical model than MP2 is desired. We found that the B3LYP/6–311 + G**//HF/6–31G* model is a very good compromise between efficiency and reliability.[52] Hence the model for calculating pK_a values in a solvent is termed (IPCM)/B3LYP/6–311 + G**//HF/6–31G*. Comparison of the *APA* values, calculated in acetonitrile, with the experimental data gave an excellent linear least-squares fit correlation:

$$pK_a(\mathrm{MeCN}) = 0.4953(\mathrm{MeCN}) - 119.7 \qquad (6)$$

It appears that, by using Eqn. (6), pK_a gradually increases along the series **6, 7a** and **8**, culminating in **9** and **10**, with the high values of 28.8 and 29.4, respectively (Table 1). The high basicity of poly-3-aminopropylguanidines is surprising at first sight in view of their size and partial self-solvation. Obviously, there is no interference of internal and external solvation as is usually the case in highly polar media such as water.[23–25] This feature makes polyaminopropylguanidines very good candidates for superbases in non-polar solvents.

As a final comment, it is interesting to note that the solvent effect in **9**(zig-zag) and **9H$^+$**(zig-zag) is larger



9 (zig-zag) **9H$^+$ (zig-zag)**

Figure 7. Structural representation of the unfolded trisaminopropyl derivative of guanidine **9** and its conjugate acid **9H$^+$**

than that in their corresponding intramolecular hydrogen bonded forms **9** and **9H**$^+$. The reason for this is simple: the nitrogen atoms in **9** and **9H**$^+$ are partially shielded by 'internal self-solvation' by three corona rings. The (IPCM)/B3LYP/6–311 + G**//HF/6–31G* model shows that the difference in total energy (including ZPVE) between **9**(zig-zag) and **9** in acetonitrile is 5.5 kcal mol^{-1}. Analogously, **9H**$^+$(zig-zag) is less stable than **9H**$^+$ in CH_3CN by 13.1 kcal mol^{-1}. Consequently, the contribution of the triple corona effect to *APA* in acetonitrile is 7.6 kcal mol^{-1}, which should be compared with the corresponding gas-phase estimate of 18.3 kcal mol^{-1}. In spite of the fact that the IMHB effect in **9** is 58% smaller in CH_3CN, its presence leads to a respectable basicity of **9** with a pK_a value 28.8 (see above).

CONCLUSION

We found that multiple aminopropyl substitutions of the initial *N*,*N*′,*N*″-trimethylguanidine lead to high intrinsic proton affinities and basicities culminating in $APA = 268.4$ kcal mol^{-1} in *N*,*N*′,*N*″-tris(3-aminopropyl)-guanidine (**9**) and $APA = 275.5$ kcal mol^{-1} in **10**. The reason behind the high proton affinity is identified as a strong cationic resonance occurring in the central guanidine moiety and the strength of the intramolecular hydrogen bonding, which is enhanced upon protonation. Clearly, cooperative action of three IMHBs is very effective in **9**, contributing substantially (~18 kcal mol^{-1}) to the absolute proton affinity of this highly basic molecule. Mono- and bis-3-aminopropylguanidines exist in several tautomeric forms. Their stabilities vary by a few kcal mol^{-1}. The most stable tautomers and conformers are those which have the largest number of intramolecular hydrogen bonds formed between pairs of N(sp^3) nitrogen atoms, acting as hydrogen bond donors (HBD), and their N(sp^3) partners acting as hydrogen bond acceptors (HBA). It is also shown that the compounds considered are very basic in acetonitrile. The highest pK_a values are found in **9** (pK_a = 28.8) and **10** (pK_a = 29.4), which indicates that these two compounds could be very useful in acid–base chemistry.

Acknowledgement

We thank the John von Neumann Institut für Computing des Forschungszentrums, Jülich, for computer time.

REFERENCES

1. Lowry TM, Richardson KS. *Mechanism and Theory in Organic Chemistry*. Harper and Row: New York, 1976.
2. Bamford CH, Tipper CFH (eds). *Comprehensive Chemical Kinetics*, Vol. 8, *Proton Transfer*. Elsevier: Amsterdam, 1977.
3. Stewart R. *The Proton: Applications to Organic Chemistry*. Academic Press: Orlando, FL, 1985.
4. Taylor R. *Electrophilic Aromatic Substitution*. Wiley: Chichester, 1990.
5. Maskill H. *The Physical Basis of Organic Chemistry* (5th edn). Oxford Science Publications: Oxford, 1995.
6. Fornarini S. *Mass Spectrom Rev.* 1996; **15**: 365–389.
7. Eckert-Maksić M, Maksić ZB, Klessinger M. *Int. J. Quantum Chem.* 1994; **49**: 383–396; *J. Chem. Soc., Perkin Trans. 2* 1994; 285–289.
8. Raczyńska ED, Maria P-C, Gal J-F, Decouzon M. *J. Phys. Org. Chem.* 1994; **7**: 725–733.
9. Schwesinger R. *Angew Chem., Int. Ed. Engl.* 1987; **26**: 1164.
10. Schwesinger R, Misfeldt M, Peters K, von Schnering HG. *Angew. Chem., Int. Ed. Engl.* 1987; **26**: 1165.
11. Maksić ZB, Kovačević B. *J. Org. Chem.* 2000; **65**: 3303–3309.
12. Schwesinger R, Schlemper H, Hasenfratz C, Willaredt J, Dimbacher T, Breuer T, Ottawa C, Fletschinger M, Boele J, Fritz M, Putzas D, Rotter HW, Bordwell FG, Satish AV, Yi GZ, Peters E-H, von Schnering HG. *Liebigs Ann.* 1996; 1055–1081.
13. Koppel IA, Schwesinger R, Brener T, Burk P, Herodes K, Koppel I, Leito I, Mishima M. *J. Phys. Chem. A* 2001; **105**: 9575–9586.
14. Maksić ZB, Vianello R. *J. Phys. Chem. A* 2002; **106**: 419–430.
15. Alder RW. *Chem. Rev.* 1989, **89**: 1215; Alder RW. *Tetrahedron* 1990; **46**: 683–713.
16. Llamas-Saiz AL, Foces-Foces C, Elguero J. *J. Mol. Struct.* 1994; **328**: 297–323.
17. Staab HA, Saupe T. *Angew. Chem., Int. Ed. Engl.* 1988; **27**: 865–879.
18. Raczyńska ED, Decouzon M, Gal J-F, Maria P-C, Gelbard G, Vielfaure-Joly J. *J. Phys. Org. Chem.* 2001; **14**: 25–34.
19. Gal J-F, Maria P-C, Raczyńska ED. *J. Mass. Spectrom.* 2001; **36**: 699–716.
20. Alcami M, Mó O, Yáñez M. *Mass. Spectrom. Rev.* 2001; **20**: 195–245.
21. Alcami M, Mó O, Yáñez M. *J. Phys. Org. Chem.* 2002; **15**: 174–186.
22. Yamdagni R, Kebarle P. *J. Am. Chem. Soc.* 1973; **95**: 3504–3510.
23. Meot-Ner (Mautner) M, Hamlet P, Hunter EP, Field FH. *J. Am. Chem. Soc.* 1980; **102**: 6393–6399.
24. Meot-Ner (Mautner) M. *J. Am. Chem. Soc.* 1984; **106**: 1265–1272.
25. Klassen JS, Blades AT, Kebarle P. *J. Phys. Chem.* 1995; **99**: 15509–15517.
26. Raczyńska ED, Maria PC, Gal JF, Decouzon M. *J. Org. Chem.* 1992; **57**: 5730–5735.
27. Raczyńska ED, Maria PC, Gal JF, Decouzon M. *J. Phys. Org. Chem.* 1994; **7**: 725–733.
28. Hernández-Laguna A, Abboud JLM, Notario R, Homan H, Smeyers YG. *J. Am. Chem. Soc.* 1993; **115**: 1450–1454.
29. Hernández-Laguna A, Abboud JLM, Homan H, López-Mardomingo C, Notario R, Cruz-Rodriguez Z, Haro-Ruiz MD, Botella V. *J. Phys. Chem.* 1995; **99**: 9087–9094.
30. Maksić ZB, Kovačević B. *J. Chem. Soc., Perkin Trans. 2*, 1999; 2623–2629.
31. Maksić ZB, Kovačević B. *J. Phys. Chem. A* 1999; **103**: 6678–6684.
32. Maksić ZB, Glasovac Z, Despotović I. *J. Phys. Org. Chem.* 2002; **15**: 499–503.
33. Alder RW, Bowman PS, Steele WRS, Winterman DR. *J. Chem. Soc., Chem. Commun.* 1968; 723.
34. Wozniak K, He H, Klinowsky J, Jones W, Barr TL. *J. Phys. Chem.* 1995; **99**: 14667–14677.
35. Szemik-Hojniak A, Zwier JM, Buma WJ, Bursi R, van der Waals JH. *J. Am. Chem. Soc.* 1998; **120**: 4840–4844.
36. Platts JA, Howard ST, Wozniak K. *J. Org. Chem.* 1994; **59**: 4647–4651.
37. Peräkylä M. *J. Org. Chem.* 1996; **61**: 7420–7425.
38. Howard ST. *J. Am. Chem. Soc.* 2000; **122**: 8238–8244.
39. Raab V, Kipke J, Gschwind R, Sundermeyer J. *Chem. Eur. J.* 2002; **8**: 1682–1693.
40. Kovačević B, Maksić ZB. *Chem. Eur. J.* 2002; **8**: 1694–1702.
41. Kovačević B, Maksić ZB, Vianello R, Primorac M. *New J. Chem.* in press.
42. Maksić ZB, Kovačević B. *J. Phys. Chem. A* 1998; **102**: 7324–7328.
43. Maksić ZB, Kovačević B, Kovaček D. *J. Phys. Chem. A* 1997; **101**: 7446–7453.

44. Frisch MJ, Trucks GW, Schlegel HB, Gill PMW, Johnson BG, Robb MA, Cheeseman JR, Keith T, Petersson GA, Montgomery JA, Raghavachari K, AlLaham MA, Zakrzewski VG, Ortiz JV, Foresman JB, Cioslowski J, Stefanov BB, Nanayakkara A, Challacombe M, Peng CY, Ayala PY, Chen W, Wong MW, Andres JL, Replogle ES, Gomperts R, Martin RL, Fox DJ, Binkley JS, Defrees DJ, Baker J, Stewart JP, Head-Gordon M, Gonzalez C, Pople JA. Gaussian 94, Revision D1. Gaussian: Pittsburgh, PA, 1995.
45. Häfelinger G, Kuske FKH. In *The Chemistry of Amidines and Imidates*, vol. **2**, Patai S, Rappoport Z (eds). Wiley: Chichester, 1991; 1.
46. Mó O, Yáñez M, Essefar M, Herreros M, Notario R, Abboud JL-M. *J. Org. Chem.* 1997; **62**: 3200.
47. Lan YK, Saluja PPS, Kebarle P, Alder RW. *J. Am. Chem. Soc.* 1978; **100**: 7328–7333.
48. Kolthoff IM, Chantooni MK Jr, Bhowmik S. *J. Am. Chem. Soc.* 1968; **90**: 23–28.
49. Schwessinger R. *Nachr. Chem. Tech. Lab.* 1990; **38**: 1214.
50. Leito I, Kaljurand I, Koppel IA, Yagupolskii LM, Vlasov VM. *J. Org. Chem.* 1998; **63**: 7868–7874.
51. Miertuš S, Scrocco E, Tomasi J. *Chem. Phys.* 1981; **55**: 117–129; Miertuš S, Tomasi J. *Chem. Phys.* 1982; **65**: 239–245.
52. Kovačević B. Maksić ZB. *Org. Lett.* 2001; **3**: 1523–1526.
53. Wiberg KB, Rablen PR, Rush DJ, Keith TA. *J. Am. Chem. Soc.* 1995; **117**: 4261–4270; Foresman JB, Keith TA, Wiberg KB, Snoonian J, Frisch MJ. *J. Phys. Chem.* 1996; **100**: 16098–16104.