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Basicity of Guanidines with Heteroalkyl Side Chains in Acetonitrile

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The pK_a values of seven novel guanidine derivatives, six of them possessing heteroalkyl substituents capable of forming intramolecular hydrogen bonds, were determined in acetonitrile (MeCN) by using the UV/Vis spectrophotometric titration method. The obtained pK_a values range from 24.7 to 27.2. The most basic among the studied guanidines was found to be by ca. 4 pK_a units more basic than the well-known superbase N^1,N^1,N^3,N^3-tetramethylguanidine (TMG). The trends in the changes in the measured pK_a values were compared with the experimental (determined by the extended kinetic method) and theoretical [B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d)] gas-phase proton affinities. It was shown that basicity ordering of the bases with dimethylaminopropyl substituents in acetonitrile follows the trend encountered in the gas phase. However, this is not the case for the methoxypropyl-substituted guanidines indicating that in these molecules formation of the intramolecular hydrogen bonds is to large extent hindered due to solvation by acetonitrile.

Introduction

Guanidine derivatives continue to attract the interest of organic chemists due to their versatile chemistry and interesting biochemical properties.[1] The guanidine moiety is an important substructure in many molecules of biological importance such as arginine, creatine phosphates, and purines.[2] On the other hand, guanidinium and substituted guanidinium salts exhibit a variety of interesting properties such as denaturation of proteins by the guanidinium ion and inhibition of the DNA synthesis by, for example, hydroxyguanidine, which has led to their classification as prospective antitumor drugs.[3] The guanidine motif is also employed in the design of new materials based on supramolecular association by means of hydrogen bonding.[4] Furthermore, owing to their strong basic properties, guanidines also serve as useful catalysts in a wide range of base-catalyzed organic reactions.[5,6] More recently, the guanidine fragment was employed as an essential building block in computational tailoring and synthesis of strong organic superbases.[7–11] Particularly interesting in this regard are guanidines substituted by flexible heteroalkyl chains capable of forming multiple intramolecular hydrogen bonds (IMHBs). For all these compounds an enhancement in the gas-phase basicity was found, in full analogy with compounds of the general formula $Y(CH_2)_nX$ (Y,X = NR_2, OR; R = H, alkyl).[12]

In a recent paper, we reported the synthesis and structural features of N,N',N''-tris[3-(dimethylamino)propyl]-guanidine,[13] which in its protonated form possesses three intramolecular hydrogen bonds. Its gas-phase basicity was predicted to be comparable to that of P2 phosphazene.[7a] This compound was also found to exert catalytic activity in some organic reactions, like Knoevenagel and nitroaldol condensations, as well as transesterification of vegetable oils.[14,15] The experimental and calculated intrinsic gas-phase proton affinities (PAs) of its structural analogues **1**–**3** and **5** and **6** (Scheme 1) indicate that replacement of the propyl groups in **1** with dimethylaminopropyl or methoxypropyl chains leads to a considerable increase in the gas-phase basicity as a result of the formation of intramolecular hydrogen bonds, which are absent in alkyl fragments.[16] The aim of the present work is to determine the basicity of these interesting guanidine derivatives in acetonitrile (MeCN) by experimental measurements and computational methods. This is of considerable importance from a practical point of view, as acetonitrile is a frequently used solvent in preparative organic chemistry. The standard reference bases used in the present study are shown in Scheme 1, along with studied guanidines **1**–**7**.

The basicity of a base B in solvent S is defined by using Equation (1) and is expressed as the dissociation constant K_a of the conjugate acid HB^+ of the base B or more commonly by its negative logarithm pK_a [Equation (2)].

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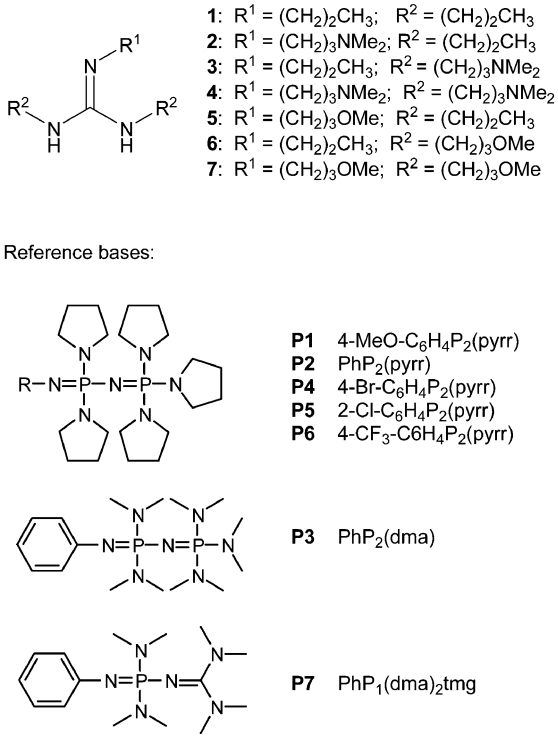


Scheme 1. Guanidine derivatives **1**–**7** studied in this work and phosphazenes **P1**–**P7** used as the reference bases in UV/Vis measurements.

$$HB^+ + S \rightleftharpoons B + HS^+ \quad (1)$$

$$K_a = \frac{a(HS^+)a(B)}{a(HB^+)} \quad (2)$$

To exclude the necessity for measuring the solvated hydrogen ion (HS^+) activity (its measurement is problematic in nonaqueous solvents), we studied the equilibrium between two bases B_1 and B_2 [Equation (3)].

$$HB_1^+ + B_2 \rightleftharpoons B_1 + HB_2^+ \quad (3)$$

This equilibrium refers to the relative basicity of the two bases B_1 and B_2, which is denoted as ΔpK_a and is defined in Equation (4).

$$\Delta pK_a = pK_a(HB_2^+) - pK_a(HB_1^+) = \log \frac{a(HB_2^+)a(B_1)}{a(HB_1^+)a(B_2)} \quad (4)$$

As can be seen, the activity of HS^+ is excluded from the equation. Assuming that the ratio $f(HB^+)/f(B)$ is the same for both bases (see ref.[18]), then the activity of species can be replaced by equilibrium concentrations in Equation (4).

Results and Discussion

Determination of pK_a values

The ΔpK_a values for the pairs of bases were obtained from the UV/Vis spectra. From each titration experiment of the mixture of bases, the ΔpK_a was determined as the mean of 10–20 values. The substituted guanidine bases measured in this work have spectral properties in the wavelength range from 215 to 235 nm, which are suitable for our measurements. All the phosphazene bases used as reference bases had an isosbestic point (the absorbance of protonated and deprotonated forms is the same) in the range 220–230 nm in MeCN solution. Therefore, the wavelength of the reference base isosbestic point can be used for measuring the protonation level of the guanidine bases in the solutions. The ΔpK_a values were calculated as described in the previous papers by Koppel and coworkers.[17]

The uncertainty in the measured pK_a values was estimated according to the approach described in ref.[18] Specifically, the standard uncertainties of the obtained pK_a values if interpreted "in the framework" of the MeCN basicity scale (that is, uncertainties to be used when comparing the different pK_a values from the scale to each other) were estimated to be 0.06 pK_a units. In the same vein, the standard uncertainties of the absolute pK_a values "detached from the scale" (that is, by treating them as negative logarithms of equilibrium constants) were found to be 0.2 pK_a units.

Computational Details

Structures of all considered guanidine derivatives were optimized at the HF/6-31G(d) and B3LYP/6-31G(d) level of theory, and the minima of all structures were verified by vibrational analysis. Several conformations of the studied species (both neutral and protonated) were examined, involving structures with intramolecular hydrogen bonds (hereafter called "cyclic") and those with unfolded chains (hereafter called "open-chain") conformers. The latter conformers will be abbreviated as X(oc), where X stands for the number specifying the guanidine derivative in question. Following a previous study of the aminopropyl-substituted guanidines[7] in calculating structures of the protonated species two possibilities were considered: (1) the first one where the proton linked to the imino nitrogen atom of the guanidine moiety and the heteroatom within the heteroalkyl chain with the heteroatom participating in the hydrogen bond are attached to the same nitrogen atom form a pseudo-six-membered ring and (2) the second, which occurs when the heteroalkyl chain and proton participating in the hydrogen bond are bound to different nitrogen atoms of the guanidine fragment, forms a pseudo-eight-membered cycle. In each of the studied species the structure of the latter type was found to be more stable. It is important to mention that formation of the pseudo-eight-membered ring structures was also found in a recent X-ray structural analysis of *N*,*N*′,*N*′′-tris[3-(dimethylamino)propyl]guanidinium hexafluorophosphate.[13] Computational optimization of the open-chain structures was carried out by assuming antiperiplanar orientation of all methylene groups in the chains. Characteristic examples of the structure involving intramolecular hydrogen bonding ("cyclic" isomer) and the corresponding open-chain isomer calculated with the HF/6-

31G(d) method are shown in Figures 1 and 2, respectively. Finally, in calculating the gas-phase proton affinities, energies of the B3LYP/6-31G(d) optimized structures were refined by B3LYP/6-311+G(2df,p) single-point calculations (Table SI1 in the Supporting Information) in order to obtain a very flexible basis set, which is required for a good description of the lone pairs on the heteroatoms. The Cartesian coordinates of all studied species calculated with the B3LYP/6-31G(d) method are given in the Supporting Information. Structures of bases **4**, **4**H$^+$, **7**, and **7**H$^+$ and their open forms were also optimized by using the IEFPCM/HF/6-31G(d) method[19] by employing UAHF atomic radii (Tables SI2 and SI3 in the Supporting Information). Key geometrical parameters of the gas-phase geometries and geometries of the pseudopolycyclic and unfolded forms of cation **7**H$^+$ are also compared in Figures 1 and 2.

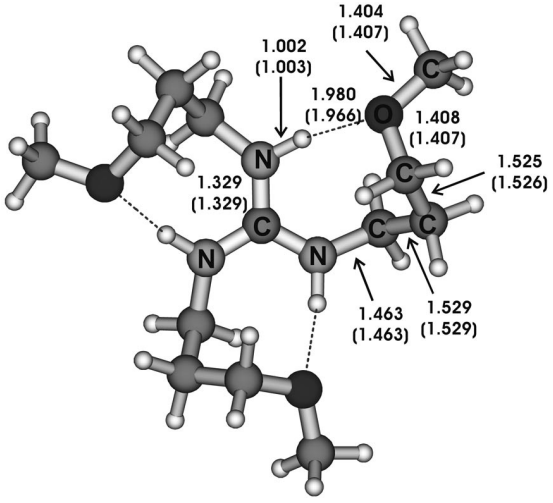


Figure 1. Schematic presentation of the geometry of the "cyclic" structure of guanidinium ion **7**H$^+$ optimized in acetonitrile and the gas phase (values in parentheses).

Total energies and energies of solvation of the considered molecules in acetonitrile were calculated by using a polarized continuum model[20] by employing the isodensity molecular surfaces of the solute molecules possessing a charge of 0.0004 eB^{-3} (IPCM). The dielectric constant ε for acetonitrile is 36.64. The solvent effect was estimated at a lower level of theory [B3LYP/6-311+G(d,p)//HF/6-31G(d)], because the computations required by the IPCM model are much more demanding.[21] The number of grid points for evaluation of isodensity surface was varied in order to achieve convergence for all calculated molecules. Full convergence was achieved by using 100 and 20 points for the $w(\phi)$ and $w(\theta)$ parameters, respectively, which represent angular integration weights over the corresponding polar coordinates.[21b] The PA(acetonitrile) values were calculated as the difference between the total energy of the neutral molecule and its conjugate acid in acetonitrile corrected for zero-point vibrational energies (ZPVEs) taken from the HF/6-31G(d) gas-phase calculations. All calculations were performed by using the Gaussian03 program package.[22] The Cartesian coordinates of the calculated species are given in the Supporting Information.

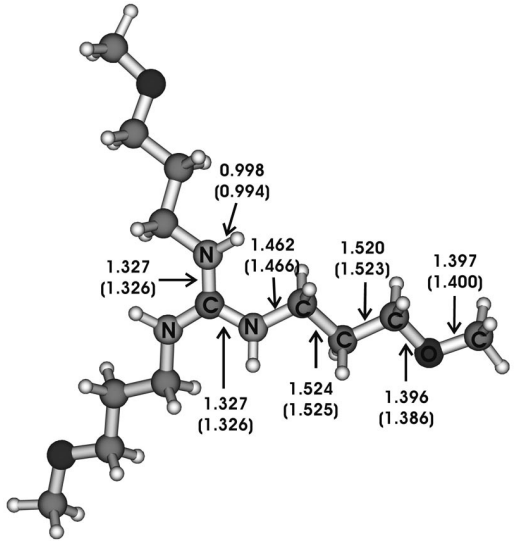


Figure 2. Schematic presentation of the geometry of the "open chain" structure of guanidinium ion **7**H$^+$ optimized in acetonitrile and the gas phase (values in parentheses).

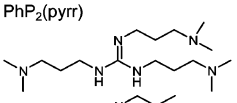
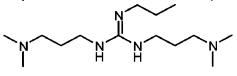
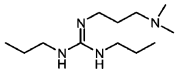
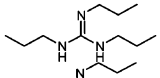
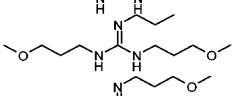
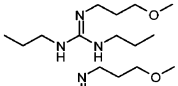
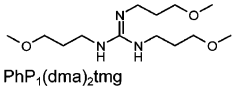
Basicity in Acetonitrile

The results of the basicity measurements in acetonitrile with the use of the UV/Vis spectrophotometric method are presented in Table 1. It is instructive to start discussion with the result obtained for **1**. This compound possesses a propyl group at each of the guanidine nitrogen atoms and does not form hydrogen bonds either in the neutral or the protonated form. Hence, its basicity is mainly governed by the resonance effect in the guanidine moiety predominantly in the protonated form[7b] coupled with a contribution associated with polarizability of the alkyl groups. Thus, it is expected that its basicity should be similar to that of previously studied polyalkyl-substituted guanidine derivatives. This is indeed the case. The measured pK_a value of 24.92 units is very close to the pK_a values of, for example, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and TMG, which in acetonitrile possess pK_a values of 26.0[17,23] and 23.4 units,[24] respectively. Replacement of the propyl groups with dimethylaminopropyl or methoxypropyl chains opens the possibility of forming intramolecular hydrogen bonds, which should additionally stabilize the protonated forms, thus raising the basicity of the parent base. Comparison of the pK_a of **1** with those of its heteroalkyl analogues shows that replacement of the propyl group at the imino nitrogen atom in **1** by a dimethylaminopropyl chain leading to **2** increases the pK_a value by 0.93 pK_a units. Similarly, double replacement of the propyl groups at the amino nitrogen atoms with dimethylaminopropyl groups leading to **3** results in an increase in the pK_a by 1.71 pK_a units. Hence, the increase in the pK_a is 0.78 units or 0.85 units per single amino nitrogen

atom, which is slightly less than that in the case of the imino nitrogen atom in **2** (0.93 units). Finally, compound **4** containing three dimethylaminopropyl groups is found to be more basic than **1** by 2.23 pK_a units. This is less than 2.64 units predicted by simple additivity indicating the presence of the saturation effect. Nevertheless, this makes compound **4** the most basic guanidine derivative in acetonitrile measured so far. On the other hand, the pK_a values of the methoxypropyl-substituted guanidines **5**–**7** appear to be slightly lower than the pK_a value of **1**. This is a surprising result, as formation of intramolecular hydrogen bonds should amplify basicity. Specifically, on passing from **1** to **7** a decrease in total basicity of 0.2 units is observed. In some more detail, replacement of the propyl groups at the amino nitrogen atoms by the three methoxypropyl chains in **1** leading to system **6** results in a decrease in the pK_a value of 0.1 units, which is 0.05 units per amino N atom. This change is practically the same as the single substitution at the imino nitrogen atom in **1** yielding derivative **5** (0.1 units). The trend in changes in a series **1**, **5**, **6**, and **7** leading to descending basicity (Table 1) roughly indicates that the intramolecular hydrogen bond(s) are nonexistent in acetonitrile, both in neutral bases and the corresponding conjugate acids. In other words, compounds **5**–**7** assume open-chain antiperiplanar conformations. The same holds for their protonated forms **5**H$^+$–**7**H$^+$. It appears that an acetonitrile molecule is a better hydrogen-bond acceptor than the ether group. Consequently, the H-bonding demand of the protonated imino nitrogen atom in methoxypropyl-substituted guanidines is saturated by a molecule of the solvent (MeCN) rather than by the oxygen atom of the side chain.

In order to check this assumption, we measured the IR spectra of the hexafluorophosphate salts of **4** and **7** in acetonitrile. Their comparison with the IR spectrum of **1**·HPF$_6$ (Figure 3) reveals that the intensity of the N–H stretching vibration (at 3360 cm^{-1}) is reduced in both heteroalkyl-substituted compounds, and the effect is more pronounced for the salt of **4**. In addition, on passing from **1**·HPF$_6$ to **4**·HPF$_6$ the C=N stretching band undergoes a redshift by 20 cm^{-1}, whereas no change is observed upon going from **1**·HPF$_6$ to **7**·HPF$_6$. These findings imply that the intramolecular hydrogen bond in **7**·HPF$_6$ in acetonitrile should be indeed significantly weaker than that in **4**·HPF$_6$, thus supporting the above conjecture. An additional piece of evidence is given in the forthcoming section.

Table 1. Results of self-consistent basicity measurements of the substituted guanidine bases and some phosphazene bases in acetonitrile.

	Base	pK_a[a]	Experimental ΔpK_a[b]
P1	4-MeO-C$_6$H$_4$-P$_2$(pyrr)	28.23	
P2	PhP$_2$(pyrr)	27.55	0.64
4		27.15	1.05
3		26.63	0.44
P3	PhP$_2$(dma)	26.46	0.95
P4	4-Br-C$_6$H$_4$-P$_2$(pyrr)	26.32	0.34
2		25.85	0.14
P5	2-Cl-C$_6$H$_4$-P$_2$(pyrr)	25.42	1.03
P6	4-CF$_3$-C$_6$H$_4$-P$_2$(pyrr)	25.29	1.04
1		24.92	0.43
6		24.84	0.56
5		24.81	0.13
7		24.74	0.56
P7	PhP$_1$(dma)$_2$tmg	24.68	0.51
			0.35
			0.45
			0.62
			0.46
			0.61
			0.16
			0.08

[a] Absolute pK_a values. [b] The numbers on the arrows are the experimental ΔpK_a values.[17]

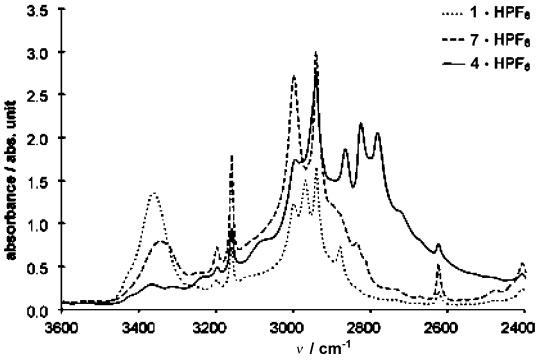


Figure 3. Section of the IR spectra of the hexafluorophosphate salts of **1**, **4**, and **7** (c = 0.05 mol L^{-1}) in acetonitrile with the characteristic NH band.

Comparison with Gas-Phase Proton Affinities

In view of the above-described difference in behavior of the dimethylaminopropyl- and the methoxypropyl-substituted guanidines in acetonitrile, it is instructive to compare the present results with the recently measured PAs of the same bases (with the exception of **4**) in the gas phase.[16] They are summarized in Table SI1, together with the relevant energetic parameters. The analysis of the data in Table SI1 shows that replacement of the propyl groups in **1** by the dimethylaminopropyl chains, as well as with the methoxypropyl groups, leads to an increase in the gas phase PA, and the effect of the methoxypropyl groups is less pronounced. Specifically, replacement of the propyl group at the imino nitrogen atom in **1** by a 3-(dimethylamino)propyl group increases the PA by 8 kcal mol^{-1}, which is by 6.5 kcal mol^{-1} higher than that on going from *N*′,*N*″,*N*‴-tripropylguanidine to *N*′,*N*‴-dipropyl-*N*″-(3-methoxypro-

Table 2. Total (E_{tot}) and hydrogen-bond-interaction energies (E_{HB})[a] of the cyclic and open chain conformers of guanidines **1**–**7** and their protonated forms in the gas phase and acetonitrile (MeCN) as calculated at the (IPCM)B3LYP/6-311+G(d,p)//HF/6-31G(d) level of theory.

Base/acid	"Cyclic" forms		"Open-chain" forms			
(B/BH$^+$)	E_{tot}(gas)	E_{tot}(MeCN)	E_{tot}(gas)	E_{tot}(MeCN)	E_{HB}(gas)[a]	E_{HB}(MeCN)[a]
1	–559.02084	–559.02725	–559.02084	–559.02725	0.00	0.00
1H$^+$	–559.42874	–559.49039	–559.42874	–559.49039	0.00	0.00
2	–692.94860	–692.95446	–692.94605	–692.95303	–1.60	–0.90
2H$^+$	–693.36295	–693.42216	–693.35250	–693.41454	–6.55	–4.78
3	–826.87445	–826.88016	–826.86941	–826.87704	–3.16	–1.95
3H$^+$	–827.29726	–827.35200	–827.27621	–827.33777	–13.21	–8.93
4	–960.79796	–960.80465	–960.79316	–960.80124	–3.02	–2.14
4H$^+$	–961.23129	–961.28221	–961.20000	–961.25969	–19.64	–14.13
5	–673.53941	–673.54542	–673.53839	–673.54690	–0.64	0.93
5H$^+$	–673.95130	–674.01082	–673.94355	–674.00813	–4.86	–1.69
6	–788.05578	–788.06238	–788.05395	–788.06516	–1.15	1.74
6H$^+$	–788.47443	–788.53115	–788.45838	–788.52378	–10.07	–4.63
7	–902.57215	–902.58047	–902.57023	–902.58304	–1.20	1.61
7H$^+$	–902.99774	–903.05134	–902.97324	–903.04076	–15.37	–6.64

[a] $E_{HB} = E_{tot}$("cyclic") – E_{tot}("open-chain").

pyl)guanidine.[16] The same holds true for the replacement of the propyl chains attached to the amino nitrogen atom. For instance, by comparing the PAs of bases **3** and **6** one observes that the latter base is less basic by 3.4 kcal mol^{-1}. It follows that in the gas phase IMHBs contribute to the stability of methoxypropyl derivatives **5**–**7** and their conjugate acids **5**H$^+$–**7**H$^+$ as intuitively expected. However, the difference in the strengths of the IMHBs in the conjugate acids and the corresponding bases is smaller than that in their dimethylaminopropyl counterparts. Concomitantly, the increase in basicity is small. This experimental evidence was corroborated by results obtained by the MP2/6-311+G(d,p)//HF/6-31G(d) and B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) methods[25] and should be considered as reliable.

In view of the importance of the intramolecular H-bonding motif in designing organic superbases, we shall present here detailed analysis of their cumulative effects. For this purpose it is useful to compare the calculated energies of the cyclic (Figure 1) and open-chain (Figure 2) conformers. As we are interested in the basicity in the gas phase and in acetonitrile, we shall use energies of the considered structures calculated at the B3LYP/6-311+G(d,p)//HF/6-31G(d) level, which are summarized in Table 2.

Taking substituted guanidine **4** as an example, we find that its open-chain conformer is less stable than the pseudopolycyclic structure by 3.0 kcal mol^{-1}. The pseudopolycyclic form of its conjugate acid, **4**H$^+$, is more stable than its fully unfolded open-chain counterpart **4**H$^+$(oc) by 19.6 kcal mol^{-1} as expected due to the increased Coulombic character of the hydrogen bonds upon protonation. The difference between these two values of 16.6 kcal mol^{-1} can be taken as a rough estimate of the contribution of the IMHBs to the PA of **4** in the gas phase. In a similar vein, a comparison between energies of cyclic conformers **7** and **7**H$^+$ and their analogues with the unfolded heteroalkyl groups **7**(oc) and **7**H$^+$(oc) suggests that cooperative intramolecular hydrogen bonds participate to 1.2 and 15.3 kcal mol^{-1}, respectively, in the stabilization of the cyclic conformers. Thus, it follows that contribution of IMHB strength to the gas phase of **7** is 14.1 kcal mol^{-1}, which is by 2.5 kcal mol^{-1} less than that in base **4**. By carrying out the same analysis in acetonitrile solution we find that contributions of the IMHBs to the stability of **4** and **4**H$^+$ are 2.1 and 14.1 kcal mol^{-1}, respectively, which is by ca. 30% lesser than that in the gas phase. On the other hand, open-chain isomer **7** is predicted to be slightly more stable in acetonitrile (by 1.6 kcal mol^{-1}), whereas the stability of **7**H$^+$ is 6.6 kcal mol^{-1} higher than that in the open-chain isomer. Geometry optimization of the considered structures in MeCN by using the IEFPCM/HF/6-31G(d) method (Table SI3) leads to similar results with only one exception. Namely, for **4**H$^+$ the latter model predicts significantly smaller contribution of the IMHBs to stability of the protonated form (7.4 kcal mol^{-1}) than in the single-point calculations (14.3 kcal mol^{-1}). It is also noteworthy that the open-chain form of **7** is found to be more stabilized (by 1.7 kcal mol^{-1}) than in the single-point IPCM calculations. In spite of that, both methods lead to the same qualitative conclusion. These results convincingly show that interaction of **7** in solution with MeCN molecules prevents formation of the IMHBs, whereas the interaction is diminished for **7**H$^+$ by 40%. This is in qualitative agreement with results of the above-mentioned IR measurements of the hexaphosphofluorate salts of **7**. An important corollary of the present analysis is that structures of bases and their conjugate acids possessing IMHBs in the gas phase could be distinctly different in solutions. Caution should be exercised particularly if the intermolecular hydrogen bonds between solute and solvent molecules are stronger than the IMHBs in solution.

Comparison of the Measured and Calculated pK_a Values of Bases 1–7 in Acetonitrile

Owing to wide interest for use of strong nitrogen and phosphorus bases in synthetic work, considerable efforts have been devoted in the past decades to develop practical

theoretical methods capable of predicting pK_a values in organic solvents.[26,27] The a priori estimates of the pK_a values from first principles[28] are unfortunately not practical in a large number of sizeable molecules. Therefore, one has to resort to simpler models of the polarized continuum (PCM)[20] and its isodensity (IPCM) variant form.[18] The latter approach was used in conjunction with the B3LYP/6-311+G(d,p)//HF/6-31G(d) method[7a,7b] for a large number of strong neutral nitrogen bases yielding a good correlation with the experimental pK_a values (derived for the set of 16 different nitrogen bases with correlation coefficient of 0.997) [Equation (5)].[27]

$$pK_a(MeCN) = 0.4953PA(MeCN) - 119.7 \quad (5)$$

Because we measured the pK_a values of guanidines **1**–**7**, we decided to check the applicability of this correlation for calculating pK_a values of these types of strong bases. It should be mentioned that for systems **5**–**7** calculations were carried out for the cyclic, as well as for the open-chain structures. The calculated PA(MeCN) and pK_a(MeCN) values of compounds **1**–**7** are summarized in Table 3.

Table 3. Solvation free energies, proton affinities, and calculated and experimental pK_a values in acetonitrile (MeCN).

Measured acids	$\Delta G_{solv.}$ [kcal mol^{-1}]	PA[a] [kcal mol^{-1}]	pK_a[b] (calcd.)	pK_a (exp.)	ΔpK_a
1H$^+$	–34.7	290.6	24.3	24.92	–0.7
2H$^+$	–33.5	293.5	25.7	25.85	–0.2
3H$^+$	–30.8	296.1	27.0	26.63	0.4
4H$^+$	–27.8	299.7	28.7	27.15	1.6
5H$^+$	–33.5	292.0	25.0	24.81	0.2
6H$^+$	–31.5	294.2	26.0	24.84	1.2
7H$^+$	–28.4	295.5	26.7	24.74	2.0
5H$^+$(oc)	–35.2	289.4	23.7	24.81	–1.1
6H$^+$(oc)	–34.0	287.7	22.8	24.84	–2.0
7H$^+$(oc)	–34.3	287.2	22.6	24.74	–2.1

[a] PA of conjugate bases **1**–**7** and **5**(oc)–**7**(oc). [b] Calculated by using Equation (5).

Analysis of the results in Table 3 reveals that the calculated pK_a values are in fair accordance with the experimental ones. However, there are some larger deviations, which call for rationalization, like, for example, those in molecules **4** and **7**, where the number of intramolecular hydrogen bonds increases upon protonation. This indicates that a part of disagreement might have its origin in neglecting the entropy contribution. More precisely, the relationship given in Equation (5) is derived for the series of amidine and guanidine derivatives lacking specific intramolecular interactions like IMHB.[17] In contrast, the structures in which the heteroalkyl chains are considered are stabilized by one or more intramolecular hydrogen bonds. This holds true in particular for the protonated forms, which in some cases possess an additional IMHB and exhibit stronger hydrogen bonds than those in their parent bases as a result of an excess amount of positive charge and an increase in Coulomb interaction. Concomitantly, reduction of a number of degrees of freedom for the internal rotations of heteropropyl chains upon protonation can be expected, thus leading to the entropy loss.[29] The next point of interest is that the trend of calculated pK_a values on passing from **1** to methoxypropyl derivatives **5**–**7** does not follow the ordering of the measured pK_a values. This is not surprising, as the PA(MeCN) values used in Equation (5) are calculated for the gas-phase geometries, implying that structural features of the considered species (including the geometry of the intramolecular hydrogen bonds in the pseudopolycyclic structures) in the gas phase and acetonitrile are the same. Therefore, in the case of methoxypropyl guanidine derivatives, where this assumption apparently does not hold, larger deviations between the calculated and measured pK_a values can be expected. It is very important to note that the pK_a(MeCN) values of bases **5**–**7**, when calculated for open-chain isomers, reproduce qualitatively the experimentally obtained ordering of pK_a values, but in this case, larger ΔpK_a deviations from experiment are encountered. Taking into account that these deviations are systematic in nature and between –1 and –2 kcal mol^{-1} and that Equation (5) is not very accurate for systems exhibiting intramolecular hydrogen bonding, it is safe to conclude that the basicities of the open-chain forms are in better accordance with the experimental values than the pseudopolycyclic ones. This is in harmony with other evidence discussed earlier (vide supra). It is fair to say that Equation (5) should be used in compounds with IMHBs only with utmost care.

Conclusions

The synthesis and spectral properties of a series of novel guanidine derivatives containing one, two, or three heteroalkyl chains, capable of forming intramolecular hydrogen bond(s) in the gas phase, was described and their pK_a values were determined in acetonitrile by using UV/Vis spectrophotometric titration. It was found that the replacement of the propyl group at the imino nitrogen atom in **1** by a 3-(dimethylamino)propyl chain leading to **2** increases the pK_a value by 0.93 pK_a units. In contrast, replacement of the propyl groups at the amino nitrogen atoms with 3-(dimethylamino)propyl groups leading to **3** results in an increase in the pK_a by 1.71 pK_a units. Finally, compound **4** having three dimethylaminopropyl substituents, was found to be more basic than **1** by 2.23 pK_a units. This makes compound **4** one of the most basic guanidine derivatives in acetonitrile measured so far, and it is of comparable basicity to P2-phosphazenes, which increases the number of strong neutral organic bases available. In contrast, the basicity of all investigated 3-methoxypropyl-substituted guanidines was found to be slightly lower than that of guanidine **1**. It is also worth pointing out that basicity ordering of the bases with the dimethylaminopropyl substituents in acetonitrile follows the trend encountered in the gas phase, whereas this is not the case for the methoxypropyl-substituted guanidines, indicating that in these molecules formation of the IMHBs is to large extent hindered due to solvation in acetonitrile.

Experimental Section

General: All solvents and reagents were purchased from commercial sources and used without further purification unless stated otherwise. THF was dried by heating at reflux and distilling over $LiAlH_4$. Dichloromethane was dried with CaH_2 and stored over 3 Å molecular sieves. Preparation of thioureas was carried out by a reaction of selected amines and CS_2 by using a previously described general procedure.[30] N^1,N^3-dipropylcarbodiimide[31] was prepared according to a slightly modified literature procedure[32] (see below). Synthesis of N',N'',N'''-tris[3-(dimethylamino)propyl]guanidine was carried out following a procedure described in the literature.[13] The same procedure was also used to prepare all other guanidine derivatives studied in this work. Gas chromatographic analyses were carried out with a Varian 3300 gas chromatograph fitted with a DB-1701 capillary column (0.32 mm × 15 m with film thickness of 0.15 μm) by using nitrogen as the gas carrier. The standard 1D ^{1}H and proton-decoupled ^{13}C NMR spectra of phosphazenes were recorded with a Bruker AC-200 NMR spectrometer at 200.13 and 50.32 MHz, respectively, whereas the NMR spectra of all other compounds were measured with a Bruker Avance 300 NMR spectrometer at 300 (1D ^{1}H) and 75.5 MHz (proton-decoupled ^{13}C), respectively. Chemical shifts were determined relative to TMS as an internal standard. IR spectra were recorded with an ABB Bomem MB102 FTIR spectrometer equipped with CsI optics and a DTGS detector.

General Procedure for the Preparation of Carbodiimides: Crude thioureas, prepared by the reaction of the desired amine and CS_2 in a 2:1 molar ratio, were dissolved in dry CH_2Cl_2. The solution was vigorously stirred and slight excess of yellow HgO was added in one portion. Stirring was continued for 2 h at room temperature. Subsequently, the solid material was filtered off with suction by means of a sintered funnel and thoroughly washed with CH_2Cl_2. The filtrate was evaporated under vacuum resulting in a colorless oil. Crude carbodiimide was purified by distillation under reduced pressure.

***N*^{1},*N*^{3}-Bis[3-(dimethylamino)propyl]carbodiimide:** Desulfurization of N^1,N^3-bis[3-(dimethylamino)propyl]thiourea (19.20 g, 0.077 mol) with yellow HgO (17.00 g, 0.078 mol) in CH_2Cl_2 (150 mL) followed by distillation under reduced pressure (3×10^{-5} mbar) afforded pure carbodiimide (13.14 g, 0.062 mol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.70 (m, 4 H), 2.20 (s, 12 H), 2.31 (t, $J_{H,H}$ = 7.3 Hz, 4 H), 3.25 (t, $J_{H,H}$ = 6.6 Hz, 4 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C, TMS): δ = 29.34, 45.23, 45.52, 56.89, 140.14 (N=C=N) ppm. IR (KBr): $\tilde{\nu}$ = 2130 (N=C=N stretching) cm^{-1}.

***N*^{1},*N*^{3}-Bis(3-methoxypropyl)carbodiimide:** Reaction of N^1,N^3-bis(3-methoxypropyl)thiourea (14.92 g, 0.076 mol) and yellow HgO (19.74 g, 0.091 mol) in CH_2Cl_2 (150 mL) followed by vacuum distillation gave pure carbodiimide (8.06 g, 0.043 mol, 0.57%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.81 (m, 4 H), 3.28 (m, 4 H), 3.34 (s, 6 H), 3.45 (t, $J_{H,H}$ = 6.2 Hz, 4 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C, TMS) δ = 31.25, 43.56, 58.69, 69.62, 140.16 (N=C=N) ppm. IR (KBr): $\tilde{\nu}$ = 2128 (N=C=N stretching) cm^{-1}.

General Procedure for the Synthesis of Guanidine Derivatives 1–7: Carbodiimide and the corresponding amine in a 1:2 molar ratio were dissolved in dry THF and stirred under reflux for 24 h. After cooling to room temperature, the solvent and the excess amount of amine were evaporated under vacuum (1332 Pa, 13 mbar), and the raw product was purified by distillation under reduced pressure affording the desired guanidine derivative in a very good yield (see below). Purity of all guanidine derivatives was checked by gas chromatographic analysis, which showed the presence of only one signal corresponding to the guanidine in question (see Experimental Section in the Supporting Information).

***N*′,*N*″,*N*‴-Tripropylguanidine (1):** Starting from N^1,N^3-dipropylcarbodiimide (3.52 g, 0.026) and propylamine (4.2 mL, 3.01 g, 0.051 mol), guanidine **1** was isolated in 73% yield (3.51 g, 0.019 mol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 0.94 (t, $J_{H,H}$ = 7.3 Hz, 9 H), 1.56 (q, $J_{H,H}$ = 7.3 Hz, 6 H), 3.02 (t, $J_{H,H}$ = 7.2 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C, TMS) δ = 11.7, 23.7, 45.3, 152.5 ppm. HRMS: calcd. for $C_{10}H_{23}N_3$ [M + H]$^+$ 186.196473; found 186.193103.

***N*′,*N*‴-Dipropyl-*N*″-[3-(dimethylamino)propyl]guanidine (2):** The same procedure as described above starting from N^1,N^3-dipropylcarbodiimide (3.28 g, 0.026 mol) and 3-(dimethylamino)propyl-1-amine (6.30 mL, 5.11 g, 0.050 mol) in dry THF (30.0 mL) afforded crude guanidine **2** as a colorless viscous oil. Distillation of the crude product at 0.01 Pa (10^{-4} mbar) yielded 81% (4.80 g, 0.021 mol, b.p. 87–92 °C/2×10^{-4} mbar) of pure **2**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 0.95 (t, $J_{H,H}$ = 7.3 Hz, 6 H), 1.57 (q, $J_{H,H}$ = 7.3 Hz, 4 H), 1.70 (m, 2 H), 2.21 (s, 6 H), 2.34 (t, $J_{H,H}$ = 6.2 Hz, 2 H), 3.03 (t, $J_{H,H}$ = 7.3 Hz, 4 H), 3.19 (t, $J_{H,H}$ = 6.2 Hz, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C, TMS) δ = 11.7, 23.4, 27.4, 41.9, 45.1, 45.3, 57.1, 153.8 ppm. HRMS: calcd. for $C_{12}H_{28}N_4$ [M + H]$^+$ 229.238672; found 229.238921.

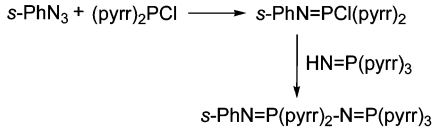
***N*′,*N*‴-Bis[3-(dimethylamino)propyl]-*N*″-propylguanidine (3):** The same procedure as described above starting from N^1,N^3-bis[3-(dimethylamino)propyl]carbodiimide (3.24 g, 0.015 mol) and propylamine (1.77 g, 0.03 mol) in dry THF (30.0 mL) afforded crude guanidine **3** as a colorless viscous oil in quantitative yield. Product was further purified by fractional distillation at 0.001 Pa (10^{-5} mbar, b.p. 103–108 °C/2×10^{-5} mbar) resulting in 3.18 g. (0.012 mol, 78%) of pure **3**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 0.94 (t, $J_{H,H}$ = 7.3 Hz, 3 H), 1.56 (q, $J_{H,H}$ = 7.3 Hz, 2 H), 1.76 (m, 4 H), 2.19 (s, 12 H), 2.34 (t, $J_{H,H}$ = 6.0 Hz, 4 H), 3.12 (t, $J_{H,H}$ = 7.3 Hz, 2 H), 3.32 (t, $J_{H,H}$ = 6.0 Hz, 4 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C, TMS): δ = 11.4, 22.7, 26.4, 40.9, 44.2, 44.9, 56.0, 155.8 ppm. HRMS: calcd. for $C_{14}H_{33}N_5$ [M + H]$^+$ 272.280871; found 272.283503.

***N*′,*N*‴-Dipropyl-*N*″-(3-methoxypropyl)guanidine (5):** The same procedure as described above starting from N^1,N^3-dipropylcarbodiimide (3.28 g, 0.026 mol) and 3-methoxypropyl-1-amine (6.00 mL, 5.24 g, 0.059 mol) in dry THF (23 mL) afforded quantitative conversion to guanidine **5**. After distillation under reduced pressure (6×10^{-5} mbar) pure **5** (4.14 g, 0.019 mol, 74%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.93 (t, $J_{H,H}$ = 7.5 Hz, 6 H), 1.54–1.62 (m, 4 H), 1.81–1.85 (m, 2 H), 3.01 (t, $J_{H,H}$ = 7.3 Hz, 4 H), 3.25 (t, $J_{H,H}$ = 4.1 Hz, 2 H), 3.33 (s, 3 H), 3.45 (t, $J_{H,H}$ = 5.6 Hz, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C, TMS): δ = 11.53, 23.23, 29.70, 41.00, 44.75, 58.60, 71.02, 153.78 ppm. HRMS: calcd. for $C_{11}H_{25}N_3O$ [M + H]$^+$ 216.207038; found 216.207379.

***N*′,*N*‴-Bis(3-methoxypropyl)-*N*″-propylguanidine (6):** The same procedure as described above starting from N^1,N^3-bis(3-methoxypropyl)carbodiimide (3.30 g, 17.6 mmol) and propylamine (3.00 mL, 2.10 g, 35 mmol) dissolved in dry THF (23 mL) afforded pure guanidine **6** (3.33 g, 14 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.95 (t, $J_{H,H}$ = 7.3 Hz, 3 H), 1.55 (m, 2 H), 1.80 (m, 4 H), 3.00 (t, $J_{H,H}$ = 7.3 Hz, 2 H), 3.16 (t, $J_{H,H}$ = 6.5 Hz, 4 H), 3.33 (s, 6 H), 3.47 (t, $J_{H,H}$ = 5.9 Hz, 4 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C, TMS): δ = 11.67, 23.62, 30.29, 41.13, 44.97, 58.56, 71.25, 153.00 ppm. HRMS: calcd. for $C_{12}H_{27}N_3O_2$ [M + H]$^+$ 246.217603; found 246.218816.

***N′*,*N″*,*N‴*-Tris(3-methoxypropyl)guanidine (7):** The same procedure as described above starting from N^1,N^3-bis(3-methoxypropyl)carbodiimide (3.28 g, 17.5 mmol) and 3-methoxypropyl-1-amine (3.60 mL, 3.14 g, 35 mmol) in dry THF (23 mL) afforded pure **7** (4.44 g, 16 mmol, 91%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.80 (m, 6 H), 3.15 (t, $J_{H,H}$ = 6.6 Hz, 6 H), 3.34 (s, 9 H), 3.46 (t, $J_{H,H}$ = 5.9 Hz, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C, TMS): δ = 30.21, 40.87, 58.57, 71.17, 153.12 ppm. HRMS: calcd. for $C_{13}H_{29}N_3O_3$ $[M + H]^+$ 276.228168; found 276.225512.

Synthesis of Reference Compounds: The synthesis and purifications of reference compounds P1, P2, P3 and P5 are described in ref.[33], and the synthesis of compounds P4 and P7 in ref.[7f] In this work the Staudinger reaction was used to synthesize new compound P6 as well as for a new synthesis of known compounds P4 and P5 according to the scheme:



where pyrr denotes the pyrrolidino group.

The reaction conditions are not optimized. The compounds were isolated as their $HBPh_4$ salts, and the free bases were liberated by means of MeOK as described in ref.[19] (a mixture of THF/MeOH was used as solvent).

4-CF_3-$C_6H_4P_2$(pyrr)·$HBPh_4$: To the solution of 4-trifluoromethylphenylazide[34] (6.9 mmol, 1.30 g) in benzene (8 mL) was added a solution of $(pyrr)_2PCl$[34] (6.9 mmol, 1.31 g) in benzene (4 mL) by syringe at room temperature under flow of argon. The mixture was stirred and heated at reflux for 1 h. To the warm mixture of $HN=P(pyrr)_3$ (4.24 g, 16.6 mmol) was added the free base[35] in benzene (3 mL), and the mixture was heated at reflux for another 4 h. The solvent was distilled off, and to the residue was added dry THF (10 mL). Precipitated $HN=P(pyrr)_3$·HCl was filtered off and THF was removed. The rest, dark brown viscous oil, was dissolved in MeOH (11 mL), and a solution of $NaBPh_4$ (3.4 g) in MeOH was added to precipitate the title compound. The raw product was recrystallized (2×; EtOH/MeCN, 3:1) to give colorless crystals (yield 24%). M.p. 209.7–210.7 °C. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ = 1.72 (m, 12 H), 1.77 (m, $J_{P,H}$ = 6.8 Hz, 8 H), 2.92 (dt, $J_{H,H}$ = 6.6 Hz, $J_{P,H}$ = 3.5 Hz, 12 H), 3.00 (m, 8 H), 4.73 (d, $J_{P,H}$ = 10.8 Hz, 1 H), 6.61 (d, $J_{H,H}$ = 8.5 Hz, 2 H), 6.87 (t, $J_{H,H}$ = 7.0 Hz, 4 H), 7.01 [t, $J_{H,H(av)}$ = 7.5 Hz, 8 H], 7.33–7.46 (m, 10 H) ppm. ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 26.2 (d, $J_{P,C}$ = 8.7 Hz), 26.4 (d, $J_{P,C}$ = 9.5 Hz), 46.8 (d, $J_{P,C}$ = 5.2 Hz), 47.0 (d, $J_{P,C}$ = 5.8 Hz), 118.1 (d, $J_{P,C}$ = 7.1 Hz), 121.6, 124.3 (q, $J_{F,C}$ = 33.0 Hz), 125.4 (q, $J_{B,C}$ = 2.8 Hz), 126.4 (q, $J_{F,C}$ = 2.8 Hz), 136.3, 142.4, 164.3 (q, $J_{B,C}$ = 49.5 Hz) ppm.$C_{51}H_{65}BF_3N_7P_2$ (905.87): calcd. C 67.62, H 7.23, N 10.82; found C 67.53, H 7.26, N 10.81.

Free Base, Reference P6: ^{1}H NMR (200.13 MHz, [D_8]THF): δ = 1.8 (m, 20 H, overlapped by solvent), 3.13 (dt, $J_{H,H}$ = 6.6 Hz, $J_{P,H}$ = 4.3 Hz, 12 H), 3.16 (m, 8 H), 6.64 (d, $J_{H,H}$ = 8.7 Hz, 2 H), 7.07 (d, $J_{H,H}$ = 8.7 Hz, 2 H) ppm. ^{13}C NMR (50.32 MHz, [D_8]THF): δ = 27.0 (d, $J_{P,C}$ = 8.2 Hz), 27.3 (d, $J_{P,C}$ = 8.5 Hz), 47.4 (d, $J_{P,C}$ = 4.0 Hz), 47.8 (d, $J_{P,C}$ = 4.7 Hz), 114.4 (q, $J_{F,C}$ = 31.5 Hz), 121.9 (d, $J_{P,C}$ = 21.8 Hz), 125.6 (dq, $J_{P,C}$ = 2.4 Hz, $J_{F,C}$ = 3.8 Hz), 159.2 ppm.

Measurements of pK_a in Acetonitrile: The measurements were carried out by using a previously developed method in one of our groups,[36] that is, by UV/Vis spectrophotometric titration of a solution, where both of the bases are present, with an optically transparent acid or base. In all experiments the simultaneous titration of two free bases of comparable basicity with an acid was carried out, and the UV/Vis spectrum was recorded after each addition of acidic titrant. Also, both bases were titrated separately. A professional glove box was used to ensure that the environment was free from humidity and oxygen. Concentrations of measured bases were in the 5×10^{-5} mol L^{-1} range during the titration experiments, concentration of acidic and basic titrants were usually around 5×10^{-4} mol L^{-1}. For a more detailed description of the experimental set up the reader is referred to ref.[17] Acetonitrile (MeCN) [Romil, >99.9%, Super purity Solvent (Far UV), water content <0.005%] was the same as that used in previous works[17,36] and was used without further purification. The water content was determined by coulometric Karl Fischer titration to be about 0.004%. A solution of methanesulfonic acid ($MeSO_3H$) (>99%) was used as acidic titrant. A solution of phosphazene base EtP_2(dma) (>98%) was used[17] as basic titrant.

Supporting Information (see footnote on the first page of this article): Procedure for the synthesis of phosphazenes P4 and P5 and their tetraphenylborate salts; copy of the ^{1}H and ^{13}C NMR spectra of all new guanidine derivatives and phosphazenes; description of the procedure for determination of the pK_a values; Cartesian coordinates of the studied neutral and protonated guanidine derivatives; summary of the measured and calculated gas-phase PAs.

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[1] J. V. Greenhill, P. Lue in *Progress in Medicinal Chemistry* (Eds.: G. P. Ellis, D. K. Luscombe), Elsevier Science Publishers, **1993**, vol. 30, pp. 206–327 and references cited therein.
[2] R. G. S. Berlinck, *Nat. Prod. Rep.* **1999**, *16*, 339–365.
[3] C. W. Young, G. Schochetman, S. Hodas, H. E. Balis, *Cancer Res.* **1967**, *27*, 535–540.
[4] a) G. Varani, *Acc. Chem. Res.* **1997**, *30*, 189–195; b) V. A. Russel, M. D. Ward, *J. Mater. Chem.* **1997**, *7*, 1123–1133.
[5] T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, 737–752 and references cited therein.
[6] a) D. Simoni, R. Rondanin, M. Morini, R. Baruchello, F. P. Invidiata, *Tetrahedron Lett.* **2000**, *41*, 1607–1610; b) D. Bensa, J. Rodriguez, *Synth. Commun.* **2004**, *34*, 1515–1533; c) W. Ye, J. Xu, C.-T. Tan, C.-H. Tan, *Tetrahedron Lett.* **2005**, *46*, 6875–6878; d) G. Gelbard, F. Vielfaure-Joly, *Tetrahedron Lett.* **1998**, *39*, 2743–2746.
[7] a) B. Kovačević, Z. Glasovac, Z. B. Maksić, *J. Phys. Org. Chem.* **2002**, *15*, 765–774; b) Z. B. Maksić, B. Kovačević, *J. Org. Chem.* **2000**, *65*, 3303–3309; c) V. Raab, J. Kipke, R. M. Gschwind, J. Sundermeyer, *Chem. Eur. J.* **2002**, *8*, 1682–1693; d) B. Kovačević, Z. B. Maksić, *Chem. Eur. J.* **2002**, *8*, 1694–1702; e) V. Raab, K. Harms, J. Sundermeyer, B. Kovačević, Z. B. Maksić, *J. Org. Chem.* **2003**, *68*, 8790–8797; f) A. A. Kolomeitsev, I. A. Koppel, T. Rodima, J. Barten, E. Lork, G.-V. Röschenthaler, I. Kaljurand, A. Kütt, I. Koppel, V. Mäemets, I. Leito, *J. Am. Chem. Soc.* **2005**, *127*, 17656–17666; g) B. Kovačević, Z. B. Maksić, *Chem. Commun.* **2006**, 1524–1526; h) I. Kaljurand, I. A. Koppel, A. Kütt, T. Rodima, I. Koppel, M.

Mishima, I. Leito, *J. Phys. Chem. B* **2007**, *111*, 1245–1250; i) E.-I. Rõõm, A. Kütt, I. Kaljurand, I. Koppel, I. Leito, I. A. Koppel, M. Mishima, K. Goto, Y. Miyahara, *Chem. Eur. J.* **2007**, *13*, 7631–7641 and references cited there.

[8] a) E. D. Raczynska, M. K. Cyranski, M. Gutowski, J. Rak, J.-F. Gal, P.-C. Maria, M. Darowska, K. Duczmal, *J. Phys. Org. Chem.* **2003**, *16*, 91–106; b) E. D. Raczynska, M. Decouzon, J.-F. Gal, P.-C. Maria, G. Gelbard, F. Vielfaure-Joly, *J. Phys. Org. Chem.* **2001**, *14*, 25–34; c) E. D. Raczynska, J.-F. Gal, P.-C. Maria, *J. Phys. Org. Chem.* **1994**, *7*, 725–733; d) E. D. Raczynska, P.-C. Maria, J.-F. Gal, M. Decouzon, *J. Org. Chem.* **1992**, *57*, 5730–5735; e) M. Decouzon, J.-F. Gal, P.-C. Maria, E. D. Raczynska, *J. Org. Chem.* **1991**, *56*, 3669–3673.

[9] a) B. Kovačević, Z. B. Maksić, R. Vianello, M. Primorac, *New J. Chem.* **2002**, *26*, 1329–1334; b) B. Kovačević, Z. B. Maksić, *Chem. Eur. J.* **2002**, *8*, 1694–1702; c) Z. B. Maksić, Z. Glasovac, I. Despotović, *J. Phys. Org. Chem.* **2002**, *15*, 499–508.

[10] a) H. A. Staab, A. Kirsch, T. Barth, C. Krieger, F. A. Neugebauer, *Eur. J. Org. Chem.* **2000**, 1617–1622; b) H. A. Staab, C. Krieger, G. Hieber, K. Oberdorf, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1884–1886; c) H. A. Staab, T. Saupe, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 865–879.

[11] R. W. F. Alder, *Chem. Rev.* **1989**, *89*, 1215–1223.

[12] a) G. Bouchoux, D.-A. Buisson, *Int. J. Mass Spectrom.* **2006**, *249–250*, 412–419; b) M. Mautner, P. Hamlet, E. P. Hunter, F. H. Field, *J. Am. Chem. Soc.* **1980**, *102*, 6393–6399; c) R. Yamdagni, P. Kebarle, *J. Am. Chem. Soc.* **1973**, *95*, 3504–3510.

[13] Z. Glasovac, B. Kovačević, E. Meštrović, M. Eckert-Maksić, *Tetrahedron Lett.* **2005**, *46*, 8733–8736.

[14] M. Eckert-Maksić, Z. Glasovac, Patent appl. HR P20040341, **2004**; M. Eckert-Maksić, Z. Glasovac, International Patent appl. PCT/HR2005/000026, **2005**.

[15] Z. Glasovac, M. Eckert-Maksić, to be published.

[16] Z. Glasovac, V. Štrukil, M. Eckert-Maksić, D. Schröder, M. Kaczorowska, H. Schwarz, *Int. J. Mass Spectrom.* **2008**, *270*, 39–46.

[17] I. Kaljurand, A. Kütt, L. Sooväli, T. Rodima, V. Mäemets, I. Leito, I. A. Koppel, *J. Org. Chem.* **2005**, *70*, 1019–1028.

[18] L. Sooväli, I. Kaljurand, A. Kütt, I. Leito, *Anal. Chim. Acta* **2006**, *566*, 290–303.

[19] a) B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *106*, 5151–5158; b) B. Mennucci, E. Cancès, J. Tomasi, *J. Phys. Chem. B* **1997**, *101*, 10506–10517; c) J. Tomasi, B. Mennucci, E. Cancès, *THEOCHEM* **1999**, *464*, 211–226.

[20] a) S. Miertuš, E. Scrocco, J. Tomasi, *Chem. Phys.* **1981**, *55*, 117–129; b) S. Miertuš, J. Tomasi, *Chem. Phys.* **1982**, *65*, 239–245.

[21] a) K. B. Wiberg, P. R. Rablen, D. J. Rush, T. A. Keith, *J. Am. Chem. Soc.* **1995**, *117*, 4261–4270; b) J. B. Foresman, T. A. Keith, K. B. Wiberg, J. Snoonian, M. J. Frisch, *J. Phys. Chem.* **1996**, *100*, 16098–16104.

[22] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision B.03, Gaussian, Inc., Pittsburgh, PA, **2003**.

[23] R. Schwesinger, J. Willaredt, H. Schlemper, M. Keller, D. Schmitt, H. Fritz, *Chem. Ber.* **1994**, *127*, 2435–2454.

[24] The pK_a value of TMG was also measured in this work. TMG was found to be a stronger base by 0.24 units than the phosphazene base 4-MeO-$C_6H_4P_1$(pyrr) and a weaker base by 0.50 units than 4-NMe_2-$C_6H_4P_1$(pyrr);[17] the pK_a value of TMG is therefore 23.4 units.

[25] In addition, for three of the investigated guanidines, namely **1**, **4**, and **7**, we also calculated enthalpies and free energies of protonation with the B3LYP/6-311+G(d,p) method, which was recently shown[7h] to give an excellent description of the experimental gas-phase basicities (GBs) of the wide range (GB varies from 190 to 265 kcal mol^{-1}) of organic bases (amines, phosphazenes, guanidines, etc.). However, this did not influence the quality of the results reported earlier in ref.[16] Specifically, at this level of theory, the PA of base **1** was found to be lower by ca 1 kcal mol^{-1} and PAs of bases **4** and **7** were higher by 1 and 2 kcal mol^{-1}, respectively, than those calculated with the B3LYP/6-311+G(2df,p)/B3LYP/6-31G(d) method (Table S1).

[26] a) J.-N. Li, Y. Fu, L. Liu, Q.-X. Guo, *Tetrahedron* **2006**, *62*, 11801–11813; b) M. Peräkylä, *J. Org. Chem.* **1996**, *61*, 7420–7425; c) S. Hwang, Y. H. Jang, D. S. Chung, *Bull. Kor. Chem. Soc.* **2005**, *26*, 585–588; d) B. Kallies, R. Mitzner, *J. Phys. Chem. B* **1997**, *101*, 2959–2967; e) F. Eckert, A. Klamt, *J. Comput. Chem.* **2006**, *27*, 11–19.

[27] B. Kovačević, Z. B. Maksić, *Org. Lett.* **2001**, *3*, 1523–1526.

[28] For example, see: a) G. Schüürmann, *Chem. Phys. Lett.* **1999**, *302*, 471–479; b) M. W. Palascak, G. C. Shields, *J. Phys. Chem. A* **2004**, *108*, 3692–3694; c) M. D. Liptak, G. C. Shields, *J. Am. Chem. Soc.* **2001**, *123*, 7314–7319; d) G. I. Almerindo, D. W. Tondo, J. R. Pliego Jr., *J. Phys. Chem. A* **2004**, *108*, 166–171; e) Z.-K. Jia, D.-M. Du, Z.-Y. Zhou, A.-G. Zhang, R.-Y. Hou, *Chem. Phys. Lett.* **2007**, *439*, 374–380.

[29] G. Bouchoux, *Mass Spectrom. Rev.* **2007**, *26*, 775–835; and references cited therein.

[30] A. F. McKay, D. L. Garmaise, H. A. Baker, L. R. Hawkins, V. Falta, R. Gaudry, G. Y. Paris, *J. Med. Chem.* **1963**, *6*, 587–595.

[31] H. Z. Lecher, K. Gubernator, *J. Am. Chem. Soc.* **1953**, *75*, 1087–1092.

[32] The reaction was conducted in dry CH_2Cl_2 at room temperature instead of in refluxing benzene, which was employed in ref.[31]

[33] T. Rodima, I. Kaljurand, A. Pihl, V. Mäemets, I. Leito, I. Koppel, *J. Org. Chem.* **2002**, *67*, 1873–1881.

[34] I. Kaljurand, T. Rodima, A. Pihl, V. Mäemets, I. Leito, I. A. Koppel, M. Mishima, *J. Org. Chem.* **2003**, *68*, 9988–9993.

[35] R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dambacher, T. Breuer, C. Ottaway, M. Fletschinger, J. Boele, H. Fritz, D. Putzas, H. W. Rotter, F. G. Bordwell, A. V. Satish, G.-Z. Ji, E.-M. Peters, K. Peters, H. G. von Schnering, L. Walz, *Liebigs Ann.* **1996**, 1055–1081.

[36] I. Kaljurand, T. Rodima, I. Leito, I. Koppel, R. Schwesinger, *J. Org. Chem.* **2000**, *65*, 6202–6208.

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