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Hyperstrong Neutral Organic Bases: Phosphazeno Azacalix[3](2,6)pyridines

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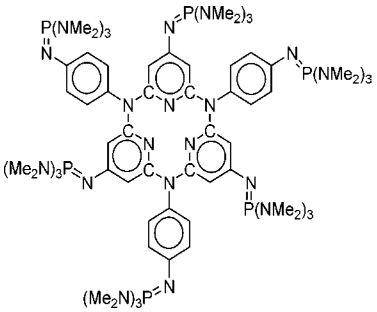
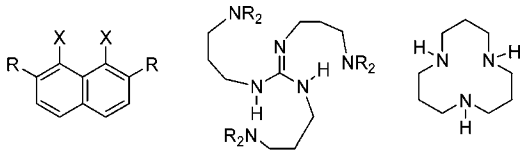
ABSTRACT



The gas-phase basicities and pK_a values in acetonitrile of tris(phosphazeno)-substituted azacalix[3](2,6)pyridine and some related compounds are examined by DFT computational method. It is shown that the hexakis(phosphazeno) derivative of azacalix[3](2,6)pyridine is a hyperstrong neutral base as evidenced by the absolute proton affinity (APA) of 314.6 kcal mol^{-1} and pK_a(MeCN) of 37.3 units. It is a consequence of the very strong bifurcated hydrogen bond (32 kcal mol^{-1}) and substantial cationic resonance effect.

It is common knowledge that neutral organic bases and superbases possess a number of advantageous properties compared to their inorganic counterparts. Therefore, it comes as no surprise that design and syntheses of the former compounds are still the focus of scientific interest. Probably the most important single contribution to the chemistry of superbases was Alder's synthesis of 1,8-bis(dimethylamino)-naphthalene (DMAN)[1,2] **1** (Figure 1), which has opened a series of investigations of this and related systems. The absolute proton affinity (APA) of DMAN of 245.3 kcal mol^{-1} is generally accepted as the threshold of superbasicity.[3,4] Increased basicity is a result of the nitrogen lone pair repulsion in the initial base and the strength of the hydrogen bonding in the final conjugate acid. This can be enhanced by the OMe substitution at the 2,7 positions (**2**), which was rationalized by a relief of steric repulsion between the methoxy groups with their neighboring amino groups



1 (X = NMe_2;R=H)
2 (X = NMe_2;R=OH)
3 (X = NMe_2;R=O^-)
4 (X = $N(Me_2)_2$;R=H)
5 (X = $NP(NMe_2)_3$;R=H)

6 (R=H)
7 (R=Me)

8

Figure 1. Pictorial representation of some known superbases.

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upon protonation.[5] The scope of proton sponges of DMAN-type was extended by Staab and co-workers by introducing inter alia different spacers.[6−8] A particularly interesting case is given by 1,8-bis(dimethylamino)naphthalene-2,7-diolate (**3**), which was experimentally observed recently.[9] It exhibits an enormous APA of 424.8 kcal mol^{-1} in the gas phase according to calculations. However, **3** is a dianion, which in turn has dramatically lower APA in DMSO. A conceptual leap in designing neutral superbases was accomplished by replacing NMe_2 groups in DMAN by guanidino and phosphazeno moieties, leading to TMGN (**4**)[10−12] and HMPN (**5**),[13] respectively. Their basicities considerably surpass that of the archetypal DMAN as a consequence of the strong resonance-assisted hydrogen bond induced by the chelated proton in the conjugate acids. It is important to stress that TMGN and HMPN possess favorable kinetics of proton transfer which makes them good candidates for catalysts.[11−13] Moreover, their nucleophilic susceptibility is low, since the excess of positive charge is efficiently dispersed over all the conjugate acids. Obviously, the formation of the intramolecular H-bond is an important factor in stabilizing the protonated species and a fruitful motif in designing superbases. This idea was explored in tailoring neutral superbases by taking advantage of the multiple intramolecular hydrogen bond (IMHB) effect in **6** and **7** guanidine derivatives.[14] The latter compound has been synthesized, characterized, and examined in detail.[15] It was shown that it exhibits very good catalytic properties in Knoevenagel condensation reactions.[16] Further, Bell and co-workers[17] found that linkage of three amino groups by three methylene groups yields bicyclic triamine **8** and that its derivatives[18] provide powerful bases being strongly stabilized by the intra-annular protonation, thus forming a IMHB network within the molecular cavity. The important feature is that these systems retain rapid proton-transfer kinetics despite the fact that the proton is placed within the bicyclic moiety. Finally, it is noteworthy that Alder designed by computational method a set of C_2-chiral diamines based on the 1,6-diazacyclodecane skeleton and which are strongly basic (both in the gas phase and MeCN) by profitting from the IMHB stabilization occurring in the corresponding conjugate acids.[19] It is important to emphasize that all of these bases exhibit high thermodynamic stability in the protonated forms (and favorable kinetics and low nucleophilicity as a rule), which makes them useful reagents. Building on these results we have undertaken to examine almost planar cyclic suprastructures involving pyridine as the essential building block.[20] Very interesting molecular frameworks are offered by azacalix[*n*](2,6)-pyridines recently prepared by Kanbara, Yamamoto, and co-workers[21,22] with varying number [*n*] of the recurring (pyridine) subunits. In particular, it turned out that the cyclic trimer **9** provide a molecular framework convenient for construction of strong neutral superbases with the proviso that suitable substituents are selected and put on the right positions. For instance, hexakis(dimethylamino) derivative **10** has gas-phase APA of 296.6 kcal mol^{-1}, its basicity is 291.3 kcal mol^{-1}, and pK_a(MeCN) = 30.9 units. It is the aim of the present letter to provide evidence that some phosphazeno derivatives exhibit hyperstrong basicity, implying that their absolute proton affinities exceed the upper borderline of superbasicity of 300 kcal mol^{-1}. The studied systems **11**−**14** are given in Figure 2. The APA values and basicities in the gas phase are calculated by the B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) method. The computational procedure and formulas are published elsewhere.[20] Perusal of the results shows that phosphazeno derivatives of azacalix[3]-(2,6)pyridines **11**, **13**, and **14** qualify as hyperstrong neutral bases in the gas phase since their APA(g) values are 302.0, 307.4 and 314.6 kcal mol^{-1}, respectively. Derivative **12** is a borderline cases with APA(g)(**12**) = 299.5 kcal mol^{-1}. It appears that methyl substitution of the amino groups decreases APA(g) by 2.5 kcal mol^{-1} and that the most efficacious amino substituent is *p*-phenyl-$NP(NMe_2)_3$ in **14**, whose protonation energy significantly enters the domain of

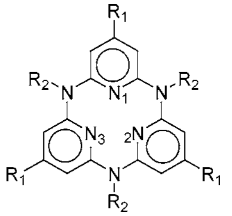

Figure 2. Pictorial representation of molecules **9** (R_1 = H; R_2 = $Phe_{para}-Me$), **10** (R_1 = NMe_2; R_2 = $Phe_{para}-NMe_2$), **11** (R_1 = $NP(NMe_2)_3$; R_2 = H), **12** (R_1 = $NP(NMe_2)_3$; R_2 = Me), **13** (R_1 = $NP(NMe_2)_3$; R_2 = $Phe_{para}-NMe_2$) and **14** (R_1 = $NP(NMe_2)_3$; R_2 = $Phe_{para}-$ $NP(NMe_2)_3$).

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the deprotonation energies of strong mineral acids and superacids. The latter conclusion also holds for **11** and **13**. The corresponding basicities are given in Table 1. The reasons behind these high APAs are found in the structural features of bases and their conjugate acids. The coordinates are given in the Supporting Information. Important interatomic distances describing cavities of the neutral and protonated bases are displayed in Table 2. The protonated nitrogen is denoted as N_1, whereas the proton is signified by $H^{\delta+}$ with the effective positive charge given in the superscript. It appears that pyridine nitrogens are the most basic sites in this family of compounds. The hydrogen bond is bifurcated, being placed and shared almost symmetricaly between the N_2 and N_3 atoms in all cases, the CH_3 derivative **12** being a notable exception. The methyl substitution introduces severe nonplanarity which is reflected in the structural parameters of **12** and in the IMHB parameters of **12**H^+. Specifically, the interatomic distances $d(N_2{\cdots}H^{\delta+})$ and $d(N_3{\cdots}H^{\delta+})$ in **12**H^+ are 1.73 and 1.81 Å, respectively, to be compared with the value of 1.72 Å in the symmetric IMHB of **11**H^+. The nonbonding contacts $d(N_1{\cdots}N_2)$ and $d(N_1{\cdots}N_3)$ are also larger in **12**H^+ than in the protonated system **11**H^+ (Table 2). One can safely conclude that the IMHB in **12**H^+ is weaker, which leads to a decrease in the proton affinity despite the inductive effect of the CH_3 groups. In contrast, the phenyl groups in derivatives **13** and **14** are almost perpendicular to the molecular framework, thus perturbing it to a lesser extent. As a consequence, the IMHB in **13**H^+ and **14**H^+ is symmetric as in **11**H^+ with practically the same structural parameters. It follows that the IMHB strengths are very close and that the increased basicity occurs due to the stronger cationic resonance effect. This conclusion is supported by increased planarization of the systems **13**H^+ and **14**H^+ (Figure S1) upon protonation and decreased pyramidalization of the amino nitrogens, which is a hallmark of the cationic resonance.

Table 1. Absolute Gas-Phase Proton Affinities APA(g) and Basicities GB(g) and the APA in the MeCN Solutions[a]

molecule	APA(g)	GB(g)	δ^+	APA(MeCN)	pK_a(MeCN)
pyridine	223.2	215.7	0.53	272.5	12.2
9	275.3	267.7	0.53	293.7	23.1(exp)
10	296.6	291.3	0.53	304.8	30.9[23]
11	302.0	296.3	0.53	307.9	35.8
12	299.5	290.3	0.51	303.6	30.4
13	307.4	298.9	0.53	307.5	33.8
14	314.6	305.9	0.53	311.1	37.3

[a] Theoretical pK_a values are estimated by eq 1 using the B3LYP/6-31+G* computational scheme. The proton charge δ^+ is calculated by Mulliken population analysis.

Table 2. The Relevant (Non)bonded Distances (in Å) Describing the Cavity of Neutral and Protonated Bases

mol	$N_1{\cdots}N_2$	$N_1{\cdots}N_3$	$N_2{\cdots}N_3$	$N_1{\cdots}H^{\delta+}$	$N_2{\cdots}H^{\delta+}$	$N_3{\cdots}H^{\delta+}$
11	2.66	2.66	2.62	–	–	–
11H^+	2.55	2.55	2.59	1.06	1.72	1.72
12	2.69	2.66	2.71	–	–	–
12H^+	2.57	2.61	2.64	1.05	1.73	1.81
13	2.67	2.66	2.72	–	–	–
13H^+	2.55	2.55	2.59	1.05	1.73	1.73
14	2.66	2.65	2.71	–	–	–
14H^+	2.55	2.55	2.59	1.05	1.73	1.73

A word on the proton charges δ^+ is appropriate here. There are several ways to define the effective charges of atoms in molecules. The results are not unique, and the question of the best criterion is still open. We shall employ here two recipes in extracting atomic charges from the total molecular wavefunctions. The first is offered by Mulliken 50:50 division of the mixed interatomic densities,[24] whereas the second is given by the natural bond orbital partitioning of the electron density to the local hybrid orbitals.[25] It appears that the effective positive charge of the bonded proton in conjugate acids is practically constant. It is +0.53|e| according to Mulliken with an exception found in **12**H^+, where it assumes +0.51|e|. It is also uniform by the NBO analysis, which yields +0.50|e| for protonated species **9**−**14**. It means that 0.5 of the electron density is transferred to the proton and that 0.5 of the positive charge of the proton is dispersed over the conjugate acids. Although both Mulliken and NBO criteria exaggerate the ionic character of the chemical bonds,[26] we shall use these estimates, keeping in mind that they are only approximations. The bottom line is that the bonded proton $H^{\delta+}$ is affecting two lone pairs of the N_2 and N_3 atom, thus contributing to a strong stabilization inter alia by appreciable Coulombic interaction. It is also important to mention that these bifurcated H-bonds are resonance assisted. Namely, they polarize N_2 and N_3 atoms and trigger the cationic resonance in the lower parts of the conjugate acids. This kind of the cationic resonance could be quite strong, and in 1,8-bis(tetramethylguanidino)naphthalene (TMGN) it is 50% of that taking place in the directly protonated guanidine fragment.[27] In order to illustrate the role of the IMHB in amplifying basicity, we consider the progenitor of the family of azacalix[3](2,6)pyridines, which is obtained by putting R1 = R2 = H and presented in Figure S2. It is denoted by **15**, whereas its open-chain protonated form is signified by **16**H^+ (Figure S3). It turns out that APAs of **15** and **16** are 267.7 and 235.3 kcal mol^{-1}, respectively, implying that the bifurcated IMHB in **15**H^+ contributes 32.4 kcal mol^{-1} to the proton affinity. Another point of interest is enhancement of basicity in the pyridine para-substituted by the $-N{=}P(NMe_2)_3$ group. It appears that the APA of pyridine (Table 1) is increased by 31.8 kcal mol^{-1} upon

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substitution. These two effects taken together yield amplification of 64 kcal mol^{-1}. The rest yielding hyperstrong basicity with APA $\geq$ 300 kcal mol^{-1} can be ascribed to the cationic resonance spread over all fragments of the suprastructures. As a final comment it should be mentioned that the use of the additional polarization and diffuse functions in optimizing the structures within the B3LYP/6-31++G** method did not change the APA of **15** at all, which lends credence to the applied methodology.

It is of interest to estimate pK_a values of hyperstrong bases in acetonitrile. According to Shields and co-workers[28] basicity of a base **B** can be computed relative to the known (experimental) basicity of base A by:

$$pK_a(\mathbf{B}\mathrm{H}^+) = pK_a(\mathbf{A}\mathrm{H}^+) + \{G_{\mathrm{gas}}(\mathbf{B}) - G_{\mathrm{gas}}(\mathbf{A}) - G_{\mathrm{gas}}(\mathbf{B}\mathrm{H}^+) + G_{\mathrm{gas}}(\mathbf{A}\mathrm{H}^+) + \Delta G_{\mathrm{sol}}(\mathbf{B}) - \Delta G_{\mathrm{sol}}(\mathbf{A}) - \Delta G_{\mathrm{sol}}(\mathbf{B}\mathrm{H}^+) + \Delta G_{\mathrm{sol}}(\mathbf{A}\mathrm{H}^+)\}/2.303\ RT \quad (1)$$

where symbols have their usual meaning. Since the considered systems are sizable and the influence of the solvent requires several iterations, the computations had to be executed at a lower level of theory than in the gas phase. This was accomplished by making use of the B3LYP/6-31+G* model. The anchor base A with the known pK_a value of 23.1 units was **9**, as measured by Kanbara, Yamamoto, and co-workers.[29] Solvation energies for all species were computed using polarizable continuum model (PCM).[30]

The absolute proton affinities APA(MeCN) and estimated pK_a(MeCN) values are given in Table 1. It should be noted that APA(g) and APA(MeCN) are not directly comparable, because they are calculated by different models. The results presented in Table 1 show that **11**, **13**, and **14** are very strong bases in acetonitrile, too, as evidenced by pK_a values of 35.8, 33.8, and 37.3 units, respectively. Thus, the considered molecules provide important rungs in the upper part of the superbasicity ladder in the gas phase and acetonitrile, which is one of the very important organic solvents.

To summarize, the parent tris(phosphazeno) azacalix[3]-(2,6)pyridine **11** and its phenyl derivatives **13** an **14** are excellent candidates for ultrastrong neutral bases in the gas phase. They show also very high basicities in acetonitrile. Since the protonation takes place within the (approximately) planar macrocycle, it is expected that kinetics of the proton transfer would be favorable in spite of the bulky peripheral substituent groups. It is beyond doubt that the protonation area is easily accessible by molecules such as acetylene and cyclopentadiene. This and other proton-transfer reactions will be studied in the future. The non-nucleophilic character of these compounds follows from the fact that the positive charge is distributed over large suprastructures of the conjugate acids. Finally, very high thermodynamic stability of the protonated species, originating in strong intra-annular bifurcated hydrogen bond acting in concert with phosphazeno substituents and appreciable cationic resonance spread over the suprastructures, indicates that this family of compounds might provide very useful chemical agents. It is worth mentioning that we also examined a number of derivatives of azacalix[4](2,6)pyridines, but they exhibited considerably lower basicities due to weaker intramolecular hydrogen bonds occurring in conjugate acids and a lower cationic resonance.[31]

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Supporting Information Available: Geometrical parameters of neutral and protonated systems **11**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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