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# Derivatives of Azacalix[3](2,6)pyridine are Strong Neutral Organic Superbases: A DFT Study

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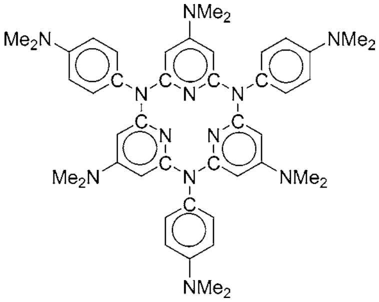
## ABSTRACT



**The gas phase basicities and p$K_a$ values in acetonitrile of azacalix[3](2,6)pyridine and its derivatives are determined by the B3LYP DFT method. It is found that all compounds of this series are neutral organic superbases. The proton attacks the inner pyridine N(sp$^2$) atom, thus forming a bifurcated intramolecular hydrogen bond. The most powerful superbase is provided by the hexakis(dimethylamino) derivative of the title compound. Its gas phase proton affinity is 296.6 kcal mol$^{-1}$, its basicity is 291.3 kcal mol$^{-1}$, and its p$K_a$(MeCN) is 30.9 units.**

Design of neutral organic bases and superbases and their synthesis attracted a lot of attention and efforts recently[1−16] because they exhibit some advantageous features compared to their inorganic counterparts.[17−20] Various structural and electronic motifs have been used in tailoring strong and ultrastrong bases. The intramolecular hydrogen bonds

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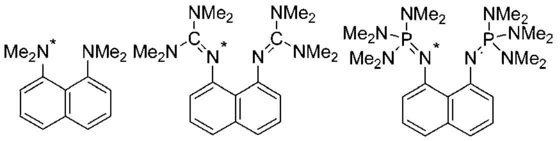
(IMHBs) belong to the most important ones since the introduction of the first proton sponge, 1,8-bis(dimethylamino)naphthalene (DMAN)[21,22] **1**, depicted in Figure 1. The protonated nitrogen is denoted by an asterisk. Its absolute proton affinity (APA) is 245.3 kcal mol$^{-1}$, which represents the threshold for the superbasicity ladder.[23] An important extension of Alder's work is introduction of the tetramethylguanidinyl and hexamethyl(triaminophosphazenyl) substituents instead of dimethylamino groups in **2** and **3**, respectively.[8,24] They possess higher kinetic basicity than paradigmatic DMAN since the basic sites are less sterically protected.



**1** **2** **3**

**Figure 1.** Schematic representation of DMAN, TMGN, and HMPN proton sponges.

An additional degree of freedom in optimizing the systems **1**−**3** is offered by a possibility of changing the naphthalene moiety by other aromatic spacers, thus varying the N···N distance of the proton pincer.[25−27] It should be strongly emphasized that the concept of the IMHB proved particularly useful if utilized in a multiple fashion. Then the cooperative and collective IMHB effect leads to a considerable stabilization of the corresponding conjugate acids.[28−30] We shall use the intramolecular hydrogen bonding here in a different context. The H-bonding will take place inside the ring of the macrocycle, which in turn represents a promising molecular framework for organic superbases. In the present work, we discuss in some detail high basicity properties of $N$-($p$-tolyl)$^3$(2,6)pyridine **4** (Figure 2) synthesized by Kanbara, Yamamoto, and co-workers recently,[31] as well as some of its derivatives. The title system **4** was prepared with $R_1 = H$ and $R_2 = Me$. In addition, we shall consider derivatives **5** ($R_1 = R_2 = Me$), **6** ($R_1 = NMe_2$, $R_2 = Me$), and **7** ($R_1 = R_2 = NMe_2$). It is intuitively expected that proximity of the pyridine rings with nitrogens pointing to the center of the macrocycle might lead to a strong IMHB possessing a three-center character. Furthermore, the amino junctions of the macrocycle should enable an efficient propagation of the cationic resonance effect upon protonation. Hence, it is anticipated that systems **4**−**7** should exhibit high basicities. The presented results corroborate this conjecture.

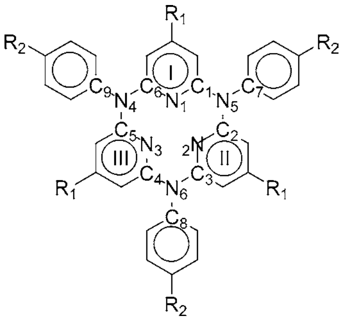


**Figure 2.** Pictorial representation of molecules **4** ($R_1 = H$, $R_2 = Me$), **5** ($R_1 = R_2 = Me$), **6** ($R_1 = NMe_2$, $R_2 = Me$), and **7** ($R_1 = R_2 = NMe_2$) and numbering of pivotal atoms.

The computational method of choice is the B3LYP/6-311+G(2df,p)//B3LYP/6-31G(d) approach, which represents a reasonable compromise between reliability and practicality, being applicable to quite large systems.[32,33] We shall not dwell on its characteristics and on formulas used in calculations APA and GB values because they are available elsewhere.[33]

The most basic sites are provided by pyridine nitrogens. The energetic data are given in Table 1. It appears that the gas phase absolute proton affinities are well above the superbasicity threshold. Moreover, hexakis(dimethylamino) derivative **7** comes close to the tentative upper borderline of neutral organic superbases of 300 kcal mol$^{-1}$ with its APA

**Table 1.** Absolute Gas Phase Proton Affinities APA(g) and Basicities GB(g) and the APAs in the MeCN Solutions. Theoretical p$K_a$ Values Are Estimated by Equation 2 Using B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) Scheme

| compound | APA(g) | GB(g) | APA(MeCN) | p$K_a$(MeCN) |
|---|---|---|---|---|
| **4** | 275.3 | 267.7 | 293.7 | 24.7 |
| **5** | 279.0 | 272.0 | 295.5 | 25.7 |
| **6** | 289.6 | 283.4 | 301.7 | 29.3 |
| **7** | 296.6 | 291.3 | 304.8 | 30.9 |

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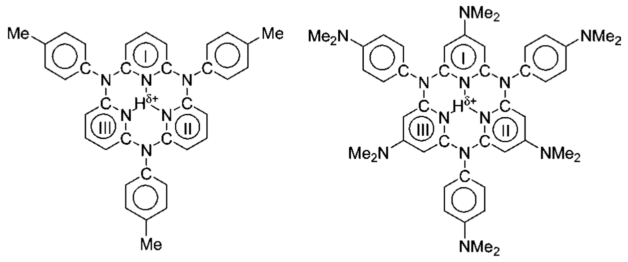
of 296.6 kcal $mol^{-1}$. Compounds **5** and **6** exhibit respectable basicities as evidenced by APAs of 279.0 and 289.6 kcal $mol^{-1}$, respectively. It follows that triple para-$CH_3$ substitution at three pyridine moieties increases APA by ~4 kcal $mol^{-1}$. Subsequent replacement of the methyl groups by $NMe_2$ substituents at three phenyls amplifies basicity by an additional 10 kcal $mol^{-1}$, thus being more significant. This is in accordance with a strong basifying effect of the $NMe_2$ group, which proved extremely useful in tailoring organic superbases.[24,27] The reason behind this is that the amino group undergoes significant planarization in the conjugated acids in order to ensure efficacious cationic resonance. It is, therefore, of interest to examine the salient structural features of the studied compounds. We selected the parent compound **4** and the most basic derivative **7** as well as their protonated form depicted in Figure 3 since a full account of all compounds lies outside the scope of this Letter. More details can be found in Supporting Information in Figures S1−4. We shall make use of the pyramidalization parameter called degree of pyramidalization,[34] for this purpose, since it describes (non)planarity of the directional covalent bond emanating from a particular atom.



**4H⁺** **7H⁺**

**Figure 3.** Schematic representation of the protonated forms **$4H^+$** and **$7H^+$**.

$$DP(\%) = [360° - \sum_{i=1}^{3} \alpha_i°]/0.9° \qquad (1)$$

Here summation goes over three apical angles of the pyramidalized atom. It appears that the system **4** is overcrowded and the repulsion between pyridine nitrogens leads to nonplanarity of the inner macrocycle. Taking $N_{(1)}$ at the ring I as a pivotal nitrogen and pyridine, respectively, it appears that rings II and III are shifted up and down by dihedral angles $N_{(2)}-C_{(2)}-N_{(5)}-C_{(1)}$ and $N_{(3)}-C_{(5)}-N_{(4)}-C_{(6)}$ of 46°. Consequently, the $N_{(1)}\cdots N_{(2)}$ and $N_{(1)}\cdots N_{(3)}$ nonbonded distances are practically equal 2.660 Å, whereas the $N_{(1)}\cdots N_{(3)}$ one is 2.705 Å. Thus, the nitrogen $N_{(1)}$ differs from $N_{(2)}$ and $N_{(3)}$, whereas the latter are placed in very similar chemical environments (Figure S1). The phenyl rings attached to $N_{(4)}$ and $N_{(5)}$ amino nitrogens close dihedral angles of 86 and 77° with the $C_{(9)}-N_{(4)}-C_{(5)}$ and $C_{(7)}-N_{(5)}-C_{(1)}$ planes, respectively. On the other hand, dihedral angles of these phenyls against $C_{(9)}-N_{(4)}-C_{(6)}$ and $C_{(7)}-N_{(5)}-C_{(1)}$ are correspondingly 70 and 63°. Deviations from full orthogonality are important because it enables transmission of the $\pi$-electron effect. Pyramidalization (DP%) of amino nitrogens is very low as evidenced by the values $N_{(4)}$(2.6%), $N_{(5)}$(2.0%), and $N_{(6)}$(0.0%), implying that they are practically planar. Protonation at $N_{(1)}$ causes dramatic structural changes. The conjugate acid **$4H^+$** becomes highly symmetric (Figure S2). More importantly, protonation at any of three pyridine nitrogens leads to the same final protonated structure of almost $C_s$ symmetry. The amino nitrogens $N_{(4)}$, $N_{(5)}$, and $N_{(6)}$ are perfectly planar. The macrocycle is planar within the accuracy of the method, and all three phenyl rings are perpendicular to the molecular plane. It is important to stress that the hydrogen bond is symmetrically shared by $N_{(2)}$ and $N_{(3)}$ atoms as evidenced by structural data. A distance between the proton denoted by $H^{\delta+}$ and $N_{(2)}$ and $N_{(3)}$ nitrogen is 1.745 Å. Further, the nonbonded distances between $N_{(1)}\cdots N_{(2)}$ and $N_{(1)}\cdots N_{(3)}$ are identical at 2.568 Å. They are considerably shortened relative to the neutral base **4**. The same holds for the $N_{(2)}\cdots N_{(3)}$ distance, which is 2.612 Å. The IMHB $N_{(1)}-H^{\delta+}\cdots N_{(2)}$ and $N_{(1)}-H^{\delta+}\cdots N_{(3)}$ angles are identical (131.5°). It follows that the IMHB in **$4H^+$** is an ideal bifurcated hydrogen bond, where the proton is equally shared by two nitrogens $N_{(2)}$ and $N_{(3)}$. It is plausible to conclude that it significantly contributes to the stability of **$4H^+$** and to enhanced basicity of **4**. The cationic resonance is reflected in lengthening $N_{(1)}-C_{(1)}$ and $N_{(5)}-C_{(7)}$ bonds and some shrinking of $C_{(1)}-N_{(5)}$ bonds (as well as their symmetric counterparts) in an alternating fashion. Interestingly, even the $N_{(6)}-C_{(4)}$ and $N_{(6)}-C_{(3)}$ bond distances are slightly shortened, whereas the $N_{(6)}-C_{(8)}$ bond is stretched. It means that the whole **$4H^+$** cation is influenced by protonation. The bond lengths in the unprotonated pyridines II and III are slightly affected, but some very small changes are noticeable (Figure S2). The structure of the superbase **7** is similar to that of the parent compound **4** concerning nonplanarity of the macrocycle (viz. Figure S3). A notable difference is given by the $NMe_2$ groups. Their nitrogens are pyramidalized by 4−5%. This is changed upon protonation at the $N_{(1)}$ atom, and the heavy atoms of the $NMe_2$ fragment (C−N−C) become practically coplanar with the host pyridine and phenyl rings, thus enabling efficient cationic resonance. Concomitantly, the C−N bond distances between the $NMe_2$ substituents and six-membered rings are lowered in **$7H^+$** (viz. Figures S3 and S4), implying that the positive charge is dispersed by the cationic resonance over all the conjugate acid including the most remote parts. The macrocycle in **$7H^+$** is not quite planar as in the **$4H^+$** case (Figure S4), but considerable planarization is introduced by protonation. The carbon−nitrogen bond lengths of the amino junction centers of the carbocycle reveal a typical resonance picture in which bonds are stretched and shrunk in an alternating way. The IMHB has a characteristic bifurcated feature, but it is not perfectly symmetrical as in **$4H^+$**. Hence, $N_{(2)}\cdots H^{\delta+}$ and

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$N_{(3)}\cdots H^{\delta+}$ distances slightly differ at 1.736 and 1.729 Å, respectively. They are smaller than the corresponding distance in **4H**$^+$ (1.745 Å), indicating a stronger bifurcated IMHB, which is compatible with the amplified basicity of **7**.

It is important to have at hand some information on the basicity of these interesting compounds in acetonitrile. The polarized continuum model (PCM) introduced by Scrocco, Tomasi, and Miertuš[35,36] proved useful in this respect. The molecular surface of the solvated system is obtained by the isodensity shell of 0.0004e $B^{-3}$, thus providing the isodensity (IPCM) polarized continuum model.[37] The dielectric constant $\epsilon$(MeCN) is 36.64. The calculations of the APAs in a solvent are much more demanding because the IPCM model requires several iterations. Hence, a more economical B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) computational scheme is necessary. The calculated APA(MeCN) can be correlated with the available experimental p$K_a$ data for 10 substituted pyridines, yielding the following linear relation obtained by the least-square fitting method:

$$pK_a(\text{MeCN}) = 0.5751 \times \text{APA(MeCN)} - 144.4 \text{ units} \quad (2)$$

The correlation is excellent as evidenced by the coefficient $R^2 = 0.993$ and the average absolute error of 0.1 unit. The results are presented in Table 1. The absolute proton affinities in MeCN are higher because the conjugate acids are additionally stabilized by interaction with an acetonitrile molecule, despite the fact that they are aprotic. It appears that **6** is a powerful superbase in MeCN, and the same holds for **7** to even greater extent.

These p$K_a$ values should be taken with a due care because formula 2 is obtained by using molecules without intramolecular hydrogen bonds.

To summarize, the title compound and its derivatives represent neutral organic superbases in the gas phase. Their APAs (GBs) are extended between 275 (268) and 297 (291) kcal mol$^{-1}$. The most basic system is given by the hexakis-(dimethylamino) substituted system **7**. The origin of the pronounced basicity of this family of molecules is identified as the cationic resonance in the conjugate acids and three-center intramolecular hydrogen bonding within the cavity induced upon protonation. The latter is of a bifurcated H-bridge type. It is perfectly symmetric in the protonated parent compound **4H**$^+$ and hexamethyl derivative **5H**$^+$. In protonated polyamino substituted azacalix[3](2,6)pyridines **6H**$^+$ and **7H**$^+$, it is almost symmetric. An equal or almost equal sharing of the proton carrying an effective $H^{\delta+}$ charge is obviously energetically very beneficial. It can be safely concluded that the strength of the IMHB increases along the series, thus contributing to the enhanced basicity. The p$K_a$-(MeCN) values of **4**, **5**, **6**, and **7** are 24.7, 25.7, 29.3, and 30.9 units, respectively, providing conclusive evidence that these compounds are strong superbases in MeCN solutions. The synthesis of **6** and **7** is therefore recommended.

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**Supporting Information Available:** Cartesian coordinates of neutral and protonated systems **4**−**7** and graphical representations of geometrical parameters of systems **4**, **4H**$^+$, **7**, and **7H**$^+$. This material is available free of charge via the Internet at http://pubs.acs.org.

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