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New Proton-Sponge-Like Macrocyclic Compound: Synergistic Hydrogen Bonds of Aminopyridine

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N,*N*′,*N*′′-Tris(*p*-tolyl)azacalix[3](2,6)pyridine (**1**) that shows a high proton affinity (pK_{BH+} = 23.1 in CD_3CN) has been classified as a new type of proton-sponge-like compound. X-ray crystallography reveals that **1** is ideal for accommodating a single proton in its cavity.

Introduction

Neutral organic bases and superbases play an important role in organic syntheses.[1–3] Since it has been reported that 1,8-bis(dialkylamino)naphthalenes with chelating nitrogens for a proton exhibit an unusually high basicity and behave as "proton sponges", many studies of related proton sponge compounds with chelating proton acceptors have been carried out.[2] Investigations have also been performed on the ability of polycyclic amines to encapsulate a proton in their cavity.[3] These polycyclic amines also exhibit a high basicity because of the synergistic effect of polycyclic amine nitrogens for accommodating a proton in their cavity.

We previously reported the preparation of *N*-substituted azacalix[*n*](2,6)pyridines (*n* = 3–8, and 10) by Pd- and Cu-catalyzed C–N bond formations.[4] Among the macrocyclic compounds, the structure of *N*,*N*′,*N*′′-tris(*p*-tolyl)azacalix[3](2,6)pyridine (**1**) is of particular interest because the arrangement of three pyridine nitrogen lone pairs in its cavity seems to be efficient for capturing a single proton. X-ray crystallography shows that the distances between pyridine nitrogen atoms (N_{py} atoms) in **1** are very short (2.602–2.671 Å),[4b] which are shorter than that between the nitrogen atoms (2.79 Å) in 1,8-bis(dimethylamino)naphthalene (**2**).[2b,2e,2g] We here report on the high proton affinity of **1** and the molecular structure of the inner monoprotonated form of **1** (**1a**).

Results and Discussion

The macrocyclic compound **1** was prepared according to our previous report.[4b] Compound **1** was monoprotonated by treatment with NH_4PF_6. The structure of **1a**·PF_6 was confirmed by spectroscopic methods, including X-ray crystallography (see below). As shown in Figure 1, the ^1H NMR spectrum of **1a**·PF_6 exhibits a new singlet signal at δ = 22.06 ppm in CD_3CN. The largely downfield-shifted proton signal indicates three strong $N_{py}\cdots H$ bridges in the cavity. The addition of excess amounts of strong acids such as $HClO_4$ and CF_3COOH seemed to lead to further protonation; however, such protonation could not be achieved by adding excess NH_4PF_6.

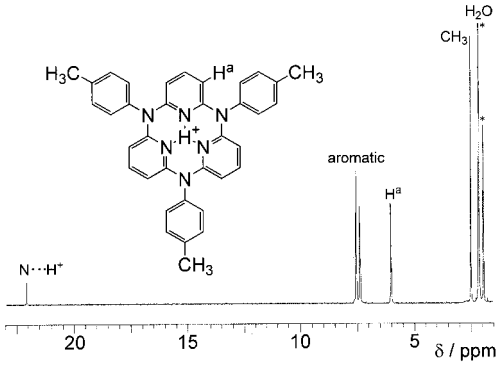

Figure 1. ^1H NMR spectrum of **1a**·PF_6 in CD_3CN. Peaks marked with an asterisk * are due to solvent impurities (CD_2HCN and H_2O).

To estimate the basicity of **1**, transprotonation experiments on **1** and the known proton sponge **2** (pK_{BH+} = 18.2–18.7 in CH_3CN)[2b,5] were carried out by ^1H NMR spectroscopy. The NMR experiments using 1:1 mixtures of **1** with the hexafluorophosphate salt of **2** (**2a**·PF_6) and of **1a**·PF_6 with **2** showed that **1** is much more basic than **2**. In neither case was any free **1** detected as shown in Equation (1).

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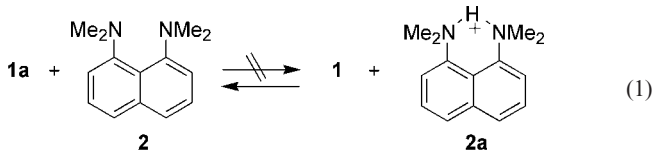
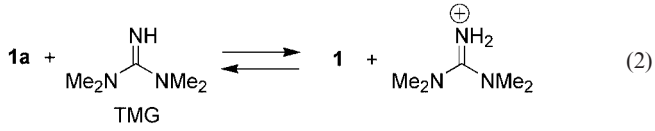


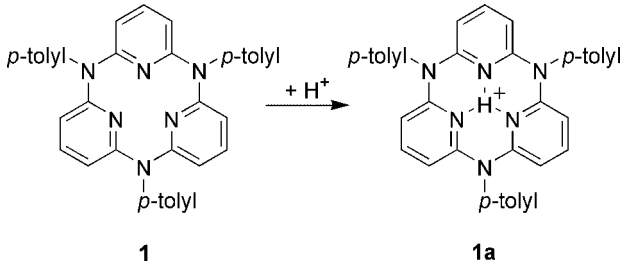
(1)

Among the organic bases tested, 1,1,3,3-tetramethylguanidine (TMG, pK_{BH+} = 23.3 in CH_3CN)[5c] was shown to be an appropriate base for the transprotonation experiments on **1a**·PF_6 [Equation (2)], on the basis of sufficiently separated signals in the ^1H NMR measurements in CD_3CN at –30 °C. The NMR spectra of 1:1 and 1:4 mixtures of **1a**·PF_6 with TMG showed 44% and 14% of **1a**, respectively (cf. Figure S1 in the supporting information). Similar transprotonation experiments comparing **1a** with TMG showed that the estimated pK_{BH+} of **1** was 23.1 ± 0.1. Accordingly, the basicity of **1** is higher by a factor of 10^8 than those of 2-aminopyridine (pK_{BH+} = 14.26–14.66 in CH_3CN) and 2,6-diaminopyridine (pK_{BH+} = 14.56 in CH_3CN).[5a,5b] This reveals a strong synergistic effect of chelating N_{py} atoms on protonation.



(2)

In contrast, homologues of **1** with larger macrocyclic compound, i.e., *N*,*N*′,*N*″,*N*‴-tetrakis(*p*-tolyl)azacalix[4](2,6)pyridine and *N*,*N*′,*N*″,*N*‴,*N*⁗,*N*⁗′-hexakis(*p*-tolyl)azacalix[6](2,6)pyridine,[4b] did not exhibit such a high proton affinity, as revealed by similar transprotonation experiments on **2a**·PF_6. In neither case was any transprotonation from **2a** to either macrocycle observed. These results indicate that the size of the cavity of **1** is appropriate for a high proton affinity. This is because the N_{py} atoms of **1** are arranged in close proximity and form three six-membered chelating N_{py}···H bridges, as shown in Scheme 1.



Scheme 1. Protonation of **1**.

When **1** and **1a** were dissolved in CD_3CN, the ^1H NMR spectrum of the resulting mixture was broad, however, the signals were separately observed at room temperature and sufficiently separated at –30 °C. This indicates that the proton exchange between **1** and **1a** is relatively slow on the NMR time scale. A similar low rate of proton exchange was observed for **2**.[2] The slow proton exchange of the captured proton in **1** is also attributed to the three stable N_{py}···H bridges in the cavity.

The high proton affinity of **1** was elucidated by X-ray crystallography. Figure 2 shows the ORTEP drawing of **1a**.[6] The crystallographic data of **1** have previously been reported.[4b] Compound **1** adopts an alternate conformation, regarding the up and down arrangements of the three N_{py} atoms from the center circle due to the destabilizing overlap of the lone electron pairs of N_{py} atoms (cf. Figure S2 in supporting information). In contrast, Figure 2 depicts that the monoprotonation of **1** leads to a well-fitted accommodation of the proton in the cavity, which induces reductions in the N_{py}···N_{py} distances [for N(2)···N(4) and N(2)···N(2)*, the distances are 2.534(5) and 2.566(4) Å, respectively] and results in the coplanarity of the macrocycle with a slight deviation of the pyridine rings from the macrocyclic framework. Compound **1a** adopts an approximate S_3 conformation, whereas the captured proton is localized unsymmetrically within nonlinear hydrogen bridges [the short N(4)–H(1) bond length was 1.18(7) Å, and the long N(2)···H(1) and N(2)*···H(1) distances were 1.63(4) Å]. These hydrogen bond lengths are somewhat longer than that of **2a**·PF_6 [the N(1)–H(1) bond length was 1.19(11) Å and the N(2)···H(1) distance was 1.45(11) Å],[2f] but are much shorter than the sum of the van der Waals radii of H and N (2.75 Å).

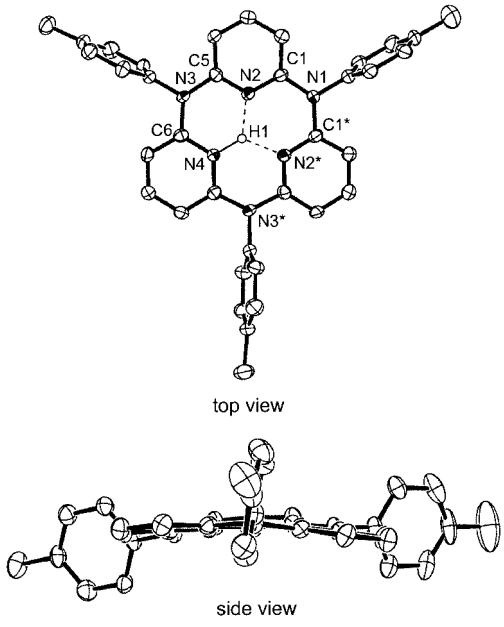


Figure 2. X-ray crystal structure of **1a**·PF_6, with thermal ellipsoids drawn at the 50% probability level; hydrogen atoms except for the captured proton and PF_6^- anion are omitted for simplicity. Selected bond length [Å], atom distances [Å], hydrogen bonding distances [Å], and torsion angles [°]: N(2)···N(4), 2.534(5); N(2)···N(2)*, 2.566(4); N(4)–H(1), 1.18(7); N(2)···H(1), 1.63(4); N(2)–C(1)–N(1)–C(1)*, –5(4); N(4)–C(6)–N(3)–C(5), –8(3); N(2)–C(5)–N(3)–C(6), 12.9(7).

As described above, the azacalix[3](2,6)pyridine **1** serves as a strong proton chelator. The macrocyclization of aminopyridine units results in the synergistic hydrogen-bonding ability of three N_{py} atoms in the cavity, leading to a marked increase in proton affinity. Because of the emergence of applications of organic superbases and proton-sponge-like compounds, the design of various macrocyclic proton chelators is of interest.

Experimental Section

***N*,*N*′,*N*′′-Tris(*p*-tolyl)azacalix[3](2,6)pyridine Hydrogen Hexafluorophosphate (1a·PF_6):** A mixture of **1** (55 mg, 0.10 mmol) and NH_4PF_6 (33 mg, 0.20 mmol) was dissolved in acetonitrile (25 mL), and stirred at room temperature for 1 h. After evaporation of the solvent, the residue was thoroughly washed with water and ether to give a pale yellow powder of **1a**·PF_6 (62 mg, 90% yield). ESI-MS: m/z = 547 $[M+H]^+$. ^{1}H NMR (300 MHz in CD_3CN): δ = 22.06 (s, 1 H), 7.55 (m, 9 H), 7.38 (d, J = 8.1 Hz, 6 H), 6.02 (d, J = 8.4 Hz, 6 H), 2.50 (s, 9 H) ppm. ^{13}C NMR (100 MHz in CD_3CN): δ = 151.8, 142.4, 141.5, 136.9, 133.0, 130.3, 106.4, 21.3 ppm. $C_{36}H_{31}F_6N_6P$ (692.64): calcd. C 62.43, H 4.51, N 12.13; found C 62.15, H 4.56, N 12.21.

Supporting Information (see also the footnote on the first page on this article): General experiments, transprotonation experiments, and X-ray crystal structures of **1** and **1a**.

Acknowledgments

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[6] Crystallographic data for **1a**·PF_6: $C_{36}H_{31}F_6N_6P$, M = 692.65, monoclinic, $C2/c$, a = 15.845(5), b = 22.025(4), c = 10.131(4) Å, β = 110.921(15)°, V = 3302.5(17) Å^3, Z = 4, $D_{calcd.}$ = 1.393 g cm^{-3}, μ(Mo-K_α) = 1.537 cm^{-1}, T = 113 K, F(000) = 1432, 12527 reflections measured, 3767 unique, 2161 observed [$I > 1\sigma(I)$], 228 variables, R_1 = 0.0635, R_w = 0.0743, GOF = 0.883. CCDC-298963 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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