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Synthesis, Characterization, and Catalytic Reactivity of a Highly Basic Macrotricyclic Aminopyridine

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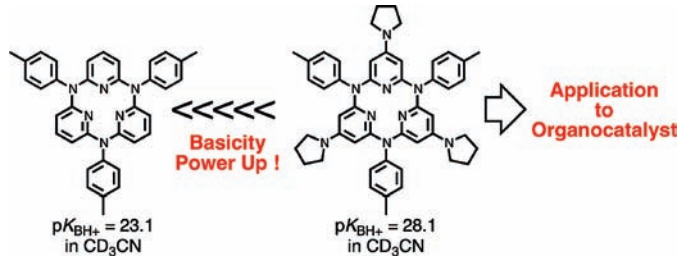
ABSTRACT



The synthesis methods, physicochemical and structural characteristics, and catalytic reactivity of new macrocyclic proton chelators, *N,N′,N″*-tris(*p*-tolyl)azacalix[3](2,6)(4-pyrrolidinopyridine) and *N,N′,N″*-tris(*p*-tolyl)azacalix[3](2,6)(4-piperidinopyridine), are studied. The introduction of pyrrolidino and piperidino groups into the pyridine unit enables the enhancement of the synergistic proton affinity of the cavity of the macrotricycle giving a high basicity (pK_{BH+} = 28.1 and 27.1 in CD_3CN), resulting in a catalytic activity for the Michael addition of nitromethane with α,β-unsaturated carbonyl compounds.

The design and synthesis of neutral organic bases and superbases have recently attracted much attention in organic chemistry.[1,2] Strong nonionic bases such as proazaphosphatranes are useful in a number of important organic transformations such as dehydrohalogenation and nitroaldol reaction, and the high pK_{BH+} of superbases enables them to effectively facilitate reactions previously restricted to ionic inorganic bases.[2] We previously reported that the macrotricyclic aminopyridine compound azacalix[3](2,6)pyridine, **1**, in Figure 1 exhibits the synergistic hydrogen bonding ability of three pyridine nitrogen atoms (N_{py} atoms) in a cavity, which is appropriate for capturing a single proton.[3] However, the estimated pK_{BH+} of **1** (23.1 ± 0.1 in CD_3CN) is still

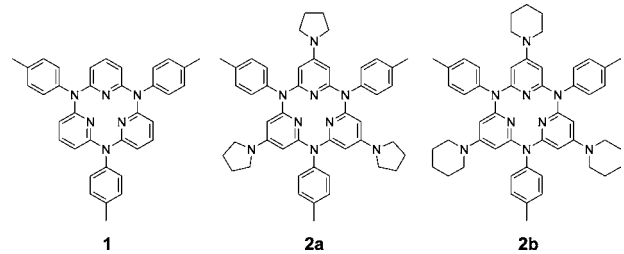


Figure 1. Azacalix[3](2,6)pyridine derivatives.

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(1) *Superbases for Organic Synthesis: guanidines, amidines and phosphazenes and related organocatalysts*; Ishikawa, T., Eds.; Wiley: New York, 2009.

(2) (a) Verkade, J. G.; Kisanga, P. B. *Tetrahedron* **2003**, *59*, 7819. (b) Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta* **2004**, *37*, 3.

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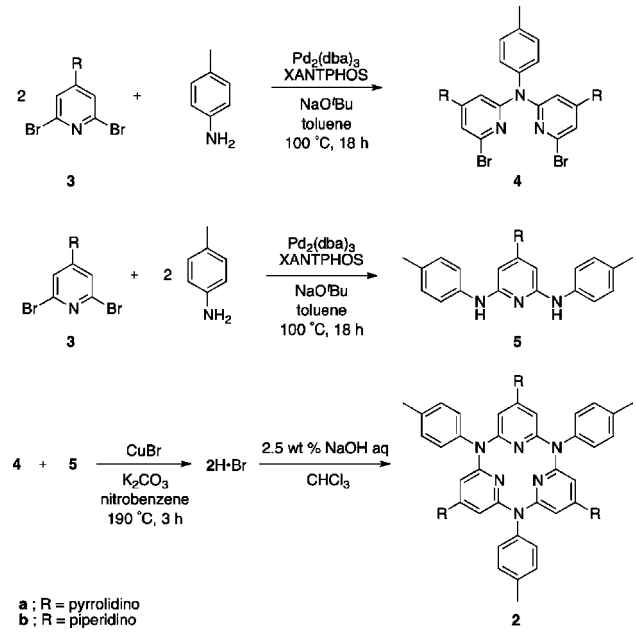
lower than that of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, pK_{BH+} = 24.3 in CH_3CN). Thus, to develop catalytically active organic superbases, the enhancement of the basicity of the macrocyclic compounds is desired.

Maksić and co-workers carried out a DFT calculation of a number of azacalix[3](2,6)pyridine derivatives and predicted that the introduction of electron-donating substituents such as a dimethyl amino group into the pyridine units will enhance the basicity of these derivatives.[4]

In accordance with Maksić and co-workers' prediction, we here demonstrate the synthesis and characterization of new azacalix[3](2,6)pyridine derivatives bearing pyrrolidino (**2a**) and piperidino (**2b**) groups. Since 4-pyrrodinopyridine (the scale of hydrogen-bond basicity, pK_{HB} = 2.93) and 4-piperidinopyridine (pK_{HB} = 2.68) show much higher basicities than pyridine (pK_{HB} = 1.86),[5] the introduction of the pyridine unit into the macrocyclic compound is expected to enhance the hydrogen-bonding ability of N_{py} atoms in the cavity. In addition, 4-(dimethylamino)pyridine (DMAP) and its derivatives are well-known catalysts for various organic syntheses.[6] In this communication, the catalytic activity of these macrotricyclic compounds for the Michael addition is also described.

The synthetic strategy for macrotricyclic compounds **2a** and **2b** was based on our previous reports.[7] 2,6-Dibromo-4-pyrrolidinopyridine (**3a**) and 2,6-dibromo-4-piperidinopyridine (**3b**) were prepared via the four-step procedure.[8] *N*,*N*-Bis[2-(6-bromo-4-pyrrolidinopyridyl)]-*p*-toluidine (**4a**), *N*,*N*-bis[2-(6-bromo-4-piperidinopyridyl)]-*p*-toluidine (**4b**), 2,6-bis(*p*-tolylamino)-4-pyrrolidinopyridine (**5a**), and 2,6-bis(*p*-tolylamino)-4-piperidinopyridine (**5b**) were prepared by the Pd-catalyzed aryl amination[9] of **3a** or **3b** with *p*-toluidine (Scheme 1). The macrotricyclic compounds **2a** and **2b** were prepared by the Cu-catalyzed aryl amination[10] of **4a** with **5a** and of **4b** with **5b**, respectively. The macrotricyclic compounds **2a** and **2b** were obtained as inner monoprotonated forms (i.e., **2a**H·Br and **2b**H·Br) owing to their high basicity. It is noteworthy that the reaction at temperature higher than 195 °C provided **2a**H·Br and **2b**H·Br in good yields (72 and 84%) without the necessity of using dilute conditions. This result indicates that the reaction systems can be driven to favor the formation of cyclic trimer; it is likely

Scheme 1. Synthesis of **2**



that the preorganization of the backbone of the intermediates is induced by the presence of proton as a template.[11] Deprotonation with an aqueous solution of NaOH (2.5 wt %) gave the neutral compounds **2a** and **2b**, and **2a**H·PF_6 and **2b**H·PF_6 were isolated by treatment with NH_4PF_6. The new compounds including **2a**H·PF_6 and **2b**H·PF_6 were characterized by NMR and ESI-MS spectroscopies and elemental analysis. As expected, the ^{1}H NMR spectra of **2a**H·PF_6 and **2b**H·PF_6 exhibit a singlet signal at 20.9 and 21.0 ppm, respectively, in $CDCl_3$ (Figure 2); the largely downfield-

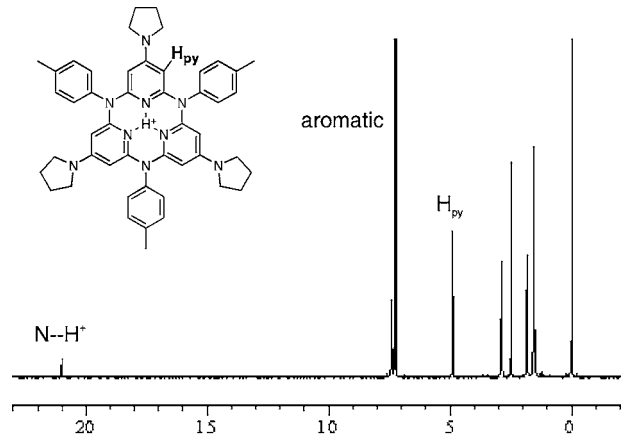


Figure 2. ^{1}H NMR spectrum of **2a**H·PF_6 (400 MHz, $CDCl_3$).

shifted proton signal reflects the synergistic hydrogen bonding ability of N_{py} atoms in the cavity.[3] The detailed synthetic procedures and characterization of the compounds are summarized in the Supporting Information.

(3) Kanbara, T.; Suzuki, Y.; Yamamoto, T. *Eur. J. Org. Chem.* **2006**, 3314.

(4) (a) Despotović, I.; Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2007**, *9*, 1101. (b) Despotović, I.; Kovačević, B.; Maksić, Z. B. *Org. Lett.* **2007**, *9*, 4709.

(5) (a) Hennemann, M.; Clark, T. *J. Mol. Model.* **2002**, *8*, 95. (b) Berthelot, M.; Laurence, C.; Safar, M.; Besseau, F. *J. Chem. Soc., Perkin Trans. 2* **1998**, 283.

(6) (a) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436. (b) Aoki, S.; Kotani, S.; Sugiura, M.; Nakajima, M. *Tetrahedron Lett.* **2010**, *51*, 3547. (c) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570.

(7) (a) Suzuki, Y.; Yanagi, T.; Kanbara, T.; Yamamoto, T. *Synlett* **2005**, 263. (b) Miyazaki, Y.; Kanbara, T.; Yamamoto, T. *Tetrahedron Lett.* **2002**, *43*, 7945.

(8) Abe, H.; Masuda, N.; Waki, M.; Inouye, M. *J. Am. Chem. Soc.* **2005**, *127*, 16189.

(9) (a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.

(10) (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (c) Selby, T. D.; Blackstock, S. C. *Org. Lett.* **1999**, *1*, 2053, and references therein.

The structure of the monoprotonated form of **2a** was also elucidated by X-ray crystallography; the ORTEP drawing of **2a**H·Br is shown in Figure 3.[12] Although one of the

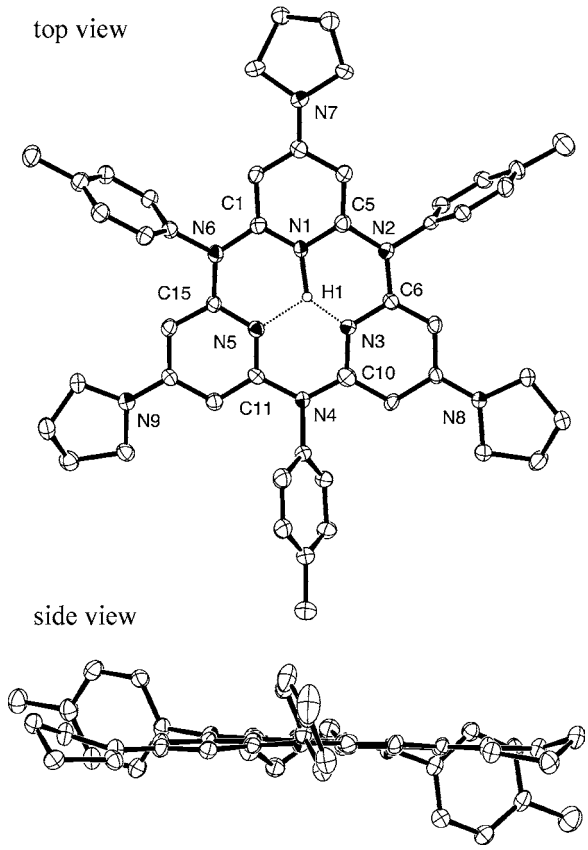
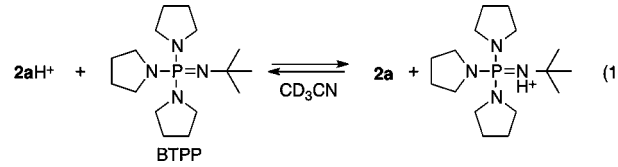


Figure 3. ORTEP drawing of **2a**H·Br with thermal ellipsoids shown at the 30% probability level. Hydrogen atoms except for the captured proton, Br anion, and solvated dichloromethane molecules are omitted for clarity.

pyrrolidino groups and a solvated dichloromethane molecule were disordered, the monoprotonation of **2a** led to a coplanarity of the macrocyclic framework with a slight deviation of the three pyridine rings; the angles between pairs of these pyridine rings are 2.99° and 6.01°, respectively. The captured proton is located unsymmetrically within nonlinear hydrogen-bonded bridges. The short N(1)−H(1) bond length is 1.33(7) Å, and the long N(3)···H(1) and N(5)···H(1) hydrogen bond lengths are 1.40(8) and 1.67(8) Å, respectively. These hydrogen bond lengths lie in a similar range found in **1**H·PF_6.[3]

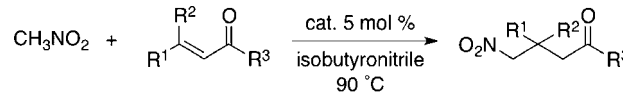
To estimate the basicities of **2a** and **2b**, transprotonation experiments on **2a**H·PF_6 and **2b**H·PF_6 with known organic bases were carried out by ^{1}H NMR spectroscopy.[3,13] Among the organic bases tested, *tert*-butylimino-tri(pyrrolidino)phosphorane (BTPP, pK_{BH+} = 28.4 in CH_3CN)[14] was the most appropriate base for the transprotonation experiments on **2a**H·PF_6 and **2b**H·PF_6 (eq 1). Since the proton exchange between **2a**H·PF_6 and BTPP was relatively slow on the NMR time scale at room temperature, the pK_{BH+} of **2a** was estimated to be 28.1 ± 0.1 from the ^{1}H NMR spectra of the mixtures of **2a**H·PF_6 and BTPP with various molar ratios. Similar transprotonation experiments on **2b**H·PF_6 with BTPP gave the estimated pK_{BH+} of **2b** to be 27.1 ± 0.2. Since these pK_{BH+} data are higher than that of **1** by a factor of 10^4−10^5, the introduction of pyrrolidino and piperidino groups into the pyridine unit allows us to enhance the proton affinity of N_{py} atoms in a cavity, resulting in a high basicity.

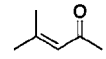
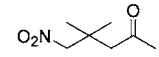
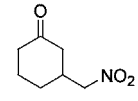
In the ^{1}H NMR spectrum of **2a**H·PF_6, the addition of CD_3OD caused the disapperance of the signal at δ = 20.9



indicating that the proton in the cavity could be replaced in solution. This result motivated us to utilize **2a** and **2b** as catalysts for the Michael addition of nitromethane with mesityl oxide and 2-cyclohexenone. Table 1 summarizes the results of the model reactions using some organic base catalysts; the reactions were carried out in accordance with the literature.[15] The Michael addition was achieved using **2a** and **2b** as base catalysts, whereas no catalytic reaction

Table 1. Michael Addition of Nitromethane with Mesityl Oxide and 2-Cyclohexenone Using **2a** and **2b**, **1**, BTPP, and DBU as the Base Catalysts



Entry	Michael acceptor	Catalyst: Base	Catalyst: pK_{BH+} in CD_3CN	Product	Yield[a] (%)
1[b]		BTPP	28.4[d]		95
2[b]		**2a**	28.1		95
3[b]		**2b**	27.1		75
4[b]		DBU	24.3[d]		0
5[b]		**1**	23.1		0
6[c]		BTPP	28.4[d]		98
7[c]		**2a**	28.1		97
8[c]		**2b**	27.1		86
9[c]		DBU	24.3[d]		34
10[c]		**1**	23.1		0

[a] Yield of isolated analytically pure compound. [b] The reaction time was 12 h. [c] The reaction time was 6 h. [d] pK_{BH+} in CH_3CN

(11) (a) *Template Synthesis of Macrocyclic Compounds*; Gerbeleu, N. V., Arion, C. B., Burgess, J., Eds.; Wiley-VCH: New York, 1994. (b) Cao, Y.; Wang, L.; Bolte, M.; Vysotsky, M. O.; Böhmer, V. *Chem. Commun.* **2005**, 3132.

(12) Selected data for **2a**H·Br·2CH_2Cl_2: $C_{50}H_{56}BrCl_4N_9$, M = 1044.77, monoclinic, $P2_1/n$, a = 10.3682(14), b = 16.537(2), c = 28.698(4), β = 90.958(2), V = 4919.9(12) Å^3, Z = 4, D_{calcd} = 1.356 g cm^3, μ = 1.10 mm^{-1}, T = 90 K, $F(000)$ = 2088, observed reflections 10 767 (all data), variables 573, R_1 = 0.1019 ($I > 2\sigma(I)$), R = 0.1545, R_w = 0.3464, GOF = 1.361. See the Supporting Information for details.

was observed using **1**. These results exemplify that the enhancement of the basicity of the macrotricyclic compound is efficient for the deprotonation of nitromethane. Although DBU was reported as a catalyst for the Michael addition of nitroalkane,[16] **2a** and **2b** served as superior catalysts for the model reactions (Table 1, entries 2, 3, 7, and 8).

As described above, according to Maksić's prediction based on the DFT calculation, we demonstrated the enhancement of the basicity of azacalix[3](2,6)pyridine by the introduction of pyrrolidino and piperidino groups into the pyridine unit. Since **2a** and **2b** served as an efficient base catalyst for the Michael addition, the method outlined in this paper is expected to contribute to the molecular design of neutral organic superbases. To expand their range of applications, further studies including other catalytic reactions are in progress.

Acknowledgment. The authors thank Prof. M. Ichinohe for useful discussion of X-ray analysis. The authors are grateful to the Chemical Analysis Center of University of Tsukuba for X-ray diffraction study, elemental analyses, and NMR spectroscopy.

Supporting Information Available: Synthesis and characterization of all compounds. NMR and X-ray crystallographic data in CIF format for **2a**H•Br. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Schwesinger, R.; Hasenfratz, C.; Schlemper, H.; Walz, L.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed.* **1993**, *32*, 1361.

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(16) Simoni, D.; Rondanin, R.; Morini, M.; Baruchello, R.; Invidiata, F. P. *Tetrahedron Lett.* **2000**, *41*, 1607.