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HIGHLY SYMMETRICAL CAGE COMPOUNDS, IN WHICH ALL SIX, EIGHT OR TEN LONE PAIRS ON NITROGEN ATOMS AT BRIDGEHEAD OR INTERVENING PYRIDINE RINGS ARE ORIENTED TOWARD THE CENTRAL CAVITY[1]

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Summary: Three dimensional cryptands 2, 3, 4 were synthesized in one step. The compounds 3 and 4 were obtained as their alkali metal cryptates. Complexation ability was enhanced by increasing the number of intervening pyridine rings.

We previously reported the synthesis and structural elucidation of 1, "hexametaxylylenetetramine".[2]

X-ray analysis showed that 1 had a rigid and highly symmetrical binding site, but the cavity size was too small to include guest species except protons.

If any or all benzene rings in 1 are replaced by heterocycles with a lone pair such as pyridine, the inclusion ability may be improved. From the molecular model consideration(CPK) and X-ray analysis of 1, each cage compound 2 - 4 has a cavity to include guest species: e.g., 4 has a cavity 3.8 Å in diameter.

In this communication, we report a synthesis and properties of the cage compounds 2, 3, and 4.

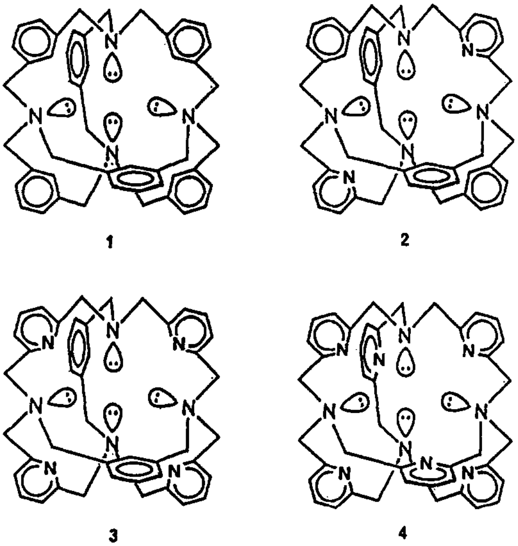
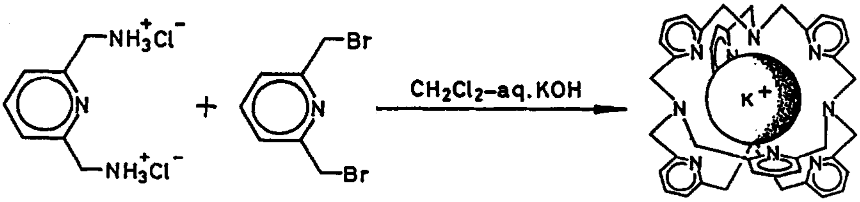
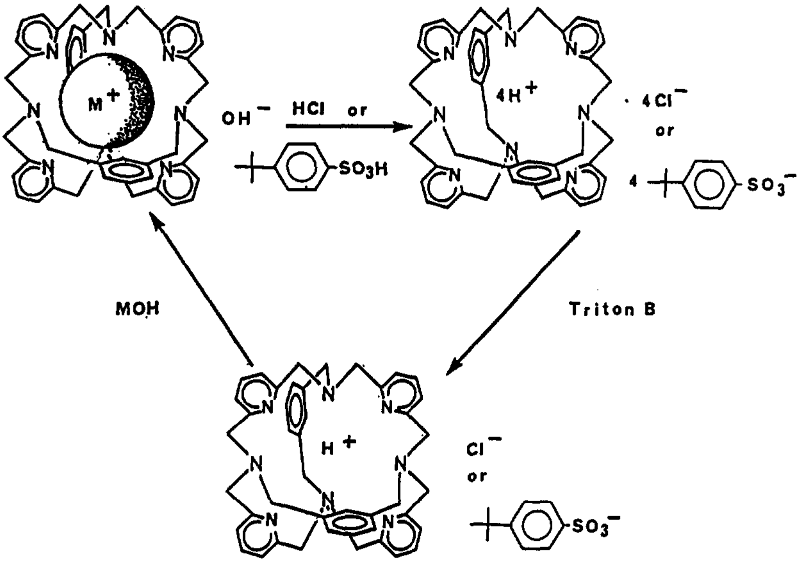

1 2
3 4

Fig. 1.



Scheme 1



Scheme 2

Synthesis[3]: A typical procedure is as follows(synthesis of 3).

In a 1-l, four-necked flask, a mixture of 2,6-bis(aminomethyl)benzene (4.0g, 0.03mol), 250ml of CH_2Cl_2 and 30ml of 5N KOH solution was heated under reflux with vigorous stirring. A solution of 2,6-bis(bromomethyl)-pyridine(6.3g, 0.023mol) in 150ml of CH_2Cl_2 was added to the mixture over a period of 5hr and additional heating was continued for 2hr. The organic phase was separated and dried over K_2CO_3. Evaporation of the solvent afforded a yellow oil and the oil was dissolved into a small amount of a mixture of $CHCl_3$ and C_6H_6. After several hours, precipitated colorless granules were collected by filtration. Recrystallization from CH_2Cl_2-C_6H_6 afforded 152mg of 3•KOH. In these reactions, the desired macrocycles 2, 3, and 4 were the only isolable products in 8.3%, 4.3% and 2.4% yield[4,5], respectively, and no other possible isomers[6] were detected.
Surprisingly, 3 and 4 were obtained as metal cryptates(Scheme 1[7]).
The source of potassium ion is the KOH added to neutralize generating HBr during the coupling reaction. Fast atom bombardment mass spectra of the cryptates $3 \cdot K^+$ and $4 \cdot K^+$ showed $(M+K)^+$ peaks, and addition of 0.1N HCl into glycerol matrix reduced the intensity of the $(M+K)^+$ peaks, but increased the intensity of protonated molecular peaks $(M+H)^+$.

In contrast to 3[8] or 4[8], metal free 2[8] was obtained. In general, oxygen is superior to nitrogen as a ligand atom for the alkali metal complexation.[9]

Interestingly, despite the donor atoms in these macrocycles being only nitrogens, strong alkali metal complexation was observed. This may be due to the three-dimensional and highly symmetrical arrangement of nitrogen atoms in the macrocycles to very effectively include spherical alkali metal ions.

Demetallation of the cryptate 3·K$^+$ was achieved by heating it with 3N HCl. An aqueous solution of the hydrochloride, 3·4HCl, was treated with an excessive amount of strong base, benzyltrimethylammonium hydroxide. However, the product was not the desired proton-free 3 but its mono-protonated salt, 3·HCl (Scheme 2). When the same treatment was applied to the 4·K$^+$ with 3N HNO$_3$, 4·HNO$_3$ was obtained.

IR spectrum of the mono-nitrate, 4·HNO$_3$, showed a strong band at 1340cm^{-1}. In ^{1}H-NMR(60MHz, CDCl$_3$), chemical shift of the methylene protons of 4·HNO$_3$ (δ , 3.83ppm) is lower than that of the corresponding methylene protons of 2 (δ , 3.53ppm). After ion exchange resin(OH form) treatment of 4·HNO$_3$, the strong band at 1340cm^{-1} disappeared, but the chemical shift of the methylene protons was identical with that of 4·HNO$_3$. The final proton could not be removed. The absorption of the methylene protons of 3·HCl or 4·HNO$_3$ was a sharp singlet at room temperature. Thus, the proton within the cavity may be rapidly flitting among the nitrogen atoms in the NMR time scale.

Deprotonation of 3·HCl or 4·HNO$_3$ was possible only in the presence of M$^+$ and OH$^-$, and the metal complex was regenerated(Scheme 2).

The number of remaining protons was confirmed by the integration of t-butyl protons of p-tert-butylbenzenesulfonate of 3, p-C_4H_9-$C_6H_4SO_3^-$·(3+H)$^+$ in the NMR spectrum(Scheme 2).

Metal picrate extraction experiments were carried out to estimate metal ion complexation ability of these macrocycles. Metal picrates(Li$^+$, Na$^+$, K$^+$, Rb$^+$, Cs$^+$) in basic aqueous phase were extracted quantitatively into organic phase(CH_2Cl_2 or CHCl$_3$) in the presence of 3·H$^+$ or 4·H$^+$. But 1 did not extract any of the metal ions and 2 showed only a moderate tendency.

Further studies on the mono-protonated salts, heavy metal complexes, and anion complexation of these compounds are now in progress.[10]

Acknowledgement. We are grateful to Dr. R. Isobe of Kyushu University, Faculty of Pharmaceutical Sciences for FAB mass spectra measurements.

References and Notes

1. Presented at The 18th Symposium on Structural Organic Chemistry, Toyama, October, 1985; Abstr. No.B2-09.
2. H.Takemura, T. Hirakawa, T. Shinmyozu, and T. Inazu, Tetrahedron Lett., 25, 5053(1984).

3a. To synthesize these cage compounds, we employed the one step coupling procedure, which is much simpler than those of other highly structured cryptands.

3b. E.Graf and J.-M. Lehn, J. Am. Chem. Soc., 97, 5022(1975), ibid., 98, 6403(1976).

3c. F. P. Schmidtchen, Angew. Chem. Int. Ed. Engl., 16, 720(1977).

4. The yields are based on the bromides.

5a. In the preparation of <u>4</u>, 2,6-bis(aminomethyl)pyridine dihydrochloride was employed instead of its free base, because the free amine(colorless crystals, mp 43.2-46.2°C; in ref. 5b described as an oily substance) is very miscible with water and the extraction procedure reduced the yield.

5b. E. Buhleier, W. Wehner, and F. Vögtle, Justus Liebigs Ann. Chem., <u>1978</u>, 537.

6. The NMR data of <u>2</u>, <u>3</u> and <u>4</u> exclude other possible cage structures such as shown in Fig. 2. Furthermore, preliminary X-ray analysis of <u>3</u>$\cdot KClO_4$ shows that K^+ ion locates in the central cavity of <u>3</u>. To be published.

7a. When the reaction was carried out in refluxing dioxane, the desired <u>3</u> was not obtained without KOH treatment of the resultant product.

7b. When a phase transfer catalyst($n\text{-}Bu_4NI$) was employed, KI cryptate, <u>3</u>•KI, was obtained instead of KOH cryptate, <u>3</u>•KOH, and yield was slightly improved.

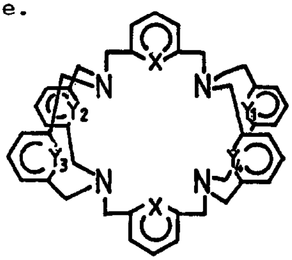
8a. <u>2</u>: mp>378°C(dec, corr). ^1H-NMR(60MHz,δ,$CDCl_3$) 3.46(16H, s, benzene-CH_2-), 3.53(8H, s, pyridine-CH_2-), 8.30(4H, bs, benzene-H), 7.05(12H, s, benzene-H), 6.9-7.6(6H, AB_2, pyridine-H). EI-MS, m/z 682(M^+). Anal. Calcd. for $C_{46}H_{46}N_6$:C, 80.91;H, 6.79;N, 12.31. Found:C, 80.63;H, 6.76;N, 12.20.

8b. <u>3</u>$\cdot 1/2K_2CO_3$: mp>305°C(dec). ^1H-NMR(60MHz,δ,$CDCl_3$) 3.41(8H, s, benzene-CH_2-), 3.58(16H, s, pyridine-CH_2-), 7.20-7.84(6H, AB_2, pyridine-H), 7.25(6H, m, benzene-H), 6.95(2H, bs, benzene-H). EI-MS, m/z 684(M^+). FAB-MS, m/z 723[$(M+K)^+$].
<u>3</u>•4HCl: Anal.Calcd. for $C_{44}H_{44}N_8\cdot 4HCl\cdot 9H_2O$;C, 53.23;H, 6.70;N, 11.29. Found;C, 53.13;H, 6.61;N, 11.26.

8c. <u>4</u>$\cdot 1/2K_2CO_3$: mp>300°C(dec), ^1H-NMR(90MHz,δ,$CDCl_3$), 3.58(24H, s, -CH_2-), 7.05-7.72(18H, AB_2,pyridine-H).EI-MS, m/z 686(M^+). FAB-MS, m/z 725[$(M+K)^+$].
<u>4</u>$\cdot Cs^+$:Anal. Calcd. for $C_{42}H_{42}N_{10}\cdot CsCl\cdot H_2O$;C, 55.48;H, 5.32;N,15.40. Found;C, 55.84;H, 5.28;N, 15.69.

9. M. Hirooka, H. Yanagida, M. Ohara, and K. Koga, "Host-Guest Chemistry", Kodan-sha, p128, 1984.

10. Properties and structures of the mono-protonated salts will be described elsewhere.



	X	Y_1	Y_2	Y_3	Y_4
1	N	CH	CH	CH	CH
2	CH	N	N	CH	CH
3	CH	N	CH	N	CH
4	N	N	N	N	N

Fig. 2.

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