Reaction of 2,6-Dimethyl(diacetoxyiodo)benzene with Propargylsilane 1a. With use of the general procedure, reaction of 0.105 g (0.3 mmol) of 2,6-dimethyl(diacetoxyiodo)benzene with 0.084 g (0.6 mmol) of **1a** (80% purity) in the presence of 0.1 g of $MgSO_4$ and 0.043 g (0.3 mmol) of BF_3-Et_2O was carried out at -20 °C for 2 h. ^1H NMR of the crude product showed the formation of 1-(2,4-dimethyl-3-iodophenyl)-2-propyne (**11a**) (47%) and 1-(2,4-dimethyl-3-iodophenyl)-1,2-propadiene (**12a**) (30%). Preparative TLC afforded **11a** (33.8 mg, 42%) and **12a** (18.4 mg, 23%). **11a**: IR ($CHCl_3$) 3300, 2925, 2120, 1560, 1445, 1375, 1185, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (d, J = 7.8 Hz, 1 H), 7.06 (d, J = 7.8 Hz, 1 H), 3.57 (d, J = 2.6 Hz, 2 H), 2.52 (s, 3 H), 2.46 (s, 3 H), 2.18 (t, J = 2.6 Hz, 1 H); MS m/z (relative intensity) 270 (83, M^+), 143 (73), 128 (100), 115 (40). HRMS Calcd for $C_{11}H_{11}I$ (M^+): 269.9907. Found: 269.9898. **12a**: IR ($CHCl_3$) 2960, 2920, 1940, 1580, 1445, 1375, 1005, 990, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (d, J = 7.8 Hz, 1 H), 7.04 (d, J = 7.8 Hz, 1 H), 6.38 (t, J = 6.7 Hz, 1 H), 5.11 (d, J = 6.7 Hz, 2 H), 2.55 (s, 3 H), 2.45 (s, 3 H); MS m/z 270 (M^+). HRMS Calcd for $C_{11}H_{11}I$ (M^+): 269.9907. Found: 269.9921.

Reaction of 2,4,6-Trimethyl(diacetoxyiodo)benzene with Propargylsilane 1a. With use of the general procedure, reaction of 0.109 g (0.3 mmol) of 2,4,6-trimethyl(diacetoxyiodo)benzene with 0.084 g (0.6 mmol) of **1a** (80% purity) in the presence of 0.1 g of $MgSO_4$ and 0.043 g (0.3 mmol) of BF_3-Et_2O was carried out at -20 °C for 2 h. ^1H NMR of the crude product showed the formation of 1-(2,4,6-trimethyl-3-iodophenyl)-2-propyne (**11b**) (21%), 1-(2,4,6-trimethyl-3-iodophenyl)-1,2-propadiene (**12b**) (37%), and 1-(2,4,6-trimethylphenyl)-2-propyne (**13**)[28] (25%). The products were separated by preparative TLC. **11b**: IR ($CHCl_3$) 3300, 3005, 2110, 1445, 1375, 1260, 1135, 965, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.96 (s, 1 H), 3.56 (d, J = 2.6 Hz, 2 H), 2.62 (s, 3 H), 2.42 (s, 3 H), 2.33 (s, 3 H), 1.98 (t, J = 2.6 Hz, 1 H); MS m/z (relative intensity) 284 (100, M^+), 157 (26), 142 (38). HRMS Calcd for $C_{12}H_{13}I$ (M^+): 284.0064. Found: 284.0079. **12b**: IR ($CHCl_3$) 2925, 1940, 1445, 1375, 1150, 965, 865, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.96 (s, 1 H), 6.20 (t, J = 7.0 Hz, 1 H), 4.91 (d, J = 7.0 Hz, 2 H), 2.58 (s, 3 H), 2.42 (s, 3 H), 2.28 (s, 3 H); MS m/z (relative intensity) 284 (30, M^+), 256 (12), 157 (100), 132 (92), 128 (26), 115 (34). HRMS Calcd for $C_{12}H_{13}I$ (M^+): 284.0064. Found: 284.0054. **13**:[28] ^1H NMR ($CDCl_3$) δ 6.86 (s, 2 H), 3.46 (d, J = 2.8 Hz, 2 H), 2.37 (s, 6 H), 2.26 (s, 3 H), 1.95 (t, J = 2.8 Hz, 1 H). Deiodination of **11b** with butyllithium in THF at -78 °C for 2 h gave **13** in 71% yield.

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(28) Heimgartner, H.; Zsindely, J.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 1113.

Syntheses and Properties of Highly Symmetrical Cage Compounds: Pyridine Analogues of Hexa-*m*-xylylenetetraamine

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Abstract: Syntheses and properties of pyridine analogues, **2-4**, of "Hexa-*m*-xylylenetetraamine", **1**, are discussed. The analogues containing four or six pyridine rings, **3** and **4**, serve as cryptands and generate stable, kinetically inert metal ion cryptates and proton cryptates. The proton cryptates could not be deprotonated even by strong bases. Ion-exchange resin treatment of the proton cryptates, $H^+\subset$**3**$\cdot NO_3^-$ and $H^+\subset$**4**$\cdot NO_3^-$, gave proton cryptates whose counter anion is a hydroxide ion. These compounds were gradually converted into water cryptates. The dynamic behavior of the proton cryptate, potassium cryptate, and water cryptate was studied by a temperature-dependent NMR method. The analogues containing two pyridine rings, **2**, and its derivatives, **2**-OMe and **2**-Cl, were synthesized. Their alkali metal ion selectivity and complexation ability were compared by alkali metal picrates extraction experiments to investigate the effect of the number of pyridine rings as well as the effect of the substituents on the complexation ability. Inversion of bridgehead nitrogens of **1** are restricted; this was supported by methylation or protonation experiments of the bridgehead nitrogens. Enantiomeric interconversion of methylene moieties around the bridgehead nitrogens was frozen at low temperatures; therefore, resolution of these enantiomers in ^1H NMR spectra was achieved by using the optically active reagent, (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

Introduction

In recent years, the chemistry of macrocycles has been remarkably developed, and many studies on designing host molecules and[1,2] inclusion of ions and molecules[3-8] as well as the construction of reaction sites[9-11] have been reported. Guest recognition of the host molecule is determined by the cavity size, topology of the coordinating groups, and hydrophilicity or hydrophobicity of the cavity of the host molecules. Furthermore, guest binding is profitable when the host molecule is preorganized, and a host-guest complex is more stable when the cavity is isolated from the outside influences of the host molecule.

Therefore, we report the syntheses and properties of highly structured, preorganized cryptands, **1-4** (Figure 1). Each compound has a cavity which is isolated from the outside influences around the molecule. It is expected that shielding of the cavity by the thick aromatic walls of such compounds causes effective ion separation on complexation and that anion activation will be

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(1) Potvin, P. G.; Lehn, J.-M. Progress in Macrocyclic Chemistry. *Synthesis of Macrocycles*; Izatt, R. M., Christensen, J. J., Eds.; John Wiley & Sons: New York, 1987; Vol. 3, pp 167-239.
(2) (a) Lehn, J.-M. *Acc. Chem. Res.* **1978**, *11*, 49. (b) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89. (c) Lehn, J.-M. *Pure Appl. Chem.* **1978**, *50*, 871. (d) Lehn, J.-M.; Vierling, P. *Tetrahedron Lett.* **1980**, *21*, 1323. (e) Gokel, G. W.; Garcia, B. J. *Tetrahedron Lett.* **1977**, 317. (f) Lincoln, S. F.; Brereton, I. M.; Spotswood, T. M. *J. Am. Chem. Soc.* **1986**, *108*, 8134.
(3) Vögtle, F.; Müller, W. M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 712.
(4) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1986**, *51*, 4440.
(5) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Marti, K.; Sampson, R. M.; Kalleymeyn, G. W. *J. Am. Chem. Soc.* **1988**, *110*, 2554.
(6) Goaller, R. L.; Handel, H.; Labbe, P.; Pierre, J.-L. *J. Am. Chem. Soc.* **1984**, *106*, 1694.
(7) Grammenudi, S.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1122.
(8) Vögtle, F.; Müller, W. M.; Werner, U.; Losensky, H.-W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 901.

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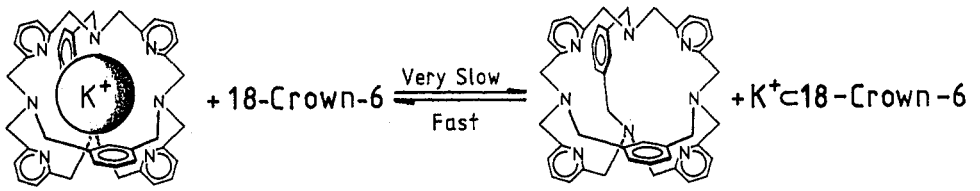
Scheme I. Equilibrium between $K^+\subset 3$ and 18-Crown-6



stronger than other types of macrocyclic compounds. In preceding communications, we reported the synthesis and structural elucidation of the parent compound, **1** (hexa-*m*-xylylenetetraamine),[12] as well as the syntheses of its pyridine analogues, **3** and **4**, and their alkali metal cryptates.[13]

X-ray crystallographic analysis revealed the rigid and unique structure of compound **1**; the bridgehead nitrogens of **1** are located at the apexes of an imaginary tetrahedron, and the lone pairs of the nitrogens are oriented toward the center of the cavity of the compound. Although **1** has an adequate structure as a cryptand, its cavity is filled with six aromatic inner protons. The cavity, therefore, becomes too small to include any chemical species except protons. This problem was overcome by substitution of the benzene rings by pyridine rings. Furthermore, a pyridine ring itself serves as a donor unit and the concentration of the pyridine lone pairs in the cavity enhances the guest binding ability. Bell et al. described that unsaturated nitrogen has a greater dipole moment than an ether oxygen or saturated nitrogen and showed that hosts containing unsaturated nitrogen have a strong affinity to alkali or alkaline earth metal ions.[19,20] Thus, compounds **3** and **4** should show strong binding properties as cryptands.

A few reports have been available dealing with tetrahedral coordinating type cryptands; they reported that such cryptands could include cations or anions.[14,15] Most of these cryptands are constructed with aliphatic chains and heteroatoms. But a few cases are known that the inclusion abilities of cryptands possessing heteroaromatic rings are greatly affected by their donating abilities of the heteroaromatic rings.[16-19] The compounds, **2**–**4**, containing pyridine rings act as the cation and anion cryptands. Especially, compounds **3** and **4** interact strongly with a proton and form stable proton cryptates. These unique properties reflect the thickness of the hydrophobic wall of aromatic rings and hydrophilic cavity which is filled with lone pairs of nitrogen atoms. Unique structural features of compound **1**—inhibition of bridgehead nitrogen inversion, protonation, and an enantiomeric motion of methylene moieties—are also discussed.

Results and Discussion

Synthesis of Cryptands 1–4. The synthetic route of these compounds has been previously reported.[12,13] Synthetic strategies of several types of three-dimensional macrocyclic compounds required many steps, and the starting materials are sometimes difficult to synthesize.[7,14b,15a,16,30] However, the synthetic routes of these highly symmetrical cage compounds, **1**–**4**, are very simple. In general, the syntheses of tertiary amines avoid the reaction between halogeno compounds and primary amines because the products will be a very complex mixture. However, the syntheses of these macrocycles were achieved by a one-step procedure employing primary amines and halogeno compounds. The yields were low, but the one-step procedure is an attractive one to synthesize such highly symmetrical macrocycles. In this procedure, the yields did not depend on the amine/bromide ratio or reaction conditions. Thus, the yields were not optimized.

Alkali Metal Cryptates. Although compounds **1** and **2** were isolated as metal free ligands, the cryptands, **3** and **4**, were isolated as potassium cryptates from the reaction mixture. Metal binding ability was greatly affected by the number of pyridine rings which construct the framework of the host molecule. Demetalation of these alkali metal cryptates were achieved by heating them with strong acids. Ammonium salts thus obtained were treated with a strong organic base, benzyltrimethylammonium hydroxide (Triton B), but resultant materials were not proton-free ligands but their monoprotonated materials. Alkali metal picrates extraction experiments using the proton cryptates, $H^+\subset 3$ and $H^+\subset 4$, showed quantitative extraction of picrates (Li^+–Cs^+). Thus, selectivity of these ligands among the alkali metal ions could not be determined. On the basis of the cavity size of **3** and **4** and the results of the picrate extraction experiment using compound **2** (described below), Rb^+ or Cs^+ fit in the cavity better than K^+. The cryptand, reported by Lehn et al., which has a cavity of similar size and tetrahedral coordination type showed the strongest affinity to Rb^+.[15a,c] These results suggest that cryptand **3** or **4** also has similar guest cation selectivity and affinity as the Lehn's cryptand. A competition experiment[20] between 18-crown-6 and $K^+\subset 3$ in DMSO-d_6 was carried out to estimate the association constant of $K^+\subset 3$, but both ^1H and ^{13}C NMR spectra showed no shift or line broadening of the peak resulting from K^+ exchange. Spectral change was not observed even after 2 weeks, and the spectra were identical with the sum of each signal. However, after half a year, the ^1H NMR spectrum showed a new set of peaks in the aromatic

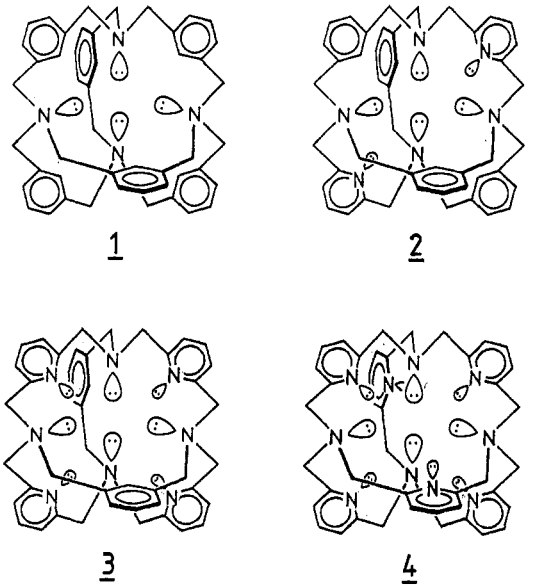
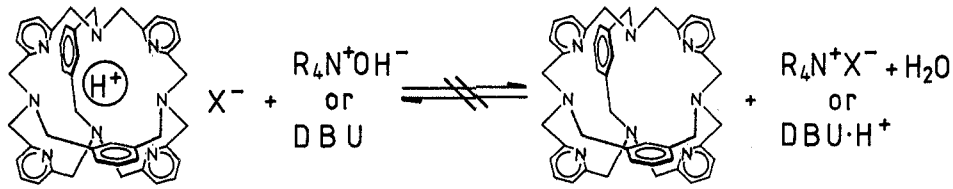


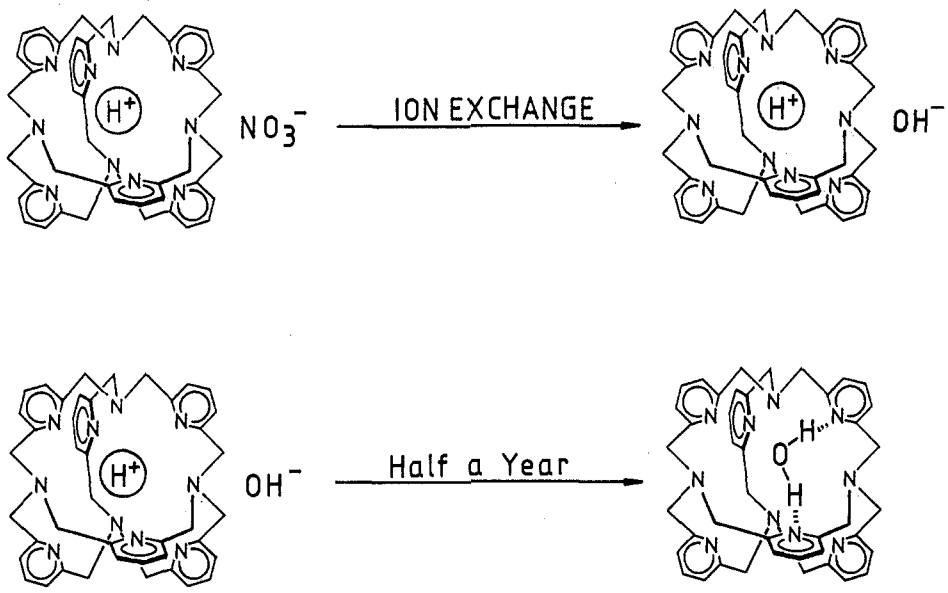
Figure 1. Structures of hexa-*m*-xylylenetetraamine and its pyridine analogues.

(9) Wambach, L.; Vögtle, F. *Tetrahedron Lett.* **1985**, *26*, 1483.
(10) Lutter, H.-D.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1125.
(11) Diederich, F.; Schürmann, G.; Chao, I. *J. Org. Chem.* **1988**, *53*, 2744.
(12) Takemura, H.; Hirakawa, T.; Shinmyozu, T.; Inazu, T. *Tetrahedron Lett.* **1984**, *25*, 5053.
(13) Takemura, H.; Shinmyozu, T.; Inazu, T. *Tetrahedron Lett.* **1988**, *29*, 1789.
(14) (a) Schmidtchen, F. P. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 720. (b) Schmidtchen, F. P. *Chem. Ber.* **1980**, *113*, 864. (c) Schmidtchen, F. P. *Tetrahedron Lett.* **1984**, *25*, 4361.
(15) (a) Graf, E.; Lehn, J.-M. *J. Am. Chem. Soc.* **1975**, *97*, 5022. (b) Graf, E.; Lehn, J.-M. *J. Am. Chem. Soc.* **1976**, *98*, 6403. (c) Graf, E.; Lehn, J.-M. *Helv. Chim. Acta* **1981**, *64*, 1040. (d) Graf, E.; Kintzinger, J.-P.; Lehn, J.-M.; LeMoigne, J. *J. Am. Chem. Soc.* **1982**, *104*, 1672.
(16) Kiggen, W.; Vögtle, F.; Franken, S.; Puff, H. *Tetrahedron* **1986**, *42*, 1859.
(17) Rodriguez-Ubis, J.-C.; Alpha, B.; Plancherel, D.; Lehn, J.-M. *Helv. Chim. Acta* **1984**, *67*, 2264.
(18) Caron, A.; Guilhelm, J.; Riche, C.; Pascard, C.; Alpha, B.; Lehn, J.-M.; Rodriguez-Ubis, J.-C. *Helv. Chim. Acta* **1985**, *68*, 1577.
(19) Bell, T. W.; Firestone, A. *J. Am. Chem. Soc.* **1986**, *108*, 8109.
(20) Bell, T. W.; Guzzo, F. *J. Am. Chem. Soc.* **1984**, *106*, 6111.

Scheme II. Interaction between Proton Cryptate and Bases



Scheme III. Generation of Water Cryptate from Proton Cryptate



region derived from K^+ subtraction from $K^+\subset$**3** by 18-crown-6 (Scheme I).

Assuming that equilibrium has been achieved at this point, the association constant of $K^+\subset$**3** is estimated by comparing the integral ratio of each aromatic signal of **3** and $K^+\subset$**3**.

$$3 + K^+ \overset{K_a}{\rightleftharpoons} K^+\subset 3$$

$$18\text{-crown-6} + K^+ \overset{K_1}{\rightleftharpoons} K^+\subset 18\text{-crown-6}$$

$$K^+\subset 3 + 18\text{-crown-6} \overset{K_2}{\rightleftharpoons} 3 + K^+\subset 18\text{-crown-6}$$

$$K_a = \frac{[K^+\subset 3]}{[3][K^+]} = \frac{[K^+\subset 3][18\text{-crown-6}]}{[3][K^+\subset 18\text{-crown-6}]} \times \frac{[K^+\subset 18\text{-crown-6}]}{[K^+][18\text{-crown-6}]}$$

$$= \frac{K_1}{K_2}$$

Since the logarithm of the stability constant of $K^+\subset$18-crown-6 in DMSO ($\log K_1 = 3.21$) has been reported,[21] K_a can be calculated from the observed $[K^+\subset 3]/[3]$ ratio and the concentration of $K^+\subset$18-crown-6 which is equal to [**3**]. The obtained value, $\log K_a = 5.2 \pm 0.1$, is 2 orders of magnitude greater than that of 18-crown-6, thus the result reflects the enhancement of stability of the complex by three-dimensional coordination. A competition experiment between $K^+\subset$**4** and $H_2O\subset$**4** (described below) was also carried out at high temperatures in DMSO-d_6 solution, but, even at 180 °C, the exchange of K^+ ion was not observed. Thus, dissociation of $K^+\subset$**3** is very slow even at high temperatures, and the previously described results showed the kinetic inertness of the cryptates of **3** and **4**.[15c,d] It is known that in solution the exchange of alkali metal cations encapsulated in cryptands is slow. Also, the step determining the metal ion dissociation rate depends on the conformational changes of the cryptates.[2f,15c] Because **3** and **4** have more rigid molecular skeletons and thicker aromatic rings surrounding the cavities than such cryptands, conformational changes are more difficult and therefore both the dissociation and the solvation of the guests become more difficult. So far, kinetic inertness equal to the stability of the cryptates, $K^+\subset$**3** and $K^+\subset$**4**, can be understandable.

Proton Cryptates. Attempted deprotonation of $H^+\subset$**3** and $H^+\subset$**4** by heating with a large excess of Triton B did not give the proton-free **3** and **4**, respectively. Interaction between $H^+\subset$**3** and strong base DBU was not observed in the ^{1}H NMR spectrum in methanol-d_4. Even after a month, the signals are essentially identical with those of the starting $H^+\subset$**3** (Scheme II).

Estimation of the basicities of **3** or **4** could not be achieved because these proton cryptates did not equilibrate with bases in the solution. Compared with the high basicities of **3** and **4**, the pK_a values of the conjugate acid of **1**, **1**·4HCl, are $pK_1 = 3.4$, $pK_2 = 4.9$, $pK_3 = 6.4$, and $pK_4 = 8.1$ (methanol/water = 80/20, w/w). The pK_a value of the reference compound, tribenzylamine hydrochloride, was estimated to be 5.64 in the same medium. Thus, the concentration of nitrogen lone pairs strongly enhances the basicity by about 2.5 pK_a units in **1** ($pK_4 = 8.1$). Since compounds **3** and **4** have four and six pyridine lone pairs, respectively, their cavities greatly stabilize the hydrogen bonds. Furthermore, aromatic moieties surrounding the cavity increase the hydrophobicity. These conditions demonstrate the high basicity of the cavity and give kinetically inert proton cryptates, $H^+\subset$**3** and $H^+\subset$**4**.[22,23]

Proton sponge also stabilizes proton by the linear and very short hydrogen bond, N–H^+–N,[24] but proton cryptates, $H^+\subset$**3** and $H^+\subset$**4**, have different types of hydrogen bonds in their relatively big spherical cavities. In general, a strongly hydrogen-bonded proton signal appears at low magnetic field in the ^{1}H NMR spectrum,[24b,c] but, in this case, the proton incorporated in **3** or **4** could not be detected, even at −90 °C, in the range of 0–20 ppm. The ^{1}H NMR spectra from room temperature to −90 °C suggest

(21) Kohltoff, I. M.; Chantooni, M. K., Jr. *Anal. Chem.* **1980**, *52*, 1039.

(22) Alder, R. W.; Moss, R. E.; Sessions, R. B. *J. Chem. Soc., Chem. Commun.* **1983**, 997.

(23) Cheney, J.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1972**, 487.

(24) (a) Staab, H. A.; Saupe, T. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 865. (b) Staab, H. A.; Saupe, T.; Krieger, C. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 731. (c) Saupe, T.; Krieger, C.; Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 451.

that the proton cryptates retain their symmetry. Therefore, a proton in the cavity would rapidly exchange among the lone pairs[25] even at low temperatures. N–H^+–N bond stretching in the IR spectra could not be observed clearly.[26] So far, the types of hydrogen bonds in the spherical cavity could not be proved whether they are a single minimum potential type or a double minimum potential type.[26] However, strong hydrogen bonding of the proton appears in the case of these proton cryptates and closely resembles a single minimum type.

Deprotonation using an anion exchange resin has been reported in the case of [1.1.1]cryptand.[23] Thus, this method was applied to the deprotonation of the proton cryptates. Two methanol solutions, one of $H^+\subset$**3**$\cdot NO_3^-$ and the other of $H^+\subset$**4**$\cdot NO_3^-$, were made to pass slowly through an anion exchange column (OH^- form). However, resultant materials were $H^+\subset$**3**$\cdot OH^-$ and $H^+\subset$**4**$\cdot OH^-$, respectively; proton-free **3** and **4** could not be detected. The ^1H NMR spectra of these compounds were identical before and after the treatment of the anion-exchange resin. The solutions of $H^+\subset$**3**$\cdot OH^-$ and $H^+\subset$**4**$\cdot OH^-$ are basic and changed the color of the pH test paper. These materials may act as the phase-transfer catalysts. Chloroform-d_1 solutions of these materials absorbed the moisture from air and produced $CHCl_3$. This phenomenon was also observed in the case of $K^+\subset$**3**$\cdot OH^-$ and $K^+\subset$**4**$\cdot OH^-$ or the mixture of aqueous NaOH and $Bu_4N^+I^-$ in $CDCl_3$. The homo-gated decoupling technique on ^1H NMR measurements showed that chloroform and water molecules were part of the following equilibrium:

$$CDCl_3 + H_2O \underset{}{\overset{H^+\subset 3\cdot OH^-}{\rightleftharpoons}} CHCl_3 + HDO$$

These results exclude the possibility of $H_2O\subset$**3** and $H_2O\subset$**4**.[27] These materials have interesting structures in which one proton of the water molecule is far apart from the OH^- moiety by the ligands. From a space-filling model consideration, the OH^- ion is small enough to enter the cavity, but, practically, the OH^- does not react with the proton incorporated in the cavity easily. Electronic repulsion between π electrons of the aromatic rings and negative charge of the OH^- hinder the approach of OH^- to included H^+.

Water Cryptates. The materials, $H^+\subset$**3**$\cdot OH^-$ and $H^+\subset$**4**$\cdot OH^-$, are stable crystals, but, upon standing for about half a year, generation of another species was observed by ^1H NMR spectra. Two characteristic peaks, $(M + H)^+$ and $(M + H_2O)^+$, observed in the FAB mass spectra of these new materials suggested that $H^+\subset$**3**$\cdot OH^-$ and $H^+\subset$**4**$\cdot OH^-$ were gradually converted into water cryptates (Scheme III).

J.-M. Lehn reported the water cryptate,[2a,c] in which the cryptand includes a water molecule in its diprotonated form and the water molecule is hydrogen bonded in a tetrahedral binding type. Exchange of the water molecule is slow, and the cryptate is stable. But details of the spectral or chemical data are not available. It is known that aza crown ethers also generate water complexes[2d,e] in their protonated forms. In all of them water molecule inclusion occurs by hydrogen bonding between water and protonated nitrogens. In case of $H_2O\subset$**3** and $H_2O\subset$**4**, the water molecule is included inside the neutral ligands by hydrogen bonding. In contrast to Lehn's water cryptate, protonated forms of **3** and **4** did not generate water cryptates. Attempted X-ray analysis of $H^+\subset$**3** excluded the possibility of $H_3O^+\subset$**3**.[27]

Further experiments to ensure whether diprotonated **3** and **4** form water cryptates are now underway.

In the ^1H NMR spectra of $H_2O\subset$**3** and $H_2O\subset$**4**, water proton–^{14}N coupling was observed. The proton signal of the included water molecule appeared as a triplet of equal intensities at 8.59, 8.39, and 8.20 ppm at room temperature (CD_2Cl_2, J = 52.7 Hz).[28]

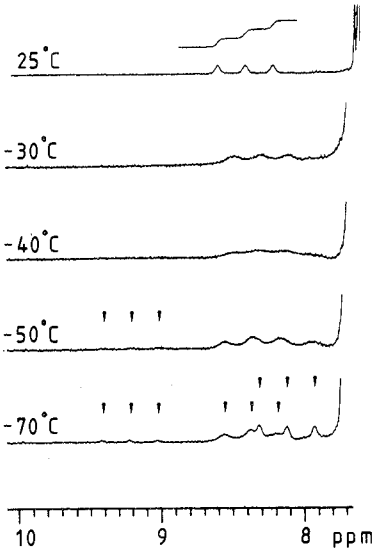


Figure 2. ^1H NMR spectra (270 MHz, CD_2Cl_2) of the water protons of $H_2O\subset$**4** at various temperatures. ▼ shows the position of the peaks.

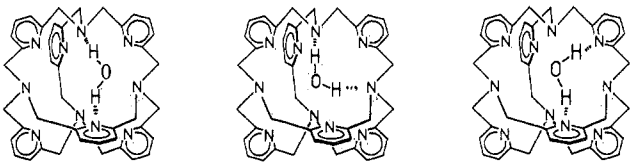


Figure 3. Three types of hydrogen bonding of included water molecule in the cavity of **4**.

In DMSO-d_6 solution the peaks appeared at a slightly upfield region than those in CD_2Cl_2, but, from room temperature to 150 °C, no temperature-dependent phenomenon was observed except for the sharpening of the signals. At low temperatures, the signal of a water molecule broadened and coalesced at about −40 °C, and then three sets of the triplet appeared below −50 °C (Figure 2). We interpret this result as indicating that, above −40 °C, the water molecule moves slowly, but, below −50 °C, movement of the water molecule is frozen; therefore, three kinds of hydrogen bonding, i.e., Py–H_2O–Py, Py–H_2O–N, and N–H_2O–N (N represents the bridgehead nitrogen), occurs at low temperatures (Figure 3). In the IR spectrum, O–H stretching of the included water molecule appeared as a very broad band at 3700–2700 cm^{-1}. The spectrum indicates that an encapsulated water molecule moves slowly and is strongly hydrogen bonded to nitrogen atoms. This result is consistent with the result of the ^1H NMR spectra. By the temperature-dependent ^1H NMR spectra, dynamic properties of the water cryptates were observed. Figure 5 shows the changes of the methylene proton signal at various temperatures. Below −30 °C, in concert with the broadening of the water proton signals, the methylene signal showed an unsymmetrical pattern, and finally, at −70 °C, the signal showed a complex splitting. At low temperatures, the torsional motion of the methylene groups around the bridgehead nitrogens is frozen and gives geminal coupling between axial and equatorial protons. Furthermore, overlapping of couplings between axial or equatorial methylene proton and the three types of unsymmetrically hydrogen-bonded protons of the included water molecule result. The complex splitting of the methylene signal indicates the unsymmetrical hydrogen bonding of water molecule at low temperatures.

Anion Inclusion. The anion complexation of several types of cryptands containing bridgehead nitrogens in acidic media has been observed by using the ^1H and ^{13}C NMR spectroscopic methods.[14a,15b,30] Compounds **2**, **3**, and **4** formed Cl^- cryptates in the D_2O/CF_3COOD(TFA-d_1) mixture.[29,30] These phenomena

(25) Cesario, M.; Dietrich, C. O.; Edel, A.; Guilhem, J.; Kintzinger, J.-P.; Pascard, C.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1986**, *108*, 6250.

(26) Alder, R. W.; Moss, R. E.; Sessions, R. B. *J. Chem. Soc., Chem. Commun.* **1983**, 1000.

(27) An X-ray crystallographic analysis of $H^+\subset$**3**$\cdot ClO_4^-\cdot CHCl_3\cdot 2H_2O$ has been carried out, but a satisfactory R value was not obtained. However, the possibility of $H_3O^+\subset$**3** was excluded. X-ray crystallographic analyses of proton cryptates and water cryptates will be described elsewhere.

(28) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley & Sons: New York, 1981; pp 197–198.

(29) Park, C. H.; Simmons, H. E. *J. Am. Chem. Soc.* **1968**, *90*, 2431.

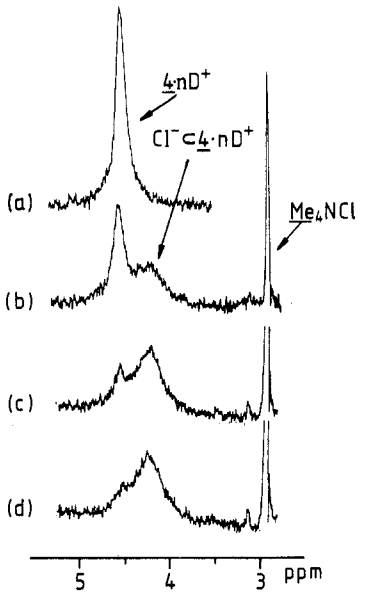


Figure 4. ^{1}H NMR spectra of methylene protons of **4**·nD$^+$ on Cl$^-$ complexation in TFA-d_1/D$_2$O by the addition of Me$_4$NCl: (a) 0.0, (b) 0.45, (c) 1.0, and (d) 1.5 mol equiv 30 °C, [H$^+$⊂**4**·NO$_3$] = 7.9 × 10^{-2} M, TFA-d_1/D$_2$O = 50/50 v/v, (equiv, 30 °C).

were observed by ^{1}H NMR spectra. Figure 4 shows the changes in the methylene signal of **4**·nD$^+$ in the mixture of TFA-d_1 and D$_2$O by the addition of tetramethylammonium chloride.

The methylene signal of compound **4** in the mixture of TFA-d_1 and D$_2$O solution appeared at 4.5 ppm as a broad singlet. Addition of Me$_4$NCl to the solution immediately gave a new broad peak at 4.25 ppm (Figure 4). The new signal grew by the addition of an increasing amount of Me$_4$NCl accompanied by the decrease in intensity of the peak at 4.5 ppm. The new peak must be the methylene signal of Cl$^-$⊂**4**·nD$^+$. To estimate the association constant of the Cl$^-$ cryptate, the overlapped two methylene signals were separated by a computational method, and the integral ratio of each signal was used to calculate the association constant. The association constant, K_a, was calculated by using the following equation:

$$\mathbf{4}\cdot n\mathrm{D}^+ + \mathrm{Cl}^- \rightleftharpoons \mathrm{Cl}^-\subset\mathbf{4}\cdot n\mathrm{D}^+$$

$$K_a = [\mathrm{Cl}^-\subset\mathbf{4}\cdot n\mathrm{D}^+]/[\mathbf{4}\cdot n\mathrm{D}^+][\mathrm{Cl}^-]$$

Thus, K_a = 8.4 L mol^{-1} and ΔG = −1.3 kcal mol^{-1} at 25 °C were obtained. The thermodynamic parameters, ΔH and ΔS, were estimated by using the variable temperature method of the ^{1}H NMR spectra. The plots of ln K_a versus T^{-1} showed a linear relationship indicating the formation of the 1:1 complex: ΔH = −4.7 kcal mol^{-1}, ΔS = −11.6 cal mol^{-1} K^{-1}. Compounds **2**, **3**, and **4** did not form anion cryptates with other anions such as Br$^-$, I$^-$, and BF$_4^-$. Considering that the diameter of the cavity of **4** is 3.8 Å, it is obvious that anions larger than Cl$^-$ (Br$^-$, 3.8 Å; I$^-$, 4.4 Å; diameter) cannot be encapsulated by **4**·nD$^+$. Due to the rigid structure of **4**, the association constant of Cl$^-$⊂**4**·nD$^+$ is smaller than that of the cryptand which has a cavity of similar size but has a flexible structure as reported by Lehn et al.[15b] Selectivity of Cl$^-$/Br$^-$ could not be estimated because Br$^-$⊂**4**·nD$^+$ could not be detected. Nevertheless, the rigidity and preorganized structure of **4** should promise a high Cl$^-$/Br$^-$ selectivity.

Comparison of Molecular Mobility among H$^+$⊂4, H$_2$O⊂4, and K$^+$⊂4. The torsional motion around the bridgehead nitrogen (Figure 11) of inclusion compounds H$^+$⊂**4**, H$_2$O⊂**4**, and K$^+$⊂**4** was compared by using the temperature-dependent ^{1}H NMR method (Figure 5). It is expected that molecular mobility would be affected by the size of the included chemical species.

Compound H$^+$⊂**4** shows a sharp methylene signal ($W_{1/2}$ = 2.5 Hz, CD_2Cl_2, where $W_{1/2}$ is the observed line width at the half-height of the signal) at room temperature. The signal did not coalesce even at −90 °C. On the other hand, cryptate K$^+$⊂**4** shows a relatively broad methylene signal ($W_{1/2}$ = 11 Hz, CD_2Cl_2) at room temperature. It coalesced at −15 °C and then split into an AB quartet below −30 °C. Calculation of $\Delta G^\ddagger$ of the conformational change (Figure 11) using the Eyring equation[31] gave 11.8 kcal mol^{-1}. These cryptates are more flexible than compound **1** ($\Delta G^\ddagger$ = 13.0 kcal mol^{-1}). Water cryptate has a line width at half-height, $W_{1/2}$ = 6.9 Hz (CD_2Cl_2), at room temperature, and the signal did not show a clear coalescence temperature (∼ −30 °C). The comparison of coalescence temperatures of three cryptates shows that the more bulky included species made the motions of the cryptates slower. Similar torsional motion of the NH_4^+ cryptate has been reported.[15d] The NH_4^+ is strongly bounded in the cavity of the cryptate. The $\Delta G^\ddagger$ for this motion is much smaller than that of our cryptates. From these results, the torsional motion mobility is not affected by the strength of interaction between included species and cavity but is affected by the bulkiness of the included species and the rigidity of the ligand.

Table I. Distribution Ratios of Rubidium Picrate in $CHCl_3$ at 20 °C[a]

host	D
2-Cl	8.05 × 10^{-3}
2	0.168
2-OMe	0.544

[a] For Table I [host] = 1.1 ∼ 1.2 × 10^{-3} M, [Pic$^-$] = 1.0 × 10^{-3} M, and [RbOH] = 0.1 M.

Effect of Substituents on Metal Ion Inclusion. Guest binding ability of the host molecule mainly depends on the cavity size, number of lone pairs on heteroatoms, and their spatial orientations. Once these requirements are fixed in a molecule, the binding ability of the host can be changed by controlling the electron density of the lone pairs intruding into the cavity. In order to study the effect of substituents on guest binding ability, we synthesized **2** and its derivatives having electron-withdrawing or -donating substituents on the pyridine rings at the 4-position (Figure 6).

Bradshaw et al. have reported the substituents effect on macrocycles containing the 4-substituted pyridine ring; they showed that the increasing basicity of the pyridine ring increased the dissociation energy barrier of the complexes.[32]

Compounds **2**, **2**-OMe, and **2**-Cl having two pyridine coordination units also have metal ion complexation ability, although it is weaker than those of **3** and **4**. Alkali metal picrate extraction experiments were carried out to estimate the selectivity among the alkali metal ions and the effect of substituents on the metal binding ability. At first, metal ion selectivity of compound **2** was examined. The results are shown in Figure 7. Extraction of the picrates by **2** took many hours (24–48 h) because of the high hydrophobicity of **2**.

Cavity size of **4** (3.8 Å, diameter) is adequate for the inclusion of the cesium ion, but the cavity of **2** can only accept the ions smaller than 2.4 Å (diameter) since it is filled with four inner benzene protons. However, the results showed that the affinity of **2** is a maximum for the rubidium ion (3.0 Å, diameter); therefore, structural rearrangement of **2** must occur. Four benzene rings must move so as to provide the spherical and large size of the cavity when the rubidium ion is included. Space-filling model considerations support this expectation. In the case of compound **3**, moving of the benzene rings is clearly observed in the ^{1}H NMR spectrum. Inner benzene protons of H$^+$⊂**3** appear at 8.21 ppm, but the protons of K$^+$⊂**3** appear at 6.95 ppm. This drastic upfield shift of the inner benzene protons indicates structural rearrangement by the inclusion of metal ions. A similar explanation may be also applicable in the case of **2**.

Secondly, the effect of substituents on metal binding was examined with use of **2**, **2**-Cl, and **2**-OMe by comparing the ex-

(30) Wester, N.; Vögtle, F. *Chem. Ber.* **1980**, *113*, 1487.

(31) $\Delta G^\ddagger$ (J/mol) = $RT_c(22.96 + \ln T_c/\delta\nu')$, where $\delta\nu' = (\delta\nu^2 + 6J^2)^{1/2}$.

(32) Bradshaw, J. S.; Maas, G. E.; Lamb, J. D.; Izatt, R. M.; Christensen, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 467.

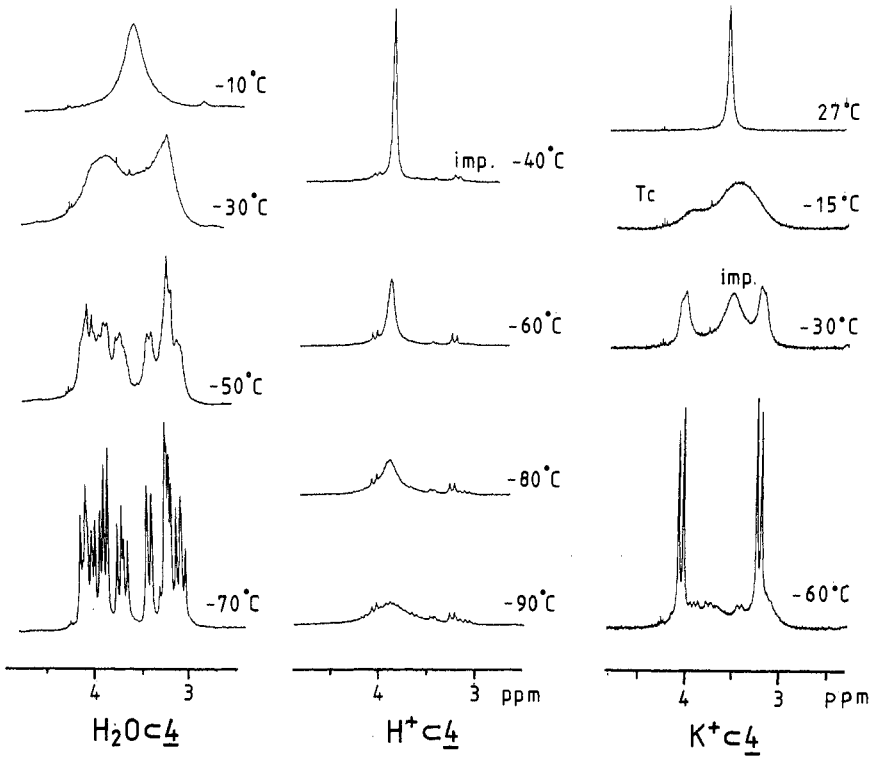


Figure 5. ^1H NMR spectra (270 MHz, CD_2Cl_2) of the methylene protons of $H_2O\subset$**4**, $H^+\subset$**4**, and $K^+\subset$**4** at various temperatures.

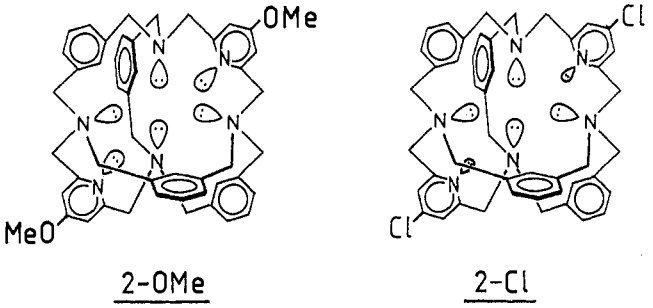


Figure 6. Structures of analogues of compound **2**.

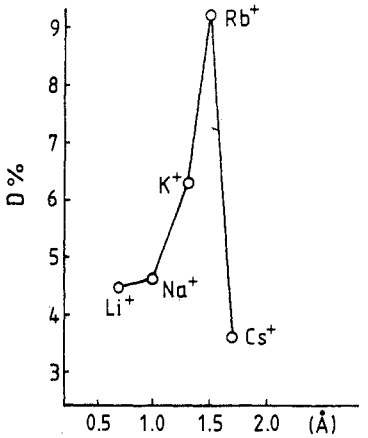


Figure 7. Plots of distribution ratios of metal picrates in $CHCl_3$ vs ionic radii of alkali metals: host = **2**; [**2**] = 1.2×10^{-3} M; $[Pic^-] = 1.0 \times 10^{-3}$ M; [MOH] = 0.1 M.

tractability of rubidium picrate. The results are shown in Table I. The effects of the substituents are apparent in the distribution ratios, and this supported the results of Bradshaw's studies. In this series of macrocycles, it is obvious that the complexation ability is strongly affected by the donating ability of the pyridine nitrogens. The number of the pyridine ring is also important as well, since the complexation ability of **3** and **4** is much stronger than that of **2** (Table II).

Table II. Distribution Ratios of Alkali Metal Picrates in $CHCl_3$ at 20 °C[a]

	metal ions				
host	Li^+	Na^+	K^+	Rb^+	Cs^+
1	0	0	0	0	0
2	4.49	4.62	6.29	9.17	3.58
3	100	100	100	100	100
4	100	100	100	100	100

[a] For Table II [host] = $1.0 \sim 1.2 \times 10^{-3}$ M, $[Pic^-] = 1.0 \times 10^{-3}$ M, and [MOH] = 0.1 M.

Attempted Methylation of Bridgehead Nitrogens of 1. A structural elucidation of compound **1** was achieved by X-ray crystallographic analysis.[12] The result shows that the lone pairs of bridgehead nitrogens are directed toward the center of the cavity. From the consideration of the space-filling model, it is expected that nitrogen inversion is inhibited, and inversion of even one nitrogen causes considerable distortion of the molecule. This feature is different from that of certain macrocycles possessing bridgehead nitrogens.[14a,c,30,33]

To confirm the rigidity, methylation or protonation of the bridgehead nitrogens was attempted. The reaction between **1** and methyl triflate (Magic Methyl) in $CDCl_3$ was monitored with its ^1H NMR spectrum at 21 °C. The spectrum of the mixture gradually changed. After 182 h, **1** was completely consumed, but the N^+–Me signal was not observed. Addition of tribenzylamine to this mixture immediately reproduced the starting material, **1**. The reaction at 50 °C was also carried out. The spectrum was identical with that obtained in a similar experiment at 21 °C at the beginning, but, after 52 h, insoluble materials precipitated. The precipitate was purified by preparative TLC on silica gel ($CHCl_3$–15% MeOH). The major component was separated from a small amount of the recovered starting material, but the ^1H NMR spectrum of this material showed no N^+–Me signal. In another experiment, a mixture of compound **1** and methyl iodide was heated in a sealed tube at 220 °C. From the reaction mixture, 1,3-bis(iodomethyl)benzene, a product of the Hofmann degradation of **1**, was obtained. These results show the difficulty of electrophilic attack on the bridgehead nitrogens; interaction be-

(33) Simmons, H. E.; Park, C. H. *J. Am. Chem. Soc.* **1968**, *90*, 2428.

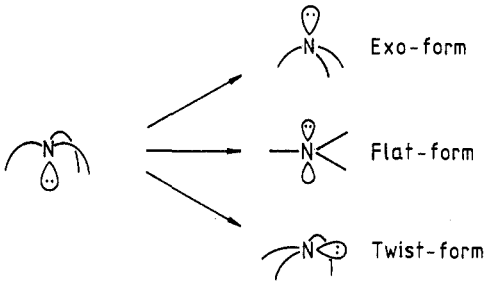


Figure 8. Possible conformational arrangements of bridgehead nitrogen of **1**.

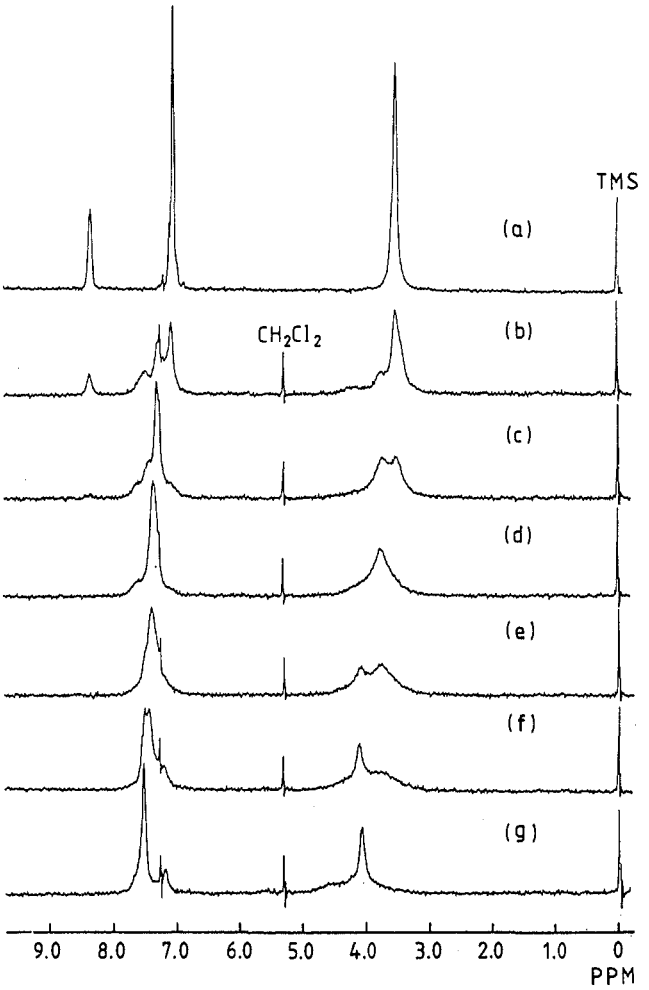


Figure 9. ^{1}H NMR spectral changes of **1** in $CDCl_3$ by addition of a TFA/$CDCl_3$ solution: (a) 0.0, (b) 1.0, (c) 2.0, (d) 3.0, (e) 4.0, (f) 5.0, and (g) 8.0 mol equiv.

tween nitrogens and the methyl cation is so weak because N-methylation occurs only when the lone pair of the bridgehead nitrogen is attacked by the methyl cation, but such conformation of compound **1** is very difficult by the distortion of the molecule and steric hindrance. Under vigorous conditions, however, the degradation took place.

Instead of inversion of the nitrogens, a twisted or flat form of nitrogens can be anticipated in the interaction between the methyl cation and bridgehead nitrogens (Figure 8). Interaction may occur either in the flat or the twisted form of the bridgehead nitrogens which are also unfavorable for generating N-methylated materials because of the strain and steric hindrance.

Protonation on Bridgehead Nitrogens of 1 in an Aprotic Solvent. The interaction between bridgehead nitrogens and a proton, which is much smaller than the methyl cation, was examined in an aprotic solvent. The ammonium salt formation in an aprotic solvent and in aqueous solution gave different results. ^{1}H NMR measurements during protonation experiments were performed by adding a

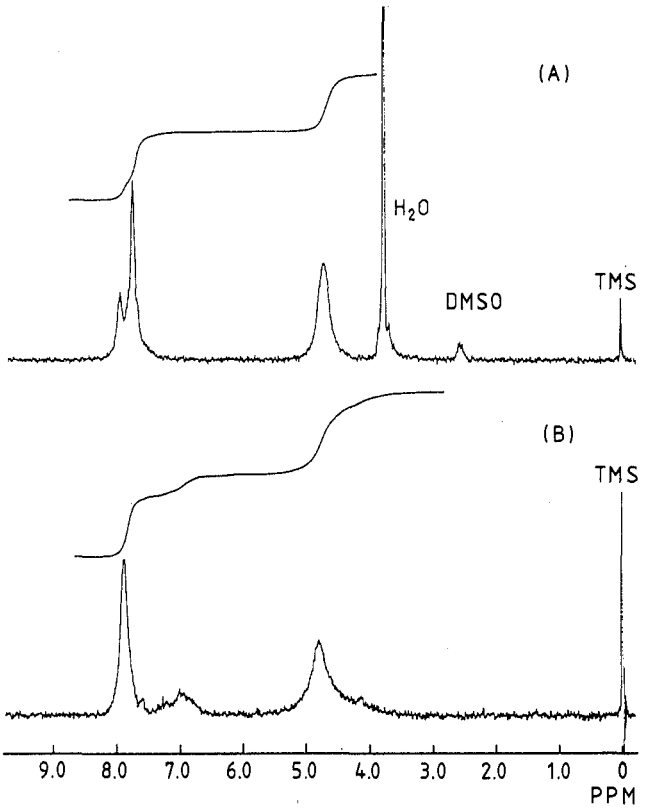


Figure 10. ^{1}H NMR spectra of (A) **1**·4HCl in DMSO-d_6 and (B) **1** in TFA-d_1.

constant volume of a solution of CF_3COOH (TFA) in $CDCl_3$ into a solution of **1** in $CDCl_3$ (Figure 9). The spectra were clearly changed by adding the acid solution with generation of the protonated species. After the generation of several protonated species, the spectra gave a simple pattern which showed one species by the addition of excess TFA. Inner aromatic protons shifted to higher field as compared to the outer aromatic protons. In case of the hydrochloride **1**·4HCl, inner aromatic protons appeared at lower field as compared to the outer aromatic protons (Figure 10, in DMSO-d_6). The inner benzene protons of the proton-free **1** also appear at lower field as compared to the outer benzene protons. Thus, **1** retains its conformation by the protonation in protic solvents. But in aprotic solvents like $CDCl_3$, **1** suffers certain conformational changes. These results are different from the case of the protonation behavior and conformational changes of [1.1.1]cryptand in aqueous or nonaqueous solutions.[35] Addition of a large amount of methanol into the $CDCl_3$ solution of **1**·*n*TFA caused precipitation of the proton free **1**. But the hydrochloride solution did not give proton free **1** by the addition of methanol or water, although endo protonated **1**·4HCl is very acidic (pK_1 = 3.4) causing easy release of one proton from the small cavity by electrostatic repulsion.[34] Thus, protonation in aprotic solvents does not generate inside protonated species, namely endo protonated species, but generates outside protonated species.[33,35-37] The possible structures of the outside protonated **1** are likely to be the twisted or flat form rather than the exo form because it is very strained. The twisted or flat form should also have considerable strain, so addition of a nucleophilic reagent such as methanol into a solution of the outside protonated species caused easy release of protons and reproduced stable species—proton free **1**.[37] In contrast to this, endo protonated **1**·3HCl is stable to bulky

(34) Dimethyl sulfoxide-d_6 solution of **1**·4HCl gradually generated **1**·3HCl, but further deprotonation did not occur (^{1}H NMR spectra).

(35) (a) Smith, P. B.; Dye, J. L.; Cheney, J.; Lehn, J.-M. *J. Am. Chem. Soc.* **1981**, *103*, 6044. (b) Cheney, J.; Kintzinger, J.-P.; Lehn, J.-M. *Nouv. Chim.* **1978**, *2*, 411.

(36) Alder, R. W.; Casson, A.; Sessions, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 3653.

(37) Alder, R. W. *Acc. Chem. Res.* **1983**, *16*, 321.

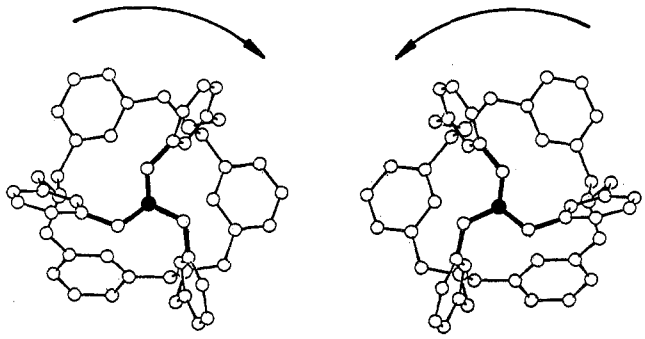


Figure 11. Enantiomeric interconversion of methylene moiety around the bridgehead nitrogen of **1**.

bases such as triethylamine. The addition of a large amount of triethylamine into a solution of **1**·3HCl in methanol showed no further deprotonation, although the pK_a value of triethylamine is much larger than that of **1**·3HCl, **1**·2HCl, and **1**·HCl. This result reflects the stabilization of **1**·3HCl, **1**·2HCl, and **1**·HCl by internal hydrogen bonding in the cavity and high hydrophobicity of the cavity surrounded by the aromatic ring wall. In fact, the titration experiment of **1**·4HCl for the determination of the pK_a values required a very long time in order to determine the pK_2, pK_3, and pK_4.

Enantiomerism of Compound 1. Compound **1** has a rigid structure, and inversion of the nitrogens is restricted. Thus, allowed motions of the molecule are only flipping of the benzene rings and rotation of the methylene moieties around the bridgehead nitrogens (Figure 11). The ^1H NMR signal of the methylene protons is very broad at room temperature ($W_{1/2}$ = 214 Hz, 400 MHz, CD_2Cl_2), suggesting the latter motion is relatively slow. On the other hand, the signal of methylene protons of $H^+\subset$**4** is sharp ($W_{1/2} \approx$ 2.5 Hz, 270 MHz, CD_2Cl_2) as previously described. This shows that the six inner benzene protons of **1** considerably affect the motion of the molecule.

The methylene moieties around the bridgehead nitrogens exist in either a clockwise or counterclockwise fashion as shown in Figure 11, and these two isomers are enantiomeric to each other. At around room temperature, these isomers interconvert slowly. The free energy for this interconversion was estimated to be 13.0 Kcal mol^{-1} by using a temperature-dependent NMR technique.[38]

It is expected that the recognition of two isomers at low temperature is possible, because this interconversion may freeze. Addition of the optically active reagent, (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol,[39] into a solution of **1** in CD_2Cl_2 at −50 °C resulted in the splitting of methylene signals (Figure 12).

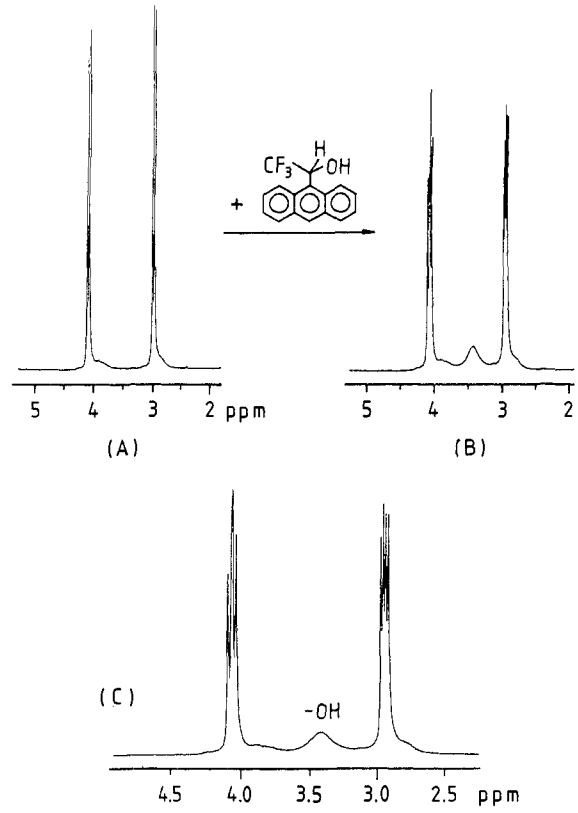


Figure 12. ^1H NMR spectra of methylene protons (400 MHz, CD_2Cl_2, −50 °C) of (A) **1**, (B) **1** plus 3.4 equiv of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, and (C) magnified spectrum of (B).

Experimental Section

All melting points are uncorrected. NMR spectra were recorded on Hitachi R-20B (60 MHz), JEOL GSX-270 (270 MHz), and JEOL GX-400 (400 MHz) spectrometers. UV/vis spectra were recorded on a JASCO UVIDEC-650. Methylation and protonation experiments of **1** and Cl^- inclusion experiments of **4** were carried out with a Hitachi R-20B NMR spectrometer. 4-Chloro-2,6-bis(bromomethyl)pyridine was prepared from 4-chloro-2,6-bis(carbomethoxy)pyridine which was prepared according to the literature method.[40] Reduction of the ester by $NaBH_4$–$CaCl_2$ gave 4-chloro-2,6-bis(hydroxymethyl)pyridine (85%). Bromination of this compound by HBr/AcOH yielded 4-chloro-2,6-bis(bromomethyl)pyridine (65%). This was converted to the amine dihydrochloride by the Gabriel method (100%). 4-Methoxy-2,6-bis(aminomethyl)pyridine dihydrochloride was prepared from 4-methoxy-2,6-bis(carbomethoxy)pyridine by the methods[40] similar for 4-chloro-2,6-bis(aminomethyl)pyridine dihydrochloride.

Synthesis of 2-Cl. In a 1-L, four-necked flask, a mixture of 250 mL of dichloromethane, 50 mL of 2.5 N aqueous KOH, 2.83 g (11.6 mmol) of 4-chloro-2,6-bis(aminomethyl)pyridine dihydrochloride, and a small amount of tetrabutylammonium iodide were vigorously stirred and heated under reflux. To this mixture was added a solution of 1,3-bis(bromomethyl)benzene (5.03 g, 19.1 mmol) in 150 mL of dichloromethane with a motor-driven syringe over 5 h. Additional stirring and refluxing were continued for 2 h. The organic layer of the reaction mixture was separated and dried over K_2CO_3, and then the solvent was evaporated to dryness. Column chromatography on alumina (CH_2Cl_2–1.5% MeOH) of the resultant oily product afforded a white powder (255 mg, 7.1% based on the bromide): mp > 312 °C dec; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.27 (s, 4 H, benzene-H), 7.10–7.01 (m, 12 H, benzene-H), 7.04 (s, 4 H, pyridine-H), 3.49 (s, 8 H, pyridine-CH_2–), 3.50, 3.39 (ABq, 16 H, benzene-CH_AH_B–, J = 12.7 Hz); EI-MS, m/e 750 (M^+). Anal. Calcd for $C_{46}H_{44}N_6Cl_2\cdot CH_2Cl_2$ (recrystallized from CH_2Cl_2–MeOH): C, 67.47; H, 5.54; N, 10.04. Found: C, 67.55; H, 5.50; N, 10.07.

Synthesis of 2-OMe. This compound was prepared by the reaction between 4-methoxy-2,6-bis(aminomethyl)pyridine dihydrochloride and 1,3-bis(bromomethyl)benzene under similar reaction conditions for the synthesis of **2**-Cl. The reaction mixture was treated as previously described, and the resultant material was column chromatographed on alumina (CH_2Cl_2–1% MeOH). The white powder thus obtained was recrystallized from CH_2Cl_2–CH_3CN: yield 12.3% (based on the bromide): mp > 306 °C dec; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.31 (s, 4 H, benzene-H), 7.08–6.99 (m, 12 H, benzene-H), 6.56 (s, 4 H, pyridine-H), 3.78 (s, 6 H, $-OCH_3$), 3.46 (s, 8 H, pyridine-CH_2–), 3.49, 3.40 (ABq, 16 H, J = 12.7 Hz, benzene-CH_AH_B–); EI-MS, m/e 742 (M^+). Anal. Calcd for $C_{48}H_{50}N_6O_2$: C, 77.60; H, 6.78; N, 11.31. Found: C, 77.38; H, 6.69; N, 11.10.

Preparation of $H^+\subset$3·ClO_4^-. The potassium complex of **3** was dissolved in hot 3 N HCl, and the solution was left to stand overnight. Precipitated colorless granules of the hydrochloride were collected and washed with water. The hydrochloride was dissolved in a minimum amount of methanol, and a large excess of benzyltrimethylammonium hydroxide solution (40% in MeOH) was added to the methanol solution of the hydrochloride. A small amount of water was added to the mixture, and the precipitate was collected by suction filtration and washed with water. The white powder thus obtained was dissolved in methanol, and the solution was slowly passed through an anion exchange column (Muromac 1-X8, ClO_4^- form). The resulting solution was evaporated to dryness, and recrystallization of the residual perchlorate from the $CHCl_3$–CH_2Cl_2 mixture gave analytically pure colorless needles: mp > 310 °C dec; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.21 (s, 2 H, benzene-H), 7.68, 7.66, 7.63, 7.25, 7.22 (AB_2, 12 H, pyridine-H), 7.16–7.18 (m, 6 H,

(38) Alder, R. W.; Orpen, A. G.; Sessions, R. B. *J. Chem. Soc., Chem. Commun.* **1983**, 999.

(39) (a) Dietrich-Buchecker, C. O.; Edel, A.; Kintzinger, J.-P.; Sauvage, J.-P. *Tetrahedron* **1987**, *43*, 333. (b) Mitchell, D. K.; Sauvage, J.-P. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 930.

(40) Markees, D. G.; Kidder, G. W. *J. Am. Chem. Soc.* **1956**, *78*, 4130.

benzene-H), 3.72, 3.63 (ABq, 16 H, pyridine-CH_AH_B-, J = 13.2 Hz), 3.42 (s, 8 H, benzene-CH_2-); Anal. Calcd for $C_{44}H_{44}N_8 \cdot HClO_4 \cdot CHCl_3 \cdot 2H_2O$: C, 57.45; H, 5.36; N, 11.91. Found: C, 57.36; H, 5.11; N, 11.90.

Preparation of $H^+ \subset 4 \cdot OH^-$. A solution of the proton cryptate, $H^+ \subset 4 \cdot NO_3^-$, in methanol was passed through an anion exchange column (Muromac 1-X8, OH^- form). Evaporation of the eluent to dryness and recrystallization of the residue from CH_2Cl_2-MeOH gave colorless prisms: ^1H NMR ($CDCl_3$, 270 MHz) δ 7.48, 7.46, 7.43, 7.00, 6.97 (AB_2, 18 H, pyridine-H), 3.83 (s, 24 H, $-CH_2-$).

Preparation of Water Cryptate $H_2O \subset 4$. Powder of the proton cryptate $H^+ \subset 4 \cdot OH^-$ was left to stand for half a year. The water cryptate thus generated was separated from the proton cryptate by preparative TLC on silica gel (Merck $60PF_{254}$, CH_2Cl_2/MeOH = 80/20, v/v). The content of water cryptate in the powder of $H^+ \subset 4 \cdot OH^-$ was higher than that of crystallized $H^+ \subset 4 \cdot OH^-$: FAB-MS, m/z (%) 704 (M + 18, 100), 687 (M + 1, 33.4); ^1H NMR (CD_2Cl_2, 270 MHz) δ 8.59, 8.39, 8.20 (t, J = 52.7 Hz, N--H-O), 7.66, 7.63, 7.60, 7.20, 7.17 (AB_2, 18 H, pyridine-H), 3.59 (s, 24 H, $-CH_2-$).

Competition Experiment between $K^+ \subset 3$ and 18-Crown-6. A solution of 18-crown-6 (0.05 mL, 0.160 M) in DMSO-d_6 was added to a solution of $K^+ \subset 3 \cdot ClO_4^-$ (4.81 mg) in 0.55 mL of DMSO-d_6. The initial concentrations of $K^+ \subset 3 \cdot ClO_4^-$ and 18-crown-6 were 9.74×10^{-3} and 1.33×10^{-2} M, respectively. The mixture was prepared in a NMR sample tube and left to stand at room temperature. At an appropriate interval, ^1H and ^{13}C NMR were observed at 25 °C (270 MHz). After half a year, the integral of each aromatic proton signal was recorded and used for the association constant determination.

pK_a Measurement of 1·4HCl. A 10-mL aqueous methanol solution (methanol/water = 80/20, w/w) of 1·4HCl (1.63×10^{-3} M) was titrated with 0.1 N NaOH solution at 25 ± 0.1 °C. Ionic strength was kept constant at I = 0.01 by LiCl. The titration curve was analyzed by calculation, and pK_a values thus obtained were compared to the pK_a values obtained from the half neutralized points. Two sets of values were identical within an experimental error.

Picrates Extraction Experiments. Equal volumes (5 mL) of chloroform (TOKYO KASEI, spectrophotometric grade) solution of the ligand (1.0×10^{-3}-1.2×10^{-3} M) and aqueous alkali metal picrate solution ([PicH] = 1.0×10^{-3} M, [MOH] = 0.1 M, M^+ = Li^+-Cs^+) were vigorously stirred with a magnetic stirrer in a Teflon sealed vial at 20 ± 2 °C for 48 h. The extraction was complete in 24 h, but stirring was continued for an extended period of time. After centrifugation, the organic phase was carefully transferred by a syringe, and the picrate concentration was determined spectrophotometrically at 374 nm (ϵ = 1.86×10^4). The distribution ratio, D, was calculated by the following equation:

$$D = [Pic^-]_{org}/[Pic^-]_{aq}$$

Anion Inclusion. ^1H NMR spectra were recorded on a Hitachi R-20B (60 MHz) spectrometer. The compound $H^+ \subset 4 \cdot NO_3^-$ (17.8 mg, 2.37×10^{-5} mol) was dissolved in 0.28 mL of a CF_3COOD-D_2O (50/50, v/v) mixture. To this solution was added 0.019 mL of a solution of tetramethylammonium chloride in D_2O (2.6 M). Temperature-dependent ^1H NMR spectra were observed in the range of 34-74 °C. The concentration ratio, $4 \cdot nD^+/Cl^- \subset 4 \cdot nD^+$, was determined by the integration of each methylene proton signal, which was separated by a computational method. The plots of ln K versus T^{-1} were optimized by a least-squares procedure, and ΔH and ΔS were determined by the slope and the equation $\Delta G = \Delta H - T\Delta S$.

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Mercuration of Cyclopropane

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Abstract: Mercury(II) acetate reacts with cyclopropane to form, after treatment with bromide, $BrHgCH_2CH_2CH_2OAc$. The stereochemistry of this reaction has been determined by use of cyclopropane-*cis*-1,2,3-d_3 and comparison of the vicinal coupling constants in the unlabeled and the deuterated propane product. The temperature dependence and absolute magnitude of these couplings indicate that the terminal carbons in the labeled product have an erythro rather than a threo relationship. The erythro structure is consistent with a double-inversion mechanism, whereby both electrophilic attack by mercury and nucleophilic attack by acetate occur with inversion. This stereochemistry is most consistent with a corner-mercurated intermediate. Initial edge attack is not excluded, provided that the edge-mercurated intermediate rearranges quickly to the corner-mercurated species without alteration of stereochemistry.

Although cyclopropanes are much less nucleophilic than alkenes, they are subject to attack by reactive electrophiles such as the proton and bromine, chlorine, and mercury(II).[2] Halogenation has been particularly well studied both theoretically and experimentally. In unsubstituted cyclopropane[3] and in many substituted cyclopropanes, the electrophilic attack by Br_2 or Cl_2 occurs with retention (probably at the edge rather than the corner), and the nucleophilic attack occurs with inversion. Electrophilic attack by mercury(II) has been examined extensively with a variety of substituted cyclopropanes.[4] Although there is no exclusive stereochemical pathway for the electrophilic attack, inversion is most commonly observed, and inversion is the normal pathway as well for the nucleophilic pathway. Transition metals normally attack by edge attack with retention.[5]

Mercuration of unsubstituted cyclopropane has only recently been examined preparatively and found to give 1,3 addition

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(2) DePuy, C. H. *Fortschr. Chem. Forsch.* **1973**, *40*, 73-101.

(3) Lambert, J. B.; Chelius, E. C.; Schulz, W. J., Jr.; Carpenter, N. E. *J. Am. Chem. Soc.* **1990**, *112*, 3156-3162.

(4) Lukina, M. Y. *Russ. Chem. Rev.* **1962**, *31*, 419-439. Nesmeyanova, O. A.; Lukina, M. Y.; Kazanskii, B. A. *Dokl. Akad. Nauk SSSR* **1963**, *153*, 114-117 (888-891 in English). Ouellette, R. J.; Robins, R. D.; South, A., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1619-1624. Sokolov, V. I.; Rodina, N. B.; Reutov, O. A. *J. Organomet. Chem.* **1969**, *17*, 477-480. Deboer, A.; DePuy, C. H. *J. Am. Chem. Soc.* **1970**, *92*, 4008-4013. Jensen, F. R.; Patterson, D. B.; Dinizo, S. E. *Tetrahedron Lett.* **1974**, 1315-1318. DePuy, C. H.; McGirk, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 2366-2367. DePuy, C. H.; McGirk, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 1121-1132. Balsamo, A.; Battistini, P. C.; Macchia, B.; Macchia, F. *J. Org. Chem.* **1975**, *40*, 3233-3237. Coxon, J. M.; Steel, P. J.; Whittingdon, B. I. *J. Org. Chem.* **1989**, *54*, 3702-3709.

0002-7863/91/1513-1331$02.50/0