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Nitrogen-bridged macrocycles: synthesis, structures and inclusion phenomena

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Contents

Abstract

Synthetic methods of nitrogen-bridged macrocyclic host molecules such as highly symmetrical cage compounds **3**–**6** and their bond isomers **8**, **10**, azacalix[n]arenes **16**, **18** and **20**, and

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tetraaza[3^4]cyclophanes **24** and **31**, are summarized. The new class of macrocycles **3–6** were designed and synthesized by one-step coupling reactions. In the compounds, pyridine or benzene units are connected by four bridgehead nitrogens, and both pyridine and bridgehead nitrogen lone pairs are directed into the cavity. The bridgehead nitrogen inversion is inhibited by the rigid structure. Because of the preorganized structure of **5** and **6** with four and six pyridine donors, respectively, they strongly bind alkali metal and ammonium ions, as exemplified by the fact that they are obtained as the K^+ complexes in the coupling reactions. The compound **5** showed Rb^+ selectivity among alkali metal ions, and the structure of its K^+ complex was confirmed by X-ray structural analysis. The hosts **5** and **6** also form very stable proton cryptates ($H^+ \subset 5 \cdot OH^-$ or $H^+ \subset 6 \cdot OH^-$). They are relatively stable, but very slowly changed into water cryptates ($H_2O \subset 5$ or $H_2O \subset 6$). The cation affinity of the host can be controlled by attaching electron-donating or -withdrawing substituents on the pyridine rings. A Cl^- ion formed the complex with **6** in acidic solution, but Br^-, I^- and other anions larger than Cl^- could not be encapsulated by **6**. The azacalixarenes, a new family of calix[*n*]arenes, have more rigid structure than the corresponding oxacalix[*n*]arenes and calix[*n*]arenes because of the strong intramolecular hydrogen bonds between phenolic hydroxyl groups and nitrogen lone pairs.

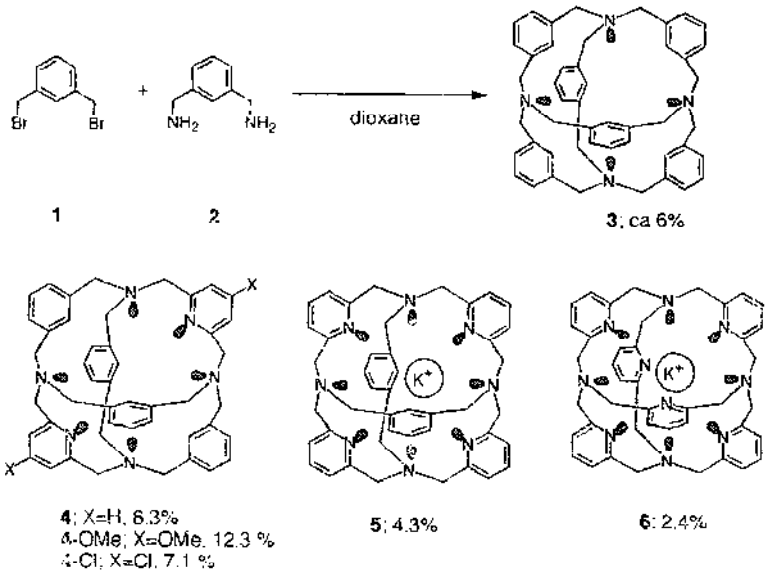
Keywords: Cage compound; Inclusion phenomena; Macrocycle; Nitrogen bridge

1. Introduction

Recent advances in host–guest chemistry demand more and more sophisticated artificial host molecules. In order to realize such molecules, the availability of the appropriate synthetic methods of the host themselves or their intermediates is of primary importance [1,2]. We briefly describe the simple and widely applicable coupling methods specifically for nitrogen-bridged macrocycles.

By using one of these coupling methods, we designed and synthesized a new class of highly symmetrical cage compounds **3–6**, where the parent compound **3** is called "hexametaxylylenetetramine" since the six methylenes of hexamethylenetetramine (urotropin) are replaced by the metaxylylene moiety. The macrocycles **4–6** are the pyridine analogs of **3** [3–6] (Scheme 1). They are highly symmetrical ligands which have a rigid and preorganized structure adequate for the inclusion of spherical cations. The preorganized structures of the hosts and the geometry of the donor sites are important for the host's complexation ability and for the recognition of the guests. Highly symmetrical spatial arrangements of the binding sites and the converging of dipoles increase the affinity to spherical guest species.

The nitrogen atom is chosen as the joint and donor atom because (i) a nitrogen atom has a large dipole moment and binds a wide variety of guest species by dipole interactions and hydrogen bonds, and (ii) anion inclusions are expected by protonation or quaternarization of nitrogens. The hosts **5** and **6** generate kinetically and thermodynamically stable inclusion complexes owing to the effective separation of an ion pair when an ion is included in the cavity, since the hydrophilic cavity is deeply hidden by the hydrophobic aromatic rings and thus unaffected by the outer environments. We also briefly introduce the synthesis and properties of azacalix[*n*]arenes **16**, **18** and **20**, aza analogs of calix[*n*]arenes.



Scheme 1. Synthetic scheme of hexametaxylylenetetramine **3** and its pyridine analogs **4**–**6**.

2. Results and discussion

2.1. Synthesis

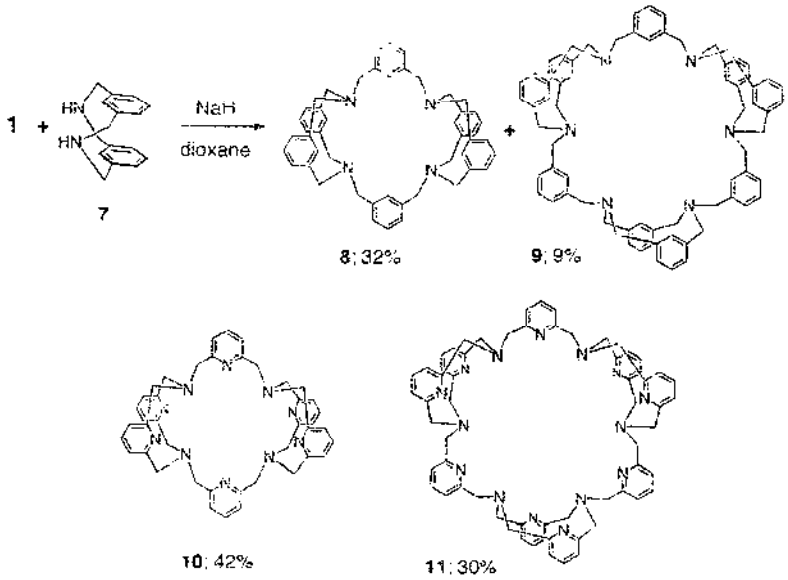
In this section, we summarize the synthetic methods for nitrogen-bridged macrocycles such as the hosts **3**–**6** and their bond isomers **8**, **10**, azacalix[*n*]arenes **16**, **18** and **20**, and tetraaza[3^4]cyclophanes **24** and its related compounds **31**, **33** and **34**.

2.1.1. Synthesis of a new class of highly symmetrical cage compounds

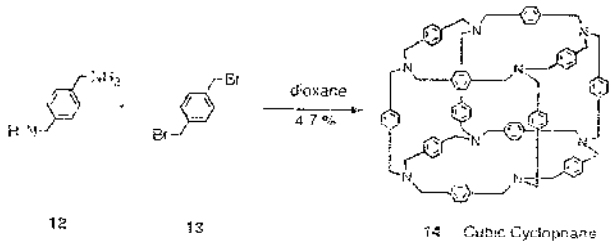
The host **3** was readily synthesized by the coupling between bromide **1** and 1,3-bis(aminomethyl)benzene **2** (Scheme 1). A similar reaction between 2,6-bis(bromomethyl)pyridine and 2,6-bis(aminomethyl)pyridine hydrochloride under phase transfer conditions (PTC) afforded $K^+ \subset$ **6**. The analogs **4** and **5** were prepared in a similar fashion. Although the yields were low, the one-step procedure is an attractive way to synthesize such highly symmetrical macrocycles. In this series of macrocycles, the compounds with more than four pyridine rings were obtained as their alkali metal complexes. The source of the alkali metal ion is the base (KOH) used in the reaction. The template effects were not observed: replacement of the base

by NaOH gave similar coupling yields. Even in the absence of the base, **5** was obtained as $H^+ \subset 5 \cdot X^-$.

Their bond isomer **8** was prepared by the coupling of 2,11-diaza[3.3]metacyclophane **7** with the bromide **1** to afford dimeric **8** and trimeric products **9** [3,4,6]. Pyridine analogs **10** and **11** were also prepared in a similar fashion (Scheme 2) [4,7]. Interactions with different kinds of guest molecules for **10** are expected, since its geometry and binding sites are quite different from those of **6** [4b]. This method was successfully applied to the synthesis of "cubic cyclophane" **14** (Scheme 3) [8,9].



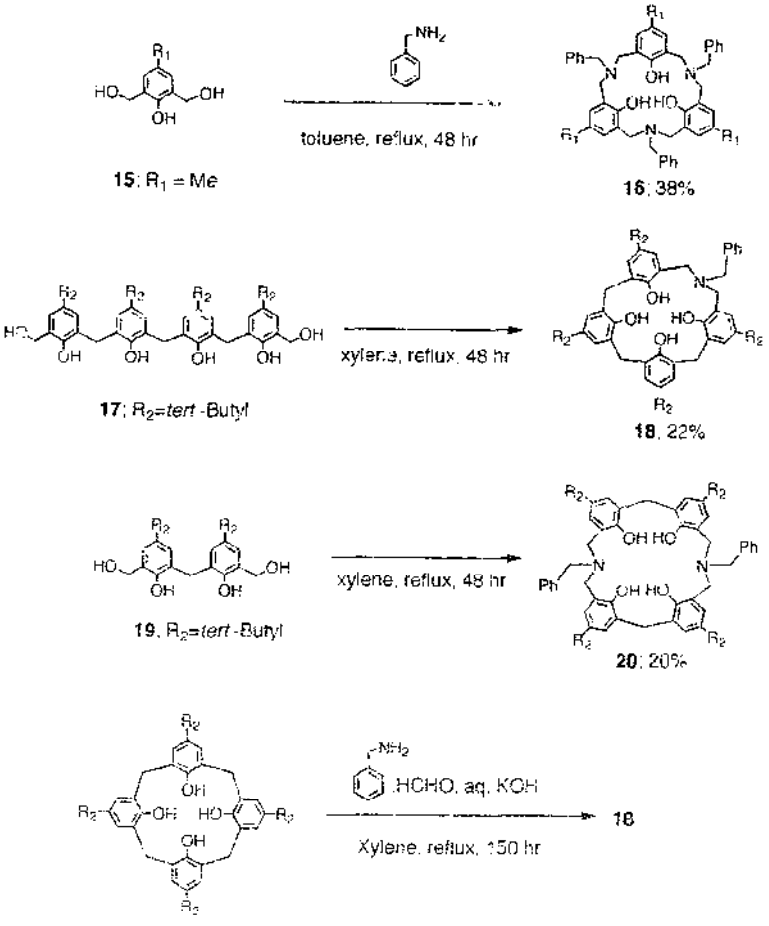
Scheme 2. Synthesis of azamacrocycles **8**–**11** by the direct alkylation of amines.



Scheme 3. Direct synthesis of cubic cyclophane **14**.

2.1.2. Synthesis of azacalix[n]arenes

We developed a simple cyclization method for the synthesis of new members of the calix[n]arene family, azacalix[n]arenes **16**, **18** and **20** (Scheme 4). Removal of water as the toluene azeotrope from the reaction mixture of 4-methyl-2,6-bis(hydroxymethyl)phenol **15** and benzylamine in toluene afforded hexahomotri-azacalix[3]arene **16** exclusively [10]. The dihomoazacalix[4]arene **18** and tetrahomodiazacalix[4]arene **20** were obtained in a similar way. The selective formation



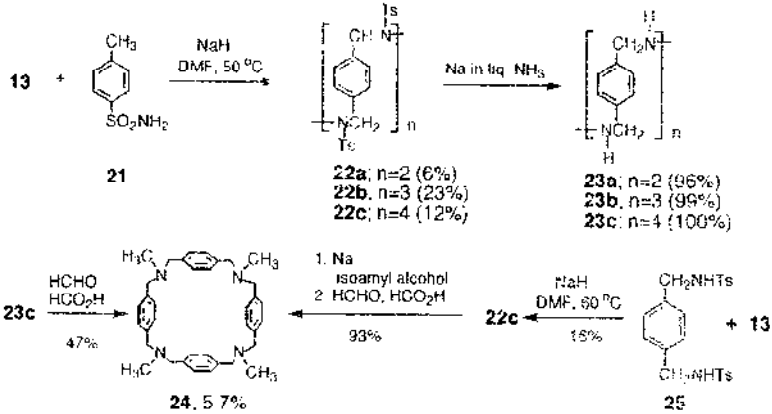
Scheme 4. Synthesis of azacalix[n]arenes 16, 18 and 20

of calix[3]arene derivative **16** can be explained by the template effect by the hydrogen bonds between phenols and benzylamine in nonpolar solvents. This one pot cyclization method facilitates introduction of various functionalized side-arms such as picolyl or chiral methylbenzyl groups into the azacalixarene structures without using N- or O-protecting groups. Introduction of a picolyl side-arm into the [3.3.3] structure greatly enhances the affinity to an alkali metal ion compared to **16**, but the selectivity decreased remarkably. The picolyl side-arm acts as a good donor, but the flexibility of the molecule reduces the selectivity [10c]. Interestingly, **18** can be prepared from calix[4]arene by a reaction with benzylamine, paraformaldehyde, and catalytic amounts of KOH (8%) (Scheme 4).

2.1.3. Synthesis of tetraaza[3^3]cyclophanes and their related compounds

Another interesting host molecule (for reviews, see Ref. [11]) is tetraaza[3^4]cyclophanes, in which *N,N′,N″,N‴*-tetramethyl-2,11,20,29-tetraaza[3.3.3.3]paracyclophane **24** [12,15] and its water-soluble derivatives [13] (for reviews, see Ref. [14]) have been one of the most extensively studied artificial host molecules. The host **24** forms 1:1 "intracavity inclusion complexes" with small organic molecules such as dioxane [12e,15], $CHCl_3$ or CH_2Cl_2 [13c] in the crystalline state. We briefly review the coupling methods for the synthesis of [3*n*]azacyclophanes (*n* = 2, 4).

In the first synthesis of **24**, the cyclic amide formation method was used as the coupling reaction [12e,13d]. As alternative synthetic methods, we developed the *p*-toluenesulfonamide [16], trifluoroacetamide [17] and cyanamide methods [18]. *p*-Toluenesulfonamide is one of the most widely used nitrogen sources for the synthesis of azamacrocycles. One- and two-step coupling procedures were developed for the synthesis of **24** (Scheme 5). The former is rather suitable for preparing *N*-tosyl[3^2]- and [3^3]azacyclophanes **22a** and **22b** [16,19], whereas two-step coupling procedures

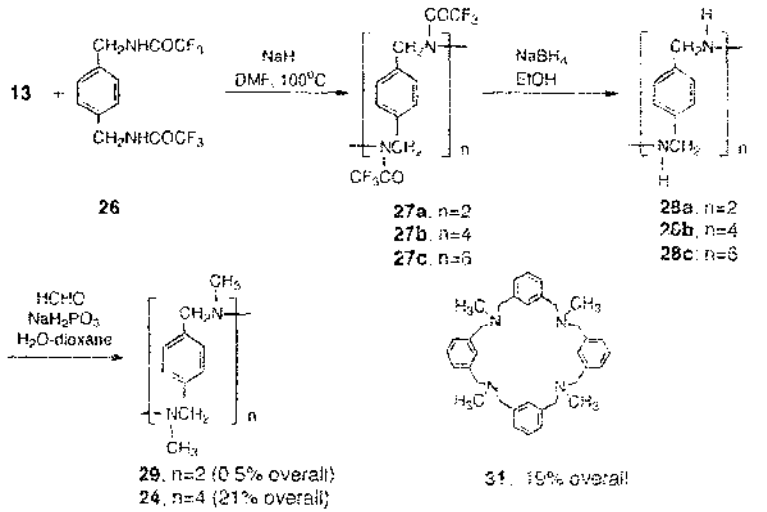


Scheme 5. Synthesis of $(Ts)_nN_n$[3^n]azacyclophanes by one-step and two-step *p*-toluenesulfonamide method

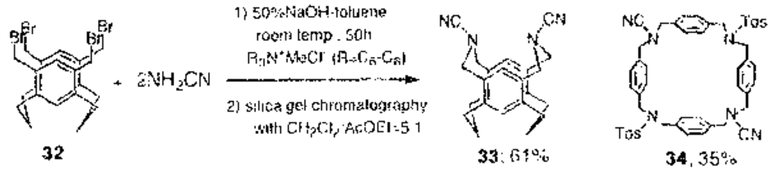
involving the reaction of once-formed *p*-toluenesulfonamide adduct **25** with the corresponding bromide **13** is suited for the selective synthesis of **24** [20,21], since the yield of **24** becomes higher than that in the one-step procedure and the troublesome separation of the trimer and tetramer can be avoided (Scheme 5). PT conditions are more promising and give better yields of [3^3]cyclophanes as compared with the single-solvent systems [22].

The trifluoroacetamide method offers a more facile and practical synthetic method for **24** and its meta analog **31**, and allows their preparation in gram quantities in a single experiment (Scheme 6) [17,23]. This method also has the advantage that the trifluoroacetyl groups are readily removed by $NaBH_4$ [24] or alkaline hydrolysis [25] after the coupling.

We have found that the dialkylation reaction of commercially available cyanamide with the corresponding bis(bromomethyl) compound in the presence of an alkali under PTC [26] afforded various *N*-cyano[3^n]cyclophanes [18]. As a typical example, the coupling of bromide **32** [27] with cyanamide affo ded tetrabridged cyclophane **33** (Scheme 7). This method is also applicable to the synthesis of tetraaza[3^4]paracyclophane with two different N-protecting groups **34**. This method is suitable for the synthesis of acid-sensitive and sterically constrained azacyclophanes.



Scheme 6. Synthesis of Me_nN_n[3^n]para- and metacyclophanes (n = 2, 4^a and azacyclophanes with [3.3]metacyclophane framework by the trifluoroacetoamide method.



Scheme 7. Synthesis of diaza[3^3]cyclophane 33 and $(Ts)_2(CN)_2N_4$[3^4]paracyclophane 34 by the cyanamide method.

2.2. Structures

The highly symmetrical structure (Td symmetry) of 3 was confirmed by X-ray crystallographic analysis. It has tetrahedrally arranged bridgehead nitrogen atoms, which retain the rigid structure. The lone pairs of bridgehead nitrogens and benzene inner protons are oriented toward the center of the cavity. Thus in the case of **4**, **5** and **6**, the pyridine lone pairs can be directed toward their cavities, as shown by the crystallographic analysis of $K^+ \subset$ **5**·ClO_4 (Fig. 1). The attempted N-methylation and protonation experiments showed that the inversion of the four bridgehead nitrogens of **3** from inside to outside is inhibited [5,6].

Although the structure of **3** is adequate as a cryptand, the cavity is filled with six aromatic inner protons. The diameter of the cavity of **3** (1.8 Å estimated by the CPK

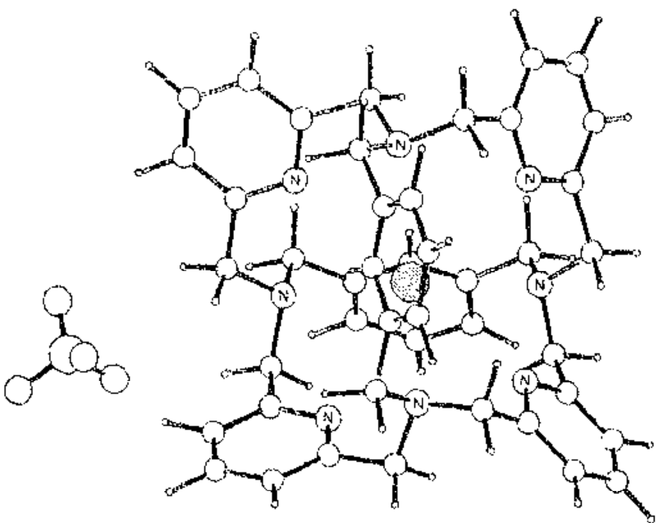


Fig. 1. X-ray structure of $K^+ \subset$ **5**·ClO_4·$CHCl_3$ (chloroform molecule is omitted; ✻ shows K^+ ion).

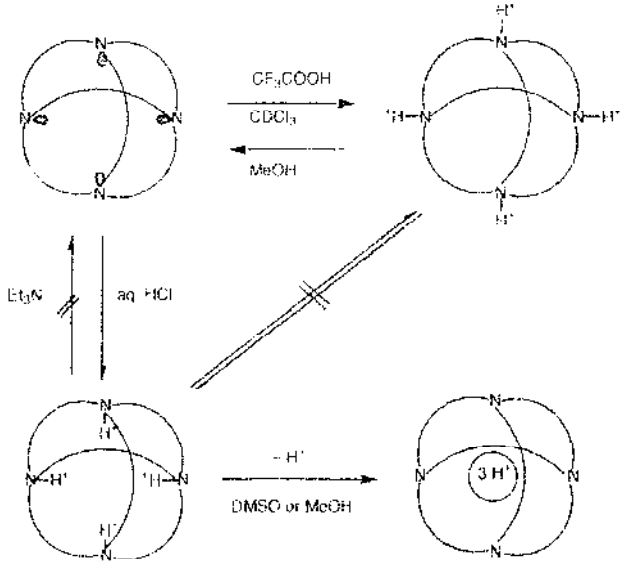
model and X-ray crystallography data) is too small to include chemical species such as alkali metal ions. Substitution of the benzene rings by pyridine rings enlarges the cavity size up to 3.8 Å for **6**, making it large enough to encapsulate several chemical species. Furthermore, the pyridine ring itself acts as a good donor unit, and the converging of the pyridine lone pairs in the cavity enhances the guest's binding ability. Bell and coworkers pointed out that unsaturated nitrogen has a greater dipole moment (1.53 D, $CH_3N{=}CH_2$) than that of an ether oxygen (1.30 D, Et–O–Et) or a saturated nitrogen (0.61 D, Me_3N). They showed that the macrocycles "torands", which contain unsaturated nitrogens, have strong affinity to alkali or alkaline earth metal ions [28]. Other macrocyclic compounds constructed by bipyridyl or bisphenanthroline rings show strong cation affinity [29,30]. The compounds **5** and **6** have four or six unsaturated nitrogen atoms, respectively, and each has four saturated bridgehead nitrogen atoms. Thus, their cavities are filled with 16 or 20 electrons, respectively. Actually, **5** and **6** interact strongly with alkaline metal cations, and especially with a proton.

Another structural feature of this series of compounds is the twisting motion of the methylene groups around the bridgehead nitrogens between enantiomeric structures as shown in Scheme 8, whose energy barrier ($\Delta G^{\ddagger}$) and rate constant were estimated to be 13.0 kcal mol^{-1} and 668 s^{-1} at 269 K for **3**. The existence of the enantiomeric pair was confirmed by ^{1}H NMR spectra at low temperatures; the addition of Pirkle's reagent, (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol into a solution of **3** at −50°C results in the splitting of the AB pattern of the methylene signal. This shows that the twisting motion is frozen at low temperatures. Similar rotations around the molecular axes have been described in some cage-type compounds [30,31].

2.3. *Properties of a new class of highly symmetrical cage compounds as amine bases*

The compound **3** shows different protonation behavior in protic or aprotic solvents; protonation with CF_3COOH in $CDCl_3$ gives **3**·4H$^+$, but, the addition of MeOH (very weak base) to the solution immediately regenerates **3**, whereas protonation in aqueous solution gives different types of ammonium salt. The ammonium salt, **3**·4HCl, was gradually converted into **3**·3HCl in MeOH or in DMSO solution, but further deprotonation cannot be observed. The addition of triethylamine into the solution of **3**·3HCl does not affect further deprotonation. The bulkiness of the base hinders the removal of the protons from the cavity (Scheme 9). In addition to the

Scheme 8. Twisting motion around bridgehead nitrogen.



Scheme 9. Protonation behavior of 3 in aprotic and protic solvents.

deprotonation properties, the two ammonium salts showed different ^{1}H NMR spectra. Consequently, protonation takes place on the outside of the molecule in an aprotic solvent, whereas protons of **3**·4HCl are placed inside the cavity and easily release one proton by electric repulsion in MeOH or in DMSO. The pKa values of the conjugate acid, **3**·4HCl, are $pK_1 = 3.4$, $pK_2 = 4.9$, $pK_3 = 6.4$, and $pK_4 = 8.1$ in MeOH–water (80wt%–20wt%). The pKa value of the reference compound, tribenzylamine hydrochloride, was estimated to be 5.64 in the same medium. The convergence of the nitrogen lone pairs enhanced the basicity of **3** by 2.5 pKa units ($pK_4 = 8.1$) compared to tribenzylamine [5,6].

On the other hand, **5** or **6** with more than eight nitrogen atoms show strong affinity toward a proton. As described below, the proton cryptates $H^+ \subset \mathbf{5}$ and $H^+ \subset \mathbf{6}$ are exceptionally stable toward bases, and direct deprotonation could not be achieved in the presence of a large excess of tetraalkylammonium hydroxide or DBU. Anion exchange resin (OH$^-$ form) treatments of these proton cryptates, $H^+ \subset \mathbf{5}X^-$ or $H^+ \subset \mathbf{6}X^-$ ($X^- = NO_3^-$, Br^-) do not give proton-free **5** or **6**, but generate $H^+ \subset \mathbf{5}{\cdot}OH^-$ or $H^+ \subset \mathbf{6}{\cdot}OH^-$ [5,32]. Interestingly, the ammonium proton could not be detected by ^{1}H NMR spectra even at low temperatures (about -90 °C) down to 30 ppm, probably owing to the complete broadening of the signal caused by the rapid exchange of the proton among lone pairs.

2.4. The hosts as cation receptors, stability of the complex and cation selectivity of the hosts

The alkali metal picrate extraction experiments showed that **3** has no complexation ability but **4** has weak affinity toward the cations; the substitution of two benzene rings of **3** into two pyridine rings increased the complexation ability of the host. The study of the selectivity of alkali metal ions in **4** by liquid–liquid extraction experiments showed an affinity toward Rb^+. Further substitution of the benzene rings with the pyridine rings of the system greatly enhanced the cation affinity. The association constant of **5** with the K^+ ion in DMSO-d_6 was estimated to be $\log K_a = 5.2 \pm 0.1$ by competition experiments between 18-crown-6 and $K^+ \subset \mathbf{5}$ [5]. The stability is 100 times greater than that of 18-crown-6. The crystal structure of $K^+ \subset \mathbf{5}$-(IO_4^-) is almost the same as that of **3**, where the K^+ ion is located at the center of the cavity, and bridgehead and pyridine nitrogens are directed to the K^+ ion (Fig. 1) [6].

The compounds **5** and **6** are ideal ligands for spherical cations, and especially for ammonium ion, because preorganized tetrahedral or octahedral coordination sites are present. By the competitive reaction between the potassium complex, $K^+ \subset \mathbf{5}$ and NH_4^+ in DMSO, the association constant of $NH_4^+ \subset \mathbf{5}$ was estimated to be $\log Ka = 6.3 \pm 0.1$. In contrast to the spherical NH_4^+, the primary alkyl ammonium salt RNH_3^+ did not form complexes with **5** and **6**. Attempted complexation reactions between $K^+ \subset \mathbf{5}$ and butylamine hydrochloride or $H^+ \subset \mathbf{5}$ and butylamine were unsuccessful. Steric hindrance and lack of guest symmetry greatly hindered the complexation.

The stability and selectivity of **5** toward alkali metal ions were estimated by competitive reactions between $K^+ \subset \mathbf{5}$ and alkali metal picrates in DMSO-d_6. The ratios of $M^+ \subset \mathbf{5}$/$K^+ \subset \mathbf{5}$ in the solution is estimated by the ^1H NMR integral ratio of the inner benzene proton signals of $M^+ \subset \mathbf{5}$ and $K^+ \subset \mathbf{5}$ since they appear at different positions. The exchange rate between the two kinds of alkali metal ions, one inside the cavity and the other in the solution, is very slow. More than three days were necessary to achieve the equilibria ($K^+ \subset \mathbf{5} + M^+ \rightleftarrows M^+ \subset \mathbf{5} + K^+$) at 25 °C after mixing the substrates.

Fig. 2 shows the plots of $\log Ka$ vs. the ionic radii of M^+ (including NH_4^+). The compound **5** has a Rb^+ selectivity similar to **4**, although the stability of the complex is much higher than that of **4**. Lehn's cryptand also has Rb^+ selectivity because of its similar cavity size (3.6 Å in diameter) [33]. In the $CHCl_3$ solution, the association constant of $K^+ \subset \mathbf{5}$ is expected to be much greater than that in DMSO. By a competitive reaction between $K^+ \subset \mathbf{5}$ and [2.2.2] cryptand in D_2O-saturated $CDCl_3$ was monitored by ^1H NMR spectra [34]. Also in this case, the reaction between them was very slow and three months were necessary to achieve the equilibrium: $K^+ \subset \mathbf{5} + [2.2.2]\text{cryptand} \rightleftarrows K^+ \subset [2.2.2]\text{cryptand} + \mathbf{5}$. As a result, an association constant of the reaction, $\mathbf{5} + K^+ \subset \mathbf{5} \rightleftarrows K^+ \subset \mathbf{5}$ in D_2O-saturated $CDCl_3$ was estimated to be $\log K_a = 15.1$.

In order to remove the K^+ ion from $K^+ \subset \mathbf{5}$, a solution of the complex in water–MeOH (1:1) (by volume) was heated in a sealed tube at 150 °C for 7 days [35]. In spite of the severe conditions, the starting material was recovered and metal-

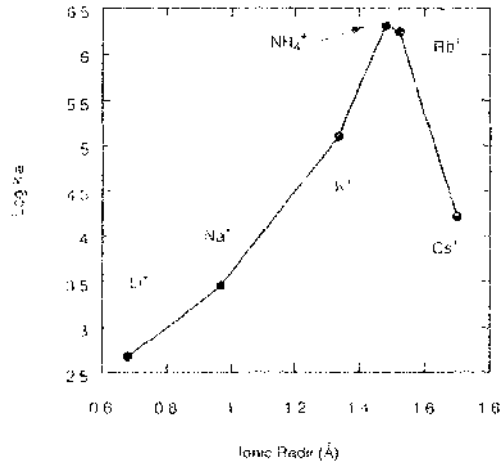


Fig. 2. Plots of association constants of $M^+ \subset 5$ vs. ionic radii of M^+.

free ligand was not detected. The K^+ ions in the complexes, $K^+ \subset 5$ or $K^+ \subset 6$, can be removed by dissolving the metal complexes in strong acids like aq. HCl, CF_3COOH or dil. H_2SO_4. Treatment of the resultant ammonium salts with $R_4N^+OH^-$ gave mono-protonated materials, $H^+ \subset 5$ or $H^+ \subset 6$.

2.5. *Molecular movement of the cation complexes*

The inner benzene protons of **5** are good probes of information about the cavity. Fig. 3 shows the relationship between the sizes of the guest metal cations and the ^1H NMR shifts of the inner aromatic protons, also the coalescence temperatures (T_c) of the methylene signal of $M^+ \subset 5{\cdot}Br^-$. The chemical shifts of the inner aromatic protons of $M^+ \subset 5$ depend on the size of M^+. A larger guest M^+ makes the molecular movements of the complex slower (Fig. 4). However, interestingly the Li^+ complex has a higher coalescence temperature than expected, but the reason is unclear so far (1:1 complexation was confirmed in all cases).

On the other hand, the chromatographic properties (R_f values) of the metal complexes, $M^+ \subset 5{\cdot}Br^-$ (Li^+–Cs^+) do not depend on the cation size. Cram and coworkers reported differences in the R_f values of the carceplexes series and they suggested some interactions between the guests in the cavity and the outer phase of the carceplexes [36]. In the case of $M^+ \subset 5$, the metal cations in the cavity do not interact with the outer environment. Although there are slight differences of molecular structures and the masses of the complexes, these are not the main factors accounting for the differences in chromatographic properties. This phenomenon can be explained by the total induced dipoles: since the guest cations are located at the center of the

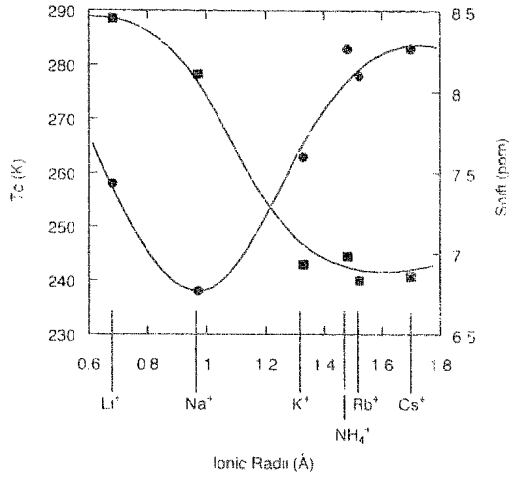


Fig. 3. Plots of chemical shifts of aromatic inner proton and coalescence temperatures (K) of M⊂**5** vs. ionic radii of guest cations: ●, coalescence temperatures of methylene signal of the complexes; ■, chemical shifts of aromatic inner proton of the complexes.

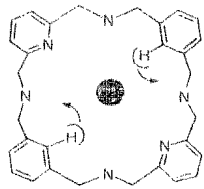


Fig. 4. Flipping of aromatic inner protons of M⊂**5** depends on the size of guest cations, M⁺. Pyridine units in front and back are omitted.

cavity, the polarizability of the complexes is totally unchanged in each metal complex. Consequently, we can estimate the size of the guest cations in the cavity not chromatographically, but by the chemical shift of the inner aromatic protons or the coalescence temperatures of the methylene signal.

2.6. Relationship between cation affinity of the ligand and donor ability, and inclusion of anions and neutral chemical species

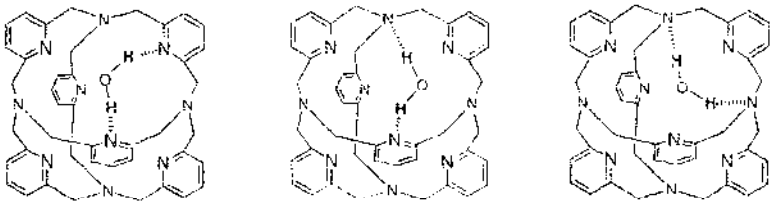
The complexation ability of **4** toward cations can be regulated from outside the cavity by attaching electron-withdrawing or -donating substituents on the pyridine rings [5,6]. The liquid–liquid extraction experiments of Rb^+ picrate showed that

the Rb^+ extraction abilities of **4**,**4**-OMe and **4**-Cl were proportional to the pKa values and dipole moments of their donor units, as expected.

A nitrogen donor can be changed into an anion receptor by protonation. In acid solutions, the positively charged cavity of $\mathbf{6}nD^+$ can incorporate anions. Thermodynamic studies on Cl^- complexation of a $\mathbf{6}nD^+$ in CF_3COOD–D_2O (1:1 by volume) solution gave the following parameters: log $K_a = 0.92$ l mol^{-1}, $\Delta H = -4.7$ kcal mol^{-1}, $\Delta S = -11.6$ cal mol^{-1} K^{-1}. The exchange rate, k_c, was also estimated by ^{1}H NMR spectra to be 150 s^{-1} (298 K). A detailed study on F^- inclusion has not been done because the ^{1}H NMR signals of $\mathbf{6}nD^+$ and $F^- \subset \mathbf{6}nD^+$ were not distinguishable from each other. Anions larger than Cl^- cannot be incorporated in the cavity (respective diameters: Cl^-, 3.6 Å; Br^-, 3.9 Å; I^-, 4.4 Å) because the cavity size of **6** is 3.8 Å in diameter. This remarkable selectivity can be ascribed to the rigid structure of **6** [5,6].

The structure of $H^+ \subset \mathbf{5}{\cdot}OH^-$ or $H^+ \subset \mathbf{6}{\cdot}OH^-$ may be considered as follows. One of the protons of the water molecule is separated from its OH^- ion by the host molecules. These complexes were stable in solid states, and the OH^- ion did not remove the proton in the cavity. The thick aromatic walls of these cage compounds generated kinetically inert, thermodynamically stable complexes. However, when $H^+ \subset \mathbf{5}{\cdot}OH^-$ or $H^+ \subset \mathbf{6}{\cdot}OH^-$ were left to stand for half a year in solid form, some parts of these materials changed to water cryptates, $H_2O \subset \mathbf{5}$ or $H_2O \subset \mathbf{6}$: the proton attracted OH^- ions into the cavity, and water cryptates were formed. Three orientations of the water molecule in the cavity were proven by ^{1}H NMR spectra at low temperatures. The combinations of hydrogen bonds between water protons and bridgehead or pyridine nitrogens give three orientation patterns; N(br)···H–O–H···N(br), N(br)···H–O–H···N(py) and N(py)···H–O–H···N(py). Here, N(br) shows bridgehead nitrogen, and N(py) shows pyridine nitrogen (Scheme 10).

Other neutral chemical species similar in size to water molecules, such as NH_3, BH_3, metal (0), Ne or Ar can be considered as possible guests. However, $NH_3 \subset \mathbf{6}$ and $BH_3 \subset \mathbf{6}$ could not be obtained following a procedure similar to that of $H_2O \subset \mathbf{6}$. In the previous experiments, $NH_4^+ \subset \mathbf{6}{\cdot}OH^-$ did not give $NH_3 \subset \mathbf{6}$, and a reaction between $H^+ \subset \mathbf{6}{\cdot}Br^-$ and BH_4^- did not give $BH_3 \subset \mathbf{6}$. The inertness of the cation complexes inhibited the reactions. Thus, in order to prepare the inclusion complexes of host and neutral chemical species, reactions between guest-free **6** and neutral



Scheme 10. Hydrogen bonding patterns of a water molecule in the cavity of **6**.

chemical species should be carried out. Several attempts to prepare these materials are being made[1].

2.7. Structure of azacalix[n]arenes

The compound **16** showed pH-dependent, strong binding properties towards UO_2^{2+} in the presence of large amounts of NaCl [10a]. The azacalixarenes have strong intramolecular hydrogen bonds between phenolic hydroxyl groups and nitrogens. The results of ^{1}H NMR and IR spectra showed that the intramolecular hydrogen bonds of the azacalix[*n*]arenes **16**, **18**, **20** are stronger than those of oxacalixarenes or calix[*n*]arenes. The ^{1}H NMR spectra showed abnormally downfield-shifted OH signals. At room temperature, the signal of **18** appeared at 11.6 ppm in $CDCl_3$. At −80°C, the signal split into six singlets, which appear in the range of 9.8–17.1 ppm in CD_2Cl_2. The IR spectra also show the existence of strong hydrogen bonds. The compound **18** has a rigid cone conformation and the free energy of flipping of the aromatic rings is larger than that of *p*-*tert*-butylcalix[4]arene [10b,c]. This rigidity also originated from the strong intramolecular hydrogen bonds. Table 1 summarizes the results of ^{1}H NMR and IR spectral features of OH groups of calix[*n*]arenes, oxacalix[*n*]arenes and azacalix[*n*]arenes.

3. Conclusions

Developments of methods to synthesize the azamacrocycles described above allow the preparation of various types of a new class of host molecules such as the cage compounds **3**–**6** and their bond isomers **8**, **10**, azacalix[*n*]arenes **16**, **18** and **20**, and tetraaza[3^4]cyclophanes **24** and **31**.

By the convergence of pyridine lone pairs in the cavity of appropriate ligand

Table 1
Free energies of aromatic ring inversion, chemical shifts of phenolic OH groups and their frequencies of O–H stretching mode in IR spectra

	$\Delta G^{\ddagger}$ (solvents) (kcal mol^{-1})	δ_{OH} (ppm)	ν_{OH} (cm^{-1})
Calix[4]arene	15.7 ($CDCl_3$)	10.2	3170
Dihomooxacalix[4]arene	13.0 ($CDCl_3$)	9.0, 9.7	3300
Tetrahomodioxacalix[4]arene	11.9 ($CDCl_3$)	9.9	3370
Hexahomotrioxacalix[3]arene **16**	–	11.2	2800
Dihomoazacalix[4]arene **18**	15.9 (DMSO-d_6) 17.8 (xylene-d_{10})	11.6	2780
Tetrahomodiazacalix[4]arene **20**	14.4 ($CDCl_3$)	10.7	3000

[a] $CDCl_3$, [b] Br dmb, [c] Too low to measure.

[1] The preparation of guest-free **5** and **6** were performed by the reactions of Co^{3+} – **5** or Ag^+ – **6** and tetraalkylammonium cyanides.

structures, stable and highly selective receptor molecules were realized. An unsaturated nitrogen atom is a better donor than an oxygen atom because it has greater dipole moment than that of the latter. The convergence of lone pairs into the cavity plays an essential role in the strong affinity for the guest species. An increase of the number of lone pairs also enhances the complexation ability. The rigid and highly symmetrical structure is suitable for the inclusion of spherical guests. The compounds **5** and **6** showed strong inclusion ability for alkali metal cations. In addition to the alkali metal ion affinities, the cavities of **5** and **6** are strongly basic: a proton in their cavity could not be removed by strong bases. The cation affinity depends on the basicity and dipole moment of the donor site. In the case of the compound **4**-OMe, and **4**-Cl, the affinity can be regulated by changing the electron density of the pyridine lone pairs by attaching electron-withdrawing or -donating substituents on the pyridine rings. Shielding the cavity with aromatic rings leads to strongly stabilized ion pairs, i.e. $H^+ \subset \mathbf{6} \cdot OH^-$. The host molecules discussed above can interact with a neutral guest (water) through hydrogen bonds and also with anions in the protonated form.

The ^1H NMR and IR spectral data showed that the azacalix[*n*]arenes **16**, **18** and **20** have more rigid structure than the corresponding oxacalix[*n*]arenes and calix[*n*]arenes because of the strong intramolecular hydrogen bonds between phenolic hydroxyl groups and nitrogen lone pairs.

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Abbreviations

[3ⁿ]CP	[3.3.⋯3]cyclophane
[3_n]CP	multi-bridged [3.3]cyclophane
⊂ (inclusion symbol)	guest ⊂ host means "guest species included in host cavity"

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