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Laterally non-symmetric aza-cryptands: synthesis, catalysis and derivatization to new receptors

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Contents

Abstract

Cryptands where the two bridgehead atoms like N or C or benzene units are connected by three bridges such that the donor atoms about the bridgeheads are different can be called laterally non-symmetric cryptands. These cryptands constitute a class which can be useful in several contemporary areas of research. The present article describes the synthesis of the cryptands and the use of metal cryptates in homogeneous catalysis, in the photochemical splitting of water to generate H_2, in the cleavage of nucleic acids as chemical nucleases. These cryptands can be derivatized to have new receptors which might be useful as well.

Keywords: Cryptands; Synthesis; Catalysis; Receptors

1. Introduction

Cryptands are useful in many fascinating areas of chemistry, biochemistry as well as materials science [1–12]. They are able to provide suitable frameworks for arrangement in space of one or more receptor sites by incorporating donor atoms. Through these sites, these molecules can act as receptors for the selective binding of substrates which can be charged (cations and anions) or of neutral molecules. The degree of rigidity in a cryptand can be tailored by introducing appropriate numbers of aromatic or ethylenic linkages in the framework. Macrobicyclic cryptands, where two bridgehead atoms like N or C or two benzene units are connected by three bridges which implies that the donor atoms about the two bridgeheads are different, constitute a class of cryptands which are laterally non-symmetric (Fig. 1). They constitute an important class of cryptands with capabilities to form inclusion complexes endowed with many interesting properties. Use of the metal cryptates as electron transfer agents, homogeneous catalysts as well as their interactions with DNA and RNA are discussed in the present review. The protonation behavior of a few cryptands is also discussed in the context of

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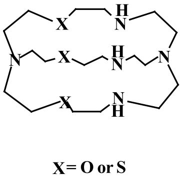


Fig. 1. An illustration of laterally non-symmetric cryptands.

their derivatization to new receptor molecules. Discussions on the structure/property relationship of the metal cryptates are avoided as these are available in several reviews [13–15].

2. Synthesis of cryptands

The high dilution technique is still the most commonly used method for cryptand synthesis. However, this technique usually takes a long time for completion which encouraged the development of other techniques such as the use of a template or low-temperature cyclization reactions. A template organizes [16] reactants with respect to each other so as to achieve a particular linking to form the desired compound. Several workers in this area [17–19] have contributed significantly to the understanding of the template effect in macrocyclization reactions.

The synthetic difficulties associated with cyclization reactions are mainly due to the movements of the reactant arms which decrease the possibility of reactive groups—coming in proximity within the reactive zone—to yield the desired macrocycle. This conformational mobility can be decreased substantially either by increasing rigidity [20] of the framework by incorporation of aromatic and unsaturated groups or running the reaction at lower temperatures [21].

Major strategies [22] devised for the synthesis of laterally non-symmetric cryptands are (I) stepwise, (II) tripodal coupling, and (III) tripodal capping.

Although stepwise synthesis mostly affords symmetric cryptands, it can also be used to obtain non-symmetric cryptands [23] (Fig. 2). However, this strategy is cumbersome and affords the desired cryptands in low overall yields.

Tripodal coupling is a more direct method where [1+1] condensation of two different tripodal units can be carried out [24]. A number of cryptands have been synthesized [24–28] by Schiff-base condensation of tripodal amines with tripodal trialdehydes (Fig. 3) followed by a reduction of the arising imino groups formed with $NaBH_4$. In this synthetic strategy, an alkali metal ion such as Rb(I) or Cs(I)) is usually employed as a template and the reaction is carried out at ~ 40 °C. However, at low temperature (~ 5 °C), the reaction can proceed with comparable yields without any templating ion due to the increased conformational stability of the podand arms. This method works well if the tripodal arms contain aromatic groups which increase the rigidity of the tripods.

Non-symmetric cryptands with large cavities (Fig. 4) can be synthesized [29] only in the presence of Rb(I)/Cs(I)-ion as the template. Un-templated reactions lead to mixtures of unidentified products. Apparently, the bigger podands cannot close-in to undergo [1+1]-condensation in absence of a template. The tripodal coupling strategy can be applied to condense a tripodal ester with a tripodal amine [30] (Fig. 5).

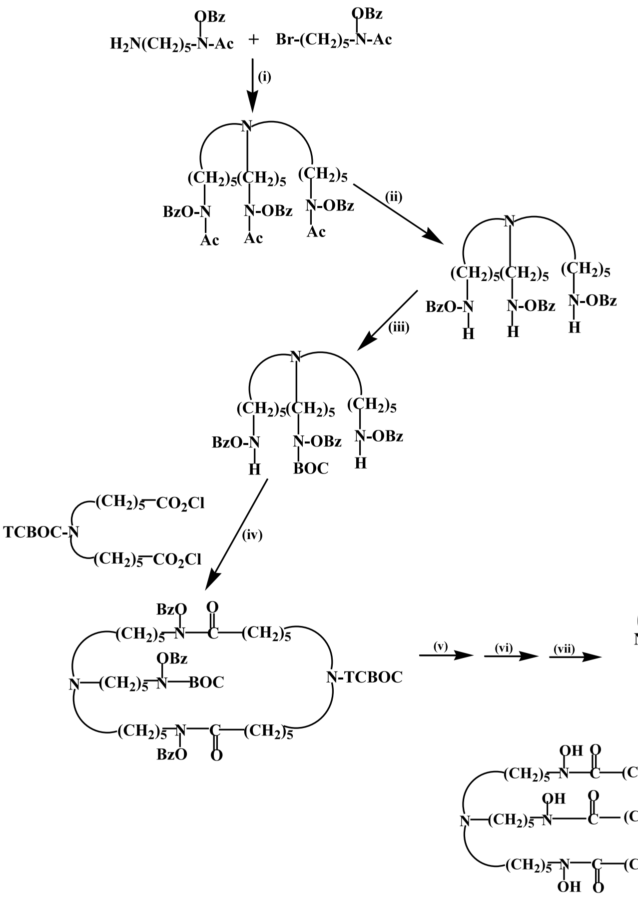
The tripodal coupling of a tri-amine with a tri-acid chloride at room temperature (r.t.) also affords [31] a non-symmetric cryptand (Fig. 6).

The tripodal capping strategy in the presence Co(III)-ion as a template has been used [32–36] to synthesize a number of non-symmetrical aza cryptands (Fig. 7). However, this strategy always gives a cryptand with Co(III)-ion included in the cavity and the removal of Co(III) is a difficult procedure. It is first reduced to the kinetically labile Co(II) state and then allowed to react with excess cyanide or concentrated boiling HBr to remove it from the cavity. The use of a kinetically labile alkali or alkaline earth metal ion, as a template in the tripodal capping reaction, is not reported. Apparently, the terminal amines are optimally oriented by the Co(III) ion for the desired capping. In one case, a cryptand with a contracted cavity has also been isolated [37] as a by-product.

3. Metal cryptates

3.1. Cryptands for metal complexation

Recognition of metal ions by cryptands remains a poorly understood phenomenon although several studies [38–41] have been carried out towards this end. The selection of donor atoms for a particular type of metal ion is based on concepts like the hard and soft acid and base principle of Pearson [42] or the A and B type of Schwarzenbach [43] or Ahrland [44]. The ethereal oxygen atom being a hard donor is generally suitable for alkali, alkaline-earth or some main-group elements, yet exceptions to this general observation also appear [45]. This is especially true if the donor set contains nitrogen and/or sulfur along with the ether oxygen atoms. On the other hand, nitrogen, sulfur and phosphorus are suitable donors for transition metal ions. Cryptands with a small cavity can accommodate a single metal ion inside. However, when the cavity is large, a single metal ion can be attached to a pre-determined site, leaving a vacant space inside. Molecules or ions can enter the cavity and become bonded to the metal ion. Besides, this space can be utilized to carry out organic transformations where the catalyst is not easily de-



(i) K_2CO_3/MeCN/24h/reflux, (ii) $Ba(OH)_2.8H_2O$/MeOH/stir/72 h,
(ii) $(BOC)_2O$/MeCN, (iv) Benzene/Py/5°C/N_2 (high dilution), (v) TFA/stir,
(vi) benzene/py/N_2, (vii) (a)Zn/HOAc, (b) MeCN/Na_2CO_3/NaI/N_2/reflux/
72 h(high dilution), (viii) a)$(Me)_2$B-Br/DCE/O°C/Ar, b) $Pd(OH)_2$/H_2/EtOH

Fig. 2. Step-wise synthesis of a laterally non-symmetric cryptand.

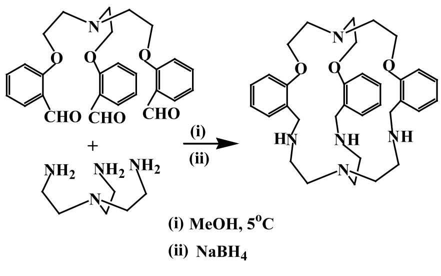


Fig. 3. Tripodal coupling of two podand units to a laterally non-symmetric cryptand.

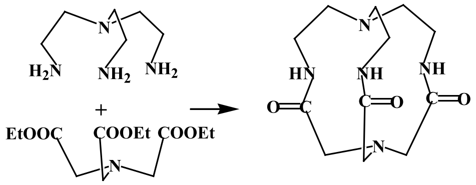


Fig. 5. Tripodal coupling of an amine with an ester.

graded due to kinetic as well as thermodynamic stability of the metal cryptate.

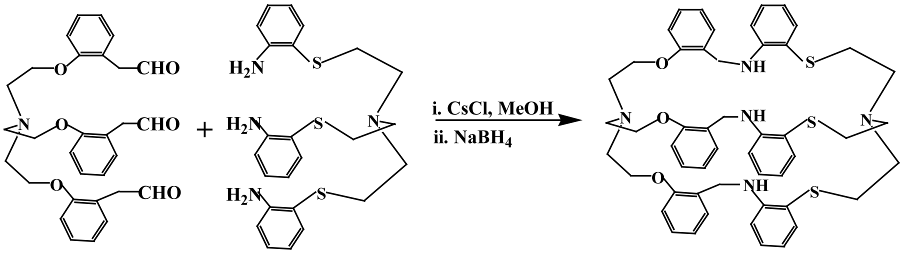


Fig. 4. Template synthesis of a cryptand with a large cavity.

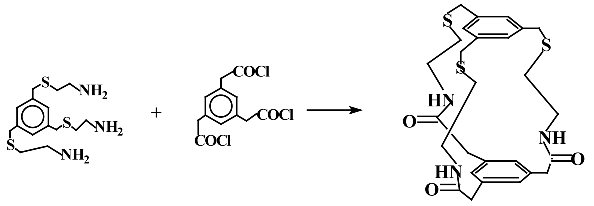


Fig. 6. Tripodal coupling of two podands with benzene bridgeheads.

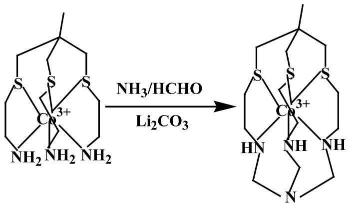
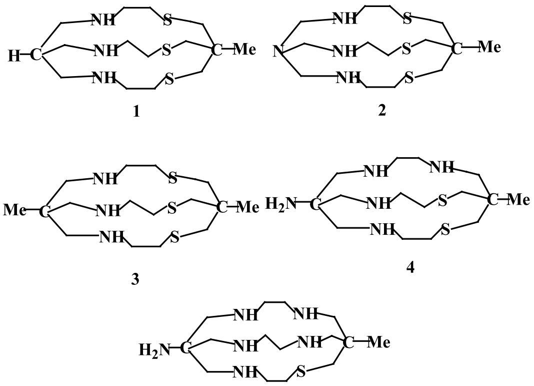


Fig. 7. Tripodal capping synthesis of a cryptand.

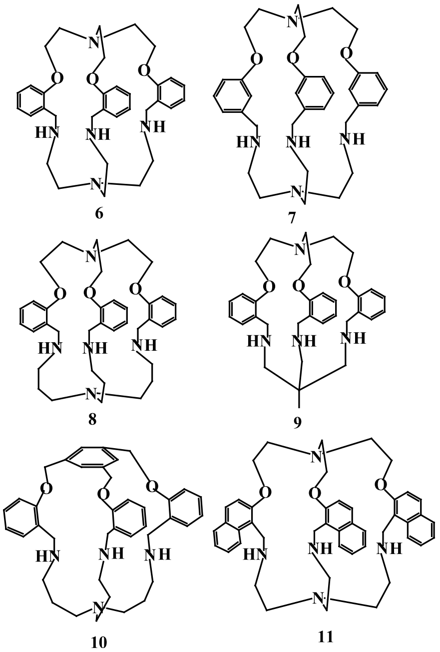


1 2 3 4 5

Fig. 8. Laterally non-symmetric cryptands with N and S as donors.

The cryptands shown in Fig. 8 have excellent ligating abilities towards transition metal ions. Each of these cage molecules binds a single transition metal ion inside. However, while Co(III) complexes with all of the ligands are known, other metal ions like Ru(III), Ni(II), etc. have been sporadically used in making complexes.

Partial replacement of nitrogen for sulfur in the original sephulcrate and sarcophagine cage molecules profoundly affects the spectroscopic properties of the Co(III) complexes. The Co(III) complexes of these ligands have been characterized in the solid state by X-ray crystallography. The small and rigid cavity binds cobalt very tightly inside and the metal ion cannot relax to its preferred geometry either in +2 or in +3 state leading to chemical as well as electrochemical reversibility of the Co(III)/Co(II) pair. The potential for this pair can be varied widely by changing the number of nitrogen and sulfur atoms in the three bridges as well as attaching electron donating or withdrawing groups to the apical atoms [37,46].



6 7 8 9 10 11

Fig. 9. Laterally non-symmetric cryptands with N and O as donors.

Each of the cryptands shown in Fig. 9 possesses a large cavity with two distinct binding sites separated by a hydrophobic spacer. The N_4 moiety derived from tris(2-aminoethyl)amine (tren) (Fig. 3) binds transition as well as heavy main-group metal ions like Pb(II) and Ag(I) while the ether moiety can be expected to be effective in the binding of harder cations. However, complexation studies [47] with these cryptands clearly show that they do not bind alkali or alkaline earth cations. The N_4 moiety, on the other hand, cannot saturate the coordination spheres of many metal ions. Therefore, the bound metal ion draws solvent molecules or counter anions from the medium to saturate its coordination requirements.

The X-ray structure of the Pb(II) cryptate of **6** shows (Fig. 10) the metal ion to be penta-coordinated from N_4O donors where one of the ether oxygen atoms is also bonded to the metal [48]. The Pb–N and Pb–O bond distances (Table 1) are very dissimilar compared with

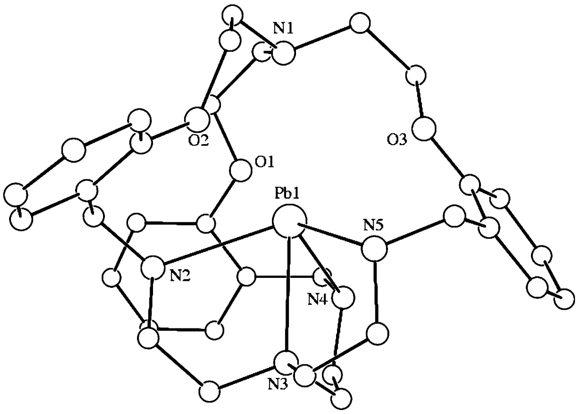


Fig. 10. A perspective view of the Pb(II)-cryptate of **6**.

Table 1
Selected distances (Å) in **6**, [H_5**6**](ClO_4)$_5$, [**6** ⊂ Pb](NO_3)$_2$, [**6** ⊂ Ag]NO_3, **8**, and [**8** ⊂ Zn](ClO_4)$_2$

		6	[H_5**6**](ClO_4)$_5$
N(1)···N(3)		6.249	5.250
N(2)···N(4)		4.036	5.529
N(2)···N(5)		4.336	5.545
N(4)···N(5)		3.536	4.589
O(1)···O(2)		4.862	4.772
O(1)···O(3)		5.365	5.282
O(2)···O(3)		3.992	5.039
[6 ⊂ Pb](NO_3)$_2$		[6 ⊂ Ag]NO_3	
Pb–N(2)	2.627(10)	Ag–N(2)	2.392(7)
Pb–N(3)	2.605(12)	Ag–N(3)	2.607(9)
Pb–N(4)	2.605(9)	Ag–N(4)	2.439(10)
Pb–N(5)	2.768(11)		
Pb–O(2)	2.768(12)		
N(1)···N(3)	5.806		5.955
N(2)···N(4)	4.058		4.059
N(2)···N(5)	4.496		4.079
N(4)···N(5)	4.235		4.005
O(1)···O(2)	4.054		4.220
O(1)···O(3)	4.271		4.425
O(2)···O(3)	4.303		4.120
	8	[**8** ⊂ Zn](ClO_4)$_2$ · 2H_2O	
N(1)···N(3)	5.291	7.263	
N(2)···N(4)	4.960	3.342	
N(2)···N(5)	6.526	3.350	
N(4)···N(5)	6.410	3.336	
O(1)···O(2)	4.974	4.589	
O(1)···O(3)	5.321	4.309	
O(2)···O(3)	5.805	4.346	
Zn–N1	2.025(7)	Nl–Zn–N2	106.5(3)
Zn–N2	2.033(6)	Nl–Zn–N4	107.8(3)
Zn–N4	2.021(7)	Nl–Zn–N5	107.6(3)
Zn–N5	2.008(8)	N2–Zn–N4	111.0(3)
		N2–Zn–N5	112.0(3)
		N4–Zn–N5	111.7(3)

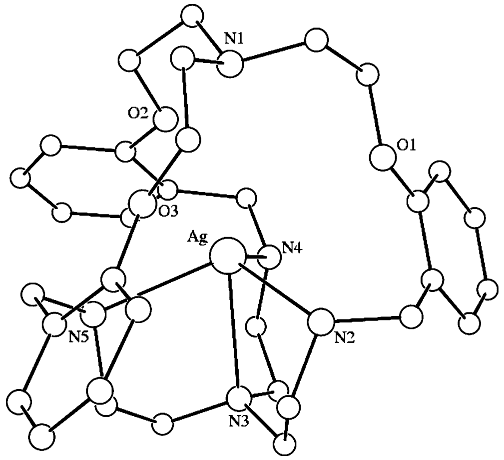


Fig. 11. A perspective view of the Ag(I)-cryptate of **6**.

those found in other Pb(II) cryptates [49]. The disparity in the bond distances suggests that the lone pair on Pb(II) is stereochemically active. It has been found [50] that the bonds most remote from the lone-pair tend to be shorter than adjacent bonds. Therefore, the lone-pair in the present complex is likely to occupy one of the axial positions with the bridgehead nitrogen occupying the other.

The coordination requirements of Ag(I) is satisfied when it is bonded to four nitrogen atoms of **6** (Fig. 11). The non-bonding distances between the nitrogen and the oxygen atoms of the cryptand do not change [48] significantly upon coordination (Table 1). This suggests that cryptand **6** is more suited for Ag(I) compared with Pb(II). In fact the extraction ability of **6** towards Ag(I) is significantly higher than that towards Pb(II) [51]. Neither Pb(II) nor Ag(I) ion bonded inside **6** shows any tendency to bind any molecule or ions to increase the coordination.

The Ni(II) ion at the N_4 end of the cavity of **6** acquires hexacoordination by binding an acetonitrile molecule from outside the cavity and a H_2O molecule inside [52] whose H atoms are bonded (Fig. 12) to the ether oxygens. This H-bonding scheme can be exploited [53] to bind a H_2S molecule to the Cu(II) ion inside the cavity of cryptand **11** (Fig. 13). Though X-ray data were not obtained, spectroscopic investigations support the type of complexation illustrated in Fig. 13.

Since the cryptand **7** possesses a much larger cavity, the H atoms of the H_2O molecule bound to Cu(II) ion cannot come close to the ether oxygens [54]. Instead, the cryptate shows a rare type of π H-bonding to the aromatic groups (Fig. 14). However, when a metal ion anchored at the tren-end (tren = tris(2-aminoethyl)amine) of the cavity binds an anion such as CN^-, SCN^- or N_3^-, the top part tilts away [27] enabling the anion to avoid the hydrophobic aromatic groups. As a result, a part of the anion remains outside the cavity (Fig. 15). In presence of the Cl^- anion, a different binding mode is observed. The Cl^- anion [47] coordinates the Ni(II) ion and at the same time forms H-bonds with amino groups present in the bridges. Both in case of **6** and **7**, the bound metal ion is pushed out of the

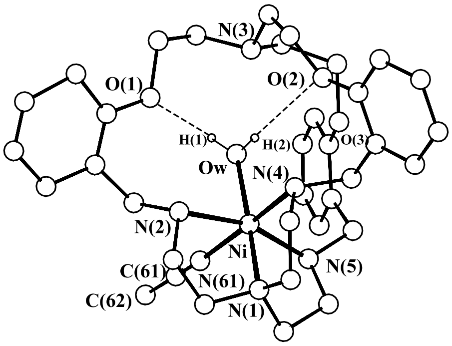


Fig. 12. A perspective view of the Ni(II)-inclusion complex of **6** showing hexacoordination.

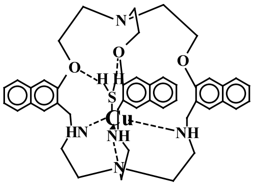


Fig. 13. A Cu(II) ion bound to one H_2S molecule inside the cavity of **11**.

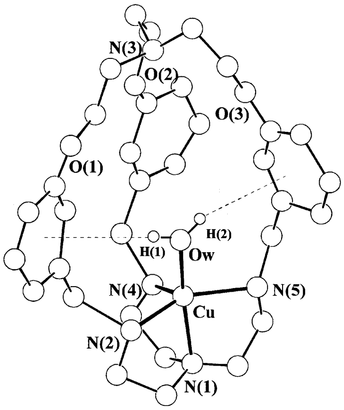


Fig. 14. A water molecule bound to Cu(II) inside the cavity of **7**.

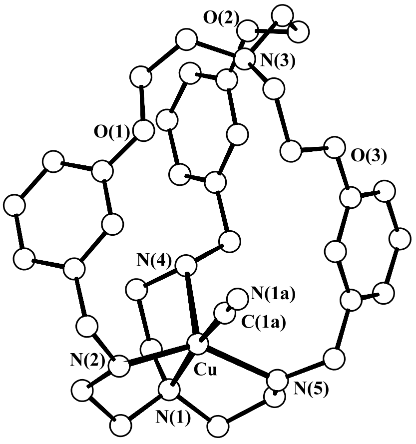


Fig. 15. A cyanide ion bound to Cu(II) inside the cavity of **7**.

plane formed by the three amino groups so that it is exposed to surroundings.

Cryptand **8**, with a trpn unit (trpn = tris(3-aminopropyl)amine) in stead of tren and *ortho*-substituted benzene groups (Fig. 9) in the three bridges, has a collapsible cavity (Fig. 16). Upon coordination to a Zn(II) ion, the cavity enlarges significantly (Table 1) and coordination geometry [55] around the Zn(II) ion becomes near to an ideal tetrahedral. The Cu(II) cryptate of this ligand can also be isolated in the solid state in pure form although no X-ray data are available. The other cryptands in this series do not afford metal cryptates in the solid state in pure form, but lead to mononuclear cryptates with a distorted tetrahedral coordination geometry, as revealed by spectroscopic studies.

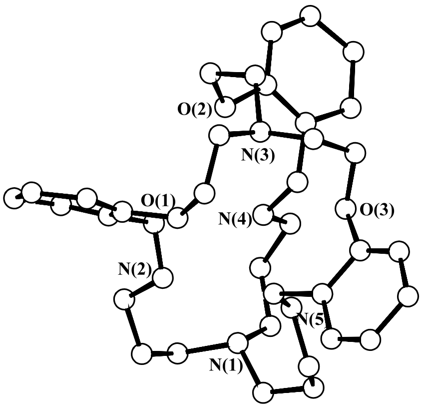


Fig. 16. The X-ray structure of the cryptand **8**.

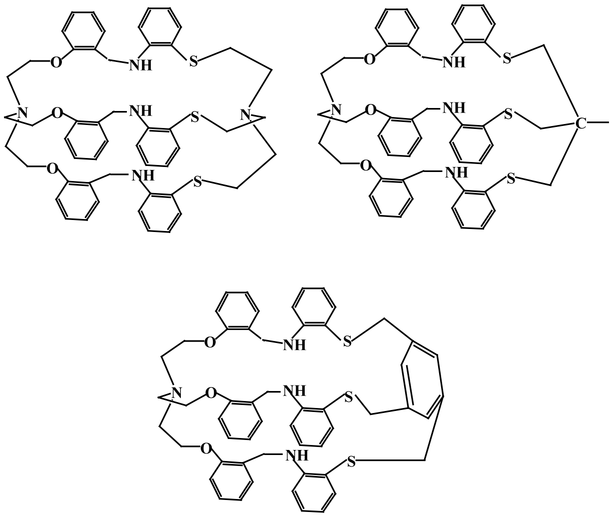


Fig. 17. Laterally non-symmetric cryptands with large cavity.

Cryptands **12**–**14** contain sulfurs in addition to nitrogen and oxygen as donors (Fig. 17) with a large cavity. These were also found to be good ligands [29] for first-row transition metal ions although only Cu(II) and Ni(II) cryptates could be isolated as pure solids. The UV–vis spectroscopic data of the Cu(II) and Ni(II) cryptates are consistent [56,57] with a distorted octahedral geometry around the metal ion with coordination from three amino nitrogens and three thioether sulfurs. The Cu(II) cryptates show only a broad EPR signal near g ca. 2.15 typical of magnetically concentrated Cu(II) complexes in the solid-state as well as in acetonitrile glass. They also show quasi-reversible Cu(II)/Cu(I) couple ($\Delta E_p = 140-180$ mV at 100 mV s^{-1} scan rate) at $E_{1/2}$ of ca. 0.5–0.6 V versus Ag/AgCl. The low value for this couple indicates that these systems are strongly reducing. Not surprisingly, when a further equivalent of $[Cu(H_2O)_6](ClO_4)_2$ is added in acetonitrile, the color of the solution changes immediately to dark green and within two hours colorless crystals of $[Cu(MeCN)_4]ClO_4$ deposit. Upon addition of more Cu(II) salt, more of the cuprous salt is formed. Such type of behavior is, however, not unprecedented [58].

3.2. Photochemical behavior of cobalt complexes

Photochemical systems for direct light-induced water splitting to produce hydrogen have been investigated quite intensively with these complexes. Such systems can be classified into homogeneous and heterogeneous where the main step of light-induced charge-separation occurs either by a homogeneous reaction (in solution) or in a semiconductor (heterogeneous). In homogeneous photochemical water splitting and H_2 production, the focus has been on different systems capable of undergoing a light-induced outer-sphere electron transfer reaction [59]. In case of cyclic water splitting based on diffusion-controlled reactions, kinetic problems diminish the quantum yield. Applying the Marcus theory in such reactions, it is generally found that the backward reactions are faster than forward reactions. The stability of photo-sensitizers and electron relay compounds pose another major problem. Co(III) inclusion complexes of cage ligands with N_3S_3 donor set (Fig. 8) have a high stability towards hydrogenation and a low reactivity towards oxygen. Hence, these compounds have been proposed [60,61] as ideal electron relay compounds for light induced H_2 formation. The electron self-exchange rate between Co(II) and Co(III) states is very fast as it occurs via an outer-sphere pathway (Eq. (1)).

$$[L \subset Co(III)]^* + [L \subset Co(II)] \rightleftarrows [L \subset Co(II)]^* + [L \subset Co(III)] \quad (1)$$

As the Scheme 1 shows, the rate of H_2 production is controlled by the generation of an excited state of the photo-sensitizer and three separate electron transfer reactions. In presence of colloidal Pt/pva catalyst [60], the reaction proceeds easily to the right. In this role, some of the Co(III) cryptates are comparable to more conventional artificial systems [62].

3.3. Catalytic properties of metal cryptates

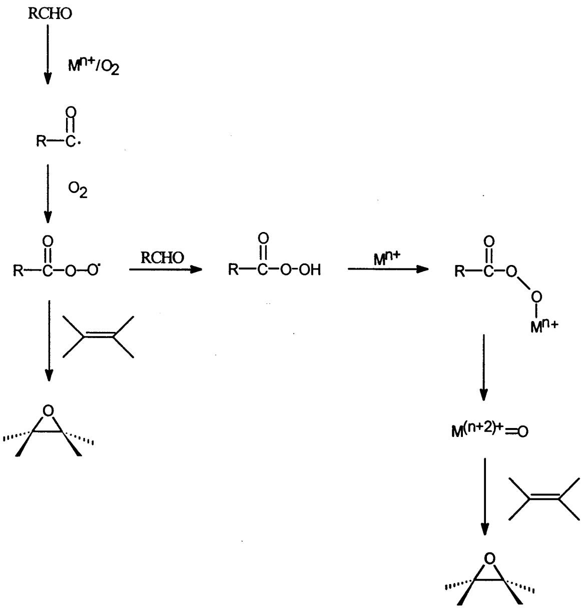
The cavity of **7** being large, it has more space for organic molecules to approach the metal bonded inside the cavity. Thus, the Cu(II) and Co(II) cryptates of **7** were probed for possible catalytic roles in the oxidation of organic substrates. Metal cryptates have been suggested to be effective as homogeneous catalysts [63] because of their increased kinetic and thermodynamic stability. Transition metal catalyzed oxidation of organic substrates with dioxygen is closely related to important biological processes like enzymatic oxygenation and therefore, can serve as biomimetic models [64]. Besides, such systems are potentially useful as the next generation low-temperature bleaching agents [65]. Impressive advances have been made to provide deeper insight into the intricacies involved during oxygen activation and its subsequent reaction with organic molecules. In these reactions, terminal oxidants such as peroxides, iodosyl benzene, hypochlorite, aldehydes, etc. oxidizes olefins to epoxides or in certain cases to the corresponding allylic alcohols and enones [66–71] and are catalyzed by various transition metal complexes. With isobutyraldehyde as the terminal oxidant, the transformation is assumed to occur via high-valent metal–oxo intermediates [71] generated from the catalyst by a number of steps (Scheme 2). In case of cryptates, the acylperoxy radical can complex with the metal ion in the cavity, forming the metal–peroxy complex. This can either transfer the oxygen atom directly to the substrate or form metal–oxo species which can transfer the oxygen to the substrate. Both the Cu(II) and Co(II) cryptates of **7** are able to oxidize a number of organic substrates with dioxygen in presence of isobutyraldehyde at ambient temperature and pressure (Table 2). While the olefinic substrates form epoxides, the benzylic substrates are converted into the corresponding ketones in excellent yields [72] with concomitant co-oxidation of the aldehyde to the carboxylic acid. Interestingly, electrophilic olefins also

$$[Ru(bpy)_3]^{2+} + h\nu \rightarrow [Ru^*(bpy)_3]^{2+} \quad \text{...........(1)}$$

$$[Ru^*(bpy)_3]^{2+} + [Co{\subset}L]^{3+} \rightarrow [Ru^*(bpy)_3]^{3+} + [Co{\subset}L]^{2+} \quad \text{........(2)}$$

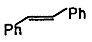
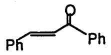
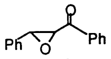
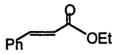
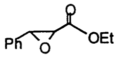
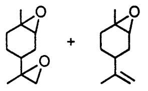
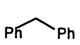
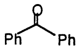
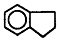
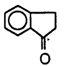
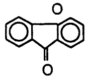
$$2[Co{\subset}L]^{2+} + 2H^+ \xrightleftharpoons{\text{catalyst}} 2[Co{\subset}L]^{3+} + H_2$$

Scheme 1.



Scheme 2.

Table 2
Catalytic oxidation of organic compounds by metal crytates

Entry	Substrate	Product	Yield % A	Yield % B
1			quant.	quant.
2			82	60
3			50	36
4			quant. (3 : 1)	75 (2:1)
5			91	
6			70	54
7			49	35

A = $[Co{\subset}7](ClO_4)_2$ and B = $[Cu{\subset}7](ClO_4)_2$

undergo oxidation under the mild conditions. During such a process, the cryptate can be recovered completely from the reaction mixture, leading to very high turnover numbers for the catalysts. A logical extension of such a system would be to derivatize the secondary amines with chiral substituents for chiral epoxidation which, however, is yet to be realized. Chiral centers can also be incorporated in the three bridges via designed synthesis.

Small molecules can interact with DNA or RNA in a number of ways like the intercalation [73] of planar aromatic molecules between the base pairs, electrostatic interaction between the complex cation and the negatively charged phospodiester backbone, etc. The π-stacking abilities of **6** and **7** (vide infra) prompted a study [74] of their binding abilities towards DNA, RNA, and oligonucleotides and also their phosphoesterase activity in the presence of lanthanide ions. The interaction of nucleic acids with cryptands is also of interest in view of their size and relative rigidity, as both factors can lead to different binding modes and affinities compared with acyclic polyamines [75]. In addition, cryptands could offer ways to provide kinetic stabilities for chemical nucleases derived from such ligands and transition metal and/or lanthanide cations [76]. If the catalytic activity were not hampered in such complexes, they would offer a starting point for the attachment of rate-enhancing co-factors. The X-ray structure of **6** shows [58] that the aromatic rings undergo π-stacking with a picrate anion. Thus, cryptand **6** as well as **7** may preferably stack with exposed bases of unfolded nucleic acid parts. Experiments with oligonucleotides as well as DNA and RNA show that both **6** and **7** destabilize the double strands which are reflected in the change in their melting temperatures [77]. Both **6** and **7** may complex lanthanide ions in their cavities [78] by binding with three ether oxygens and three amine nitrogens. However, a spectrophotometric titration [74] for the complexation of **6** with $PrCl_3$ in methanol, gave a log K value of only 2.59. Complexation in water is expected to be even weaker and cannot be measured due to solubility problems. In consequence these ligands can either block the phosphate of the substrate or can act as co-factors in the hydrolysis [79]. Highly stable and water-soluble Co(III) inclusion complexes of some of the cage ligands shown in Fig. 9 have been derivatized [80] with groups able to enhance the interaction with DNA through intercalation or electrostatic interactions. Some of these systems are shown in Fig. 18. Irradiation of the intercalated complexes at 254 nm causes single-strand cleavage of DNA while irradiation at a higher wavelength shows substantially less effective cleavage. The cleavage mechanism put forward is that the N-radical cation arising from ligand to metal charge (electron) transfer in the intercalated complex leads to oxidation of the deoxyribose moieties. This is followed by fission of the resulting deoxyribose diphosphate radical cation leading to DNA single-strand cleavage. The efficiency of the cleavage is found to be increasing with the Co(III)/Co(II) potential of the inclusion complexes.

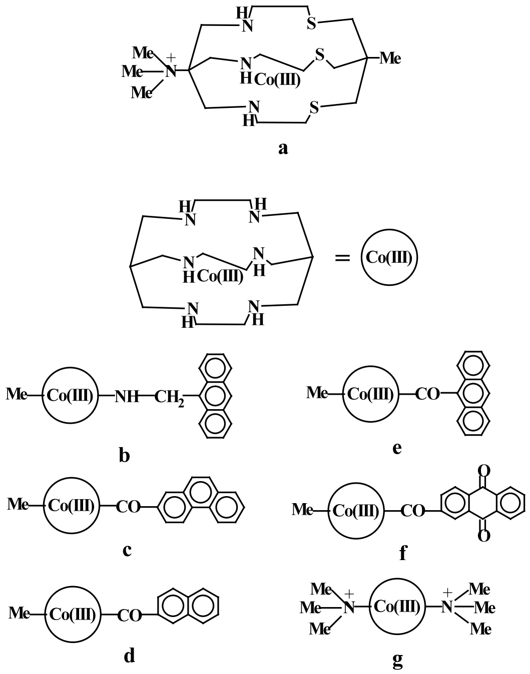


Fig. 18. Chemical structure of the Co(III) cryptates capable of interacting with DNA.

4. Protonation of cryptands

The protonation behavior of cryptands incorporating amino nitrogens depends critically on the overall structure of the cryptand and the relative positions of the nitrogen atoms in the cryptand architecture [81]. This is because subsequent to protonation of the nitrogen(s) to form NH_2^+, the species can be stabilized by relatively short H-bonding interactions. However, sometimes an exhaustive protonation can be difficult due to unfavorable build-up of positive charges especially if the cavity is small. In the pH range 2.5–10.5, cryptand **6** behaves as a tetraprotonated base $[H_4\mathbf{6}]^{4+}$ while **7** and **8** are able to form the fully protonated species $[H_5\mathbf{7}]^{5+}$ and $[H_5\mathbf{8}]^{5+}$. Cryptand **6** can form the fully protonated species only in very acidic solution. The first two protonation constants of **6** are considerably higher than the corresponding values for **7** and **8** (Table 3) while the third and fourth values are significantly lower. The higher values for the first two protonation constants of each cryptand make them topologically complementary to water molecule(s) which are tightly held inside the cavity of the protonated cryptands as found by X-ray crystallography. The cryptand **6** as well as its N-methyl derivative bind a water molecule [82] almost at the middle of the cavity and the bond angles around the water oxygen are close to being tetrahedral (Fig. 19). The cavity of **7** being larger, two water molecules are bound [54] inside where each oxygen atom is almost tetrahedral (Fig. 20). In $H_2\mathbf{6}^{2+}$ and its N-methyl derivative, the water molecule seems to be bound more strongly than in $H_2\mathbf{7}^{2+}$ due to direct participation of both the binding moieties in the former. This is, in turn, a consequence of the different bonding of the tripodal binding moieties to the benzene rings; the *ortho*-substituted cryptand allows a closer approach of the bridgehead nitrogen atoms than the *meta*-substituted one. Hence, it seems likely that efficient cooperativity of the two opposing binding subunits, as mediated by a water molecule, is responsible for the higher basicity of **6** in the first two-protonation steps. In **8**, the benzene rings are also *ortho*-substituted but unlike **6**, it is more flexible as the tris(2-aminoethyl)amine unit is replaced by a tris(3-aminopropyl)unit. An alternative explanation for such behavior may be found in the abilities of similar cryptand molecules to promote the coordination of anionic species. Inclusion of a negatively charged substrate would lead to stabilization of the positively charged receptor through charge neutralization and, depending upon the nature of the anion, through the formation of intramolecular hydrogen bonds. Accordingly, the marked loss of basicity ob-

Table 3
Logarithms of ligand protonation constants of **6**–**8** determined in 0.10 mol dm^{-3} Me_4NNO_3 at 298.1 K

Equation	**6**	**7**	**8**
$L+H^+=HL^+$	10.45(7)	9.74(6)	
$HL^++H^+=H_2L^{2+}$	10.44(2)	8.68(6)	8.9(1)
$H_2L^{2+}+H^+=H_3L^{3+}$	5.56	7.47(8)	8.8(1)
$H_3L^{3+}+H^+=H_4L^{4+}$	3.46(6)	5.6(1)	4.6(1)
$H_4L^{4+}+H^+=H_5L^{5+}$		2.4(1)	2.9(1)

Values in the parenthesis are standard deviations in the last significant figure.

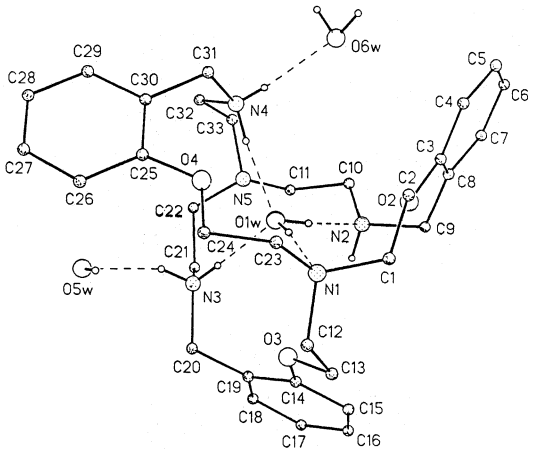


Fig. 19. A water molecule bound inside the cavity of diprotonated N-methyl derivative of **6**.

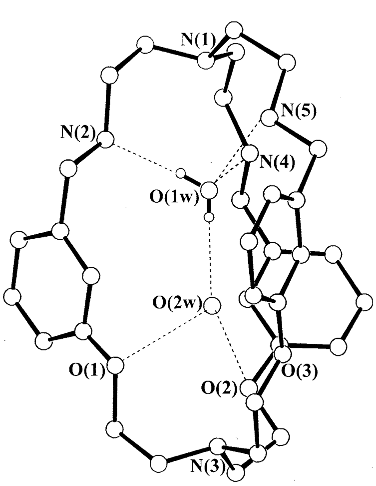


Fig. 20. Two water molecules inside the cavity of **7**.

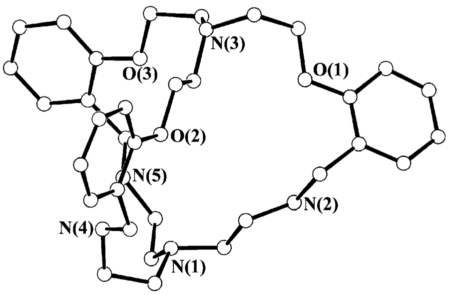
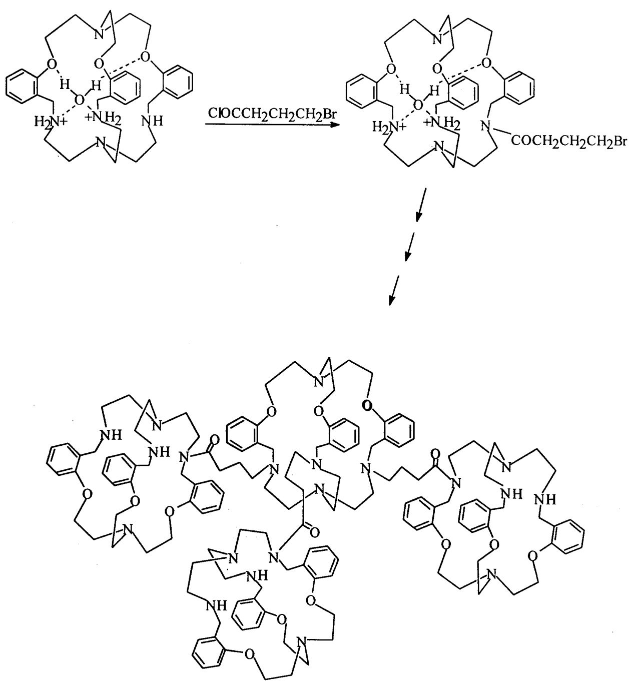


Fig. 21. A perspective view of the $[H_5\mathbf{6}]^{5+}$ cation.

served in the third and fourth protonation steps of **6** might stem from disruption of the internal structure as a result of the guest species interacting with the final protonation sites. The crystal structure of $[(H_5\mathbf{6})(ClO_4)_5]\cdot 4H_2O$ shows an empty cavity (Fig. 21) that displays evident stress stemming from the electrostatic repulsion between positive charges. As a result of electrostatic repulsion, the cavity of $H_5\mathbf{6}^{5+}$ is expanded significantly compared with that of **6**. The distances between the nitrogens in the three bridges are mainly affected while at the same time, the O···O distances between the ether oxygens are less affected (Table 1). Also, the bridgehead nitrogen atoms assume an endo-exo conformation. When protonated with picric acid the aromatic groups in the three bridges in **6** are arranged in a propeller shaped orientation and undergo synergic hydrogen bonding and face-to-face π-stacking with picrate anion forming a supramolecular array in the solid state (Fig. 22). Both **6** and **8** stack in solution as well which is consistent with their ^{1}H-NMR studies at r.t. [83].



Scheme 3.

5. New receptors

The chemistry of metal cryptates has mainly focused on utilizing the cavity of the cryptand and its tailoring with respect to shape, size, number as well as type of donor atoms, etc. The cryptands incorporating secondary amino groups in the three bridges like the ones described here, can be easily derivatized to give new receptors. The stability of the diprotonated aqua cryptates of **6** and **7** offer possibilities for selective derivatization. In fact, it is possible to derivatize the third amino group without disturbing the other two which are protonated. This way, mono-derivatization of the cryptands **6** can be achieved [84] with the formation of specific side-arm and the system can behave as a dendron unit; three such units can be connected to another cryptand forming first generation dendrimers although in a poor yield. Cryptands may be protected by forming the corresponding di-BOC species which can be purified easily by column chromatography. The pure di-BOC derivative of **6** can be used to form first generation

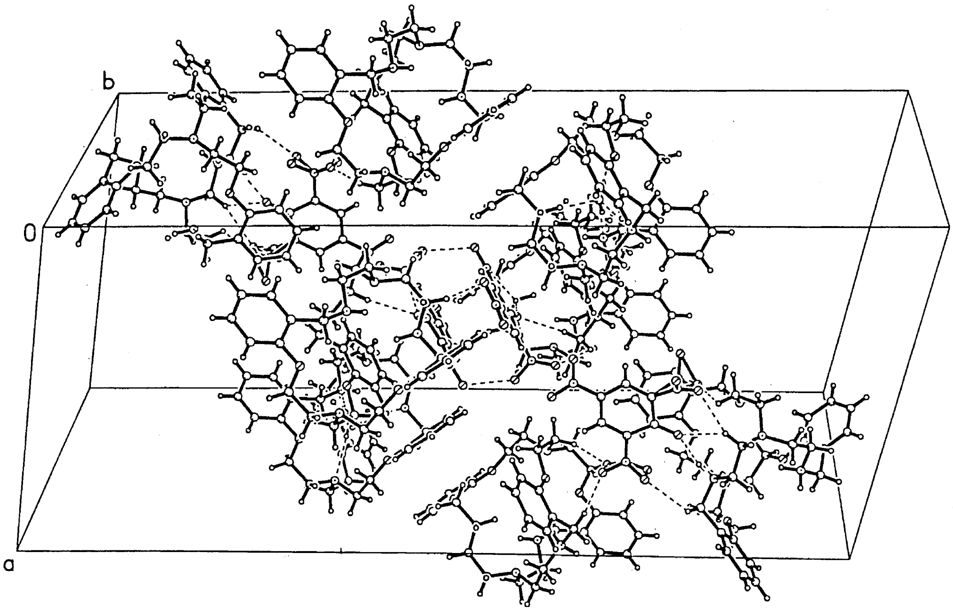


Fig. 22. Packing diagram of $[H_2\mathbf{6}]^{2+}$ cation and picrate anions showing intermolecular π-stacking and H-bonding interactions.

dendrimers (Scheme 3) in higher yields [84]. Higher generation cryptand based dendrimers can be made following the same synthetic strategy. An advantage of this synthetic strategy is that it is modular and different types of cryptands can be added at each generation which leads to a variety of molecules. Moreover, the cryptands at the periphery can be functionalized to impart specific properties to these molecules. Calixarenes as hosts are an important class of molecules in supramolecular chemistry [85]. Both the upper and the lower rim of calixarenes are readily amenable to modification and they have been widely used as three-dimensional molecular platforms for the construction of molecules endowed with selective host-guest chemistry. For example, the lower rim has been transformed to have calix-*mono*-crowns [86], or calix-*bis*-crowns [87] which have a high selectivity towards alkali cations. In calix-*bis*-crown compound, several alkali metal ions including NH_4^+ ion have been shown to oscillate from one crown ether loop to the other one. Azamacrocycles [88] and porphyrins [89] have also been attached to calixarenes to have new receptors. The cryptand **6** can be [90] attached to the lower rim of calix[4]arene via spacers to obtain yet another class of novel receptor molecule (Fig. 23). However, these novel receptors are yet to be explored for simultaneous binding of ions and neutral molecules which might be of interest as new catalytic systems.

6. Conclusions

Thus, the present review gives an account of the growth that occurred in the chemistry of laterally non-symmetric cryptands. These molecules can be designed to impart a desired degree of rigidity so as to enforce unusual coordination geometries onto metal ions entering the cavity. In addition, small molecules or ions can bind the metal ion forming cascade complexes. The vacant space in the cavity of such cryptates can be used for the oxidation of olefins to epoxides in high yields. If chirality can be introduced in any one or all of the three bridges in a nonsymmetric cryptand, chiral epoxidation reactions might be possible. When the cavity is small and rigid, a metal ion trapped inside can exhibit rapid electron transfer and can be useful in the photochemical conversion of solar energy. The protonation behavior of some of the cryptands can be exploited to obtain new receptor molecules for binding several metal ions at the same time. It is also possible to have cryptand based dendrimers which might be useful as molecular devices upon further derivatization of the peripheral cryptands. Laterally non-symmetric aza cryptands afford an easy and definite way to be selectively derivatized with groups containing donor atoms for binding a metal ion thereby making exo-cyclic coordination feasible. The exo-cyclic coordination can be exploited to effect metal-driven assembly of cryptands. Studies along these lines are in progress in our laboratory. It is thus clear that these molecules will continue to attract the attention of chemists in the years to come.

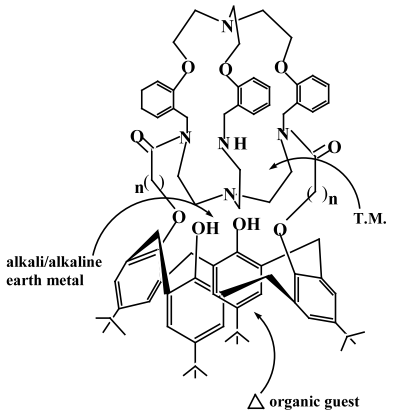


Fig. 23. Chemical structure of a cryptand-calix[4]arene hybrid molecule.

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