Macrobicyclic Cryptands

Macrobicyclic Cryptands:

Synthesis and Applications

By

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PREFACE

Recent years have witnessed an explosive growth of literature on the supramolecular chemistry of macrobicyclic cryptands. These compounds have proven to be enormously useful in several areas of chemistry, biology as well as materials science. While working in this field, we realized there was enormous scope to work with cryptands and a need to put all aspects of this important subject in one volume for the students and researchers in supramolecular chemistry.

This monograph starts with an extensive discussion on the synthesis of cryptands giving both the synthetic strategy and methods useful for beginners and the experienced alike. It provides chemical structures of a large number of cryptands that are discussed in later chapters. The contents should help the reader to design more complex structures for specific targets besides using them as starting points for varied applications. Especially, the chiral cryptands that are fewer in number have yet to show their presence. Cryptands with long alkyl chains attached for greater lipophilicity are quite useful in phase transfer catalysis. Laterally nonsymmetric cryptands that form single metal cryptates leaving an empty space in the cavity, can be excellent systems for catalysis. Moreover, a suitably designed cryptand can be used as a platform to assemble more than one metal ion in close proximity to mimic the active sites of some metalloenzymes. Also, they can exhibit cooperativity in the activation of small substrates. This book gives a lengthy treatment on several aspects of metal ion sensing and different techniques in sensing. It also provides a discussion on nonlinear optical activity that can be used in suitably designed cryptands. Another topic of utmost importance is cryptand based synthetic amphiphiles. A new generation of cryptand based amphiphiles can be synthesized easily that spontaneously form vesicular structures. Several new initiatives can be made with these molecules that self-assemble to complex structures or behaves well in a Langmuir-Blodgett trough.

This monograph is by no means intended to be exhaustive but is an attempt to provide only a few examples on each topic with adequate references. We had no option but to omit a few examples that are unintentional. It would have been impossible for us to write a monograph comprehensively describing so many different topics without active help from our coworkers and our family members as well. We thank all of them and would assume responsibility for all mistakes.

Kolkata, India, 2023
Parimal K. Bharadwaj
Dulali Bharadwaj

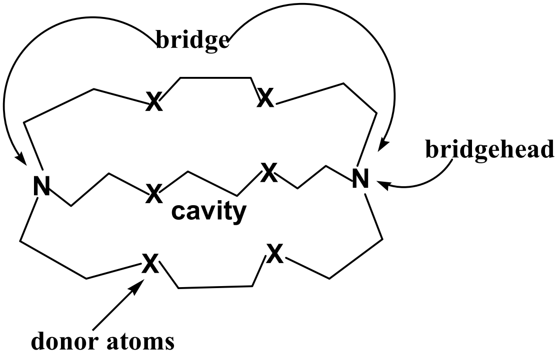
CHAPTER 1

INTRODUCTION

Cryptands are molecules with bicyclic or polycyclic structures. However, in the present book the term "cryptand" will be reserved for compounds where two bridgehead atoms such as C, N, P, etc. are connected by three bridges. Few cryptands with mixed bridgeheads are also known. It is also possible to build cryptand molecules with benzene or multi-aromatic systems as bridgeheads. Cryptands have structural features that make them an important component of supramolecular chemistry with wide ranging applications in chemical, biological and material sciences. These molecules are characterized by several donor atoms in the three bridges whose nature as well as the topology can be built-in during synthesis to accommodate guests such as metal ions, anions, neutral molecules, or their mixtures inside the cavity to form *cryptates*. The selectivity of a cryptand towards guests depends mainly upon the number and nature of the donor atoms and their spatial distribution amongst other parameters. The organic framework plays an important role in defining the solubility characteristics as well as stability of the cryptate formed. In some cases, different photoactive, electroactive, alkyl, or chiral groups can be attached to a cryptand that increases its scope(s) for different contemporary fields of research. Since the discovery of crown ethers (Pedersen, 1967, 2495-2496) with mostly planar topology, a logical extension was to make molecules that delineate a three-dimensional cavity to completely isolate a guest included in the cavity. The first batch of cryptands with different shapes and sizes were synthesized (Dietrich, Lehn, and Sauvage, 1969, 2885-2888) to study them as host molecules for cations, anions, and neutral molecules. Most cryptands are flexible in shape to different degrees that is advantageous for binding a guest because the host can adjust the molecular shape around the guest to achieve maximum thermodynamic stability in equilibrium. In the cryptand design, these aspects should be kept in mind. On the other hand, shape persistent organic cage molecules (Kiggen, and Vogtle, 1984, 712-713) (Pieters, Cuntze, Bonnet, and Diederich, 1997, 1891−1900) of similar shape have seen an explosive growth since 2009 have much more rigid frameworks. These molecules are not covered here.

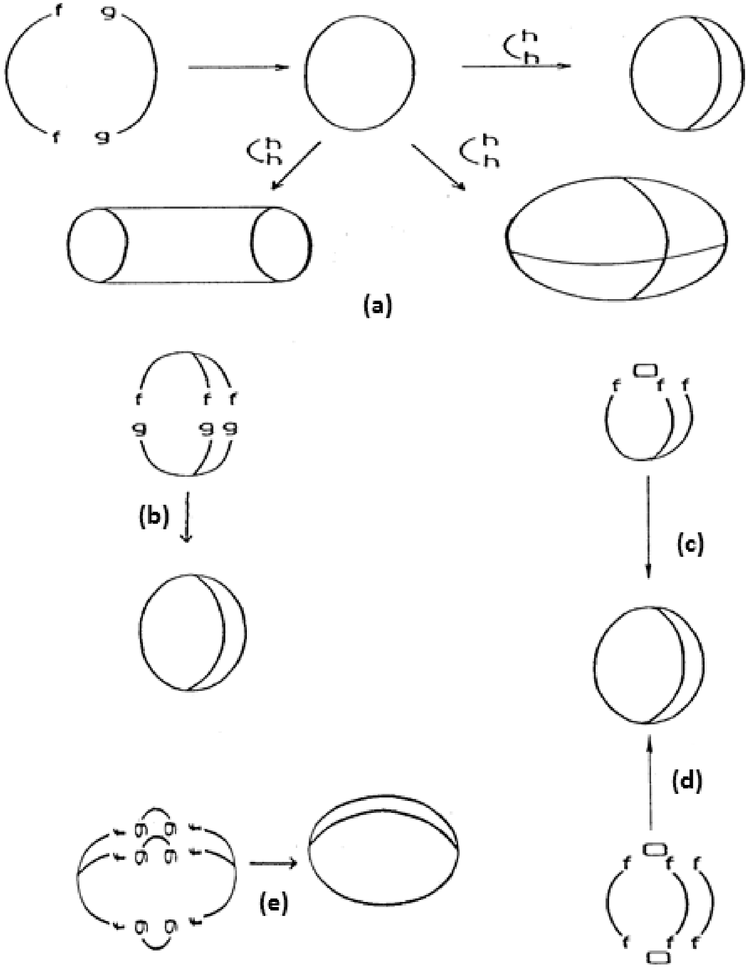
1.1 Characteristic structural features of a macrobicyclic cryptand

The characteristic structural features of a macrobicyclic cryptand are shown schematically here. Molecules with nitrogen as bridgeheads are most common although quite a number of cryptands are known with carbon bridgeheads. Also, there are examples [Caminade, and Majoral, 1994, 1183-1213) of other heteroatoms as bridgeheads such as phosphorus or aromatic groups. Several cryptands with mixed bridgeheads are also reported (Höhn, Geue, Sargeson, and Willis, 1989, 1644-1645). Cryptands usually incorporate a number of identical or different donor atoms in the bridges, whose relative positions can be varied via ligand design. The nature of the donor atoms is very important to discriminate and recognize a substrate. Ethereal O atoms as donors prefer binding of alkali/alkaline earth or lanthanide metal ions. Other heteroatoms like N, S, P, etc. show a great tendency to complex transition metal ions. On top of the overall architecture of a cryptand, judicious arrangement of the donor atoms determines the type of recognition, e.g., linear, trigonal, tetrahedral, spherical, and so on.



Scheme 1.1 Characteristic features of a typical cryptand molecule.

1.2 Synthesis of cryptands

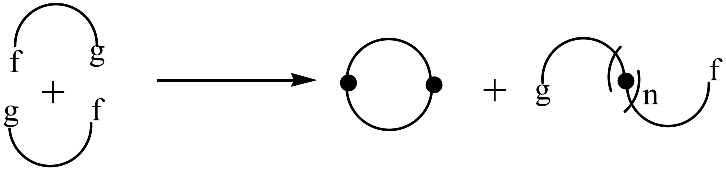


Scheme 1.2 Five basic synthetic strategies for the synthesis of cryptands.

Since the early years of its discovery (Dietrich, Lehn, and Sauvage, 1969, 2885-2888), several synthetic protocols have been put forward by researchers in this field. Synthesis of these molecules has two aspects: (I) strategy and (II) methodology. Commonly adopted synthetic strategies developed (Lehn, 1973, 1-69) over the years are termed as (a) stepwise, (b) tripodal coupling, (c) tripodal capping, (d) single, and (e) double capping (Scheme 1.2) as the five basic strategies. Several other synthetic strategies have been reported although they can be treated as mere extension of these five basic strategies. An excellent article on the synthesis of macrobicyclic cryptands is available (Dietrich, 1996, 153-211).

1.2.1 Stepwise synthesis

This is the oldest and most common synthetic strategy for cryptand synthesis. Here, in the first step, a macrocycle is built from two acyclic precursors which sometimes might be nontrivial. Instead of the desired cyclization process, the two components can react to form mostly a mixture of linear oligomers (Scheme 1.3). In this case, value of **n** can vary widely, and the reaction usually ends up having a mixture of products. The macrocycle, if at all forms, will be in low yields and sometimes difficult to isolate. To solve this problem, metal ions have been used as templates to hold the reactive groups in proper positions in the macrocyclization reactions. A template provides instructions for the formation of a single product in a chemical reaction of two or more reactants which otherwise have the potential to react in a variety of ways affording different products. The use of a template in enhancing the yield of a desired product is known as the *template effect*. The template effect (Curtis, 1960, 4409-4413) (Melson, and Busch, 1965, 1706-1710) can be of kinetic or thermodynamic origin or can be a combination of both.



Scheme 1.3 An illustration showing two linear molecules can be combined in two different ways.

Once a macrocycle is formed, a third acyclic component can be attached to form the cryptand. Even in this step, there are possibilities of several undesired products. To minimize the formation of oligomeric products, the reactions are sometimes carried out under high dilution conditions (see later). This method allows synthesis of cryptands where the three bridges can be different. While this method shows versatility, in practical terms, stepwise synthesis is cumbersome. Often, it becomes a lengthy procedure to isolate the desired cryptand from a mixture of products. At each stage, chromatographic purification may be required. Nevertheless, a large number of cryptands were synthesized adopting this strategy, especially in the early years. An example of stepwise synthesis is shown in Figure 1.1 below.

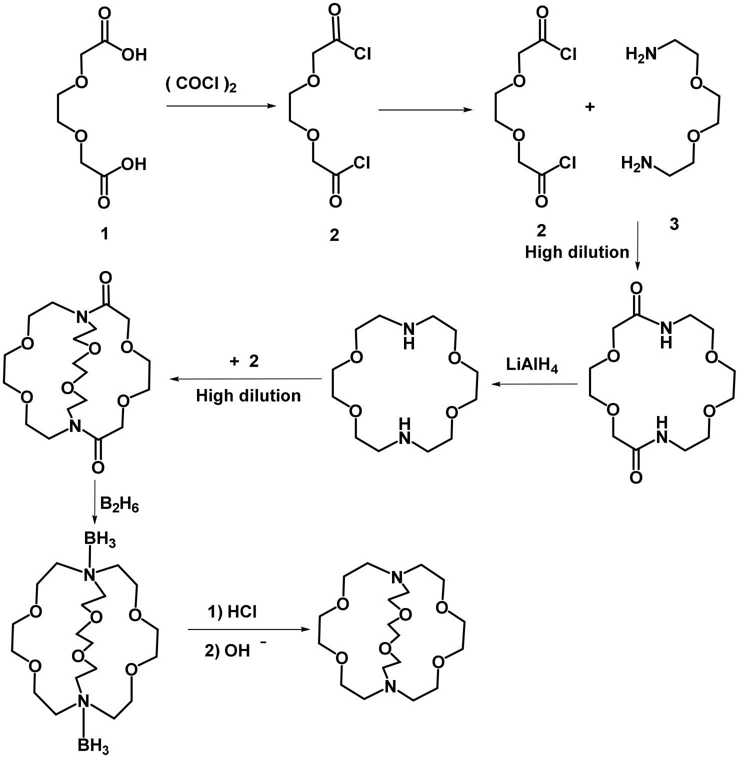


Figure 1.1 Stepwise synthesis of a cryptand

In the stepwise syntheses, yields are generally low i.e., less than 10%. In favorable cases, however, better yields have been observed. Particularly, double N-alkylation of tetraoxadiazamacrocycle by acyclic dihalide, ditosylate or dimesylate in boiling acetonitrile solvent in presence of excess base like Na_2CO_3, K_2CO_3 or Cs_2CO_3 can afford cryptands in good yields. In many cases, a macrocycle with pendant arms can be used to construct the cryptand. Another method (Jurczak, Ostaszewski, 1989 2175-2179) include the formation of cryptand by reacting a suitable macrocycle with αω-diiodoalkane under very high pressure. An important aspect of stepwise synthetic strategy is that both laterally symmetric and asymmetric cryptands with different rigidity and topology of the donor atoms can be synthesized. A list of representative cryptands synthesized adopting stepwise strategy are collected in Chart I.

1.2.2 Tripodal coupling

In tripodal coupling (Scheme 1.2 b), [1+1] condensation of two tripodal units are carried out in a one-pot synthesis (Ragunathan, and Bharadwaj, 1992, 7581-7584). Formation of a macrobicyclic product by tripodal coupling is not straightforward. Numerous intermolecular reactions can compete with the desired condensation pathway. Therefore, a low yield of the desired cryptand is expected. To surmount this problem, occasionally a metal ion has been used as a template. The templating metal ion should form a kinetically labile complex. Otherwise, it may be difficult to remove the metal ion post synthesis. Sometimes, allowing the reaction to proceed at low temperature using rigid aromatic groups in the tripodal units can improve the yield. A number of cryptands have been synthesized by Schiff base condensation of tripodal amines with tripodal trialdehydes at 40° C under a dinitrogen blanket using Rb^+ or Cs^+ ion as a template. The intermediate Schiff base can be easily reduced with $NaBH_4$. The entire operation requires < 12 h and the yields are usually high (range, 40–60%). Other alkali metal ions such as Na^+ or K^+ are not useful as they are highly solvated. The Schiff base condensation involves initial attack on the carbonyl carbon by the lone pair of nitrogen; hence, availability of this lone pair is important. When a transition metal ion is used as the template, it coordinates strongly to the lone pair of amino nitrogen attenuating its nucleophilicity. So, the reaction does not proceed in the desired direction even when the temperature is raised to a higher value using a different solvent. The cryptands once formed, are isolated through fractional crystallization or column chromatography. Comparable yields of the products are also obtained (Smith, Barr, Brainard, Ford, et. al, 1993, 7939−7941) when some of these reactions are carried out at a low temperature (~ 5° C) without employing any templating ion. This technique works really well if the tripodal units incorporate aromatic groups for increased rigidity. However, choice as well as amount of solvent although empirically determined is crucial for the success of this method. For the reaction shown below (Fig 1.2), methanol has been found to be the solvent of choice. The aldehyde is taken in methanol in a round bottom flask and the solution of the amine in methanol is added dropwise at a slow rate. The tripodal aldehyde is slightly soluble in methanol at low temperature and a dilute methanolic solution of the amine is added dropwise at such a rate that the previous drop should completely dissipate before a new drop is added. This mimics a high dilution reaction condition. Many cryptands have been synthesized in recent years adopting the tripodal coupling strategy and using different reactions in addition to Schiff base condensation. An important point to remember here is the fact that by this strategy, the cryptand can be obtained in less time (<12 h) compared to the stepwise synthesis. It is to be noted that a moderate dilution condition should be maintained; otherwise, a [2+2] condensation product (Fig 1.3) along with other side products might form as the major product. Another important point is that in tripodal coupling, the two tripodal reactant units should be of similar size. When there is a large size mismatch, [2+2] condensation may take place instead of the usual [1+1] reaction even under

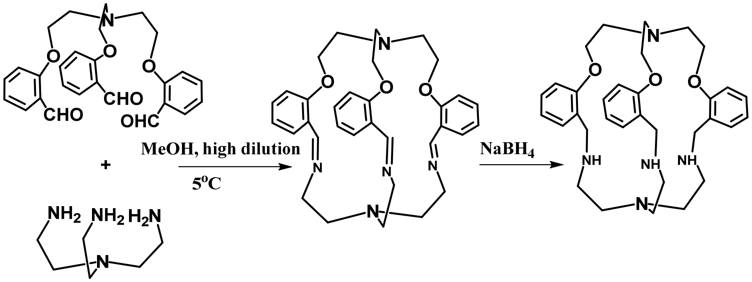


Figure 1.2 Synthesis of a cryptand by the tripodal coupling strategy.

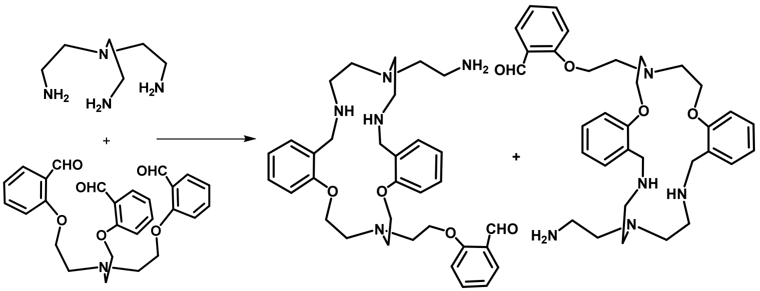


Figure 1.3 Formation of [2+2] condensation product under high concentration

high dilution. The system shown in Fig 1.4 illustrates this point. Here, tripodal coupling via Schiff base reaction has been shown as an illustrative example. There are many types of facile reactions that have been utilized in the formation of cryptands via tripodal coupling. Chart II shows some of the cryptands synthesized adopting this strategy.

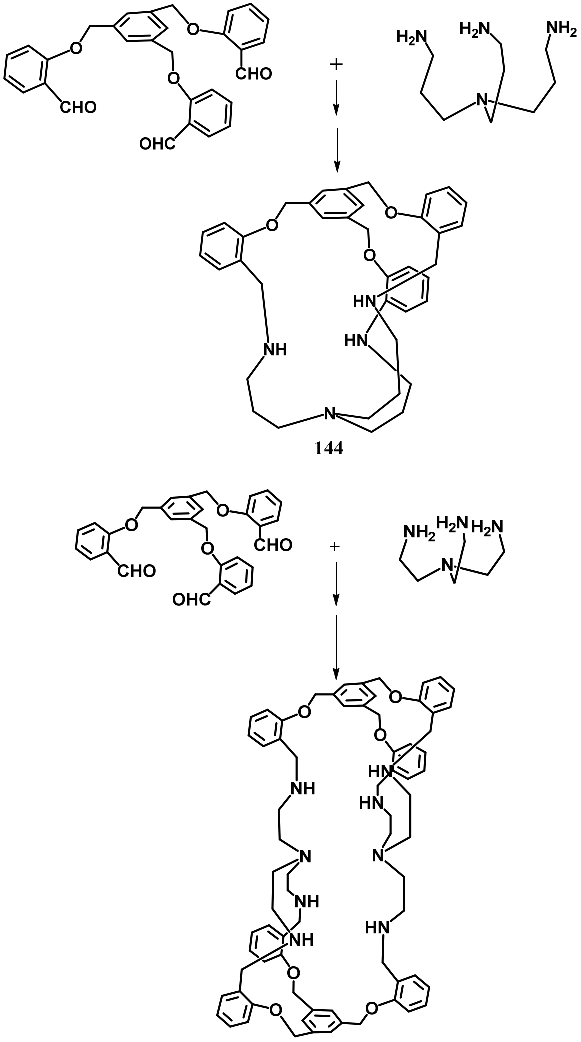


Figure 1.4 The [1+1] and [2+2] tripodal coupling reactions.

1.2.3 Tripodal *mono*- and *bis*-capping

In the tripodal *mono*-capping strategy (Scheme 1.2c), Co^{3+} has been chosen as a template in bringing about the reaction to the desired cage compound. The idea behind using Co^{3+} as a template is that six-coordinate Co^{3+} is kinetically inert. So, it can hold the reactive ends quite nicely and in proper orientation (Geue, Hambley, Harrowfield, Sargeson, and Snow, 1984, 5478-5488) to facilitate capping. However, in the case of laterally nonsymmetric cryptands, only moderate yields are achieved. The presence of thioethers in the tripodal reactant leads to reduction of Co^{3+} to kinetically labile Co^{2+} ion. Additionally, a thioether is a poor donor compared to the amine. Both these factors lead to the loss of the cobalt ion from the podand under the capping conditions and result in poor yield of the desired product. Another problem with this strategy is the fact that once the podand is capped, the Co^{3+} ion inside the cavity is both kinetically as well as thermodynamically inert making its removal to isolate the free cryptand a difficult task. The encapsulated Co^{3+} ion is first reduced to Co^{2+} by means of a strong reducing agent like Zn dust. In the form of Co^{2+} ion, it can be removed using cyanide ion or concentrated boiling HBr.

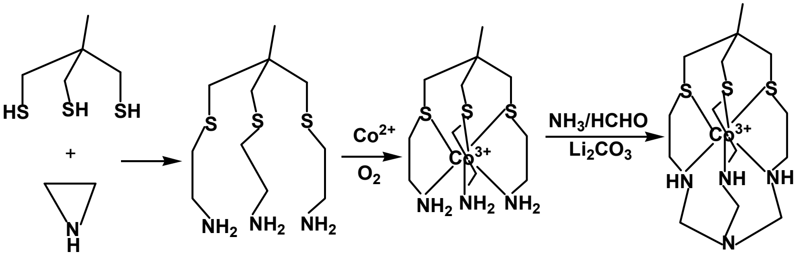


Figure 1.5 An example of tripodal mono-capping strategy.

The capping strategy can be used to form a macrobicyclic cage with a contracted cavity (Osvath, Sargeson, McAuley, Mendelez, *et al.*, 1999, 3634-3643). Figure 1.6 shows the proposed reaction sequence for its formation. Figure 1.7 gives an example of synthesizing a functionalized cage molecule. The yield of the products is moderate and the desired macrobicycle usually has donor atoms one carbon away from the bridgehead that makes it quite rigid at least in one end. Several cages with different donor set and bridgeheads have been synthesized. Chart III provides a partial list of the compounds. In a slightly different *bis*-capping method (Scheme 1.2d), *tris*-ethylenediamine complex of Co^{3+} is synthesized first. It is then allowed to react with ammonia and formaldehyde in several

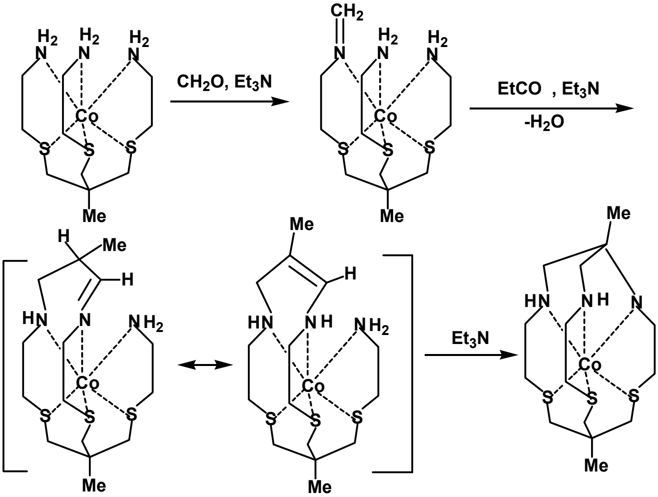


Figure 1.6 Synthesis of a contracted macrobicyclic product

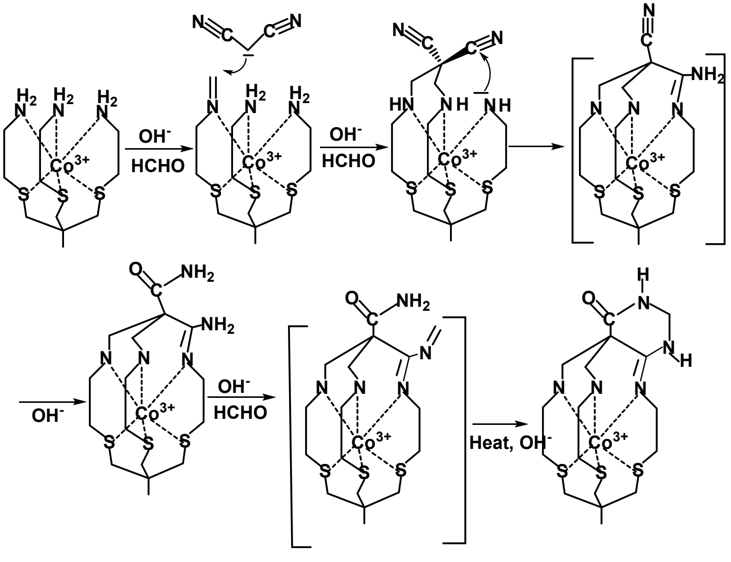


Figure 1.7 Synthesis of a functionalized cage molecule

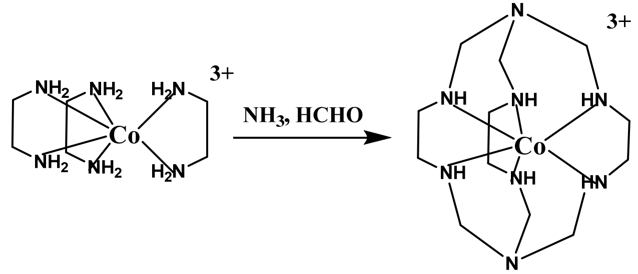


Figure 1.8 An example of the *bis*-capping method

steps to cap both sides to have (Fig 1.8) the macrobicyclic compound (Gahan, Hambley, Sargeson, and Snow,1982, 2699-2706) with Co^{3+} ion inside the cavity. Here, ammonia formally acting as a tribasic acid under the preparative conditions and the product is more rigid compared to the previous ones. In principle, any other tribasic acid might, therefore, be expected to provide a substitute for ammonia and thus several macrobicycles with different bridgeheads can be synthesized.

1.2.4 Tripodal double-capping

In this strategy, two tripodal components are allowed to react with three linear spacers in a [2+3] condensation (Scheme 1.2e) to form a cryptand with a large cavity. Twelve reactive groups interact in this method with the possibility of many side reactions. Surprisingly, several cryptands were synthesized in excellent yields adopting this strategy. Early attempts to obtain the cryptands by the [2+3] condensation of triethanolamine with the appropriate dichloride in an inert solvent and in presence of a strong base like sodium hydride afforded low yields of the products. Later, it was found (Hunter, Nelson, Harding, McCann, *et al.* 1990, 1148-1151) that *tris*(2-aminoethyl) amine (TREN) can undergo facile Schiff base condensation with dialdehydes in presence of a group 2 metal ion as templates to form the cryptand easily and in good yields.

Independently, alkali metal ions like Rb^+ and Cs^+ in methanol solvent have been used in the synthesis of this (Ragunathan, and Bharadwaj, 1992, 1653-1656) and several other cryptands (Fig 1.9) adopting the [2+3] condensation strategy. This strategy is widely used at present in synthesizing cryptands having large cavities. When the linear component has aromatic group(s) it becomes somewhat rigid, and no templating metal ion may be necessary especially when the reaction is carried out under high dilution condition at low temperature. In sharp contrast, *tris*(3-aminopropyl) amine (TRPN) affords the cryptand in poor yields under similar experimental conditions where a number of side products are also formed. It may be due to the three arms in TRPN having much higher degrees of freedom compared to those in TREN. Chart IV gives a list of representative cryptands synthesized adopting the [2+3] strategy. It should be noted here that a few examples where the three bridges are not identical are also shown in Chart IV for easier discussion in later chapters.

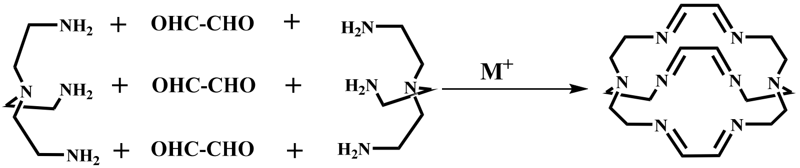


Figure 1.9 Synthesis via the double-capping strategy

Three interesting all aza cryptands (Fig 1.10) are shown below which have been synthesized (Dietrich, Lehn, Sauvage, and Blanzat, 1973, 1629-1645) via replacement of hydrogens of ammonia or amines by aliphatic halides.

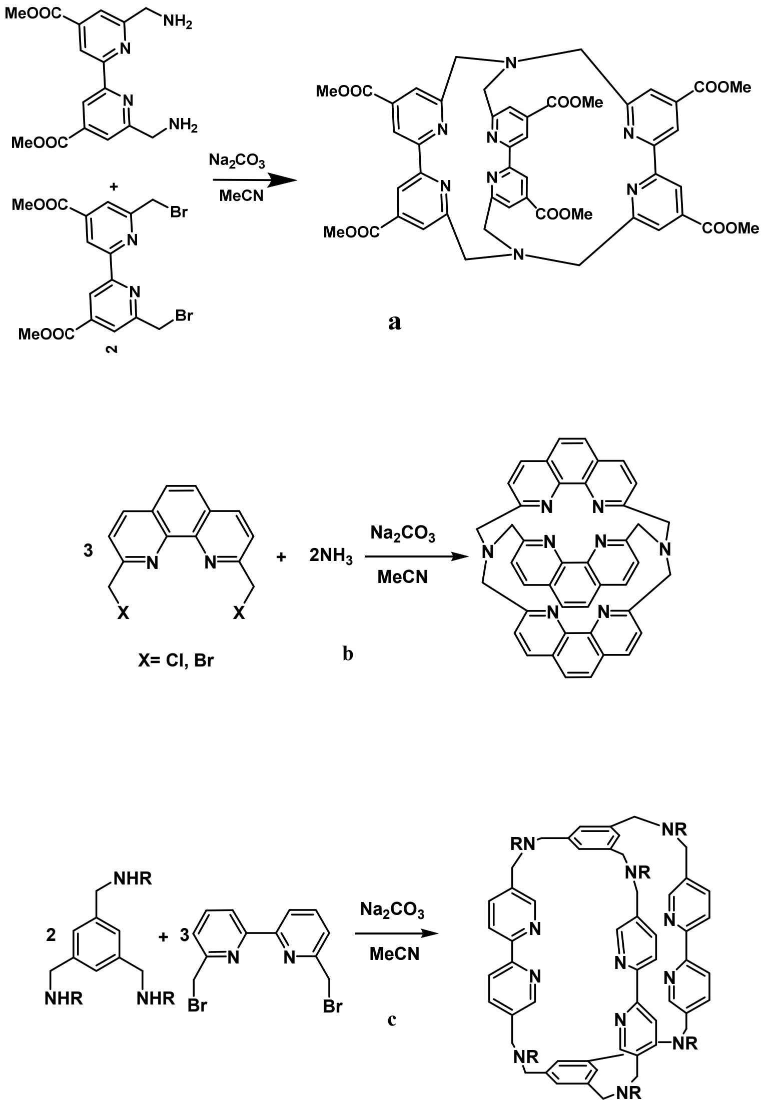


Figure 1.10 Cryptands synthesized adopting [2+3] condensation strategy.

1.2.5 Methodology

The commonly adopted methods can be described as (a) high dilution, (b) use of templates, (c) rigid group principle, and (d) low temperature.

1.2.6 High dilution method

Allowing reactions to proceed under high dilution is the most commonly used technique in the synthesis of macrocycles (macropolycycles) starting from acyclic reactants. Usually, in this method, the reactants are added simultaneously into a reaction flask already having a large quantity of solvent. The appropriate concentration level for the cyclization step is, however, determined empirically. Under high dilution conditions, the reaction should be facile to reduce the scope of forming undesired side products. Most importantly, the high dilution condition is to provide long residence time for the intermediate to complete the desired intramolecular reaction. However, the final product must be stable under the prevailing reaction conditions. An apparatus for controlling the reaction (Fig 1.11) conditions in the high dilution synthesis has been described. This apparatus consists of motorized burette, which can add measured quantities of the reactants to the reaction vessel at a very slow rate. The temperature of the reaction can be easily maintained by placing it in a thermostat. Although the high dilution technique has been known for a long time, it was Ziegler who developed (Ziegler, *Methoden der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, 1955, Vol. 4, Part 2, p. 178) and widely used this method for macrocyclization reactions. Detailed theoretical studies (Illuminati, and Mandolini, 1981, 95-102) regarding the factors that influence a macrocyclization process and practical hints (Rossa, and Vögtle, 1983, 1-86) are available. Generally, high-dilution method takes long time to complete and large volume of solvent is required that should be recycled whenever possible.

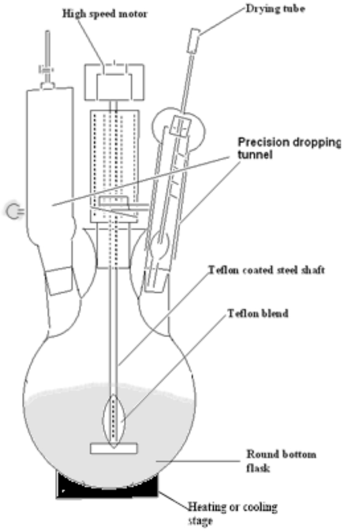


Figure 1.11 The equipment generally used to carry out a reaction under high dilution.

1.2.7 Use of templates

As high dilution synthesis takes a long time to complete, sometimes few days, other methods like use of a template have been widely accepted whenever possible. A template organizes (Busch, 1992, 389-395) the reactants with respect to each other to achieve a particular linking to form the desired compound. A template is usually a metal ion although anions as well as neutral molecules have been used sometimes as templates. The use of a template in enhancing the yield of a desired product is known as the *template effect*. The template effect of a metal ion can be of kinetic or of thermodynamic origin or a combination of both. Pioneering research by Curtis in the macrocyclization of isomeric Ni^{2+} complexes (Curtis, 1960, 4409-4413) (Curtis, 1968, 3-47) and research by Busch and coworkers (Melson, and Busch, 1965, 1706-1710) paved the way for template synthesis. Both transition as well as non-transition metal ions have been used as templates in cryptand synthesis (Geue, Hambley, Harrowfield, Sargeson, and Snow, 1984, 5478-5488) (Hubin, and Busch, 2000, 5-52). When a kinetically inert metal ion is used, the final product is isolated as a metal cryptate; removal of the metal ion can sometimes be difficult.

Kinetically labile alkali, alkaline earth, and some main group metal ions can also be efficient templates in directing cyclization reactions and in the event of any encapsulation, can be trans-metalated easily.

1.2.8 Rigid-group principle

According to rigid-group principle, (Baker, McOmie, and Ollis, 1951, 200-201) the synthetic difficulties associated with cyclization reactions from acyclic components owe mainly to the possibility of rotation about the bonds in the molecule. Unfavorable rotation effectively lowers the possibility of reactive groups coming in proximity within the reactive zone to yield the desired macrocycle. To lower the conformational mobility of an acyclic compound, rigidity may be increased in the structure by incorporating aromatic groups or unsaturation to aid in pre-organizing the reactive fragments to react in a directed fashion thereby reducing the possibility of oligomerization.

1.2.9 Low temperature synthesis

Low temperature synthesis is a relatively recently developed technique. Smith and coworkers (Smith, Barr, Brainard, Ford, *et al.*, 1993, 7939−7941) reported the synthesis of an octaaza cryptand (Fig 1.12) starting from TREN and glyoxal using the double capping strategy at 273 K. Maintaining a low temperature for the reaction decreases the movement of the reactive groups, that minimizes polymerization to a great extent even if there is no templating metal ion used. Of course, the functional groups should react readily at low temperatures to make the synthesis a success. Utilizing this technique, many cage molecules have been isolated in excellent yields in recent years.

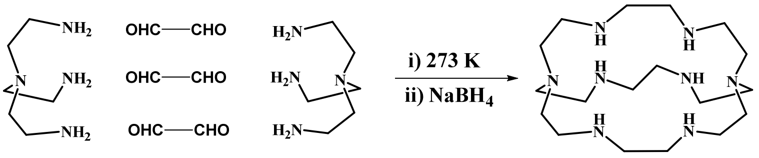


Figure 1.12 Octaaza cryptand synthesized at low temperature.

1.2.10 High pressure synthesis

An interesting method of synthesizing cryptands involves synthesis (Jurczak, and Pietraszkiewicz, 1985, 183-204) under high pressure. This method works well for the system where the molar volume of the reactants is more than that of the transition state. Double quaternization of a macrocycle with a linear component works well under a pressure of ~10 K bar at ordinary/slightly elevated temperature. Several cryptands incorporating bis-quaternary bridgeheads have been reported. Some of them are shown in Chart I. As an example, when the macrocycle and *bis*-(2-iodoethyl) ether in acetone (0.08 M) are exposed to 10 kbar pressure for 20 h, the bis-quaternary salt precipitates almost quantitatively. Demethylation of the quaternary salt can be achieved by reacting with Ph_3P in DMF (Fig 1.13).

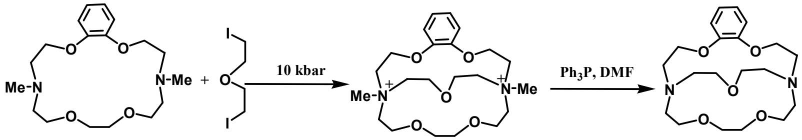
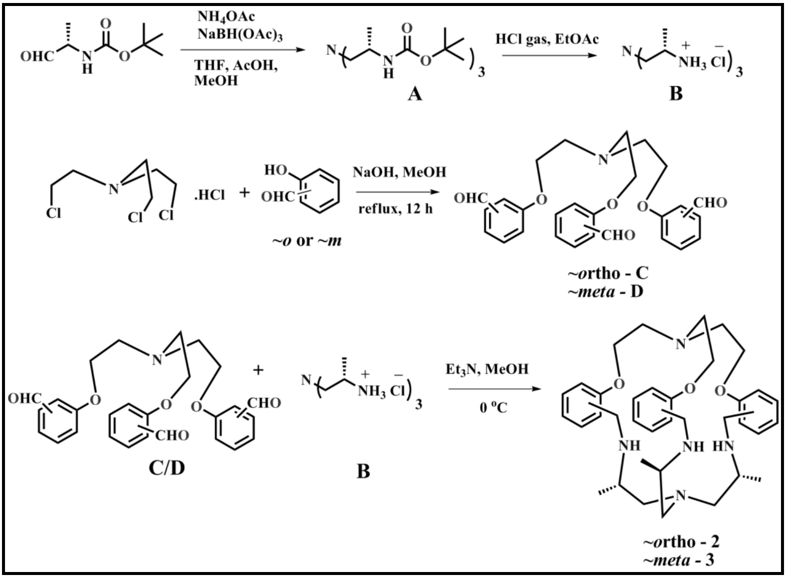


Figure 1.13 Synthesis of cryptand under high pressure and its subsequent demethylation reaction

1.3 Chiral cryptands

Few chiral cryptands have been reported thus far and a list of chiral cryptands are shown in Chart V. This certainly will increase at a rapid pace in the future. Chirality in the cryptands can result by introducing (De, Bhattacharya, and Bharadwaj, 2017, 11443-11449) a chiral molecule like L-proline by substitution in the bridges, using flexible cryptands capable of adopting many conformations including helical ones, and above all, by having chiral centers. Particularly interesting are the chiral cryptands **236** and **237** that can be easily synthesized (Pal, Sanchari, Ph.D. Thesis, IIT Kanpur, 2016) by the tripodal coupling strategy taking N^1,N^1-*bis*(2-aminopropyl) propane-1,2-diamine in place of TREN and allowing it to react with a tripodal trialdehyde (Scheme 1.4). This chiral tripodal amine can be used to design a myriad number of chiral cryptands. As a matter of fact, most of the cryptands listed in Chart II and Chart IV where TREN is one of the components, the chiral tripodal amine can be used. Chiral cryptands can extend the scope of research in terms of chiral recognition, asymmetric catalysis, and so on, that remained mostly an unexplored area.



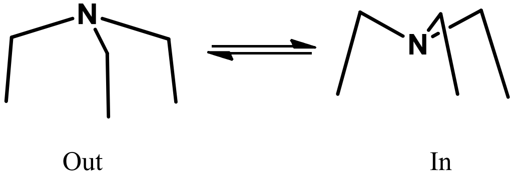
Scheme 1.4 Synthetic Scheme for the cryptands, **236** and **237**

1.4 Topology

The subunits used for the construction of cryptands determine the nature of the cavity in terms of its overall shape, size, and flexibility. These subunits incorporate donor atoms at strategic positions to define the binding topology of the cavity. When the bridges are built with saturated chains, they provide greater flexibility of the cavity whereas unsaturation or aromatic groups can lead to steric constraints and a rigid cavity. Functional groups like amide, ester, etc. facilitate polar group binding and additional ligand stiffening. The more rigid the cavity, the greater will be its discriminatory power against the guests that are smaller than the cavity, since it will require severe ligand deformation. An ideal situation for substrate binding will arise if the ligand donor set and shaping groups are pre-organized to accommodate the substrate with minimum ligand deformation.

1.5 Conformation

There are two regions in a cryptand that can undergo conformational changes. When the bridgehead is tertiary nitrogen, it can invert at room temperature:



The cryptand in such cases can exist in three different conformations (Fig 1.14) as *exo-exo, exo-endo* and *endo-endo* that are critical in the complexation process. The *endo-endo* conformation with both bridgehead nitrogen along with the heteroatom lone pairs directed into the cavity are important in forming the inclusion complexes. When the cryptand forms an inclusion complex, greater stability is to be expected when the conformation of both in the free as well as in the complexed states are same. In another case, when there is a possibility of restricted rotational freedom in the bridging part, interesting conformations can result. In the cryptand shown in Figure 1.15, the two pyrazole rings are in *anti*--conformation when crystallized but in presence of a metal ion, the rings become *syn* to bind a metal ion (Verma, Tomar, and Bharadwaj, 2019, 369-375) in an exocyclic fashion.

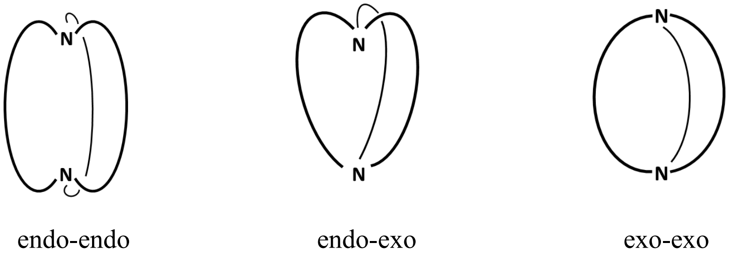


Figure 1.14 The three conformations of cryptands with N-bridgeheads

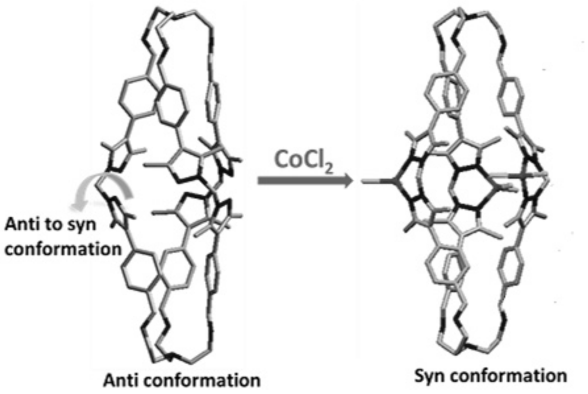


Figure 1.15 Crystal structures showing change of *anti* to *syn* conformation of the *bis*-pyrazole moiety of the cryptand upon metal complexation. Hydrogen atoms are omitted for clarity.

1.6 Layer effect

When a cation or an anion is included in the cavity, the bound species is buried deep inside the cavity and the cryptand provides an organic covering to it. This bound species is well isolated from the medium and the counter ion outside the cage. The nature of the organic skin may be lipophilic or lipophobic that in turn determines the solubility characteristics. In some cases, like activation of anions or its use in phase transfer catalysis, depends upon its solubility in nonpolar organic solvents. The stability of the complex depends upon the thickness of the organic skin of the host cryptand as it determines the extent of interaction between the medium and the guest. Aryl groups are crafted into the cryptand to get rigidity and pronounced layer effects.