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Macrocyclic ligands have been prepared by various one-step cyclooligomerization processes. This short review covers one-step cyclization reactions involving the formation of four to twenty or more new covalent bonds. The new macrocycles reviewed include cyclophanes, biscrown ethers, cryptands, macrolides, cage compounds, calixarenes, homocalixarenes, cucubiturils, and supercryptands all prepared by one-step syntheses.

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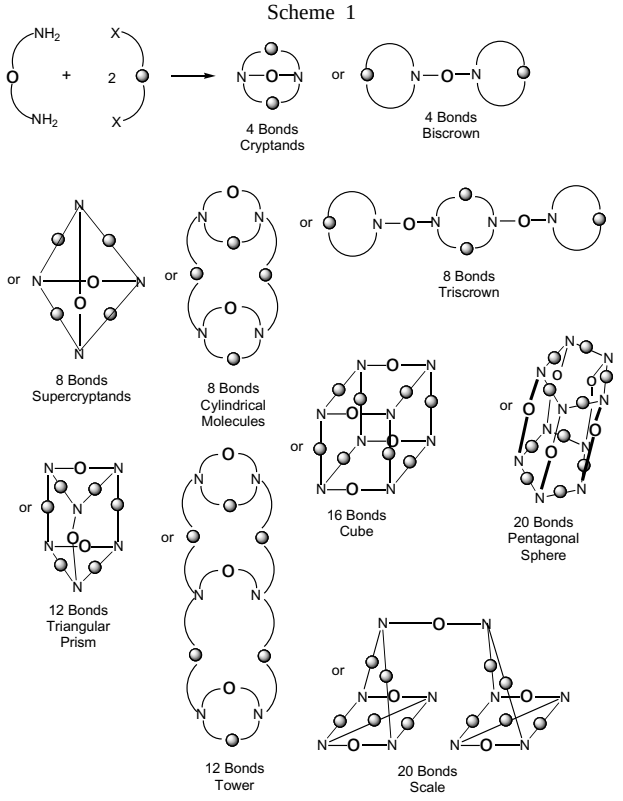
Introduction.

Synthetic polymer chemistry was developed before synthetic macrocyclic chemistry. Organic polymers cannot be synthesized without having macrocyclic compounds as side products and *vice versa*. The preferential formation of only one product often depends on the conditions of the reaction. Cyclic products are usually not wanted in linear organic polymers because of their deleterious effect on polymer characteristics. During polymerization reactions, thousands of new bonds are formed while cyclization reactions result from only a few formed bonds [1,2].

In the synthesis of macrocyclic ligands, different macrocyclic compounds can form from the same ratio of starting materials. For example, starting from a 1:2 ratio of diamine and dihalide (or ditosylate), it is possible to obtain macrocyclic ligands that form with 4-20 or more new bonds (see Scheme 1). Formation of a particular structure depends on reaction conditions such as template effects, temperature, concentration of starting materials, and other unknown factors. Up to now, cryptands, biscrown ethers, supercryptands, cylindrical polycyclic compounds and cubic compounds have been prepared by direct one-step methods. However, nearly every day additional new and unique structures are added to this list [3,4].

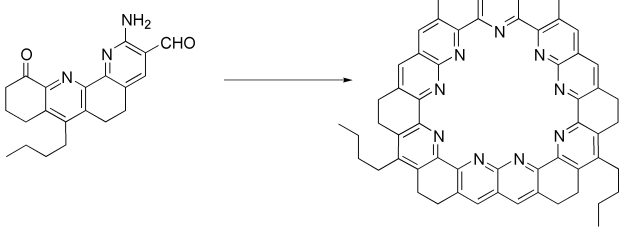
Scheme 1



In this review, we show a few one-step cyclization reactions that form specific macrocyclic compounds. The more bonds that are formed during cyclization starting with simple starting materials, the more complicated are the produced macrocyclic products. We hope that this review will help in the search for new routes for "cyclooligomerization" to form new and unique macrocyclic compounds. Also, it provides information for non-synthetic chemists that will allow them to prepare desired macrocyclic compounds in order to study their physical and chemical properties. The main purpose of this review is to give examples of some of the most important syntheses of macrocyclic compounds and to show the fastest approach to these complicated molecules. Many reviews and books are devoted to the synthesis of macrocyclic compounds [1,5-10], but no review has been published with an emphasis on one-step syntheses by the formation of many new bonds.

A special place in the synthesis of macrocyclic compounds belongs to the synthesis of torands, especially one that is formed from an aromatic ketoaminoaldehyde during a triple cyclopolymerization reaction (Scheme 2).

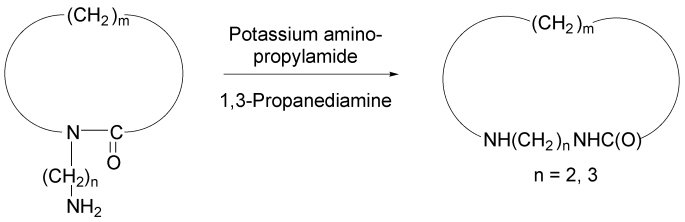
Scheme 2



Friedlander condensation and cesium hydroxide templated trimerization gave an expanded torand in 50% yield [9,11].

Another cyclization reaction that is unusual is the so called "zip" reaction, which causes a ring expansion by the insertion of a side chain. For example, conversion of a lactam into a cyclic aminoamide with ring enlargement has been achieved using potassium aminopropylamide in 1,3 propanediamine (Scheme 3). In this way, a 13-membered lactam has been transformed into a 33-membered cyclic aminoamide by five successive introductions of a $CH_2CH_2CH_2N$ unit into the ring (Scheme 3) [12,13].

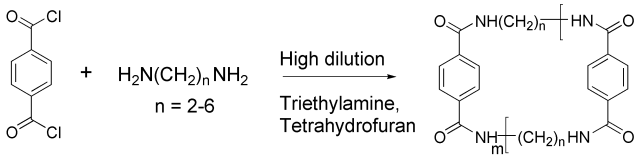
Scheme 3



Macrocyclic Compounds Formed by Two to Twelve New Bonds.

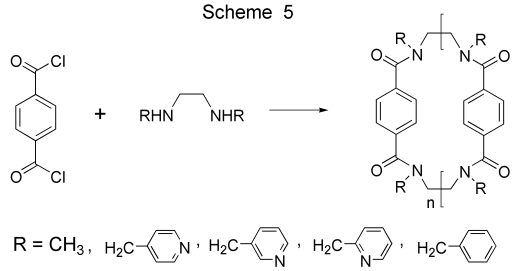
The reaction of an aromatic diacid dichloride with a diamine followed by reduction is a common method for producing 1:1, 2:2, 3:3 and higher-order cyclocondensation products. The most detailed study of this type of cyclocondensation reaction was done by Raymond and coworkers for the reactions of terphthalyl dichloride with various diamines as shown in Scheme 4 [14]. Where n = 2, the cyclocondensation products included the trimer (m = 2) (the product of three diacid dichlorides with three diamines) to the hexamer. Where n = 4, dimer to pentamer (m = 3) products were isolated; and where n = 6, dimer to pentamer (m = 4) products. The yields of pentamer and hexamer products were less than 1%. The best yields were for the dimer (24%), a 28-membered ring, in the reaction using 1,6-diaminohexane (n = 6) and for the trimer (17%), a 30-membered ring, in the reaction with ethylenediamine (n = 2) [14].

Scheme 4



Vögtle and coworkers studied the cyclocondensation reactions of terephthalyl dichloride and various derivatives of ethylenediamine (Scheme 5) [15,16]. Where R = benzyl, the 3:3 cyclo-condensation product (n = 2) was isolated in a 25% yield and the 4:4 adduct in a 3% yield.

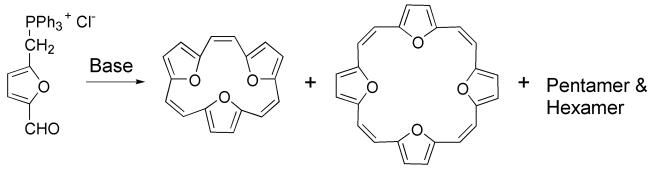
Scheme 5



Macrocyclic Compounds Formed by Three to Six New Double Bonds.

Some interesting furan-containing macrocycles have been prepared using the base catalyzed Wittig Reaction as shown in Scheme 6 [17]. In this case, 5-formylfuran-2-ylmethyltriphenylphosphonium chloride cyclocondensed to form the trimer to hexamer products with three to six double bonds. These products were isolated in low yields.

Scheme 6

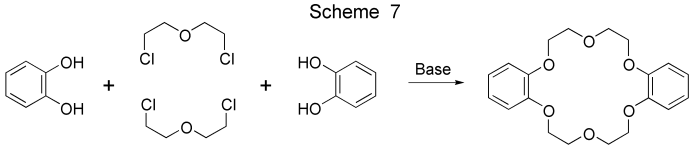


Macrocyclic Compounds Formed by Four New Bonds.

The best example of this reaction type is the 2:2 cyclization reaction. This reaction is carried out under high dilution techniques or with a template. The high dilution reaction usually produces a 1:1 cyclization compound as a by-product. If one of the reactants contains a rigid molecule, the possibility of producing 1:1 cyclization products is reduced. The concentration of the reactants also influences the types of addition products. High concentrations favor the formation of 2:2 addition products, however, more linear polymer is also formed. One example of a rigid difunctional molecule that reacted by 2:2 rather than 1:1 cyclization is catechol, which reacted with 1,5-dichloro-3-oxapentane to form dibenzo-18-crown-6 exclusively (Scheme 7) [18].

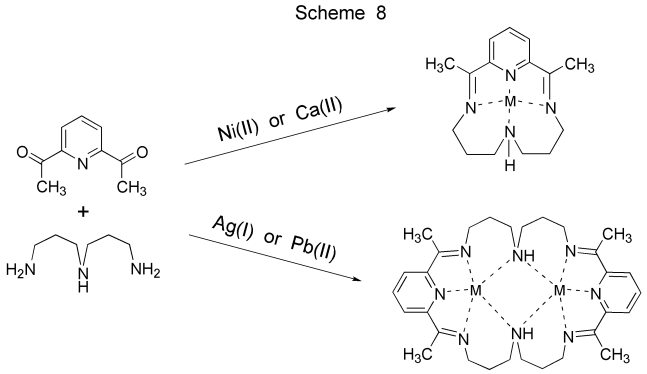
An important result of templated synthesis using polyamines coordinated with metal ions is that it allows the preparation of peraza macrocycles without the need for protecting groups on the nitrogen atoms. This reduces the number of steps needed in a synthetic sequence. The

Scheme 7



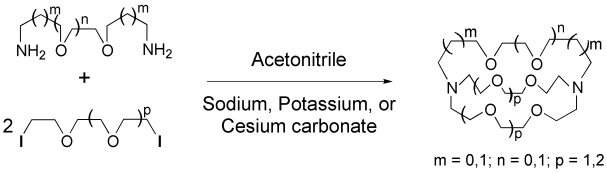
appropriate templated cation allows for the formation of macrocycles by 1:1 or 2:2 cyclo condensations. It is important to note that even small cations can produce 2:2 cyclization products because two cations can be coordinated inside a large cavity. The reaction between 2,6-diacetylpyridine or 2,6-diformylpyridine and 3,3'-iminobispropylamine are appropriate examples. First, as shown in Scheme 8, 2,6-diacetylpyridine was treated with bis(3-aminopropyl)amine in the presence of Ni(II), Cu(II), Mn(II), Co(II) or Zn(II) salts resulting in the formation of cyclic complexes of the 1:1 condensation products [19,20]. Templated cyclocondensation of the above compounds in the presence of Ag(I), Pb(II), Ca(II) or Sr(II) gave the binuclear Ag(I) and Pb(II) and mononuclear Ca(II) and Sr(II) complexes of the 28-membered ligand resulting from 2:2 cyclization [21-23]. This process is complicated by the formation of a ring-contracted form when the reaction is carried out using Ca(II) or Sr(II) salts. The ring contraction process is evident when diethylenetriamine is used in the reaction. The contracted 20-membered ring is converted to the 24-membered ring by a transmetallation process with a transition metal ion [23,24].

Scheme 8



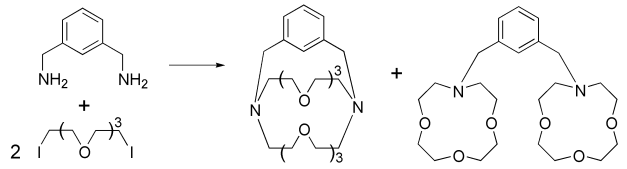
There is large interest in the chemistry of the cryptands because of their strong complexing properties. A great number of papers concerning the chemistry of the cryptands have been published. Only a few cryptands can be purchased and they are very expensive. The most convenient method for preparation of cryptands would be the one-step reaction of a diamine with two equivalents of an oligoethylene glycol dichloride first tried by Kulstad and Malmsten [25]. Although they were unsuccessful, we repeated their work and found that some [2.2.2] was produced. However, since there were so many side products in that reaction, we studied the preparation of many other cryptands by one-step procedures before we learned how to make [2.2.2] in one step. It is most convenient in any synthesis procedure to use starting compounds that are available from commercial sources such as ditosylates and diiodides. With that in mind, we discovered a convenient one-step method to prepare a variety of cryptands by treating one mole of available α,ω-diamines with two moles of available α,ω-diodides as shown in Scheme 9 [26-30].

Scheme 9

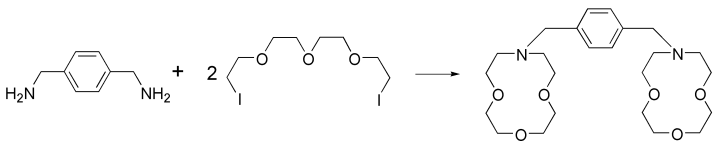


Often, unexpected by-products are obtained during cyclization reactions. For example, Krakowiak, *et al.* prepared the desired cryptand and a biscrown ether by-product in the same reaction starting from 1,3-bis(aminomethyl)benzene and 1,11-diodo-3,6,9-trioxaundecane (Scheme 10) [26]. In the case of using 1,4-bis(aminomethyl)benzene, only the bisaza-12-crown-4 was isolated (Scheme 11). Evidently, in this latter example, the biscrown is much easier to form than the [15]paracyclophane ring leading to the cryptand.

Scheme 10

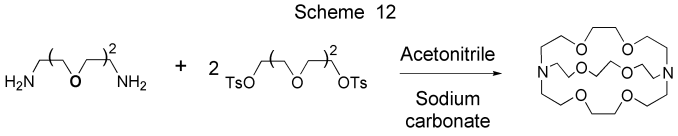


Scheme 11



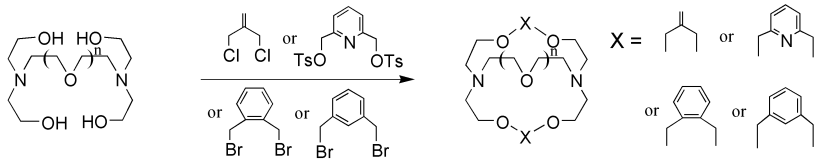
The most important cryptand, [2.2.2], was finally prepared in good yields using the ditosylate starting material instead of the diiodide (Scheme 12). Other cryptands such as [2.2.1], [3.3.1], [3.3.2], and [3.3.3] were also prepared in good yields by this 2:1 bicyclization process using the appropriate ditosylates [31].

Scheme 12



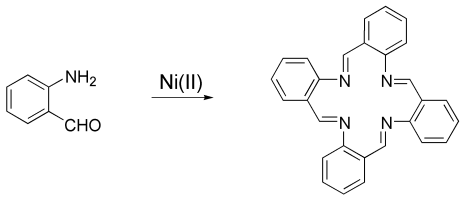
A number of unsymmetric cryptands have been prepared in our laboratory by a different one-step ring closure procedure [32]. Easily formed tetraalcohols were treated with two equivalents of a dichloride, dibromide, or ditosylate to produce the new unsymmetric cryptands in yields up to 50% (Scheme 13).

Scheme 13



Self-condensation of *o*-aminobenzaldehyde in the presence of Ni(II) produced a mixture of cyclic trimers and tetramers [33]. Even though this is not a 2:2 cyclization reaction because only a single starting material was used, four new bonds were formed as shown in Scheme 14 for the tetramer [34-36].

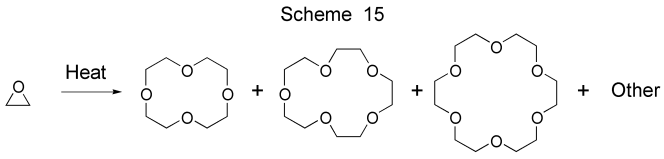
Scheme 14



Macrocyclic Compounds Formed by Four to Six New Bonds.

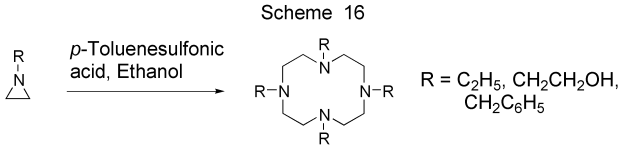
Small three-membered heterocyclic compounds such as aziridine and ethylene oxide can open and react to form larger macrocyclic compounds. For example, cyclooligomerization of ethylene oxide gave many new cyclic products. Using the proper conditions, this process gave a mixture of crown compounds as shown in Scheme 15. Dale and coworkers [37,38] have shown that product composition can be influenced by adding a "templating cation". Addition of copper or zinc tetrafluoroborate, for example, gave a product mixture containing greater than 90% of the cyclic pentamer (15-crown-5) [38].

Scheme 15



Aziridine molecules readily polymerize and, in some cases, macrocycles can be isolated from the product mixture [39,40]. For example, 1-benzylaziridine reacted to give good yields of tetra-*N*-benzyl-substituted peraza-12-crown-4 as shown in Scheme 16 [39,40]. These cyclic tetramers were formed under conditions that should have given the polymers. 1-Methyl- and 1-phenylaziridine gave only polymers under the same conditions.

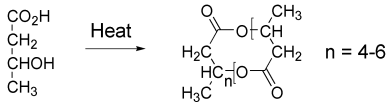
Scheme 16



Macrocyclic Compounds Formed by Five to Seven New Bonds.

The macrolide compounds are important macrocycles formed from the hydroxycarboxylic acids. Seebach and coworkers obtained interesting results for the cyclolactolization of (*R*)- and (*S*)-3-hydroxybutanoic acid as shown in Scheme 17 [41]. At room temperature, the cyclic pentamer, hexamer and heptamer were formed in approximately equal amounts with a total yield of 50%. The ratio of the products was 59:30:9 in favor of the pentamer over the heptamer at 110°.

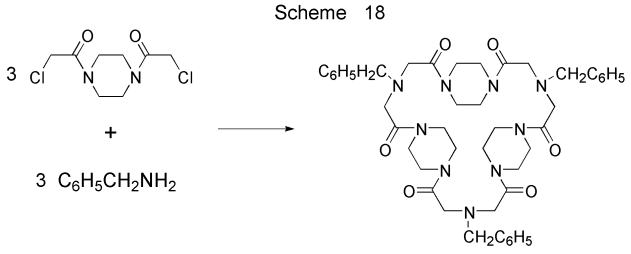
Scheme 17



Macrocyclic Compounds Formed by Six New Bonds.

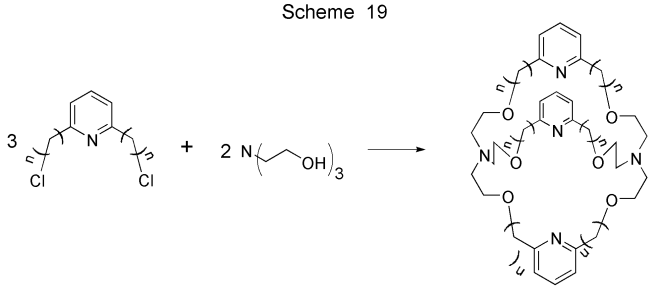
Products of 3:3 cyclization reactions are generally byproducts from high dilution 1:1 or 2:2 cyclizations [42,43]. These large cyclic products can be isolated by careful chromatography. Often 3:3 cyclization is the main product because the 1:1 and 2:2 cyclization products cannot form. An example of a 3:3 cyclization is the preparation of the piperazine-containing cyclic hexamide shown in Scheme 18 [44].

Scheme 18



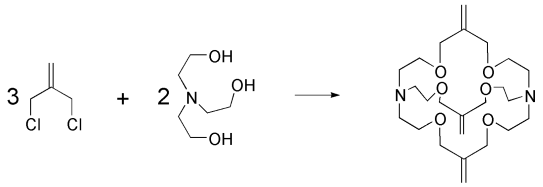
Cyclocondensation of 3 molecules of a dihalide (or diacid dichloride) with 2 molecules of a trialcohol or triamine forms cryptands wherein six C-O or six C-N bonds are formed. For example, cryptands were formed from triethanolamine and 2,6-bis(chloromethyl or 2,6-bis(chloroethyl)pyridine as shown in Scheme 19 [45,46]. The reaction was carried out in xylene or dimethylformamide in the presence of sodium hydride to give low

Scheme 19



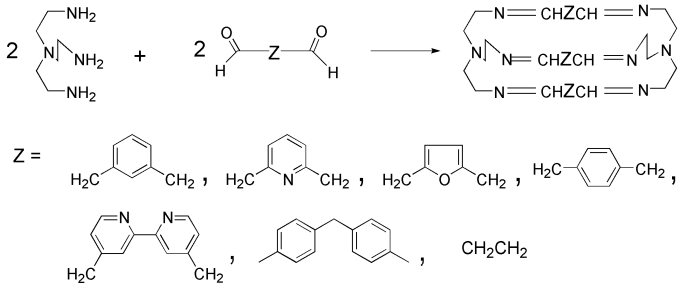
yields of the products. A much higher yield was observed for the 3:2 cyclocondensation of 2-(chloromethyl)-3-chloropropene with triethanolamine (Scheme 20) [47].

Scheme 20



The 3:2 cyclocondensation reaction has also been used to prepare cryptands containing six Schiff base functions [48-53]. In this case, two molecules of tris(2-aminoethyl)-amine were condensed with three molecules of an aliphatic or aromatic dialdehyde as shown in Scheme 21. Many of the hexaimines were then reduced to form the saturated hexaaza cryptands.

Scheme 21

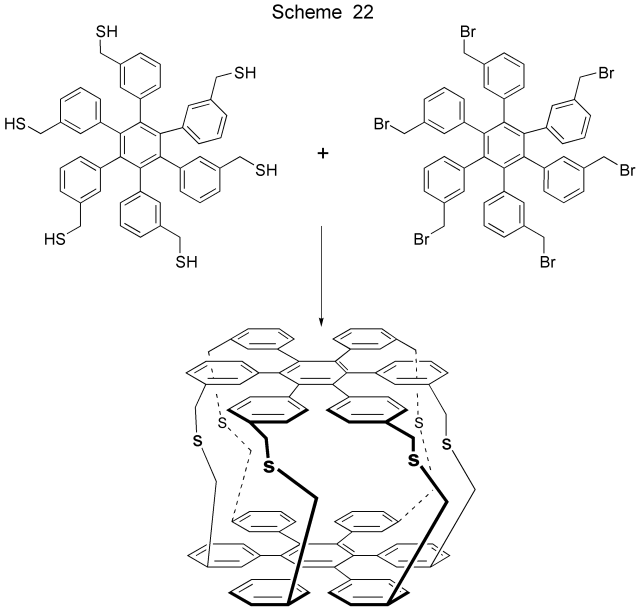


Kissener and Vögtle prepared a remarkable cage compound composed of two benzene rings connected together by six aromatic bridges in one step as shown in Scheme 22 [54]. They reacted the two starting materials in very high dilution using cesium carbonate as the base to give the product in 0.1% yield. The yield was improved to 0.5% in a later reaction process. Other cage compounds containing three decks were also prepared with a total yield of 6% for a mixture of two isomers [55,56].

Macrocyclic Compounds Formed by Eight New Bonds.

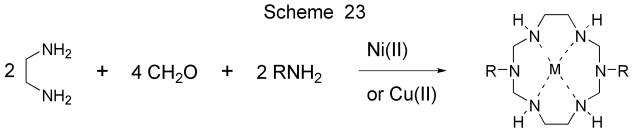
Formaldehyde, aldehydes and ketones are often used for the formation of bonds during the synthesis of macrocyclic compounds. For example, Suh and Kang [57] prepared

Scheme 22



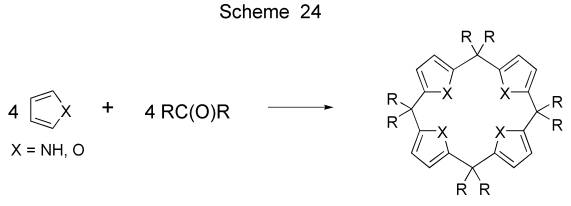
hexaazacrowns by the templated condensation of ethylenediamine, formaldehyde and an alkylamine in the presence of Cu(II) or Ni(II) (Scheme 23).

Scheme 23



If rigid subunits are to be incorporated, the various acyclic intermediates may be pre-organized in the correct conformation for cyclization. Sometimes these reactions are quite spectacular. An early example is the reaction of pyrrole and ketones in the presence of acid, which gave excellent yields of the macrocycle in a 4+4 cyclization reaction (Scheme 24) [58,59]. Similar reactions were observed with furan [60,61].

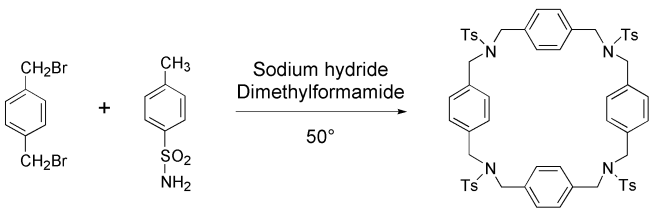
Scheme 24



Inazu and coworkers developed the synthesis of cyclophanes in one step using a few different approaches [62]. As alternative synthetic methods, they introduced

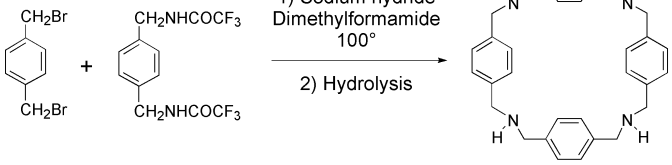
p-toluenesulfonamide as a reactant (Scheme 25) [63]. During this reaction, the authors isolated products of 2:2, 3:3 and the desired 4:4 cyclization. The use of *p*-phenylenebistrifluoroacetamide offers a more facile and practical

Scheme 25



synthetic method to prepare the cyclophanes and allows the preparation of these macrocycles in gram quantities (Scheme 26) [64].

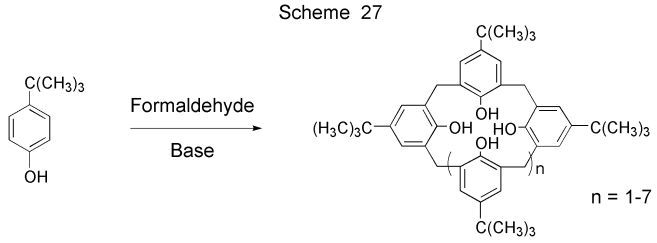
Scheme 26



Macrocyclic Compounds Formed by Eight to Forty New Bonds.

In general, the base catalyzed condensation of *p*-substituted phenols and formaldehyde yields a complex mixture of linear and cyclic oligomers and the outcome of the reaction is difficult to control. There are, however, a few cases in which the reaction can be controlled. For example, when the starting phenol bears a bulky substituent at the *p*-position, the condensation reaction can be directed to cyclic products in excellent yields (Scheme 27). The wide ranging investigations of Gutsche and coworkers [65-69] and others [70-73] have resulted in both reproducible and high yield procedures for the synthesis of *p*-*t*-butylcalixarenes

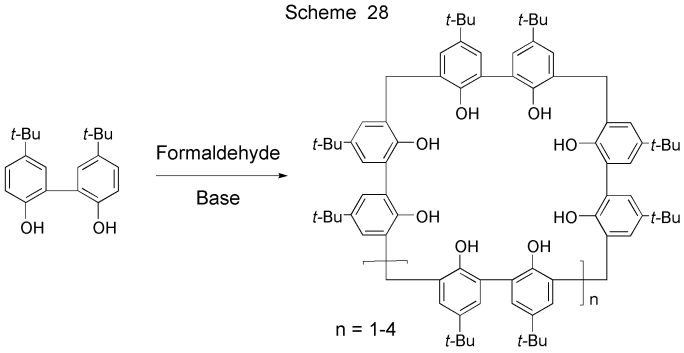
Scheme 27



containing an even number of phenolic rings. The hexamer was formed when alkali metal cations with large ionic radii (K^+, Cs^+) were used and the tetramer was formed when a higher temperature was applied. It is important to emphasize that a step-by-step synthesis of these compounds is difficult so that it is more convenient to use the one-step procedure. Calixarenes containing an odd number of phenolic rings are less accessible but can be produced with an average yield by a one-step synthesis [74].

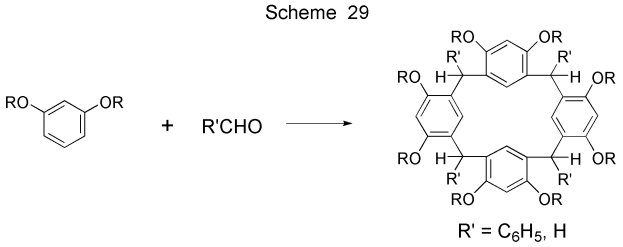
The base catalyzed condensation of 5,5'-di-*t*-butyl-2,2'-dihydroxybiphenyl with formaldehyde gave a calixarene-like macrocyclic compound as shown in Scheme 28 [75-77]. Macrocycles with three, four and eight 2,2'-dihydroxybiphenyl units have been prepared.

Scheme 28



Condensation of resorcinol with aldehydes forms calix[4]resorcinarenes, but only one member of the family is known (Scheme 29) [78], although a calix[5]arene with resorcinol connected in a different position is also known [79]. It is most likely that resorcinarenes of other ring sizes can be produced in a manner similar to that used for the syntheses in the calixarene family. The resorcinarenes are starting materials for other classes of compounds such as the cavitands [80,81].

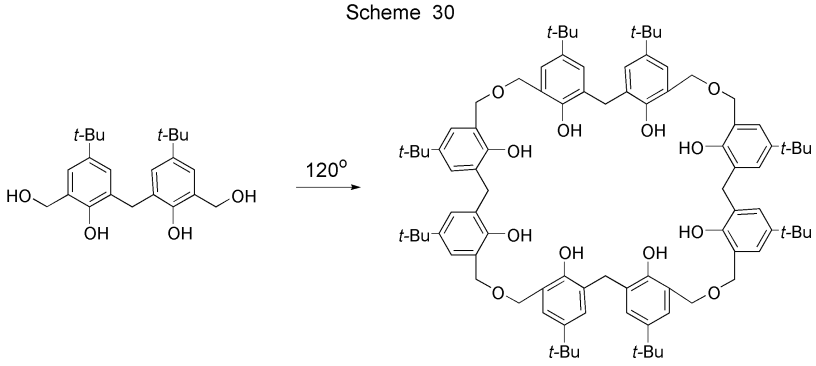
Scheme 29



The homooxacalixarenes are calixarene analogues in which some or all of the CH_2 units bridging the aromatic rings in the calixarenes are replaced by CH_2OCH_2 units. Usually, this family of compounds is prepared by the dehydration of phenols. For example, a large homooxacalixarene was isolated after heating a bis(hydroxymethyl)-bisphenol to a high temperature as shown in Scheme 30 [82,83].

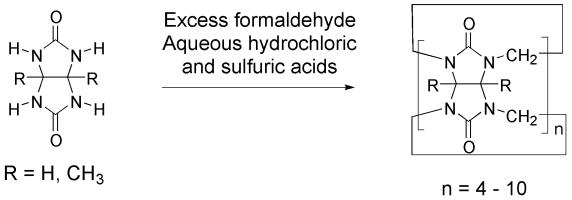
Another group of macrocyclic compounds that was reported nearly 100 years ago by Behrend *et al*. [84] waited until recently for the method of their preparation to be discovered. These workers isolated the compounds from an acidic condensation of glycoluril with an excess of formaldehyde. The structure of the compound was published 75 years later by Freeman *et al*. [85] and it proved to be cucurbit[6]uril (Scheme 31). It was another 10 years before another example of this class of compounds, cucur-

Scheme 30



bit[5]uril with 10 methyl groups, was prepared [86]. Cucurbit[6]uril and cucurbit[5]uril have been tested for different applications [87,88]. The preparation of any cucurbit[n]uril from n = 4-10 (Scheme 31) was published only a year ago [89,90]. The authors also detected larger compounds up to n = 12. The calixarenes have more proven applications than do the cucurbituril compounds because the cucurbituril compounds do not have functional groups that would allow them to be used as building blocks or platforms to create new supramolecular structures.

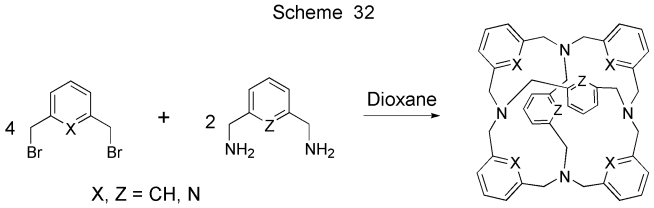
Scheme 31



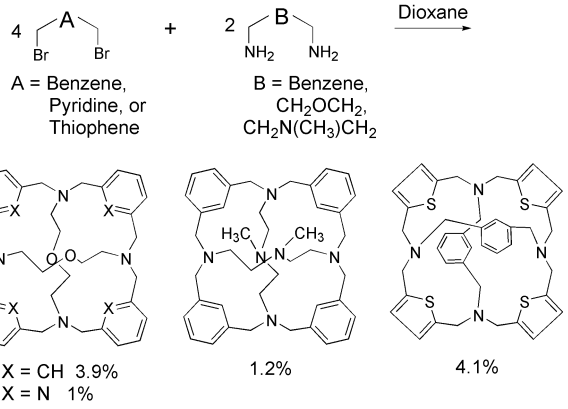
Macrocyclic Compounds Formed by Twelve New Bonds.

Recent advances in host-guest chemistry demand more and more sophisticated artificial host molecules. Step-by-step synthetic methods are not practical because multi-step syntheses involve many protecting and deprotecting steps. A one-step method to the more sophisticated compounds is a much better approach even with very low yields. Often purification of the complicated product requires very careful column chromatography. The so-called supercryptands (spherical macrotricyclic ligands) can be prepared easily if rigid aromatic units are present in the starting compounds (Scheme 32) [62,91-94]. Unfortunately, this synthetic approach is not useful for the preparation of small supercryptands with aliphatic connecting groups because small five- or six-membered rings, such as morpholine or piperazine, will preferentially form. Some aliphatic connecting group-containing supercryptands shown in Scheme 33 have been prepared, but in small yields [95-97]. However, reactions of the appropriate starting materials do not always give the desired supercryptands but often lead to other macrocyclic compounds as shown in Scheme 34 [96].

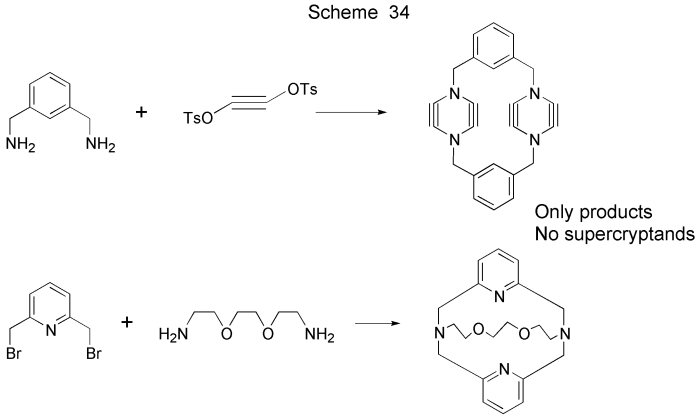
Scheme 32



Scheme 33



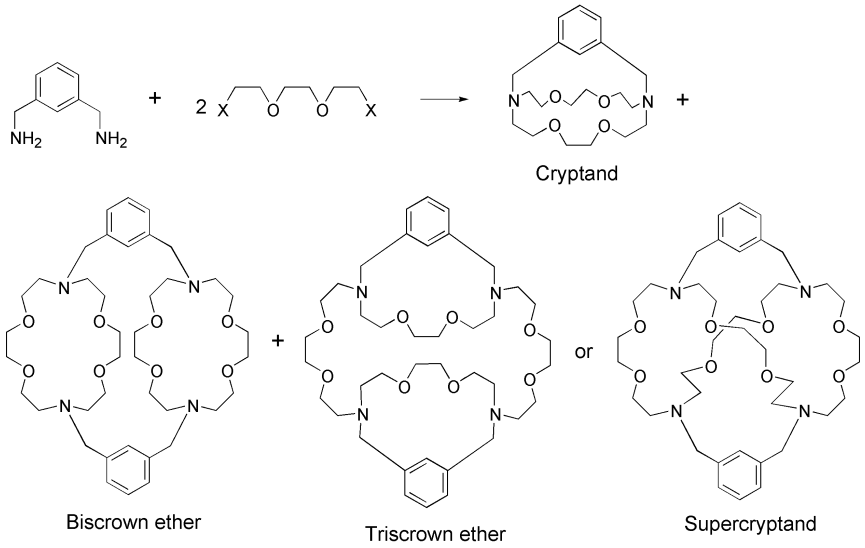
Scheme 34



Krakowiak, *et al*. in the reaction shown in Scheme 35, produced cryptands, biscrown ethers, and a supercryptand or a triscrown ether [26]. After reacting the two starting materials in a 1:2 ratio, they separated two products of a 4:2 cyclocondensation. One product was characterized as

the biscrown ether shown in Scheme 35 [26]. The other is either the triscrown or the supercryptand. The exact structure has not yet been determined.

Scheme 35



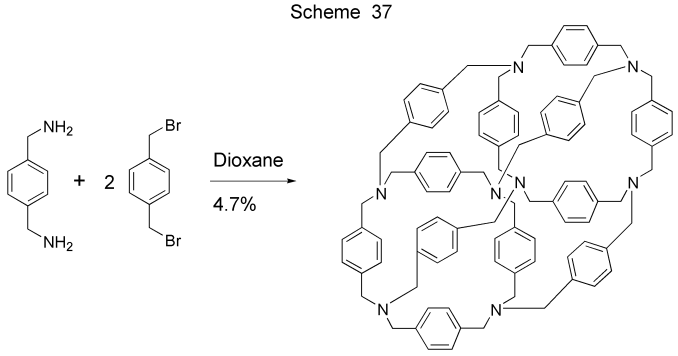
Sargeson and coworkers have used an external template to prepare an octaazacryptate which was obtained in greater than 95% yield by condensation of the tris(ethylenediamine) cobalt(II) ion with formaldehyde and ammonia as shown in Scheme 36 [98,99].

Scheme 36

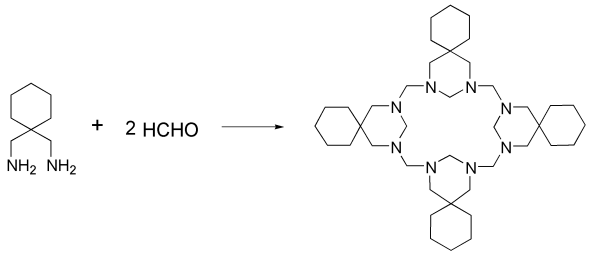
Macrocyclic Compounds Formed by Sixteen New Bonds.

A square prism (cubic) compound was first prepared by a multistep synthesis in a 2% yield [100,101]. Later, the same compound was prepared by a one-step process (Scheme 37) with a better yield (4.7%). Another example is the condensation of 1,1-bis(aminomethyl)cyclohexane with formaldehyde to form a polymer, which upon heating readily isomerized to a cyclic compound (Scheme 38) [102].

Scheme 37



Scheme 38



Summary.

One-step syntheses of macrocyclic compounds are very convenient methods to prepare many cyclic compounds. The only drawbacks are that the yields are low and purification steps sometimes require repeated column chromatography. Some macrocycles can only be prepared by a one-step synthesis because a multi-step synthesis is not practical and would take too long (for example for the calixarenes). On the other hand, unsymmetric macrocyclic compounds can only be prepared using a multi-step method.

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