New Trends in the Chemistry of Condensed Heteromacrocycles Part A: Condensed Azacrown Ethers and Azathiacrown Ethers

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This paper is dedicated to Prof. Dr. Klaus Hafner

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Contents

This review article, covering the literature from 1990 to 2001, deals with the main strategies for the synthesis of condensed azacrown ethers and condensed azathiacrown ethers as well as their specific syntheses. Reactivities and applications of these compounds in different areas are in focus.

Introduction.

Heteromacrocycles represent an important point of departure from traditional heterocyclic chemistry. The bulk of these compounds contains twelve or more members and they are aliphatic rather than aromatic. Heteromacrocycles generally complex cations internally using four or more donor groups to stabilize the Lewis acid. It is reasonably safe to say, however, that a major motivation in the macrocycle area for the synthesis of so many novel structures was to develop complexing agents. Crown ethers, which were discovered by Pedersen [1] at Du Pont in 1967, represent a class of these compounds. Since Pedersen reported the synthesis and complexing properties of crown ethers, there has been a great interest in the crown compounds as complexing agents for various cations and anions.

Many changes have been made to the basic crown ether structure in an attempt to find molecules with superior properties and proper applications in various areas. Different kinds of crown ligands have been synthesized including the lariat ethers, azacrown ethers, cryptands, calixarenes, spherands and other preorganized macromolecules.

It is noteworthy to mention that the Nobel Prize for chemistry in 1987 was awarded to Charles J. Pedersen, J. M. Lehn and D. J. Cram for their development of crown ethers and other macroheterocyclic ligands.

This review covers all condensed azacrown ethers synthesized in the last ten years. We have concentrated on azacrown ethers condensed with aromatic and/or heteroaromatic rings. A compilation of azacrown compounds prepared to about 1992 is given by Gokel and co-workers [2] and Bradshaw and co-workers [3].

Azacrown ethers are those heteromacrocycles that contain one or more nitrogen atoms. The present discussion focuses on compounds in which nitrogen replaces an atom in an otherwise standard crown ether. We have also included the compounds containing sulfur in addition to nitrogen and oxygen. These compounds have complexation properties that are intermediate between those of all-oxygen crowns which strongly complex alkali and alkaline earth metal ions, and those of all-nitrogen cyclams which strongly complex heavy metal cations. These mixed complexation properties make the azacrown interesting to researchers in many areas [4-6]. The azacrowns have important uses as radioisotope complexing agents for treatment of tumors [7,8]. Many functionalized azacrown macrocycles have shown a wide range of biological activities [9]. Certain azacrown compounds have been covalently attached to silica gel or other solid support. These silica gel bound aza-crown compounds have been used for selective separation of specific metal ions from mixtures of metal ions [10]. In addition, azacrown ethers are important synthons for the preparation of functionalized mono- and polycyclic ligands [11].

As mentioned above, this review focuses on azaheteromacrocycles condensed with aromatic and/or heteroaromatic ring systems. The insertion of such systems into the macroring provides rigidity and are able to participate in complexation through their soft donor atoms. In addition, the aromatic units facilitate the modification of macrocyclic hosts with various UV and/or fluorescent active groups [12],

proton ionizable fragments [13] and functional groups, which can be attached to proteins to provide radionuclide carriers for medicals diagnosis and therapy [14].

Nomenclature.

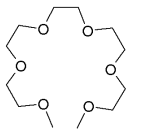
Macroheterocycles are given trivial names, which are relatively simple. For example dibenzo[18]crown-6 (**vi**) is a crown ether with an 18-membered macrocyclic ring containing six oxygen atoms with two benzo substitutents. The first number in the crown name designates the number of atoms in the ring (usually given in square brackets). The second number gives the number of oxygen (or other donor) atoms. Condensed aromatic rings are denoted with a prefix such as benzo-, triazolo-, pyridino-,…. etc.

A more generalized system of nomenclature for such neutral organic ligands was developed by Vögtle and Weber (1979) and later modified by Cram (1986), in which any monocyclic system such as the crown ether is termed a corand. Open chain molecules such as (**i**) are called podand, bicyclic or oligocyclic systems (for example **iv**) are termed cryptands and rigid, *p*-methylanisole-based system **vii** are given the name spherand.

In general for purely oxygen donor ligands, the historical crown nomenclature is retained. Under this system, all of the above crown ethers belongs to the general class of corands. The name of dibenzo[18]crown-6 **vi** becomes $18(O_6)2_6$corand-6), meaning a 18-membered ring monocyclic compound containing six oxygen atom linked by six spacers containing two carbon atoms each to give a total of six donor atoms. Similarly, the azacrown compound **ii** is called $18(O_5N_1)2_6$ corand-6). The cryptand has a somewhat different nomenclature. Each host is denoted by a series of numbers indicating the number of donor atoms in each of the bridges between the bridgehead atoms. Thus **iv** is termed [2.2.2]cryptand.

The term "lariat ethers" refers to a crown ether or similar macrocyclic derivatives with one or more podand side arms (for example **iii**) to enhance the cation complexing ability. Lariat ethers are members of a hydrid corand-podand family.

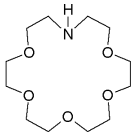
All of these ligands have been synthesized with binding of metal cation guests in mind and thus the nomenclature must distinguish between the free (uncomplexed) ligand and the metal complex. This is achieved by use of the ending *-and* to mean uncomplexed ligand and the ending *-ate* for the metal complex. Thus metal complexes of podands are termed *podates*, corand complexes are called *corates* and cryptand complexes are called *cryptates*. To avoid confusion with the literature as far as possible, IUPAC names for all the representative examples are also given.



i

Podand

1-(2-Methoxyethoxy)-2-{2-[2-(2-methoxyethoxy)-ethoxy]ethoxy}ethane

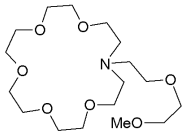


ii

16-aza-18-crown-6

$18(O_5N_1)2_6$corand-6)

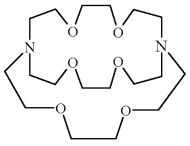
1,4,7,10,13-Pentaoxa-16-azacyclooctadecane



iii

Lariat ether

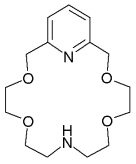
16-{2-(2-Methoxyethoxy)ethyl}-1,4,7,10,13-pentaoxacyclooctadecane



iv

[2.2.2]Cryptand

4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane

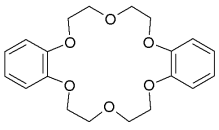


v

Pyridinoazacrown ether

Pyridino-18-crown-6

3,6,12,15-Tetraoxa-9,21-diazabicyclo-[15.3.1]henicosa-1(20),17(21),19-triene

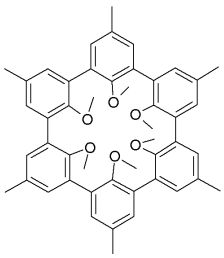


vi

Dibenzo-18-crown-6

Dibenzo-$18(O_6)2_6$corand-6)

6,7,9,10,17,18,20,21-Octahydrodibenzo[b,k] 1,4,7,10,13,16-hexaoxacyclooctadecine



vii

Spherand

31,32,33,34,35,36-hexamethoxy-4,9,14,19,24,29-Hexamethylheptacyclo-[25.3.1.1(2,6).1(7,11).1(12,16).1(17,21).1(22,26)]hexatriaconta-1(31),2(32),3,5,7(33),8,10,12(34),13,15,17(35),18,20,22(36),23,25,27,29-octadecaene

Azacrown Precursors.

The preparation of azamacroheterocycles requires the preparation of the appropriate amine precursors. A survey of the general methods for the preparation of starting materials have been previously reviewed [3]. Some of these methods have been included in this review.

A- Diamines.

Dietrich and co-workers [15] used the Gabriel synthesis to prepare triethylene glycol diamine (**1**). In this sequence, triethylene glycol was treated with PBr_3 in pyridine to form the dibromide. Reaction with potassium phthalimide in DMF gave the expected bis(phthalimide), which was cleaved using hydrazine followed by acid. Reaction of the dibromide with *N*-tosylbenzylamine affords the *N*-tosyl-*N*-benzyl derivative **2a**. This can be detosylated to afford the bis(*N*-benzyl) derivative **2b** [16]. A more straightforward approach to the diamine precursor **1** was reported by King and Krespan [17] who heated the triethylene glycol dichloride with ethanolic ammonia. Several groups have prepared triethylene glycol diamine (**1**) by conversion of its chloride into the corresponding diazide. The azide is then reduced using $LiAlH_4$ [18].

The nitro group has been used successfully as an amine precursor in the preparation of certain dibenzodiazacrowns. Thus, 2-nitrophenol is treated with diethylene glycol dihalides and K_2CO_3 in DMF. The resulting dinitro derivative **3a** is subsequently reduced using stannous chloride and acid to give the diamine **3b** [19].

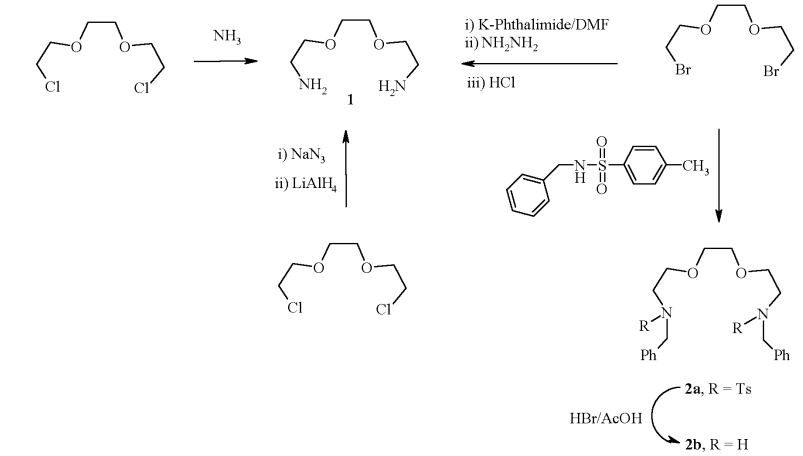
B- Amino- and Diaminodiols.

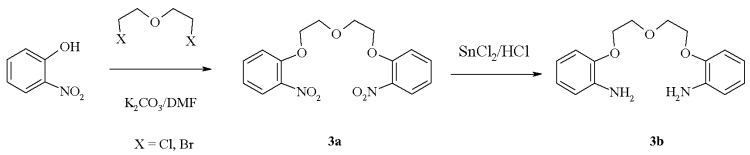
Okahara and co-workers [20] prepared a number of *N*-alkylamino diols **6** that were not symmetrical by reacting the monochloride derivatives **4** of the oligoethylene glycol with *N*-alkylethanolamines **5** in the presence of Na_2CO_3 as the base.

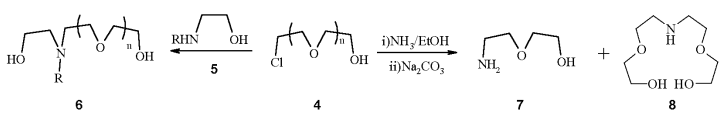
On the other hand, Krespan [21] found that when 2-(2-chloroethoxy)ethanol (**4**) (n = 1) was heated with ammonia in ethanol a mixture of 2-(2-aminoethoxy)ethanol

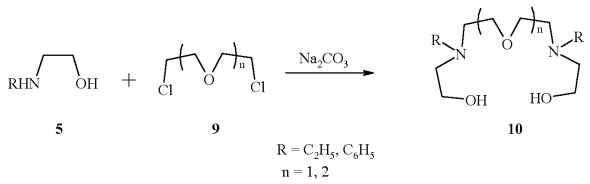
(**7**) and the symmetrical 6-aza-3,9-dioxaundecane-1,11-diol (**8**) was isolated.

Under similar conditions, Bradshaw and co-workers [22] reported the synthesis of *N*,*N*'-dibenzyldiazaoligoethylene glycol **10** in high overall yield by reacting dihalide **9** with *N*-ethyl- or *N*-benzyl substituted ethanolamine **5**.

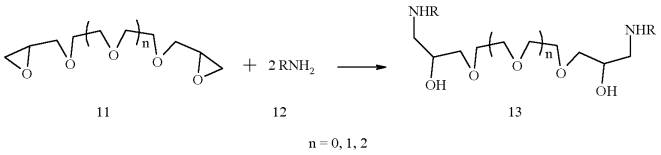








Okahara and coworkers [23] used an epoxide ring-opening reaction to prepare some interesting diaminodiol ethers **13** that are capable of ring closure either through the diamine or the diol by reacting bisepoxy polyether **11** with an excess of the alkylamine **12** .



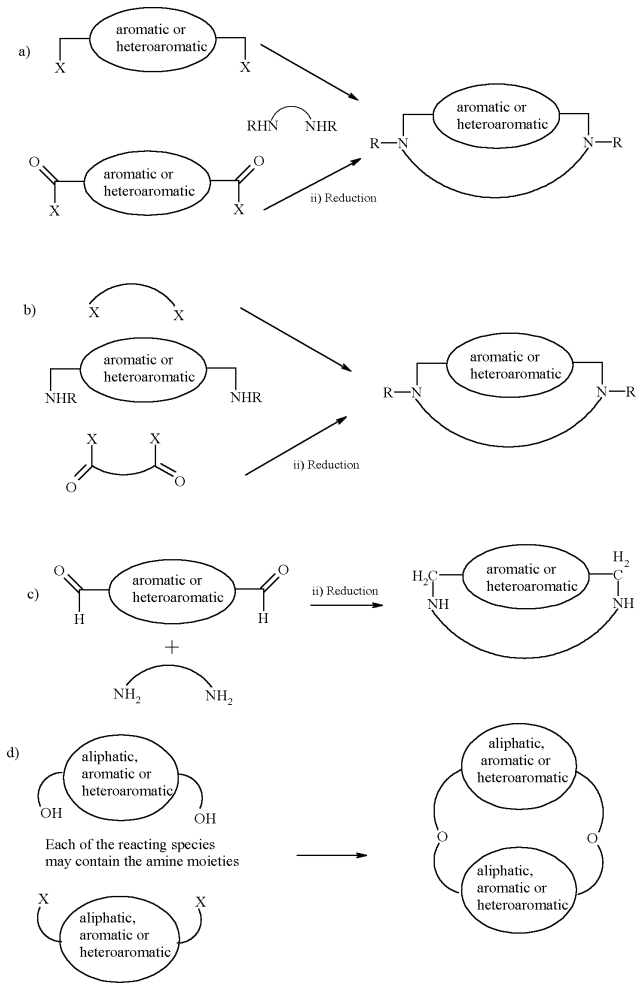
Main Strategies for the Preparation of Azamacrocycles Condensed with Aromatic and/or Heteroaromatic Rings.

In general, syntheses of azacrowns were performed by cyclization of primary or secondary amines with dihalides, activated diacid derivatives or dialdehydes. Reacting species containing heteroatoms and aliphatic or aromatic fragments (between interacting centers) have been used for cyclization (the following Scheme, parts a-c).

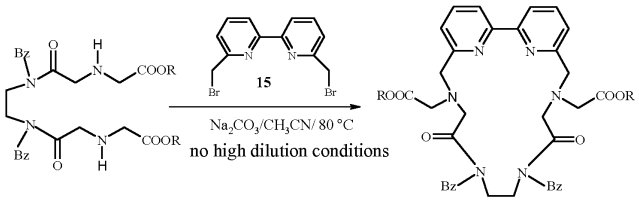
Cyclizations are possible using other end functional groups, particularly hydroxy, where amine moieties are in the center of the starting bis bifunctional materials. These reactions were used mostly in 1:1, 2:2 and intramolecular cyclization processes (the following Scheme, part d).

In general, the problems encountered in the synthesis of macroheterocycles are those typical of reactions forming large rings, namely, low yields and polymerization. Using, in the cyclization step, a rapid reaction under high dilution conditions, can minimize these difficulties. The presence of rigid groups also increases cyclization yields by reducing the number of conformational degrees of freedom in the secomacrocycle. As a result of restricted rotations, there are relatively small losses in entropy on cyclization, allowing ring closure to occur in relatively high yields without a need for a preorganization of the starting materials [24,25].

In some cases, cyclization yields may be enhanced by using alkali metal cations as templates to keep the chains together during the reaction. The reaction mechanism usually involves two successive SN_2 reactions. After the initial alkylation the metal cation apparently acts as a "template" to bring the two reacting ends of the long chain close together for a rapid reaction [26,27]. This template effect is less pronounced in the formation of azacrowns because the softer N-donor atoms form weaker complexes with the alkali metal cations.



The relatively high yield of the azamacrocycles **16a**, **b** in the following macrocyclization reactions have been explained in terms of both template and entropy effects [28].



14a, **16a** R = Et, yield = 67 %
14b, **16b** R = Bz, yield = 95 %

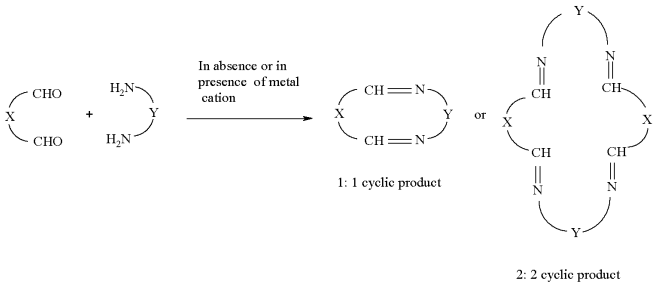
Thus, reaction of 6,6'-bis(bromomethyl)-2,5-bipyridine (15) with diamine 14a in refluxing acetonitrile and in the presence of Na_2CO_3 as a base gave the NaBr complex of the macrocycle 16a in good yield (67%) without the use of high dilution technique. This is certainly the result of a template effect of the sodium ion. It has also been noted that replacement of ethyl ester group by a benzyl group in

the diamine compound (14b vs. 14a) produced a better cyclization yield (93%). This may be a result of restricted conformational freedom in 14b, caused by the bulkier benzyl group and consequently a small loss of entropy in the cyclization process.

General Methods for the Synthesis of Condensed Azamacrocycles.

A- Synthesis of Condensed Azamacrocycles from their Precursor Macrocyclic Schiff Bases.

The first approach to azamacrocycles involves the formation of cyclic Schiff bases. The synthetic strategy depends on the cyclocondensation between bis amines and the appropriate bis aldehyde to give the corresponding Schiff bases followed by reduction. The cyclocondensation reactions are known to occur either in the absence or in the presence of metal ions. The latter can serve to direct the condensation preferentially to cyclic rather than oligomeric and/or polymeric products and to stabilize the macrocycle once formed. The reactions proceed to give "1+1" macrocycles or "2+2" macrocycles depending, together with other factors, on the size of the template ion (when it is used) and the chain length of both the diamine and the dialdehyde [29-31].

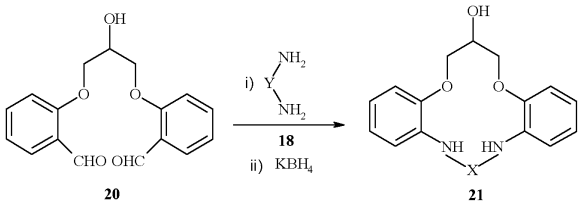


Specific Synthesis of Macrocyclic Schiff Bases.

a) Dibenzomacrocyclic Schiff Bases.

Lindoy and co-workers [32-35] pioneered the synthesis of dibenzomacrocycles having a mixture of heteroatoms **19** by reduction of the precursors macrocyclic Schiff bases. The synthetic strategy depends on the cyclocondensation of the bis amines **18** and the appropriate bis aldehydes **17** to give the corresponding Schiff bases followed by reduction. The bis aldehydes **17** were prepared by alkylation of salicylaldehyde with the appropriate dihaloalkane in basic solution.

Similarly, Zhao and co-workers [36] reported the synthesis of hydroxydibenzo-azacrown ethers **21** in 44-77% yields by cyclocondensation of 1,3-bis(2-formylphenoxy)-2-propanol (**20**) with diamines **18** followed by potassium borohydride reduction.

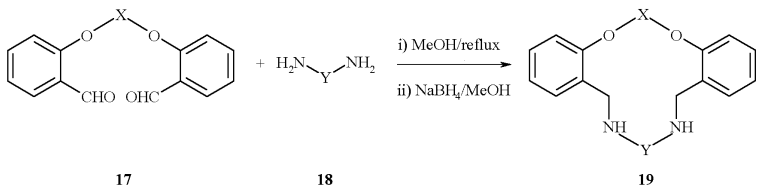


Y = $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_2NH(CH)_2$, $(CH_2)_2NH(CH_2)_nNH(CH_2)_2$, n = 2, 3

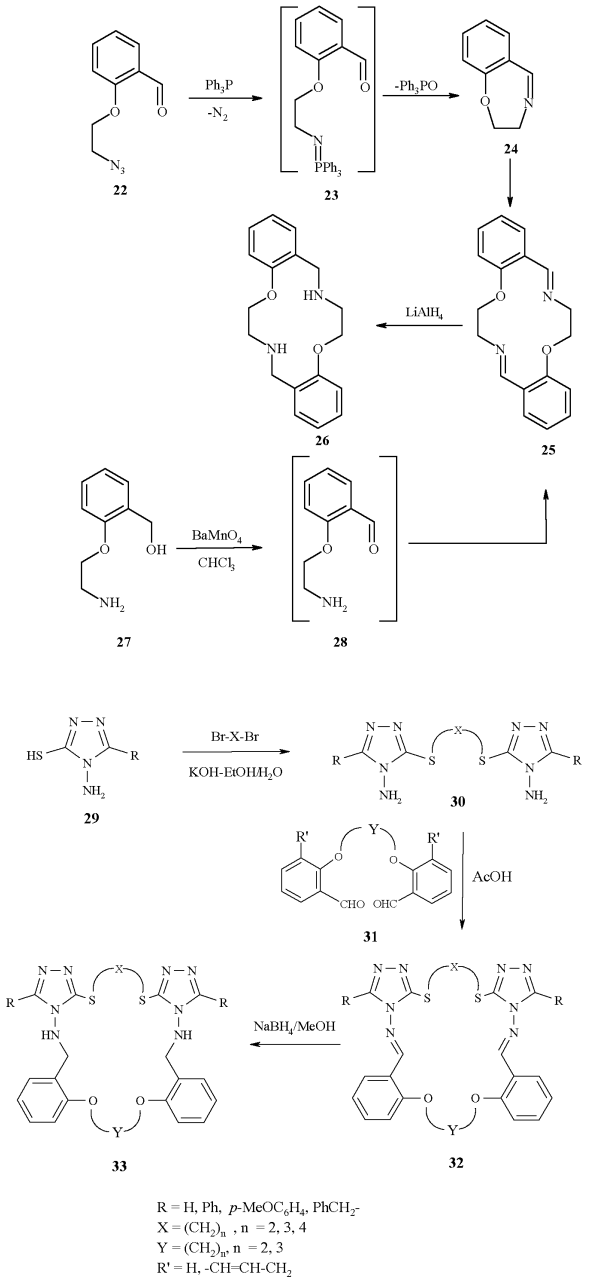
Wild and co-workers [37,38] reported the synthesis of 14-membered diimine macrocycle **25** with a *trans* arrangement of the N_2O_2 donor groups by reacting 2-(2-azidoethoxy)benzaldehyde (**22**) with triphenyphosphine in diethyl ether to give **23** *via* an aza-Wittig reaction. The reaction proceeds presumably *via* seven-membered 2,3-dihydro-1,4-benzoxazepine (**24**). The latter underwent dimerization to give **25**. Reduction of diimine **25** with $LiAlH_4$ gave the *trans* N_2O_2 diamine macrocycle **26**. Diimine **25** could also be isolated in satisfactory yield by first oxidation of 2-(2-aminoethoxy)benzyl alcohol (**27**) with barium manganate to give aldehyde **28** followed by self condensation to give the target **25**.

b) Triazolomacrocyclic Schiff Bases.

Ibrahim and co-workers [39,40] reported the synthesis of some 20-22-membered macrocyclic Schiff bases **32** as outlined in the following Scheme. These macrocycles contain nitrogen, oxygen and sulfur in the macrocyclic ring as donor atoms and are fused to two benzo and two triazole rings. Thus, 4-amino-1,2,4-triazole derivatives **29** were treated with the appropriate dibromoalkane to give the corresponding α,ω-bis(4-amino-1,2,4-triazol-3-yl-



X = $(CH_2)_n$, n = 1, 2, 3
Y = $(CH_2)_2$-A-$(CH_2)_2$, A = O, S, NH
= $(CH_2)_2NH(CH_2)_3$
= $(CH_2)_3NH(CH_2)_2$

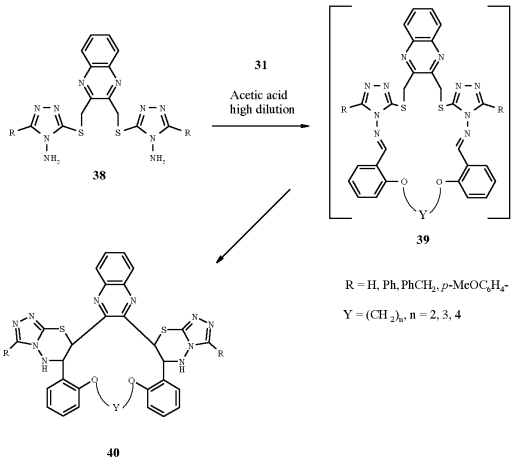


R = H, Ph, *p*-$MeOC_6H_4$, $PhCH_2$-
X = $(CH_2)_n$, n = 2, 3, 4
Y = $(CH_2)_n$, n = 2, 3
R' = H, -CH=CH-CH_2

sulfanyl)alkane **30**. Cyclocondensation of **30** with the appropriate α,ω-bis(2-formylphenoxy)alkanes **31** in glacial acetic acid under high dilution conditions gave the corresponding Schiff bases **32**. The latter underwent reduction with sodium borohydride in methanol to give the corresponding macrocycles **33**.

Elwahy and co-workers [41,42] attempted to modify the structure of **32** by intoducing pyridine or quinoxaline rings in addition to the triazole rings. The bis aldehydes **34** and **35** were chosen as starting materials and were allowed to react with bis amines **30** in glacial acetic acid under high dilution conditions. Unfortunately, bis aldehydes **34** and **35** underwent intramolecular cyclocondensation to give the corresponding bis(benzo[6]furan-2-yl) derivatives **36** and **37**, respectively.

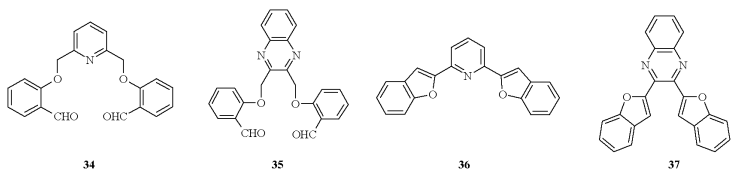
Elwahy and co-workers [43] reported another attempt to prepare macrocyclic Schiff bases **39** containing the quinoxaline moiety in addition to the triazol rings by reacting bis amines **38** with the appropriate bis aldehydes **31** in refluxing acetic acid. Interestingly, the reaction did not give macrocycle **39** but rather gave the condensed heteromacrocycles **40**. The reaction probably proceeds *via* initial formation of the corresponding macrocyclic Schiff bases **39** followed by intramolecular cyclization.

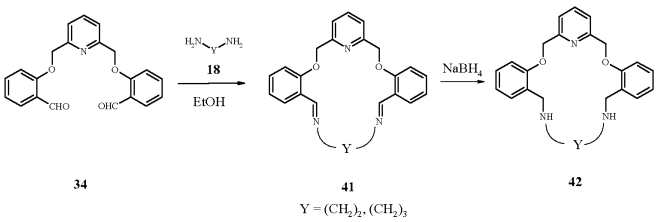


R = H, Ph, $PhCH_2$, *p*-$MeOC_6H_4$-
Y = $(CH_2)_n$, n = 2, 3, 4

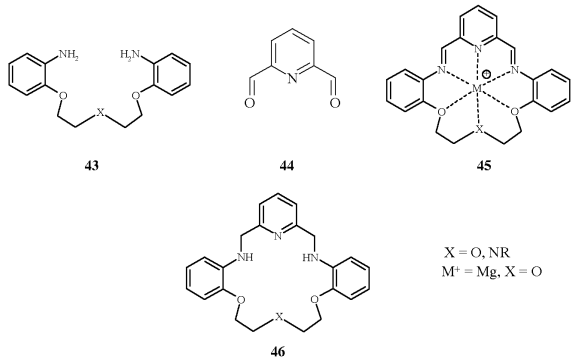
c) Pyridinomacrocyclic Schiff Bases.

Lindoy and co-workers [44] along with others [45] have reported the synthesis of pyridino-azacrown ethers **42** (Y = CH_2) *via* Mn(II)-templated cyclocondensation of the precursor dialdehyde **34** and diamine **18** followed by an *in situ* reductive demetallation of the manganese (II)Schiff base intermediate **41** by $NaBH_4$. Attempts to synthesize ligand **42** (Y = $(CH_2)_3$) by the same route failed and so a non-template approach was used. Fenton and co-workers [46] used a similar approach to prepare **42** (Y = CH_2OCH_2).

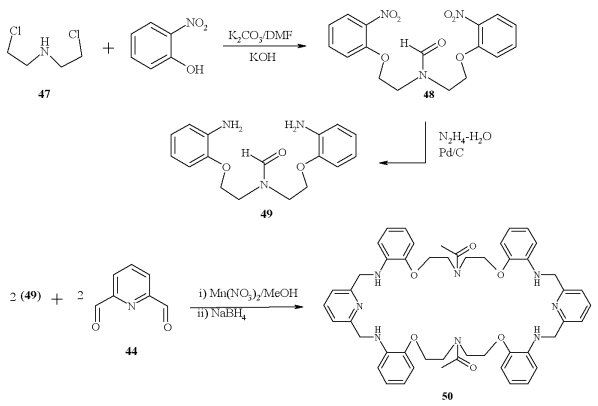




On the other hand, Fenton and co-workers [47,48] and He and co-workers [49] reported the synthesis of modified derivatives of **41** in which the imine likage is directly attached to the pyridine ring by metal-templated cyclocondensation of diamines **43** with 2,6-diformylpyridine (**44**). The N_3O_3 oxaazamacrocycle **45** was obtained as its metal complex. *In situ* reductive demetallation of **45** with $NaBH_4$ gave the corresponding metal free macrocycles **46**.



Using bis-amine **49**, Fenton and co-workers [50] reported the synthesis of macrocycle **50** as outlined in the following Scheme. Thus, the reaction of *o*-nitrophenol

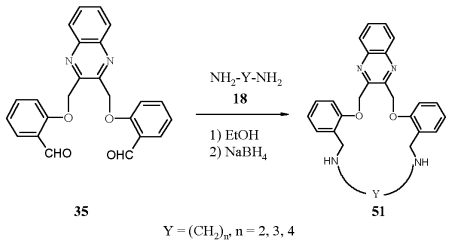


with bis(2-chloroethyl)amine (**47**) in DMF containing K_2CO_3 led to the formation of the dinitro compound **48** which underwent reduction to give the corresponding diamine **49**. A metal-templated cyclocondensation of the latter with pyridine-2,6-dialdehyde (**44**) produced a [2+2] macrocycle **50**. As this [2+2] product is formed rather than the anticipated [1+1] macrocycle, it is possible that *N*-formylation of the linker unit has a significant influence on the reaction pathway.

Using metal-templated [2+2] macrocyclization of the appropriate bis amines with the corresponding bis aldehydes, a number of tetraimine macrocyclic derivatives were synthesized [51-53].

d) Quinoxalinomacrocyclic Schiff Bases.

Elwahy [42] described the synthesis of quinoxalinoazacrown ethers **51** by reacting dialdehyde **35** with the diamines **18** in refluxing ethanol to give the corresponding macrocyclic Schiff base followed by $NaBH_4$ reduction.



B-Synthesis of Macrocyclic Polyether Lactams as Precursors for Azamacrocycles.

In this part we focus on macrocyclic polyether di-and tetralactams not only for being valuable intermediates for the synthesis of azacrowns and related compounds but also for their wide applications in selective noble metal complexing [54,55] and as metal ion selective electrodes [56]. For example, incorporation of an amide linkage in a polyether macrocycle has been found to modify the binding properties of crown ether compounds to favor alkaline earth cations over alkali metal cations [57-59].

The published methods for preparation of macrocyclic di- and tetralactams include the following:-

1 - Reaction of α,ω-dicarboxylic acid derivatives (diester, or diacid dichloride) with various diamines.

2 - Reaction of bis amines with dihalo compounds (containing amide moieties).

3 - Reaction of diol or bis phenol (containing amide moieties) with the appropriate (dihalo compounds).

In most cases, the reactions were carried out under high dilution conditions, which require simultaneous addition of the reactants to a large volume of solvent over an extended period to avoid undesired side products. Macrocyclic tetralactams are produced in some cases as by-products.

Most of the macrocyclic lactams reviewed in the next pages can be readily transformed into the corresponding azacrown compounds using, for example, BH_3 x Me_2S [60].

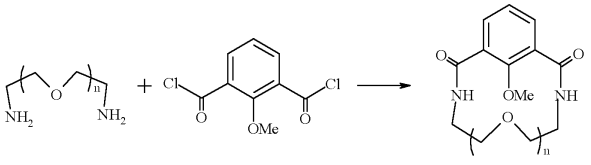
Specific Synthesis of Macrocyclic Polyether Lactams

Preparation of such systems are classified depending on the starting materials as follows:-

1- The Action of Diacid Dichloride on Diamines.

a) Macrocyclic Dilactams Containing One Benzene Unit.

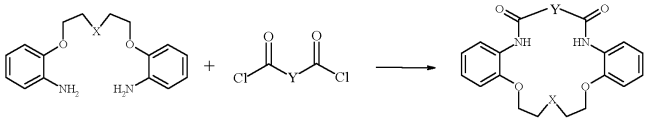
Bartsch and co-workers [61] reported the synthesis of macrocyclic dilactams **54** by cyclocondensation of diamine **52** with diacid dichloride **53** in THF/TEA under high dilution conditions.



52 **53** **54**

b) Macrocyclic Diamides Containing Two or Three Benzene Units.

Under similar conditions to that described by Bartsch and co-workers [61], Formanovskii's group [62,63] and Zhang's group [64] have prepared macrocyclic diamides **56** in 27-96% yield by cyclocondensation of diamine **43** with the appropriate diacid dichloride **55**.

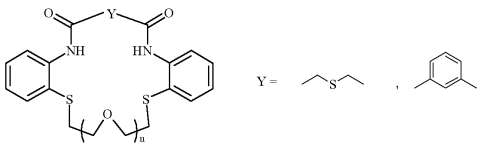


43 **55** **56**

X = O, S, NTs, $(CH_2)_n$,

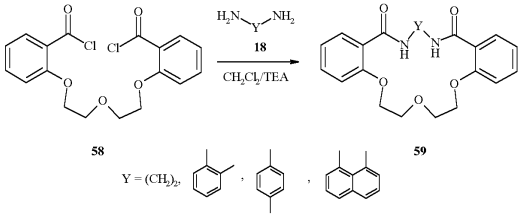
Y = $(CH_2OCH_2)_m$, $(CH_2SCH_2)_m$, $(CH_2NTsCH_2)_m$, m = 0-3, $(CH_2)_n$, n = 1, 2

Similarly, Kumar and co-workers [65] have prepared macrocyclic diamides **57** (n = 1-3) by cyclocondensation of the diacid dichloride **55** with the appropriate diamines.



57

Sharghi and co-workers [66,67] reported the synthesis of some new macrocyclic dibenzotrioxadiamides **59** in which the carbonyl group of the amide moiety is attached directly to the aromatic ring by reaction of the dicarboxylic acid dichloride **58** with the appropriate diamines **18** in CH_2Cl_2. The cyclization does not require high dilution techniques or template metal ions and provides the expected dilactams in high yields ranging from 80% to 95%.

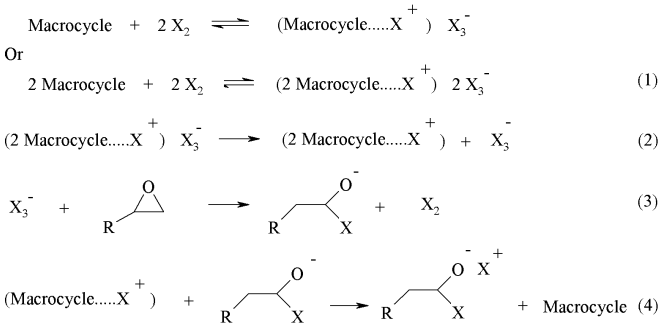


58 **59**

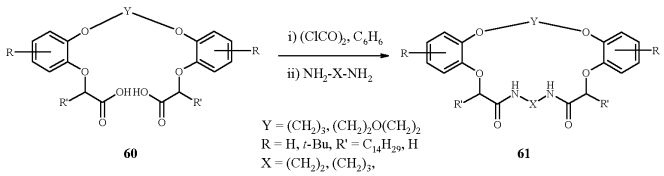
Y = $(CH_2)_2$,

Sharghi and co-workers [68] succeeded in synthesizing a number of macrocyclic diamides in good yields from the reaction of a diacid dichloride with primary diamino compounds in the presence of magnesium oxide-silica gel at room temperature. One advantage of this method is that the reaction proceeds under mild conditions using inexpensive inorganic solids. Moreover, synthetic versatility, no side reactions, no HCl evolution, ease of work up, regenerability of inorganic solids and short reaction time can be considered as advantages of this method.

Sharghi and co-workers [67] also reported the use of derivatives of macrocyclic diamides **59** as catalysts in the highly regioselective halogen promoted cleavage of epoxides with elemental halogen. The epoxides were subject to cleavage by elemental halogen (I_2 and Br_2) in the presence of these catalysts under mild reaction conditions in various aprotic solvents. In this study, reagents and conditions were discovered with which the individual halohydrins are synthesized in high yield and with more than 95% regioselectivity. The results can be discussed in terms of a four step mechanism: (1) formation of charge-transfer complex between catalyst and halogen in which halogen ion (X_3^-) exists as a contact ion pair, (2) release of halogen nucleophile from the complex, (3) reaction of the active nucleophile at the less sterically-hindered site in the epoxide, and (4) regeneration of the catalyst. The major advantages of this method are high regioselectivity, simple regeneration of the catalyst, its re-use through several cycles without a decrease in activity, and ease of workup of the reaction.



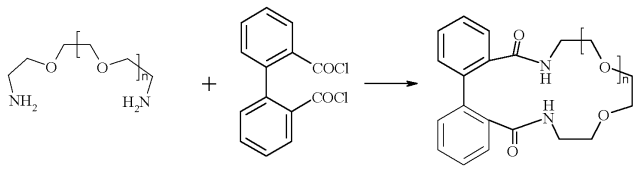
Bartsch and co-workers [69] apply a similar approach for the synthesis of lipophilic macrocyclic polyether diamides **61** as outlined in the following Scheme.



60 **61**

The lipophilic acyclic polyether dicarboxylic acids **60** were converted into diacid dichlorides with oxalyl chloride. Cyclization was accomplished by rapid addition of a mixture of the diamine and triethylamine in CH_2Cl_2 to a stirred solution of the diacid dichloride in CH_2Cl_2 at 0 °C.

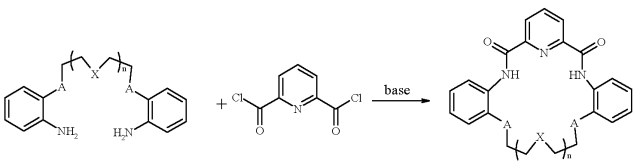
On the other hand, Simonov and co-workers [70] used the high dilution technique to prepare macrocyclic diamide **64** containing the biphenyl moiety by reacting bis amine **62** with 2-{2-(chlorocarbonyl)phenyl}benzoyl chloride (**63**) in basic solution.



62 **63** **64**

c) Macrocyclic Diamides Fused with Pyridine Ring.

Kumar and co-workers [65] and other research groups [71-73] have prepared a number of macrocyclic diamides **67** fused with two benzene units and containing pyridine as a subcyclic unit by reacting the appropriate bis amines **65** with pyridine-2,6-dicarbonyl dichloride (**66**) in basic solution.



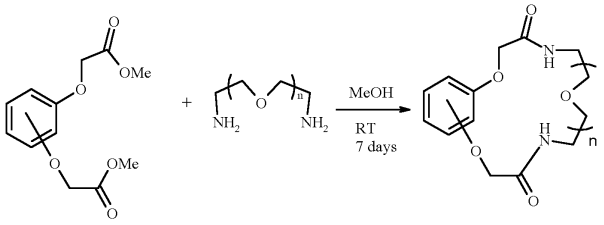
65 **66** **67**

n = 1-3, X = O, S, CH_2, NHTs
A = O, S

2-The Action of Diesters on Diamines.

a) Macrocyclic Diamides Fused with One or Two Benzene Units or Binaphthyl Units.

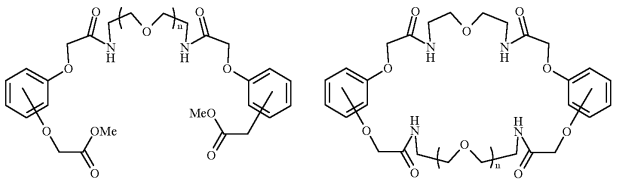
Jurczak and co-workers [74] reported the synthesis of some benzomacrocyclic diamides 69a-c by stoichiometric condensation of a series of diesters 68a-c with diamines 52. They have found that yields of macrocyclic diamides decreased with increasing distance between the ethereal oxygen atoms in the diesters.



68 a-c **52** **69a-c**

a, *o*-; b, *m*-; c, *p*-

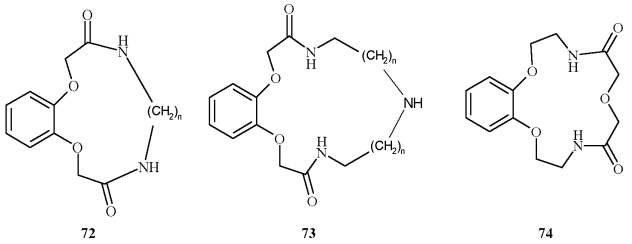
When using diesters **68b**, **68c**, diamidodiesters **70** and macrocyclic tetraamides **71** were obtained together with the target macrocyclic diamides **69b**, **69c**.



70 **71**

m-, n = 2
p-, n = 1, 2

Kumar's group [75] and Jurczak's group [76] used a similar approach to prepare a series of benzomacrocyclic diamides **72-74**.

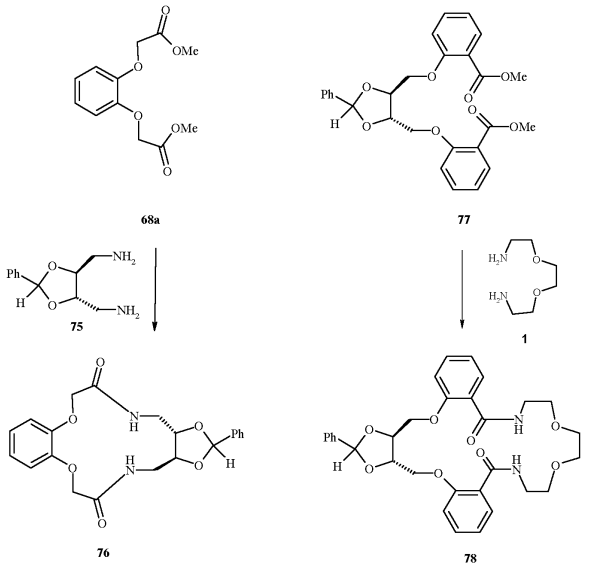


72 **73** **74**

n = 2, 3

Jurczak and co-workers [77] also reported the synthesis of chiral macrocyclic diamides **76** and **78** starting from the chiral diester **77** or the chiral diamine **75** as outlined in the following Scheme.

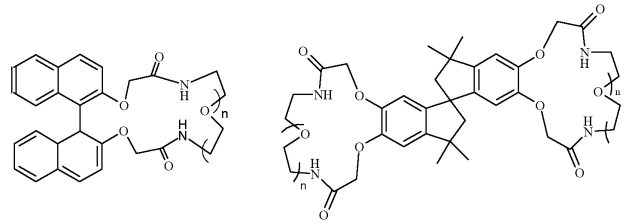
Under similar conditions, macrocyclic diamides **79** and bis(macrocyclic diamide)s **80** have been obtained by reacting the appropriate diesters with the corresponding diamines.



68a **77** **75** **1** **76** **78**

b) Macrocyclic Diamides Fused with Heterocyclic Units.

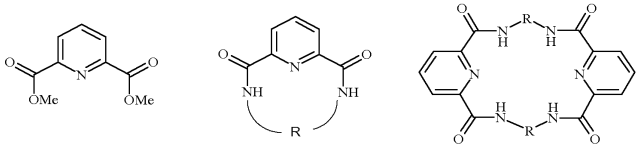
Pyridino-macrocyclic diamides **82** were obtained by cyclocondensation of dimethyl pyridine-2,6-dicarboxylate (**81**) with the appropriate diamines. Some macrocyclic tetramides **83** were isolated in some reactions depending on the structure of the amines [78].



79 **80**

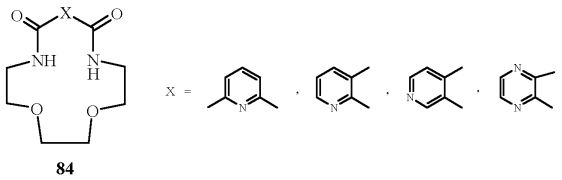
n = 1, 2

Sodium methoxide was found by Jurczak and co-workers to be an effective catalyst in the reaction of diesters with diamines to give the corresponding macrocyclic diamides. The time of the reaction was shortened by about 20 times as compared with previous results. Under these conditions pyridino-, and pyrazinomacrocyclic diamides **84** were obtained in good yields [79].



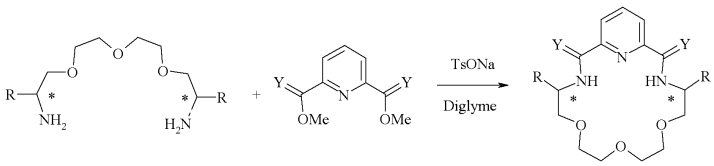
81 **82** **83**

R = $(CH_2)_2O(CH_2)_2$,
$(CH_2)_2O(CH_2)_2O(CH_2)_2$,
$(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2$,
$(CH_2)_3O(CH_2)_4O(CH_2)_3$,
$(CH_2)_3O(CH_2)_2O(CH_2)_2O(CH_2)_3$



84

Bradshaw and co-workers [80] reported the synthesis of chiral pyridinomacro-cyclic diamides **87a** and **87b** in yields of 29% and 25%, respectively, by cyclization of diamines **85a** and **85b** with dimethyl 2,6-pyridinedicarboxylate (**81**) in the presence of sodium tosylate. Pyridinodiamido-crowns **87a** and **87b** were refluxed with Lawesson's reagent in toluene to give dithionoamido-crowns **87c** (88%) and **87d** (90%). Ligands **87c** and **87d** were also prepared in yields of 28% and 8%, respectively, by reacting diamines **85a** and **85b** with *O,O'*-dimethyl 2,6-pyridinedicarbothioate (**86**) in the presence of sodium tosylate.

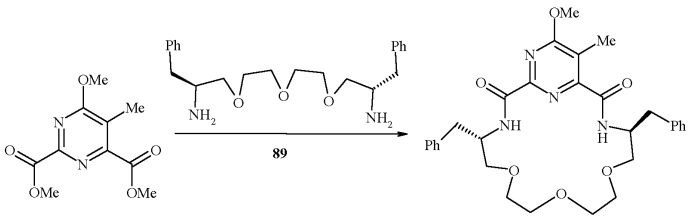


85a, R = Ph
85b, R = $PhCH_2$-

81, Y = O
86, Y = S

87a, Y = O, R = Ph
87b, Y = O, R = $PhCH_2$-
87c, Y = S, R = Ph
87d, Y = S, R = $PhCH_2$-

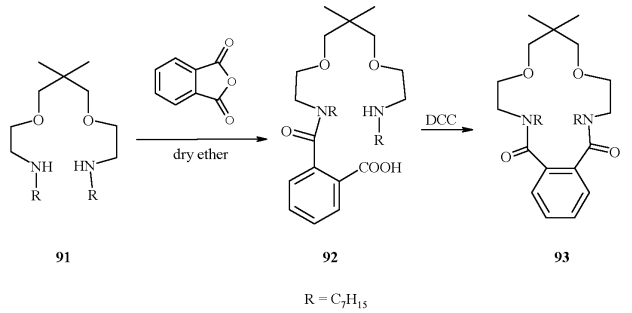
Redd, Bradshaw and co-workers [81] also prepared chiral dibenzyl-subsituted pyrimidino-crown diamide **90** by reacting dimethyl 4-methoxy-5-methyl-2,6-pyrimidine dicarboxylate (**88**) with the diamine derivative of chiral dibenzyl-substituted tetraethylene glycol **89** in basic conditions.



88 **89** **90**

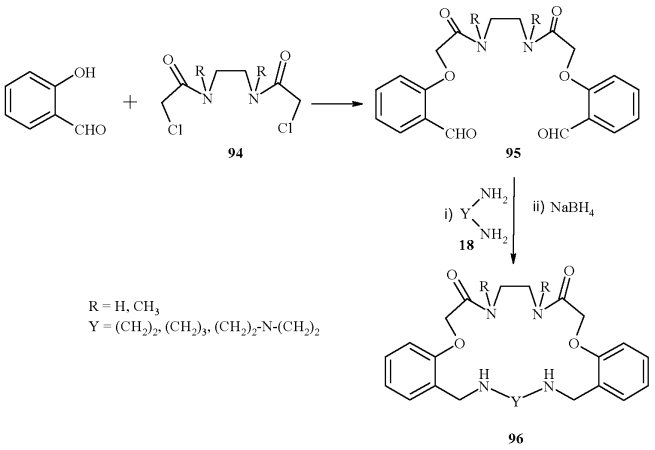
3- The Action of Diacid Anhydrides on Diamines.

Attiyat and co-workers [56] reported the preparation benzodioxadiamide **93** from *N,N*-diheptyl-5,5-dimethyl-3,7-dioxanonanediamine (**91**) by first treating it with phthalic anhydride to give the corresponding monoamide **92**, which was cyclized *in-situ* using *N,N*-dicyclohexylcarbodiimide (DCC) to give the corresponding cyclic dioxadiamide **93**.



4- From Cyclic Schiff Bases Containing Bis-Diamide in the Ring.

Lindoy and co-workers [82] reported the synthesis of some nitrogen-oxygen dibenzo-macrocyclic ligands containing two amide groups **96** by cyclocondensation of the dibenzo-containing diamidodialdehydes **95** with the appropriate diamines **18** followed by reduction of the intermediate cyclic Schiff bases. The dialdehydes were prepared by treating 2 equivalents of salicylaldehyde with bis(α-chloroamide)s **94**.



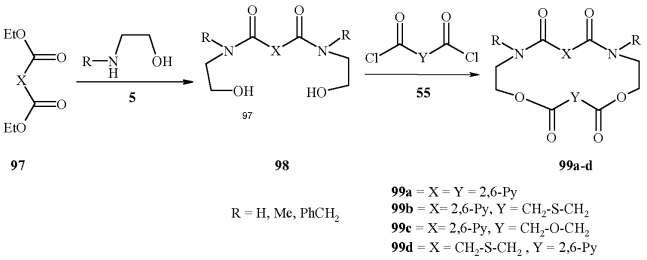
Reinhoudt and co-workers [83] used a similar approach to synthesize chiral derivatives of 96.

5- From the Reaction of Diacid Dichlorides and Diols Containing Bis-Amides.

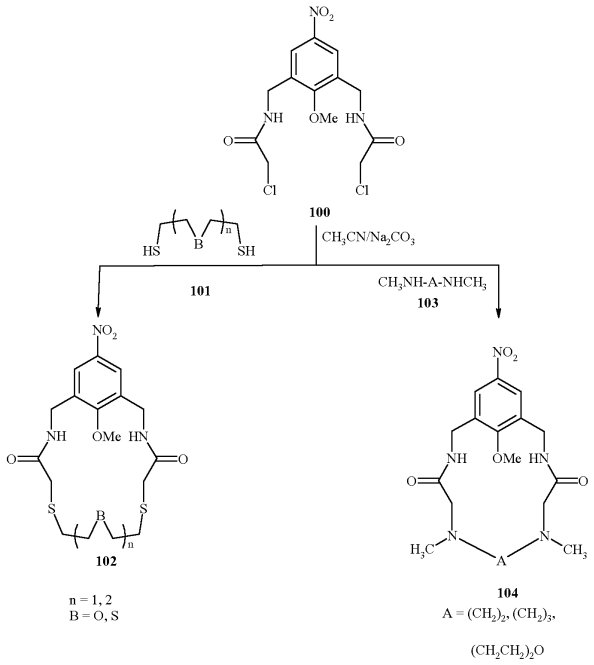
Kumar and co-workers [84-86] prepared diamide-diester macrocycles **99a-d** with pyridine and thioether ligating units by treatment of the appropriate diacid dichloride **55** and the corresponding diols **98**. The diols **98** were obtained by aminolysis of each diester of diethyl pyridine-2,6-dicarboxylate (**97**) (X = 2,6-pyridinyl) and diethyl thiodiglycolate with the appropriate amino alcohol **5**.

6-Reaction of Diamines or Dithiols with Dihalides.

Bradshaw and co-workers [87,88] prepared *p*-nitroanisole-containing macro-cycles **102** and **104** in 35-80% yields by reacting the bis(α-chloroacetamide) compounds **100** with the appropriate dithiols **101** or diamines **103** in refluxing acetonitrile containing sodium carbonate under high dilution conditions. Nucleophilic cleavage of the internal methoxy group of macrocycles **102**, **104** with LiI occurred smoothly in refluxing pyridine to give the corresponding *p*-nitrophenol-containing macrocycles. The amidomethylation reaction (Einhorn reaction) was used to prepare bis(α-chloroacetam-ide) compounds **100** in one step from commercially available starting materials.



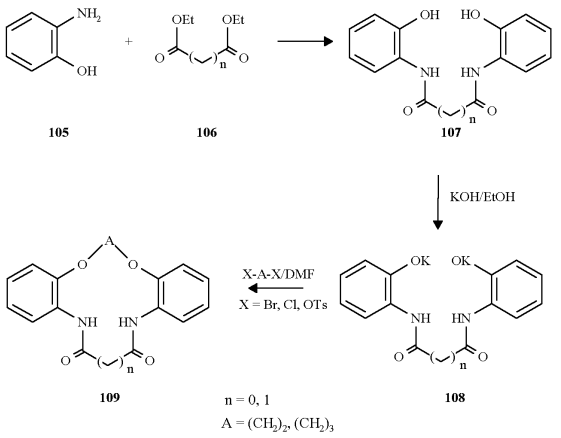
Some interesting 2+2 macrocyclization by-products were isolated from the above reactions in 1-5% yields. Higher yields of these products would be expected if the cyclization reaction were run in more concentrated solution.



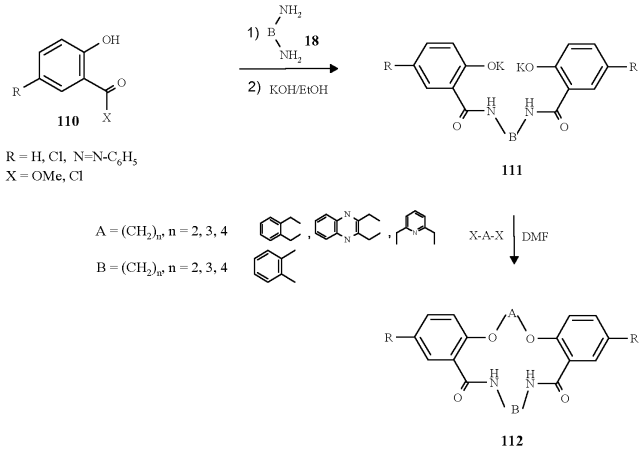
7- Reaction of Bis Phenols with Dihalo or Ditosylate Compounds.

Ibrahim and Elwahy [89] reported the synthesis of some 13-16-membered macrocyclic diamides **109** by treating dipotassium salts **108** (obtained upon treatment of the corresponding bis(phenol)s **107** with ethanolic KOH) with the appropriate dihalides in refluxing DMF. Compounds **107**

were readily obtained by condensing *o*-aminophenol **105** with the appropriate diester **106** in refluxing xylene.

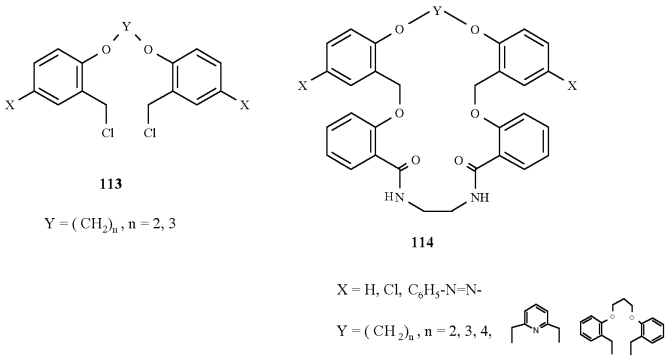


Similarly, the 14- and 17-membered macrocyclic dibenzo- and tribenzodioxadiamides and trioxadiamides **112** have been prepared by the same authors in moderate to good yields (40-90%) by treating dipotassium salts **111** (obtained by first treatment of methyl salicylate (**110**) (X = OMe) or 2-hydroxybenzoyl chloride derivatives **110** (X = Cl) with the appropriate diamines **18** to give the corresponding bis(phenols) **111** followed by treatment with ethanolic KOH) with the appropriate dihaloalkanes or ditosylates in DMF [90,41,42].



Ibrahim and co-workers [91] have also prepared derivatives of ring system **112** containing bis azo groups suitably located in the molecules to act as potential chromophores useful for spectrophotometric applications. Other derivatives of **112** with allyl substituents have also been prepared aiming at their use as promising monomers for the synthesis of polymer-supported macrocycles [40]. Attaching the crown compounds to a polymeric backbone facilitates its retrieval and alleviates the need to use such compounds on a large scale which is inhibited by their expense.

Ibrahim, Elwahy, Abbas, and co-workers [92,93,41] also reported the synthesis of some 23-, 24- and 31-membered macrocyclic diamides **114** in 40-50% yields by reacting dipotassium salt [B = $(CH_2)_2$] **111** with dihalo compounds **113**. The latter were prepared from salicylaldehyde by first alkylation with the appropriate dihalo compounds to give the corresponding dialdehydes followed by reduction with $NaBH_4$ and subsequent chlorination with $SOCl_2$ in chloroform solution.



The exceptional good yields in the macrocyclization of the dipotassium salt can partly be explained as a result of the restricted rotational freedom in the dianion (Figure I) caused by high resonance stabilization and hydrogen bonding. This results in a relatively small loss in entropy on cyclization allowing ring closure to occur in high yields without a need for preorganization of the starting materials [90].

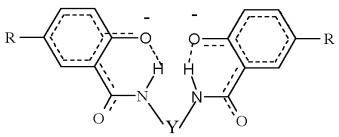


Figure I

C- Direct Synthesis of Condensed Azacrown Ethers.

In this section, we focus on the direct synthesis of condensed azacrown ethers without passing through intermediate macrocyclic schiff bases or macrocyclic lactams.

The reported methods for the direct synthesis of condensed azamacrocycles include the following:-

1. Reaction of α,ω-diamines with the appropriate dihalo or ditosylate compounds.
2. Reaction of diol or bisphenol (containing amine moieties) with the appropriate dihalides or ditosylate compounds.
3. 1,3-Dipolar cycloaddition reactions of each of azide and nitrilimine to alkenyl or alkynyl moieties.
4. The use of Mannich reaction [94-96] as a tool for preparation of phenol- containing azacrown ethers. Mannich reactions have also been used to functionalize

the azacrown compounds with phenolic unit as side arms. The reaction proceeds *via* initial conversion of secondary amine to a (methoxymethyl)amine which is an active electrophilic reagent in the Mannich reaction and reacts readily with electron rich aromatic compounds such as phenols.

Introducing phenolic units into the framework of mono- and polycyclic ligands is important for many reasons. First, phenolic groups with the OH functions inside the macrocycle cavity are potential complexing sites for metal cations and some organic substances. Second, the phenolic OH groups of a macrocyclic system as well as the *para* position of the phenol ring can be functionalized with different substituents, which can affect the complexing ability of the ligands. In addition the phenolic group are appropriate sites for attaching the macrocycles to inorganic solid support.

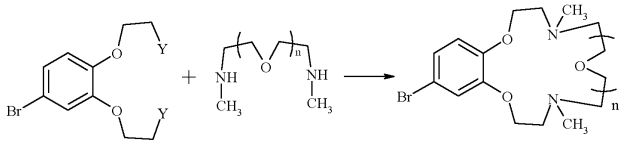
The Mannich reaction, as a method for modification of azacrown macrocycles with hydroxybenzyl function, has some advantages when compared to alkylation of the azacrown by benzyl halides. In fact, aminomethylation of the phenols allow the preparation of azamacrocycles containing both electron donating and electron withdrawing groups in the substituted phenolic rings. The preparation of such compounds by alkylation is not always convenient because of the difficulties in preparing the starting benzyl halides and the necessity of protecting the phenolic hydroxy group.

Specific Synthesis of Azacrown Ethers.

1- Azacrown Ethers Fused to Aromatic Derivatives.

a) One Benzo Unit.

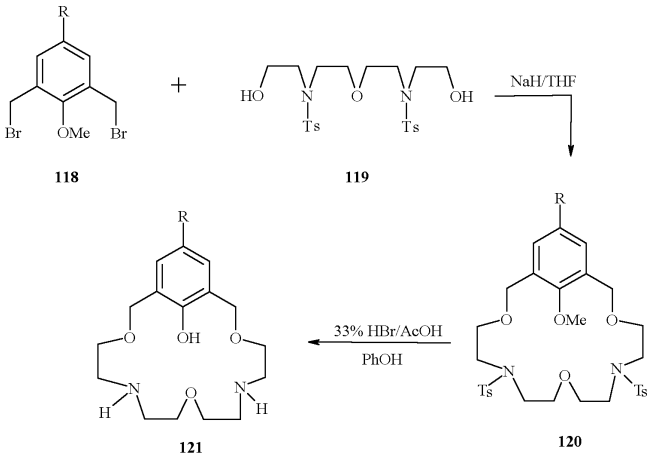
Gromov and co-workers [97] reported the synthesis of monobenzodiazacrown ethers **117** by reacting 4-bromo-1,2-bis(2-haloethoxy)benzenes **115** with polyoxaalkanes **116** containing terminal NHMe groups.



115 **116** **117**

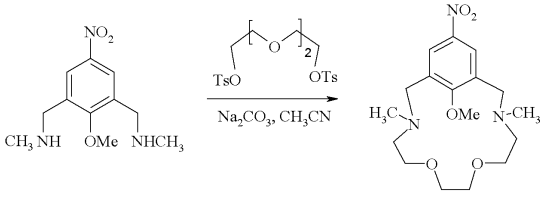
Y = halogen
n = 1, 2

Xue and co-workers [98] reported the synthesis of new phenol containing diazacrown ethers **121** by adding a suspension of NaH in THF to a mixture of 2,6-bis(bromomethyl)-4-substituted anisole **118** (R = CH_3, Cl) and 3,9-ditosyl-6-oxa-3,9-diazaundecane-1,11-diol **119** to give the azacrown ether derivatives **120**. Treatment of the later with 33% HBr in acetic acid and excess phenol led to detosylation and demethylation to afford 50% yields of the diazacrown ethers **121**.



118 **119** **121** **120**

Bradshaw and co-workers [88] used the bis amine **122** as a rigid building block containing the chromophoric NO_2 group to prepare the monobenzodiazamacrocycle **123** by ring closure of **122** with triethylene glycol ditosylate in acetonitile containing Na_2CO_3.



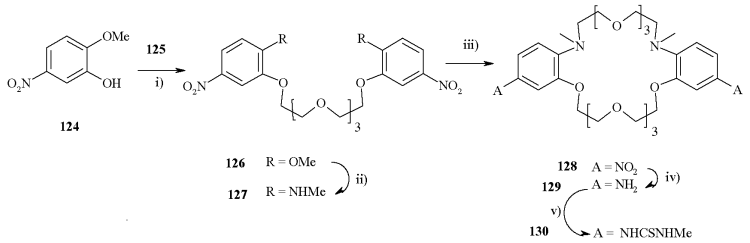
122 **123**

b) Two Benzo Units.

Kubo and co-workers [99] reported the synthesis of a multisite receptor capable of cooperative complexation of cationic and anionic species in an induced fit fashion. The synthetic strategy is shown in the following Scheme.

The commercially available compound **124** was reacted with 3,6,9-trioxaundecane-1,11-diyl bistosylate **125** in the presence of K_2CO_3 to produce podand **126** followed by nuleophilic reaction with $MeNH_2$ to afford **127** in quantitative yield. Again the Williamson synthesis with **125** was performed to give the synthon **125** which underwent reduction to produce **129**. Subsequent reaction with MeNCS led to the formation of the azamacrocycle **130**.

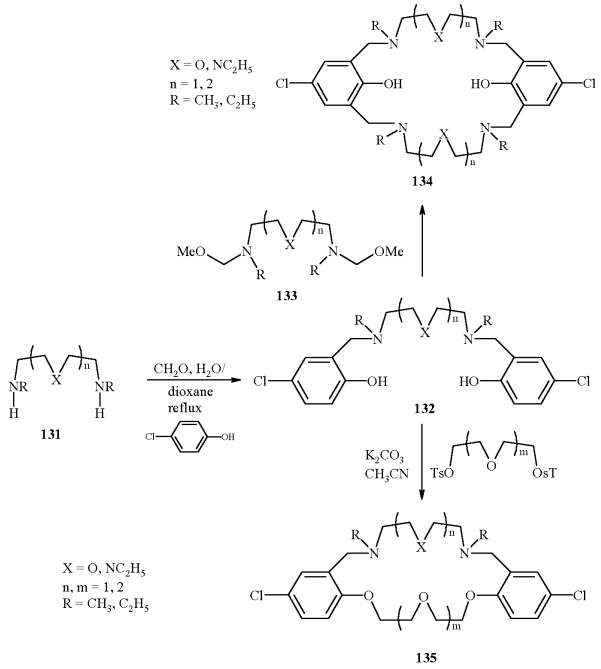
Using the Mannich reaction, Bradshaw and co-workers [100] synthesized a series of dibenzoazacrown ethers **134** by ring closure of the bis phenol **132** with bis(methoxymethyl)-substituted diamines **133** on positions *ortho* to the OH-group. Starting intermediates **132** were prepared from *p*-chlorophenol, the appropriate secondary diamine **131**



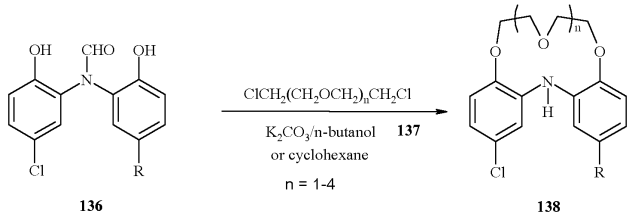
Reagents and conditions: i) 3,6,9-trioxaundecane-1,11-diyl bistosylate (**125**), K_2CO_3, dry acetone, reflux; ii) methanolic solution of $MeNH_2$ (40% v/v) in sealed tube, 100 °C; iii) 3,6,9-trioxaundecane-1,11-diyl bistosylate (**125**), NaH, dry DMF, 80 °C; iv) 10% Pd/C, H_2 (2 atom), EtOH, rt; v) MeNCS, CH_2Cl_2, 40 °C, 40%.

and paraformaldehyde in refluxing aqueous dioxane (or refluxing xylene).

Using the bisphenol **132**, the same authors constructed dibenzomacrocycles **133** by reacting **132** with the appropriate oligoethylene glycol ditosylate in refluxing CH_3CN containing K_2CO_3.

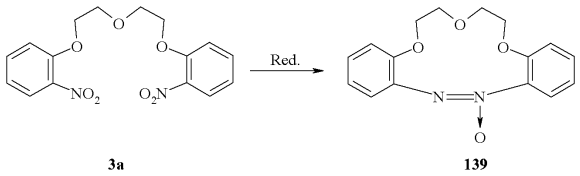


Töke and co-workers [101] used the bis phenol **136** to prepare a series of dibenzopolyoxamonoazacrown compounds **138**. Thus bis-alkylation of **136** with bis(chloro) ethers **137** in *n*-butanol containing K_2CO_3 afforded 10-51% yields of **138**.



It should be emphasized that during the cyclization of **133**, the *N*-formyl group cleaved resulting in the free macrocycle **138** with a secondary amine function in each case. The presence of this protective group however, proved to be necessary at least in the first stage of the bis-alkylation process to avoid the formation of *N*-alkylated products.

Biernat and co-workers [102] reported the synthesis of 13-membered dibenzo-azacrown ether **139** with an azoxy subunit in the macrocycle by the reduction of the open chain dinitro compound **3a** using stannite under strong alkaline conditions.



c) Azacrown Ethers Containing a Phenyldinaphthomethane Subunit.

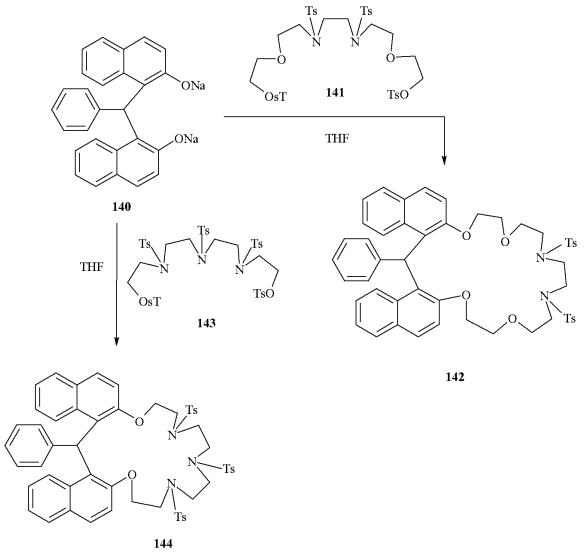
Clegg and co-workers [103] reported the synthesis of two azacrown ethers, **142** and **144**, containing a phenyldinaphthomethane subunit by reacting disodium salt **140** with the appropriate ditosylate **141** and **143**, respectively, in THF.

2- Azacrown Ethers Fused with Heterocyclic Rings.

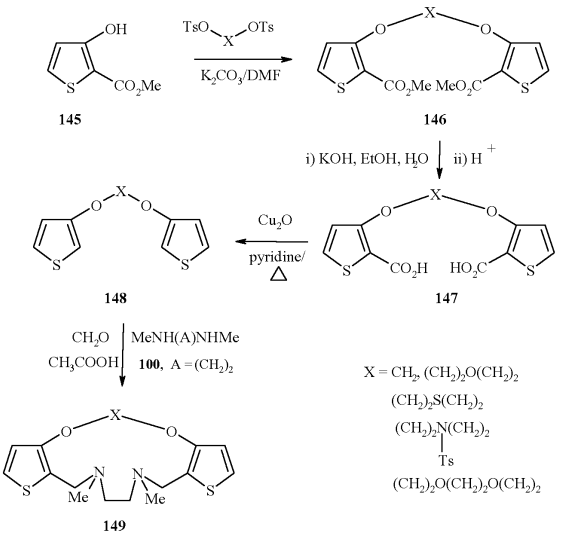
a)Azacrown Ethers Fused with 5-Membered Heterocycles.

i) Thiophene.

Several thiophene containing macrocycles **149** have been reported by Barker and co-workers [104]. The preparation of these compounds was accomplished according to the following Scheme. Initial bridging of the 2-carbomethoxy-3-hydroxythiophene (**145**) was accomplished by reaction with the appropriate ditosylate to give the diester **146**. Once bridged, the carbomethoxy protecting group was hydrolyzed to give **147**. Subsequent decarboxylation by heating in pyridine in the presence of cuprous oxide catalyst gave **148**. After the thiophene-2-position



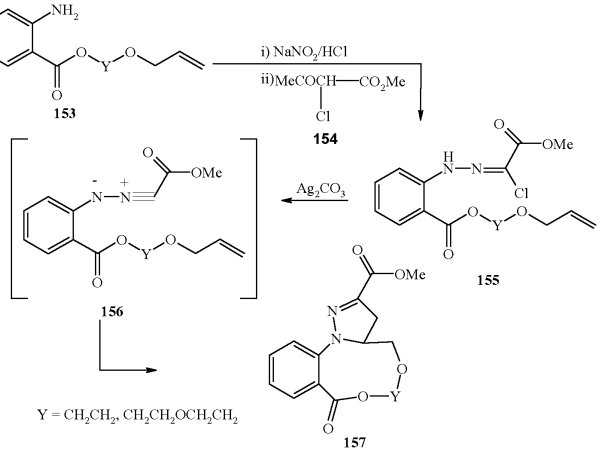
was revealed, Mannich reaction with diamine **100** closed the ring to afford **149**.



Likewise, Halfpenny and co-workers [105] reported the synthesis of thiophene containing azacrown ether **152** by ring closure of 3,4-bis[5'-(3''-thienyloxy)-3'-oxapentyloxy]thiophene (**151**) upon reaction with piperazine *via* the Mannich reaction. Compound **151** was obtained in 5 steps starting from diethyl 3,4-dihydroxythiophene-2,5-dicaroxylate (**150**).

ii) Pyrazole.

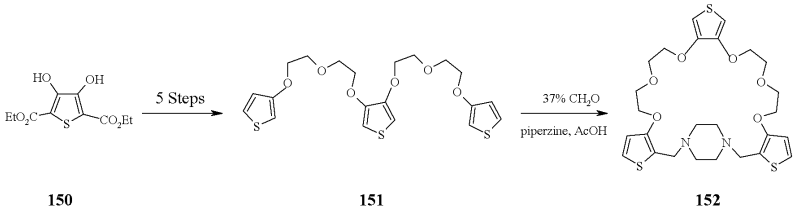
Zecchi and co-workers [106] described an application of the intramolecular nitrilimine cycloaddition methodology to the synthesis of azacrown ethers **157** having the nitrogen incorporated in the pyrazole ring. According to the usual procedure the nitrilimine **156** was generated *in situ* upon basic treatment of the corresponding hydrazonyl chloride **155** followed by intramolecular cycloaddition of the nitrilimine group to the ethenyl moiety. Compound **155** was obtained by diazotization of **153** followed by coupling with methyl chloroacetoacetate (**154**).

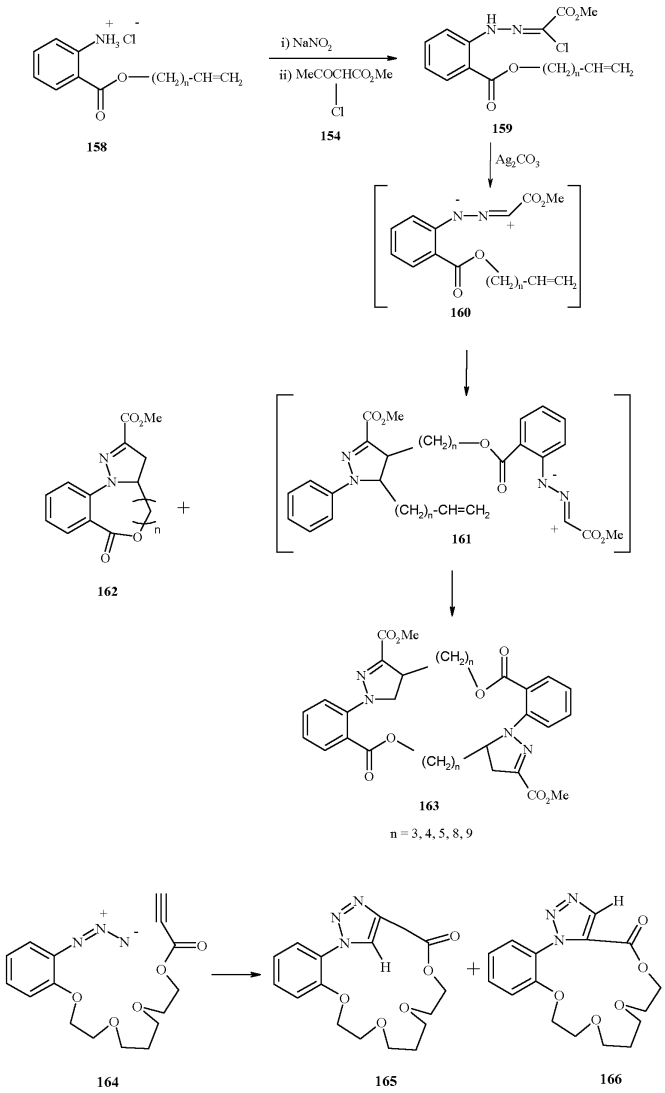


On the other hand, diazotization of amine hydrochloride **158** followed by coupling with methyl chloroacetoacetate **154** afforded the hydrazonyl chloride **159**. The nitrilimine **157** generated *in situ* upon basic treatment of **159** gave intramolecular cycloadduct **162** together with their bis cyclic analogs **163**. The latter was formed *via* initial intermolecular cycloaddition to give **161** followed by intramolecular cycloaddition. The synthetic strategy is outlined in the following Scheme [107].

iii) 1,2,3-Triazole.

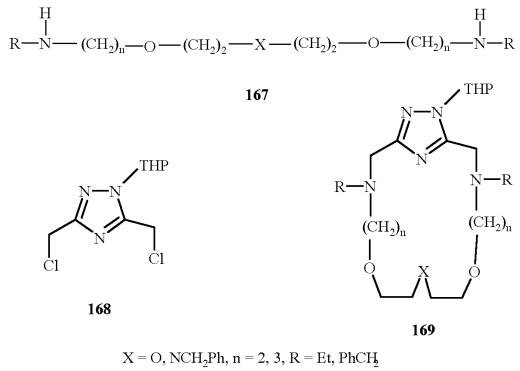
L'abbe and co-workers [108] also used the 1,3-dipolar cycloaddition reaction as a tool for the formation of 1,2,3-triazoloheteromacrocycles **165** and **166** *via* intramolecular cycloaddition of the azide moiety of compound **164** to its ethynyl group.



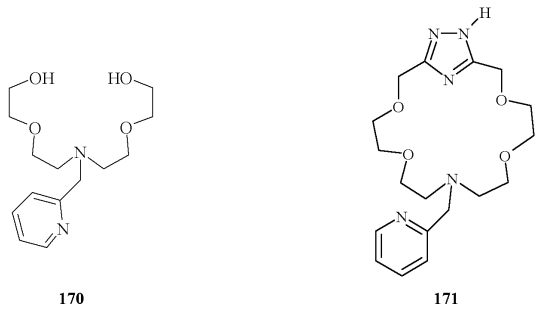


iv) 1,2,4-Triazole.

Bradshaw and co-workers [109] obtained the 1,2,4-triazolomacrocycles **169** by reacting the appropriate polyamines **167** with 2-tetrahydropyranyl-3,5-bis(chlorometh-yl)-1,2,4-triazole **168**.

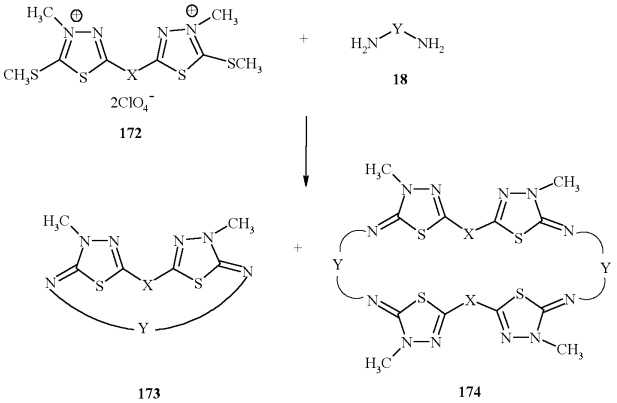


Bradshaw and co-workers [110] have also prepared triazolomacrocycle **171** by cyclization of the protected aminodiol **170** with **168** in THF containing NaH. The THP-protecting group of **169** and **171** was cleaved in methanol saturated with HCl.



v) 1,3,4-Thiadiazole.

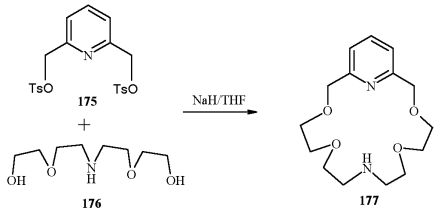
Molina and co-workers [111] reported the synthesis of heteromacrocycles **173** and **174** containing 1,3,4-thiadiazole rings as subunits. The macrocyclization step in this methodology involves the non-templated reaction of bis(4-methyl-5-methylthio-1,3,4-thiadiazolium) diperchlorate **172** with the appropriate diamino compound **18**, which was carried out in the presence of triethylamine, with dry DMF as solvent. The 2,2'-spacer could be aliphatic, aromatic or heteroaromatic, while the structure of the 5,5'-spacer can be chosen by the diamino compound used as a reagent. The stoichiometry of the macrocycle, thus obtained, seems to be dependent on the length and rigidity of both the 2,2' and 5,5'-spacers.



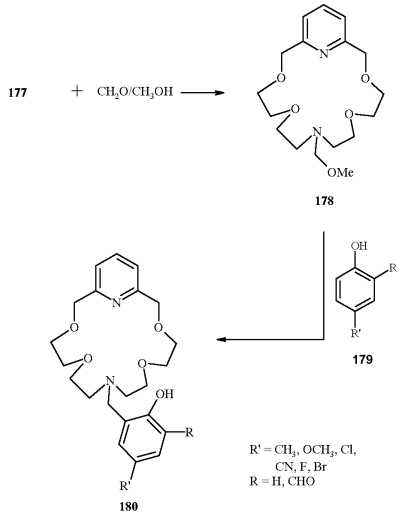
b) Azacrown Ethers Fused with 6-Membered Heterocycles.

i) Pyridine.

Bradshaw and co-workers [110] reported the synthesis of pyridinomonoazamacrocycle **177** by reacting aminodiol **176** with ditosylate **175** in THF containing NaH.



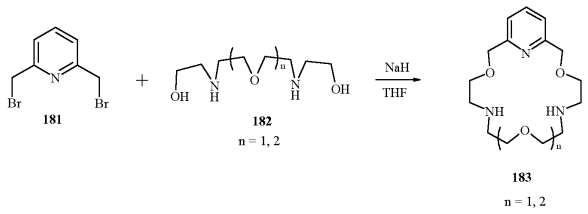
The same authors [112] also reported the use of Mannich reaction as a tool to attach phenolic units to the crown ring as side arms as outlined in the following Scheme.



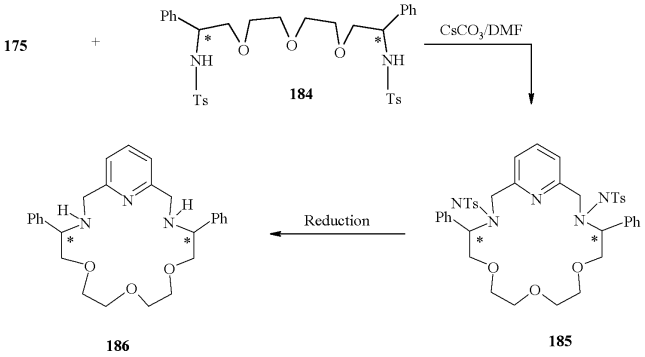
The *N*-methoxymethyl derivative **178** was prepared through the condensation of **177** with paraformaldehyde in dry methanol. Treating of **178** with various phenols **179** (R =H) in refluxing benzene give the proton ionizable pyridinoazacrown ethers **180**.

Mannich reaction is also a useful approach for the preparation of oxime and Schiff base-containing azacrown ethers *via* reaction of **178** with 5-bromosalicylaldehyde **179** (R = CHO) to produce the corresponding *N*-(2'-hydroxy-3-carbonyl)-substituted azacrown derivatives **180** followed by reaction with the appropriate amines.

Xue and co-workers [113] reported the synthesis of pyridinodiazacrown ether **183** by the reaction of 2,6-bis(bromomethyl)pyridine (**181**) with the appropriate diol **182** as outlined in the following Scheme.



On the other hand, Bradshaw and co-workers [80] reported the synthesis of chiral pyridinodiazacrown ethers **186** by first reacting the bis tosylamide **184** with 2,6-pyridine dimethyl ditosylate (**175**) in the presence of base to give **185** followed by removal of the *N*-tosyl groups using sodium amalgam in the presence of dibasic sodium phosphate in methanol.



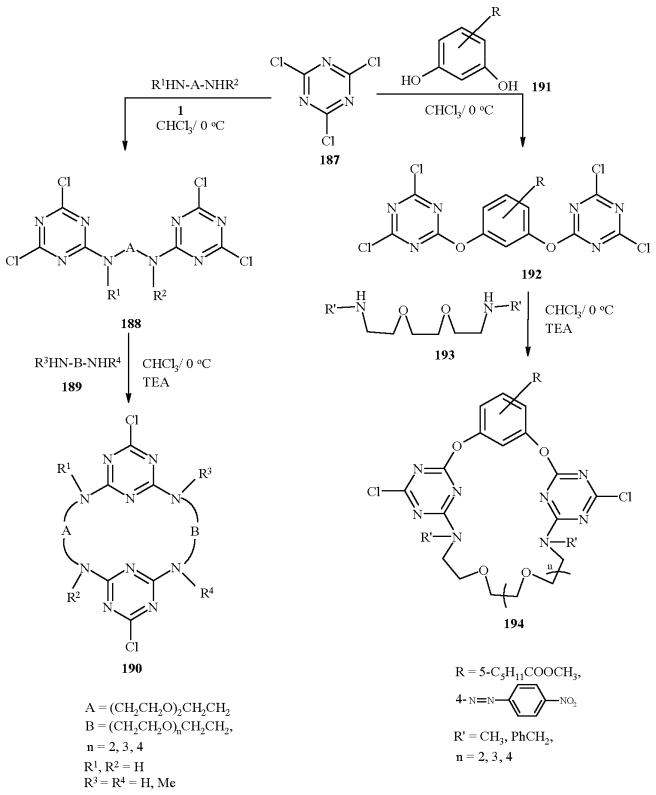
ii) 1,3,5-Triazine.

Graubaum and co-workers [114,115] reported the synthesis of macroheterocycles **190** and **194** containing 1,3,5-triazine subcyclic units by reacting each of bis(4,6-dichloro-1,3,5-triazin-2-yl)diamine **188** and bis(4,6-dichloro-1,3,5-triazin-2-yloxy)benzene **192** with the appropriate diamines **189** and **193**, respectively. Compounds **188** were obtained by aminolysis of 2,4,6-trichloro-1,3,5-triazine **187** with diamine **1**. However, **192** was obtained by the reaction of **187** with 1,3-dihydroxybenzene derivatives **191**.

Reactivity and Applications of Azacrown Ethers.

A) Cation Complexation.

The azacrown ethers have complexation properties that are intermediate between those of the all-oxygen crowns and those of the all nitrogen cyclams. An N for O replacement generally weakens binding of alkali metal cations. On the other hand, addition of nitrogen atoms favors transition metal cation binding. Cation complexation constants were determined for various mixed-donor macrocyclic ligands in 95% methanol for monovalent silver and for divalent cobalt, nickel, copper, zink, cadmium and



lead. The ligands vary not only in the identity of the heteroatoms but also in their relative replacement. Ring size varies from 16 to 19 members and spacing between heteroatoms varies from one carbon to four. For all of the cations studied, altering oxygen to nitrogen increases cation binding strongly. This is expected for transition metal ions and opposite to the trend observed for alkali metal cations. Generally, the vast families of heterocyclic structures containing O, S and N that have been tested are useful as cation binders. The selectivities of such molecules for alkali, alkaline earth or transition metals depend upon ring size and the number and nature of donor atoms. Smaller rings with more S or N atoms will favor transition metals while larger rings having all or mostly oxygen donors will favor alkali metals [116-121]. Many structure changes have been made to azacrown structure to enhance their complexation abilities. A great improvement in complexation ability and selectivity has been observed when proton ionizable units were attached to the crown ring as side arms or introduced inside the macrocyclic cavity [13,109]. Phenolic groups are widely used proton ionizable substituents. Deprotonation of the phenolic groups in alkaline media is an additional factor in increasing their complexing ability and selectivity. Proton ionizable crown compounds also alleviate the need to have hard anions (chloride, nitrate, sulfate) to cotransport with the metal cations across bulk liquid and liquid surfactant membranes [93-95,99,122,123].

In addition to the applications of crown compounds in selective metal extraction, many other applications depend also on their abilities to form complexes with metal cations [124]. For example, their abilities to form complexes with some radioisotopes have provided a means to deliver the radioisotope to specific sites in the body in order to improve Tc-based diagnostic imaging agents for the heart, kidney and brain [125]. One of the most interesting reported medical applications of some functionalized macrocyclic compounds and their metal complexes is their use as antibody labeling through the covalent attachment of the macrocycles or their complexes to the antibodies [126]. The extraction of certain isotopic cations by crown compounds plays an important role in treatment of nuclear waste to separate the long-living radioactive elements from the waste effluent in order to reduce to a minimum the volume of materials that need highly secure underground storage [127,128].

Moreover, the ability of crown compounds to convert hydrophilic metal ions into large hydrophobic cationic species soluble in organic solvents of low polarity has been widely exploited in organic synthesis. Problems of co-solubility between reaction reactant and reagent can be overcome allowing the reaction to be carried out under mild conditions. Reagent solubilization, phase transfer catalysis, anion activation, cation inhibition along with several of applications have been previously discussed [124, 129,130].

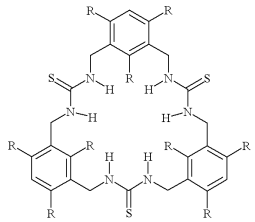
B) Anion Complexation.

For most of the anion receptors, anion binding is due to coulombic interaction (in positively charged receptors) and/or interaction with Lewis acid sites (in organometallic receptors). However, in nature, neutral anion binding proteins are known which bind the anions only *via* hydrogen bonding interactions [131-139].

A number of molecules possessing urea or thiourea groups have been designed as neutral receptors for various anions. These groups have the strong hydrogen bonding ability of urea and thiourea groups. For example, compound **A** showed selective binding to AcO^- while compound **B** showed selective binding to $H_2PO_4^-$ [128,131]. Complex formation with anions was followed by ^1H NMR spectroscopy. The urea hydrogen atom resonance was broadened and shifted downfield over 1 ppm upon complexation of the anion.

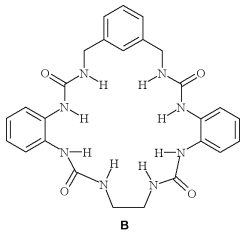
C) Dication Complexation.

Heteronuclear metal ion receptors have been designed for simultaneous binding of soft-transition and hard-alkali or alkaline earth ions in one molecule or supramolecular aggregate [111]. These receptors have received considerable attention because bringing two metal ions together (intermetallic distance < 4 Å) affects the redox properties

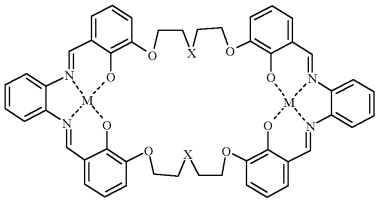


A

R = H, Et



B

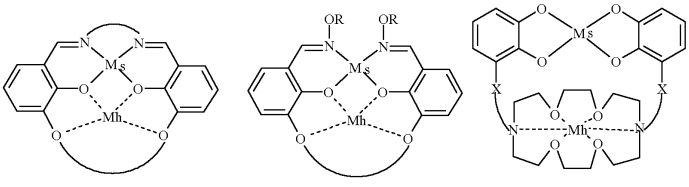


M = Cu, Zn, Ni
X = O, S

Figure III

of the complexed transition metal cation. Other areas of interest are bimetallic activation and catalysis [140]. In order to perform "double" coordination, the ligand should possess two sets of binding sites. One site is a multidentate ligating fragment for complexation with alkali or alkaline earth metal ions and the other is one, or several soft chelating groups providing the transition metal ion with an appropriate geometry for coordination.

A number of heteronuclear metal ion receptors and their complexes have been reported [140]. Reinhoudt and coworkers [141] elaborated approaches to the synthesis of salen and salophen type complexes having polyglycol chains as multidentate binding sites for hard cations. Schiff base-substituted aromatic moieties of these ligands chelate the transition metal ions mostly in square planar coordination (Figure II a, b). Replacement of the polyglycol chains with cyclic crown ether fragments should result in enhanced affinity towards a hard cation and provide the receptors with additional rigidity. Hosseini and coworkers [142] developed catechol-based diazacrown ether receptors (Figure II c) which were expected to coordinate a transition metal ion through the 1,2-dihydroxy groups of the catechol in either square planar or tetrahedral modes and bind alkali or alkaline earth metal ions by the azacrown portion.



a b c

Ms = soft metal ion
Mh = hard metal ion

Figure II

Dinuclear copper complexes without a bridging ligand are interesting as models for copper proteins [143]. Heterodinuclear complexes (Figure III) can be easily obtained by complexation of "hard" cations like alkaline and alkaline earth cations in the crown ether cavities of these macrocyclic ligands with immobilized transition-metal cations [53].

D) Cation-Anion Complexation.

Ion pair recognition, the simultaneous complexation of cationic and anionic guest species by multisite receptors is a new, emerging and topical field of coordination chemistry [144-148]. These heteroditopic ligands can be designed to exhibit novel cooperative and allosteric behavior whereby the binding of one charged guest can influence, through electrostatic and conformational effects, the subsequent coordination of the pairing ion. Such systems have potential as new selective extraction and transportation reagents for ion pair species of environmental importance. This includes extraction of toxic anion guest species from simulated aqueous nuclear waste *via* cooperative ion-pair binding effects [147]. Incorporation of thiourea units as efficient anion-binding sites onto the building block of crown compounds (for example compound **127**) can create a multisite receptor for a unique coordinative recognition of cationic and anionic species [98].

On the other hand, molecules containing two crown moieties separated by a polyamine linking group will sandwich cations and it has been postulated that the linker between the two crown rings, which will form a pocket, should be capable of complexing the counter ion of the cation [144].

E) Molecular Recognition.

Crown compounds containing chiral groups on the ring can show selective complexation of one enantiomer in a racemic mixture. This chiral recognition is due to unfavorable secondary interactions between chiral host and chiral guest, which selectively destabilize the binding of one of the two enantiomers [149]. The degree of destabilization and thus, selectivity depends on the substrate and more importantly, the design of chiral receptors. Since Cram and his coworkers published their pioneering studies on the use of chiral macrocyclic ligands in enantiomeric recognition, a great number of chiral molecules have been synthesized and reviewed [150-159]. These compounds play an important role in determination of concentration and separation of single enantiomeric forms of amino acids

Molecules that possess the capacity to selectively detect enantiomers are of interest to researchers in organic,

biological, pharmaceutical and analytical chemistry. Enantiomeric recognition of organic amines and ammonium salt by chiral macrocyclic ligands is an area of molecular recognition that is receiving attention at the present time [150-154]. Examples of enantiomeric discrimination can be found in many natural processes such as enzyme-substrate interactions, immunological responses, the mechanism of drug action and the storage and retrieval of genetic information. The successful design, synthesis and use of macrocyclic ligands capable of selective recognition of other species is of great interest to workers in catalysis, separation, and other areas involving chiral molecular recognition [150-152]. The study of the enantiomeric ligands is of significance because these compounds are basic blocks of biological molecules with versatile abilities to form complexes with a variety of molecules [153-159]. Careful characterization of such synthetic systems could lead to better understanding of natural systems.

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