THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

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AZA-CROWN MACROCYCLES

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The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds constitutes one of the broadest and most complex branches of chemistry. The diversity of synthetic methods utilized in this field, coupled with the immense physiological and industrial significance of heterocycles, combine to make the general heterocyclic arena of central importance to organic chemistry.

The Chemistry of Heterocyclic Compounds, published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance which impinge on almost all aspects of modern organic and medicinal chemistry, and for this reason we initiated several years ago a parallel series entitled *General Heterocyclic Chemistry*, which treated such topics as nuclear magnetic resonance, mass spectra, photochemistry of heterocyclic compounds, the utility of heterocyclic compounds in organic synthesis, and the synthesis of heterocyclic compounds by means of 1,3-dipolar cycloaddition reactions. These volumes are of interest to all organic and medicinal chemists, as well as to those whose particular concern is heterocyclic chemistry.

It has become increasingly clear that this arbitrary distinction created as many problems as it solved, and we have therefore elected to discontinue the more recently initiated series *General Heterocyclic Chemistry* and to publish all forthcoming volumes in the general area of heterocyclic chemistry in *The Chemistry of Heterocyclic Compounds* series.

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Preface

We have been interested in the synthesis and complexing properties of macrocyclic ligands since 1968. Our work concerns, in general, the crown ethers and thioethers and their diester analogs. Our interest in the aza-crowns started in 1987 and was prompted by a desire to have macrocycles that formed very strong interactions with all types of metal ions. The 1987 Nobel Prize was awarded jointly to Charles Pedersen, Jean Marie Lehn, and Donald J. Cram for their elegant pioneering work on the synthesis and properties of macrocyclic ligands. Their work, perhaps more than any other, made people realize that molecules that have the property to recognize other molecules could be synthesized. Our own work showed that metal and organic cations could be recognized by the appropriate crown ether or thioether.

Our *Chemical Reviews* article in 1989 on aza-crown compounds made us realize the wealth of great chemistry available in the aza-crown macrocycles field. This review prompted us to look more fully into this field and has resulted in writing this book. As with any endeavor where one looks at the predecessors and current practitioners in one's area of expertise, one finds some tremendous individuals who have made or are making great strides in the field. We know that a list of important people in the aza-crown field will most likely be incomplete, but that shouldn't keep one from mentioning some individual researchers whose names come quickly to mind. Some of these are as follows:

E. Blasius (polymer-containing macrocyclic ligands)
A. V. Bogatskii and I. G. Lukyanenko (prepared hundreds of aza-crown macrocycles)
D. H. Busch (template syntheses of the aza-crown macrocycles)
N. F. Curtis ("Curtis" reaction—first to report the aza-crown macrocycles)
G. W. Gokel (lariat aza-crown macrocycles)
E. Kimura (syntheses of numerous peraza-crown macrocycles)
J. M. Lehn (biological-like aza-crown macrocycles)
L. F. Lindoy (numerous benzoaza-crown macrocycles)
M. Okahara (ring closure of diols with tosyl chloride)
P. Paoletti (complexing properties of peraza-crown macrocycles)
J. E. Richman and T. J. Atkins (tosylamide ring-closure reactions)
H. Stetter (first prepared macrocyclic diamides)
I. Tabushi ("Tabushi" synthesis using diamines and diesters)
F. Vögtle (great variety of aza-crown macrocycles)

This book contains four introductory chapters covering uses of the aza-crown macrocycles, the synthesis of starting materials, and general ring-closure reactions. The remaining chapters cover the synthesis of aza-crown macrocycles containing one or more ring nitrogen atoms, benzene rings, and those macrocycles containing other heteroatoms such as sulfur. Two lengthy chapters on the peraza-crown macrocycles come next followed by a chapter on macromolecular systems containing the aza- and peraza-crown macrocycles. A final short chapter containing practical information on the synthesis of the aza-crown macrocycles is also included. A complete listing of all aza-crown macrocycles prepared through about July, 1991 is given in tables at the end of Chapters V–XII. We estimate that over 3800 individual aza-crown macrocycles are included. We apologize for the few macrocycles we may have overlooked. The tables are arranged first by ring size and then by the complexity of the various substituents attached to ring atoms.

We wish to thank the many people who helped us along the way. Daria Zamecka-Krakowiak helped in every phase of the work. She found material in the library, put together most tables, compiled and checked all the references, and, most importantly, made all the drawings on CHEM DRAW™. This work could not have been done without Daria's expert help. Two part-time secretaries, Laura Sullivan and Devin Greenhalgh, did the bulk of the typing. The Chemistry Department secretaries, particularly Debbie Smith and Peggy Erickson, also helped in so many ways.

We express our gratitude to Professor E. C. Taylor and the editorial people at John Wiley and Sons for their patience and help during this work.

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Provo, Utah
November, 1992

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CHAPTER I

Aza-crown Macrocycles: An Overview

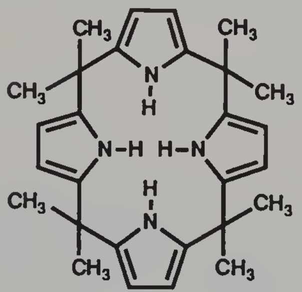
A. INTRODUCTION

Macrocyclic ligands containing heteroatoms are important complexing agents for cations, anions, and neutral molecules. The aza-crown macrocycles, which are the subject of this book, play an important role in the macrocyclic ligand field. Macrocycles included in this book have ring sizes of at least nine members and have three or more heteroatoms with at least one nitrogen atom in the ring. We estimate that about half of all synthetic macrocycles belong to this class. The nitrogen atom has a much stronger association with transition-metal ions than does the oxygen atom. Nitrogen is less electronegative, so the electron pair is more available for complexing purposes.

The aza-crowns have metal ion complexing properties that are intermediate between those of the all-oxygen crowns, which strongly complex alkali and alkaline-earth metal ions, and those of the peraza-crowns (cyclic amines), which strongly complex heavy-metal cations. These complexing properties make the nitrogen-containing macrocycles interesting to researchers in many areas (Izatt et al., 1985, 1991; Lindoy and Baldwin, 1989; Kimura, 1986). The macrocycles have important uses as synthetic receptors in molecular recognition processes (Sutherland, 1986) and, in some cases, anion complexing properties that are similar to those in certain biological systems (Hosseini et al., 1987; Lehn, 1985; Yohannes et al., 1985). They have an enhanced complexing ability for ammonium salts (Lehn and Vierling, 1980; Izatt et al., 1985, 1991) and for transition-metal ions over the all-oxygen crown compounds (Izatt et al., 1985; Lamb et al., 1979; Hancock, 1986).

The era of macrocycles containing amine functions started over 100 years ago when Baeyer (1886) prepared tetraazaquaterene (**1**). Hinsberg and Kessler (1905) prepared similar nitrogen-containing macrocycles. Cyclic amines (like **2**) were first reported by Alphen (1937), and the dibenzoaza-crowns (**3**) were first prepared by Krässig and Greber (1953, 1956). The important complexing properties of the peraza macrocycles were known before the milestone discovery of the all oxygen-containing crown ligands (**4**) by Pedersen (1967, 1988).

The metal-ion-templated synthesis of a peraza macrocycle was reported more than 30 years ago. The macrocycle resulted from the reaction of tris(1,2-diaminoethane)nickel(II) perchlorate with acetone to form a 14-membered macrocyclic ligand–Ni(II) complex (**5**) (Curtis, 1960; Curtis and House, 1961). Numerous examples of this and other metal-ion-templated reactions have been investigated in the intervening years (Black and Hartshorn, 1972–1973; Busch, 1964; Curtis, 1968). Slightly earlier, the methyl-substituted peroxa-12-crown-4 (**6**) was reported along with unambiguous evidence for its ability to solubilize the alkali metal ions in organic solvents (Down et al., 1959).



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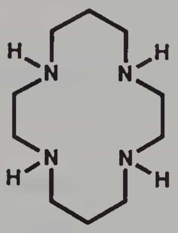

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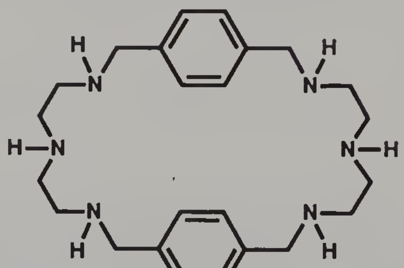

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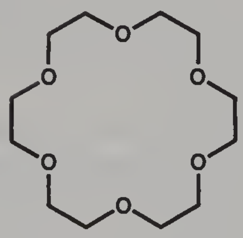

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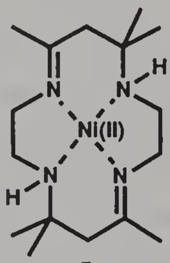

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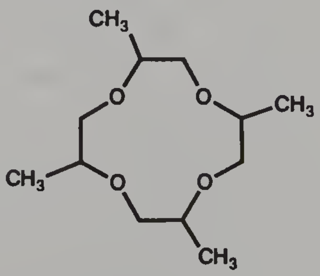

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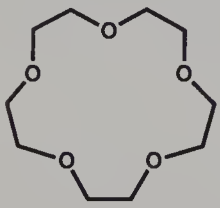
This chapter contains information on the nomenclature of the aza-crown macrocycles and a brief review of their complexing abilities and selectivities for various cations, anions, and neutral organic molecules. Some information on important medicinal uses for these compounds is also included. The last section gives a few general comments about the compounds that are covered in this book.

B. NOMENCLATURE OF THE AZA-CROWN MACROCYCLES

Two types of nomenclature for these macrocycles are used in this book. Mainly, we use the crown nomenclature proposed by Pedersen (1967) in his article on the crown ether compounds. In his nomenclature, the total number of ring members is given first followed by the word "crown." Then the number of heteroatoms is given. The 18-membered ring containing 6 oxygen atoms is 18-crown-6 (see **4** above) and the 15-membered ring is 15-crown-5 (**7**). The position of nitrogen heteroatoms that replace the oxygen atoms in the aza-crown macrocycles is numbered in Pedersen's crown nomenclature. Thus, 1,10-diaza-18-crown-6 (**8**) is the 18-crown-6 macrocycle where two oxygen atoms on opposite sides of the macroring have been replaced by NH groups. The sulfur-containing macrocycles are named in the same manner. Compound **9** is thia-15-crown-5.

The second method used to name the nitrogen-containing macrocycles was proposed by Busch and coworkers (Dabrowiak et al., 1972). The size of the macrocycle is given in a bracket followed by the number and types of heteroatoms. Structure **10** is $[14]N_4$. This macrocycle is often called *cyclam*. The 15-membered ring with four nitrogen atoms and one oxygen atom is $[15]N_4O$ (see **11**). We have modified this nomenclature by leaving out the "ane" following the brackets. The original proposal used "ane" to denote a saturated macrocycle. This book is devoted to saturated macrocycles, so the "ane" part of the Busch et al. nomenclature is not needed. This nomenclature method does not indicate the position of the nitrogen atoms in the ring. For example, there can be two $[15]N_2O_3$ structures. The crown nomenclature discussed above does distinguish between the two structures as 1,4-diaza- or 1,7-diaza-15-crown-5 (**12** and **13**, respectively).



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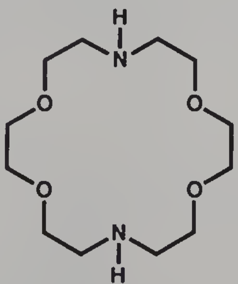

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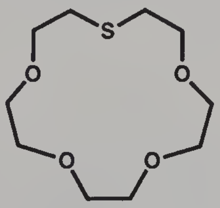

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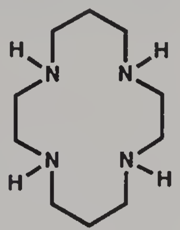

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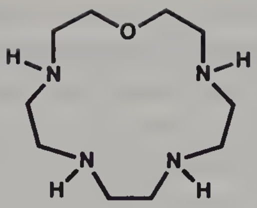

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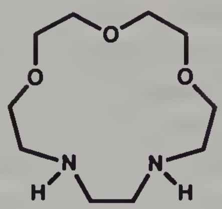

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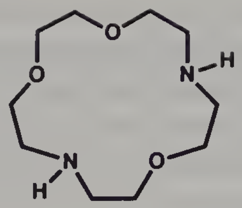

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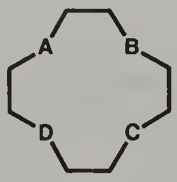
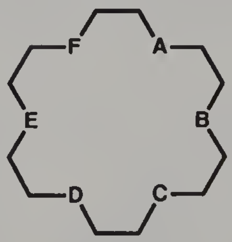
C. COMPLEXING ABILITIES OF THE AZA-CROWN MACROCYCLES

1. Introduction

The most important characteristic of the polyether and polyamine macrocycles is their ability to form complexes with cations, anions, and neutral organic molecules. There are many reviews on the complexing abilities of the crowns and aza-crowns (Bianchi et al., 1991; Hiraoka, 1982; Izatt and Christensen, 1978, 1987a, 1987b; Izatt et al., 1985, 1991; DeLong and Reinhoudt, 1981; Lindoy, 1989a; Melson, 1979; Patai, 1980). The aza-crown macrocycles generally form 1:1 complexes with metal ions with the ion located in the central cavity of the macrocycle. However, there are bi- and trinuclear complexes where two or three metal ions complex with one macrocycle, especially where the macrocycle is large and the cation small. Substitution of oxygen by nitrogen in ligands such as 18-crown-6 and dibenzo-18-crown-6 results in macrocycles that have less affinity for the alkali metal ions, such as K^+, than did the parent peroxa-crown. The log *K* values in these cases decrease in the order of decreasing electronegativity of the heteroatom O > N (containing an alkyl substituent) > N (containing a proton) (Frensdorff, 1971). However, replacing the oxygen donor atom by nitrogen resulted in increased affinities for the heavy-metal ions such as Ag^+ and Pb^{2+}. For example, the log *K* values in water for Pb^{2+} interactions with the 12- and 18-membered macrocycles are as follows: $[12]O_4$(**14**), 2.0; $[12]NO_3$(**15**), 4.1; $[12]N_2O_2$(**16**), 6.3; $[12]N_3O$(**17**), 10.5; $[12]N_4$(**18**), 15.9 and $[18]O_6$(**19**), 4.4; $[18]N_2O_4$(**20**), 6.9; $[18]N_4O_2$(**21**), 9.0; $[18]N_6$(**22**), 14.1 (Hancock and Martell, 1989). Increased interactions for



14 A-D = O
15 A = NH; B-D = O
16 A, C = NH; B,D = O
17 A-C = NH; D = O
18 A-D = NH

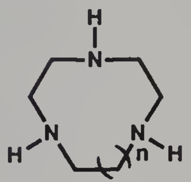


19 A-F = O
20 A, D = NH;
B, C, E, F = O
21 A, D = O;
B, C, E, F = NH
22 A-F = NH

Ca^{2+}, Sr^{2+}, and Ba^{2+} also have been observed for $[15]N_2O_3$(**13**) where the two ring nitrogen atoms contain substituents that have alkyl chains containing hydroxy functions (Wester and Vögtle, 1978). These examples of changing the macrocycle–metal ion interaction by changing the macrocycle cavity size, type of donor atoms, and substituents show some of the reasons for the great interest in these compounds. The design and synthesis of macrocycles having selectivity for a desired cation or group of cations are now possible. Some features of aza-crown macrocycle interactions with metal ions and the specific types of aza-crown macrocycles needed for specific applications are given as follows.

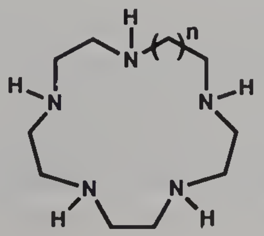
2. The Macrocyclic Effect

The peraza macrocycles, in general, form more stable complexes with a variety of metal ions than do the open-chain polyamines containing the same number of amine groups. This characteristic is called the *macrocyclic effect*. Triaza-crown macrocycles, in nearly every case, form 1:1 complexes with metal ions that are thermodynamically more stable than those with diethylenetriamine. Only complexes of the open-chain triamine with Cu^{2+} and Hg^{2+} are more stable than those with the cyclic triamines (Bianchi et al., 1991). Triaza-9-crown-3 (**23**) forms stronger complexes with most cations than the larger triazacyclodecane (**24**), triazacycloundecane (**25**), or triazacyclododecane (**26**) (Bhula et al., 1988; Chaudhuri and Wieghardt, 1987).



23 n = 1
24 n = 2
25 n = 3
26 n = 4

The tetraazacycloalkanes, particularly the 14-membered cyclic tetraamine (cyclam) (**10**), exhibit the macrocyclic effect due to a more favorable enthalpy contribution to complex stability (Hancock and Martell, 1988). Complexes of the pentaaza-crown macrocycles have been studied extensively from a thermodynamic point of view (Bianchi et al., 1991). With the exception of Ni^{2+}, $[15]N_5$ formed the most stable complexes with all the metal ions studied with the stability order as follows $[15]N_5$(**27**) > $[16]N_5$(**28**) > $[17]N_5$(**29**) (Bianchi et al., 1991).



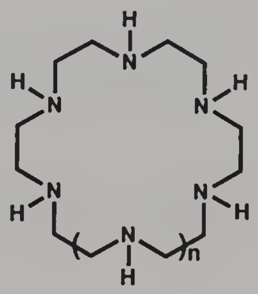
27 n = 1
28 n = 2
29 n = 3

The hexaazacycloalkanes have complexing properties that lie between those of the smaller peraza-crown macrocycles, which exhibit the macrocyclic effect and the large peraza macrocycles, which do not. Compound [18]N_6(**22**) forms complexes in water with the transition metals and also with K^+, Sr^{2+}, Ca^{2+}, and La^{3+} ions. It is interesting that [18]N_6(**22**) has a higher affinity for Ca^{2+} than does [18]O_6(**19**) (Bianchi et al., 1991).

3. Large Cavity Peraza-crown Macrocycles

The peraza-crown macrocycles that have large cavities do not exhibit the macrocyclic effect. These large macrocycles have several features in common: (1) they are polybases producing highly charged protonated species in solution in the neutral pH range that could serve as model reagents for the study of nucleotide complexation; (2) they are suitable for anion-coordination studies; and (3) because of the large number of donor atoms, they can form polynuclear metal ion complexes that could prove useful in the search for more effective catalysts.

The possibility for these polyaza-crown macrocycles to bind more than one metal ion in the macrocyclic framework has aroused the interest of several research groups. The work to date has been limited to the first-row transition elements, Zn^{2+} and Cd^{2+}. Since second- and third-row transition elements are important as catalysts and since several of these elements have large affinities for nitrogen, it is likely that future work may involve them. In general, large polyazacycloalkanes can form mono-, di-, and trinuclear (with copper) species, as well as polyprotonated complexes. The dinucleating and trinucleating abilities of these ligands increase as ring size increases. Mononuclear and dinuclear complexes are formed by Cu^{2+} with [21]N_7(**30**); Ni^{2+}, Zn^{2+}, and Cd^{2+} with [24]N_8(**31**); and by Co^{2+} with [27]N_9(**32**) (Bencini et al., 1987a, 1987b). All macrocycles with rings larger than these form only binuclear complexes with these specific metal ions. In addition, Cu^{2+} forms both binuclear and trinuclear species with [33]N_{11}(**34**) and [36]N_{12}(**35**) (Bencini et al., 1988). The general trend of stability of binuclear complexes is: $Co^{2+} < Zn^{2+} < Ni^{2+} < Cu^{2+}$ (Bencini et al., 1989a). Co_2L^{4+} type complexes with [30]N_{10}(**33**), **34**, and **35** predominate over a rather wide pH range, which is a favorable condition for study of O_2 uptake (Bencini et al., 1989a).

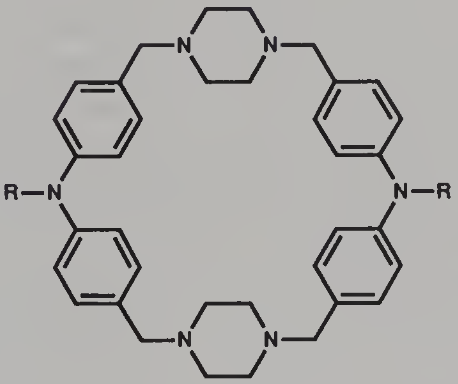


30 n = 2
31 n = 3
32 n = 4
33 n = 5
34 n = 6
35 n = 7

The stability of mononuclear complexes of Ni^{2+} with azacycloalkanes increases from $[9]N_3$(**23**) to $[18]N_6$(**22**), and then decreases for $[21]N_7$(**30**) and $[24]N_8$(**31**) (Bencini et al., 1989b). Crystallographic data show that Ni^{2+} is coordinated by six of the nitrogen atoms of **30**. The fact that only the monoprotonated form of Ni^{2+}-$[21]N_7$ is present in solution supports this idea (Bencini et al., 1989b).

4. Aza-cyclophanes

Azacyclophanes, macrocycles with cyclophane subunits incorporated into the ring, have sizable internal cavities and are able to interact with neutral molecules (Schneider et al., 1988, Murakami et al., 1989a), cations (Kihara et al., 1989; Schneider and Junker, 1986), and anions (Murakami et al., 1989b; Murakami and Kikuchi, 1988) through hydrophobic host–guest interactions that are scarcely affected by external factors such as pH, temperature, and ionic strength. A novel azacyclophane consisting of diphenylamine and piperazine skeletons (see **36**) was synthesized and was found to be an effective ligand for alkali metal and ammonium cations; thus, the log $K(CHCl_3)$ value for Li^+ interaction is 8.06. This ligand is effective in the selective extraction of Li^+ from H_2O to $CHCl_3$. Corey–Pauling–Koltun (CPK) molecular models showed that the cavity of this ligand is too large to include the bare Li^+, but $Li(H_2O)_6^+$ could fit into the cavity forming hydrogen bonds with the piperazine moieties and two molecules of the coordinated water (Kihara et al., 1989).



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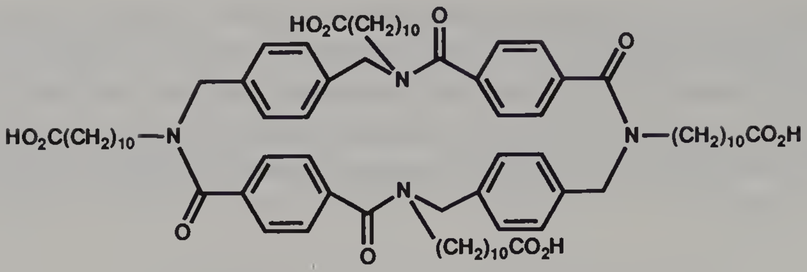
Macrocycles consisting of crown ether and cyclophane subunits and having properties of both crown ethers and cyclophanes have been synthesized (Saigo, 1990; Saigo et al., 1990; Ferguson et al., 1989). Attachment of long alkyl chains on the macrocycle skeleton provides a deeper cavity and allows the introduction of catalytically active groups not only into the cyclic skeleton but also into each alkyl chain (see **37**). These properties of azacyclophanes, as well as their high substrate specificity due to their intrinsic geometric



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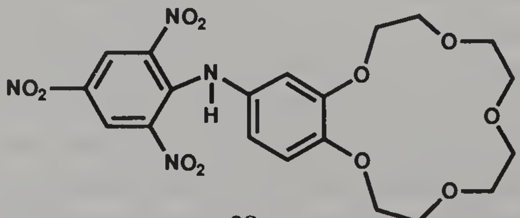
requirements for host–guest interactions, give them the potential to be superior enzyme models (Murakami, 1983).

5. Chromogenic Macrocycles

The idea of designing crown ether dyes that have chromogenic functional groups within the molecules and are able to serve as photometric reagents selective for alkali and alkaline-earth metal ions arose over a decade ago (Takagi et al., 1977). During the 1980s, a substantial number and variety of these compounds were prepared (Takagi and Ueno, 1984; Takagi and Nakamura, 1986). In these compounds, the chromogenic groups bear a dissociable proton (or protons) and ion exchange between the proton and appropriate metal cations causes the color change (Nakashima et al., 1983; Shiga et al., 1983; Takagi and Nakamura, 1986). The chromogenic groups can also be uncharged. In this case, both the electron donor and acceptor are within the chromogenic crown ether dye and the metal cation coordinated to either the donor or acceptor site induces a change in the charge-transfer band of the dye (Dix and Vögtle, 1980, 1981; Hollmann and Vögtle, 1984; Takagi and Ueno, 1984; Takagi et al., 1989).

Chromogenic macrocycles that are useful for selective extraction of cations and for determining cation concentrations, particularly Na^+ and K^+ at the parts per million (ppm) level, have been synthesized (Nakashima et al., 1986; Nakamura et al., 1981, 1982a, 1982b; Takagi et al., 1977) (see **38** for example). Takagi and coworkers synthesized chromogenic macrocycles that are selective for Ca^{2+} (see **39**) and extract other alkaline-earth cations in the order $Ca^{2+} > Sr^{2+} > Ba^{2+} >> Mg^{2+}$ (Shiga et al., 1983). Kaneda and coworkers synthesized chromogenic macrocycles and developed a sensitive spectropho-



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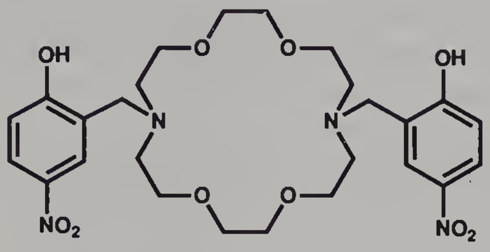
tometric method for their use in the colorimetric determination of Rb^+ and Cs^+ (see **40**)(Nakashima et al., 1983). The same group of scientists reported



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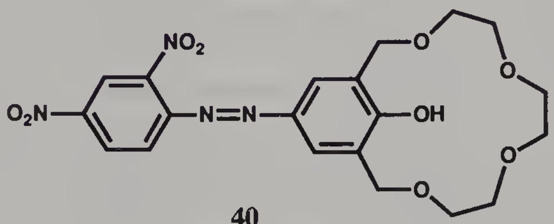

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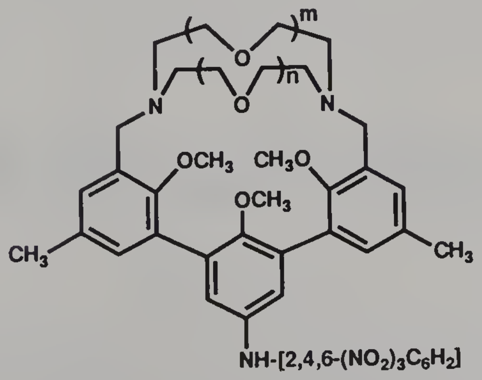
the first examination of amine-selective (Kaneda et al., 1989a) and enantiomeric-amine-selective (Kaneda et al., 1989b) coloration properties of chromogenic macrocycles.

Recently, creativity in chromogenic macrocycle synthesis has expanded. New spherand species have been synthesized that act as highly preorganized chromogenic-specific indicators for Li^+ and Na^+ (Cram et al., 1985), and an azophenol dye has been prepared with "perfect" selectivity for Li^+ (Kaneda et al., 1985). Many of these chromogenic macrocycles and more complicated species such as the hemispherands and cryptohemispherands have found commercial use for Na^+ and K^+ assays in body fluids (see **41**) (Helgeson et al., 1989; Czech et al., 1990).



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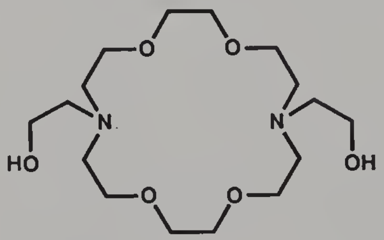
6. Lariat Crown Ethers

The number of reported lariat crown ethers bearing one, two, or more side arms has increased dramatically in the past few years. The lariat crowns are crown ethers with side arms containing donor atoms at the end. These lariat donor atoms can complex with cations above and/or below the complex, thereby increasing complex stability (Gokel et al., 1987). Macrocycles bearing pendant carboxylic acid functions are good examples of the lariat crowns. Carboxylate groups interact with metal cations; for example, $[12]N_4$ containing pendant carboxylates forms the most stable lanthanide complexes known ($\log K = 22.86\text{–}29.2$) (Cacheris et al., 1987; Loncin et al., 1986). The cavity of the ligand is too small to accommodate a lanthanide cation, so the ligand ring acts as a frame to constrain the nitrogen atoms and the carboxylate groups into a nearly spherical arrangement.

In general, side arms, especially those containing donor groups, enhance the binding strength of the lariat crown ethers toward cations, in comparision with the crown ether analogs without side arms, by cooperative ring–side arm interaction (Gatto et al., 1986). Gokel and coworkers showed by X-ray crystallography that the two-armed lariat crown ether of 4,13-diaza-18-crown-6 (see **42**) enveloped Na^+ and K^+ cations in a three-dimensional manner displaying cryptand-like behavior (Arnold et al., 1987). Side arms without donor groups do not interact directly with ring-bound cations, but influence the binding by their interaction with the solvent (Arnold et al., 1988a). The complexation phenomena exhibited by lariat crown ethers are influenced by the cavity size–cation size relationship, ligand flexibility and conformation, total number of donor atoms, and solvation energies for the cation, macrocycle, and complex (Arnold et al., 1988b).



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D. COMPLEX SELECTIVITIES OF THE AZA-CROWN MACROCYCLES

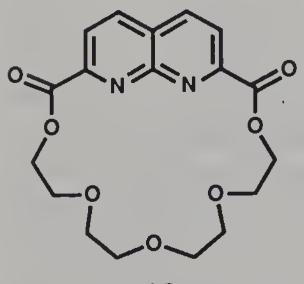
1. Introduction

The main target in macrocycle ligand design is to synthesize macrocycles that are able to discriminate among different cations. Many factors influencing the selectivities of macrocycles for cations have been determined. These factors may be divided roughly into several groups, including macrocycle cavity dimensions; shape and topology; substituent effects; conformational flexibility/rigidity; and donor atom type, number, and arrangement (Bianchi et al., 1991; Cram, 1988; Izatt et al., 1985, 1991; Izatt and Christensen, 1987a, 1987b; Lindoy, 1989b; Pedersen, 1988; Raevskii, 1990; Vögtle and Weber, 1989).

2. Rigidity, Side Arms, and Donor Atoms

Macrocycles of the "rigid" type (e.g., small cryptands and other preorganized macrocycles) discriminate between cations that are either smaller or larger than the one that exactly fits into the cavity (peak selectivity). Macrocycles of the "flexible" type (e.g., larger polyether crowns and cryptands) discriminate principally among smaller cations (plateau selectivity) (Vögtle and Weber, 1989).

Incorporating benzene, cyclohexane or pyridine rings, and/or other constituents into macrocyclic skeletons leads to a more rigid macroring and may alter the strength and selectivity of ligand interaction with a cation. An example is that of a 20-membered crown ether with an incorporated 1,8-naphthyridine ring (see **43**), which shows excellent selectivity for Ba^{2+} ($\log K = 7.16$) over Ca^{2+} ($\log K = 4.91$) in $CDCl_3$ (Chandler et al., 1988). Chiral groups incorporated into the correct location of a macrocyclic framework may allow separation of optically active enantiomeric cations (see **44**) (Bradshaw et al., 1990; Huszthy et al., 1991; Izatt et al., 1985; Stoddart, 1981; Vögtle and Weber, 1989; Zhu et al., 1992). Selectivities may be modified also by variation of the side arms. 4,13-Diaza-18-crown-6 containing two carboxylate groups on side arms shows unique selectivity toward lanthanide cations as a group (Chang and Rowland, 1983). 18-Crown-6 derivatives with amine-containing substituents (see **45**) are effective in K^+ transport through a CH_2Cl_2 membrane and are highly selective in transport experiments for K^+ over Na^+ (Nakatsuji et al., 1986).



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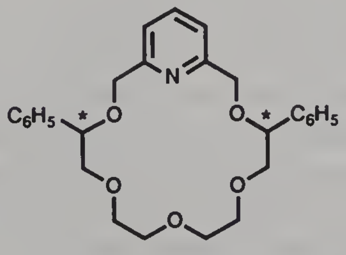

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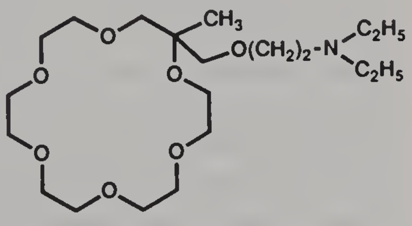

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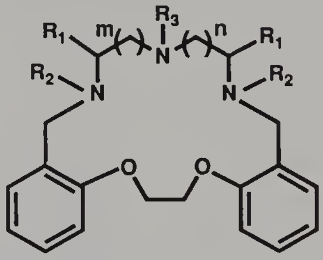
The number, kind, and arrangement of donor atoms also play important roles in macrocycle selectivities. Oxygen donor atoms in classical crown ethers have the largest affinities for alkali, alkaline-earth, and lanthanide cations;

nitrogen donor atoms favor transition-metal cations; and sulfur donor atoms interact preferentially with Ag^+, Pb^{2+}, and Hg^{2+} (Vögtle and Weber, 1989). For example, the extremely large stability differential among macrocycles (e.g., up to 10^{10} for Cu^{2+}) may be achieved solely through variation of number, kind, and location of donor atoms within the specific ligand frame employed (Adam et al., 1987).

3. Structural Dislocations

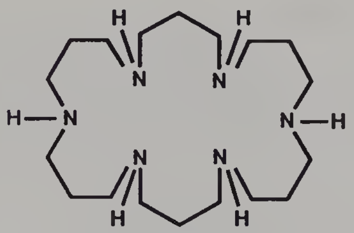
Recently, Lindoy and Adam and their coworkers conducted a series of investigations on cation discrimination by structural dislocation (Adam et al., 1983a, 1983b, 1986, 1987, 1988; Lindoy, 1989b). Structural dislocation is associated with a sudden change in the *K* value for cation–macrocycle interaction for a particular metal ion with a series of closely related macrocyclic ligands (Adam et al., 1983b, 1986). In one example, the interaction of 17-, 18-, and 19-membered dibenzo macrocycles (see **46–52**) containing three nitrogen and two oxygen atoms in the ring with Cd^{2+} and Zn^{2+} in 95% CH_3OH was examined. The log *K* values of Cd^{2+} with the 19-membered macrocycles were considerably lower than expected from the log *K* values for the 17- and 18-membered macrocycles. The observed dislocation along the Cd^{2+} series appears to be a crossover from coordination of the ether groups in the 17- and 18-membered macrocycles to their lack of coordination in the 19-membered macrocycle (Adam et al., 1988; Chen et al., 1984; Buschmann, 1988, 1989; Soong et al., 1990; Gholivand and Shamsipur, 1986). The influence of solvent (Marolleau et al., 1990; Schmidt et al., 1983) and counteranion (Bünzli and Giorgetti, 1985; Pett et al., 1988; Kim et al., 1987a, 1987b; Zavada et al., 1985; Solovev et al., 1987; Stover et al., 1985; Motekaitis et al., 1982) on macrocycle selectivities are also well known and have been studied thoroughly.



46 $R_1, R_2, R_3 = H$; m, n = 1
47 $R_1 = CH_3$; $R_2, R_3 = H$; m, n = 1
48 $R_1 = H$; $R_2, R_3 = CH_3$; m, n = 1
49 $R_1, R_2, R_3 = H$; m = 1, n = 2
50 $R_1, R_2, R_3 = H$; m, n = 2
51 $R_1, R_2 = H$; $R_3 = CH_3$; m, n = 2
52 $R_1, R_2, R_3 = H$; m = 1; n = 3

4. Selectivity For Anions

Macrocyclic polyamines that can be fully or nearly fully protonated in the neutral pH range appear to be the best ligands for the biologically important carboxylate and adenosine phosphate anions because the formation of these anions occurs in these pH regions. Lehn and Dietrich and their coworkers have synthesized macrocyclic polyamines [24]N_6(**53**) and [32]N_8(**54**), based on propylene units (Dietrich et al., 1981), and macrocycles with mixed nitrogen–oxygen donor atoms connected by ethylene units, [27]N_6O_3(**55**) (Dietrich et al., 1981) and [24]N_6O_2(**56**) (Hosseini and Lehn, 1987; Hosseini et al., 1983). These macrocycles are similar to those found in natural systems.



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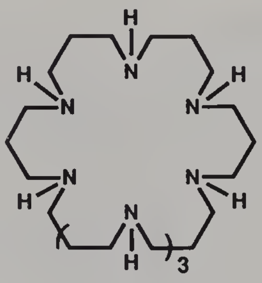

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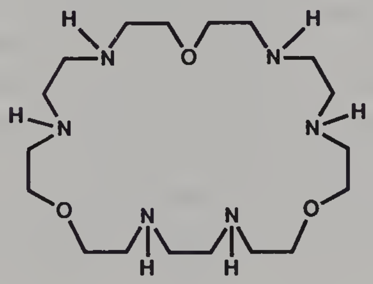

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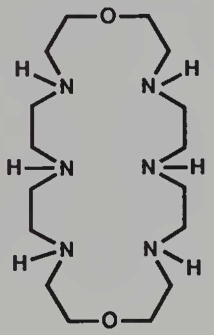

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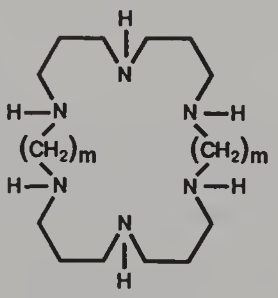
Both types of protonated macrocycles were found to form stable and selective complexes with both inorganic [i.e., SO_4^{2-}, $Co(CN)_6^{3-}$, and $Fe(CN)_6^{4-}$] and organic (i.e. carboxylate and nucleotide) polyanions in aqueous solution in the neutral pH range. Since selectivity in these systems depends on electrostatic and geometric effects, modification of macrocyclic cavity shape and size should allow one to control the selectivity sequence (Dietrich et al., 1981). The interactions of **53** and **54** in their less than fully protonated forms with carboxylate and nucleotide anions have been investigated recently (Hosseini and Lehn, 1988).

Macrocyclic penta- and hexaamines [15]N_5(**27**) and [18]N_6(**22**), based on ethylene units, are selective in their triprotonated forms at neutral pH for polycarboxylate anions that occur in the catabolic tricarboxylic acid cycle in which the two carboxylate groups are near each other, and are ineffective toward other carboxylate and monocarboxylate anions (Kimura et al., 1981). These macrocyclic polyamines also form stable 1:1 complexes at neutral pH with phosphate anions such as the inorganic phosphates, AMP, ADP, and ATP (Kimura et al., 1982a) and with physiologically essential CO_3^{2-} (Kimura et al., 1982b). Bis(macrocyclic polyamine) ligands synthesized recently by Kimura and coworkers show enhanced polyanion binding due to probable formation of sandwich-type complexes (Kimura et al., 1990). Gelb and coworkers studied the interactions of tetraprotonated macrocyclic hexaamines with inorganic anions (tri- and tetraprotonated forms in the case of SO_4^{2-}) and found that the process of desolvating macrocycle and anion solvation spheres is a driving force in complexation (Cullinane et al., 1982; Gelb et al., 1985, 1986).

Large polyazacycloalkanes produce highly charged protonated species in the neutral pH range. Complexation of such large polyazacycloalkanes as [27]N_9(**32**), [30]N_{10}(**33**), and [33]N_{11}(**34**) with large polyanions, $Fe(CN)_6^{4-}$ and $Co(CN)_6^{3-}$, have been examined (Garcia-Espana et al., 1985; Bencini et al., 1987c). It was found that these macrocycles did not show selectivity toward the anions studied. This result is consistent with strong interactions, mainly Coulombic in nature, between the anion and the protonated ligand. The greater the extent of protonation of the ligand, the more stable is the complex. An X-ray crystallographic study of the octaprotonated **33**–$Co(CN)_6^{3-}$ complex shows that the anion lies outside the ligand cavity (Bencini et al., 1987c). The same authors reported recently how small structural modifications in highly organized tricarboxylic acid molecules cause drastic changes in the degree of complexation with the polyaza-crown macrocycle **32** (Bencini et al., 1991a).

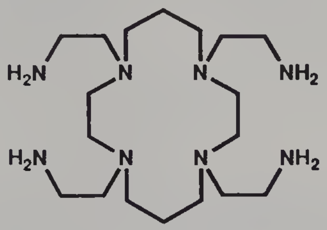
Ditopic macrocyclic polyamines containing 1,3-diamine and longer units, [24]N_6(**53**), [32]N_6(**57**), and [38]N_6(**58**), were designed as receptors for dianions (Hosseini and Lehn, 1982, 1986). All of the polyamines studied form



57 n = 7
58 n = 10

stable and highly selective complexes with organic dicarboxylate anions, $^{-}O_2C\text{-}(CH_2)_m\text{-}CO_2^-$. These macrocycles display linear molecular recognition based on ditopic binding between two triammonium units of the macrocycle and the two terminal CO_2^- groups of the dicarboxylate anion. The most stable complex is formed when the macrocycle is fully protonated and the length of the dicarboxylate anion complements the site separation of the macrocycle.

Recently it was reported that the small macrocycle *N*,*N*′,*N*″,*N*‴-tetrakis(2-aminoethyl)[14]N_4(**59**) can interact with anions. It was proposed that protons attach first to the primary amino groups of the side arms and second to the tertiary nitrogens of the macrocycle. Thus, because of the initial protonation in the side arms, the flexibility of this receptor might lead to better matching in its interaction with anions (Bencini et al., 1991b).



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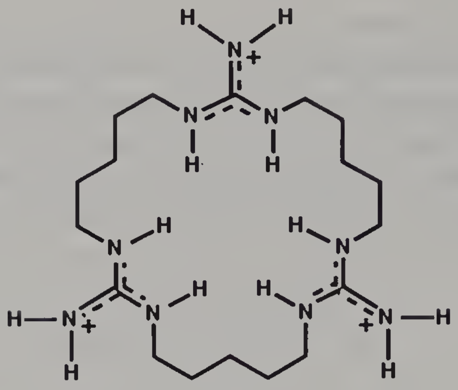
5. Selectivity for Organic Molecules

Aza-cyclophane-type macrocycles possess large cavities of different sizes that have pronounced hydrophobic character and form host–guest inclusion complexes with charged or uncharged organic compounds in aqueous solution by hydrophobic and/or electrostatic interactions. In these complexes, the matching of the shape and size of the macrocycle hydrophobic cavity to the shape of the hydrophobic anion is important for optimum complex stability. In addition, increasing the hydrophobic volume of the cavity improves complex formation (Koga and Odashima, 1989). Aza-cyclophane-type macrocycles are able to select guests by recognition of the steric structure and charge of the guests. Their complexes with dianions are stronger than those with corresponding monoanions. They form strong complexes with anions having naphthalene rings, weaker but relatively strong complexes with anions having benzene rings, and only weak complexes with anions having nonaromatic structures (Odashima et al., 1981). Macrocycles bearing quaternary ^+N charges in the cavity bind aromatic guests, including anions, 60 times stronger than aliphatic guests of similar shape. The differences in log K values are much smaller with the same macrocycles bearing no charges (Schneider et al., 1989).

Macrocycles containing guanidinium moieties as binding sites (see **60**) were synthesized by Lehn and coworkers (Dietrich et al., 1978). These macrocycles were expected to be effective and selective ligands for phosphate, di- and triphosphate, AMP, ADP, and ATP anions. However, the PO_4^{3-} complex was found to have low stability and there was almost no macrocyclic effect (Dietrich, 1984; Dietrich et al., 1978).



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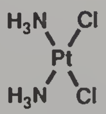
Achieving selective complexation between receptors and substrates of biochemical interest has been a driving force in the design of macrocycles suitable for selective binding of organic anions. As in the case of cations, selectivities of macrocycles toward anions are governed by many parameters. An important parameter involving spherical anions is the match between anion size and macrocycle cavity diameters. The geometry and topology of macrocyclic cavities are other parameters that influence selectivity. Arrangement of and distance between binding sites in ditopic polyammonium macrocycles, such as [38]N_6(**58**) and [24]N_6(**53**), result in a selectivity pattern toward dicarboxylate anions corresponding to a process of linear molecular recognition (Hosseini and Lehn, 1982, 1986). Usually, macrocycle selectivities for anions are governed by several factors simultaneously. Macrocyclic penta- and hexaamines were found to recognize only the dicarboxylates having suitable geometry and electronic arrangement (Kimura et al., 1981).

E. MEDICINAL USES OF THE AZA-CROWN MACROCYCLES

There are important new applications of the aza-crown macrocycles for medicinal purposes. The perturbation of metabolic processes based on biological metal ion–ligand coordination can produce a disease or even death. Conversely, undesirable biological processes can be prevented by using certain metal ion–ligand interactions. For example, the weak complexing ability of chlorine to the central platinum ion of *cis*-platin (**61**) allows *cis*-platin to have antitumor activity (Haiduc and Silvestru, 1989). When applied in a biological



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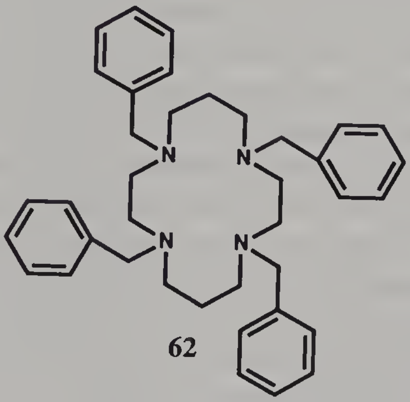
system, the labile chlorine dissociates, allowing the platinum ion to interact with the DNA molecules of the cancer tissue. This is a common mode of antitumor activity by a chelating agent. Other drugs such as metallocene dichloride and diorganotin dihalide use this type of antitumor action (Reedijk et al., 1987). Up to the mid 1980s, only metal ion complexes of linear ligands had been tested. More recently, tetrabenzyl[14]N_4(**62**) complexes containing copper, gold, and silver have been tested for antitumor activity (Farrell, 1989; Haiduc and Silvestru, 1989).



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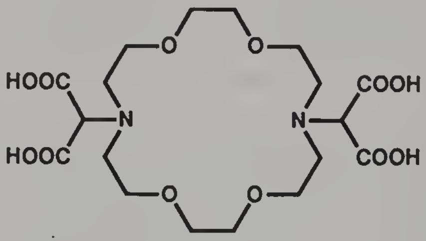
Other antitumor active compounds such as the bleomycin, antracycline, and streptomycin antibiotics have a different mode of action. Antitumor activity is manifested by DNA binding to the antibiotics followed by DNA strand cleavage. Cleavage requires oxygen and a metal ion that can form a complex. Fe^{2+} is the most effective metal ion in vivo and in vitro (Farrell, 1989; Sugiura et al., 1986). Busch and Cairns (1987) have taken the first steps in finding the right ligands to bind Fe^{2+} and dioxygen.

A novel method to localize and treat tumors by means of a ligand–radioisotope complex attached to an antibody is now being tested. The cyclic polyamines are ideal ligands for this purpose because they can be attached to an antibody and form strong complexes with the appropriate radioactive metal ions (Cox et al., 1989; Craig et al., 1989; Kaden et al., 1989; Moi et al., 1987, 1988; Morphy et al., 1988, 1989; Parker et al., 1989; Riesen et al., 1989). The cyclic amines form complexes with radioactive metal ions that are kinetically inert with respect to dissociation either by the pH of body fluids or reaction with the common metal ions in body fluids.

Early experiments in tumor localization and treatment using C-functionalized EDTA and DTPA chelates were not promising because the complexes with Cu^{2+} and In^{3+} were labile in body fluids and mixed complexes with Ca^{2+}, Mg^{2+}, and Zn^{2+} formed. Since the radioactive metal ions can damage liver and bone marrow, it is very important to use ligands that form very strong complexes with those cations. Recently, a complex of Bi^{3+} and a DTPA incorporating rigid cyclohexane rings between the nitrogen atoms has exhibited good in vivo stability and has promise for ^{212}Bi-radioimmunotherapy (Brechbiel et al., 1991). Aza-crown macrocycles of 9–14 ring members and with acetic or phosphoric acid groups attached to each nitrogen atom appear to be good candidates to replace DTPA or EDTA for this application. A number of these macrocycles were tested and the only inefficient labeling was found for the complex of [12]N_4-tetraacetate and ^{90}Y where divalent cations such as Ca^{2+} and Zn^{2+} effectively competed for the ligand (Broan et al., 1991). The aza-crown macrocycles do show great promise, but more work is needed (Gansow et al., 1991). More detailed discussions concerning the complexation of radioisotopes for radioimmunotherapy have been published in recent reviews (Jankowski and Parker, 1992; Liu and Wu, 1991; Parker, 1990).

Aza-crown macrocycle–metal ion complexes are effective proton relaxation enhancement agents in aqueous solution and in rat tissue. The magnitude of enhancement is such that proton relaxation is detectable in magnetic resonance images obtained by clinical nuclear magnetic resonance (NMR) imagers (Jackels et al., 1986). Recent work shows promise for the use of paramagnetic complexes with macrocycles as contrast agents in medicinal NMR imaging. The best metal ions appear to be Fe^{3+}, Gd^{3+} and Mn^{2+} because of their high magnetic moments and relaxation efficiencies (Comblin et al., 1991; Geraldes et al., 1991; Kumar et al., 1991; Lauffer, 1987).

The oldest medicinal application for chelating agents is the inmobilization of toxic metal ions such as arsenic, lead, mercury, and nickel. Immobilization of excess amounts of essential metal ions such as iron or copper has also been done by chelating agents. In general, the linear chelating agents are being used for these purposes (Bulman, 1987; Jones, 1991), but the aza-crown macrocycles are now being tested. The tetrasodium salt of [18]N_2O_4–*N*,*N*′-dimalonic acid (**63**) is capable of promoting the excretion of radiostrontium



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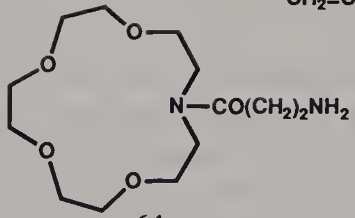
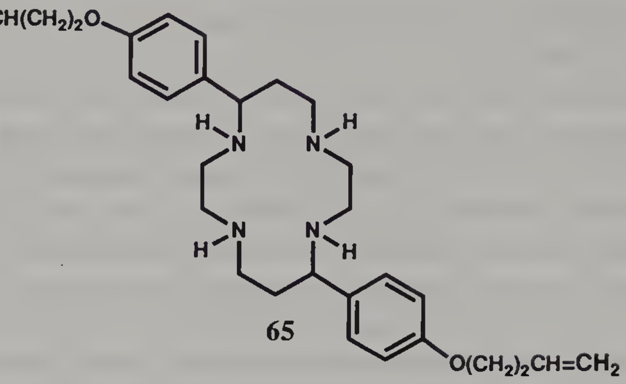
and radiocerium that had been administered into animal bodies (Varga et al., 1990). Derivatives of [14]N_4(**10**) (cyclam) even in low doses have a good efficiency in reducing the lethal response to nickel. These macrocycles significantly enhance the urinary and biliary excretion of Ni^{2+} and restore the altered levels of other trace metal ions such as Cu^{2+}, Zn^{2+}, and Fe^{3+}. They are more efficient in this application than linear chelating agents such as EDTA or triethylenetetraamine (Athar et al., 1987; Misra et al., 1988).

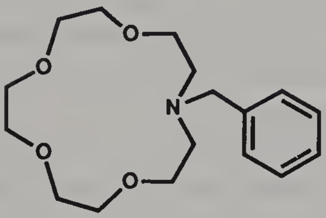
[12]N_4(**18**) (cyclen) is efficient in eliminating Cu^{2+} from animals (Pilichowski et al., 1983).

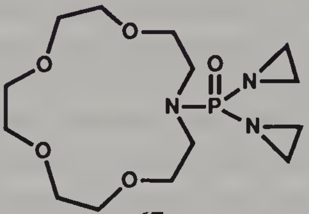
There have only been a few preclinical studies using the aza-crown macrocycles. The toxicity of the crowns has been somewhat studied. Crown ethers are more toxic than the aza-crown macrocycles because toxicity arises from the slow leakage of potassium ions out of and sodium ions into cells (Gokel, 1991). Dibenzo-18-crown-6 is much less toxic than the other crown ethers because it is much less soluble in water. Complexed ligands are much less toxic than the uncomplexed ligand. For example, complexes of [12]N_4-tetraacetate are not toxic while the uncomplexed ligand will remove metal ions from cells (Lauffer, 1987). Thus, it is important to have stable complexes when the macrocycles are used for medicinal purposes.

Some miscellaneous medicinal studies using macrocyclic ligands are worthy of mention. Several crown ethers have exhibited antimicrobial activity (Adimado et al., 1991; Voronkov and Knutov, 1990). [15]NO_4 and [18]N_2O_4 containing pharmacophoric groups have shown psychotropic properties in that, in doses of 50 mg/kg, they partially restored memory after training and scopolamine induced amnesia (Voronina et al., 1988, 1990). It has been suggested that amino acid derivatives of certain macroheterocyclic compounds exert a stimulating effect on learning and memory (Garibova et al., 1990). Derivatives of [15]NO_4 (see **64**) are the most practical macrocycles to study for medicinal uses because they are less toxic than [18]N_2O_4(**20**) and appear to have anticonvulsant activity (Karaseva et al., 1990; Raevskii et al., 1988). The *N*-acylaza-crown macrocycles also have anticonvulsant activity, but they have a higher toxity level (Voronina et al., 1990). Derivatives of [14]N_4 (cyclams) (see **65**) exhibited significant antiarrhytmic activity (Hankovszky et al., 1984), as did the smaller nine-membered macrocycles (Mikiciuk-Olasik and Kotelko, 1987; Mikiciuk-Olasik et al., 1983). The effect of *N*-benzylaza-15-crown-5 (see **66**) on blood pressure in the femoral artery has been studied. The mechanism of the vasodilating action of **66** may be due to an inhibitory effect on the calcium-dependent release of noradrenaline from terminals of the sympathetic nerves (Gurbanov et al., 1988). Others have tested 125 crown ethers and concluded that these materials are a new class of antihypertensive drugs (Kovalev et al., 1990). An experimental study of cardiovascular effects and cardiotropic action of a [15]NO_4 derivative was performed (Kovalev et al., 1988). Sosnovsky and Lukszo (1991) reported that **67** shows a high degree of antineoplastic activity and may be a drug for the future. Kimura (1985) has suggested that the aza-crown macrocycles could be used in the treatment of kidney stones. The aza- and peraza-crown macrocycles also were tested for other pharmacologic activity (Bogatskii et al., 1984; Lukyanenko et al., 1985; Voronkov et al., 1982). Other aza-crown macrocycles containing pharmacophoric groups have been prepared (Elben and Vögtle, 1978; Elben et al., 1979; Vögtle and Elben, 1978; Vögtle, 1991) and some with peptide side arms (Kulikov et al., 1990; White et al., 1989).


64


65


66


67

F. MISCELLANEOUS USES OF THE AZA-CROWN MACROCYCLES

The aza-crown macrocycles are important synthons for the synthesis of the cryptands (Dietrich et al., 1973; Lehn, 1978), other macropolycyclic ligands (An et al., 1992), nitrogen pivot lariat crown ethers (Schultz et al., 1985), and other species requiring one or two nitrogens in the macroring (Löhr and Vögtle, 1985; White et al., 1987). Certain aza-crowns have been used as catalysts in nucleophilic substitution and oxidation reactions (Kauser, 1983; Liotta, 1989; Voronkov and Knutov, 1988; Weber, 1983; Yatsimirski, 1990) and in the chromatographic separation of metal cations (Sakai et al., 1986; Takagi and Nakamura, 1986; Weber, 1984). Other aza-crowns have been covalently attached to silica gel or other solid supports (Bradshaw et al., 1989a, 1989b, 1991; Sahni and Reedijk, 1984). The silica-gel-bound aza-crowns can be used for the selective separation of specific metal ions or groups of metal ions from mixtures of metal ions (Bradshaw et al., 1989a, 1991). Polyesters and polyamides containing aza-crown units have some ion-binding properties (Gramain et al., 1980; Nishimura et al., 1981). Other topics concerning aza-crowns attached to or part of polymer systems are given in Chapter XII. Recent topics in this area include the selective extraction of Hg, Pd, Pt, Au, Ag, Ru, Ir, Cu, and Pb cations (Pshezhetsky et al., 1990); synthesis and properties of thermally stable macrocyclic polymers (Koton et al., 1990); application of sorbents containing diaza-18-crown-6 in the luminescent analysis of the lanthanides (Beltyukova et al., 1990); immobilized macrocycles in mixed stationary phases in chromatography (Pletnev et al., 1990); and sorbtion of metals with immobilized N—O macrocycles (Pasekova et al., 1990).

The uses of the aza-crown macrocycles are multiplying as shown above. New research is reported almost daily. The titles of a few recent articles are instructive: (1) "Macrocyclic Polyamines [16]N_3 and [21]N_4: Synthesis and a Study of Their ATP Complexation by ^{31}P Nuclear Magnetic Resonance Spectroscopy" (Prakash et al., 1991); (2) "Removal of Dyes from Solution with the Macrocyclic Ligands" (Buschmann et al., 1991a, 1991b); (3) "Iron–Cyclam Complexes as Catalysts for the Epoxidation of Olefins by 30% Aqueous Hydrogen Peroxide in Acetonitrile and Methanol" (Nam et al., 1991); (4) "Lipid-Bound Macrocycles as New Immobilized Ligand Systems for Effective Separation of Metal Cations" (Tsukube et al., 1991); (5) "Application of Macrocyclic Ligands to Ion Chromatography" (Lamb and Smith, 1991); (6) "Chromatographic Separation of Metal Cations on Silica Gel Chemically Modified with a Polymeric Diaza-18-crown-6 Derivative" (Basyuk, 1991); and (7) "Column Preconcentration of Trace Metals from Sea Water with Macroporous Resins Impregnated with Lipophilic Macrocycles" (Blain et al., 1991).

An extensive number of crowns have been synthesized. Several of these materials can be purchased. For example, Merck, Aldrich, Janssen, and Fluka list a number of aza-crowns, including 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane. These compounds are extremely expensive. The design of new and inexpensive procedures to prepare these important ligands is an important need. Partial compilations of aza-crown macrocycles prepared prior to about 1980 are reported by Gokel and Korzeniowski (1980) and from 1981 to 1987 by Bradshaw and coworkers (Krakowiak et al., 1989).

G. GENERAL COMMENTS

This book covers the syntheses of all aza-crown macrocycles up to the middle of 1991. We have concentrated on nitrogen-containing macrocycles of at least nine ring members and with at least one nitrogen in the macroring. We have included the benzoaza-crowns, but crowns containing other aromatic, unsaturated, or saturated subcyclic units are not included. Macrocycles containing the pyridine subcyclic group have been reviewed by Newkome and Gupta (Newkome et al., 1984). A survey of general methods for the preparation of starting materials is also included. Specific methods for the preparation of monoaza-crowns, diaza-crowns, polyaza-crowns, benzoaza-crowns, and the peraza-crowns, such as the cyclams, are included in this book. Only macrocycles where the specific synthetic method for their preparation have been published are listed in the tables in the various chapters of this book. The synthesis of cyclic peptides in general is not included, although some syntheses of the cyclic peptides that are similar to the aza-crowns are presented. New methods for preparation of saturated aza-crowns from the cyclic peptides are included (Moi et al., 1988).

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CHAPTER II

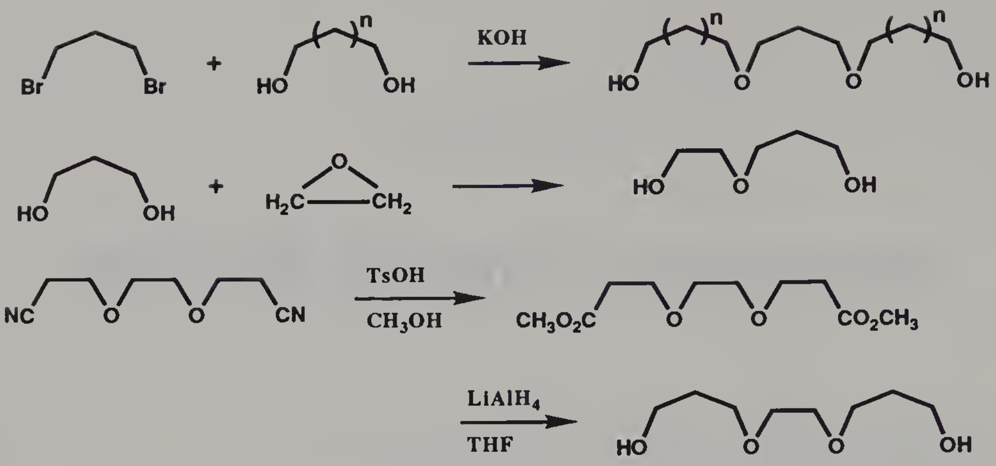
Preparation of Starting Materials

Syntheses of aza- and peraza-crowns require the use of diols (glycols), amino ethers, polyamines, and/or aminodiols. Often, these important building blocks are not available and need to be prepared in the laboratory. Unfortunately, methods for the preparation of these starting materials have not been published in an organized manner, although there are two brief reviews (Bradshaw et al., 1992; Krakowiak et al., 1989a). This chapter presents the many methods for synthesis of these important materials.

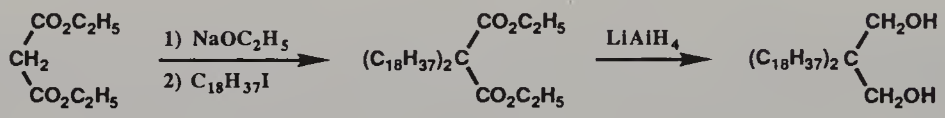
A. PREPARATION OF DIOLS (GLYCOLS)

Most of the simple oligoethylene glycols and other diols used for the synthesis of macrocyclic compounds are commercially available. Methods for their preparation have been published (Bartsch et al., 1989; Bradshaw et al., 1976; Cornforth et al., 1973; Coudert et al., 1986; Dale and Kristiansen, 1972; Gallaugher and Hibbert, 1936; Kimura et al, 1987; Koizumi and Hanai, 1956; Kravchenko et al., 1972; Laurie, 1928; Nakatsuji et al., 1987; Newcomb et al., 1977; Perry and Hibbert, 1936). Most of the reported procedures use the classical Williamson ether synthesis and provide yields in the 20–45% range. Glycols with propylene units other than 1,3-propanediol are not commercially available. They can be prepared from inexpensive starting materials as shown below for the preparation of three glycols (Kitazawa et al., 1984; Kotelko, 1967; Olsher and Jagur-Grodzinski, 1981).

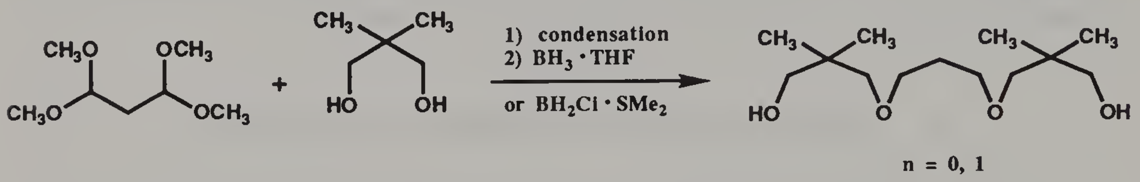
Glycols with side chains are generally not available but are very desirable since crown ethers with active side groups (hydroxy or allyl, for example) or with long-chain lipophilic groups are often needed. Cornforth and coworkers



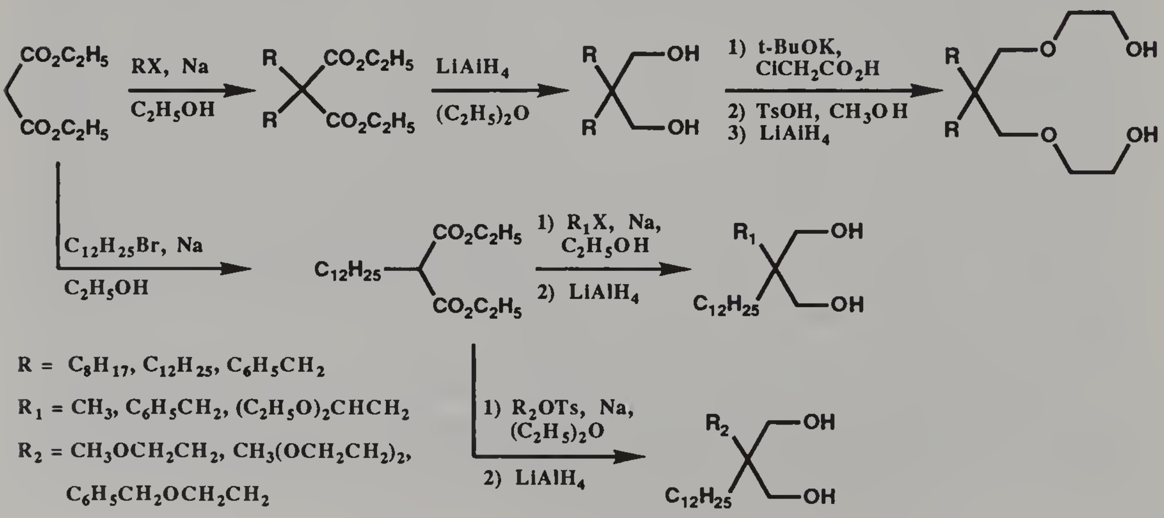
made a lipophilic diol, 2,2-dioctadecylpropane-1,3-diol, from diethylmalonate (Cornforth et al., 1973). Alkyl-substituted polyether diols have also been



prepared by a selective reductive cleavage of C—O bonds in bis(cycloacetals) using borane or the monochloroborane–dimethyl sulfide complex (Castro et



al., 1988). Malonate esters have been used as starting materials for the preparation of many alkyl-substituted propylene glycols (Kimura et al., 1986;

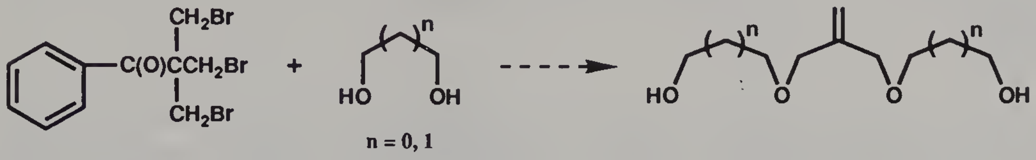


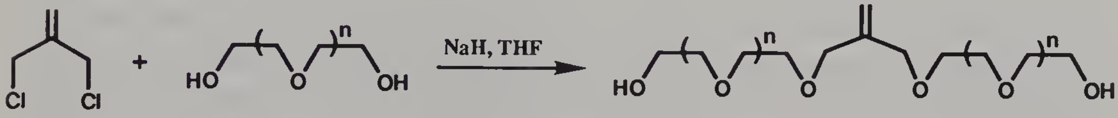
$R = C_8H_{17}, C_{12}H_{25}, C_6H_5CH_2$

$R_1 = CH_3, C_6H_5CH_2, (C_2H_5O)_2CHCH_2$

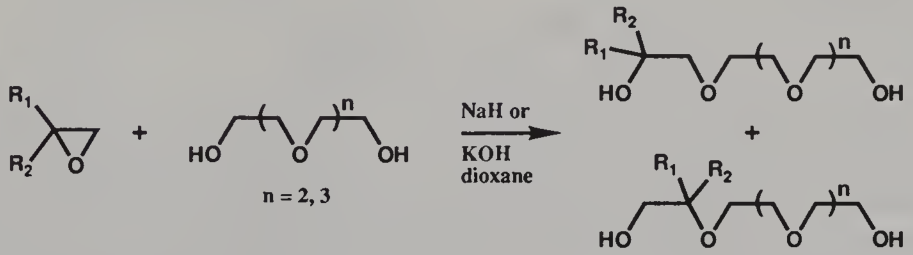
$R_2 = CH_3OCH_2CH_2, CH_3(OCH_2CH_2)_2,$
$C_6H_5CH_2OCH_2CH_2$

Kitazawa et al., 1984). Diols with propylene units containing a methylene (=CH_2) substituent (Krakowiak et al., 1990; Nerdel et al., 1970; Olsher et al., 1991) are useful because the methylenyl unit can be easily converted to a hydroxymethyl group by the hydroboration procedure or to a keto group by oxidation (Nerdel et al., 1970; Tomoi et al., 1979). Use of these 1,3-propanediol derivatives gave crowns with a propylene unit between oxygen atoms.



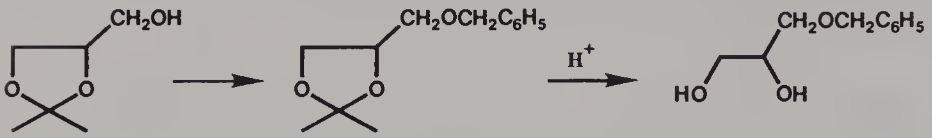


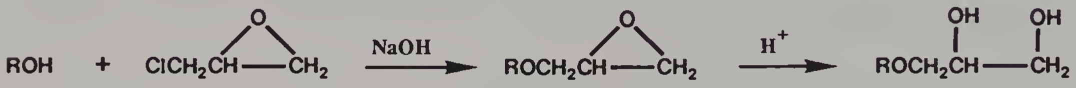
In general, crowns with ethylene bridges form more stable complexes with metal cations than those with propylene bridges. Okahara and coworkers (Ikeda et al., 1980, 1984) developed a method for preparation of substituted oligoethylene glycols using substituted ethylene oxides. The glycol containing two substituents on the first carbon was the major product of this reaction. Gandour and coworkers used a similar reaction to prepare hydroxymethyl-substituted oligoethylene glycols (Jungk et al., 1983). Recently, Bradshaw and coworkers have produced alkyl-substituted glycols by the above process (Bradshaw et al., 1986a; McDaniel et al., 1989).

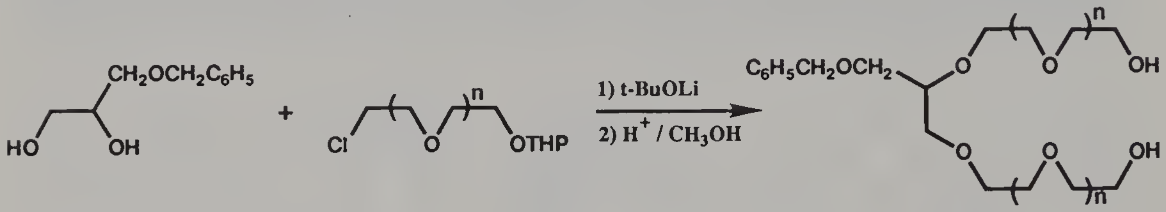


Many alkyl-substituted ethylene glycols can be purchased. Of particular interest is 3-allyloxy-1,2-propanediol, which is a great building block for preparing macrocycles containing an (allyloxy)methyl or hydroxymethyl substituent. Polyethylene glycols substituted with methyl and allyloxymethyl groups were prepared by the reaction of 1,2-propanediol, 3-allyloxy-1,2-propanediol, and ethylene oxide in the presence of BF_3–ether. The various polyethylene glycols were isolated by fractional distillation (Kuo et al., 1978).

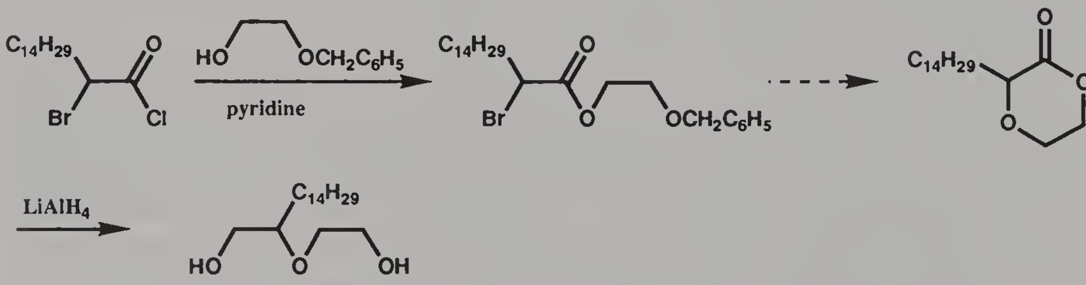
(Benzyloxy)methyl-substituted ethylene glycol, first prepared by Howe and Malkin (1951), has been used by many workers to prepare oligoethylene glycols with the (benzyloxy)methyl substituent in the middle of the ethylene oxide chain. This diol was prepared from the 1,2-isopropylidene-blocked glycerol or from the epichlorohydrin (Czech, 1980; Dishong et al., 1981; Gokel et al., 1980; Nakatsuji et al., 1983). The substituted ethylene glycol was then reacted with THP-protected oligoethylene glycol monochloride, followed by hydrolysis to remove the THP protecting group, to form the (benzyloxy)methyl-substituted oligoethylene glycol with a greater number of ethyleneoxy units (Bartsch et al., 1989; Czech, 1980; Czech et al., 1983a, 1983b, 1985; Son et al., 1984). The (benzyloxy)methyl group was converted to hydroxymethyl after the (benzyoxy)methyl-crown was prepared (Czech, 1980; Czech et al., 1983a; 1983b; Fukunishi et al., 1981; Son et al., 1984). Thus, the (benzyloxy)methyl-substituted glycols are important intermediates for preparation of the hydroxymethyl functionalized crowns.



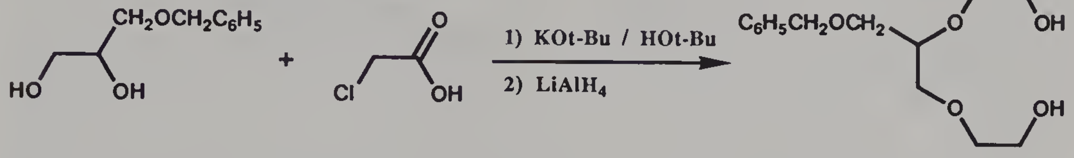




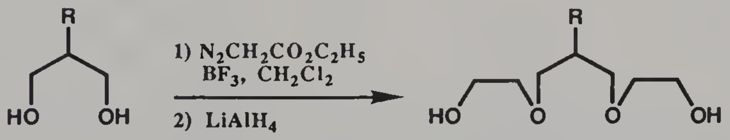
An unusual method to prepare diethylene glycol with an alkyl side chain has been reported by Montanari and coworkers (Anelli et al., 1985). As shown in the following scheme, α-bromopalmitic acid was reacted to obtain a lactone ether that was reduced to form the diol.



Reaction of (benzyloxy)methyl-substituted ethylene glycol with chloroacetic acid followed by reduction gave the substituted triethylene glycol. This latter reaction sequence, first used by Cinquini (1976) to prepare the bis-dodecyl-substituted triglycolic acid, was also used with some modifications by

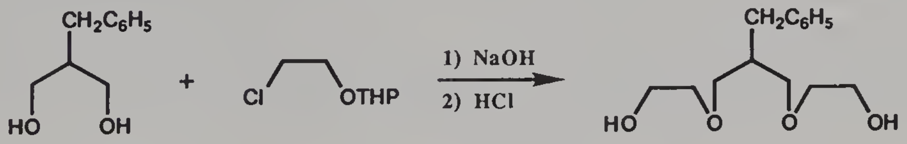


Bradshaw and coworkers (Bradshaw et al., 1986a, 1986b, 1988) and Bartsch and coworkers (Babb et al., 1986; Czech et al., 1983a, 1983b) to prepare glycols containing lipophilic or (allyloxy)methyl substituents. Montanari and Tundo (1982) also used this procedure to prepare the corresponding *tert*-butoxymethyl-substituted triethylene glycol, which was used to prepare hydroxymethyl-substituted crowns and cryptands. Similar glycols, but with a propylene bridge containing the substituent, were prepared by reacting ethyl diazoacetate rather than chloroacetic acid with the starting glycol (Sakamoto et al., 1986).

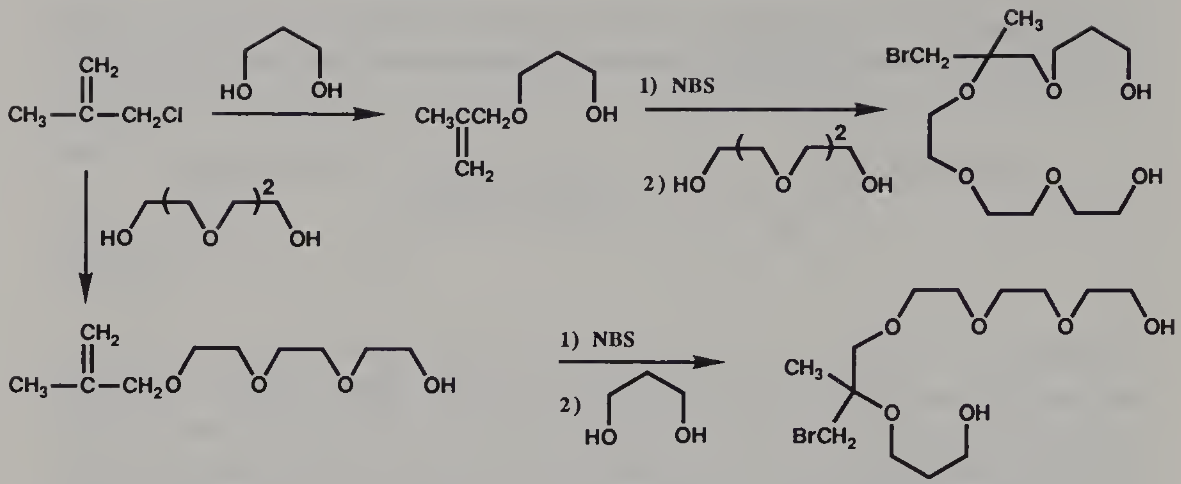


R = various alkyl groups

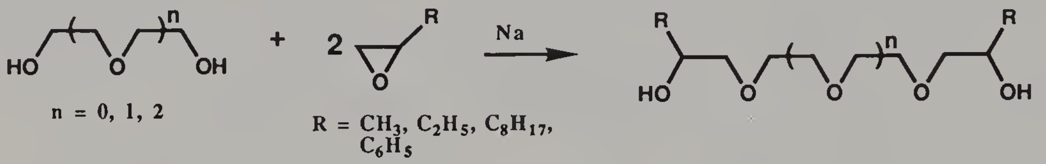
An efficient two-step method for preparation of oligoethylene glycols uses the reaction of 2 equivalents (eq) of THP-protected ω-chlorooligoethylene glycol $[Cl(CH_2CH_2O)_nTHP]$ with a diol in 50% aqueous sodium hydroxide in the presence of a phase-transfer agent to give the bis-THP protected oligoethylene glycol. The THP protecting groups are readily removed to provide the glycol in good to excellent yields as shown for the preparation of a relatively simple diol (Bartsch et al., 1989).

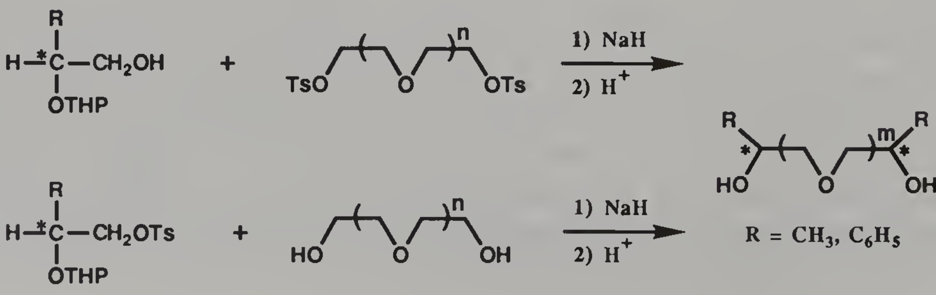


Okahara and coworkers have recently proposed some interesting bromomethyl-substituted glycols that also had a propylene bridge either on the oxygen next to the carbon containing the bromomethyl group or beta to that carbon (Nakatsuji et al., 1988; Wakita et al., 1990). These two types of products were formed in a two-step synthesis where the position of the bromomethyl substituent was fixed by the order of addition of trimethylene glycol or triethylene glycol.



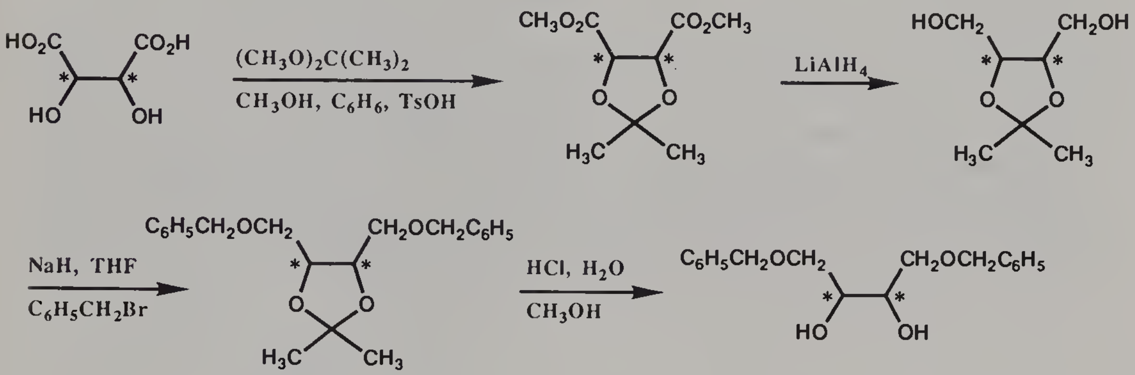
Oligoethylene glycols with symmetrically substituted terminal alkyl substituents have been prepared by the sodium-metal-catalyzed reaction of a lower oligoethylene glycol with 2 eq of a substituted epoxide (Bradshaw and Jolley, 1979; Jolley and Bradshaw, 1980; McDaniel et al., 1989). The reactions generally gave good yields (30–60%) of the di-substituted oligoethylene glycols, which often could be purified by distillation. One problem with this reaction is the formation of varying amounts of the 2-substituted isomer formed by attack of the alkoxide on the substituted carbon of the epoxide. The isomers can best be characterized from the NMR spectrum of their corresponding ester or tosylate derivatives. Chiral di-substituted oligoethylene glycols have been prepared by another method that requires the preparation of a chiral THP-protected alkyl- or phenyl-substituted ethylene glycol, which was then reacted with a ditosylate followed by deprotection to give the chiral oligoethylene glycol (Bradshaw et al., 1984, 1990a; Cooper and Walborsky, 1981; Huszthy et al., 1991; Jones et al., 1982). Alternatively, the THP-protected glycol could be converted to a tosylate and reacted with a diol in the presence of sodium hydride as shown below (Mack et al., 1976, 1983).



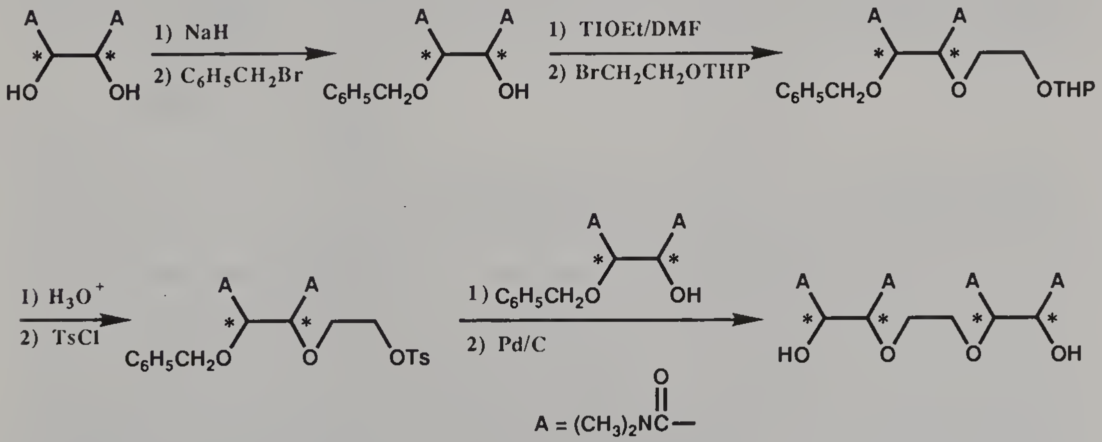


Many other chiral glycols have been prepared. These glycols were used to prepare various chiral crown ether ligands. A few of the chiral glycols are discussed in the next few pages.

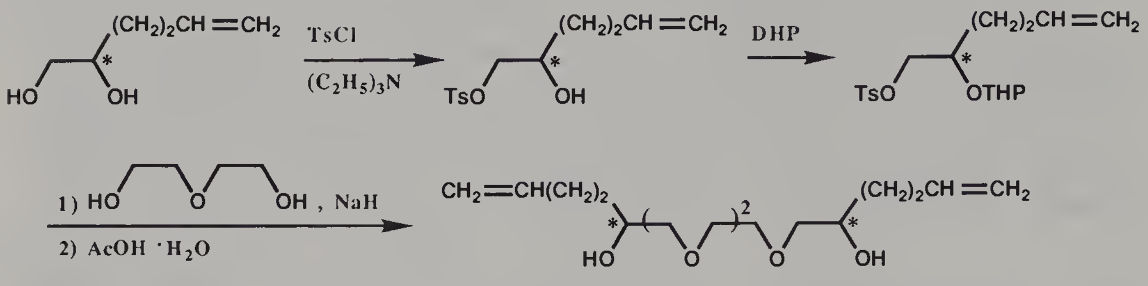
Stoddart and coworkers have reported chiral triethylene glycols prepared from D-mannitol (Curtis et al., 1977). Tartaric acid has been used most often to prepare a variety of chiral di-substituted ethylene glycols (Ando et al., 1978; Behr et al., 1980; Girodeau et al., 1975). The preparation of 1,4-di-*O*-benzyl-L-threitol is a good example of the use of tartaric acid (Mash et al., 1989). This compound has been used for the construction of chiral crown ethers that are useful as enzyme model systems (Fyles et al., 1984; Helgeson et al., 1979; Sasaki et al., 1985). Other examples of the preparation of chiral glycols and crowns and their applications are listed in a review by Stoddart (1987).

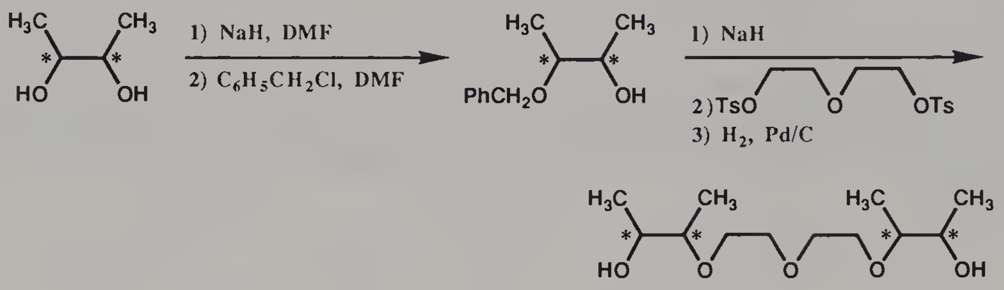


Another interesting preparation of a chiral tetracarboxamide-substituted triethylene glycol was reported recently by Fyles and coworkers using a benzyl protecting group on the original tartaramide compound and using thallous ethoxide to avoid epimerization of the chiral center (Dutton et al., 1989).

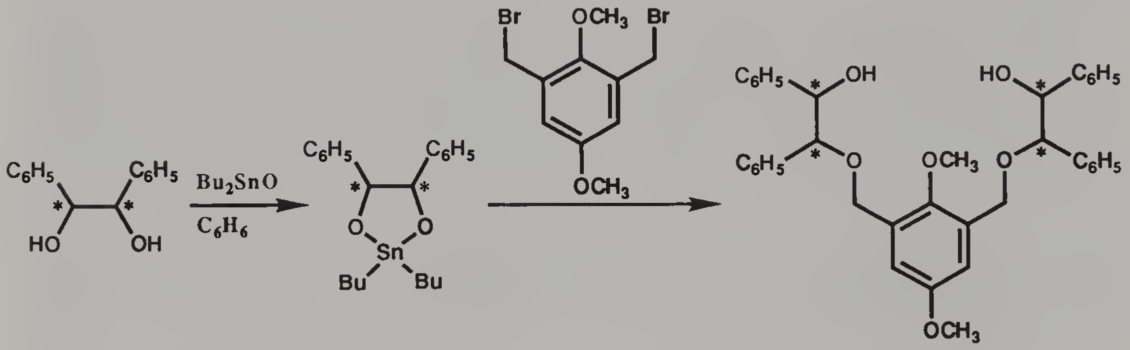


A similar use of benzyl and THP protecting groups and the selective formation of a primary tosylate has led to the preparation of chiral diallylsubstituted and tetramethyl-substituted tetraethylene glycols (Bradshaw et al., 1990a). An interesting chiral tetraphenyl-substituted diol containing a





benzene ring in the backbone has been prepared by Misumi and Kaneda (1989) using a dibutyltin derivative of chiral 1,2-diphenylethylene glycol.

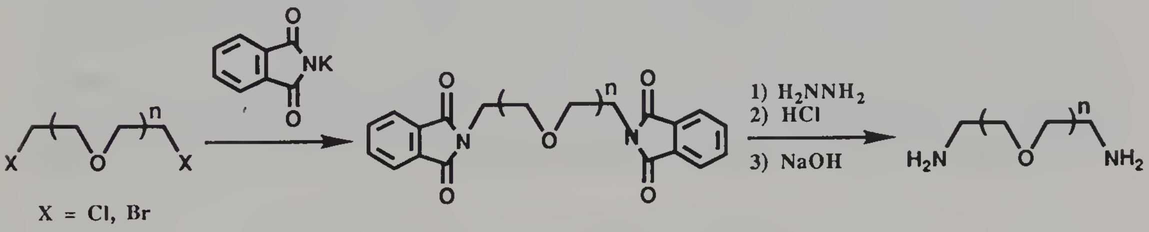


Some chiral starting materials containing more than two hydroxy groups have been used for the syntheses of macrocycles. Tetraols, for example, can react at two hydroxy functions, leaving the other hydroxy functions to bond the product to solid supports or on ion-selective electrodes (Bogatskii et al., 1984). Tetraols can also react to form bis-crowns (Bogatskii et al., 1984; Lukyanenko et al., 1986). 1,2,3,4-Butanetetraol was prepared from tartaric acid (Bogatskii et al., 1984), and 2,3-bis(hydroxymethyl)-1,4-butanediol was prepared from sodium malonate (Lukyanenko et al., 1986). The nonchiral spiro tetraols, which were used to build bis-crowns, were prepared from pentaerythritol (Weber, 1979, 1982).

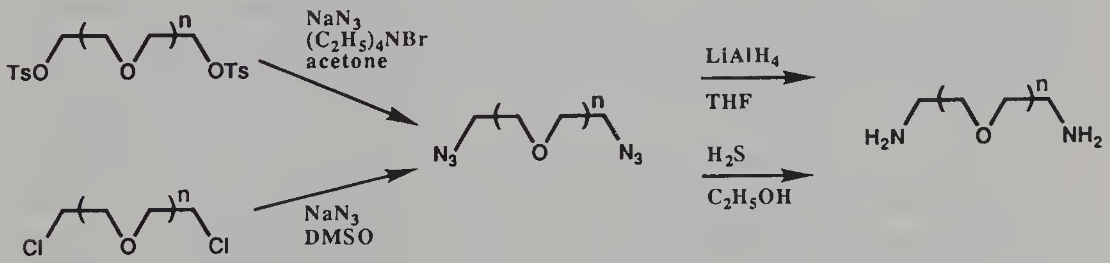
B. PREPARATION OF DIAMINO AND POLYAMINO ALIPHATIC ETHERS

It is important to have simple and inexpensive methods for preparation of the diamine starting materials needed for cyclization to form the diaza-crown compounds. Many of the oligoethylene (or oligopropylene) polyamines and their *N*-methyl and *N*-ethyl analogs can be purchased. We present here some of the methods that have been used to prepare the diamino and polyamino aliphatic ethers that are not available.

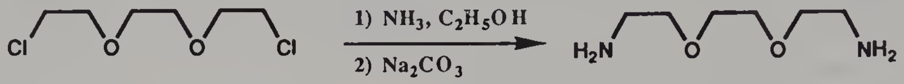
First, methods for preparation of the primary diamino aliphatic ethers are presented. These materials can be used to prepare polyamines (see Chapter II, Section C). A modified Gabriel synthesis, using the reaction of potassium phthalimide with a dihalide followed by hydrolysis using hydrazine was one of the first methods used to prepare the diamino ethers (Bogatskii et al., 1980; Dietrich et al., 1973; Dwyer et al., 1953; Sun et al., 1985). Krakowiak and Kotelko (1982, 1983b) used this method to prepare a variety of diamino ethers containing both ethylene and propylene connecting groups. The 1,5-diamino-3-oxapentane is available but expensive. Longer diamino ethers must be prepared in the laboratory.



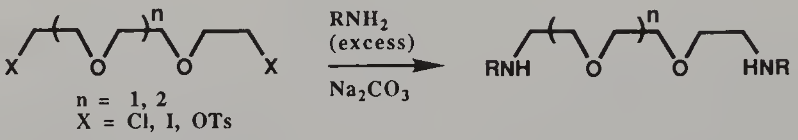
Reduction of diazido-substituted ethers to the diamine form has been reported by a number of workers (Desreaux et al., 1977; Gansow et al., 1981; Gatto et al., 1986a; Kulstad and Malmsten, 1979). The starting diazido ethers were prepared by treating either the ditosylate or dichloro derivatives of the oligoethylene glycols with sodium azide. The reduction of the diazide can be done with lithium aluminum hydride or hydrogen sulfide in ethanol as shown. These reactions gave an overall yield of 65–85%; however, care must be taken because the diazide can be explosive.



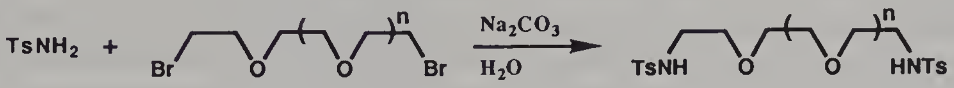
A more direct approach to the 1,8-diamino-3,6-dioxaoctane was reported in 1974 by King and Krespan. They used the Hofmann reaction of a chlorocompound with ammonia by reacting 1,8-dichloro-3,6-dioxaoctane with ethanolic ammonia and sodium carbonate in an autoclave to give the diamine in a 71% yield (King and Krespan, 1974). Their reaction was similar to that for the preparation of bis(3-aminopropyl)ether by Wiley (1946). The ditosylate derivative of triethylene glycol has been used in place of the dichloride for the above reaction. In this case, 30% aqueous ammonium hydroxide was used. The yields for this reaction were lower, but an autoclave was not necessary (Bradshaw et al., 1987). This method of preparing diamino ethers is probably not a general one. It is likely that the reaction of 1,5-dichloro-3-oxapentane with ammonia would give morpholine not the desired 1,5-diamino-3-oxapentane (Boon, 1949; Gatto et al., 1986a).



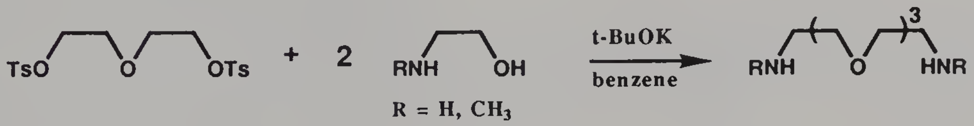
This procedure is also convenient for the preparation of *N*,*N*′-dialkyl (or ditosyl) derivatives of 1,8-diamino-3,6-dioxaoctane and higher homologs. The procedure uses the reaction of the readily available dihalo or ditosylate derivatives of the oligoethylene glycols with an excess of alkyl or arylamine (Bradshaw and Krakowiak, 1988; Gatto et al., 1989; Kikui et al., 1984; Sonveaux, 1984). This process is not applicable to preparation of the diamine derivatives of diethylene glycol since the reaction of an amine with the dihalide yields only *N*-alkylmorpholine as mentioned above (Boon, 1949; Gatto et al., 1986a). Gokel and coworkers used the more reactive diiodide in this reaction to prepare some *N*,*N*′-dialkyldiamines in yields of 70–85% (Gatto et al., 1986a). Bradshaw and Krakowiak (1988) have optimized the reaction with the dichloride using only a 4-fold excess of the amine in the presence of sodium carbonate and using a Dean–Stark apparatus to remove water formed in the reaction to obtain an 82% yield of the *N*,*N*′-dibenzyl derivatives. Recently, Gokel and coworkers also used the 1,2-bis(2-chloroethoxy)ethane in excess benzylamine to prepare the 1,10-dibenzyl-4,7-dioxa-1,10-diazadecane (Gatto et al., 1989).

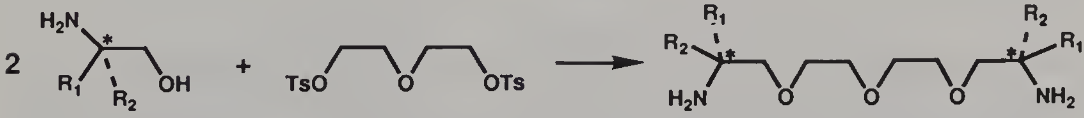


The *N*,*N*′-ditosyldiamino ethers can be prepared in a one-step reaction using *p*-toluenesulfonamide and the appropriate dihalide. This procedure is certainly easier than the three-step method of first forming the diamine and then reacting it with tosyl chloride (Bogatskii et al., 1980; Desreaux et al., 1977; Sun et al., 1985). In the new method, 1,8-dibromo-3,6-dioxaoctane (or its next-higher homolog) was added to the tosylamide in saturated aqueous sodium carbonate to give a high yield of the *N*,*N*′-ditosyldiamine (Lukyanenko et al., 1988). The reaction of 1,8-dichloro-3,6-dioxaoctane with *p*-toluenesulfonamide in a different solvent gave a low yield of 1,10-ditosyl-1,10-diaza-18-crown-6 rather than the open chain *N*,*N*′-ditosyldiamine (Rashoffer and Vögtle, 1978). Similar results were reported by Pappalardo and coworkers for the reaction of *p*-toluenesulfonamide and 1,2-bis-(2-iodoethoxy)ethane in DMF, except they also isolated *N*-tosylaza-9-crown-3 in addition to the 1,10-ditosyldiaza-18-crown-6 (Bottino et al., 1988).

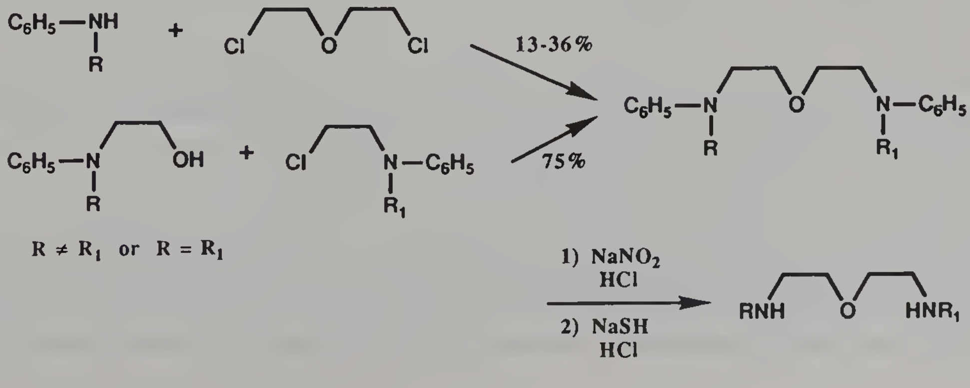


Böhmer and coworkers found that 2-aminoethanol reacted with a ditosylate using potassium *t*-butoxide as base to form the diamino ether in a 30% yield (Kern et al., 1979). They also prepared the *N*,*N*′-dimethyl derivative. Sutherland and coworkers used this same technique to prepare a chiral diamino ether in high yields (Chadwick et al., 1984). Secondary amines were prepared in much the same fashion. Some mixed oligo(ethyleneoxy)dipropylamines, $NH_2(CH_2)_3(OCH_2CH_2)_nO(CH_2)_3NH_2$, can be purchased from Tokyo Kassei. These materials are inexpensive and can be used to form the aza-crowns.



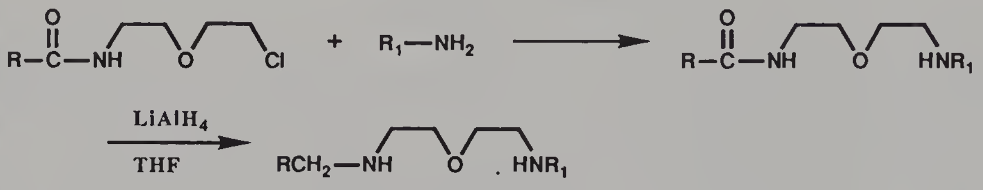


Boon (1949) prepared the 1,5-bis(methyl- or ethylamino)-3-oxapentanes by two methods as shown. The initial diamino ether contained phenyl protecting groups that required a two-step method for removal. Boon also isolated

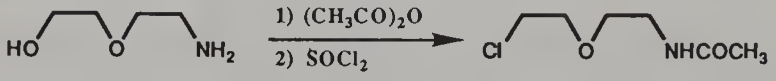


N-phenylmorpholine as a by-product when the dichloride was reacted with aniline (R = H). The second method allows the preparation of unsymmetric derivatives where the R groups substituted on each of the two nitrogen atoms are different (Boon, 1949).

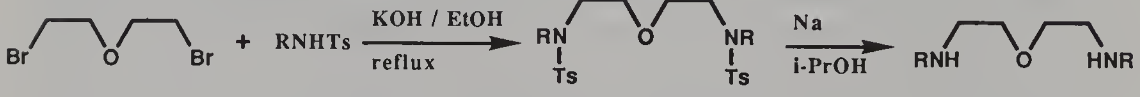
Recently, Bradshaw and coworkers reported the synthesis of *N*,*N*′-dialkyldiamino ethers with ethyl or benzyl on one amine nitrogen atom and any alkyl group (including ethyl or benzyl) on the other amine nitrogen (Bradshaw et al., 1990b). The overall yields of these reactions were not high because the primary amine also reacted with two alkyl chlorides, giving the unwanted *N*,*N*,*N*′-trialkyl-substituted products. Even so, this procedure is important because there is no other general method for preparing these unsymmetrically substituted *N*,*N*′-dialkyldiamines. The key building blocks, *N*-[2-(2-chloroethoxy)ethyl]acetamide and its benzamide analog, were prepared from available 2-(2-aminoethoxy)ethanol in high yields (Bradshaw et al., 1990b; Krakowiak et al., 1989b; Krakowiak and Bradshaw, 1991).



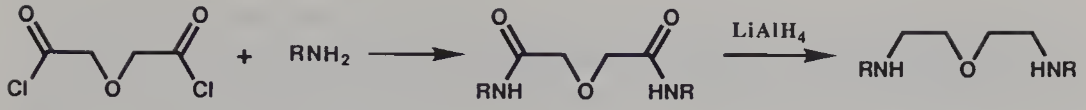
R_1 = various
R = C_6H_5, CH_3



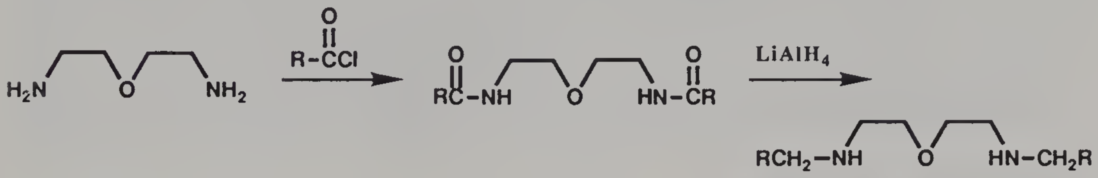
N-Tosyl-substituted amines have also been used to prepare secondary diamino ethers. Petranek and Ryba (1980) reacted *N*-tosylbenzylamine or the aniline analog with the dibromo derivative of diethylene glycol to form the bis(*N*-tosylamino) derivatives. The tosyl blocking groups were removed by using sodium in isopropyl alcohol. *N*,*N*′-Dimethyldiamino ethers were prepared by Krakowiak and Kotelko (1983a) by tosylating bis(2-aminoethyl)ether, subsequently alkylating the *N*,*N*′-ditosyl derivative in base, and removing the tosyl group by HBr/phenol in acetic acid.



An excellent method for preparation of the *N*,*N*′-dialkyl derivatives of 1,5-diamino-3-oxapentane involves the formation of a bisamide followed by reduction with lithium aluminum hydride (Krakowiak and Kotelko, 1983a; Pietraszkiewicz, 1984). Diamines with a wide variety of alkyl substituents from

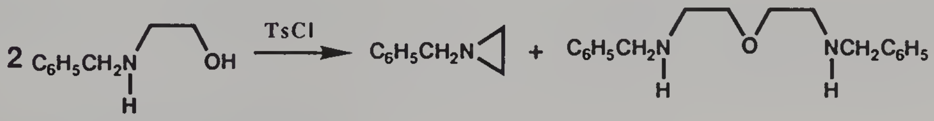


methyl to 3-(*N*,*N′*-diethylamino)propyl were prepared in moderate yields. Others have used this procedure, except borane was used as the reducing agent (Gatto et al., 1986a, 1986b). Gokel and coworkers also prepared the *N*,*N′*-dialkyldiamino ether by treating the diamine with an acid chloride followed by reduction of the resulting bisamide (Gatto et al., 1986a). This is a

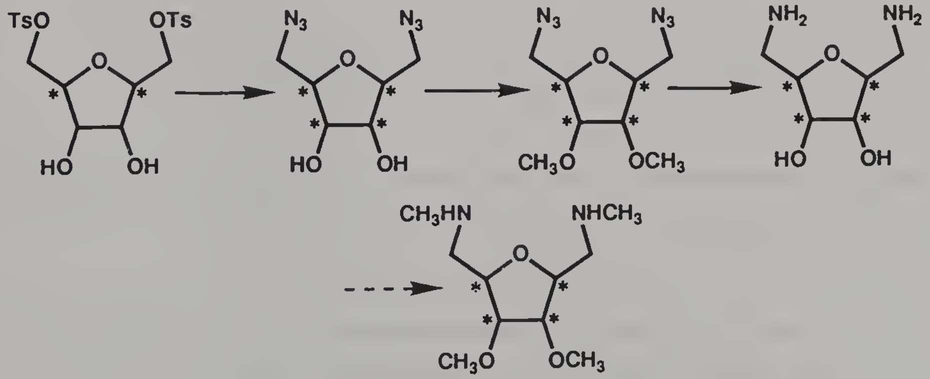


reasonably good method of preparing these diamines, but the starting 2,2′-bis(aminoethyl)ether is several times more expensive than diglycolyl dichloride used in the preceding method.

N,*N′*-Dibenzyl-1,5-diamino-3-oxapentane was prepared in a low yield by a one-step dimerization of *N*-benzylethanolamine (Bradshaw et al., 1990b). The main product was the *N*-benzylaziridine.



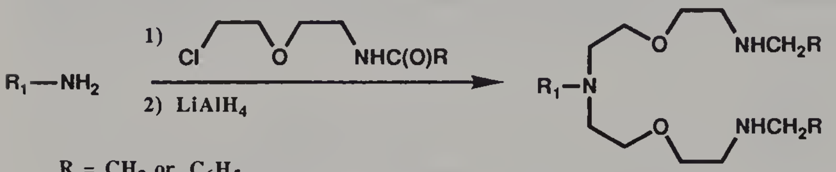
Lehn and Potvin (1988) have prepared an interesting chiral diamino ether based on the *N*,*N′*-dimethyl-1,5-diamino-3-oxapentane structure. Starting with a ditosylate derivative of D-mannitol, they were able to produce the 2,5-anhydro-1,6-di-*C*-(*N*-methyl)amino-1,6-dideoxy-3,4-di-*O*-methyl-D-mannitol as shown.



Diamino ethers containing one or more additional amine groups in the chain have been prepared. These polyamino ethers contain terminal NHC_2H_5

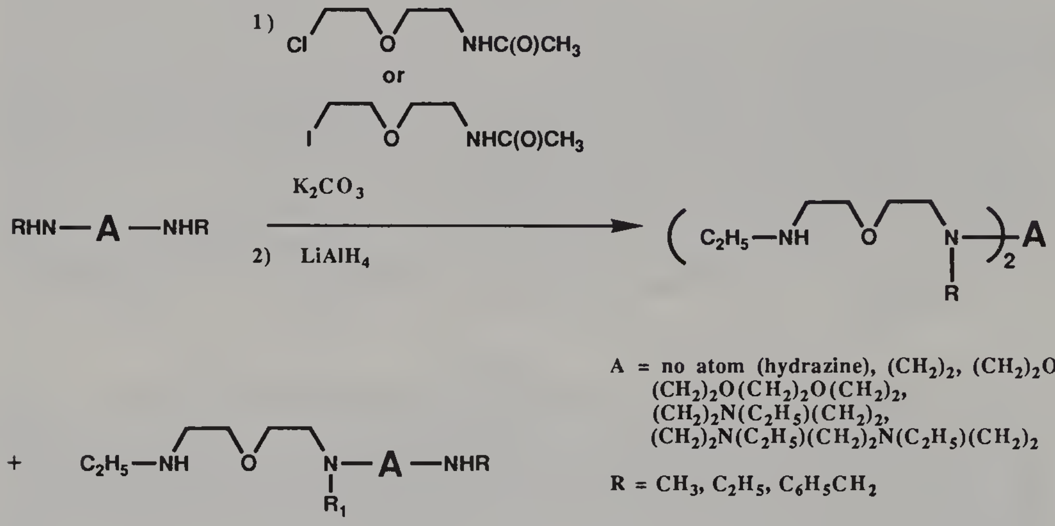
or $NHCH_2C_6H_5$ functions (Bradshaw et al., 1990b; Krakowiak and Bradshaw, 1991; Krakowiak et al., 1989b, 1989c, 1990). The procedure used the reaction of *N*-[2-(2-chloroethoxy)ethyl]acetamide or its benzamide analog with an amine, diamine, or polyamine and the subsequent reduction of the amide functions as shown in the following two schemes. When the reaction to form the tetraamine (excluding any amine groups in A) was run with an excess of *N*-[2-(2-chloroethoxy)ethyl]acetamide in toluene or DMF, mostly the diadduct was formed. A greater amount of the monoadduct was formed when the acetamide derivative was the limiting starting material (Bradshaw et al., 1990b; Krakowiak et al., 1989b, 1989c). It was possible to prepare higher-order polyoxa amines when the polyamino products shown in the schemes were further reacted with *N*-[2-(2-chloroethoxy)ethyl]acetamide followed by reduction (Krakowiak et al., 1989b).

Triamines



$R = CH_3$ or C_6H_5
$R_1 = HO(CH_2)_2O(CH_2)_2$-, benzyl

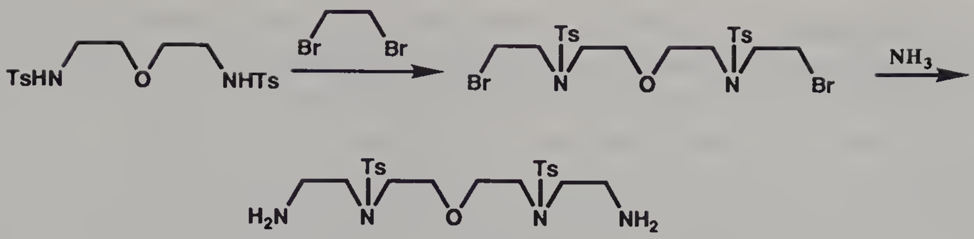
Tetraamines and Polyamines



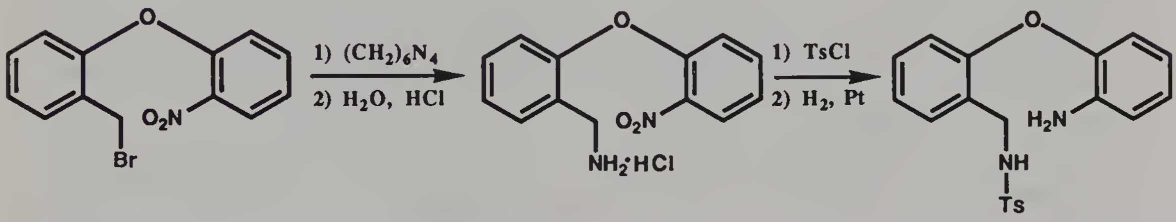
A = no atom (hydrazine), $(CH_2)_2$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_2O(CH_2)_2O(CH_2)_2$, $(CH_2)_2N(C_2H_5)(CH_2)_2$, $(CH_2)_2N(C_2H_5)(CH_2)_2N(C_2H_5)(CH_2)_2$

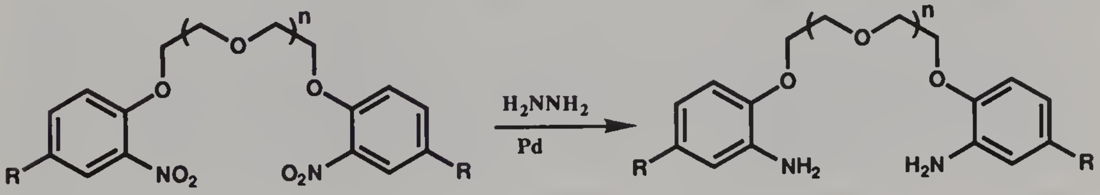
$R = CH_3$, C_2H_5, $C_6H_5CH_2$

Lehn and coworkers prepared a tetraamino ether similar to those shown above except the two internal amines contained tosyl groups (Dietrich et al., 1983). They reacted an excess of 1,2-dibromoethane with *N*,*N*′-ditosyl-1,5-diamino-3-oxapentane to form an open chain dibromide as shown. Use of an excess of the dibromide suppressed the formation of a nine-membered ring. The oxadiaza dibromide was then reacted with ammonia to form the product.



Only a few of the many aromatic diamino ethers used to prepare macrocycles will be mentioned here. A reduction process has been used to prepare aromatic diamines from nitro- and azide-containing ethers. The preparation of an aromatic diamine using known methods was reported by Glinka (1982), who treated an aromatic nitro halide with hexamethylenetetraamine followed by hydrolysis to give an aromatic nitro amine. The nitro amine was reduced to the diamine after tosylation. A palladium-catalyzed hydrazine or amalgamated aluminum reduction of some bisnitro aromatic compounds appears to be a good method for the preparation of dianiline-substituted ether compounds (Biernat et al., 1979, 1987; Bradshaw et al., 1987).





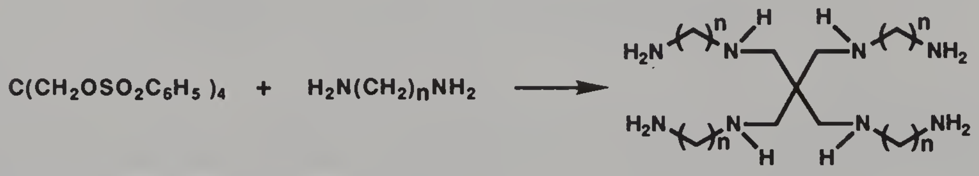
C. PREPARATION OF POLYAMINES

Polyamines containing terminal primary or secondary amine functions are important starting materials for the polyaza- and peraza-crowns. The most common method of preparing these terminal diamines from readily available dihalogen compounds is the Gabriel synthesis using phthalimide (Gibson and Bradshaw, 1968). The use of hydrazine hydrate hydrolysis of the imide (Dwyer et al., 1953; Ing and Manske, 1926) instead of acid hydrolysis has greatly improved this method for preparation of an amine. Other Gabriel reagents are very useful because mild conditions can be used for the final deprotection step (Ragnarsson and Grehn, 1991). The reaction of alkyl halides or tosylates in the Delepine reaction with hexamethylenetetraamine (Wendler, 1949) and the Hofmann reaction with liquid ammonia (Whitmore and Langlois, 1932) are often employed to prepared the bis-terminal primary amines. These last two reactions have limited application. Hexamethylenetetraamine is a poor nucleophile and will react only with very reactive alkyl halides such as the benzylic, pyridylic, or allylic halides (or tosylates) or the β-bromocarboxylic acid derivatives. Reactions with ammonia or liquid ammonia often require special equipment that is not available in most laboratories.

Many polyamines are now available from Aldrich, Fluka, Phaltz and Bauer, Sigma, and TCI chemical companies. The available compounds include tri- and tetraamines with a mix of ethylene, trimethylene, and tetramethylene units between the nitrogen atoms. Of particular interest are tetraamines where the two internal amines are tertiary and the terminal amines are secondary. These compounds can be used in the ring closure reaction to form the peraza-crowns.

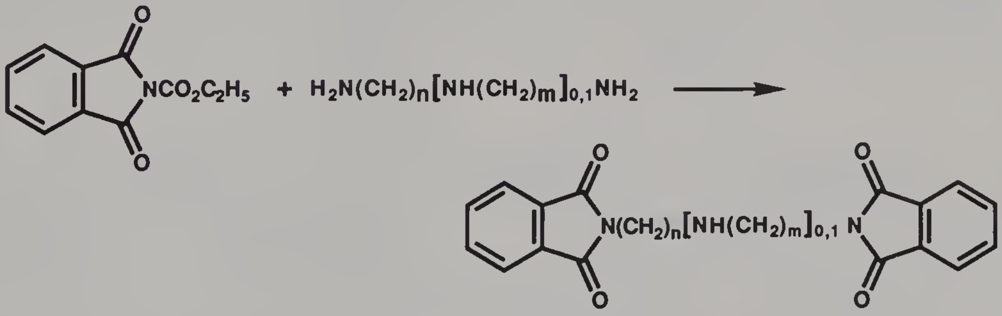
There are numerous natural polyamines such as putrescine, spermine, and spermidine. The chemistry of these and related compounds has some recent developments (Bergeron, 1986; Ganem, 1982). The preparation of these compounds is not straightforward (Carboni et al., 1988; Nordlander et al., 1984). Nordlander and coworkers list the various preparative methods and other progress in this field.

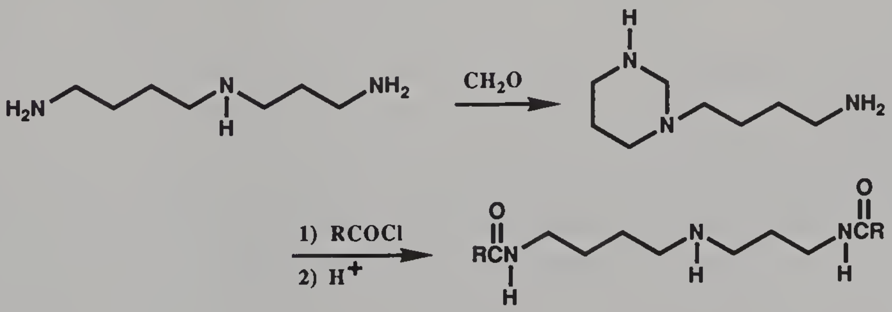
Although there are now a large number of available polyamines, there still is a need to modify them or to make longer chains with more amine groups. The most used procedure to form higher order polyamines is to use a large excess of the primary amine and a dihalide or ditosylate (Alphen, 1936; Krakowiak et al., 1980). The use of excess primary amine reactant reduces the problem of disubstitution on the amine, and the excess primary amine reactant is easy to remove by distillation. This method was used to build a complicated polyamine by reacting pentaerythritol tetrabenzenesulfonate (or tetrabromide) with ethylene- or trimethylenediamine (Geue and Searle, 1983; Phillip, 1968; Sakaguchi et al., 1985; Tomioka et al., 1984). This reaction gave three products that were separated as their Ni(II) complexes (McAuley et al., 1989). Linear polyamines also were prepared by using a large excess of the primary amine as shown in the following example (Barefield et al., 1976). Many other polyamines have been prepared in average yields by this standard nucleophilic displacement procedure (Hamilton and Alexander, 1966).



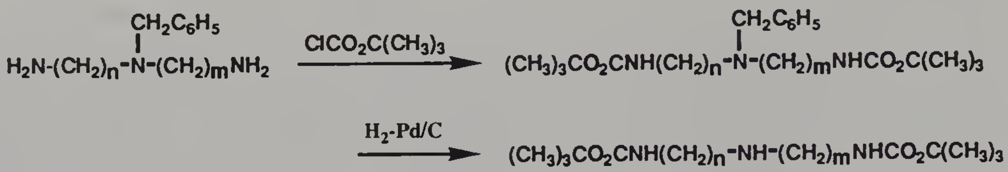
There are problems in preparing specific polyamines with only secondary amine functions or polyamines with primary terminal amine functions and tertiary internal amines (Bradshaw et al., 1992). In these cases, the terminal primary amine or internal secondary amine functions need to be protected. For example, for the preparation of 3-methyl-1,5-diamino-3-azapentane, phthalic anhydride was reacted with the two primary amines of 1,5-diamino-3-azapentane to form the bisphthalimide as a protection for the primary amines. The internal amine was then methylated and the phthalimide groups removed (Searle et al., 1979).

There are a number of other methods to selectively protect primary amines. Nefkens' reagent selectively protects primary amines as shown below (Sosnovsky and Lukszo, 1986). The reaction of spermidine with formaldehyde produced 1-(4-aminobutyl)hexahydropyrimidine, which on successive acylation and ring cleavage was transformed into the bisamide-protected triamine (Bergeron et al., 1982). Bergeron and coworkers also prepared terminally protected triamines by first preparing the triamine containing a benzyl protecting group on the internal nitrogen atom and reductively cleaving the benzyl group after the *tert*-butoxycarbonyl protecting units were added to the end



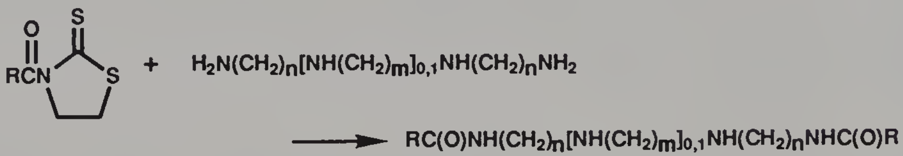


amines as shown (Bergeron and Garlich, 1984; Bergeron et al., 1981). Terminally acyl-protected polyamines also were prepared by reacting the polyamine with 1-acyl-1,3-thiazolidine-2-thione (Nagao et al., 1980, 1981).

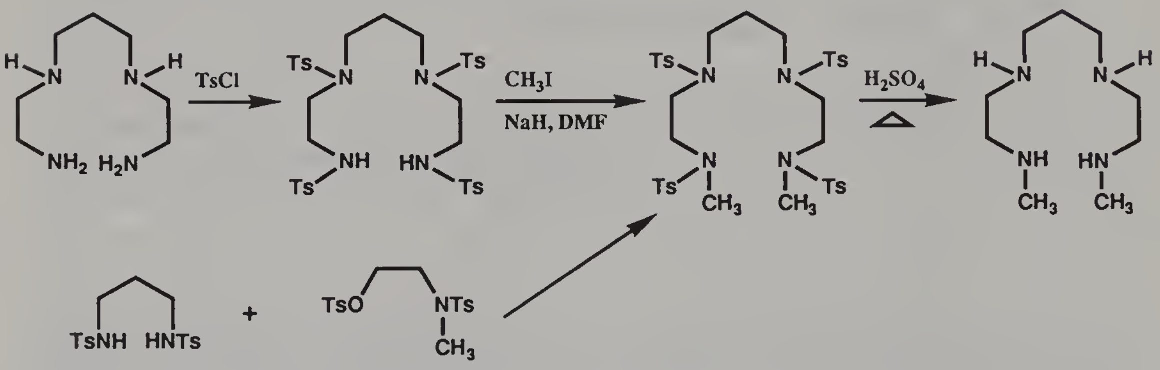


$$H_2N\text{-}(CH_2)_n\text{-}\overset{CH_2C_6H_5}{N}\text{-}(CH_2)_mNH_2 \xrightarrow{ClCO_2C(CH_3)_3} (CH_3)_3CO_2CNH(CH_2)_n\text{-}\overset{CH_2C_6H_5}{N}\text{-}(CH_2)_mNHCO_2C(CH_3)_3$$

$$\xrightarrow{H_2\text{-}Pd/C} (CH_3)_3CO_2CNH(CH_2)_n\text{-}NH\text{-}(CH_2)_mNHCO_2C(CH_3)_3$$

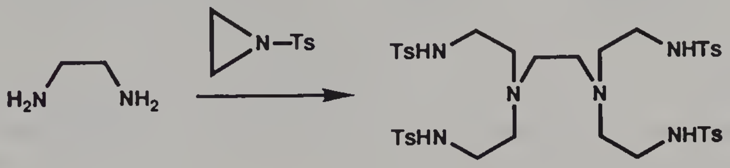


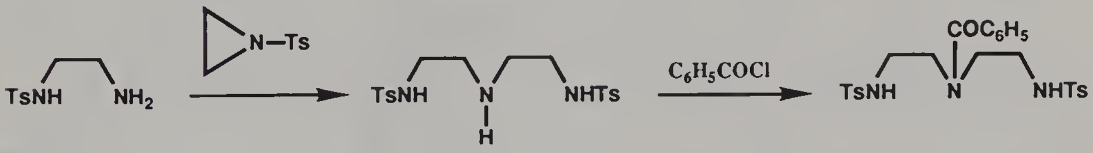
Paoletti and coworkers used *N*-tosyl protecting groups to prepare a tetraamine containing only secondary amine functions (Clay et al., 1985). The second part of the scheme shows another strategy for preparing these compounds.



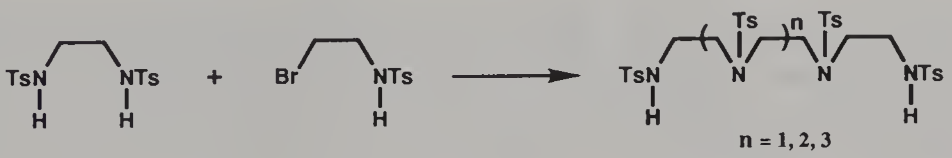
It is often easier to build a new molecule from more simple materials than to modify an available compound. Methods that allow the formation of polyamines from smaller moieties are of great interest. The formation of polyamines with ethyl, propyl, or butyl bridges between nitrogen atoms has developed in recent years. These types of compounds are important for the preparation of synthetic cyclams that are similar to natural spermine and spermidine alkaloids (Marecek and Burrows, 1986; Wasserman and Wu, 1982). Indeed, most of the interest in open-chain polyamines has focused on their use for the preparation of biologically active compounds including the peraza-crowns (cyclams).

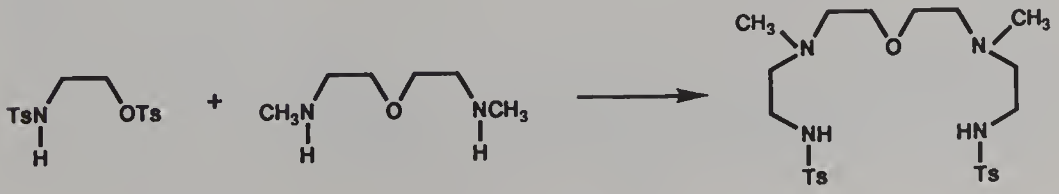
There are some useful techniques of extending the polyamine chain on one or both sides (Bradshaw et al., 1992). Nucleophilic ring opening of the aziridine molecule is one of the most used methods to extend the chain. Most of the aziridines that are used have electron-withdrawing groups (RCO, RSO_2, CN, Ar, etc.) substituted on the aziridine nitrogen atom. Other aziridines require more vigorous reaction conditions for ring opening. *N*-Tosylaziridine, which is not commercially available, has been used the most since the reaction product has the reactive *N*-tosylamine groups on the terminal positions. Paoletti and coworkers have used this procedure to prepare a complicated *N*,*N*′,*N*″,*N*‴-tetratosylhexaamine (Garcia-Espana et al., 1985). Martin and Bulkowski (1982) have also used *N*-tosylaziridine to prepare diethylene triamine with a different protecting group on the middle nitrogen atom. This type of reagent is helpful in producing macrocycles with different functional groups (Martin et al., 1982).



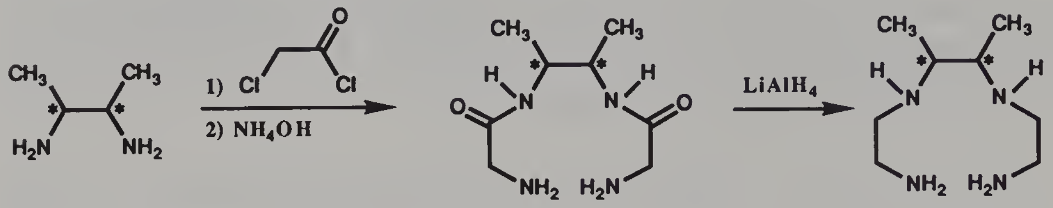


A similar reaction was observed using *N*-tosyl-2-bromoethylamine (Iwata and Kuzuhara, 1986a). The reaction of *N*-tosyl-2-bromoethylamine and *N*,*N*′-ditosylethylenediamine gave mainly the desired pertosyltriethylenetetraamine ($n = 1$), but also some pertosyltetraethylenepentaamine ($n = 2$) and pertosylpentaethylenehexaamine ($n = 3$) were isolated. Opfew and Popkov (1987) found that 2-(*N*-tosylamino)ethyl tosylate, on the other hand, only added once to each amine group of *N*,*N*′-dimethyl-3-oxa-1,5-pentanediamine to give the dimethyl ditosyl tetraamine as shown.

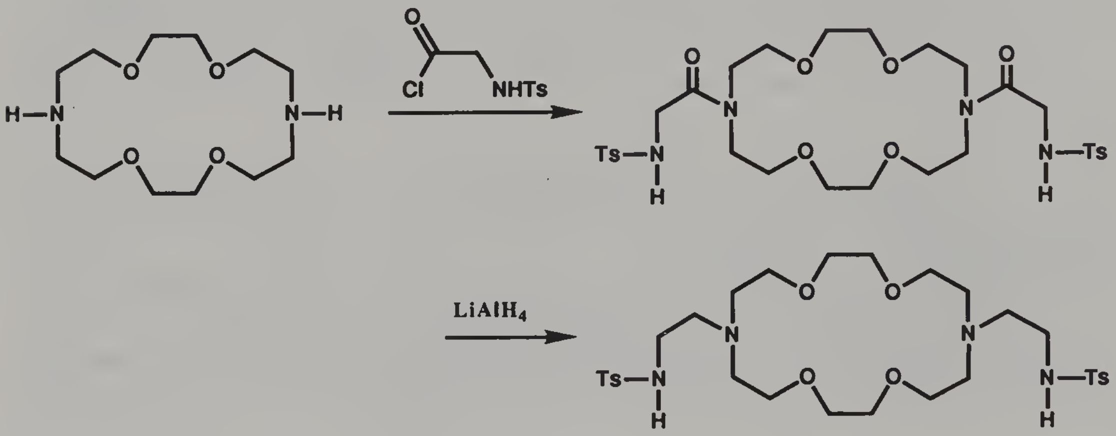




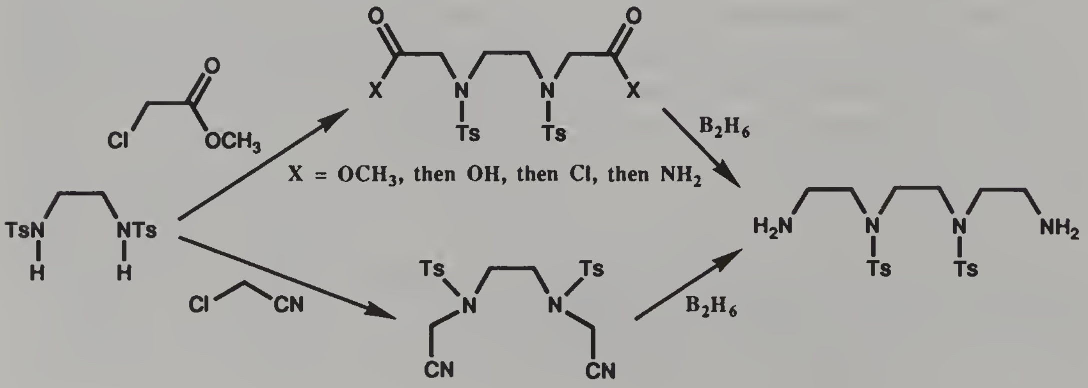
Inexpensive chloroacetyl chloride is a convenient building block to extend the polyamine chain. Goto and coworkers prepared a chiral dimethyl-substituted triethylenetetraamine using chloroacetyl chloride (Goto et al., 1973).



N-Tosylaminoacetyl chloride has also been used to add aminoethyl groups to a polyamine chain (Dragomiretskaja et al., 1987). The process requires reduction of the amide moieties as well as removal of the *N*-tosyl groups. The formation of bis-2-(*N*-tosylamino)ethyl-substituted 1,10-diaza-18-crown-6 is an example of this process.

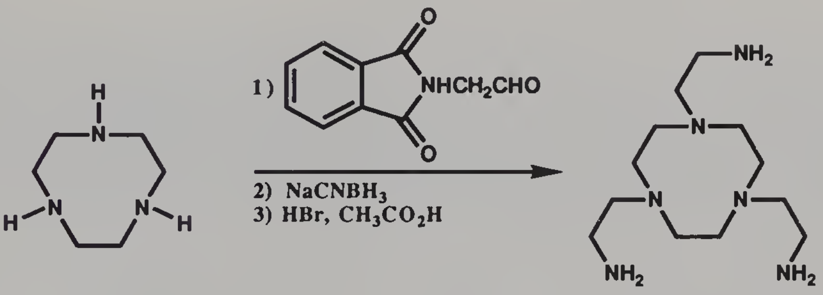


Extending the chain has allowed the five-step synthesis of a tetraamine with tosyl groups on the two center nitrogen atoms (Stetter and Roos, 1954; Stetter and Mayer, 1961; Takada et al., 1988). The procedure used the reaction of *N*,*N*′-ditosylethylenediamine with derivatives of chloroacetic acid.

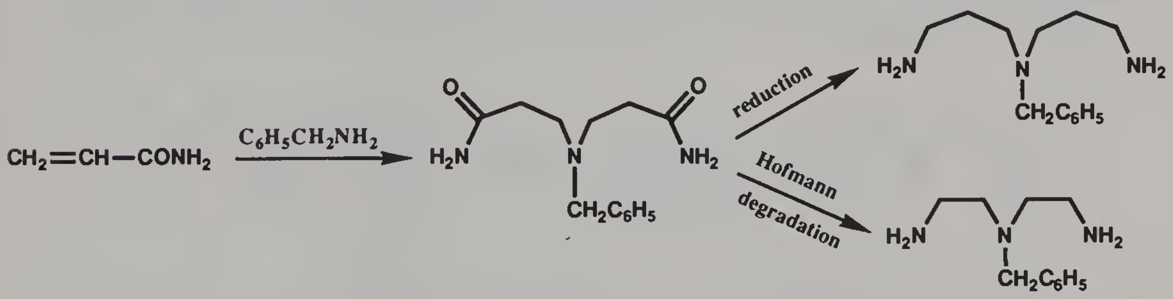


After attaching the chloroacetic acid derivatives, they can be converted to the carboxylic acid, acid chloride, and finally to the amide functions (Takada et al., 1988). A shorter process (bottom reaction in scheme above) used chloroacetonitrile followed by reduction instead of chloroacetate to give the product in an overall yield of 76% (Dietrich et al., 1989). Chloroacetonitrile was previously used to prepare secondary amines from primary amines (Overman and Burk, 1984).

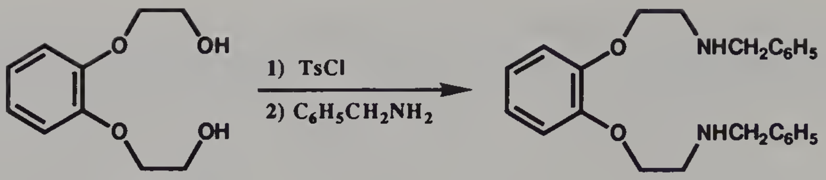
Aminoethyl side arms can also be added using phthalimide derivatives such as (2-bromoethyl)phthalimide or the acetaldehyde analog. The reaction of the aldehyde with a secondary amine requires sodium cyanoborohydride to effect the reductive alkylation of the amine (Gahan et al., 1982; Hammershoi and Sargeson, 1983).



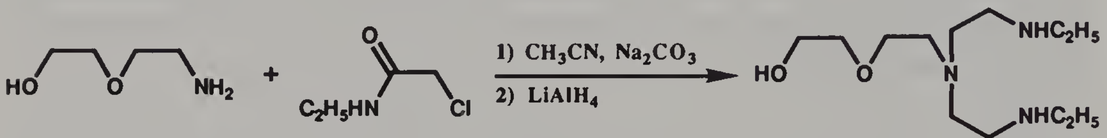
An interesting method for preparation of either 4-benzyl-4-aza-1,7-heptanediamine or 3-benzyl-3-aza-1,5-pentanediamine has been reported (Tweedle et al., 1987). Benzylamine was added to 2 eq of acrylamide to form the intermediate bisamide. The bisamide was reducted to form the bis(3-aminopropyl)benzylamine or converted to the bis(2-aminoethyl)benzylamine using the Hofmann amide degradation as shown. The Hofmann amide degradation requires sodium hypobromite or hypochlorite. The latter reagent is recommended more often (Magnien and Baltzly, 1958; Wallis and Lane, 1946).

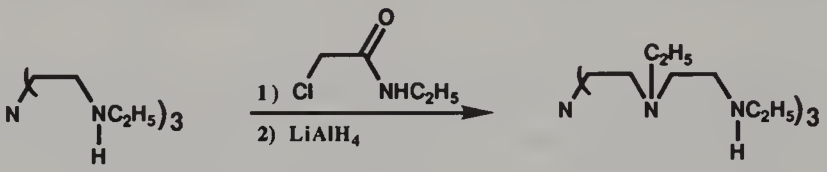


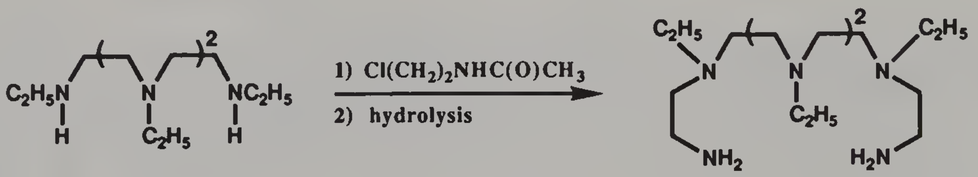
The (2-alkylamino)ethyl side arm can be introduced by reacting a suitable primary amine with the appropriate dialkyl ditosylate unit (Pedersen and Bromels, 1977). This reaction with bis(2-hydroxyethoxy)benzene also gave the benzoaza-9-crown-3 unless an excess of the benzylamine was used.



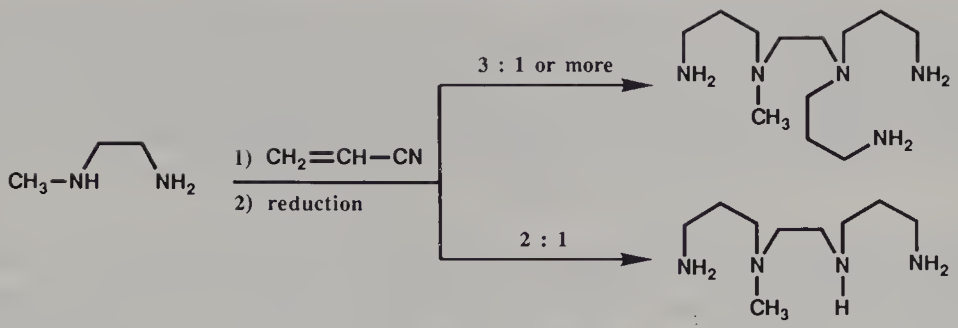
N-Alkylchloroacetamide is readily available and a convenient reagent to introduce 2-(*N*-alkylamino)ethyl groups onto an amine system (Bradshaw et al., 1989b). An interesting tri-terminal secondary amine was prepared using this procedure. Tris(2-ethylaminoethyl)amine was reacted with *N*-ethylchloroacetamide in acetonitrile in the presence of anhydrous sodium carbonate to give the triamide, which was reduced to the tri-terminal secondary amine (Bradshaw and Krakowiak, 1990). The same type of reaction using chloroacetamide (without the *N*-alkyl group) and a bis secondary amine gave only average yields of the bis-terminal primary amine products (Bradshaw et al., 1989b). It is possible to use *N*-(2-chloroethyl)acetamide rather than chloroacetamide to introduce *N*-aminoethyl substituents at the end of a polyamine (Crnic and Glincic, 1981). This reaction must be carried out in acid medium since base causes the starting material to cyclize to form 2-oxazoline rather than the linear compounds (Franco and Muchowski, 1980). These types of cyclizations are difficult to avoid, so it is best to use reagents that will not cyclize.

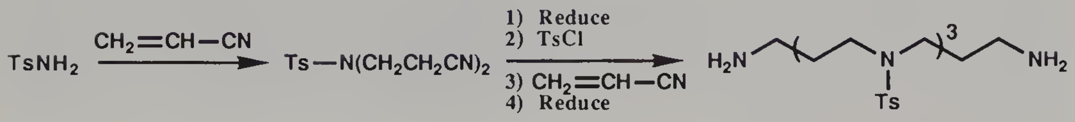




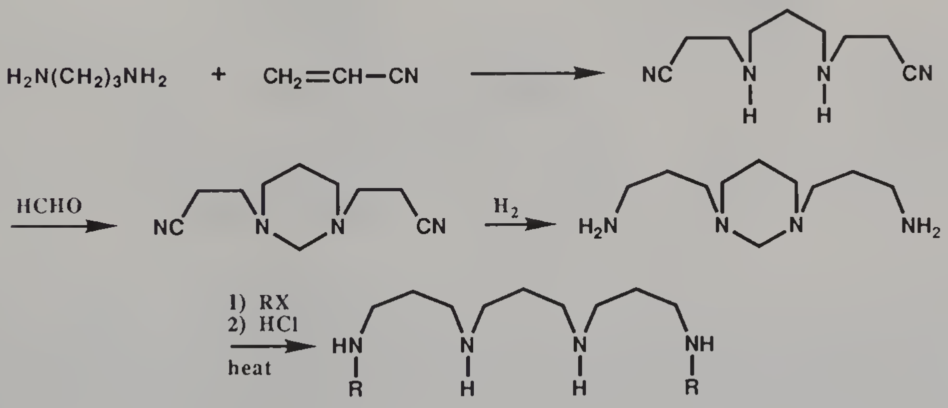


The introduction of the 3-aminopropyl side arm is straightforward. The nucleophilic addition of an amine or amide to acrylonitrile followed by reduction appears to be a general method for preparation of the terminal aminopropyl units (Barefield et al., 1976). This process can give diadduct am-

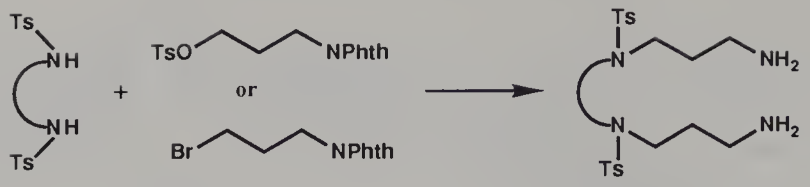




inopropyl groups to a primary amine depending on the ratio of the reactants as shown. The reduction process requires special conditions that avoid the formation of polymers. Borane, Raney nickel, or hydrogenation in the presence of acetic anhydride all form amines that are incapable of further reactions. The tosyl moieties in the above syntheses are useful as nitrogen protecting groups, but removing them is not easy (Dietrich et al., 1983). For this reason, an unusual protecting process for the trimethylene bridged systems has been developed. Polyamines with trimethylene bridges (including the natural polyamines) were treated with formaldehyde in the presence of barium hydroxide to form a cyclic diazacyclohexane system as shown. The cyclic diamine was opened by treatment with hydrochloric acid or by heating after other amine alkylation reactions were carried out (Dutasta et al., 1988; Ganem, 1982).

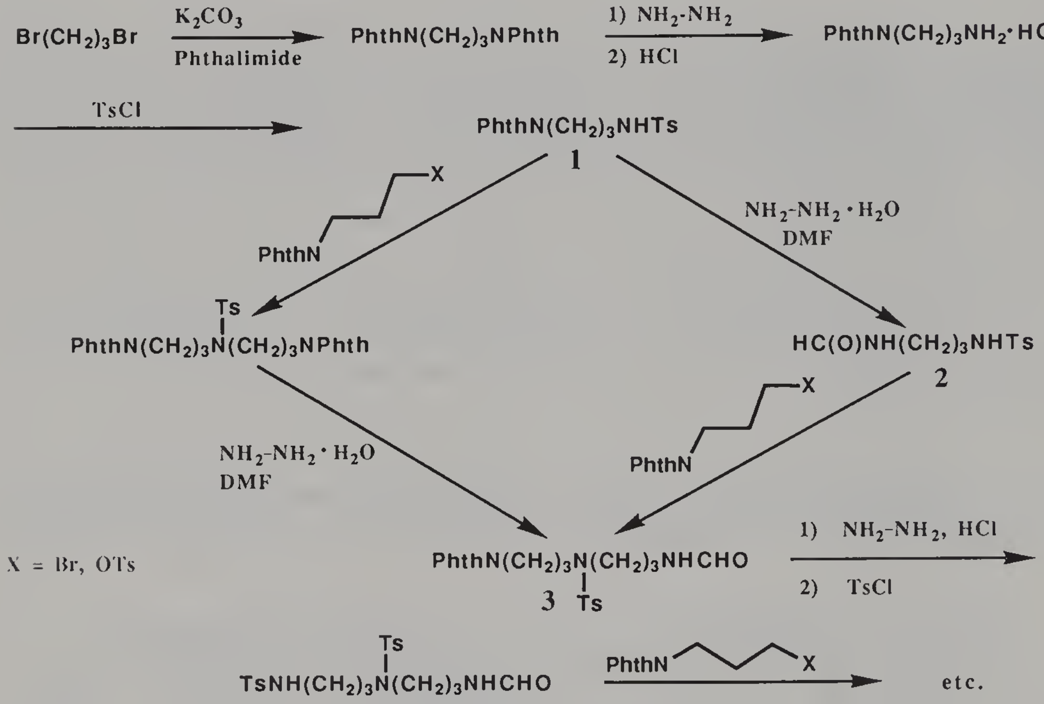


3-Bromopropylphthalimide (commercially available) or the tosylate analog are excellent synthons for the preparation of polyamines containing trimethylene bridges. Iwata and Kuzuhara (1985, 1986b, 1989a, 1989b), who used this interesting method, also were able to prepare the 3-(*N*-tosylamino)pro-

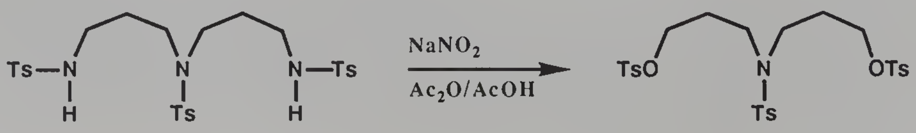


Phth = phthalimide

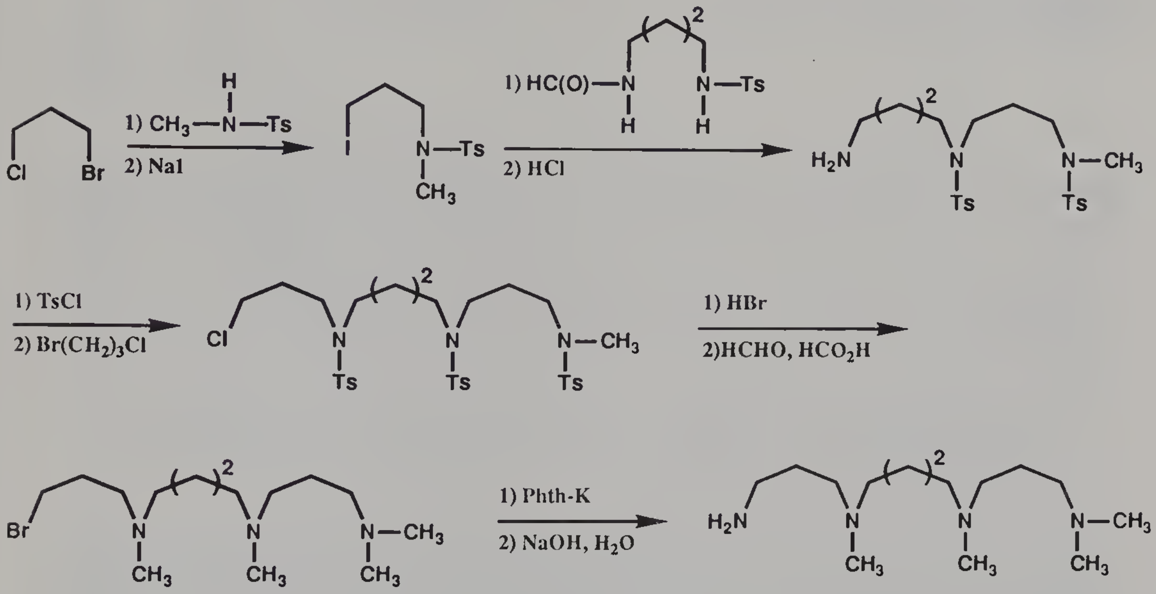
pylphthalimide (**1**), which can be reacted with hydrazine in DMF in such a way (Iwata and Kuzuhara, 1986b) as to form *N*-formyl-*N*′-tosyl-1,3-propanediamine (**2**). This latter compound can be reacted with the 3-phthalimidopropyl tosylate to form formyl-protected 7-phthalimido-4-tosyl-4-aza-1,7-heptanediamine (**3**) as shown in the right-hand sequence. Compound **3** can also be prepared by adding the two reactants in reverse order as shown on the left side of the sequence.



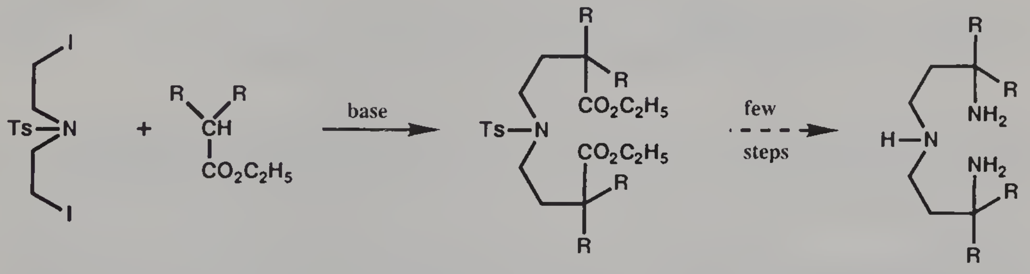
The process can be repeated by hydrolysis with hydrazine, treatment with tosylchloride, and reaction again with 3-phthalimidopropyl tosylate to form the tripropylene-tetraamine-type compound as shown on the bottom of the sequence. In this way, polyamines with a few tetramethylene, trimethylene, and ethylene bridges can be constructed. The final products will have terminal tosylamines that can be ring-closed using the Richman–Atkins procedure. It is also possible to convert the terminal tosylamines to the tosylates as shown below (Iwata and Kuzuhara, 1985).



Kiedrowski and Dörwald (1988) have reported a different strategy for preparation of polytrimethyleneamines. In their process, 1-bromo-3-chloropropane was used to extend the chain by trimethylene units. In the example shown below, *N*-formyl-*N*′-tosyl-1,4-butanediamine was extended by a multistep process utilizing both tosyl and formyl protecting groups.

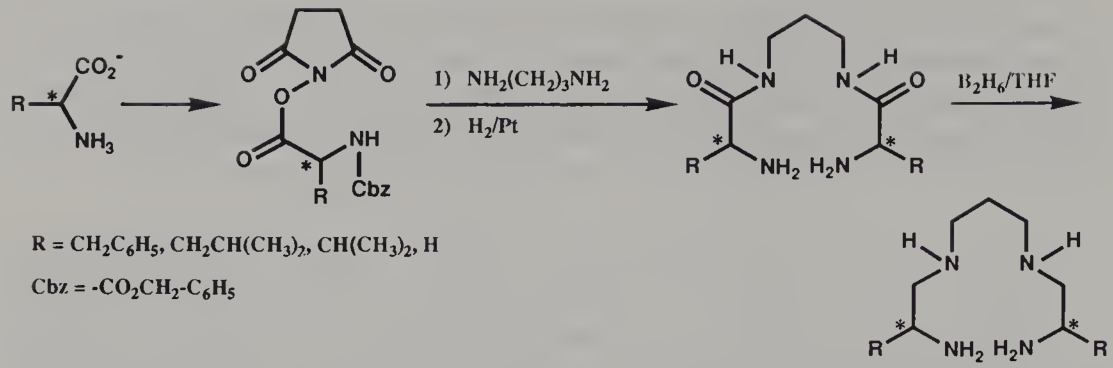


Schmidtchen (1980) has also prepared specific amines with trimethylene bridges, but with many steps as shown.



The inexpensive amino acids have been used for the synthesis of chiral polyamines. These chiral materials are then used in the synthesis of peptides or other products. One recent example of the use of L-phenylalanine, L-leucine, and L-valine to prepare chiral polyamines that, in turn, were used to prepare chiral macrocycles was published by Burrows and coworkers (Wagler and Burrows, 1988; Wagler et al., 1989). This synthesis (shown below) appears complicated, but it produced the chiral amines in overall yields of 37–62%.

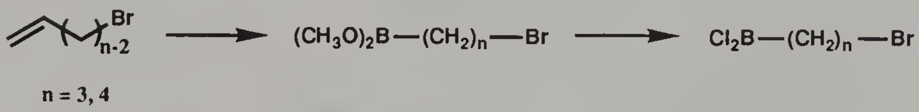
The azide moiety, which can be reduced to a primary amine, can be used to prepare secondary amines by means of a reductive alkylation using an



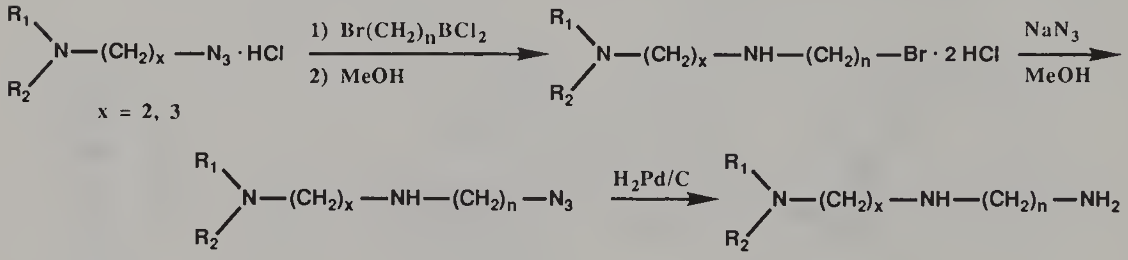
R = $CH_2C_6H_5$, $CH_2CH(CH_3)_2$, $CH(CH_3)_2$, H

Cbz = $-CO_2CH_2-C_6H_5$

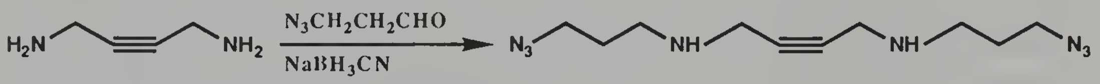
alkylborane (Brown et al., 1973, 1987). The aminoazides were easily prepared from the corresponding halides. The necessary dichloro(ω-bromoalkyl)boranes were prepared from the corresponding dimethylboronates, which were prepared by hydroboration of alkenyl bromides as follows (Carboni et al., 1988).



The procedure to extend the amine using the dichloro(ω-bromoalkyl)borane, and an aminoazide is shown below. This procedure can be used to add terminal 3-aminopropyl or 4-aminobutyl substituents.

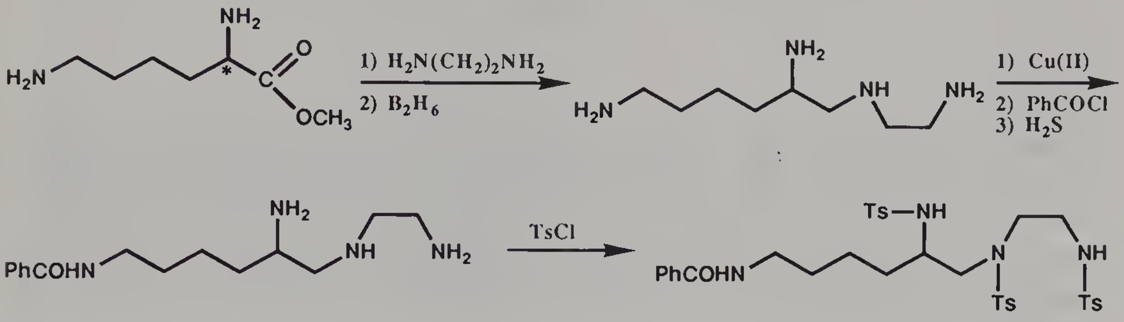


A method for preparation of a tetraamine with either a 2-butene or a 2-butyne bridge between the central amine groups was recently reported (Nagarajan and Ganem, 1986, 1987). 1,4-Diamino-2-butyne was reacted with 3-



azidopropanal in the presence of sodium cyanoborohydride. The resulting butyne-containing diaminodiazide was reduced by triphenylphosphine to give the tetraamine with the butyne moiety or with lithium aluminum hydride to give the tetraamine with a 2-butene bridge.

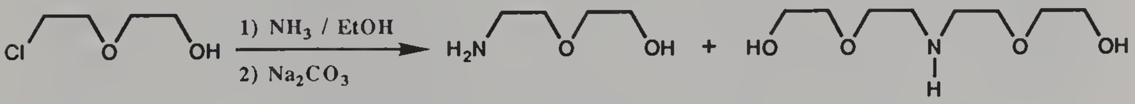
An unusual method to protect three amines in one portion of the molecule while a fourth amine in another part was benzoylated was reported by Parker and coworkers (Craig et al., 1989). The methyl ester of L-lysine was reacted with neat ethylenediamine followed by reduction to give a new tetraamine. Copper(II) was complexed with the diethylenetriamine portion of the molecule while the remaining primary amine was reacted with benzoyl chloride. The copper(II) ions were removed with hydrogen sulfide and the remaining amines were reacted with tosyl chloride. This unusual trisulfonamide-monobenzamide was used to prepare a macrocyclic ligand that contained a 4-aminobutyl substituent (Craig et al., 1989). Kaden and coworkers also used complexation with copper(II) to protect certain amines in a cyclam containing two aminoalkyl side arms. The only free amine in this complex was then reacted. In another case, a side arm containing a carboxyl group on a cyclam reacted with an external amine because the cyclam nitrogen atoms were complexed with the copper(II) (Kaden et al., 1989).



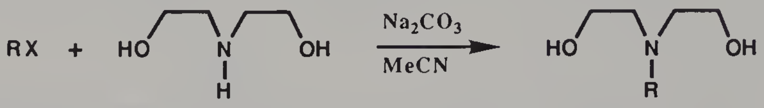
D. PREPARATION OF AMINODIOLS

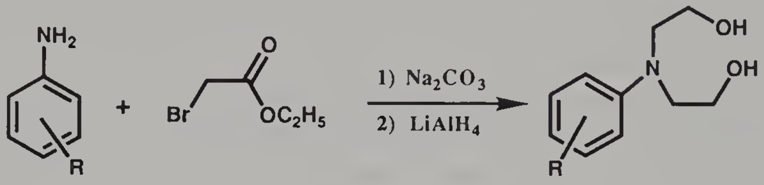
An alternate method to the use of diamino aliphatic ethers in the cyclization reaction to prepare the aza-crowns is to cyclize aminodiols. Some of the methods to prepare the aminodiols are now presented.

Krespan (1975) found that when 2-(2-chloroethoxy)ethanol was heated with ammonia in ethanol, a nearly equimolar mixture of 2-(2-aminoethoxy)ethanol and 6-aza-3,9-dioxa-1,11-undecanediol was isolated. In addition to these amino diols, King and Krespan (1974) prepared other types of amino diols starting with 2-aminoethanol or *N*-tosyl-2-aminoethanol and 1,8-dichloro-3,6-dioxaoctane or 1,5-dichloro-3-oxapentane. Gokel and coworkers prepared the *N*-alkyl derivatives of diethanolamine in good yields by treating

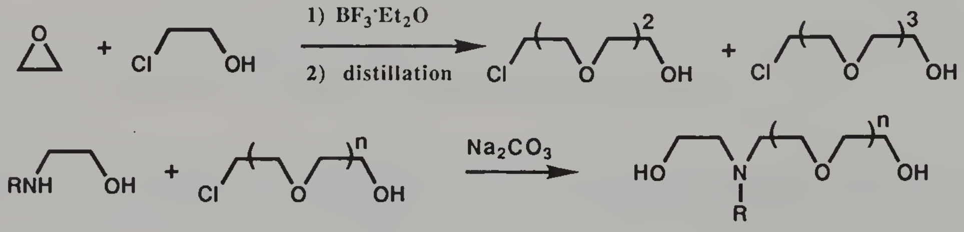


the amine with an alkyl halide using sodium carbonate as the base (Schultz et al., 1985). This reaction worked well when using methyl 2-(2-chloroethoxy)ethyl ether as the alkylating agent to prepare *N*-ethyleneoxy-substituted aminodiols, but the products from the reaction of longer chloroethoxy derivatives could not be separated from the by-product salts so that distillation was not practical. *N*-Phenyl-substituted diethanolamines were prepared by reacting various anilines with ethyl bromoacetate followed by reduction (Schultz et al., 1985).

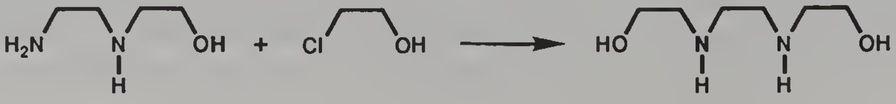




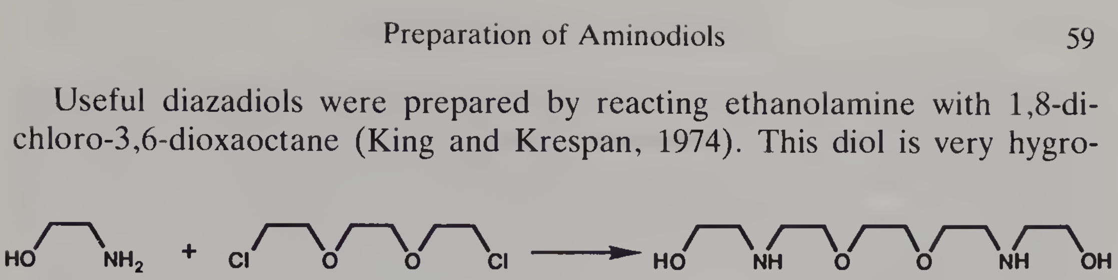
Okahara and coworkers prepared a number of *N*-alkylamino diols that were not symmetric. They first prepared the monochloride derivative of the oligoethylene glycol by reacting ethylene oxide with 2-chloroethanol in an acidic medium (Kuo et al., 1980). The oligomers were separated by distillation. The isolated monochloro derivative was then reacted with *N*-alkylethanolamine using sodium carbonate as the base. Other alkyl-substituted compounds were prepared by first reacting the amine with an excess of monochloroethylene glycol oligomer to form an amino alcohol that was further reacted with the same or another monochloro oligomer (Maeda et al., 1983a). A diamino alcohol was reacted with 2-chloroethanol using sodium carbonate as the base to form a diamino diol (Maeda et al., 1983b).



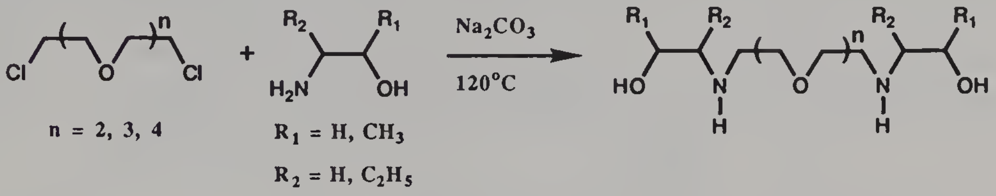
$R = C_6H_{13}, C_8H_{17}$
$n = 2, 3$



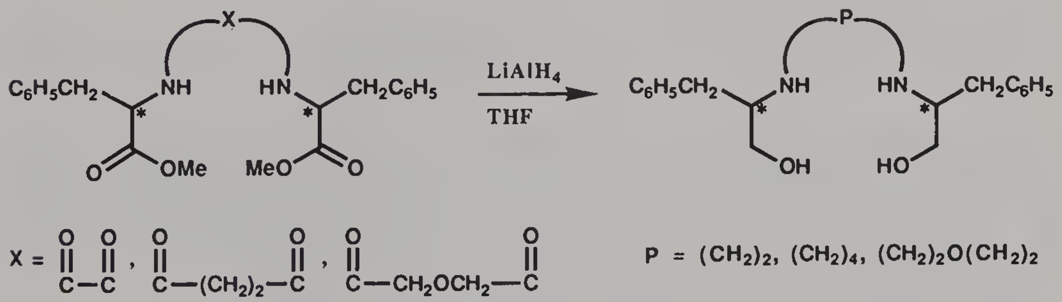
Useful diazadiols were prepared by reacting ethanolamine with 1,8-dichloro-3,6-dioxaoctane (King and Krespan, 1974). This diol is very hygroscopic but was used successfully to prepare diaza-crowns and cryptands (Krakowiak et al., 1990). It is impossible to prepare diazadiols in this manner from 1,5-dichloro-3-oxapentane because this reactant cyclizes with the primary amine to form a morpholine.



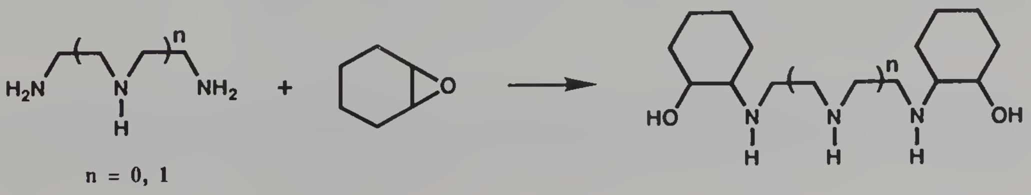
A series of diaza or triaza diols were prepared by Maeda and coworkers by three different types of reactions (Maeda et al., 1983b). With sodium carbonate as the base, ethanolamine compounds were reacted with the dichloro derivatives of the oligoethylene glycols to form the diaminodiols.



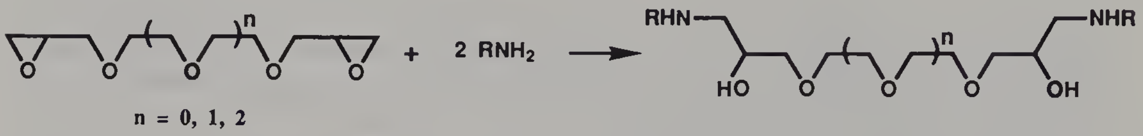
Chiral dibenzyl-substituted diaminodiols were prepared by first coupling two methyl esters of L-phenylalanine with a diacid chloride followed by reduction with lithium aluminum hydride (Vriesema et al., 1986).



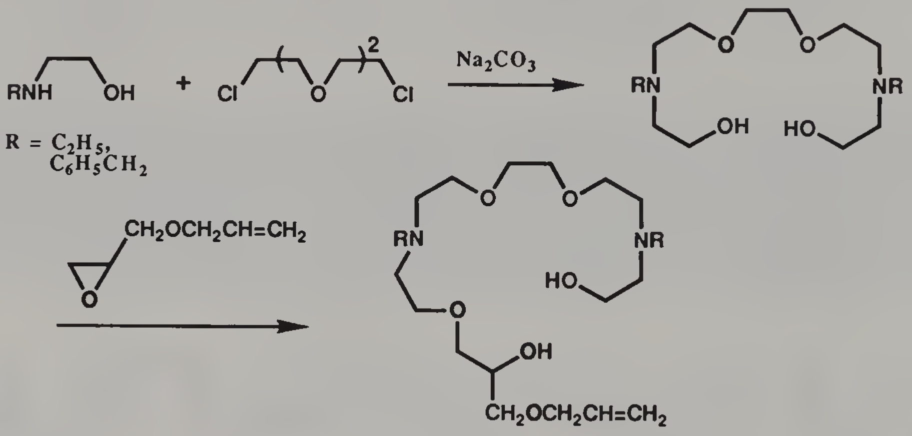
Polyaminodiols were also prepared by reacting terminal diamines with epoxides. For example, cyclohexene oxide was heated with ethylenediamine or diethylenetriamine to form oligoazadiols containing two 2-hydroxycyclohexyl units (Maeda et al., 1983b). All of these diols internally ring closed to

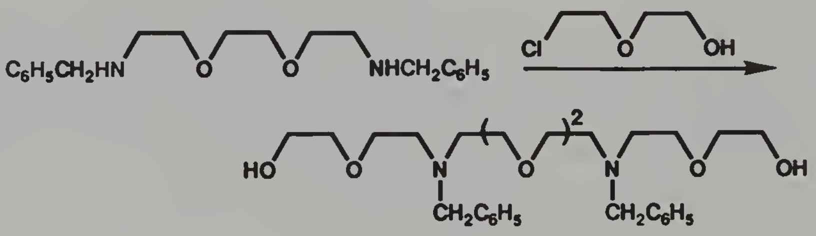


form polyaza-crowns when tosyl chloride was used (the Okahara procedure), as will be discussed later. Okahara and coworkers used a similar epoxide ring-opening reaction to prepare some diaminodiol ethers that are capable of ring closure through either the diamines or the diols (Maeda et al., 1983c). A bis(epoxy polyether) was reacted with an excess of alkylamine to form the diaminodiol material.

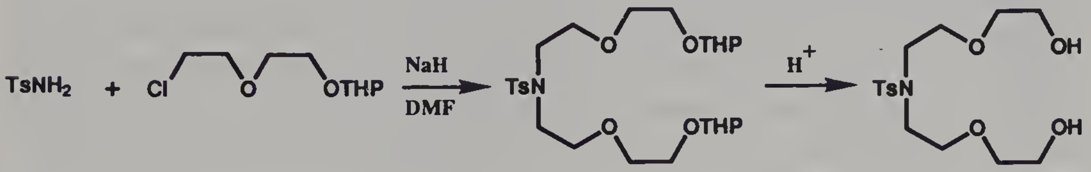


Bradshaw and Krakowiak have modified the reaction of a dihalide with *N*-ethyl or *N*-benzyl-substituted ethanolamine in the presence of a carbonate base in toluene to prepare *N*,*N*′-diethyl- and *N*,*N*′-dibenzyldiazapentaethylene glycol in high overall yields (Bradshaw and Krakowiak, 1988; Bradshaw et al., 1988). These diols were reacted with (allyloxy)methyl-substituted ethylene oxide to form the diazahexaethylene glycol containing an (allyloxy)methyl substituent. This latter diol was ring closed with tosyl chloride to form a diaza-18-crown-6, which was attached to silica gel (Bradshaw et al., 1988; Bradshaw et al., 1989c). A longer diaminodiol with each internal amine substituted with the benzyl protecting group was prepared by the same authors in another way (Bradshaw and Krakowiak, 1988).



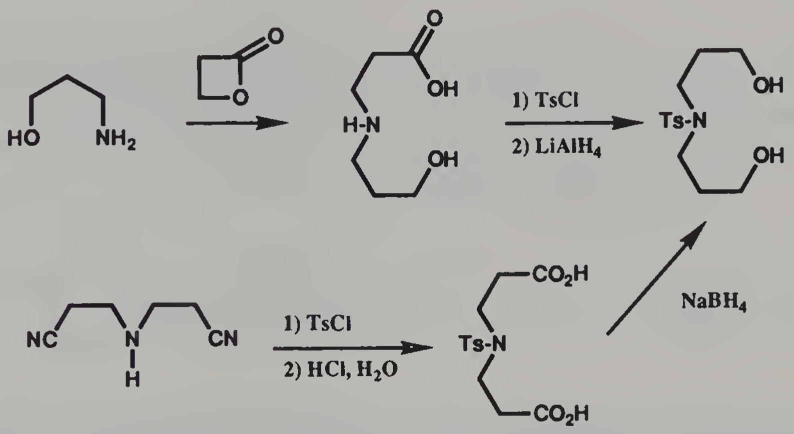


The *N*-tosylamino glycols are popular intermediates for the preparation of aza-crowns with secondary amino groups. Dale and Calverley (1982) used the reaction of *p*-toluenesulfonamide and the monochloro derivative of THP-blocked diethylene glycol to prepare the symmetrical *N*-tosylazatetraethylene glycol as shown. The same compounds were prepared without the need to

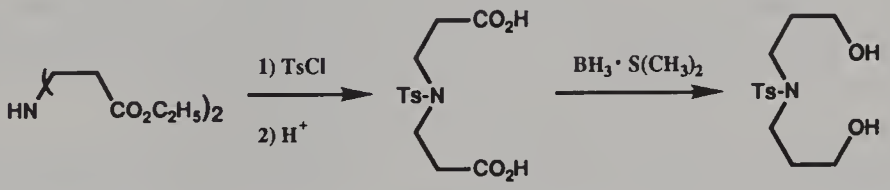


protect the 2-(2-chloroethoxy)ethanol and the subsequent deprotection step (Anelli et al., 1988). The unprotected chloroalcohol was reacted with tosylamine in DMF in the presence of sodium carbonate to give a 77% yield.

Sutherland and coworkers recently prepared diols with trimethylene bridges between the oxygen and nitrogen atoms using the two methods shown below (Pratt et al., 1988). The second method gave the best overall yield.



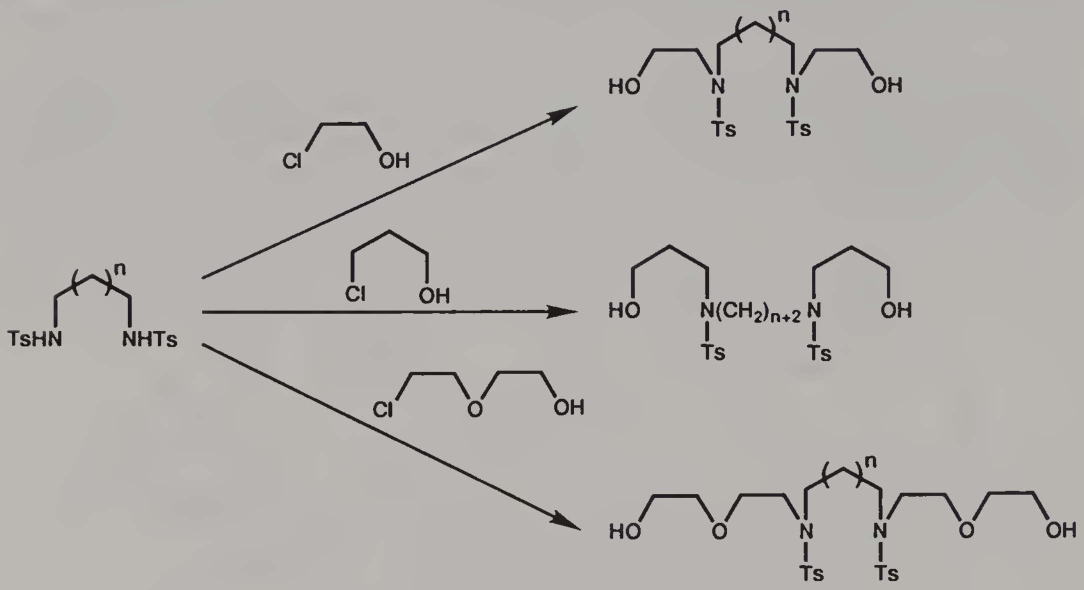
This same aminodiol was prepared by Wiest and coworkers from diethyl 3,3′-iminodipropanoate (Erhardt et al., 1980).



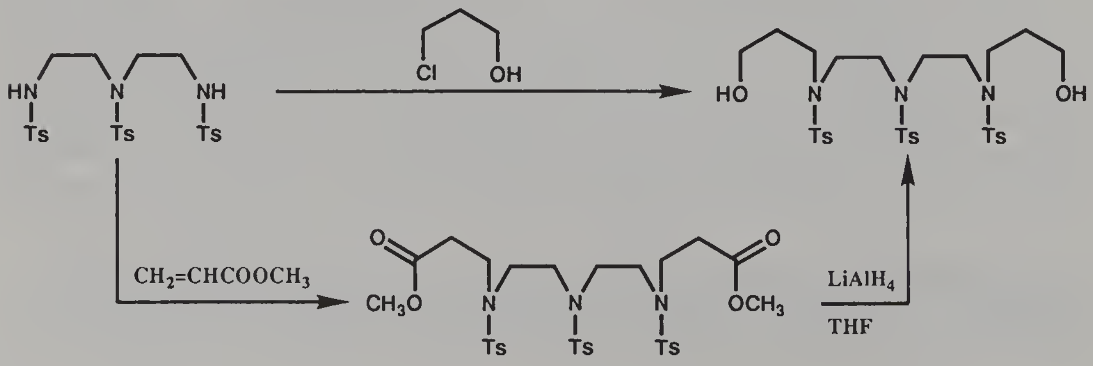
The *N*,*N*′-ditosyldiaminodiols are also very important as starting materials for the preparation of longer polyamines or polyaminodiols, or they can be used in the cyclization step for the preparation of polyaza-crowns. The *N*,*N*′-ditosyldiaminodiols were prepared by bonding arms onto *N*,*N*′-ditosylethylenediamine or by reacting *N*-tosylethanolamine with a dichloride as shown (Dietrich et al., 1981; Rashoffer and Vögtle, 1978). The reaction was carried

out in DMF in the presence of potassium carbonate or potassium *t*-butoxide to give yields of 30–65%. These *N*,*N*′-ditosyldiaminodiols have ethyleneoxy units between the nitrogen atoms.

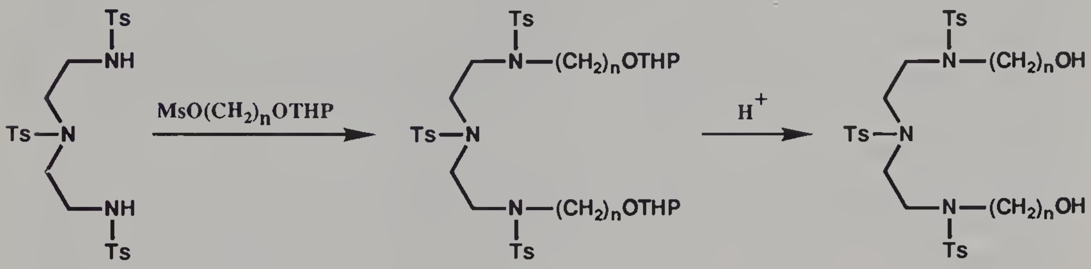
Many types of *N*,*N*′-ditosyldiaminodiols have been prepared where the nitrogen atoms are in the center of the chain. *N*,*N*′-Ditosylethylenediamine or other α,ω-ditosylaminoalkanes were reacted with an ω-chloroalcohol to give the required diols in one step (Dietrich et al., 1981; Goss, 1987; Hosseini and Lehn, 1982). Instead of 2-(2-chloroethoxy)ethanol used in the third reaction in this scheme, 3-oxaglutaric anhydride can be used followed by reduction (Carroy et al., 1986). Ethylene carbonate has been used instead of 2-chloroethanol (Bencini et al., 1988; Wagler and Burrows, 1987). In this case, *N*,*N*′-ditosyl-1,3-propanediamine was reacted with ethylene carbonate to give the ditosyldiaminodiol in a good yield (Wagler and Burrows, 1987). Marecek and Burrows (1986) also reacted *N*,*N*′-ditosyl-1,4-butanediamine with 3-chloro-1-propanol to give *N*,*N*′-ditosyl-4,9-diaza-1,12-dodecanediol, which was used to prepare a spermine-like macrocycle.



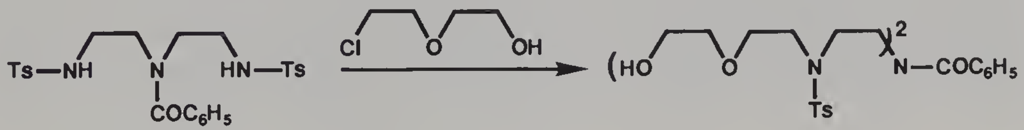
Triazadiols were prepared by the same method as above (Comarmond et al., 1982) or by a Michael addition using an *N*,*N*′,*N*″-tritosyltriamine. In the



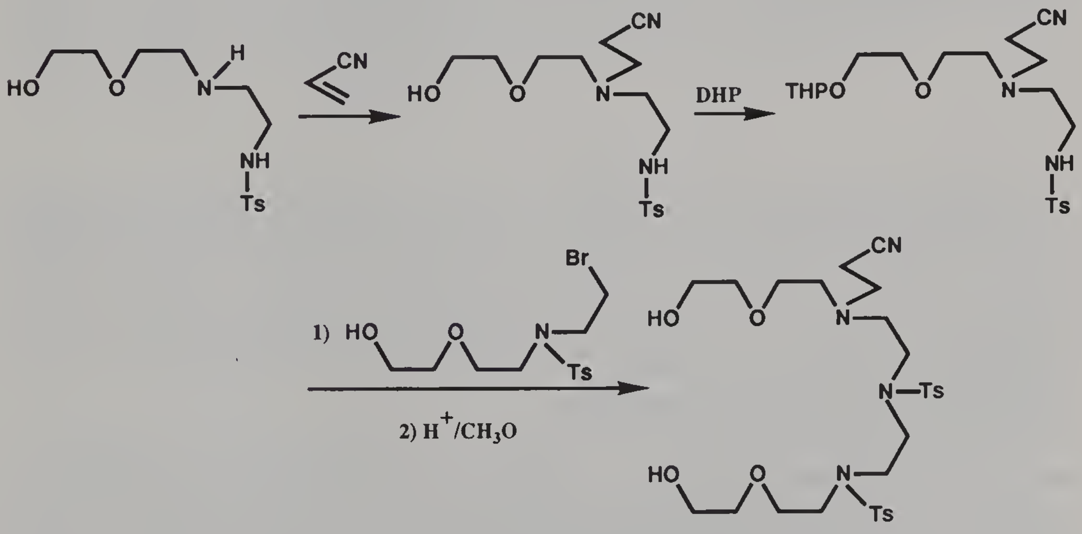
second method, methyl acrylate was reacted in DMF in the presence of potassium carbonate and the resulting diester was reduced by lithium aluminum hydride in THF. The two methods cannot be compared because yields were not reported in both cases (Dietrich et al., 1983). Martin and Bulkowski (1982) prepared similar diols by reacting the tritosyltriamine with a mono-THP-protected mesylate derivative of a diol. The protecting group was removed by acid in a second step.



Specific functionalization of a polyamine requires selective protection of the various amine groups. Other protecting groups, in addition to tosyl, include benzoyl, benzyl, and mesyl. Lehn and co-workers have prepared triaminodiols with mixed blocking groups (Hosseini et al., 1987).



Mertes and coworkers have prepared a triaminodiol containing an *N*-(2-cyanoethyl) group (Gu et al., 1989). The cyanoethyl-containing triaminodiol

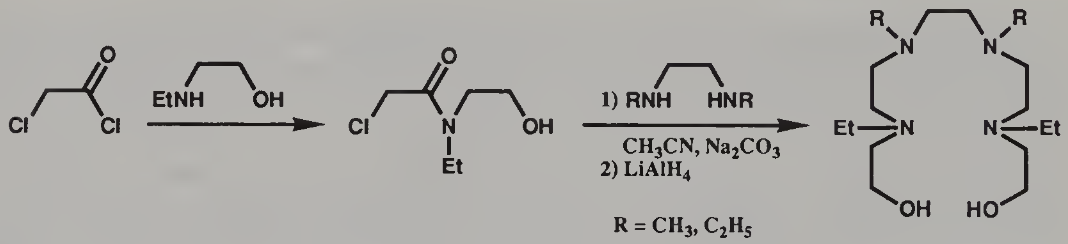


can be cyclized giving a macrocycle with a reactive side arm. In the above sequence, the starting hydroxydiamine was prepared by the reaction of 2-(2-

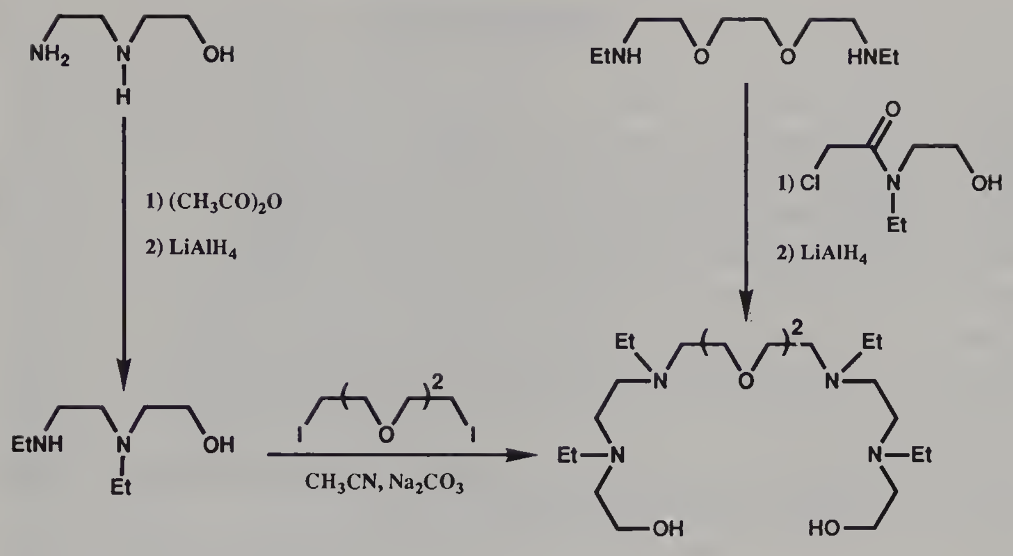
aminoethoxy)ethanol with *N*-tosylaziridine in acetonitrile. The free amine was cyanoethylated with acrylonitrile and the hydroxy group was protected using dihydropyran. This protected tosylamine was reacted with 8-bromo-6-tosyl-6-aza-3-oxaoctane [prepared from *N*-tosyl-2-(aminoethoxy)ethanol and 1,2-dibromoethane] followed by deprotection in acid to give the desired 6-cyanoethyl-9,12-ditosyl-3,15-dioxa-6,9,12-triaza-1,17-heptadecanediol (Gu et al., 1989). The number of steps in this reaction possibly could be reduced by reacting the *N*-tosyl-*N*-cyanoethylhydroxyamine (not protected) with the *N*-tosylbromohydroxy compound in DMF using sodium or potassium carbonate as base instead of sodium hydride. The carbonate bases do not remove the proton from a hydroxy group so that reaction takes place exclusively on nitrogen (Bradshaw et al., 1989a).

The *N*-tosyl groups are often difficult to remove from the final products. The yields for the reductive removal of the tosyl groups are often only moderate (Pratt et al., 1988). *N*-Tosyl groups also change the complexation properties of the aza-crowns if they are not removed. It is important to find methods to prepare the aminodiols with functionalizable nitrogen groups without the need for protecting the nitrogen atoms.

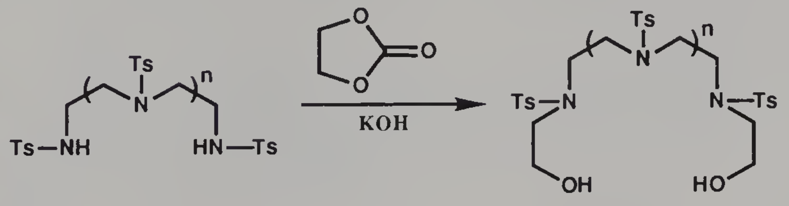
A tetraazadiol was recently prepared by first reacting chloroacetyl chloride with *N*-ethylethanolamine to form a chloro hydroxy amide (Chadwick et al., 1984; Krakowiak et al., 1989d). This latter compound was reacted with *N*,*N*′-dimethyl- or *N*,*N*′-diethylethylenediamine with subsequent reduction to give the tetraazadiol (Krakowiak et al., 1989d). This tetraazadiol was also obtained by two other methods from readily available starting materials (Krakowiak et al., 1989d). Unfortunately ethylene oxide, a hazardous material, cannot be used in these reactions. It is likely that use of ethylene oxide would be advantageous because *N*,*N*′,*N*″,*N*‴-tetraethyltriethylenetetraamine can now be purchased (Pfaltz and Bauer) and could be reacted with ethylene oxide to prepare the same diol in one step.



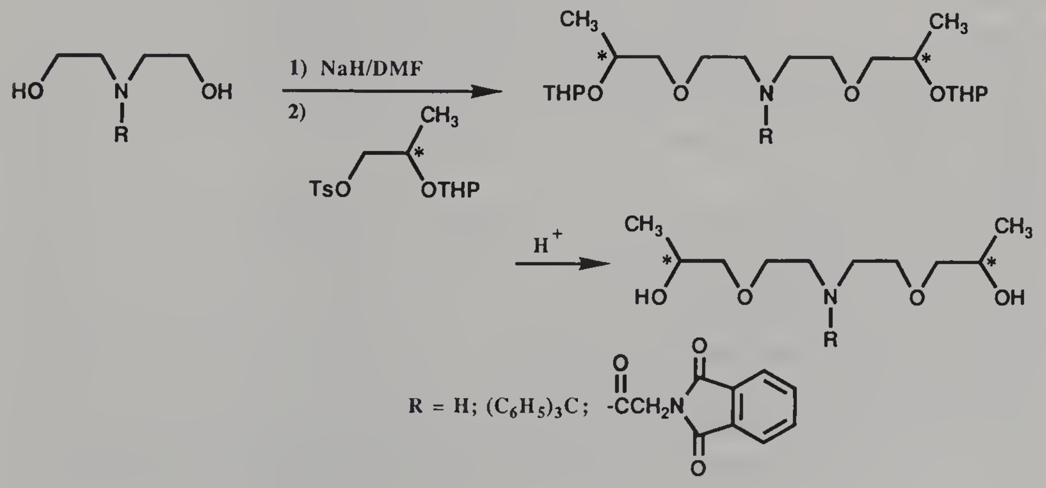
A tetraazadiol with two ether oxygens in the chain has been prepared by two methods (Krakowiak et al., 1989d). The final product was difficult to purify when using 1,8-diiodo-3,6-dioxaoctane as a reactant giving only a 20% yield. The second reaction, on the other hand, using the *N*-ethyl-*N*-(2-hydroxyethyl)chloroacetamide followed by reduction gave very good results.



Polyazadiols have been synthesized in yields of about 60% using the reaction of a pertosylpolyamine with ethylene carbonate (Bencini et al., 1987, 1988; Bianchi et al., 1985; Micheloni et al., 1985).



A chiral azadiol recently was prepared using the procedure that was developed for the preparation of glycols (Huszthy et al., 1992). This reaction was also carried out with a protecting group on the nitrogen atom.



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CHAPTER III

General Synthetic Methods for the Polyaza-crown Macrocycles

A. INTRODUCTION

There are many types of macrocyclic ligands in nature. The cyclic peptides represent a large class of naturally occurring compounds that include antibodies, ion-transport regulators, hormones, toxins, alkaloids, antibiotics, and other types of biologically active substances. A noteworthy feature of the cyclic peptides is the frequent occurrence among its members of unnatural amino acid residues: amino acid residues not found in natural linear proteins or peptides. Cyclic antibiotics were first isolated from spore microorganisms in 1950. Since then, many antibiotics have been found to have the cyclopeptide structure. Valinomycin, for example, is a cyclic dodecadepsipeptide that has a 36-membered ring arranged so that, when it complexes with potassium ion, the metal ion is coordinated to six inward-pointing ester carbonyl groups.

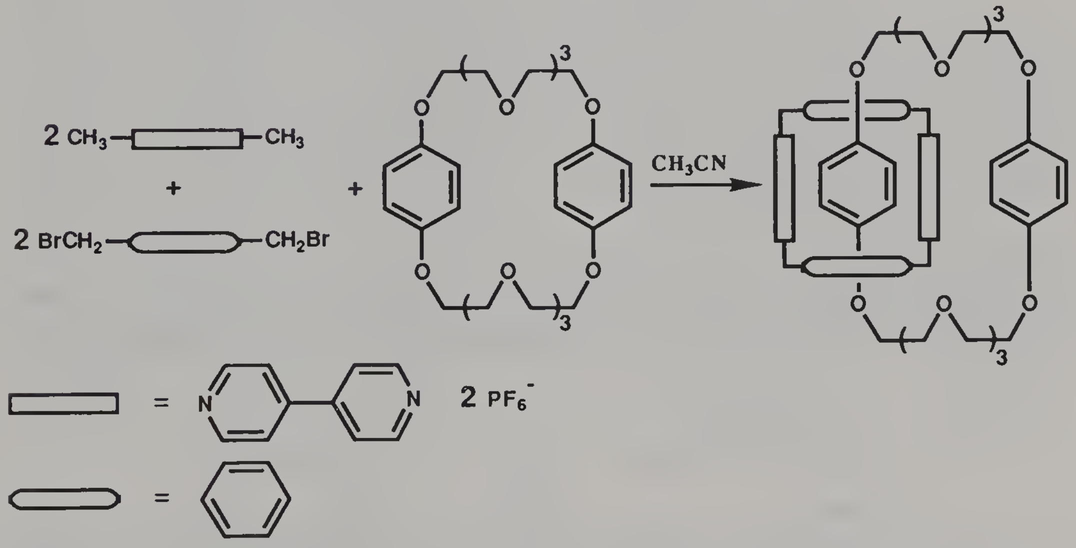
This arrangement gives valinomycin a cavity which exactly fits around the potassium ion giving valinomycin a 10^4 greater affinity for potassium over sodium ions (Wipf et al., 1970). These types of ionophores have unique abilities to transport metal ions across apolar membranes. The ionophoric peptides have been the subject of two reviews (Hilgenfeld and Saenger, 1982; Lindenbaum et al., 1979).

The cyclic peptides have other medicinal uses (Tonelli, 1986; Hirschmann, 1991). The isolation, characterization and synthesis of the peptide hormones oxytocin and vasopressin were reported 40 years ago by du Vigneaud, who was awarded a Nobel Prize. Insulin holds a very special place in the annals of peptide research because it is a life-saving drug for the juvenile diabetic. More recently, DDAVP (an analog of vasopressin) has long-lasting antidiuretic properties. Octatreotide, a cyclic octapeptide, was approved by FDA for treatment of acromegalics and for use in patients who have a special type of tumor. The fungal metabolites, cyclosporin A and FK-506, are used as immune suppressants (Devlin and Hargrave, 1989). Didemnin, a depsipeptide, has antiviral and antitumor activity (Devlin and Hargrave, 1989). The syntheses of these types of compounds are very difficult. Didemnin, for example, was only recently synthesized in the laboratory (Ewing et al., 1989; Hamada et al., 1989; Rinehart et al., 1987; Schmidt et al., 1988). These authors first formed long-chain compounds with the two functional groups appropriately spaced to form an internal cyclic compound when reacted together. This cyclopeptide method of ring closure (Ovchinnikov and Ivanov, 1982), often called the "snake" reaction where the mouth catches the tail, seldom gives high yields of the cyclic product.

Cyclodimerization is another process for the preparation of these cyclic peptides. In this case, two molecules are held together in an antiparallel fashion by intermolecular interactions (usually multiple hydrogen bonding) so that a cyclic dimer is formed when they react rather than a monomer. An example of this type of cyclic peptide formation is the synthesis of gramicidin S (Schwyzer and Sieber, 1958). Often, cyclodimerization occurs by the construction of sulfur–sulfur bonds. Recently, a template method for ring closure has been applied to the formation of cyclic peptides (Kataoka and Katagi, 1987, 1989).

The first documented synthetic macrocycle was synthesized by Baeyer via the condensation of pyrrole and acetone in the presence of mineral acid (Baeyer, 1886). Other examples, from a historical point of view, are listed in a review by Newkome and coworkers (Newkome et al., 1977). The aliphatic macrocycles were synthesized later as exemplified by Willstätter's synthesis of eight-membered rings (Willstätter and Veraguth, 1905) and Ruzicka's studies of the chemistry of muscone and civetone (Ruzicka, 1926). The synthesis of thiacycloalkanes using the reaction of sodium sulfide with an alkyl dihalide was also investigated early in the twentieth century (Braun and Tcherniac, 1907). A cyclam (cyclic amine) was first synthesized by Alphen (1937). The preparation of the peraza-crowns was first developed by Stetter (1953a, 1953b). Curtis and Busch first prepared unsaturated nitrogen-containing macrocycles (cyclic imines) followed by reduction to form the saturated cyclic amines (Busch et al., 1971; Curtis, 1960, 1968).

There has been recent interest in the preparation of interlocked macrocyclic molecules—the so-called catenanes. Willstätter first discussed the existence of molecular interlocked rings in 1912. Frisch and Wasserman (1961) stated clearly the possible routes for the synthesis of such molecules. Dietrich-Buchecker and Sauvage (1987) have reviewed this interesting topic. The first steps in catenane chemistry were made in 1983 using one-pot template syntheses from phenanthroline derivatives (Dietrich-Buchecker et al., 1983, 1984). Stoddart and coworkers have prepared a [2]catenane compound of interlocking bisparaphenylene-34-crown-8 and cyclobis(paraquat-*p*-phenylene) in the remarkably high yield of 70% (Ashton et al., 1989). The high yield was a result of a template-directed cycloaddition of the complex of a bis(pyridinium) salt and bisparaphenylene-34-crown-8 with bis(bromomethyl)-benzene.

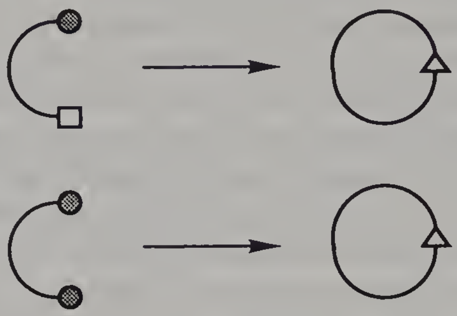


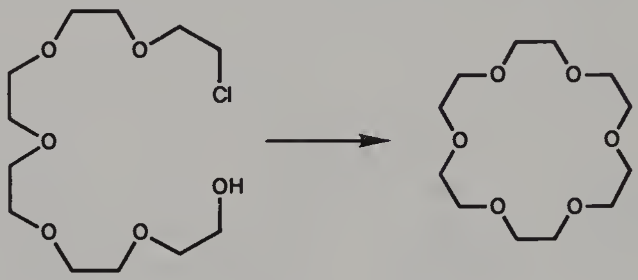
This chapter will present many of the methods for building the polyaza macrocyclic rings.

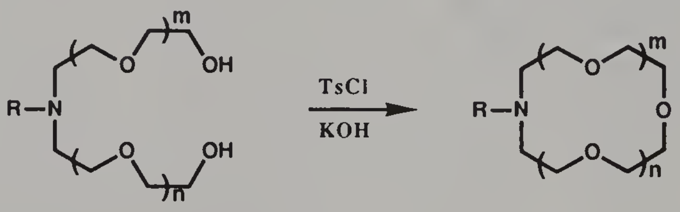
B. RING-CLOSURE METHODS

1. The Formation of One Bond

The preparation of macrocycles by the formation of one bond has found broad application in cyclic peptide chemistry. A linear compound with reactive groups on each end can react internally to form the macrocycle. The formed bond is usually of the amide or disulfide type (Kessler et al., 1989; Ovchinnikov and Ivanov, 1982; Spatola and Darlak, 1988). An early synthesis of 18-crown-6 used an internal Williamsen ether synthesis of the monochloro derivative of hexaethylene glycol (Pedersen, 1967a, 1967b). Okahara and coworkers discovered a more direct reaction of an α,ω-diol with one mole of tosyl chloride in base to give the macrocycle (Kuo et al., 1978a, 1978b, 1980; Maeda et al., 1983a, 1983b). This "Okahara" ring-closure method for preparation of macrocycles is very useful for the preparation of the polyaza-crowns because the starting material is usually available either commercially or by a one- or two-step process and cyclization yields are usually very good.



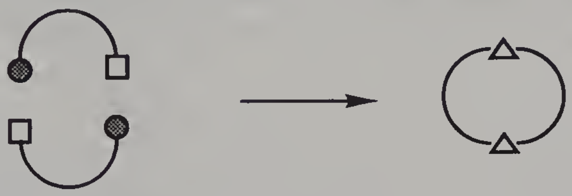




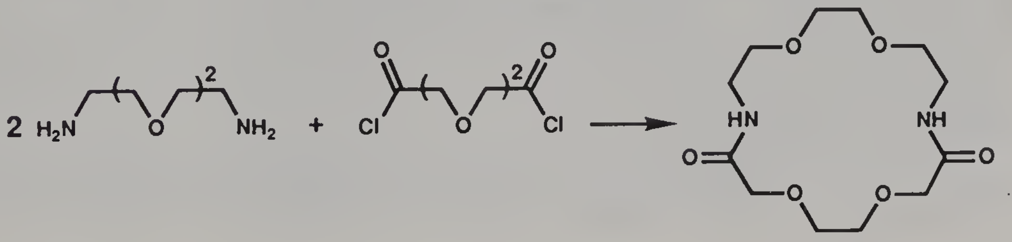
2. The Formation of Two Bonds (1:1 Cyclizations)

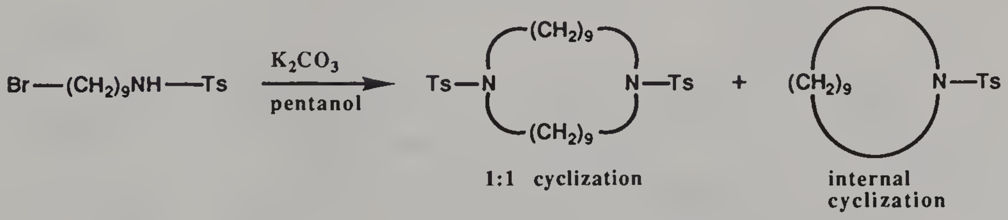
The most used method for the preparation of macrocycles is through the simultaneous formation of two bonds. Each substrate has two functional groups that are reactive with the two functional groups on the other substrate.

The two sets of functional groups can be arranged with two of the same functional groups on each molecule as shown in the first example or one of each functional group on both molecules as shown in the second example. This 1:1 cyclization process often gives high yields because of metal ion template effects, intermolecular hydrogen bonding between the two molecules, or running the reaction in high-dilution conditions.



The 1:1 cyclization process has been used extensively for the synthesis of the polyaza-crowns. A typical example of the first type of 1:1 cycloaddition is the reactions of an α,ω-diacid chloride with an α,ω-diamine to form a cyclic diamide. A second molecule of the diamine is generally used to trap the released hydrogen chloride (Dietrich et al., 1973). The preparation of *N*,*N*′-ditosyl-1,11-diazacycloeicosane is an example of the second type of 1:1 cycloaddition (Müller et al., 1952). In this case, the base deprotonated the tosyl amide increasing the nucleophilicity of the nitrogen atom. Halogen and tosylate ions are the usual leaving groups in these types of reactions. Formation of the smaller cyclic product in the above reaction shows one of the problems of using a starting material that contains one of each reactive group in the

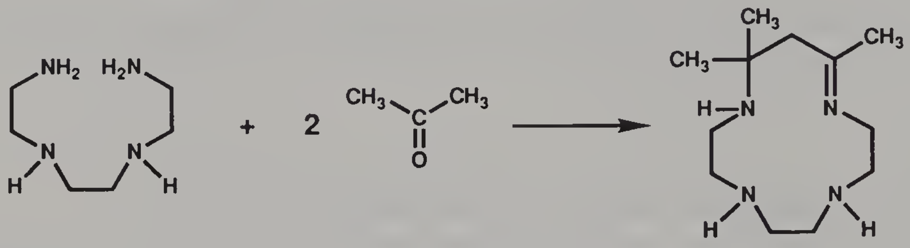




1:1 cyclization process. When the two groups in the same molecule react together, a small macrocycle forms by the one-bond forming process. It's very difficult to avoid such cyclizations, especially when five-, six-, or seven-membered rings can be formed.

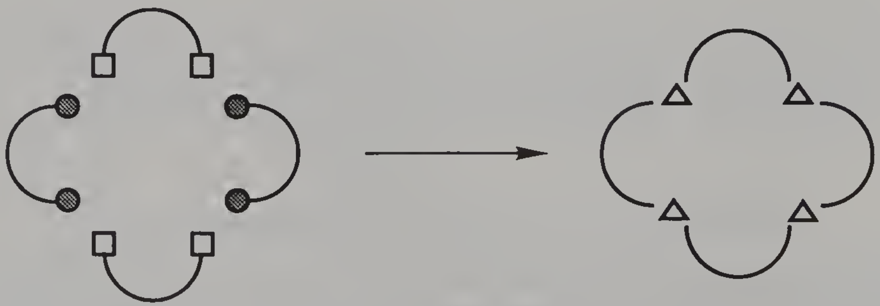
3. Reactions of Two Identical Substrates with a Third Substrate (2:1 Cyclizations)

The reaction of acetone or an aldehyde with triethylenetetraamine is an example of the 2:1 cyclization reaction. In this reaction, an unsaturated 13-membered macrocycle was obtained. This compound could be reduced to the trimethyl-substituted cyclam (Busch, 1967; House and Curtis, 1962, 1964a). The mechanism for macrocycle formation in these reactions is not known, but the authors suggested that an enolate ion of the second acetone replaces the hydroxy group on the condensation product of the first acetone and one of the primary amines. The second amine then condenses with the resulting carbonyl carbon forming the product. These reactions take place using Ni(II) or Cu(II) as template ions.



4. Reactions of Two Substrates with Two Substrates (2:2 Cyclizations)

The 2:2 cyclization process forms four new bonds between four substrates as shown. The reaction can be carried out under high-dilution techniques or with a template. The high-dilution reaction also produces the 1:1 cyclization product (and even the 3:3, 4:4, etc. products). If one of the reactants is a

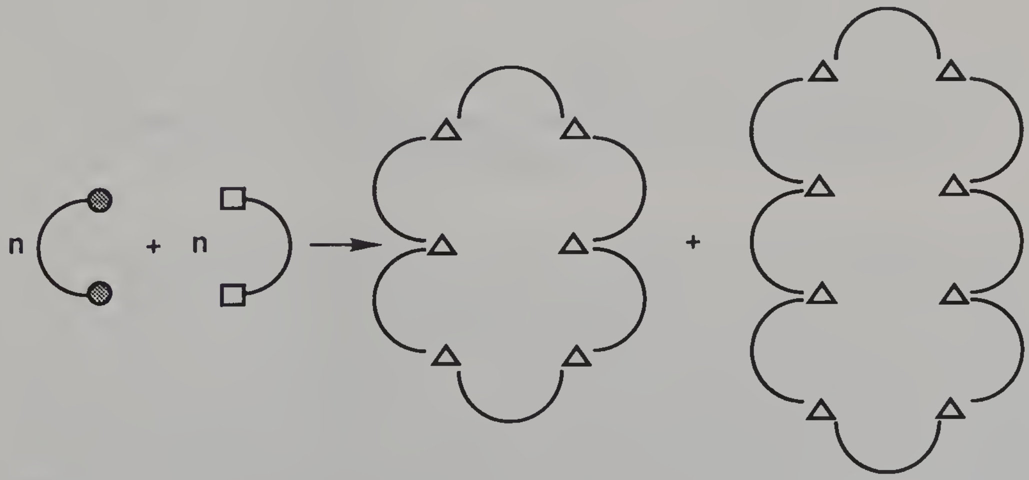


rigid molecule, the possibility of 1:1 cyclization is reduced. The concentration of the reactants also influences the types of addition products. A higher concentration favors the formation of 2:2 addition products, but also, more polymer is formed (Rossa and Vögtle, 1983).

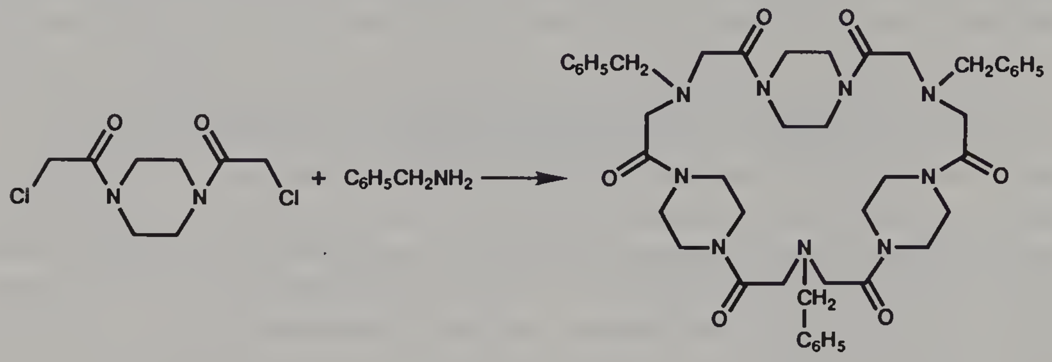
One example of a rigid difunctional molecular that reacted by 2:2 cyclization rather than 1:1 cyclization is catechol, which reacted with the dichloro derivative of diethylene glycol to form dibenzo-18-crown-6. This latter reaction was the initial discovery by Pedersen that led to the crown ether ligands that form remarkable complexes with various metal and organic cations (Pedersen, 1967a, 1967b). The diaminobenzene compounds, when reacting with dialdehyde groups, also react by a 2:2 cyclocondensation reaction (Jazwinski et al., 1987b). The 2,6-disubstituted pyridine compounds react with 1,2-difunctionalized ethane or 1,3-difunctionalized propane molecules to give exclusively the 2:2 cyclization products (Krakowiak, 1986; Lüning, 1987; Nelson, 1980; Newkome and Gupta, 1984; Weber and Vögtle, 1976). It is worth mentioning here that the template effect can favor 2:2 cyclization over 1:1 and vice versa. The size and coordination properties of metal ions can play an important role in these reactions. Sometimes smaller cations favor 2:2 cyclizations because two cations coordinated with the heteroatoms in larger macrocycles (Alcock et al., 1984; Drew et al., 1987; Fenton, 1986; Menif et al., 1989; Nelson, 1980).

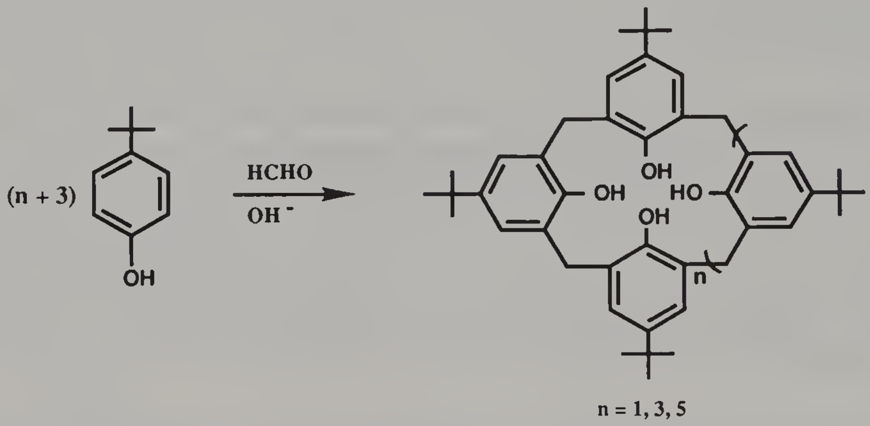
5. Reactions of Three or More Substrates with Three or More Substrates (3:3, 4:4, etc. Cyclizations)

The 3:3, 4:4, 5:5, etc. cyclization products are generally by-products from the high-dilution 1:1 or 2:2 cyclization reactions mentioned above (Krakowiak et al., 1990a; Newkome and Gupta, 1984; Newkome et al., 1989; Rossa and Vögtle, 1983). These products are isolated by careful chromatography and analyzed by mass spectrometry. The yields decrease as the size of the



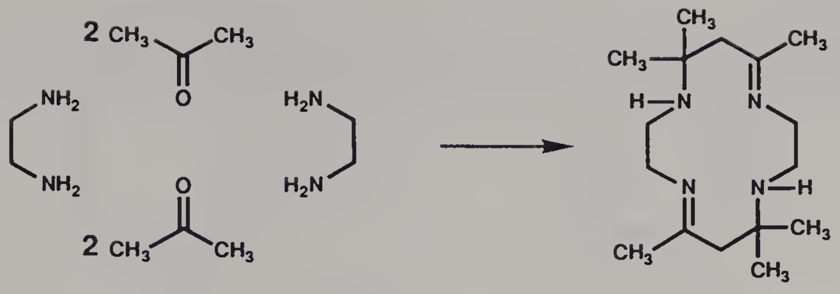
ring increases. Examples of a 3:3 cyclic condensation are shown by the preparation of the piperazine-containing hexaamide (shown below) (Krakowiak et al., 1991) and by the reaction of terephthaloyl chloride or 2,6-pyridinedicarboxylyl dichoride with substituted ethylenediamine (Vögtle and Müller, 1984). Another example of multiple condensation is in the preparation of the *p*-*t*-butylcalixarenes. Four, six, or eight molecules of *p*-*t*-butylphenol and formaldehyde were connected to form the calixarenes (Gutsche and Iqbal, 1989; Gutsche et al., 1989; Munch and Gutsche, 1989).





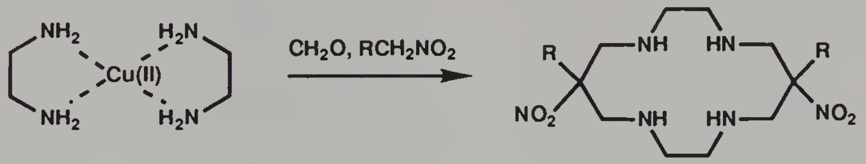
6. Reactions of Four of One Substrate with Two of Another (4:2 Cyclizations)

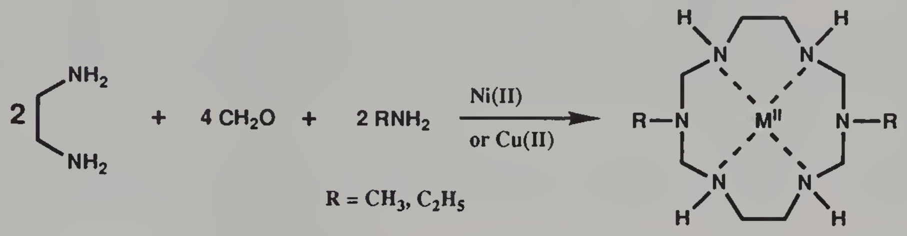
The process of forming unsaturated macrocycles from acetone or other ketones and derivatives of 1,2-diaminoethane or 1,3-diaminopropane was first reported by Curtis and coworkers (Blight and Curtis, 1962; Curtis and House, 1961; House and Curtis, 1964a). The mechanism of this reaction involves the reaction of four acetone molecules with two diamino compounds probably as mentioned above for the similar 2:1 cyclization reactions of acetone and a diamine. The reaction can be carried out with or without a template metal ion (Hay et al., 1975). The monoprotonated salt of the amine was cyclized without the template ions.



7. Reactions Involving Three Substrates

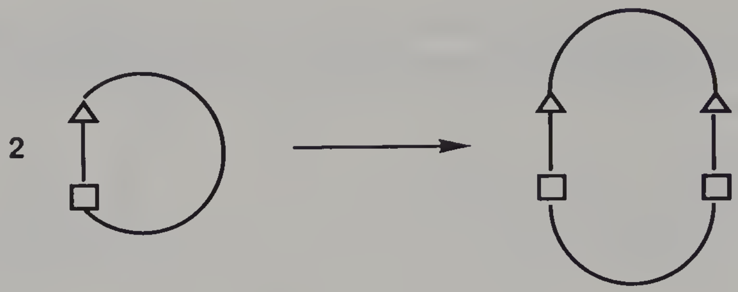
Using the appropriate template cations, macrocycles can be prepared from three different substrates. For example, the complex of copper with multidentate amines reacted with formaldehyde and nitromethane or diethyl malonate (not shown) to form a peraza-crown (Comba et al., 1986; Lawrance and O'Leary, 1987). The ratio of substrates can vary from 1:2:1 or 1:4:2 (amine:formaldehyde:activated carbon) depending on reaction conditions and substrates. Additional amines can be used instead of activated carbons (Suh and Kang, 1988). In this case, eight molecules reacted together to form a hexaaza macrocycle.





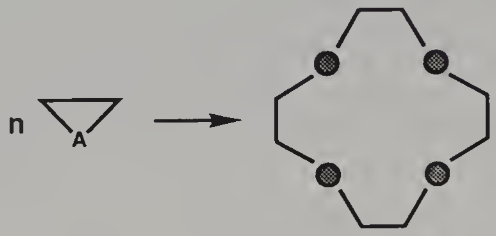
8. Ring Dimerizations

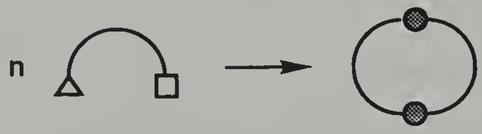
There are cases where an already formed nitrogen-containing small ring reacts when heated to form a macrocycle with twice the number of ring members. The dimerization is favored by a template ion. Seven-membered rings open and dimerize to the 14-membered ring and 9- to 18-membered. This method has given a high yield of carbon-substituted cyclams (Kasprzyk



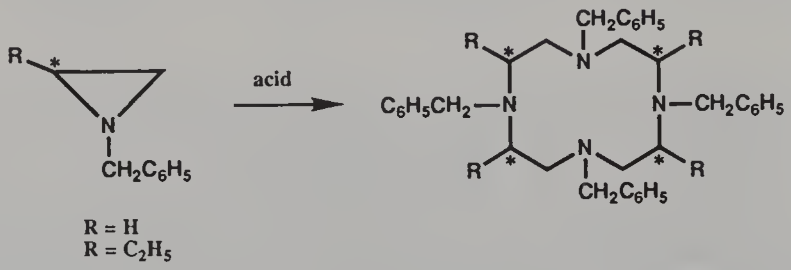
and Kolinski, 1984). There is also a report of reducing the ring size from 14 to 7 members (Bergman and Brynolf, 1989).

9. Oligomerizations of Small Rings or Linear Reactants

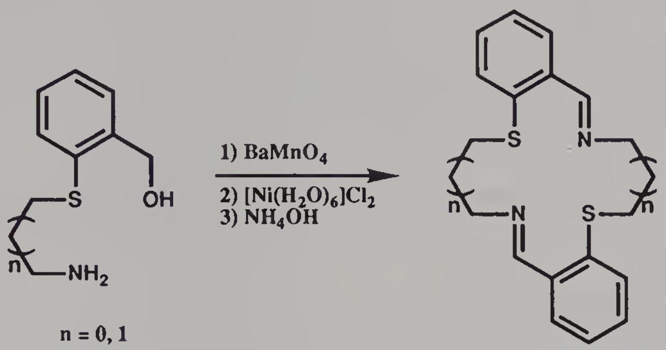




The derivatives of ethylene oxide and aziridine can be used to build macrocycles. Substituted aziridine or ethylene oxide self-condenses on ring opening to form cyclic trimers, tetramers, and so on (Dale and Daasvatn, 1976; Dale et al., 1974; Hansen and Burg, 1968; Tsuboyama et al., 1970). The size of the macrocycle depends mainly on what starting material is used. In the case of *N*-benzylaziridine, the macrocycle formed was the tetraaza-12-crown-4.

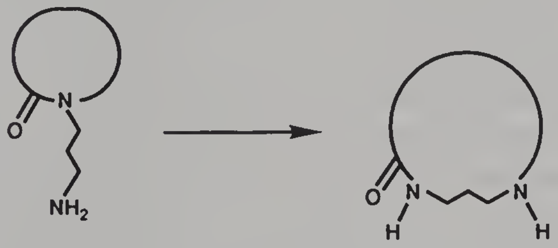


Open-chain compounds also react to give these types of macrocycles. For example, 2-(hydroxymethyl)-6-(bromomethyl)pyridine reacted in the presence of sodium hydride to give the dimer, trimer, and tetramer (Newcomb et al., 1977). Also 2-(3-amino-1-thiapropyl)phenylmethanol or the corresponding 2-(4-amino-1-thiabutyl)phenylmethanol self-condensed in the presence of barium manganate to give dimeric compounds (Martin et al., 1987).



10. Ring Expansions

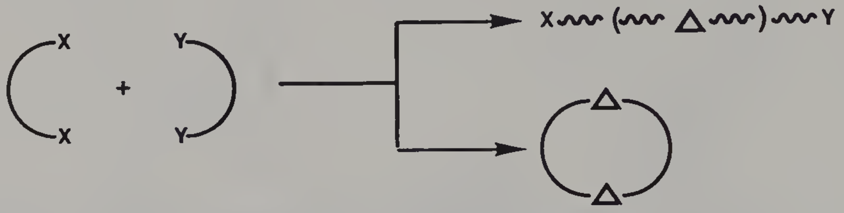
The "zip" reaction (ring expansion from a small to a larger cyclic amide) has been used by many researchers to enlarge heteromacrocyclic compounds (Guggisberg et al., 1978; Jenny and Hesse, 1981; Kramer et al., 1977, 1978a, 1978b, 1979), especially for syntheses of natural products (Bienz et al., 1987). Cyclic lactams substituted at the nitrogen atom by a 3-aminopropyl moiety were readily transformed to the larger macrocyclic aminoamide under base catalysis. The yield for these reactions was often as high as 90%. It is possible to prepare macrocycles with more than three nitrogen atoms in the ring by this process.

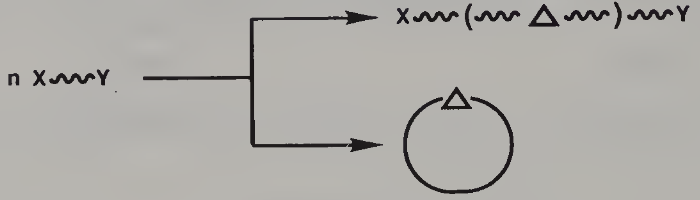


C. SPECIFIC CONDITIONS FOR RING CLOSURE

1. Formation of Macrocycles versus Polymers

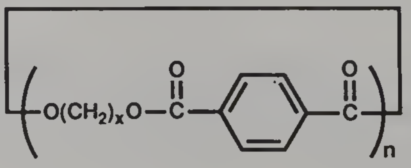
It is important in the cyclization process to maximize the yields of the desired macrocycle by choosing strategies that inhibit the competing linear polymerization reaction. Since the reactants for both cyclization and polylinear compound formation are the same, special conditions must be used to avoid polymerization or polycyclization (3:3, 4:4, etc. cyclization processes). The polymerization process is favored in reactions carried out without solvents





or where the substrates are in concentrated form and in the presence of certain additives. The 1:1 or 2:2 cyclization reactions are usually slow and are favored at low temperatures in dilute solutions and by using special catalysts as templates. Polymerization can be prevented if cyclization is carried out at concentrations not exceeding 10^{-3} molar (Ziegler et al., 1933). This rule can be transgressed in some individual cases where a preferred quasicyclic conformation favors ring closure and impedes bimolecular reactions from one starting material.

Polymer chemistry developed first, followed by cyclic chemistry (especially the crowns and peraza-crowns). Cyclic products are not wanted in linear polymers because of their deliterous effect on polymer characteristics. Exceptions include polythiazoles, polyimidazoles, and polytriazoles, which are produced by a polycyclization process. Macrocycles are often isolated during the synthesis of polymers. The polycondensates are particularly rich in the cyclic oligomers (Foti et al., 1982; Goethals, 1977; Semlyen, 1976; Zahn and Gleitsman, 1963). Other polymerization reactions also gave some cyclic oligomers under special conditions (Ballistreri et al., 1980; Foti et al., 1981). Some commercial polymers have some cyclic oligomers that can be extracted and structurally determined by mass spectrometry (Lünderwald et al., 1976). Terephthalate–alkylene copolymers, when prepared by melt polymerization, contain up to 1.5% of terephthalate–alkylene cyclic oligomers as part of the polymeric mixture. Where the polymer contains ethylene units ($x = 2$), the cyclic trimer ($n = 3$) predominates (East and Girshab, 1982; Wick and Zeitler, 1983). Even so, cyclic oligomers where $n = 7$–9 were observed. About equal



amounts of the cyclic dimer and trimer were observed where butylene units ($x = 4$) were present. Other oligomers with more complicated structures can form in these reactions (Shiono, 1979).

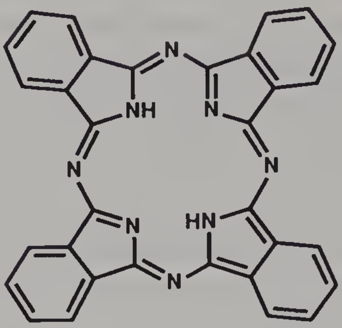
The cyclic oligomers often are found in high-temperature polymer degradation products (Foti and Montaudo, 1985). Those cyclic oligomers, which evaporate in the high-vacuum ion source of the mass spectrometer at temperatures below 200°C, can be detected without the need for prior isolation. The start of thermal decomposition can be observed for polyamides by the total ion current at temperatures above 350°C. Under those conditions polyamides are degraded by ring chain equilibration into cyclic oligomers that are normally the cyclic dimers, trimers, etc. (Lünderwald and Menz, 1978; Lünderwald et al., 1978; Wiley, 1979).

From the preceding discussion, it can be seen that appropriate conditions must be maintained to maximize the 1:1 or 2:2 cyclization reactions. Cyclocondensations of two or four substrates (1:1 or 2:2 cyclizations) are favored in high dilution and with template cations. Often internal hydrogen bonding helps to favor the cyclic reaction product. A more complete discussion of cyclization versus polymerization in these polycondensation reactions in high-dilution conditions has been published (Fastrez, 1987).

2. Template-Mediated Cyclization Reactions

The procedures to prepare macrocycles are many and varied. One fundamental problem with the preparation of macrocyclic ligands concerns the orientation of reactive sites so that they give macrocyclic products rather than the acyclic polymer. In general, most of the synthetic methods can be classified into two categories: (1) generation of the cyclic product is controlled by the presence of a metal "template" ion that interacts with the heteroatoms, and (2) generation of the cyclic product is done in high dilution without a metal "template" ion. Often hydrogen bonding between reacting molecules serves as the template. For many years the synthesis of macrocycles was largely unsuccessful and wasteful because of the low yields of cyclic products, the many side products, and the large volumes of solvents needed. There are, however, notable exceptions where good yields of certain macrocycles were obtained.

Baeyer first reported a 4:4 cyclization product for the reaction of pyrrole and dry acetone catalyzed by the addition of one drop of hydrochloric acid (Baeyer, 1886). The macrocycle was later isolated in an 88% yield in a less violent reaction (Rothemund and Gage, 1955). Metal derivatives of the phthalocyanines were obtained when *o*-diaminobenzene, *o*-cyanobenzamide, or related compounds were pyrolized with metals or their salts (Braun and Tcherniac, 1907). This was possibly the first observed template synthesis of a macrocyclic ligand.



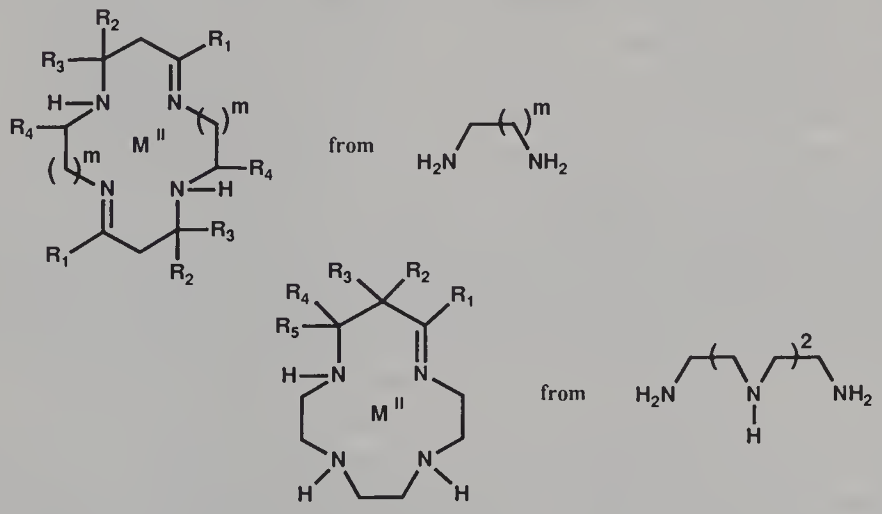
The effect of metal ions in promoting certain cyclization reactions has been recognized for a long time. In 1928, during the synthesis of phthalimide in an iron vessel, a dark by-product was isolated. This by-product proved to be the ferrous ion complex of phthalocyanine. The role of the ferrous ion as a template in the cyclization reaction was not recognized until much later (Hurley et al., 1967; Thompson and Busch, 1962, 1964a, 1964b). Busch recognized that the coordination sphere of the metal ion could hold the reactive groups in the correct positions for the cyclization reaction; that is, the metal ion acts as a "template." Template syntheses tend to form macrocycles only when the geometry of the ligand is favorable for the metal ion used, and often (especially in the formation of unsaturated macroheterocycles) the macrocycle is stable only when coordinated with the metal ion.

The metal ions may play less obvious roles in the cyclization process. For example, metal ions may mask or activate individual functional groups or influence the reaction in other ways not directly related to the more readily defined steric influences in the reaction sequence. Template effects have been studied in some depth in only a few specific systems.

It is noteworthy that the first macrocyclic polyamine was produced as a side product in 1937 (Alphen, 1937) and the first cyclic polyether was prepared the same year (Luttringhaus, 1937; Luttringhaus and Ziegler, 1937). The first template synthesis of a peraza unsaturated macrocycle without aromatic nitrogen-containing groups using Ni(II) or Cu(II) was published in 1961 (Curtis and House, 1961; House and Curtis, 1962). A few years later, Pedersen published his landmark synthesis of dibenzo-18-crown-6. This macrocycle was formed in a 45% yield by reacting catechol and the dichloro derivative of diethylene glycol using sodium *t*-butoxide as the base (Pedersen, 1967b, 1971). Pedersen observed that ring closure was facilitated by the sodium ion that interacted with the oxygen atoms to give a "wrapped" intermediate from three of the molecules and allowed the fourth to close the ring (Pedersen, 1971).

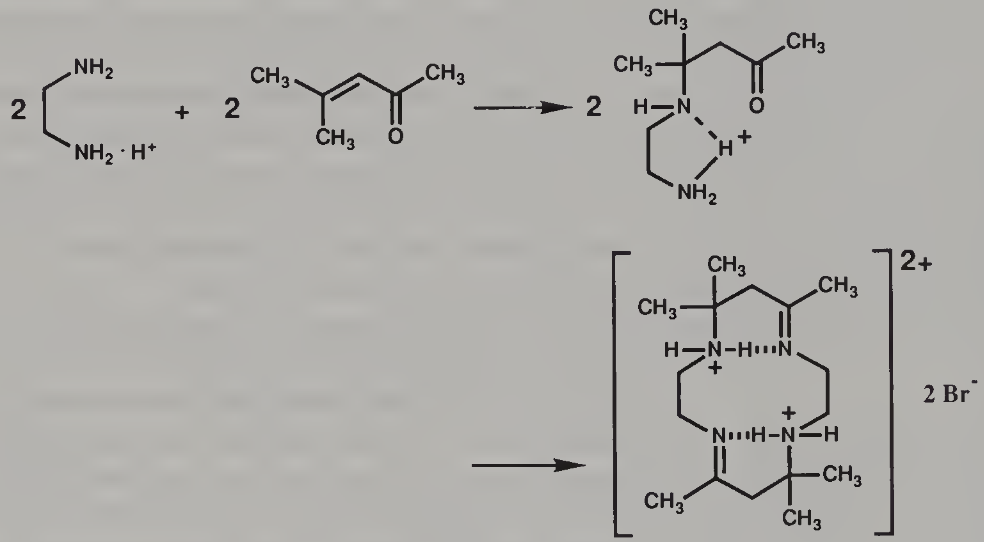
Before Pedersen's discovery was extensively tested, template reactions to form unsaturated aza macrocycles containing other nitrogen, oxygen, or sulfur heteroatoms were studied. The unsaturated cyclic aza systems have less flexibility, which restricts the number of possible modes of coordination. These factors tend to increase the kinetic stability of these systems. However, these unsaturated aza compounds seldom are stable under the reaction conditions without the coordinating metal ion. Some of the systems were reduced to the more stable saturated aza compounds followed by removal of the metal ion. Many unsaturated macrocyclic aza compounds were reported from 1961 to 1980 and often were reduced to the saturated macrocycle. Many of the macrocycles contained aromatic subcyclic units (Black and Markham, 1965; Curtis, 1968; Hancock and Martell, 1988; Healy and Rest, 1978; Laidler and Stoddart, 1980). Some of the metal-coordinated unsaturated macrocycles could not be reduced because the macrocycle decomposed under reduction conditions or the metal ion interfered in the reduction process. It is interesting that metal ion complexes with certain unsaturated aza macrocycles containing pyridine and phenanthroline can be reduced while the free unsaturated macrocycle cannot (Lüning, 1987; Lüning and Müller, 1989). Other uncoordinated Schiff-base-type macrocycles have been reduced by lithium aluminum hydride or sodium borohydride (Chen and Martell, 1991; Jazwinski et al., 1987a, 1987b; Menif et al., 1991). Other template syntheses especially for unsaturated aza macrocycles that are not part of this work on aza-crowns have been reviewed extensively (Busch, 1964, 1967; Busch and Cairns, 1987; Busch et al., 1971; Lindoy and Busch, 1975; Lindoy, 1989).

The cyclic tetraazadienes were first discovered by Curtis (Curtis, 1960; Curtis and House, 1961). These macrocycles were prepared by reacting 1,2-diaminoethane, 1,2-diaminopropane, or 1,3-diaminopropane with acetone, methyl ethyl ketone, propionaldehyde, *n*-butyraldehyde, isobutyraldehyde, or other small carbonyl compounds in the presence of Ni(II) or Cu(II) (Blight and Curtis, 1962; House and Curtis, 1962, 1964a, 1964b). Similar tetraaza macrocycles can be isolated from the reaction of triethylenetetraamine and the carbonyl compound in the presence of the metal template ions (Curtis and Hay, 1966). Compounds with two double bonds can exist in the isomeric form with both double bonds to the same molecule of diamine starting material

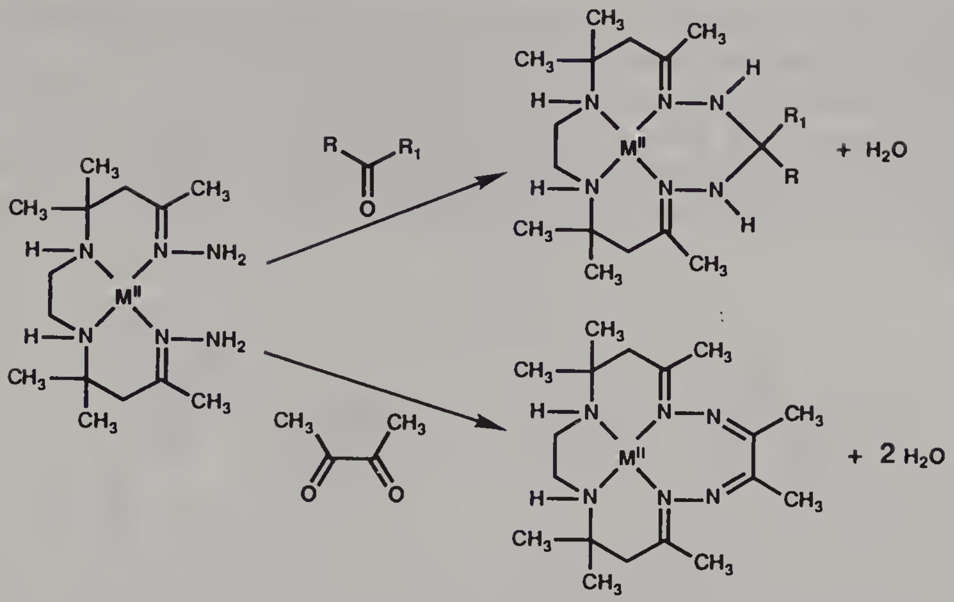


(*cis*-form). The structure of the product depends on the metal ion used.

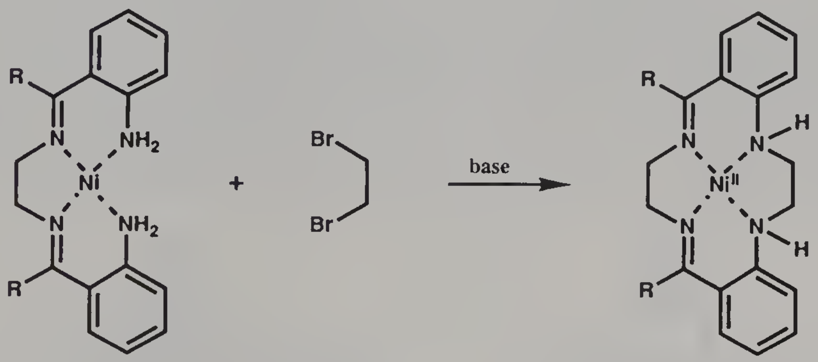
The mechanism of this reaction is not known. It is interesting that in some cases, the reaction takes place without the template ion. A hydrogen bonding network may act as the template for this latter reaction and may also serve to stabilize the macrocycle once it is formed. The hydrogen bromide salt of ethylenediamine reacted with acetone, methyl vinyl ketone, or 4-methyl-3-penten-2-one to form a macrocyclic dication (Hay et al., 1975; Kolinski and Korybut-Daszkiewicz, 1969; Sadasivan and Endicott, 1966; Tait and Busch, 1978a). In this case, the *trans*-ligand was isolated in a yield of 80% or greater as the dihydrogen bromide salt. The saturated macrocycle was formed by reduction of the nickel complex of the above cyclic diene. The saturated ligand was removed from the nickel ion in the presence of cyanide ion (Curtis, 1965, 1967; Warner and Busch, 1969). A more direct synthesis of the tetraaza macrocycle $Me_6[14]N_4$ using diamino salts followed by reduction is easier and more convenient (Tait and Busch, 1972, 1978a, 1978b). This more direct approach will be discussed more fully in Chapter X, on the synthesis of aliphatic peraza macrocycles.



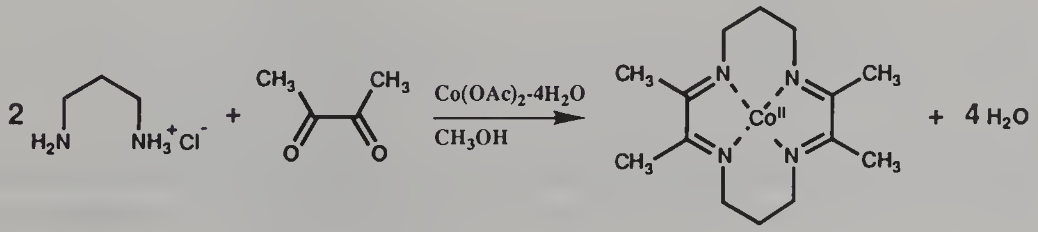
Another interesting template reaction, discovered by Curtis and coworkers, is the preparation of unsaturated aza macrocycles containing two hydrazine moieties. The intermediate bis-hydrazone complex was formed by condensation of a diazadicarbonyl compound with hydrazine in the presence of Cu(II) (Curtis et al., 1984.) The two uncoordinated *N*-amines were then reacted with a ketone or diketone to form the hexaaza macrocycle (see next page). This ring closure reaction was possible because the *N*-amino groups were not coordinated with the metal ion so that the electron pair on each nitrogen was available for nucleophilic reaction. Reaction of the uncomplexed amine with an alkyl halide will be possible only if the nonbonding electron pair on the



amine nitrogen atom is suitably oriented to undergo reaction with the approaching electrophile. The prospect that ring-closure reactions may involve complexed amine donors that may not be completely bonded to the metal ion cannot be ruled out as shown in the following example (Uhlemann and Plath, 1969).

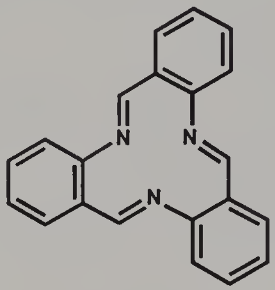


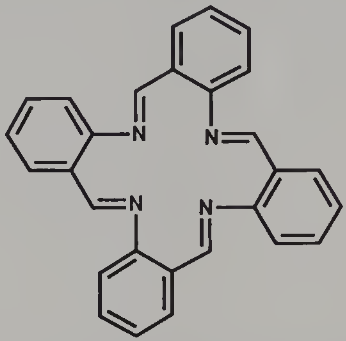
Other cyclization reactions also require a metal cation. For example, the preparation of the following cyclic Schiff base was possible only with a metal ion template (Jackels et al., 1972). Formation of the same ring system but with benzyl substituents rather than methyls also required a template ion. In



this case, Co(II) allowed the ring to close as shown above (Jackels et al., 1972; Welsh et al., 1977).

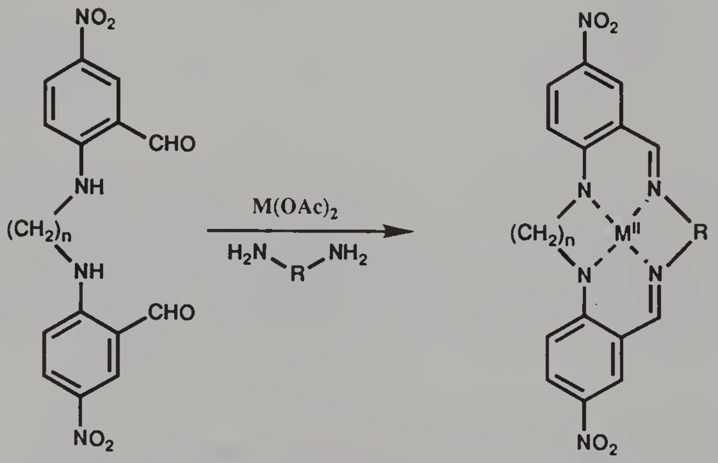
Self-condensation of *o*-aminobenzaldehyde in the absence of metal ions occurred slowly and gave a mixture of products (Bamberger, 1927; McGeachin, 1966; Seidel and Dick, 1927). Some of these products rearranged in the presence of Ni(II) or Cu(II) to give the cyclic trimer or tetramer (shown below).





The same products were obtained in better yields when *o*-aminobenzaldehyde self-condensed in the presence of Ni(II) (Melson and Busch, 1963, 1964, 1965; Tait and Busch, 1978c). Similar products were obtained with other metal ions. In general, the type of compound formed depended on the nature of the template metal ion (Busch et al., 1971; Cummings and Busch, 1970).

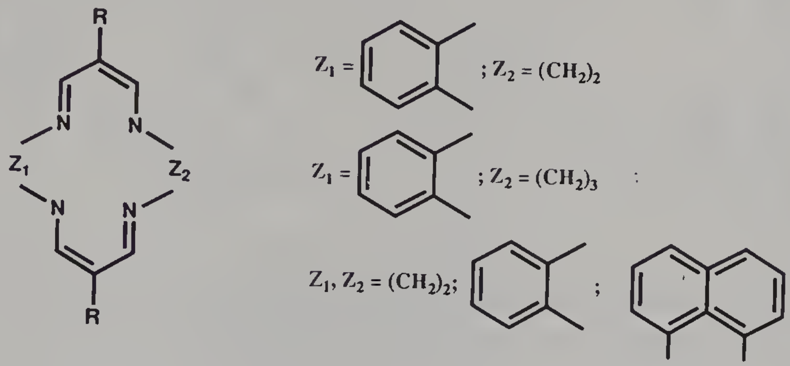
Condensation of a series of diaminodialdehydes with ethylenediamine, *o*-phenylenediamine, or 1,8-diaminonaphthalene in the presence of Ni(II), Co(II), or Cu(II) acetates gave a series of macrocyclic quadridentate complexes containing 14, 15, or 16 ring members (Black and Kortt, 1972; Black and Leane, 1970a, 1970b; Black and Srivastava, 1971; Honeybourne, 1978).



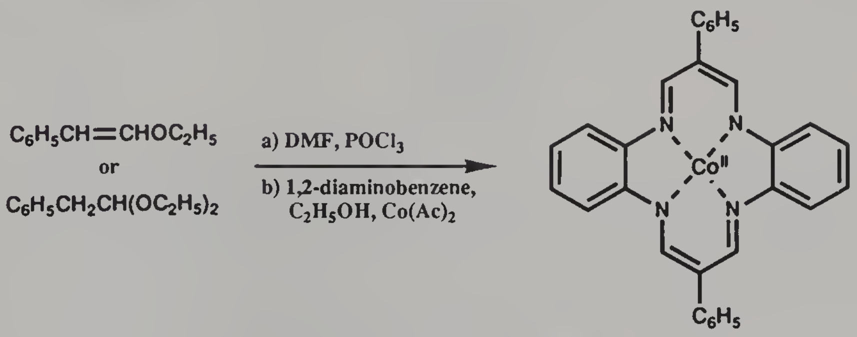
R = $(CH_2)_2$; o-C_6H_4; 1,8-$C_{10}H_6$

Bromomalonodialdehyde reacted rapidly with metal(II) diacetate complexes of *o*-phenylenediamine, ethylenediamine, 1,3-diaminopropane, and

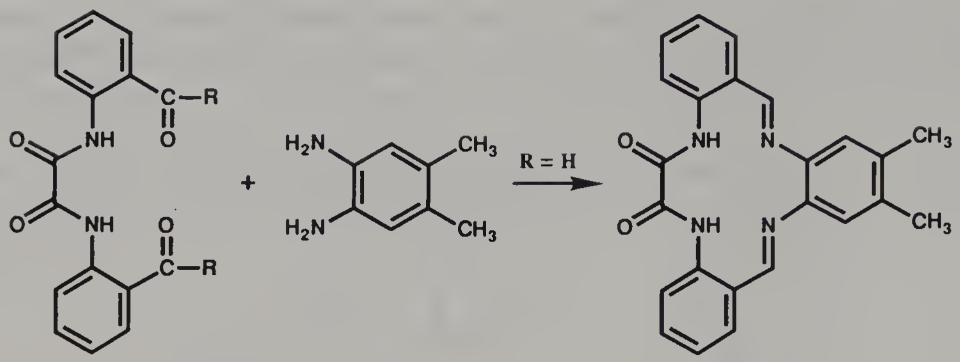
1,8-diaminonaphthalene. The yield of the macrocycle from *o*-phenylenediamine was 60% using Co(II) and near quantitative using Cu(II) (Honeybourne, 1975). These results are superior in both yield and simplicity of ring closure to the previous method for the preparation of the dibenzo macrocycle starting from propionaldehyde and using no metal ion template (Hiller et al., 1968). A similar dibenzotetraaza macrocycle was prepared by a template condensation of *o*-phenylenediamine with pentane-2,4-dione in the presence of Ni(II) ions (Goedken et al., 1973). The metal ion was removed by treatment with hydrochloric acid, and the macrocycle was isolated as the hydrochloride salt. Neutralization with base afforded the neutral ligand.



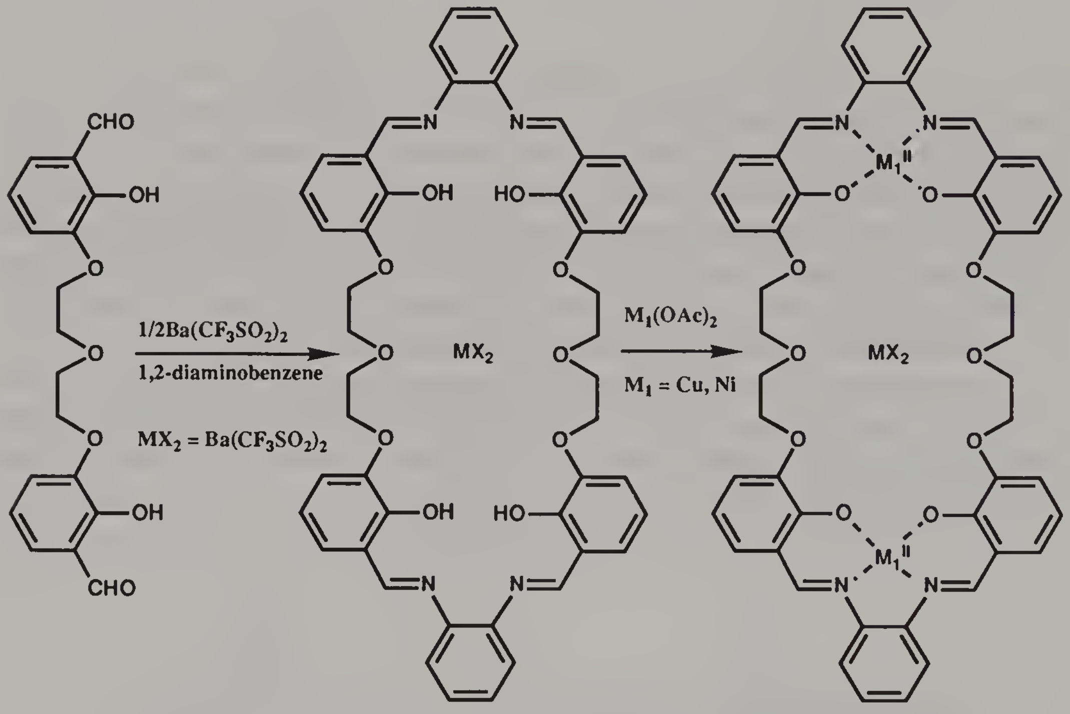
As noted above, the template effect increases the yield in most cases. The macrocycle complex system shown below was obtained in only 2% yield without a template ion and 28% using Ni(II) or 33% using Co(II) as template ions (Makin et al., 1988).



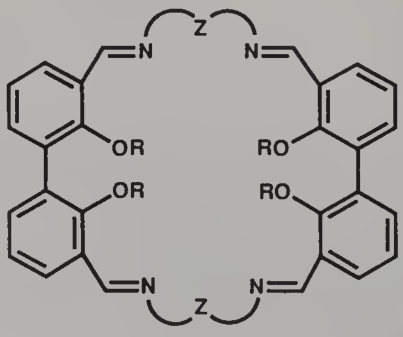
A similar system was prepared with or without the template effect. In this case, reaction without a metal ion gave a higher yield (93%)(R = H) than the yield using Ni(II) (82%)(R = CH_3)(Christodoulou et al., 1990). Reaction without a metal ion where R = CH_3 gave no product. The final compounds can bind two different metals ions—one inside the cavity and the other outside to the carbonyl oxygen atoms.



Another example of coordination of two different soft metal ions but inside the cavity by a special organized crown was reported recently (van Veggel et al., 1989). An unusual boric acid template for the preparation of Schiff-base

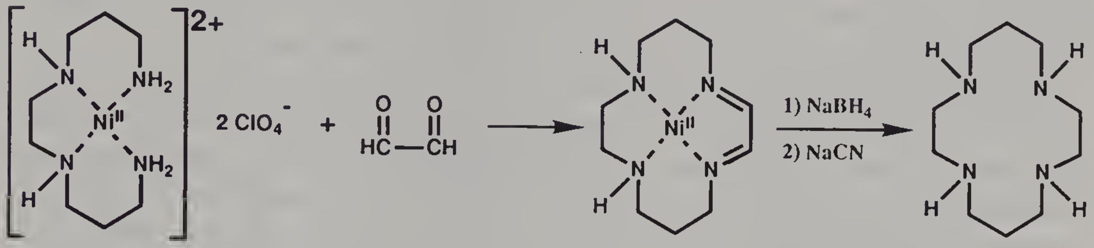


macrocycles has been used in France. Two types of macrocycles were prepared, one shown below and the second one containing naphthalene units (Moneta et al., 1988).

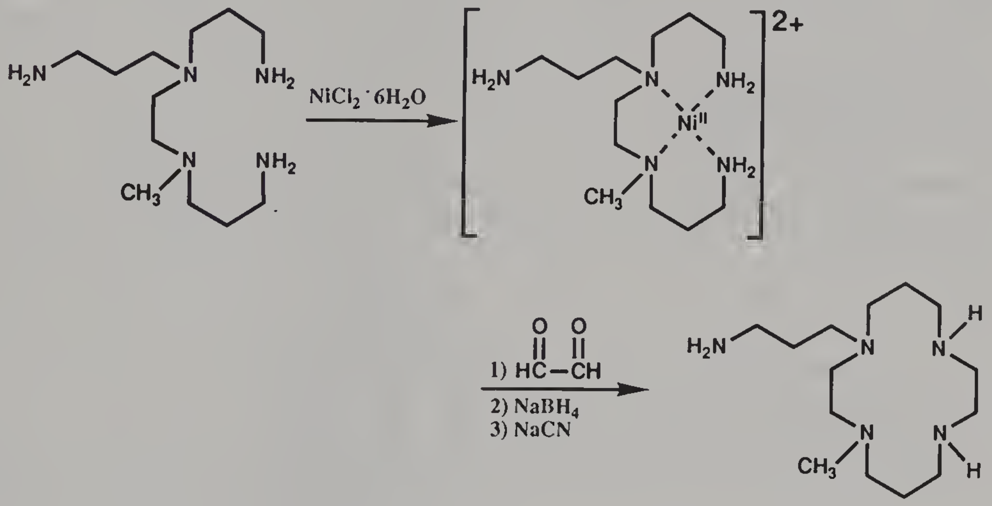


Z = (CH$_2$)$_3$, p-CH$_2$-C$_6$H$_4$-CH$_2$, o-C$_6$H$_4$

1,4,8,11-Tetraazacyclotetradecane, commonly called "cyclam," was synthesized using Ni(II) as the template ion (Barefield, 1972; Barefield and Freeman, 1980; Barefield et al., 1976a). The reaction provided a good yield (nearly 40%); however, dangerous perchlorate and cyanide ions were used in the process. A cyclization method using an *N*,*N*′-ditosylate compound and a dihalide gave a comparable overall yield of the cyclam (Stetter and Mayer, 1961). A one-step cyclization from 1,3-dibromopropane and 1,4,8,11-tetraazaundecane gave only a small yield of the cyclam (Bosnich et al., 1965).

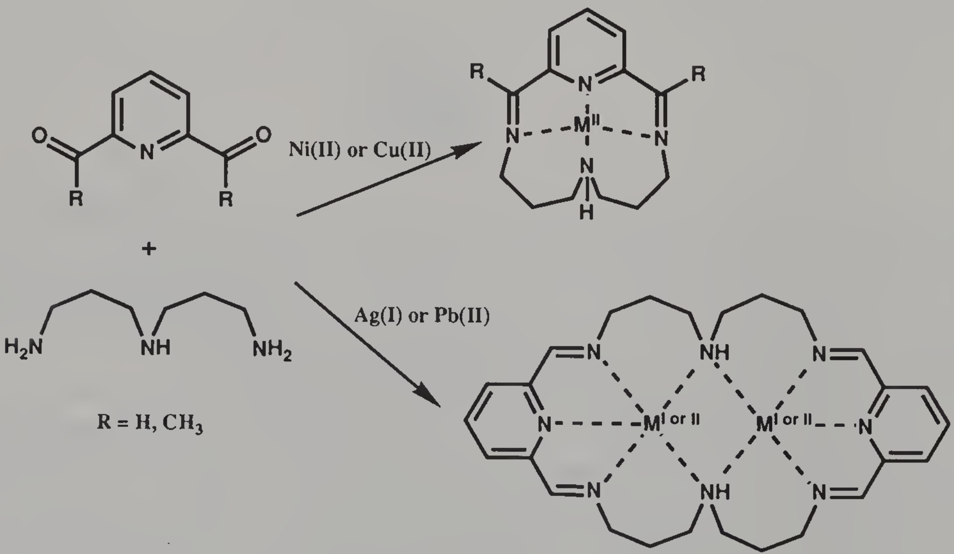


One other interesting template synthesis of a cyclam was reported by Franz and coworkers (Franz et al., 1987). The Ni(II) complex of 5-(3-aminopropyl)-8-methyl-1,5,8,12-tetraazadodecane reacted with glyoxal followed by reduction and decomplexation to give the cyclam containing methyl and 3-aminopropyl substituents on two of the ring nitrogen atoms.

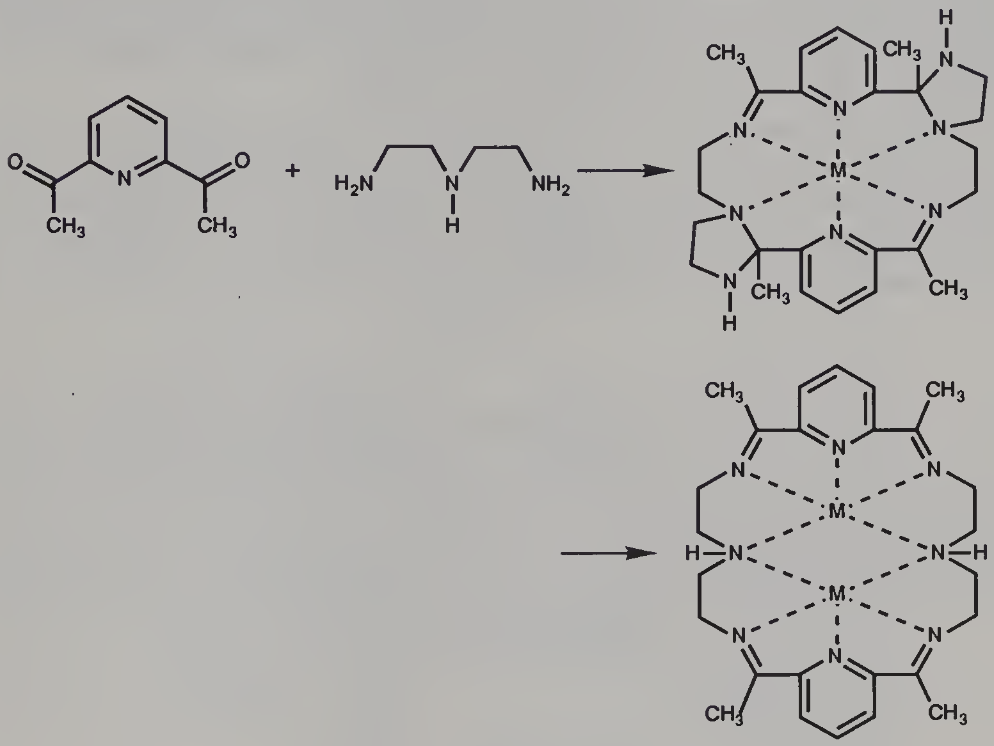


Other examples of template cyclization reactions leading to macrocycles with amine double bonds that can be reduced to the fully saturated systems will be discussed later. Often, without the template ion, small 1:1 cyclizations take place. In the case of the Curtis reaction, a seven-membered ring was formed without the template ion (Montecatini, 1968). Ethylenediamine condensed with mesityl oxide or with other α,β-unsaturated ketones to give tetrahydro-1,4-diazepines without the template ion (Elguero et al., 1969; Guareshi, 1894; Mushkalo and Shokol, 1960). However, in the case of reactions of rigid arylideneacetone or benzylideneacetophenone with ethylenediamine, the tetrahydroazepines were not the main products. The cyclic 2:2 condensation products were the main materials isolated in this case (Hideg and Lloyd, 1971). In all of these cyclization reactions, the template ion helps in the 2:2 cyclization process. The appropriately sized metal template ion allows the synthesis of the larger 2:2 cyclization products where the cavity size is slightly larger than the metal ion diameter (Nelson, 1980).

An important result of the template 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. Some examples were shown above in the Curtis cyclization reactions. The works of Nelson and coworkers and Fenton and coworkers (Drew et al., 1981; Fenton, 1986; Fenton et al., 1987; Murphy et al., 1987; Nelson, 1980) show that some saturated macrocycles with a heterocyclic subunit (pyridine, furan, or thiophene) can be formed after a two-step reaction without the need for nitrogen protecting groups. The appropriate template cation allows the formation of 1:1 or 2:2 condensations. It is important to note that even small cations can produce 2:2 cyclization products because two atoms can be coordinated inside a large cavity. The reaction between 2,6-diacetylpyridine or 2,6-diformylpyridine and 3,3′-iminobispropylamine are examples. First, as shown below, 2,6-diacetylpyridine reacted with bis(3-aminopropyl)amine in the presence of Ni(II), Cu(II), Mn(II), Co(II), or Zn(II) salts leading to the formation of complexes of the 1:1 condensation product (Karn and Busch, 1966; Rich and Stucky, 1965). Schiff-base template condensation of the above compounds in the presence of Ag(I), Pb(II), Ca(II), or Sr(II) led to binuclear Ag(I) and Pb(II) and mononuclear Ca(II) and Sr(II) complexes of the 28-membered ligand (2:2 cyclization) (Cabral et al., 1984; Drew et al., 1979, 1987). This process



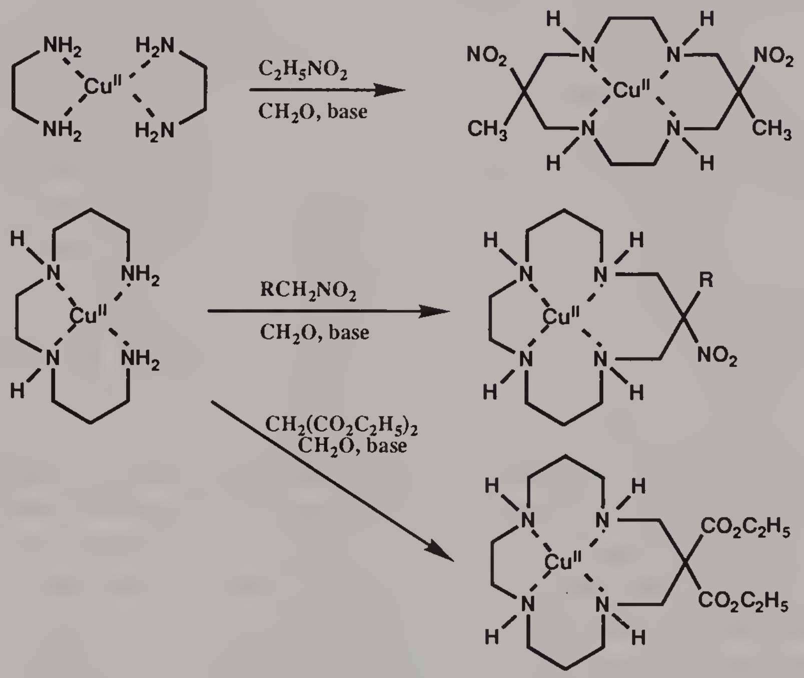
could be complicated by the formation of a ring-contracted form when the reaction was carried out using calcium or strontium salts. This ring contraction process was evident when diethylenetriamine was used in the reaction. The contracted 20-membered ring was converted to the 24-membered ring by a transmetallation reaction with a transition metal.

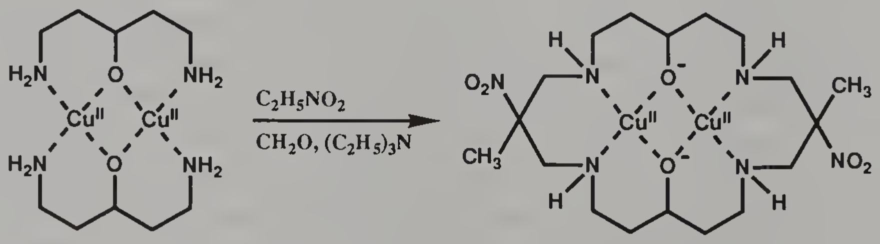


The mononuclear and binuclear complexes can be transmetallated into the opposite complex type using other metal ions. This procedure could be useful for the reduction process because the complex can be converted into a metal complex that could be reduced. For example, the Ag(I) complex of the Schiff base shown above cannot be reduced, but two successful reduction procedures have been reported for the lead thiocyanate complexes using sodium borohydride (Drew et al., 1987, Krakowiak et al., 1991). In addition, the above compounds were separated as the free bases without impurity for NMR and other analyses (Krakowiak et al., 1991).

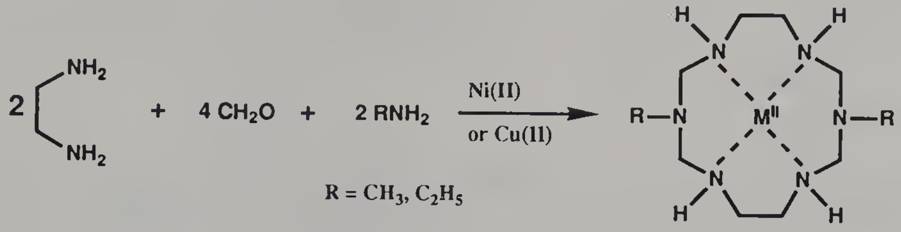
While the template cyclization technique has resulted in the isolation of many aza macrocycles that are not available by other means, its main drawback is that demetallation to produce the free ligand is not always possible because the macrocycles often are unstable in the uncoordinated state or the complex is too strong for decomplexation. In those cases, a direct synthesis is usually employed to produce the aza macrocyclic compounds that may be amenable to organic modifications. The direct synthesis procedure is usually longer. For example, in contrast to the template method, the direct approach to similar macrocycles with pyridine subcyclic units required six steps using nitrogen protecting groups (Hosseini et al., 1989). The problem of a multistep procedure or the difficulty in removing the complexed metal ion has been partially overcome by the condensation reaction of a dialdehyde with a diamine. A 2:2 cyclic condensation was noted for the reaction of 2,5-diformylthiophene with 3-thiaheptane-1,5-diamine or bis(3-aminopropyl)methylamine and for 2,6-pyridinedicarbaldehyde or 1,10-phenanthrolinediacarbaldehyde with 1,3-diaminopropane (Alcock et al., 1984; Krakowiak et al., 1991; Lavery et al., 1987). Some of the resulting unsaturated macrocycles were reduced to the fully saturated systems (Alcock et al., 1984).

Reaction of selected metal ion complexes of multidentate amines with formaldehyde and a variety of activated carbon compounds (such as nitromethane or diethyl malonate) have led to ring closure to yield polyaza macrocycles (Comba et al., 1986; Lawrance and O'Leary, 1987). Reaction with the malonate ester gave less than a 2% yield. Another approach for the construction of similar types of compounds was explored by the same authors. The precursor was prepared as a binuclear complex (Murase et al., 1982) and reacted with nitroethane in the presence of triethylamine and gave more than a 5% yield of the product (Comba et al., 1990). The same precursor, 1,5-diamino-3-hydroxypentane and acyclic dialdehydes were used for the non-

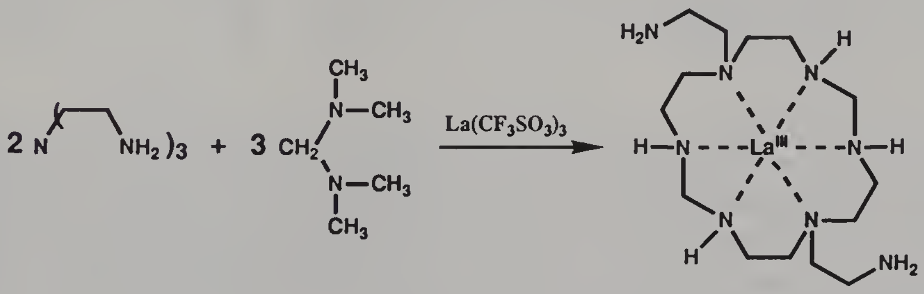




template procedure to synthesize other macrocycles and to synthesize mononuclear complexes of Co(II), Ni(II), Cu(II), and Zn(II) (Bailey et al., 1990). Three-dimensional macrocycles were also prepared using this approach (Boucher et al., 1983; Geue et al., 1984; Sargeson, 1984). A similar procedure was used to prepare 1,3,6,8,10,13-hexaazacyclotetradecane (Suh and Kang, 1988). These hexaaza macrocyclic complexes were prepared by the template condensation of ethylenediamine, formaldehyde, and an alkylamine in the presence of the metal ion as shown.

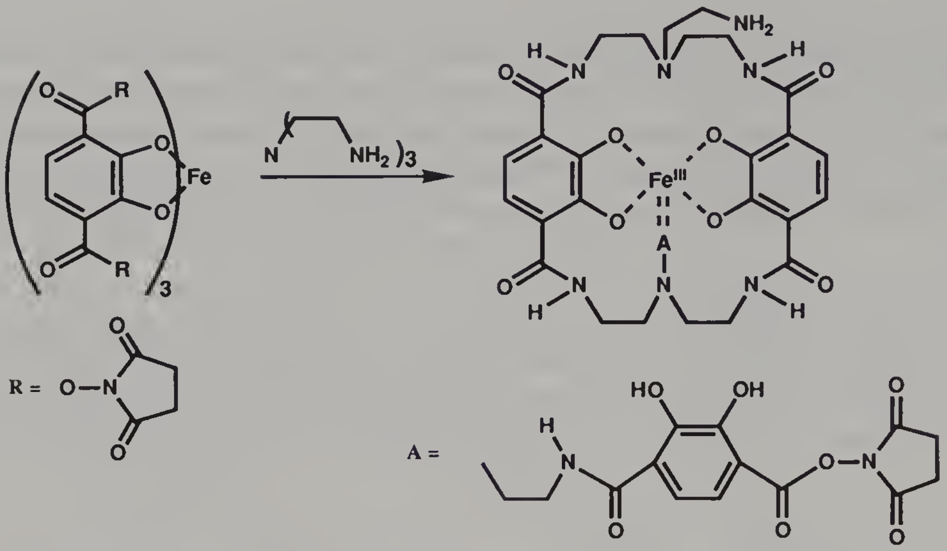


A hexaaza macrocycle containing two 2-aminoethyl pendant groups was prepared using La(III) as the template ion. The macrocycle–La(III) complex was prepared by the condensation of 3 eq of bis(dimethylamino)methane and 2 eq of tris(2-aminoethyl)amine (Smith and Raymond, 1985).

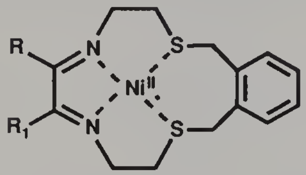


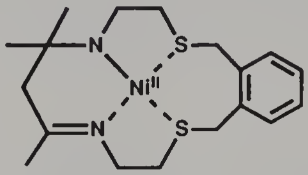
Template chemistry can be used to build complicated macrocycles because the template metal ion can hold the starting materials in the required steric arrangement. An example of the formation of a complicated macrocycle using Fe(III) as the template was recently reported by Raymond and coworkers (McMurry et al., 1987; Raymond, 1989). They obtained a 50% yield of the tetraamido macrocycle (shown on p. 98) wherein five amide linkages were formed in one step. The activated carboxyl group at the end of substituent A subsequently reacted with the aminoethyl group on the other side of the macrocycle to form a cryptand. These types of siderophores were obtained previously as mixtures of products using high-dilution techniques (McMurry et al., 1987; Rodgers et al., 1985).

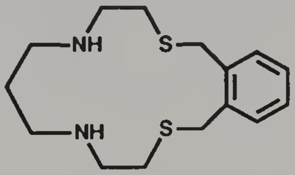
The most common template synthesis of macrocycles containing both sulfur and nitrogen atoms is the condensation of α-diketones (or acetone), β-mer-



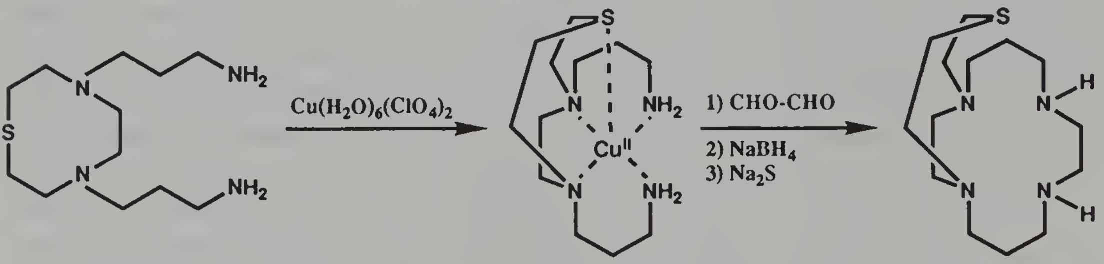
captoamines in the presence of Ni(II) ions, and α,α'-dibromo-o-xylene to give the following compound types (Busch, 1967; Drew et al., 1980; Thompson and Busch, 1962).



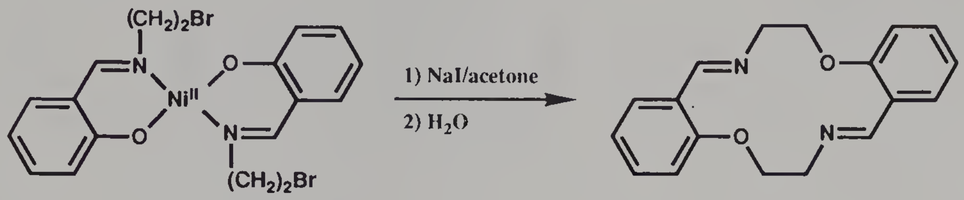


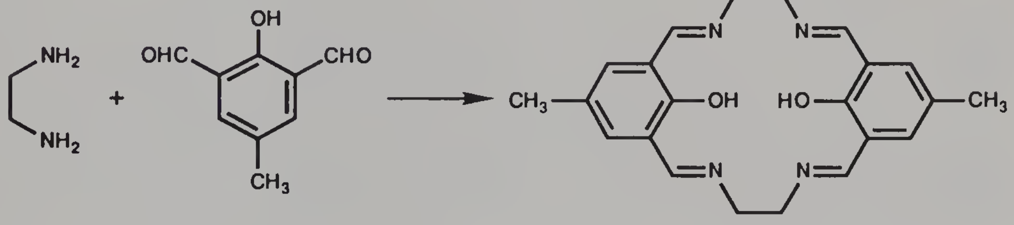


One of the first successful cyclizations using glyoxal and promoted by Ni(II) produced a 14-membered cyclic system (Barefield et al., 1976b). Fortier and McAuley (1989) reported an interesting example of a cyclization reaction using glyoxal. They produced a bicyclic system as shown below using a Cu(II) catalyst. The authors isolated the Cu(II)–ligand complex and then remove the metal ion using aqueous sodium sulfide.



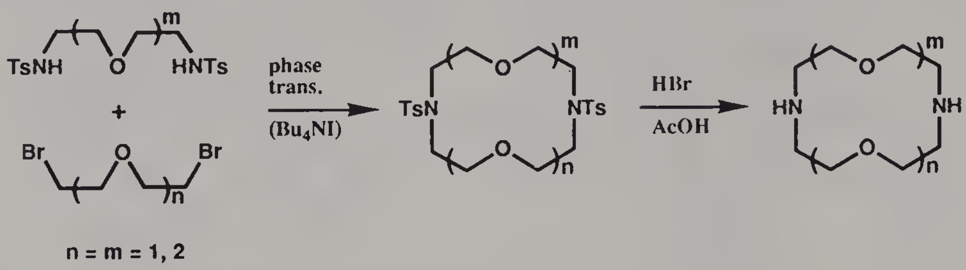
The template synthesis of macrocycles containing both nitrogen and oxygen atoms (the aza-crowns) has been the most studied synthetic method for the nitrogen-containing macrocycles. The synthesis of mixed nitrogen and oxygen donor macrocycles containing aromatic subcyclic groups are based mainly on salicylaldehyde–metal ion complexes (Kluiber and Sasso, 1970). The amine–ether macrocycle was also formed by heating the *N*-(2-bromoethyl)-salicylaldimine complex in acetone in the presence of sodium iodide. The free macrocycle was obtained by treating the complex with water. Another similar macrocyclic ligand was obtained from 2-hydroxy-5-methylisophthaldialdehyde and ethylenediamine only when a metal ion was present (Pilkington and Robson, 1970). The diphenolic macrocycle formed mononuclear complexes with Ni(II), but when the hydroxy groups were deprotonated, it formed binuclear complexes with Mn(II), Fe(II), Ni(II), Cu(II), and Zn(II) ions (Hoskin et al., 1976).



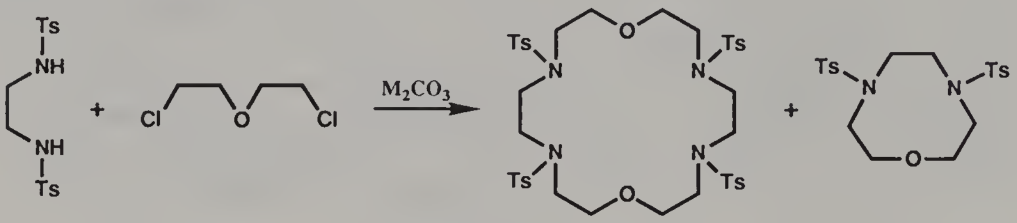


Greene observed that the formation of 18-crown-6 from a ditosylate and a diol in the presence of *t*-butoxide salts was enhanced when a potassium cation was used (Greene, 1972). This template effect was operative for the synthesis of other polyether crown compounds using alkali or alkaline-earth metal cations. Template effects have also been observed for the preparation of aza-crown ethers, although the effect is less pronounced because the softer *N*-donor atoms form weaker complexes with the alkali metal cations (Frensdorff, 1971). Richman and Atkins reported that high-dilution techniques were not required for the cyclization reaction of the disodium salt of a pertosylated oligoethylenepolyamine with sulfonated diols to form medium and large polyaza-crown compounds (Richman and Atkins, 1974; Atkins et al., 1978).

It is interesting to note that replacement of the sodium cations by tetramethylammonium ion in the Richman–Atkins procedure did not inhibit the reaction as one might expect in a template cyclization but only decreased the yield of the tetraaza-crown to about 50%. Gokel and coworkers suggested that the increase in the yield from 50% to 80% when tetramethylammonium was replaced by sodium does indicate a small template effect by the sodium ion (Gokel et al., 1982). Bogatskii and coworkers used phase-transfer conditions (Isele and Martinez, 1981) to obtain macrocyclic poly-*N*-tosylaza-crown compounds (Bogatskii et al., 1984). They reported that the yield for the cyclization step did depend on the nature of the cation. The 12-crown-4 compound formed best with lithium hydroxide while the larger crowns formed best when sodium hydroxide was used.



Biernat and Luboch have shown a definite template effect in the synthesis of tetra-*N*-tosylaza-18-crown-6 by the following reaction sequence (Biernat and Luboch, 1984).



The yield of the tetraaza-18-crown-6 product was 40% with potassium carbonate but only 10% when sodium carbonate was used. The amount of 9-crown-3 by-product was greater when sodium carbonate was used. The same reaction using diethylene glycol ditosylate instead of 2-chloroethyl ether with cesium carbonate as the base was reported recently, but with only a 20% yield (Craig et al., 1989).

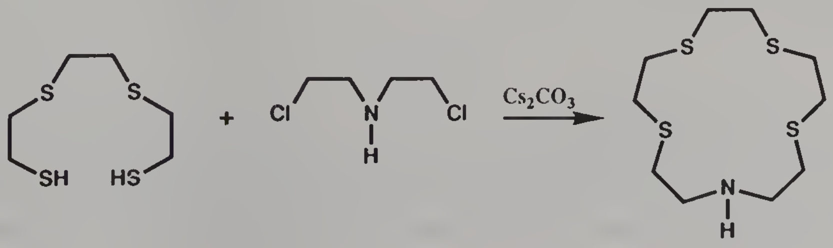
The diminished template effect in the formation of the poly-*N*-tosylaza-crowns using tosylaza starting materials has been explained by Shaw to be a result of restricted rotational freedom in the starting materials caused by the large tosyl groups (Shaw, 1975). As a result of this restricted rotation, there is a relatively small loss in entropy on cyclization, allowing ring closure to occur in relatively high yields without a need for preorganization of the starting materials. Rasshofer and Vögtle (1978) also explained the cyclization reactions to form the poly-*N*-tosylaza-crowns in terms of template, steric, and entropy effects. Thus, despite not using high-dilution conditions, the very high yields in these cyclization reactions resulted from the steric influence of the bulky *N*-tosyl groups (Chavez and Sherry, 1989; Iwata and Kuzuhara, 1989a, 1989b). It is worth noting that some of these systems were large with up to 52 ring members (12 nitrogen atoms). The bulky *N*-tosyl groups reduce the number of conformational degrees of freedom in the reactants and intermediates. It is this restriction that is thought to facilitate cyclization relative to polymerization in these systems.

Recently, several large-ring macrocyclic diamines have been prepared in DMF using cesium carbonate to deprotonate the ditosylamide groups followed by a slow addition of the dibromoalkane (Dijkstra et al., 1987; Vriesema et al., 1984). Excellent yields were reported for the 17- to 28-membered rings using cesium carbonate, but low yields and incomplete reactions were observed for the 11- and 12-membered rings and for syntheses of the larger rings when lithium, sodium, or potassium carbonates were used. A comparison of yields for the cyclization of a 28-membered diamino macrocycle using cesium carbonate for deprotonation of the *N*-tosyl groups versus using the sodium *N*-tosylate salt (the Richman–Atkins procedure) suggested that a combination of ion-pair/template effects were operative and that cesium ion had a significant advantage over the smaller sodium ion for this ring size.

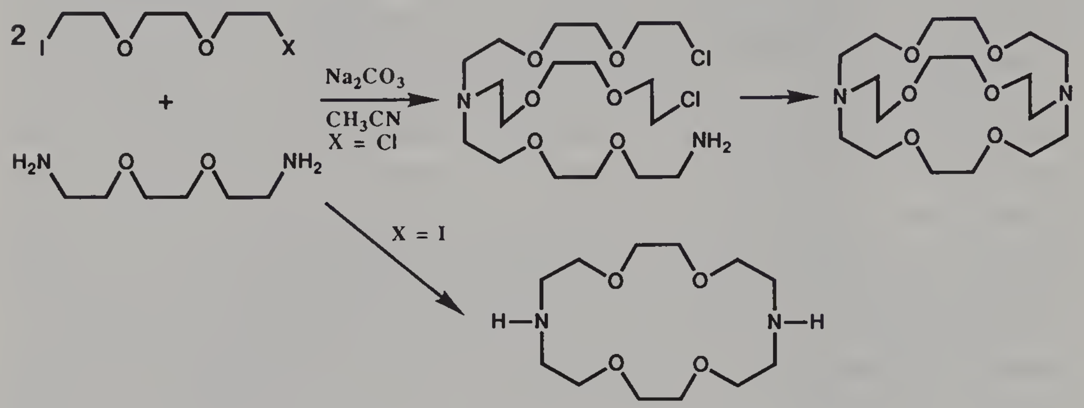
Changing the metal carbonate also affected intramolecular cyclization to form the 10-membered macrocycle with three nitrogen atoms in the ring. Isolated yields were 0%, 21%, 75%, 75%, and 0% using lithium, sodium, potassium, cesium, and silver ions, respectively (Chavez and Sherry, 1989). This indicates that potassium and cesium carbonates are excellent bases for the deprotonation of the tosylamides in DMF and that a template effect is not the most important factor in this reaction.

Cyclization reactions using tosylamides and ditosylates or dihalides is dependent on the base strength, as was pointed out by Chavez and Sherry (1989). If the base does not deprotonate the tosylamide, a reaction does not take place. It is also difficult to compare cyclization yields using various metal bases because of a concomitant decomposition of the ditosylate or dihalide coreactants in basic conditions at higher temperatures. This problem will be discussed again in the next chapter on the most common methods for the syntheses of the aza-crowns.

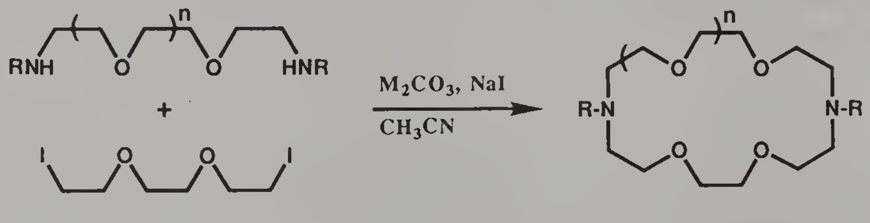
Cesium carbonate in DMF, as mentioned above, has been recognized as a cation that can give high yields for the cyclization step not in a template effect but as the so-called cesium effect. Cyclization yields in the presence of cesium carbonate in DMF were much higher in the case of small and large sulfur-containing crowns (Buter and Kellogg, 1981, 1987; Kruizinga and Kellogg, 1981). This effect is also recognized in the formation of azathia-15-crown-5. Since cesium is too large to fit into the cavity of the macrocycle, the relatively high yields of the product must be due to the "cesium effect" (Pavlishchuk and Strizhak, 1989).



Kulstad and Malmsten (1980a) reported a remarkable synthesis of 1,10-diaza-18-crown-6 and cryptand[2.2.2] from the reaction of either 1-iodo-8-chloro-3,6-dioxaoctane or 1,8-diiodo-3,6-dioxaoctane. The chloro-iodo starting material gave the cryptand while the diiodo starting material gave the diaza-18-crown-6. In the former case, the iodide reacted much faster than the chloride, allowing for the formation of an intermediate amine with three branches. This product then cyclized into the cryptand as shown. When the diiodo starting material was used, the diaza-crown resulted from a simultaneous reaction with both iodides in the presence of a template cation. The formation of the cryptand was also controlled by template and solvent effects. The best solvent was found to be acetonitrile. Sodium carbonate was the best catalyst, and no significant amount of cryptand was observed when potassium carbonate was used. These authors found that variations in the combination of metal carbonate and solvent could significantly affect the yield of diaza-18-crown-6 when using the diiodide. In acetonitrile, sodium carbonate was the best catalyst followed by potassium, cesium, and lithium carbonates, which gave decreasing yields of the cyclic product (Kulstad and Malmsten, 1979). It is instructive to note that diaza-18-crown-6 yields fell to only 4% when an excess amount of dicyclohexano-18-crown-6 was present in the reaction mixture. Presumably the crown complexes the metal cation so that it was less available to act as a template (Kulstad and Malmsten, 1980b).

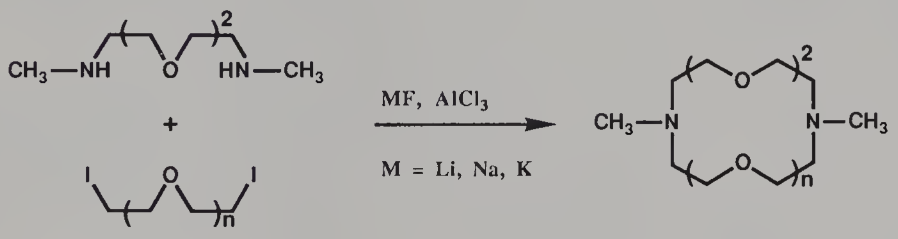


Gokel and coworkers prepared a series of nitrogen-pivot lariat crown ethers (Schultz et al., 1985). These compounds all have side arms connected to a macroring nitrogen atom. Where a side arm was incapable of coordinating a metal ion, the ring-closure reaction occurred to give a yield of about 30% or

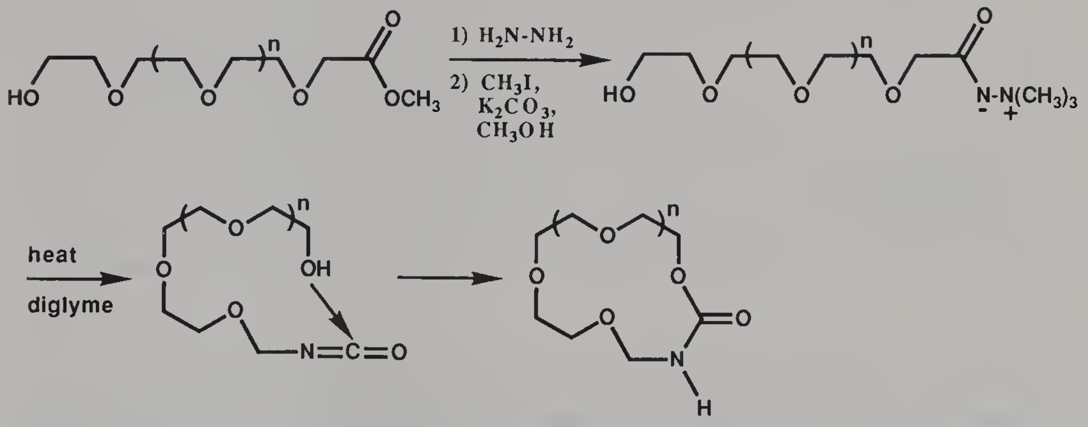


less. Where the side arm was composed of relatively rigid aryl groups containing an ether donor oxygen atom, the ring-closure reaction occurred in about 40% yield. Cyclization yields of 50% and higher were obtained where the donor atoms were attached to a flexible side arm. In the latter case, the flexible side arm allowed the donor atom to interact with the cation in the forming macroring cavity, resulting in a more stable complex and thus a higher macroring yield.

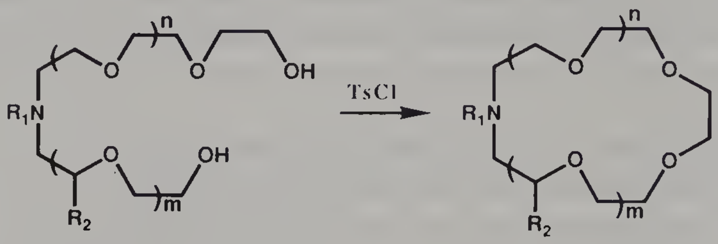
Yamawaki and Ando (1979, 1980) have shown that crown ether syntheses can occur when a potassium-fluoride-coated alumina catalyst is used. Pietraszkiewicz and coworkers have found this technique useful for the preparation of diaza-crowns (Pietraszkiewicz, 1984; Pietraszkiewicz and Jurczak, 1983). They found that the yields increased when the metal ion was changed from lithium to sodium to potassium. They explained the increase in yields as a result of greater basicity of the potassium fluoride–alumina catalyst rather than a template effect. However, the main drawback of this method is that base-sensitive groups such as the esters are affected by potassium fluoride on alumina (Pietraszkiewicz and Jurczak, 1984).



Okahara and coworkers prepared two macrocyclic monoamide compounds by heating the salt of an ω-hydroxyamide (Masuyama et al., 1985). No significant change in the cyclization yields was observed on the addition of template salts such as sodium or potassium tetrafluoroborate.

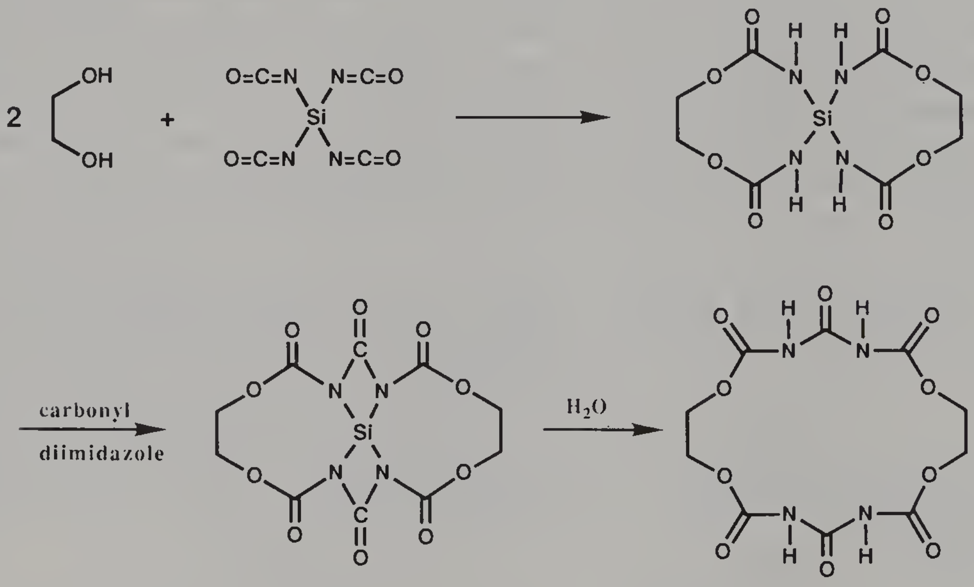


Okahara and coworkers found that the oligoethylene glycols cyclized into crown ethers upon treatment with 1 mol of tosyl chloride. This method has been used to prepare many aza-crowns (Kuo et al., 1978a, 1978b, 1980; Maeda et al., 1983b; Nakatsuji et al., 1988; Son et al., 1984). They determined that

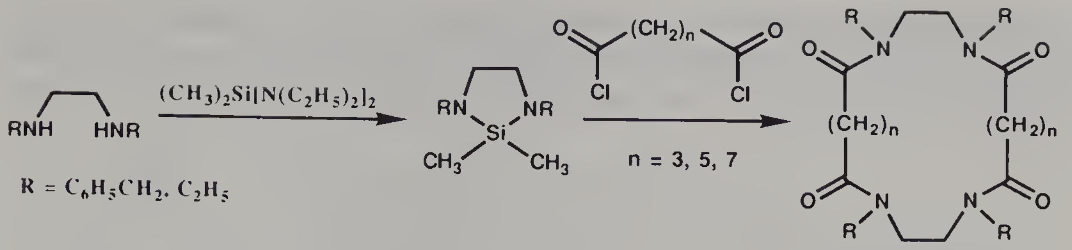


the best yields were obtained in either dioxane or a *t*-butyl alcohol–dioxane mixture with an appropriate template metal hydroxide. The Okahara ring closure reaction will be discussed in more detail in the next chapter.

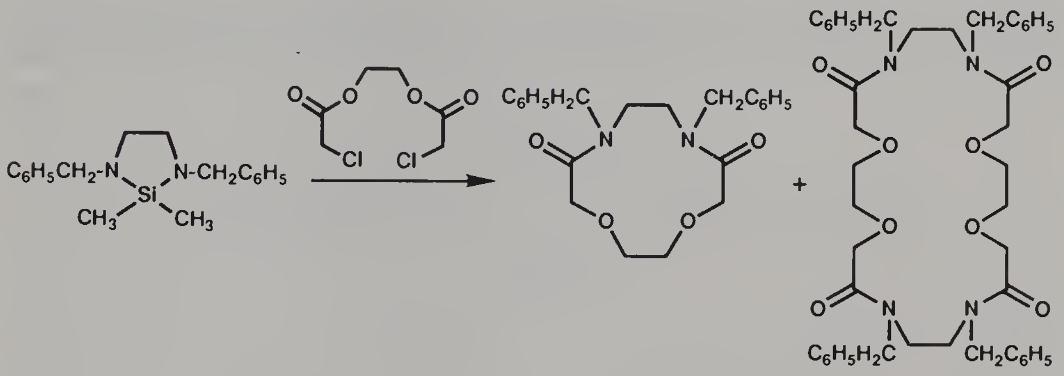
Schwartz and Shanzer have used silicon as a metaloid template for the one-step synthesis of biomimetric macrocycles (Lifson et al., 1987). Silicon functions as a covalent template by forming weak bonds to the heteroatoms and can be easily removed using mild conditions. Silicon tetraisocyanate was reacted with ethylene glycol followed by carbonyl diimidazole to give a polycyclic product that was desiliconated with water.



Another similar method for the preparation of cyclic tetraamides has been developed by the same authors (Schwartz and Shanzer, 1981; Schwartz et al., 1985). The method involved a 1,3,2-diazasilolidine intermediate formed by the reaction of a diamine with dimethylbis(diethylamino)silane. The diazasilolidine intermediate was reacted with a diacid chloride to form the macro-



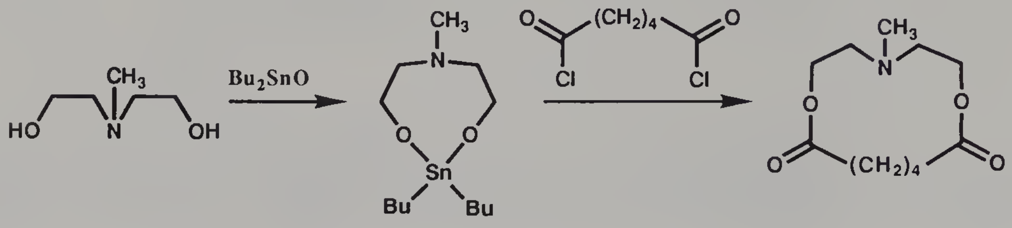
cyclic tetraamide. This procedure was used by other authors to prepare macrocyclic di- and tetraamides containing both nitrogen and oxygen atoms (Leygue et al., 1987, 1988). But in the latter case, a higher yield was obtained



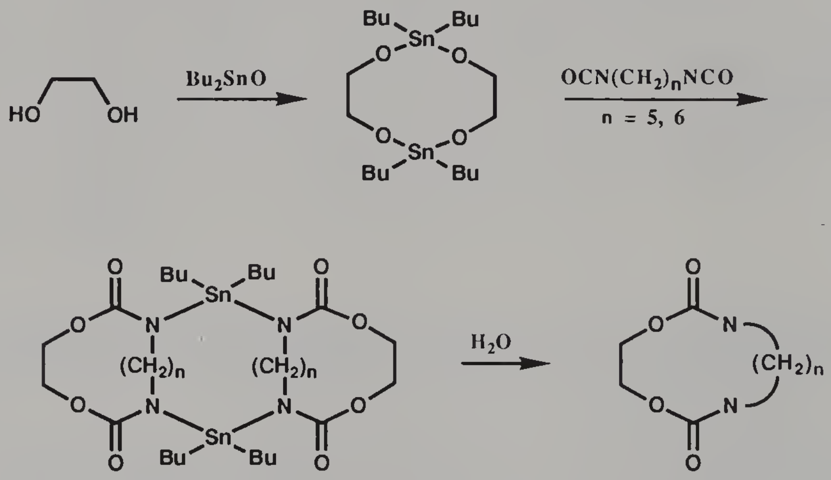
using high-dilution techniques than with the silicon-template method. In both the silicon-template and high-dilution methods, the 2:2 cyclization product was isolated in a low yield.

The same type of reaction was carried out using ethylene glycol or dimercaptan rather than the diamine to form the dioxa- or dithiasilolidine intermediates. The dioxasilolidine or its bis(trimethylsilyl) derivative did not form the cyclic compounds on reaction with a diacid chloride, while the dithia analogs reacted to give modest yields of the cyclic 1:1 and 2:2 products (Leygue et al., 1988). When high-dilution techniques were used, a greater amount of the 2:2 cycloaddition product was isolated. In general, little or no 2:2 cyclization products were observed in the silicon-template reaction. This method is best for the preparation of macrocyclic lactams, only moderately successful for macrocyclic thiolactones and not at all useful for the macrocyclic lactones.

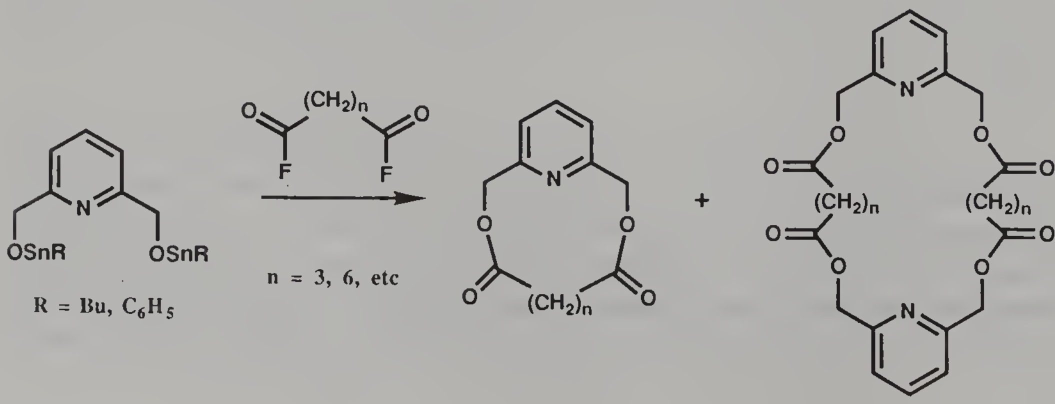
Other metalloids such as tin have also been used as template ions because they form dimeric complexes which react with electrophiles to build large cyclic molecules in a 2:2 ratio (Lifson et al., 1987). Shanzer and coworkers have studied cyclizations using a dibutyltin derivative as an intermediate (Shanzer et al., 1980, 1981, 1982, 1983; Schwartz et al., 1985). The tin intermediate acts like a template to direct the diacid chloride and diol to react to form a macrocyclic tetraester as the sole cyclic product. Ninagawa and coworkers used the Shanzer approach to prepare a macroring containing both oxygen and nitrogen atoms starting from a glycol (Ninagawa et al., 1984). This type of reaction has also been used to prepare a series of macrocyclic



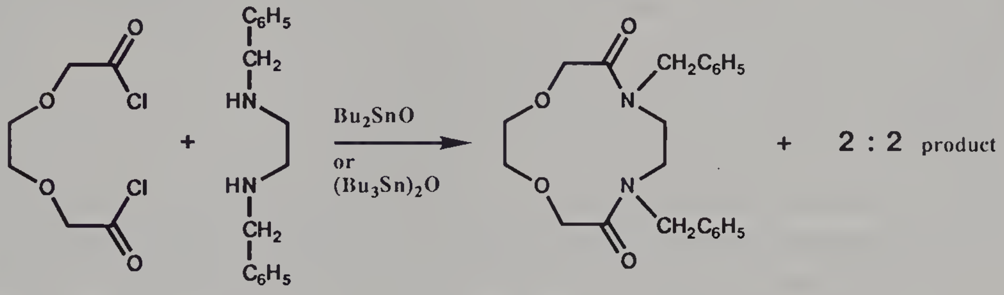
lactones and lactams (Steliou and Poupart, 1983; Steliou et al., 1980). The method can be used for the synthesis of a macrocyclic bis-urethane using an



activated tin derivative (Shanzer et al., 1980; Yeda Research, 1985). Tisnes and coworkers reacted a diacid fluoride with a tin derivative of 2,6-pyridinedimethanol (or other diols) to prepare macrocyclic di- and tetraesters containing the pyridine unit as the aza portion of the macroring (Picard et al., 1984, 1986; Tisnes et al., 1984).



The tin template cyclization reaction is useful for the preparation of macrocyclic compounds from diols, dithiols, and diamines (Leygue et al., 1988).



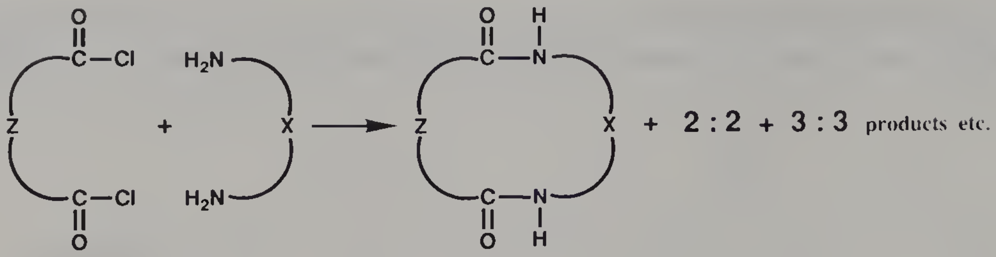
In the case of ethylenediamine or ethylene glycol, only the 1:1 cyclization product was formed. The yield was only about 30%, but separation was easy since no 2:2 product was present. With 1,2-ethanedithiol, the 12-membered ring formed in a 70–80% yield with only 3–10% of the 2:2 cyclic product.

In summary, we would like to stress that the template cyclization reactions have more advantages than disadvantages. The advantages are as follows: high-dilution conditions are not needed, polyfunctional macrocycles can be prepared without protecting groups (the metal template acts as a temporary protecting group), metal complexes of the macrocyclic ligands are usually obtained directly from the reaction, and those macrocyclic ligands that cannot be obtained metal-free are readily isolated as their complexes. The most important disadvantage is that it is not always easy to find the correct metal template, and therefore the products of the template reaction can be oligomers or other metal-directed reaction products instead of the macrocyclic compounds (Constable, 1990).

The case for template assistance in the cyclization step in the formation of polyaza-crown compounds has not been proved for many cyclization reactions. Certainly, other factors such as base strength and intramolecular hydrogen bonding need to be considered.

3. Formation of Macrocyclic Bis-amides in Normal and High-Dilution Conditions

The macrocyclic bisamides are the most used intermediates for the preparation of the polyaza- and peraza-crowns. The cyclic bis-amides are prepared by the condensation of activated diacid groups (such as the diacid dichlorides) and diamines. The cyclic bis-amides are usually prepared under high-dilution conditions to avoid as much of the polyamide and polycyclic by-products as possible. The ring-closure reaction of a diacid dichloride and diamine was the first example of a reaction to prepare cyclic compounds by the high-dilution principle (Ruggli, 1912, 1913). This cyclization reaction takes advantage of the fact that after the two groups react forming the first of a linear chain, the



remaining reactants are so dilute that the two functional groups on each end can react together to form the cyclic product rather than waiting for another open-chain reactant. In large volumes of solvent, it is statistically easier for the two ends of a short chain to find and react with each other than to find other short-chain molecules. Also, the functional groups at the ends of the two-unit chain are reactive to each other, while only half of the time that the two separate chains meet will the groups be mutually reactive.

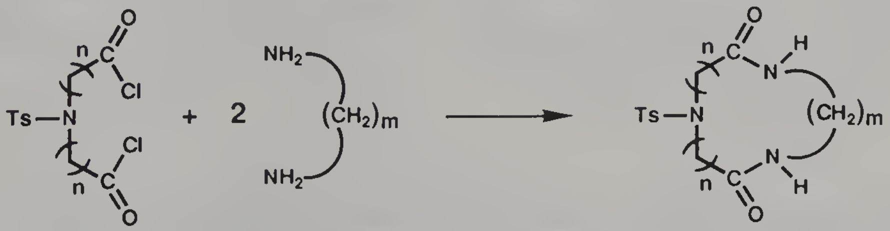
The high-dilution technique does not necessarily require large volumes of solvents. The large volumes can be reduced by factors of 10 or 20 by the precision addition of the two reactants by syringe pumps or other means. In this way, a very dilute stationary concentration of the reactants is maintained so that the cyclization reaction is favored over polymerization. Thus, the ideal amount of reactants that favors cyclization is always present in the solvent.

Factors other than reactant concentration also affect the cyclization reaction. Some of these factors include reaction temperature, time, type of solvent, speed of stirring, starting reactant concentration, and type of apparatus used. It has long been known that one of the important factors in macrocycle formation is the number of macroring members. Studies of ring formation to form cyclic carbonyl compounds have shown that the medium sized rings (11 to 13 members) are more difficult to form than the larger sized rings (Mandolini and Vontor, 1979). In the case of the perhydroheterocyclic rings with oxygen and nitrogen atoms, this size effect is not as serious because the carbon–heteroatom bond angles are different and the macrorings with the heteroatoms have fewer hydrogen substituents to occupy the space within the ring cavity. Rings of 9–11 members are the most difficult of the heterocyclic compounds to prepare. For example, azacyclooctane was prepared in a 60% yield while azacyclodecane was prepared in only a 3% yield (Müller et al., 1952). This effect is often used to form very large macrocycles. Reactants that would form 9- or 10-membered rings in a 1:1 cyclization will generally react in a 2:2 fashion to give the 18- or 20-membered rings. This 2:2 cyclization (or even a 3:3 process) is even more pronounced where reactants contain rigid aromatic rings. These rigid reactants do not allow a 1:1 (and sometimes a 2:2) cyclization to take place. It is often possible to form these products under non-high-dilution conditions where two (1:1), four (2:2), six (3:3), etc. molecules cyclize together (Krakowiak et al., 1990a; Newkome et al., 1989). Generally, the use of low concentrations of the two reactants increases 1:1 cyclizations (unless rigid molecules are involved) and decreases the 2:2

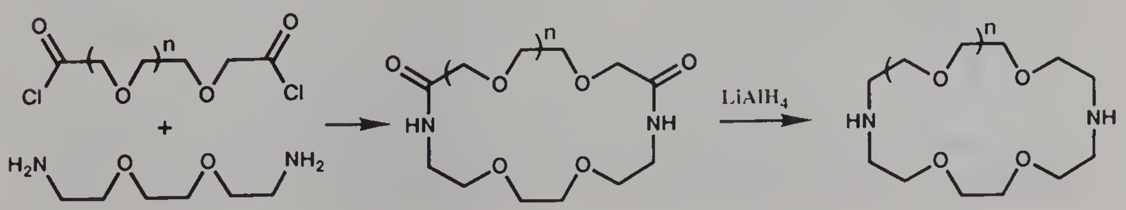
and higher order cyclizations. Usually, the 4:4 and higher-order cyclizations are difficult to observe because of their low yields. Thus, it is possible to design a synthesis for the appropriate ring size: 9–11 ring members by a high dilution 1:1 reaction and 18–22 ring members by a less-high-dilution technique. The 2:2 cyclization reaction is favored for rigid systems such as the dibenzo cyclophanes. In this case, the concentration of the reactants can be manipulated to give the desired 2:2 or 3:3 cyclization products in the highest possible yields. A geminal dimethyl effect can also influence the formation of macrocyclic rings (Borgen and Gaupset, 1974; Friedman and Allen, 1965).

High-dilution cyclizations are usually carried out at room temperature or lower for aliphatic diamines and at reflux for the aromatic amines in an apolar solvent such as benzene or toluene using excess diamine or adding triethylamine or proton sponge (An et al., 1992) as the HX scavenger. Very vigorous stirring and using the proper-shaped stirrer are also important in high-dilution reactions. The use of syringe pumps to precisely add the reactants is superior to the use of dropping funnels. The dosing Teflon addition tubes for the two reactants should be as far from each other as possible. It is best to have one in the bottom of the reaction flask and the other one on top to give the statistically lowest possible concentration of the two reactants in the solvent before they react.

A few typical examples will show the wide application of high dilution in the preparation of the cyclic bis-amides. Stetter prepared many bisamide macrocycles using high-dilution conditions (Stetter and Marx, 1957). Under strict dilution conditions, the reaction of the diacid chloride with different diamines gave about a 50% yield of the cyclic bis-amide. Macrocycles larger than 25 ring members were obtained in about 40% yield (Schmidtchen, 1980; Stetter and Marx, 1957).

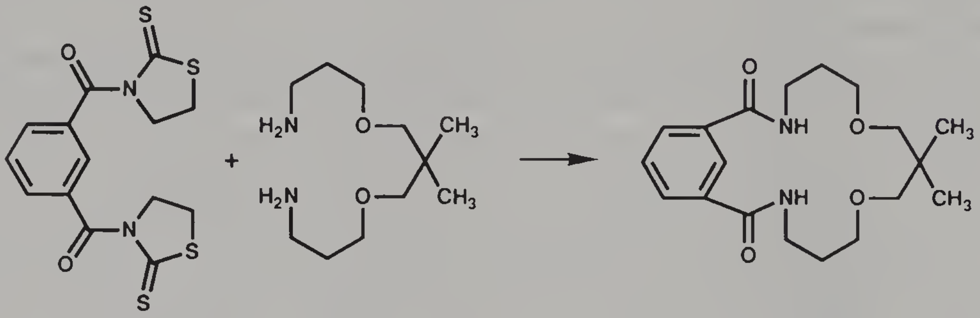


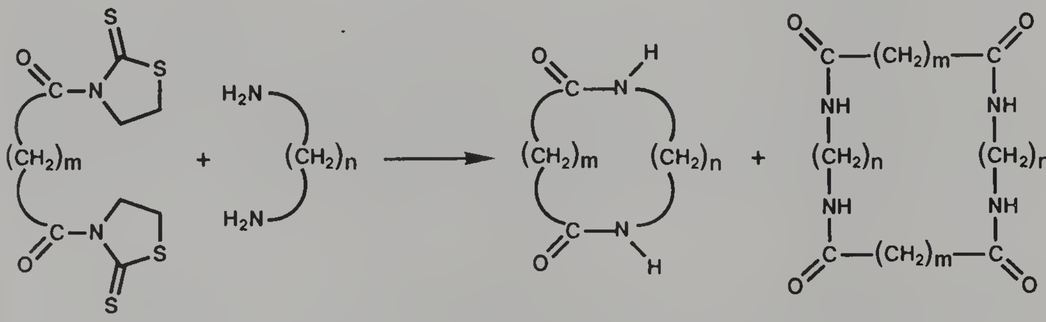
The reaction of a diacid dichloride with a diamine to effect ring closure followed by reduction of the resulting diamide was the first method used to prepare the diaza-crown compounds. Lehn and coworkers prepared diaza-18-crown-6 by this method (Dietrich et al., 1969, 1973). The intermediate



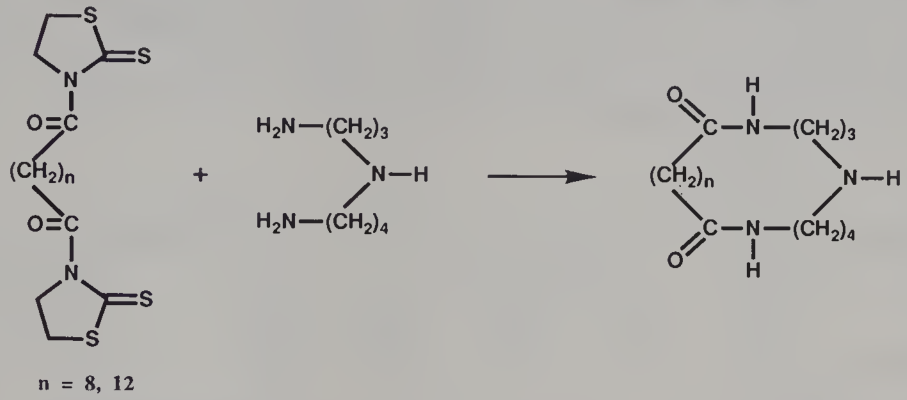
macrocyclic dilactams were isolated in moderate to good yields. The bisamides usually were reduced by lithium aluminum hydride in THF to give high yields of the diaza-crown compounds.

Bartsch and coworkers found that if the reaction was carried out at 0 °C, a slower reaction resulted with higher yields (Babb et al., 1986; Czech et al., 1988). In cases where the reaction rate is slow, such as when one of the reactants is an ester or an active ester, the reaction does not require high-dilution techniques. Even in those cases, high dilution does improve the cyclization yield by 10–30%. Substitution of a thiazolidine-2-thione or 3,5-dimethylpyrazolidine for a chloro group in the acid chloride greatly increases the rate, and the reaction can be carried out under high- or moderate-dilution conditions. Activation of the diacid by forming the bis(thiazolidine-2-thione) derivative is carried out by reacting the diacid with thiazolidine-2-thione in the presence of dicyclohexylcarbodiimide (DCC) together with a catalytic amount of 4-(dimethylamino)pyridine or the thalium salt of thiazolidine-2-thione in dichloromethane. Bis(thiazolidine-2-thione) derivatives are reactive toward amines and do not yield hydrochloric acid as a by-product (Nagao et al., 1980a, 1981a). A yield of 91% was observed for the formation of the cyclic diamides with 6% of cyclic tetraamide by-product (result of a 2:2 cyclization). No cyclic 8–12-membered diamides could be made by this process, but rather the cyclic 16–24-membered tetramides by a 2:2 cyclization. However, diamides of 14, 18, and 22 ring members could be formed by the 1:1 cyclization process.

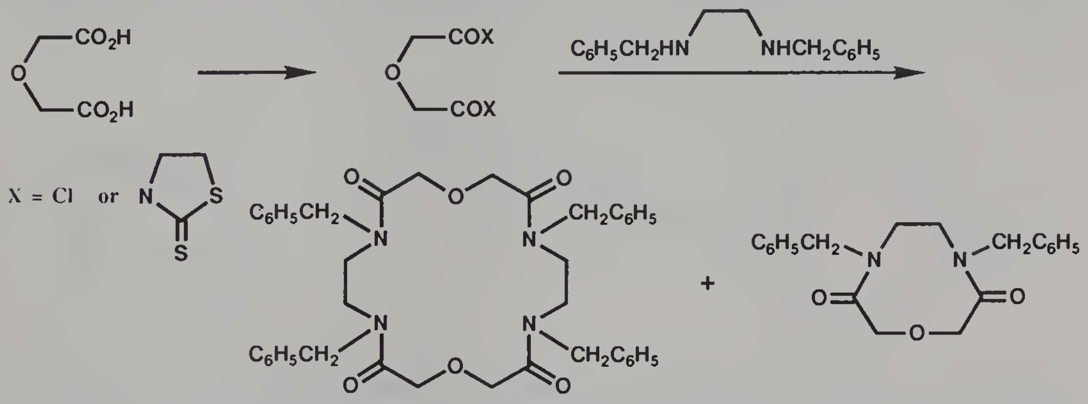


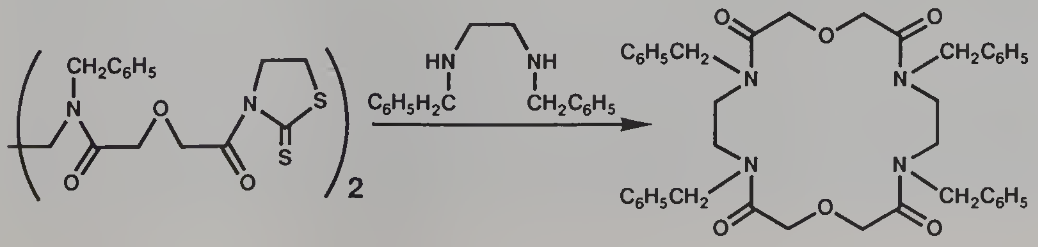


It is interesting that when the bis(thiazolidine-2-thione) derivative of a dicarboxylic acid was reacted with a polyamine, the two terminal primary amine groups reacted to form the cyclic diamide in an 89% yield (Nagao et al., 1980a, 1981a). The by-product, wherein the internal secondary amine reacted with an activated carboxyl group, was not observed. Thus, the thiazolidine-2-thione activating group is selective for a primary amine over a secondary one, which is important for some natural-product-type syntheses. A small amount (about 5%) of the 2:2 cyclization product was observed in this reaction.



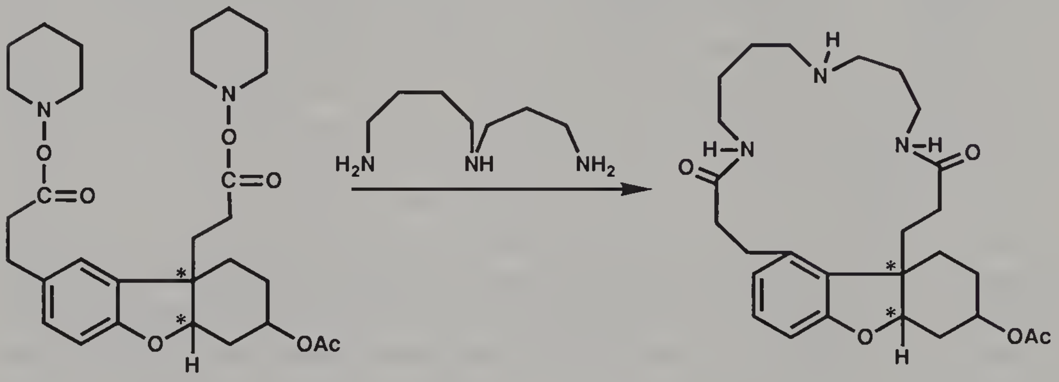
When reacting diglycolyl dichloride or its bis(thiazolidine-2-thione) derivative with *N*,*N*′-dibenzylethylenediamine, the 18-membered cyclotetraamide was prepared in 20–25% yields (Cazaux et al., 1989). The 1:1 cyclization product, diaza-9-crown-3, was also isolated in a 20% yield. The authors did not optimize this reaction because they prepared the tetraaza-18-crown-6 by another route. First, they prepared a long linear bis(thiazolidine-2-thione) derivative and closed the ring with the diamine. The overall yields of the two



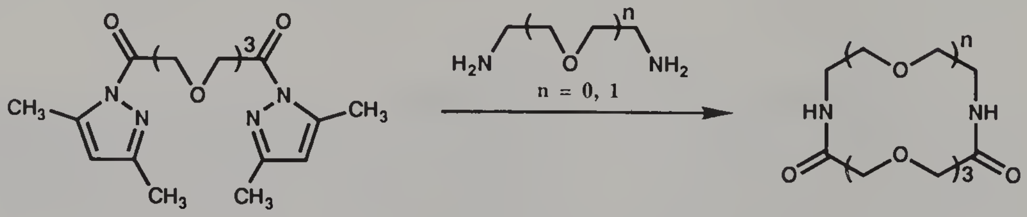


pathways were about 25%, but separation of the product was easier in the second route because none of the 9-crown-3 was produced.

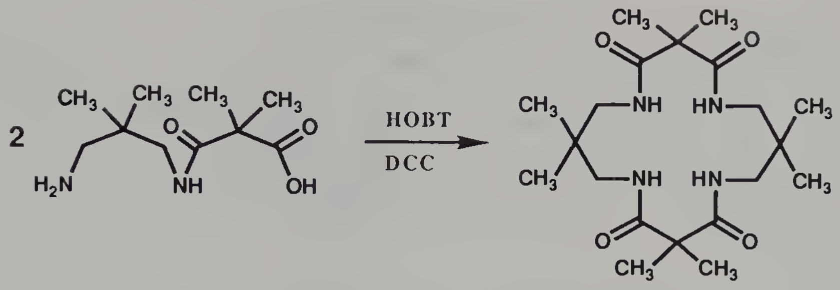
Spermine- and spermidine-type macrocyclic alkaloids were prepared using the same carboxylic acid activating groups (Nagao et al., 1980b, 1981b) or using derivatives of *N*,*N*′-diacylhydroxyamine (Husson et al., 1971; Poupat, 1976). Isobutyl chloroformate also was reacted with a diacid to form an active derivative that was reacted with a diamine in much the same manner (Bartsch et al., 1987).



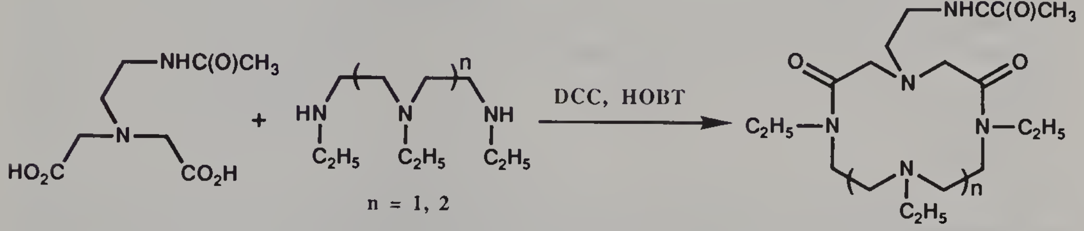
Biernat and Luboch (1984) used the bis(3,5-dimethylpyrazolide) of tetraglycolic acid (prepared by reacting the crude acid with the pyrazole in the presence of *O*-ethylphosphoric acid) for the preparation of a macrocyclic bis-amide in excellent yields and under normal reaction conditions. The *N*,*N*′-bis-carbonylimidazole has also been used to produce macrocycles. In this case, hydroxy and activated carbonyl groups were reacted (Katagi and Kuriyama, 1982). Other information about the uses of active esters can be found in books concerning peptide syntheses (Bodanszky, 1979, 1988).



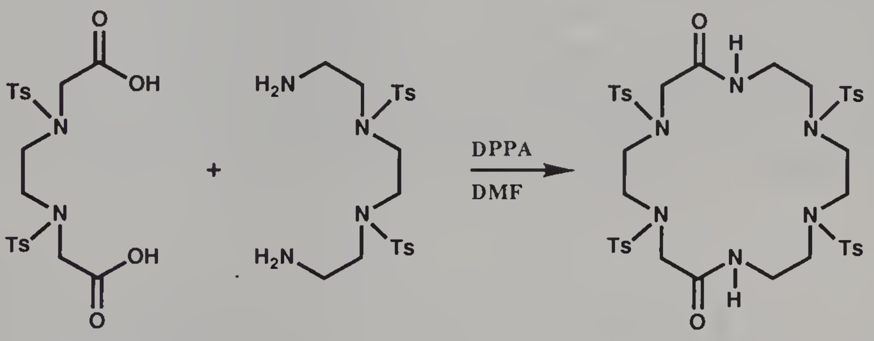
The above mentioned methods for preparation of cyclic bis-amides were patterned after peptide chemistry reactions where amide bonds dominate. Also in peptide chemistry, DCC, and DCC plus 1-hydroxybenzotriazole (HOBT) have been used in amide formation reactions. Using this procedure, 16-membered peraza-crowns have been prepared in 50–55% yields for the cyclization step (Vellacio et al., 1977). The carboxyl group can also condense with secondary amines in DMF in the presence of 1.1 mol of DCC and 1.2 mol of HOBT per mole of the dicarboxylic acid (Krakowiak et al., 1989).



The triamide in the latter case was reduced to the triamine using diborane (not shown).

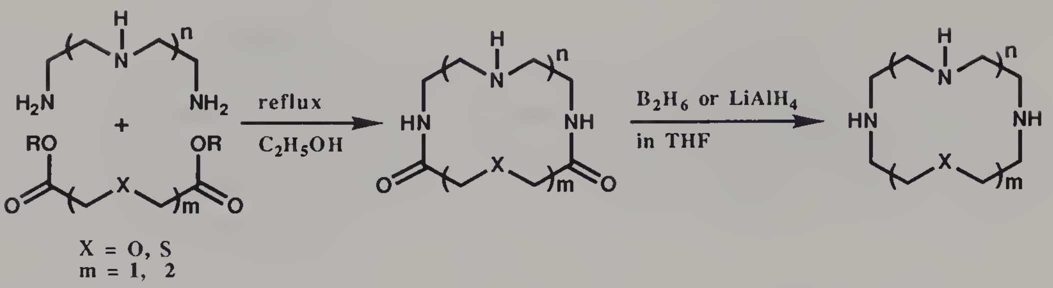


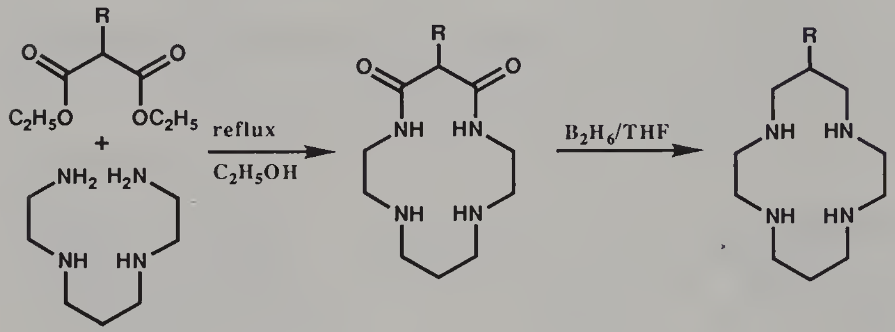
Diphenylphosphoryl azide (DPPA) has also been used as an activating agent for the ring closure of dicarboxylic acids with polyamines to give high yields of the cyclic bis-amides (Qian et al., 1990). Cryptands have also been



prepared using this technique. There are many other activating agents for these types of reactions in peptide chemistry, but they are expensive and thus their use is limited.

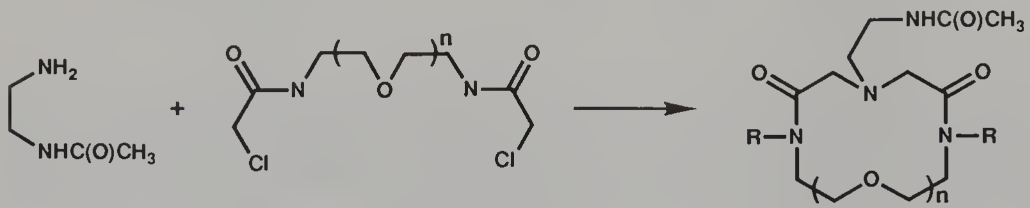
The simultaneous addition of the two starting materials over an extended time period is not convenient. Tabushi and coworkers found that high-dilution techniques were not required for the reaction of diesters (including malonates) with diamines to form the cyclic bis-amides (Tabushi et al., 1976, 1977). The cyclic diamides were reduced to form the polyaza-crowns. This method, along with the *N*-tosyl method for ring closure, are the most common procedures for the preparation of peraza-crowns. The yields for these ester plus amine

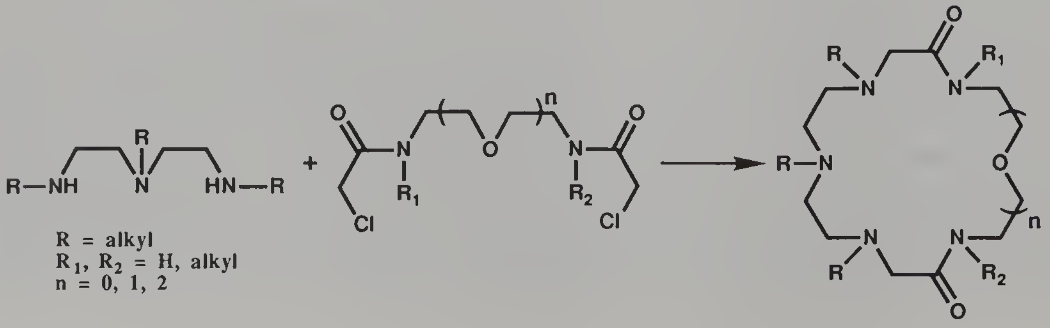




ring-closure reactions were reported to be in the range of 12–67%. The usual yield was about 30% after reaction for a few weeks in refluxing ethanol.

Bradshaw, Krakowiak, and coworkers have designed methods to prepare aza-crowns and peraza-crowns with *N*-pendant side chains containing amines and hydroxy groups as well as peraza-crowns with one or two unsubstituted ring nitrogen atoms (Bradshaw et al., 1988, 1989a, 1989b; Krakowiak et al., 1989, 1990b, 1991). This process does not require high dilution; however, in some cases the cyclic bis-amides could be formed in 10–20% higher yields using ultra-high-dilution conditions. The method is simple, as shown below, and can give 30–80% yields depending on the size of the macrocyclic ring. These "crab-like" cyclizations will be discussed in more detail in the next chapter.





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CHAPTER IV

Common Methods for the Formation of Polyaza Macrocyclic Rings

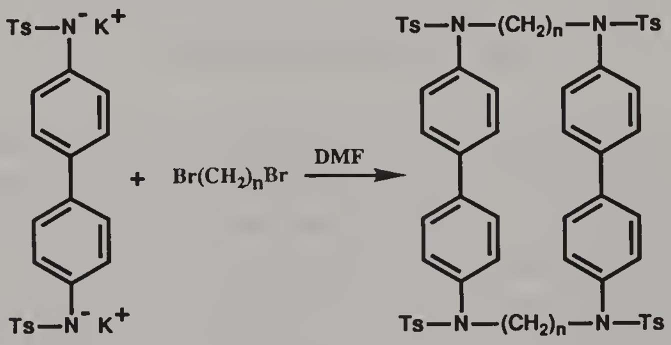
A. INTRODUCTION

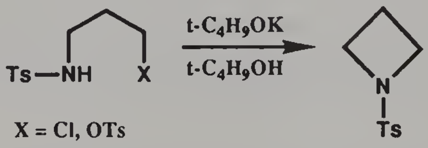
The previous chapter contains a discussion of the main, general methods for cyclization reactions to prepare aza-crowns. The two main methods use either a metal template or high-dilution conditions in the ring-closure step. Many ring-closure reactions that do not require high dilution or metal templates were also discussed in Chapter III. From a very large family of ring-closure reactions, a few methods are generally more useful than the others. A few of these common procedures were used in the beginning of macrocyclic chemistry, while other convenient methods have been discovered more recently. The "Richman–Atkins" procedure is probably the most widely used process for macroring closure, but the "Okahara" process is also an important one for the preparation of the aza-crowns. This chapter will highlight these and other time-tested procedures to close the macroring and will discuss new processes for these important synthetic reactions.

B. RING CLOSURE USING SULFONAMIDES (OFTEN CALLED THE RICHMAN–ATKINS REACTION)

The use of reactive sulfonamides for ring closure allows the formation of macrocycles with secondary amine groups in the ring. The procedure uses the reaction of the dimetal salts of a polysulfonamide with a dihalide or disulfonate (ditosylate or dimesylate). The sulfonyl groups (nearly always tosyl moreties) of the resulting per-*N*-sulfonyl-substituted polyaza-crown are cleaved to form a polyaza-crown containing secondary amine groups. The template method to produce the polyaza-crowns (discussed in Chapter III) is more convenient since there are no tosyl protecting groups to be removed. However, it is difficult to predict all the conditions that are needed to give good results in the template cyclization reaction. Also in the template reaction, one must choose the proper metal ion to form the intermediate complex and the resulting macrocyclic diamide must be reduced and the metal ion removed. All of these processes are not always predictable. Thus, the shorter and more direct procedure is not always useful, while the sulfonamide method predictably yields the desired products.

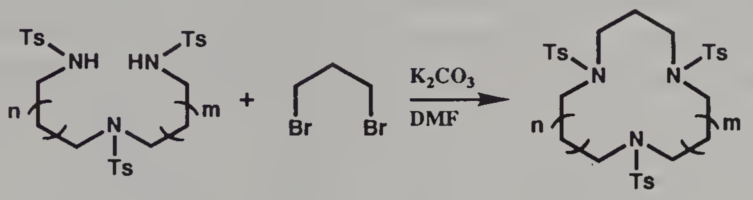
The first use of a tosylamide in a cyclization reaction was reported nearly 100 years ago in German patents for the preparation of 1,4-ditosylpiperazine by Marckwald and Droste-Huelshoff (1898). Azetidine was also prepared by this process, as well as 1,5-diazacyclooctane using the appropriate halide and tosylamide (Bleier, 1899; Howard and Marckwald, 1899). A similar method was applied to macrocycles by Stetter and Roos (1954, 1955) when they reported the 2:2 cyclization reaction of an α,ω-dihalide with the dipotassium salt of an aromatic bis-sulfonamide as shown. Ring closure of an *N*-tosyl compound was also noted with tosylate leaving groups as shown for the synthesis of *N*-tosylazetidine in yields of 55–93% (Vaughan et al., 1961).





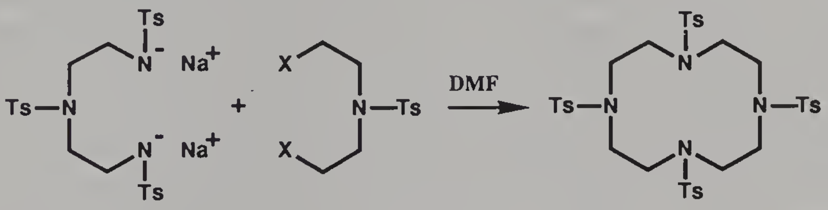
Tosylate ester starting materials were found to provide greater yields in the formation of the crown compounds (Dale and Kristiansen, 1971, 1972) in contrast to the use of the dichloride derivatives of the oligoethylene glycols (Pedersen, 1967).

The preparation of triaza macrocycles by the reaction of 1,3-dibromopropane with various *N*,*N*′,*N*″-tritosyltriamines was reported by Koyama and Yoshino (1972). It is surprising, but the best yield (25%) was obtained for the 10-membered ring while the 12-membered ring was prepared in only an 8% yield. These yields were improved later by other researchers (Atkins et al., 1978; Chavez and Sherry, 1989).



m, n = 0, 1

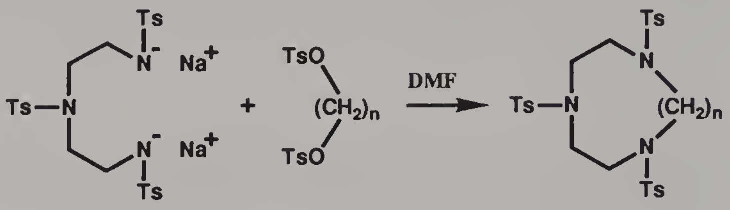
Richman and Atkins (1974) reported the generality of the sulfonamide method to prepare the polyaza-crowns. They used a ditosylate ester starting material rather than a dihalide. A similar reaction was reported at the same time by Cram (1977) in a patent filed in 1974. The so-called Richman–Atkins cyclization reaction is the reaction of the polysulfonamide or its disodium or dipotassium salt with a ditosylate or a dimesylate. The interior sulfonamide groups are believed to be necessary to force the open-chain compounds into macrocycle-like conformations, thus helping in the cyclization reaction. Three research groups tested the conditions needed for this ring-closure reaction by studying the effects of solvent, base metal ion, and starting materials on the yields for the cyclization step (Atkins et al., 1978; Högberg and Cram, 1975; Rasshofer and Vögtle, 1978; Rasshofer et al., 1976). The best solvent proved to be DMF. DMSO and hexamethylphosphoramide were also good solvents, but they are not as convenient as DMF. The best cyclization yields were realized when tosylate and mesylate esters were used instead of the dihalides (80% vs. 25% for the preparation of 1,4,7,10-tetraazacyclododecane) (Atkins et al., 1978). When the ditosylate was used, large volumes of solvent were not needed. The sulfonamides of aromatic amines were also reacted with tosylate esters to form macrocycles in 20–55% yields (Högberg and Cram, 1975).



X = OTs or OMs

The sulfonamide salts are prepared by reacting the sulfonamides with sodium methoxide or ethoxide, sodium hydroxide, potassium *t*-butoxide, potassium carbonate, potassium phthalimide, or cesium carbonate. The salts may be isolated, but they are moisture-sensitive and are usually prepared and used immediately.

Atkins and coworkers synthesized a variety of macrocycles using this procedure (Atkins et al., 1978). The size of the ring was varied according to the size of the α,ω-ditosylate used for ring closure. The yields of the macrocycles varied from 84% (n = 3) to 40–50% (n = 6). Thus, a 10-membered ring was formed in the highest yield. Others have confirmed that the yields of the 9- and 10-membered rings are the highest in the sulfonamide ring-closure reaction (Briellmann, 1987; Koyama and Yoshino, 1972). The yields for ring closure to prepare the 11- to 13-membered rings can be 70–80% by using other conditions and methods (Chavez and Sherry, 1989).



Two research groups studied the syntheses of 36 different macrocycles (Atkins et al., 1978; Rasshofer et al., 1976). The yields averaged about 60% but varied from 7% to 90%. The yields of certain macrocycles prepared by both research groups varied by as much as 50%. These variations can be attributed to different reaction conditions, particularly in the methods used to prepare the amide salts, reaction temperatures, purity of starting materials, and reaction times. Careful drying of the solvent and prevention of atmospheric moisture from contacting the moisture sensitive amide salts generally increases the yields for the cyclization step in these reactions (Bhula et al., 1988).

On the other hand, *N*-tosylated aza-crowns were formed in good yields (50–94%) from the reaction of the bis-sulfonamides with dibromides or ditosylates in aqueous alkali–toluene or benzene mixtures in the presence of quaternary ammonium salt phase-transfer catalysts. Some cyclizations did not depend on alkali concentration, but for the tri- or tetraaza-crowns, 50% alkali solutions were preferred. In the synthesis of *N*,*N*′-ditosyldiaza-18-crown-6 via the interaction of the bis-sulfonamide with a dibromide, dichloride, diiodide, or ditosylate using 50% aqueous sodium hydroxide–toluene or benzene solution in the phase-transfer reaction, the cyclization rate varied according to the leaving group, $\mathrm{Br} \geq \mathrm{OTs} > \mathrm{I} \gg \mathrm{Cl}$. In dilute alkaline solution (7.5%), the diiodide was more reactive than the ditosylate. This could be a result of the greater activity of water in the solution so that hydrolysis of the tosylate is more rapid and, therefore, there would be less tosylate to react with the amide (Bogatskii et al., 1984; Lukyanenko et al., 1987, 1988).

In other experiments, the ditosylate ester reactant was found to decompose during the slow cyclic condensation reaction using carbonate bases. This decomposition of the ditosylate was accelerated at higher temperatures so that a marked decrease in cyclization yield was observed (Iwata and Kuzuhara, 1989a). The ditosylate derivative of ethylene glycol decomposed in a *t*-butyl alcohol–dioxane mixture in the presence of potassium *t*-butoxide (Bradshaw and Krakowiak, 1988).

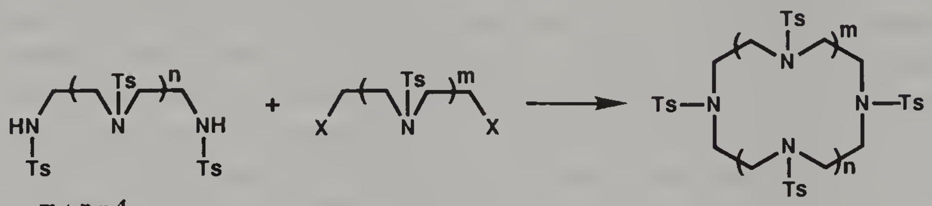
Other impurities besides water can effect these reactions. Dimethylamine or formaldehyde impurities in DMF would decrease cyclization yields. DMF can be purified by azeotropic distillation with benzene or drying with barium oxide, alumina or potassium hydroxide and distillation under vacuum (Vogel, 1989). Some authors omit this procedure by buying spectro-quality DMF and drying it over molecular sieves until used. Purified DMF needs to be kept in dark storage bottles because light may decompose it. The purity of the starting polyamines and diols is important. Most of the needed polyamines with ethylene bridges and some with propylene bridges can be purchased, but they need to be purified. One compound, triethylenetetraamine, was listed in one company's catalog as 95% pure in 1989 but was found to be only 65% pure. The oligoethylene glycols are listed as 99% pure and generally can be used as received. *p*-Toluenesulfonyl chloride can contain some *p*-toluenesulfonic acid (Fieser and Fieser, 1967) and should be recrystallized from *n*-hexane, or the impure acid chloride can be used in excess.

The pertosylamides are easy to prepare and purify because they are generally solids. In contrast, the permethanesulfonamides and perbenzenesulfonamides are usually liquids. Tosylation of the polyamines is most often carried out in pyridine (Atkins et al., 1978; Bencini et al., 1988; Newcomb et al., 1977). The resulting solid is readily purified by recrystallization from alcohol. Tosylation can be carried out in a two-phase water and ether or benzene system using sodium or potassium hydroxide as the base (Buttafava et al., 1986; Koyama and Yoshino, 1972; Martin et al., 1977; Stetter and Mayer, 1961). Diaminoethers have been tosylated in this manner (Krakowiak and Kotelko, 1982, 1983a, 1983b; Weber and Vögtle, 1976). Water can be used as the solvent with sodium hydroxide (Searle and Geue, 1984) or potassium carbonate (Dietrich et al., 1983) as the base. Sometimes, the same sulfonamide prepared by different processes had different physical properties. For example, *N*,*N'*,*N''*-tritosyl-4-aza-1,7-heptanediamine prepared by different research groups had the following melting points: 148–150°C (Stetter and Mayer, 1961), 134°C (Iwata and Kuzuhara, 1982), 144–148°C (Dietrich et al., 1983), 138–140°C (Searle and Geue, 1984), and 134°C (Krakowiak and Bradshaw, 1991). These differences can be explained if the starting materials were not of the same quality or the different pathways provide different impurities for the tosylated products.

Tosylation of the glycol to prepare the ditosylate ester starting material is most often done using pyridine as the solvent and base (Bailey et al., 1978; Dale and Kristiansen, 1972; Kyba et al., 1977). The method is not complicated, but the ditosylate product sometimes is a liquid, especially when polyethylene glycol was used, and must be purified by column chromatography.

Kabalka and coworkers reported only a 50% yield of the ditosylate in pyridine using 2 eq of tosyl chloride, and the recovered material was a mixture of the desired ditosylate and the corresponding chloride (Kabalka et al., 1986). These authors reported that better results were obtained using chloroform as the solvent with some pyridine as the base. Other methods for the preparation of the ditosylate esters, such as using dioxane and water with sodium hydroxide as the base, have been used (Cornforth et al., 1973; Ouchi et al., 1984). A new method uses powdered sodium or potassium hydroxide in THF. In this case, after the reaction, methylene chloride is added and the solvent is filtered and evaporated (Bradshaw et al., 1990a). This method gave superior results especially for the preparation of 2,6-pyridinedimethyl ditosylate from the corresponding diol. Ether, THF, or dichloromethane were also used as the solvent with triethylamine as the HCl scavanger to give good yields of the ditosylates (Bencini et al., 1988; Bradshaw et al., 1991; Buttafava et al., 1986; McAuley et al., 1984). The dimesylate starting materials were also prepared using methylene chloride and triethylamine at low temperatures (Atkins et al., 1978; Crossland and Servis, 1970) or in pyridine (Pilichowski et al., 1985).

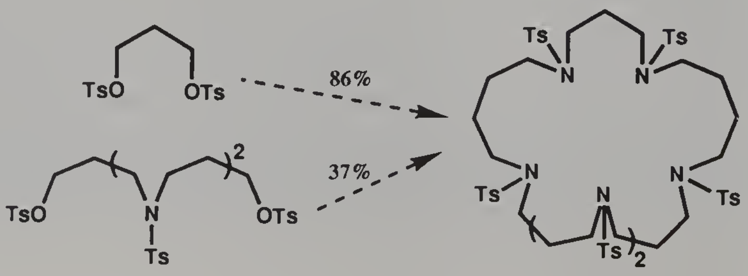
Pertosylated peraza-crowns can be prepared by the Richman–Atkins procedure by many pathways depending on the size of the starting materials.



m + n = 4
m, n = 0 - 4
X = OMs or OTs

The larger rings have more possible pathways. For example, peraza-18-crown-6 can be prepared by five pathways (*m* = 0, 1, 2, 3, or 4 and *n* = 4, 3, 2, 1, or 0, respectively). The choice of the best and most convenient preparative method depends on the availability of precursor diols, aminodiols, and polyamines.

Recent research shows that coupling the electrophile containing the shortest chain length with the nucleophile containing the longest chain length gave the best yields (Iwata and Kuzuhara, 1989a, 1989b). It appears that this rule can apply for the formation of the larger rings. No such differences were

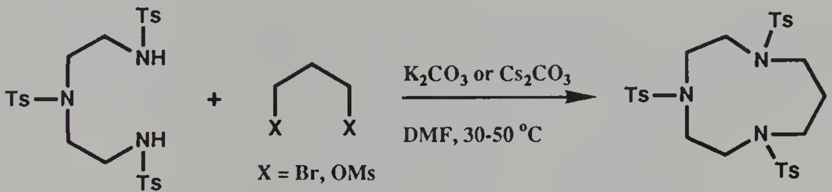


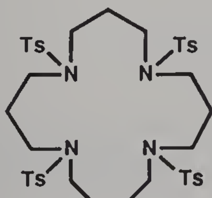
noted for the formation of smaller rings except in the case of 1,2-ethaneditosylate, which often decomposed under the conditions of the reaction. Even so, inexpensive 1,2-ethanedibromide or ditosylate can be used in excess to increase the cyclization yields (Chavez and Sherry, 1989).

Other nitrogen protecting groups such as the benzyl, trityl, and mesyl moieties are often used on the interior nitrogen atoms of the starting polyamines. These large groups also tend to force the open-chain polyamines into conformations favorable for ring-closure reactions (Hediger and Kaden, 1983; Martin et al., 1982).

The Richman–Atkins cyclization procedure (using dimesylate or ditosylate ester starting material) for the preparation of medium-sized rings (12–18 members) does not require high-dilution conditions. Indeed, it has been suggested that solutions saturated with the reactants gave even higher yields of the cyclization products (Bhula et al., 1988). High dilution does increase the yields for macrocycles larger than 18 ring members (Bencini et al., 1987a, 1987b, 1988; Iwata and Kuzuhara, 1989a, 1989b).

Up to about 1986, most of the reactions were carried out at high temperatures (about 100°C) with some exceptions (Iwata and Kuzuhara, 1986; Krakowiak et al., 1984). Recent studies of the sulfonamide ring-closure process has shown that the reaction is best carried out at temperatures from room temperature to about 50°C (Chavez and Sherry, 1989; Iwata and Kuzuhara, 1986, 1989a, 1989b). For the first time, high yields of the macrocycle were obtained at low temperatures using a dibromo starting material (Chavez and Sherry, 1989). The dimesylate ester also gave high yields of product after 24 hr at 30°C. The ditosylates, which are 5 times more reactive than the corresponding dibromides (Iwata and Kuzuhara, 1986), gave nearly quantitative yields of [17]N_4 and [21]N_5 under the same reaction conditions (Iwata and Kuzuhara, 1989a). It is interesting that the same [17]N_4 (see the structure below), which was prepared as mentioned above in nearly quantitative yields using the ditosylate of 1,3-propanediol, was prepared in only a 56% yield from 1,4-dibromobutane at a higher temperature using cesium carbonate as the base in DMF (Vriesema et al., 1984).





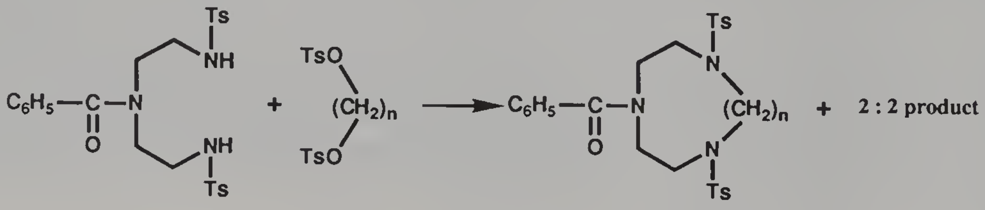
[17]N_4

The difference in reactivity between the ditosylate and the dibromide is not necessarily the reason for these results since the reaction with 1,4-dibromobutane was done at a much higher temperature. In this case, the dibromide could have partially decomposed accounting for the lower yield of product.

The choice of a base is also important in the sulfonamide cyclization method. Cesium and potassium carbonates are the best bases for this reaction. The stronger bases increase the rate of decomposition of the ditosylate esters or dihalides at higher temperatures, which in turn decreases the yield of the macrocycle. For example, the reaction of the disodium salt of the ditosylamide reacted rapidly in DMF but gave a lower yield than when potassium carbonate was used with the diamide (Iwata and Kuzuhara, 1989a). Thus, when potassium or cesium carbonate was used, the reaction gave nearly quantitative yields of cyclization products at moderate temperatures but at a much longer reaction time.

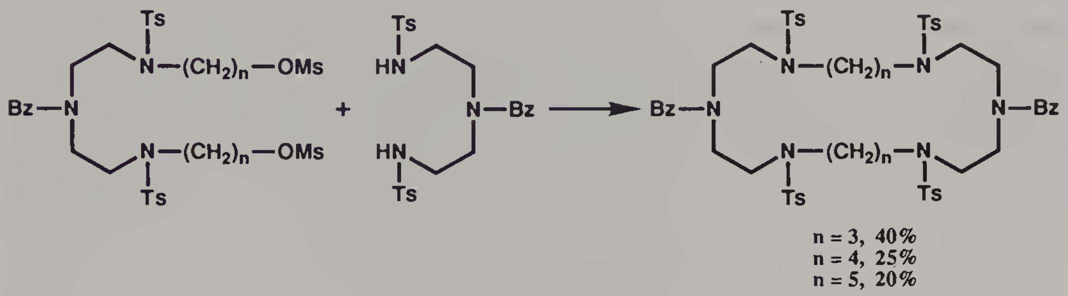
There are critics of the sulfonamide ring closure method. Briellmann and coworkers reported that, although the 9- to 13-membered cyclic trisulfonamides were prepared in 31% to 57% yields, isolation of products was difficult (Briellmann et al., 1987). Up to six products were shown by TLC analysis. Sometimes the impurities could be removed by crystallization, but most often, careful column chromatography was needed. With the larger 11- and 13-membered macrocycles, the 2:2 cyclization products, [22]N_6 and [26]N_6, were also isolated in 11% and 3% yields, respectively. In the synthesis of the smaller 9- and 10-membered macrocycles, no 2:2 cyclication products were observed. When formed, the 2:2 cyclization products were hard to separate because often 1:1 and 2:2 cyclization products have similar R_f values in chromatography. Richman and Atkins (1974) also reported 10–15% of the 2:2 cyclization products during the preparation of 12- or 13-membered cyclic triamines. They suggested that reactants of similar lengths gave the best yields of the 1:1 cyclizations, although they gave no details.

Martin and coworkers also observed a considerable amount of 2:2 cyclizations when they prepared 11- and 13-membered triaza macrocycles (Martin et al., 1982). The internal nitrogen atom of their bis-sulfonamide contained



n = 2, 85% + <1%
n = 4, 30% + 20%
n = 6, 56% + 17%

a benzoyl group. Notice that less than 1% of the 2:2 cyclization product was observed when they formed a 9-membered cyclic triaza compound. Naemura and coworkers obtained more complicated chiral cyclic macrocycles but with ethoxy substituents in a 20% yield for the 1:1 and an 8% yield for the 2:2 cyclization products (Naemura et al., 1989). The same 2:2 cyclization products as shown above were easier to obtain by a 1:1 cyclization of the appropriate di-*N*-tosyl-containing dimesylate esters with the polysulfonamide as shown (Martin and Bulkowski, 1982; Soga et al., 1980; Takahashi et al., 1984). In this case, no 2:2 cyclization to form very large rings was observed.

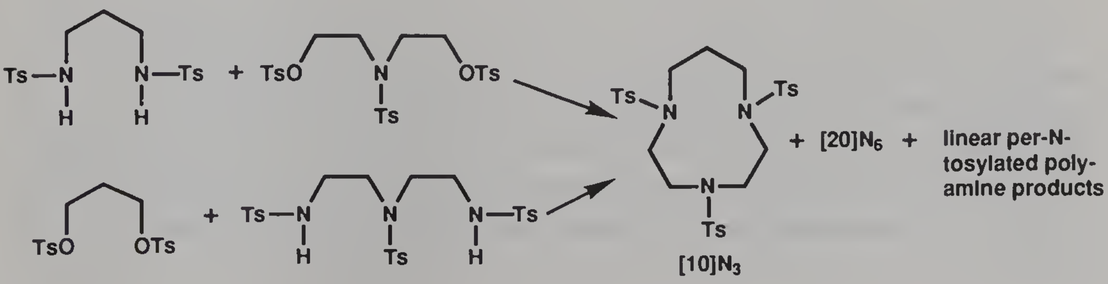


n = 3, 40%
n = 4, 25%
n = 5, 20%

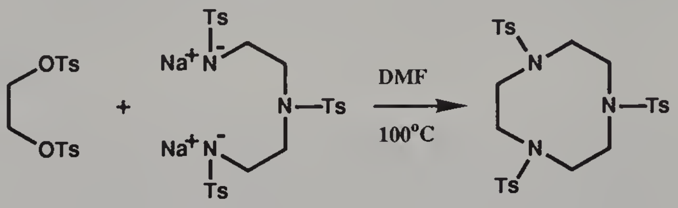
Often 2:2 cyclization is the desired reaction. Biernat and Luboch (1984) reported the preparation of $[18]N_2O_4$ in 30–40% yields by a 2:2 process using potassium carbonate as the base instead of sodium carbonate, which favored the $[9]NO_2$ macrocycle. Others used cesium carbonate for the formation of $[18]N_2O_4$ in a yield of 20% (Craig et al., 1989a). If the starting material has a rigid structure with terminal reactive functional groups, the 2:2 cyclization process is greatly enhanced and no 1:1 cyclization occurs. This type of reaction, for example, produces the cyclophanes and pyridinophanes (Stetter and Roos, 1955).

Separation of the 1:1 and 2:2 cyclization products from each other can be done not only by column chromatography but also by complexation with the appropriate metal cation. For example, the Cu(II)–$[24]N_6$ binuclear complex was isolated from $[12]N_3$, the 1:1 cyclization product (Schaber et al., 1988). Similar results were obtained by Margulis and Zompa (1979), who separated the Ni(II) complex of $[20]N_6$ from $[10]N_3$, the 1:1 cyclization product.

Higher-order cyclization products (2:2, 3:3, etc.) are not the only byproducts that are observed in these reactions. In a few cases, noncyclic products were also observed. A considerable amount of per-*N*-tosylated-3,7,10,13-tetraazahexadecane-1,16-diamine and per-*N*-tosylated-$[20]N_6$ (the 2:2 cyclization product) were obtained during the synthesis of $[10]N_3$ by the following reactions (Angley et al., 1980; Searle and Angley, 1981).

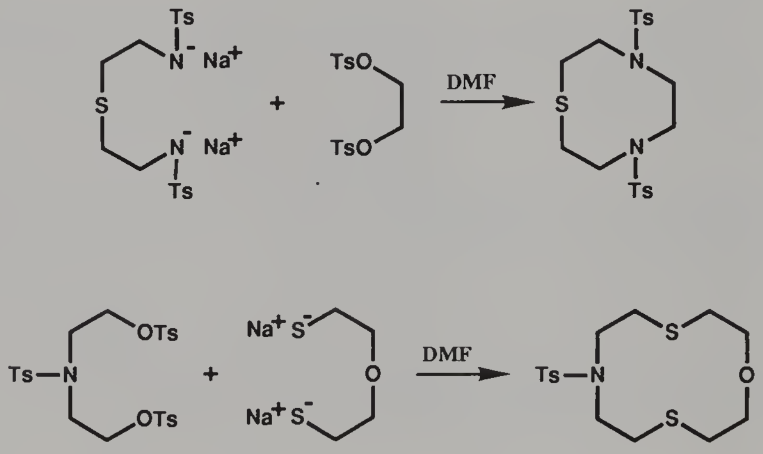


Graham and Weatherburn (1981) obtained the [10]N_3 without side products from the ditosylate ester of 1,3-propanediol. However, no cyclization was observed for this type of reaction using the ditosylate esters of 1,2-propanediol, 1,3-butanediol, 2,3-butanediol, or 2,2-dimethyl-1,3-propanediol under the same reaction conditions (Graham and Weatherburn, 1983). These latter results could be explained by the decomposition of the ditosylate esters under strong basic conditions as was observed for the ditosylate ester of ethylene glycol (Bradshaw and Krakowiak, 1988; Dale and Kristiansen, 1972). The ditosylate ester of ethylene glycol can react to form the peraza macrocycles in less drastic conditions in DMF as shown below (McAuley et al., 1984).

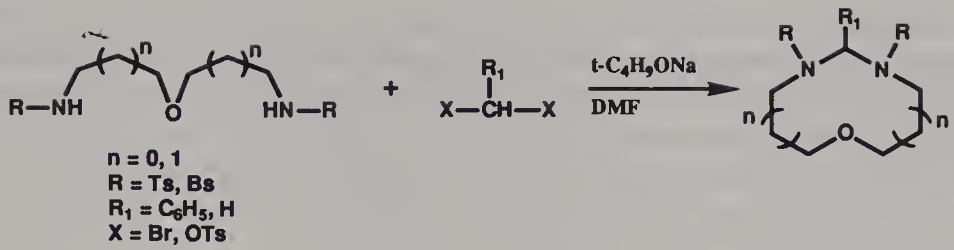


The ditosylate ester of 2,2-dimethyl-1,3-propanediol also did not decompose when used to form the peraza macrocycles under mild conditions (Krakowiak, 1982).

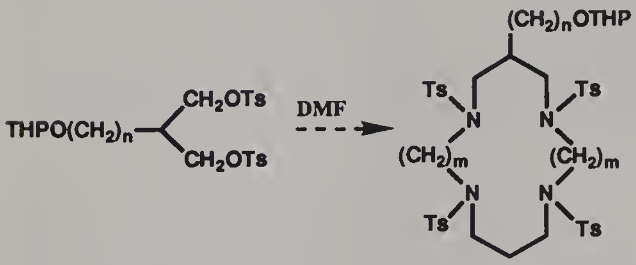
The sulfonamide cyclization method has been used to prepare not only aza- and peraza-crowns but also sulfur-containing macrocycles as shown (Boeyens et al., 1985; Gahan et al., 1982; Hart et al., 1983).

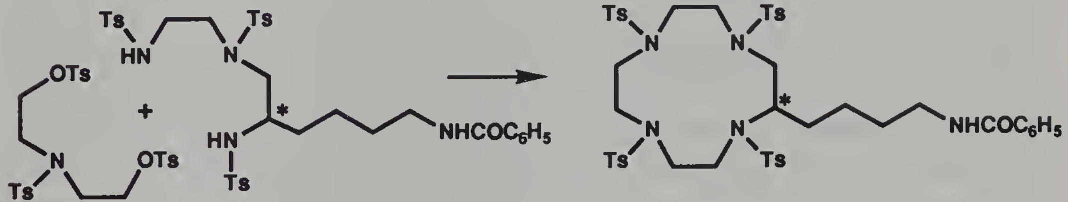


The sulfonamide method has been used to prepare aza-crowns with a methylene unit between nitrogen atoms or nitrogen and oxygen atoms. The bis-sulfonamide was reacted with dibromomethane, benzal bromide, or methylene ditosylate (Krakowiak and Kotelko, 1982, 1983a, 1983b, Krakowiak et al., 1983) or with bis-chloromethyl ether (Krakowiak et al., 1984). Unfortunately, the macrocycles were not stable after the *N*-tosyl groups were removed.

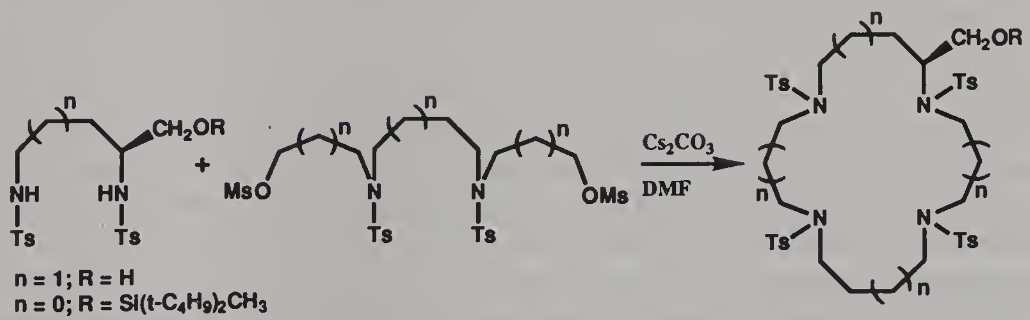


Aza-crowns and cyclams containing functional groups on ring carbon atoms or on pendant groups attached to ring carbon atoms have been prepared by the sulfonamide cyclization process. Usually the pendant functional group was protected before the cyclization reaction and then deprotected afterward (Benabdallah and Guglielmetti, 1988; Cox et al., 1989). Burrows and co-



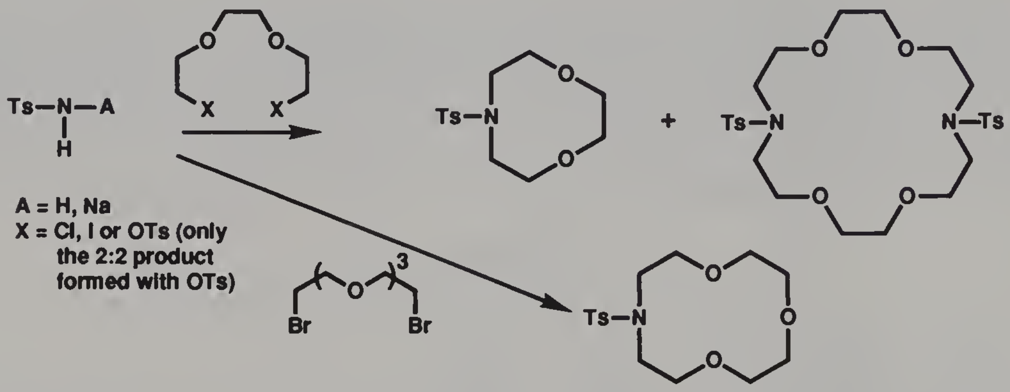


workers have prepared peraza-crowns containing a hydroxy moiety with and without the use of a hydroxy protecting group (Marecek and Burrows, 1986; Wagler and Burrows, 1987). In their reaction process, fewer steps were needed



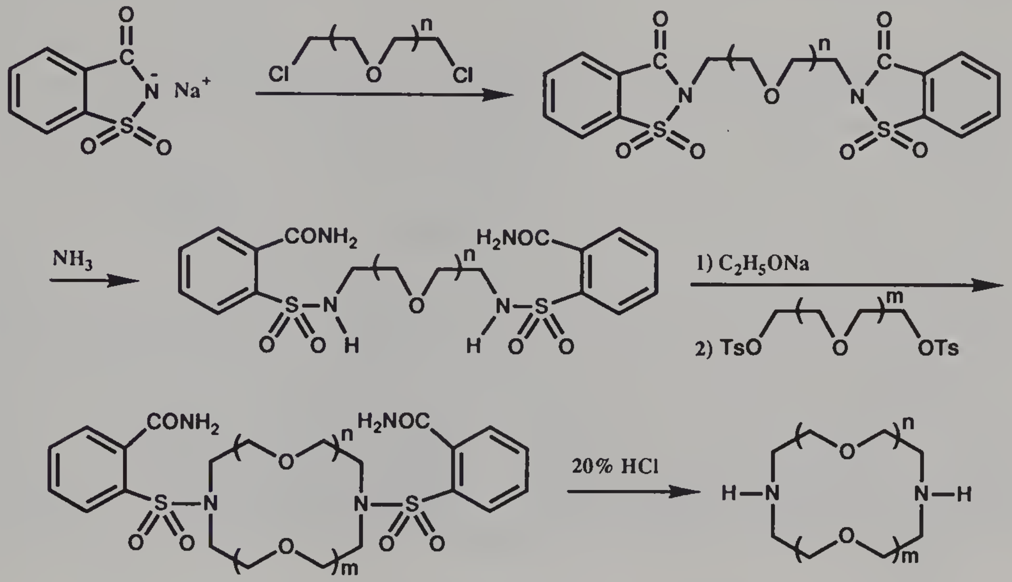
for the overall synthesis and cyclization yields were, with one exception, in the 55–80% range.

The ring-closure reaction using *p*-toluenesulfonamide can be a one-pot process (Bottino et al., 1988; Ostaszewski et al., 1988; Pappalardo et al., 1985; Rasshofer and Vögtle, 1978). Either the sulfonamide or its sodium salt and the dihalide or ditosylate ester were reacted in DMF. This type of process was used earlier to prepare similar compounds (Marckwald and Droste-Huelshoff, 1898; Paudler et al., 1966) and was used by Högberg and Cram (1975) to prepare benzoaza-crowns. This one-pot synthesis was used most successfully to prepare diaza-crowns (Bottino et al., 1988; Ostaszewski et al., 1988; Rasshofer and Vögtle, 1978). Treatment of *p*-toluenesulfonamide with a ditosylate ester in the presence of catalytic amounts of tetrabutylammonium chloride in DMF gave higher yields of the *N*,*N*′-ditosyldiaza-crowns (Ostaszewski et al., 1988).

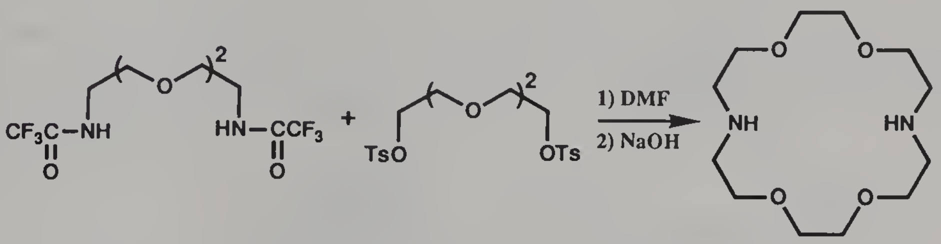


In summary, the sulfonamide cyclization reaction can give quantitative yields, especially for the 9–20-membered rings. The reaction temperature needs to be 20–40°C for the best results with potassium or cesium carbonate as the base. The formation of 2:2 cyclization by-products (especially during the formation of 11- to 13-membered rings) does not detract from the general utility of this cyclization process. This process is also useful for the formation of cyclophanes by a 2:2 cyclization process. It is important to note that this well studied process works and can be carried out by someone who is new to the field. It should be emphasized that although the sulfonamide cyclization process works well and is straightforward, the removal of the sulfonyl groups to form the unsubstituted aza-crowns is not always easy. There are a number of methods for the detosylation (or demesylation) step. The workup and isolation of the resulting amine products are sometimes difficult and not always predictable. This problem will be discussed in greater detail later in this chapter. Because of the difficulty in isolating the final amine products after detosylation, some authors have tried to produce the macrocycles by cyclizing other types of active amine compounds.

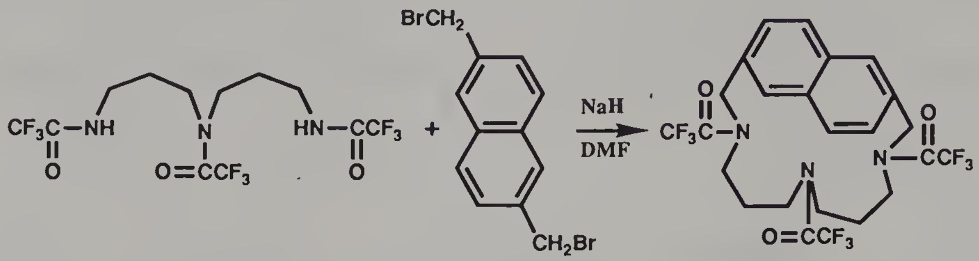
Saccharine can be used to convert an alkyl halide into a primary amine. Saccharine is reacted with the alkyl halide followed by a mild acidic cleavage of the resulting benzenesulfonylcarboxy residue (Abe, 1955; Eckenroth and Koerppen, 1896, 1897). This reaction has been used in cyclizations by first treating the dichloride derivative of a di- or triethylene glycol with the sodium salt of saccharine in DMF in the presence of sodium iodide to form the bissaccharide. This material was reacted with ammonia and then with a ditosylate to form the *N*,*N*′-bis-*o*-carbamoylbenzenesulfonyl-substituted crown as shown (Wang et al., 1989). The *N*-protecting groups were easily removed using 20% aqueous hydrochloric acid. This process will work well for the diaza-crowns but could be difficult for peraza-crowns because of the need for other *N*-protecting groups.



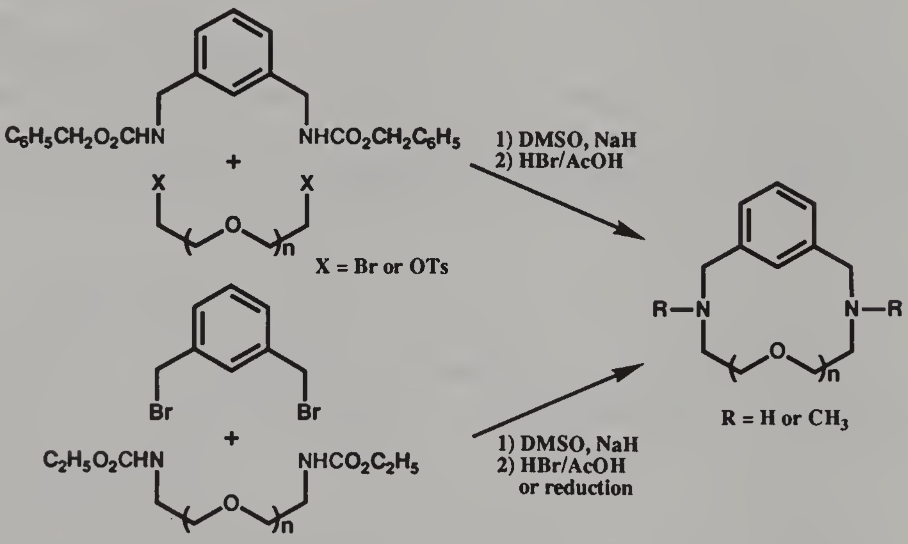
King and Krespan (1974) used the bis-trifluoroacetamide derivative of a diamine rather than the bis-sulfonamide to prepare a diaza-crown. The trifluoroacetamide is easy to prepare from the appropriate primary amine and ethyl trifluoroacetate, and the *N*-trifluoroacetyl group is readily removed after the reaction. Unfortunately, the cyclization reaction gave very poor yields of the diaza-crown. The authors suggested that the poor yield was a result of the reduced nucleoplilicity of the electrons on the nitrogen because of the electronegativity of the trifluoroacetyl unit (King and Krespan, 1974). Other examples of the use of this cyclization process have recently been published (Pratt et al., 1988). These authors studied the base-catalyzed cycloaddition of the *N*,*N*′,*N*″-tris(trifluoroacetyl) derivative of 4-aza-1,7-diaminoheptane with 4,4′-bis(bromomethyl)biphenyl. The *N*-protected 2:2 cycloaddition product was obtained in only a 5% yield but was easily deprotected to give



the hexaazacyclophane. The same reaction with 2,6-bis(bromomethyl)-naphthalene gave the smaller triaza 1:1 cyclophane adduct in a 26% yield as shown.

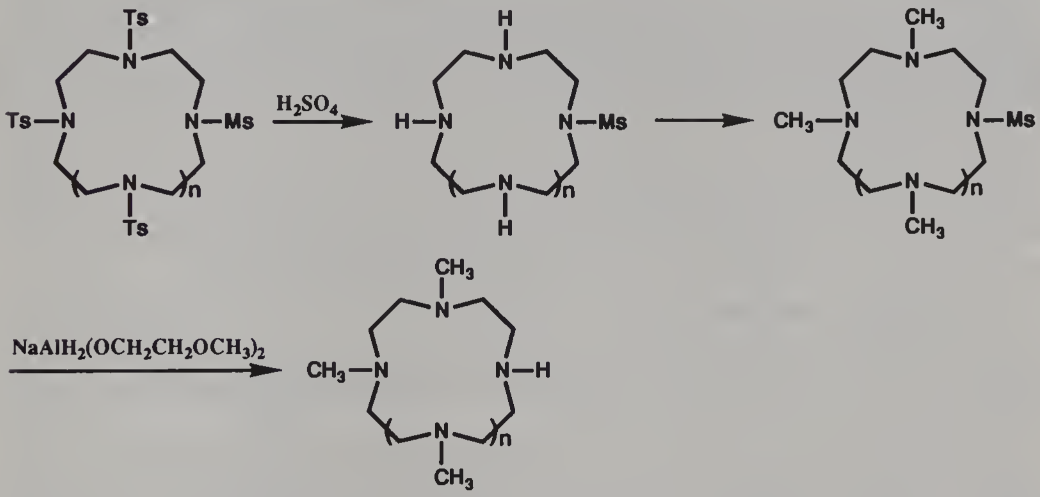


Sutherland and coworkers have used bisurethane types of compounds for ring closure and an easy removal of the carboxylate protecting groups. Pedersen and Bromels (1974) first suggested this type of protecting group for the synthesis of macrocycles. The diethyl or dibenzyl bisurethane was reacted with the ditosylate ester or dihalide in DMSO with sodium hydride as the base to give a 30–50% yield of the cyclic product (Hodgkinson and Sutherland, 1979; Hodgkinson et al., 1979; Leigh and Sutherland, 1979). The carboxylate protecting group can be removed using hydrobromic acid–acetic acid to give the amine or reduced to the methyl-substituted amine. Care must be taken with the DMSO–sodium hydride solution because of its explosive character (Vogel, 1989). As shown above, the 1,3-benzocrown could be prepared in two ways from either α,α'-dibromo-*m*-xylene or the corresponding bis-urethane produced from 1,3-bis(aminomethyl)benzene. This process has been used several times for the synthesis of macrocycles with the best yield at about 65% (Pietraszkiewicz and Jurczak, 1984). Aza-crowns with more than two nitrogen atoms were not prepared by this procedure, which shows that this method has only limited application.



Other amides have been used for ring closure with only limited success. The bis-acetamides were used to give only 20–25% yields of the macrocycle (Biernat et al., 1979; Mikiciuk-Olasik and Kotelko, 1984). A bis-formamide was used for ring closure to also give very poor yields (Krakowiak and Bradshaw, 1991).

As mentioned above, a major problem with the sulfonamide cyclization process is removing the sulfonyl groups from the cyclized product. The sulfonyl groups are usually removed under drastic conditions, which sometimes causes problems with the cyclic products. The mesyl and other sulfonamides are seldom solids, as was mentioned in the beginning of this chapter. Mesyl groups are more difficult to remove than tosyl groups and this property has been used to advantage to prepare peraza-crowns with a methyl substituent on all but one nitrogen atom (Pilichowski et al., 1985). The macrocycle with one nitrogen protected with a mesyl group and the rest with tosyl groups was treated with sulfuric acid, which removed the tosyl groups. Then the unsubstituted nitrogens were alkylated, followed by a reductive removal of the mesyl group.



C. METHODS FOR REMOVAL OF TOSYL PROTECTING GROUPS

The more prevalent tosyl groups are removed by three general methods: (1) acid hydrolysis with concentrated sulfuric acid, (2) reductive cleavage with a mixture of hydrobromic acid and acetic acid, and (3) lithium aluminum hydride reduction. Table 4.1 (Section G, near end of chapter) is a listing of compounds where tosyl groups were removed by these and other less common tosyl cleavage methods along with cleavage yields. The table is organized by cleavage method and size of the resulting aza- or peraza-crown ring.

Acid hydrolysis was done in 90–97% concentrated sulfuric acid followed by treatment with base. This method is not entirely satisfactory because some aza- and peraza-crowns decompose under very strong basic conditions and often isolation of the aza-crown is difficult (Thöm et al., 1986). Isolation of the cyclic polyamine or amine salts required solvent extraction and distillation, crystallization, sublimation, or column chromatography (reverse phase on aluminum oxide or silica gel). TLC and electrophoresis methods are used to check the purity of the product (Aoki et al, 1981; Blackborow et al., 1975; Yatsunami et al., 1981). Ion-exchange chromatography can isolate the free base from the salt rather than using solvent extraction from the basic solution (Bencini et al., 1987a, 1987b; Buoen et al., 1984; Dietrich et al., 1983; Osvath et al., 1987; Searle and Geue, 1984; Sun et al., 1985). The sulfuric acid method for removal of the *N*-tosyl groups appears to give good results for the preparation of peraza-crowns but is less satisfactory for the aza-crowns (see Table 4.1).

The hydrobromic acid–acetic acid method works well using 33–48% of hydrobromic acid in acetic acid (which can be purchased) with phenol as a bromine scavenger. Phenol is not necessary. The reaction can be carried out at room temperature for an extended period of time, under reflux, refluxed in a sealed tube for an extended period of time, or in a sealed tube at 120°C. Isolation of the product is easier than with the use of concentrated sulfuric acid. Usually, the addition of a large amount of an organic solvent such as ether causes the product to separate as the hydrobromide salt.

The lithium aluminum hydride reductive method to cleave tosyl groups is also convenient and will likewise reduce any carbonyl groups present in the macrocycle at the same time. Isolation of the products of this cleavage reaction is relatively easy.

The choice of method for removing the tosyl group can be critical. Carbon–oxygen or carbon–sulfur bonds can be cleaved by hydrobromic acid under reflux conditions. In this case, the reaction must be done at room temperature, or the lithium aluminum hydride reductive cleavage process must be used. Occasionally, other protecting groups (THP, ester, trityl or *t*-butylsilyl) must also be removed, which can be done during the detosylation process (Benabdallah and Guglielmetti, 1988; Helps et al., 1989a, 1989b; Wagler and Burrows, 1987). Also, there could be other functional groups in the macrocycle that could be changed by the drastic conditions required. Such a case was reported by Benabdallah and Guglielmetti (1988) and Hediger and Kaden (1983) where a pendant cyano group was hydrolyzed while removing the tosyl groups. Some substituents such as the hydroxy group are not changed under drastic detosylation conditions (Marecek and Burrows, 1986).

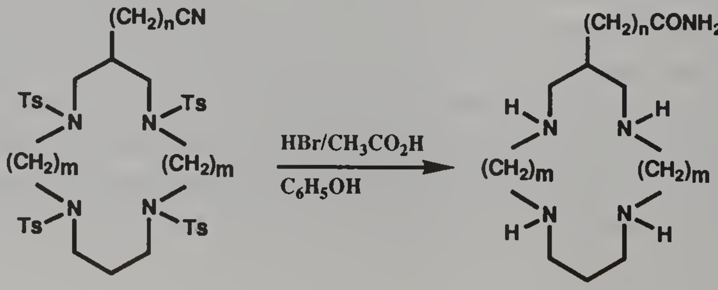
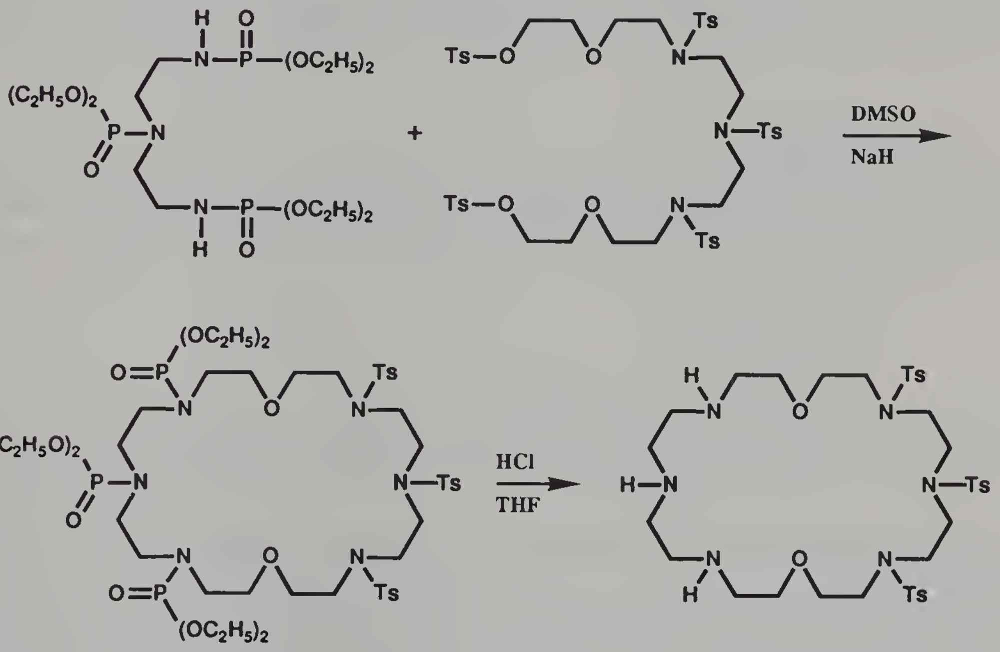


Table 4.1 lists the methods that have been used to remove the tosyl groups. There are other methods to cleave the sulfonamide functions in linear compounds but they did not work on the macrocyclic sulfonamides (Müller, 1957).

The sulfonamide method is the most important process for preparation of aza-crowns and cyclams. Recent developments in this process, such as using lower temperatures, the use of potassium and cesium carbonates, and using DMF as a solvent, allow the production of macrocycles in high yields and without the need for high dilution. A considerable number of compounds have been prepared using this technique. The tosyl moiety has been used as a nitrogen protecting group and activator in the majority of cases. Other activating groups that are easier to remove after cyclization have given poor cyclization yields. There is room for more work on this important cyclization process.

Two very recent developments show that work is continuing on this important process. Mertes and coworkers have shown that the diethoxyphosphoryl group is an excellent activator for primary amines and is easy to remove using gaseous HCl in THF (Qian et al., 1991a, 1991b). In the example shown,

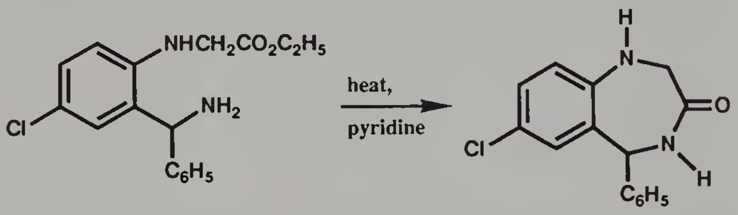


N,*N*′,*N*″-tris(diethoxyphosphoryl)diethylenetriamine was treated with a pertosylated triazaoligoethylene glycol to produce the triphosphoryltritosyl-protected hexaaza-24-crown-8. The phosphoryl groups were easily removed leaving the tritosyl-protected crown. This type of reaction allows the preparation of polyaza-crowns with different substituents on the ring nitrogen atoms. The 2-nitro-α-toluenesulfonyl group has also been suggested as a good primary amine activating group that is easy to remove. The 2-nitro-α-toluenesulfonyl chloride needed to prepare the corresponding sulfonamide is very expensive (*Aldrichimica Acta*, 1991).

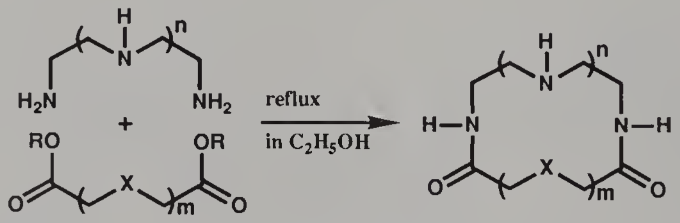
D. DIESTER–DIAMINE REACTIONS TO FORM CYCLIC DIAMIDES

The macrocyclic diamides are generally prepared by two cyclization processes. The reaction of a diacid dichloride and a diamine or polyamine under high-dilution conditions was discussed in detail in Chapter III. The second method is the cyclization reaction of a diester and a bis primary amine or polyamine that has internal secondary amino units. This reaction is slow, so long reaction times are the rule. We present here the reaction of simple diesters and diamines in the ring-closure step.

The reaction between primary amines and simple ester groups to form amides has been known since the beginning of organic chemistry. The formation of cyclic amides by this process was known before crown ethers were discovered. As an example, benzodiazepinone was prepared by a cyclic amide formation reaction as shown (Archer and Sternbach, 1966).

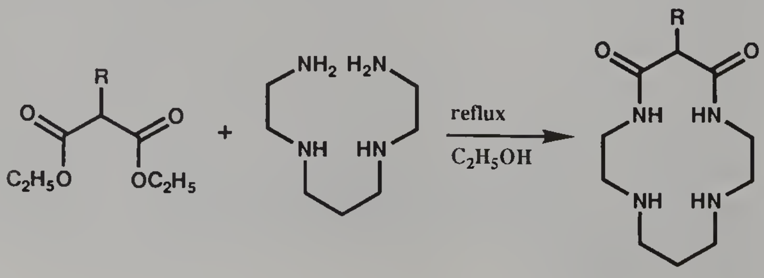


Tabushi and coworkers reported the first synthesis of a macrocyclic diamide by this process (Tabushi et al., 1976). They refluxed an α,ω-diester and an oligoethylene polyamine together in ethanol to give the macrocyclic diamide

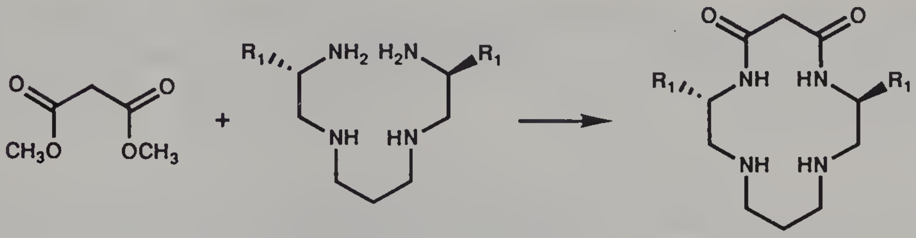


in 12–37% yields. Some of the yields were reported to be higher for unpurified cyclic products.

The same authors reported a similar reaction of a substituted diethyl malonate with 1,9-diamino-3,7-diazanonane to produce the [14]N_4 (cyclams) in 25–40% yields (Tabushi et al., 1977). Many other researchers have used the

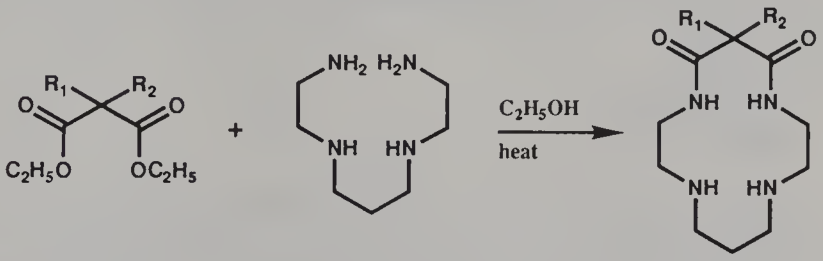


Tabushi method for the synthesis of [14]N_4-diamides. [14]N_4 ligands with methyl, ethyl, and propyl substituents have been prepared (Machida et al., 1983). The *p*-cyanophenyl derivative of [14]N_4-diamide was prepared in a 19% yield from the *p*-cyanophenyl-substituted diethyl malonate (Morphy et al., 1988). Chiral cyclic diamides were prepared from chiral tetraamines in 7–12% yields (Wagler et al., 1989).



$R_1 = CH_2C_6H_5, CH_2CH(CH_3)_2, CH(CH_3)_2$

Kimura and coworkers have used the Tabushi process to form [14]N_4-diamides with two substituent groups (Kimura et al., 1988). The two substituents were generally alkyl groups, but macrocycles with one and two fluorine substituents were also reported. The rate of formation of the fluoromacrocycles was fast. The macrocycle with two fluorine subsituents was formed in

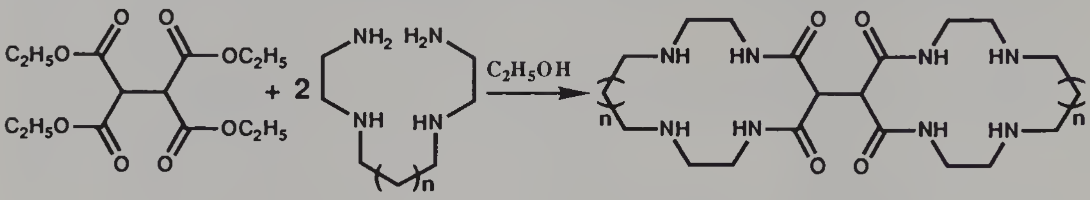


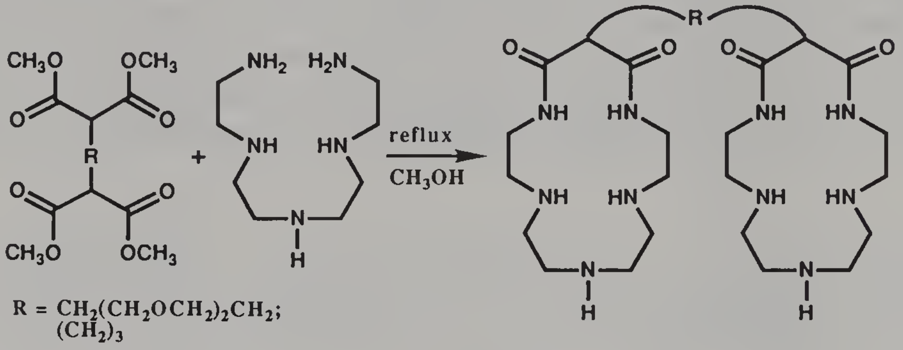
30 minutes and the one with one fluorine in about 3 days as compared to as long as a week or more with only alkyl substituents on the macroring (Kimura et al., 1988).

The diester cyclization method generally does not require high dilution. However, if substrate concentration was 5×10^{-2} *M* or less, formation of unwanted 2:2 and 3:3 cyclization products was avoided. Often the cyclam was obtained by a slow crystallization from the solution (Fabbrizzi et al., 1984). There have been no studies of solvent effects on this cyclization process other than using mixtures of THF and alcohol. It is possible that higher-boiling solvents could reduce the lengthy reaction times.

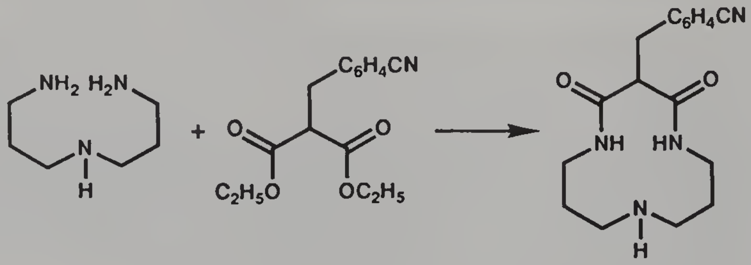
Kimura and coworkers tried to shorten the extended reaction times required for these cyclization reactions by using more reactive derivatives of malonic acid. They reacted the diazide derivative of α,α-dimethylmalonic acid with 1,9-diamino-3,7-diazanonane in chloroform for 12 hr at 0°C to give the dimethyl-[14]N_4 macrocycle in a 23% yield (Kimura et al., 1989a). This method will probably not be widely accepted because diazides are not safe materials. Attempts to improve the yields by reacting malonyl dichloride at high pressure (8–9 kbar, 50°C) or under high dilution conditions were unsuccessful (Wagler et al., 1989).

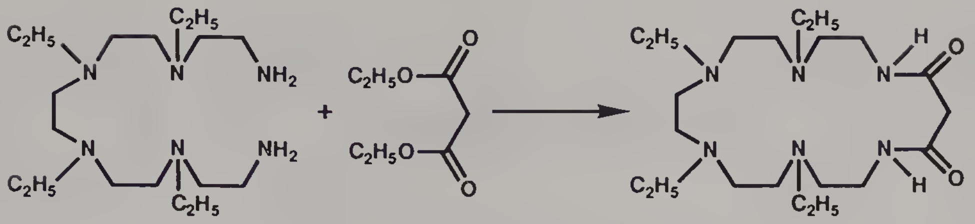
A bismalonate ester was used to prepare a bis[14]N_4 bicyclic system in a 30% yield (Buttafava et al., 1984; Fabbrizzi et al., 1984; Mochizuki et al., 1991). Larger peraza bicyclic ligands were prepared in low yields by a similar process from two malonate esters connected by diethyleneoxy or trimethylene units (Kimura et al., 1990a).



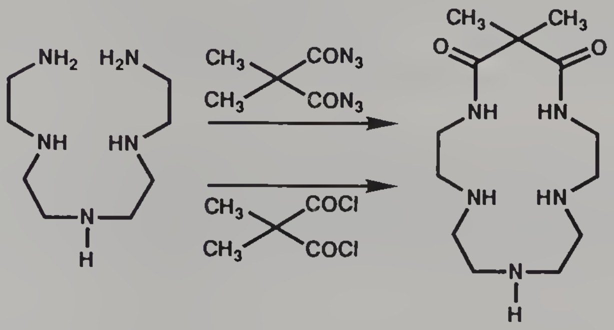


Diethyl malonate derivatives have been used to prepare peraza macrocycles that are smaller and larger than the cyclams. A [12]N_3 macrocycle was prepared in a low yield from cyanobenzylmalonic ester and a triamine (Craig et al., 1989b; Helps et al., 1989b). A [19]N_6 ligand was prepared in a 17% yield from a tetraethyl-substituted pentaethylenehexaamine and malonic ester (Bradshaw et al., 1989a). The macrocyclic diamide [19]N_6-dione was prepared from the reaction of dimethyl or diethyl malonate with 1,14-diamino-3,6,9,12-tetraazatetradecane in refluxing alcohol over a period of a few weeks (Kimura et al., 1984b, 1989b). More practical methods for preparation of these same macrocycles used the diazide or diacid chloride of malonic acid to give 16%

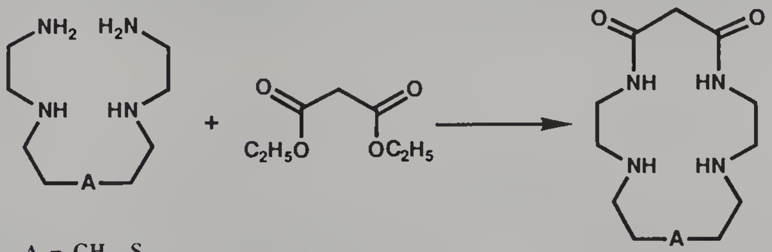




and 7% yields of the salts of the macrocycles, respectively (Kimura et al., 1989b). Kimura and coworkers prepared less symmetric [16]N_5-diamide and



[16]N_4S-diamide systems in 19% and 36% yields, respectively, by the reaction of diethyl malonate with the appropriate polyamine (Kimura et al., 1984b).

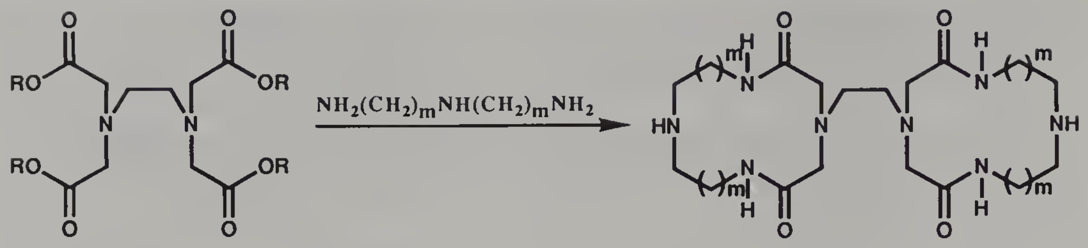


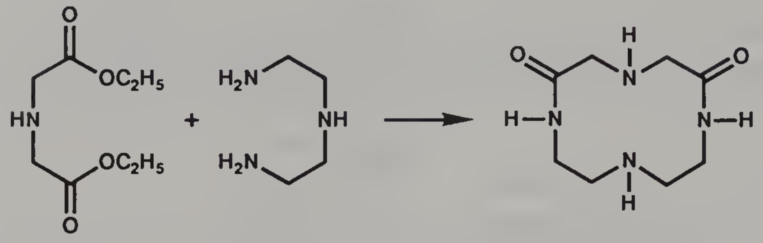
A = CH_2, S

It is interesting that the [16]N_5-diamide containing a pyridine subcyclic unit was obtained in a 64% yield (the highest yield for this type of reaction) by the reaction of diethyl malonate and 2,6-bis[1,4-diazapentyl]pyridine (Kimura et al., 1984b).

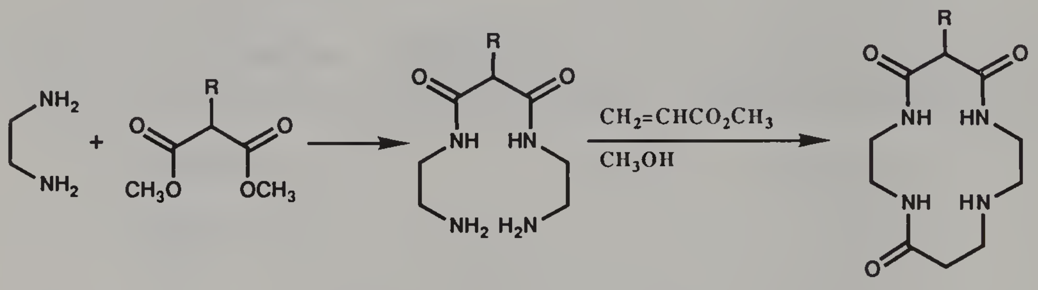
Two other ester starting materials include diethyl iminodiacetate and the tetraester derivative of EDTA. The latter tetraester was used to prepare a bistetraaza-crown, while iminodiacetate was used to make [12]N_4 (Fabbrizzi et al., 1986; Kodama and Kimura, 1981) (shown on next page). The diethyl iminodiacetate reaction also gave a small yield of a 2:2 cycloadduct, the octaazacyclotetraamide (Kimura et al., 1990a). It is interesting that diethyl oxalate has not been used as a building block in these diester cyclization reactions.

An interesting side light of the diester–diamine cyclization reaction is the Michael addition of one amine of a diamine to the carbon–carbon double bond of an acrylate ester coupled with the ester–amine reaction of the second

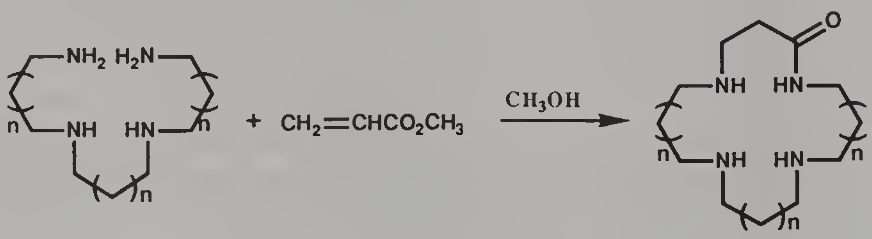




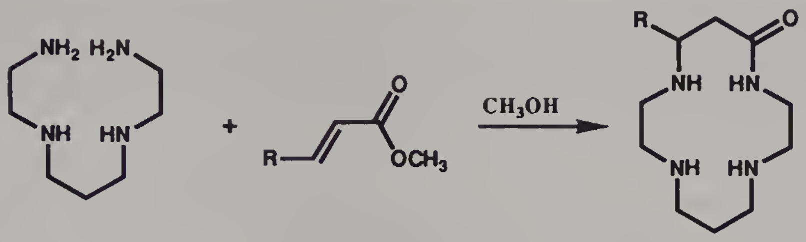
amine to the ester moiety of the acrylate to give a cyclic amide (Machida et al., 1983). The overall process gave macrocyclic triamides when a diamido-diamine starting material was used as shown below.



Substituted dimethyl malonate was reacted with a 3-fold excess of ethylenediamine in the absence of a solvent. Methyl acrylate in methanol was slowly added to the tetraaza reactant at room temperature, and the mixture was refluxed to produce the macrocycle (Kimura et al., 1984a; Machida et al., 1983). Methyl acrylate was treated with various tetraaza starting materials to prepare macrocyclic monoamides in yields of less than 30% (Machida et al., 1983).



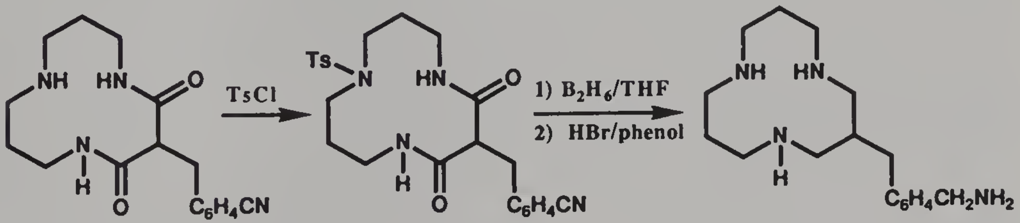
Substituted methyl acrylates, such as the cinnamates, have also been used to prepare these macrocyclic monoamide compounds (Kimura, 1986; Kimura



R = 2-pyridyl; C_6H_5; 2-HO-C_6H_4;
2-HO,5-NO_2-C_6H_3; 2,3-$(CH_3O)_2$-C_6H_3

et al., 1985, 1986a, 1986b, 1987a, 1987b). The substituent on the acrylate could be varied from phenyl to pyridyl and even imidazol (where one nitrogen atom in the imidazol ring was protected by a trityl group) (Kimura et al., 1987b). Derivatives of coumarin were also used to prepare similar macrocycles in yields of less than 20%.

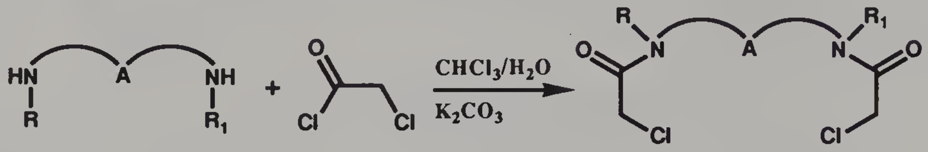
The diester (or methylacrylate) cyclization reactions give the cyclic mono-, di-, or tetraamides. These materials must be reduced to provide the polyaza-crown compounds. The reduction process is usually carried out using diborane–THF or lithium aluminum hydride. The best results were obtained with a large excess of borane, however, a stable boron complex with the macrocycle often results. It is difficult to separate the macrocycle from the complex. Reduction of [12]N_3–diamide with borane–THF always gave the stable complex. This problem was avoided by first forming *N*-tosyl[12]N_3–diamide using the ester cyclization method followed by reduction with borane-THF and detosylation with HBr/phenol (Helps et al., 1989b).



The diester cyclization route to the peraza-crowns is particularly useful for the synthesis of the 11–15-membered rings. The yields for these syntheses are not high; however, the ability to use substituted malonate esters allows the incorporation of various types of side chains. One important advantage of the diester cyclization method is that nitrogen protecting groups are not needed for the internal secondary amines of the polyamine starting materials (Wagler et al., 1989).

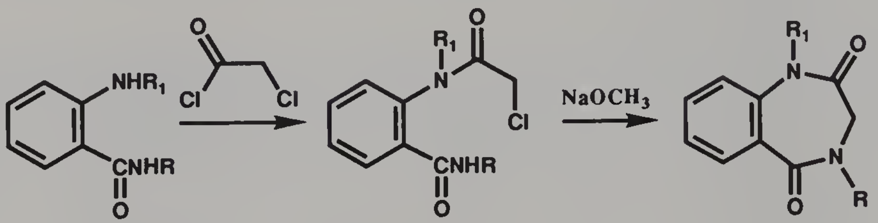
E. THE CRAB-LIKE CYCLIZATION PROCESS USING BIS-α-CHLOROAMIDES

In the crab-like cyclization process, very reactive bis-α-chloroamide intermediates are used. These intermediates, prepared by the reaction of a diamine and chloroacetyl chloride, resemble a crab with two reactive alkyl chloride groups poised and ready to react with a primary amine or a diamine to form the macrocyclic diamide (Bradshaw et al., 1989a; Krakowiak et al., 1990a).



crablike bis-α-chloroamide

Chloroacetyl chloride has been used to prepare small heterocyclic compounds (Groszkowski and Wrona, 1982; Groszkowski et al., 1985; Lee, 1964).



R = alkyl, aryl
R_1 = H, alkyl

The crab-like cyclization reaction has been used for a one-step preparation of polyaza-crowns containing one unsubstituted amine group in the macrocyclic ring or a secondary amine at the end of a pendant carbon chain. Previous syntheses of monofunctional polyaza-crowns required the use of two types of protecting groups that could be removed sequentially. These types of crowns were prepared using the Richman–Atkins procedure (Comarmond et al., 1982; Hediger and Kaden, 1978, 1983; Hosseini et al., 1987, 1988; Martin et al., 1982). Their procedures gave a polyaza-crown with one secondary amine in the ring that could be used to attach various substituents. The remaining ring nitrogen atoms contained tosyl or other removable substituents that allowed even more substitutions to take place. Barefield and coworkers prepared similar compounds using template cyclizations and benzyl protecting groups (Barefield et al., 1976, 1986a, 1986b).

In all of the syntheses for preparation of mono-functionalized polyaza-crowns, many steps were required to obtain compounds similar to those obtained by the one-step crab-like cyclization. The advantages of the crab-like synthesis of macrocycles are (1) the process is a straightforward one-step cyclization from simple and inexpensive starting materials; (2) the secondary amide nitrogen atom on the crab-like starting material is unreactive as a nucleophile, so nitrogen protecting groups are not needed; (3) the process is short, and the overall yields for the polyaza-crowns are higher than when protecting groups are employed; and (4) the chloride leaving group is activated by the neighboring amide group, but the molecule does not have the blistering properties of a β-chloroamine.

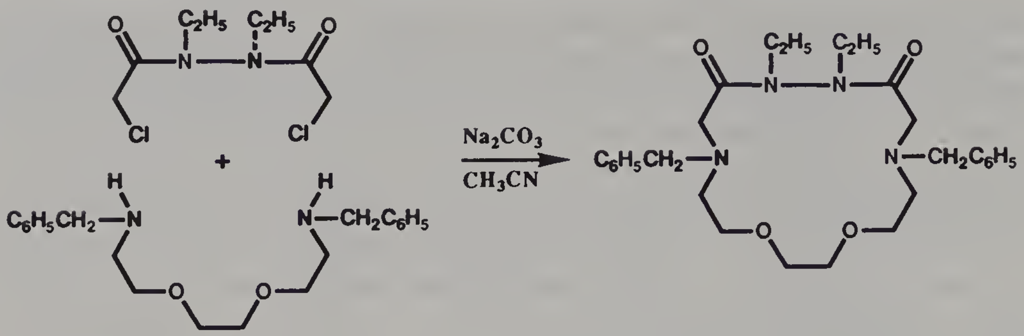
The starting bis-α-chloroamides were prepared in 70–100% yields by the reaction of the appropriate diamine and chloroacetyl chloride, usually in a water–chloroform mixture in the presence of potassium carbonate at 0–5°C as shown earlier (Bradshaw et al., 1989a). Others used chloroform or benzene–water mixtures in the presence of sodium hydroxide or aqueous sodium hydroxide for this reaction (Cottrell and Gill, 1947; Goto et al., 1973; Lin et al., 1985; Schraufstätter and Gönnert, 1962). This reaction can be done in the presence of hydroxy and carboxyl groups since the amine group is more reactive toward acetylation (Bergmann and Grafe, 1930; Birnbaum et al., 1952; Chadwick et al., 1984; Krakowiak et al., 1989a).

The crab-like bis-α-chloroamide starting materials can be prepared from simple primary and/or secondary diamines and oligooxadiamines but not from polyamines with terminal secondary and internal tertiary amine units. The internal tertiary amines were probably dealkylated by the chloroacetyl chloride, and a mixture of products resulted (Cooley and Evain, 1989). Other chloroacetylating agents such as chloroacetates and anhydrides might be useful for preparing the bis-α-chloroamides from the polyamines. Similar chloroamides can be obtained by the Ritter reaction of dialcohols, chloronitriles, and sulfuric acid (Meyers and Libano, 1961a, 1961b). The bis-α-chloroamides were usually solids, although some were viscous oils. Usually, when the reaction was carried out at 0–5°C using purified chloroacetyl chloride, the product bis-α-chloroamide did not need to be purified for the ring-closure reaction. The purity of the bis-α-chloroamide can be determined by TLC (silica gel using alcohols). Purification can be done by recrystallization of the solids or flash column chromatography of the liquids (silica gel and alcohols) (Bradshaw et al., 1989a; Krakowiak et al., 1990a, 1990b).

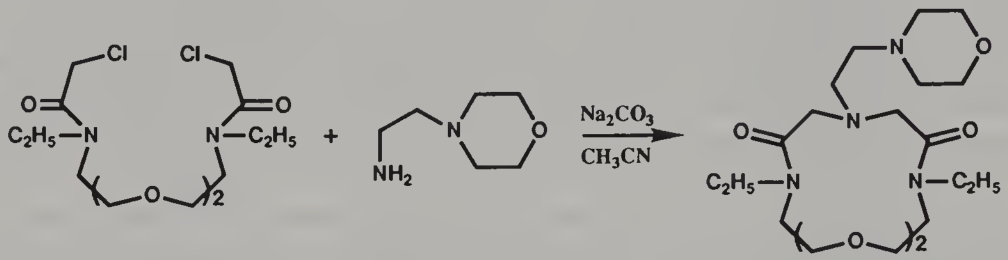
The haloacetamides are more easily cleaved by acid (0.1 *N* HCl) or base (0.01 *N* KOH or 15% NH_3 in methanol) than unsubstituted acetamides (Greene, 1981). Thus, care must be taken to avoid strong base conditions and water in the cyclization process using the bis-α-chloroamides. For this reason, the crab-like compounds probably could not be used for the preparation of macrocycles by C—O—C bond formation since a strong base is needed for the reaction of alcohols with alkyl halides.

The cyclization reaction was carried out by treating the bis-α-chloroamide with the primary amine or bis secondary amine in acetonitrile using a carbonate base to give the macrocyclic diamide in good yields. The base could be sodium, potassium or cesium carbonate, or triisobutylamine. The best results were obtained using the carbonates with no noticeable yield differences among the different cations. It may be that internal hydrogen bonding between the reacting diamine and crab-like starting materials provides a psuedotemplate and favors the cyclization process.

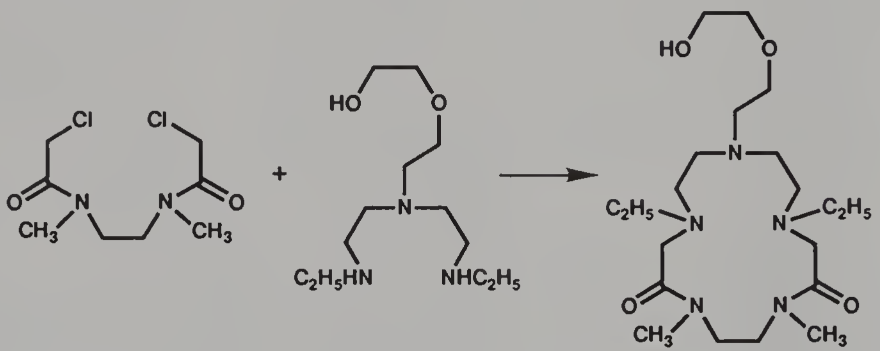
The first example of the crab-like cyclization reaction for the formation of macrocycles was in the synthesis of hydrazino-crown ethers (Bradshaw et al., 1988b). The hydrazine-containing crab-like starting material was prepared from *N,N′*-diethylhydrazine and chloroacetyl chloride.

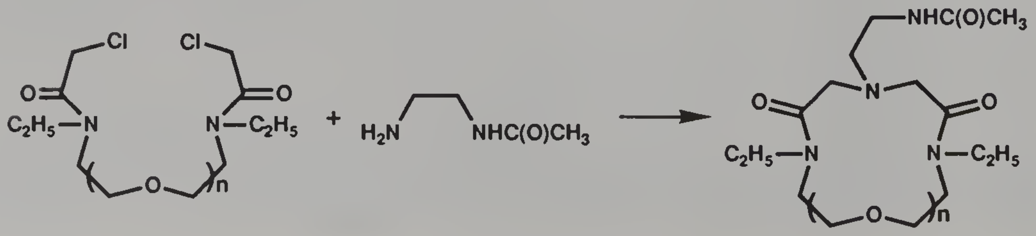


Reaction of the crab-like starting material with a primary amine formed a 1:1 cycloadduct wherein the primary amine reacted with the two alkyl chlorides of the starting material. The primary amine may have other heteroatoms or groups, such as morpholine, which, after the amides are reduced, can also coordinate with metal cations (Krakowiak et al., 1990a). Macrocycles with

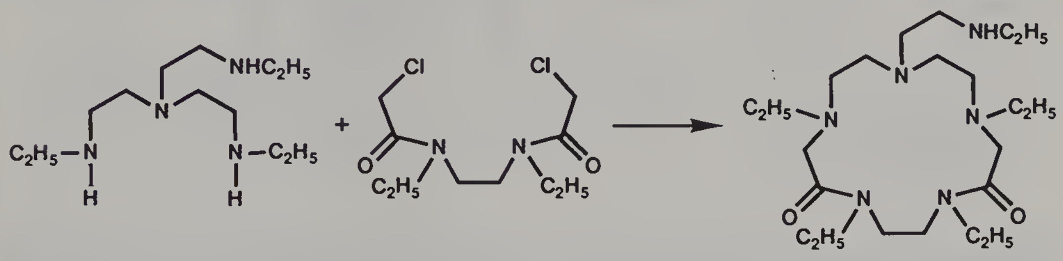


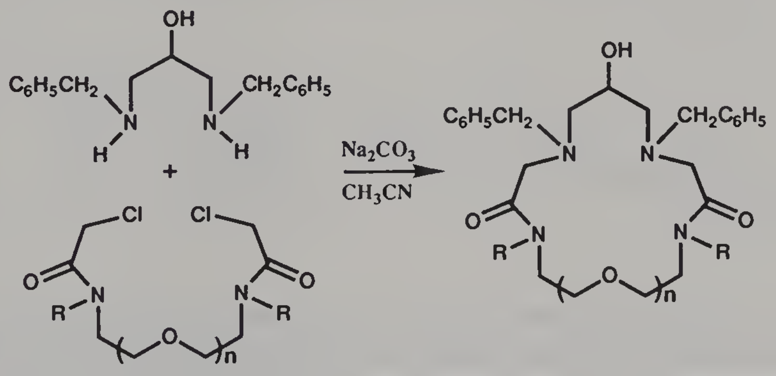
other attached groups such as $(CH_2CH_2O)_nCH_2CH_2OH$, $(CH_2)_nN(C_2H_5)_2$, and $CH_2CH_2NHC(O)CH_3$ have also been prepared. Macrocycles with hydroxy substituents are possible because the amine function is more reactive as a nucleophile using sodium carbonate as the base than the nonionized hydroxy group. The pendant amide group allows the preparation of polyaza- or peraza-crowns with reactive amine side groups after reduction (Krakowiak et al., 1989b).



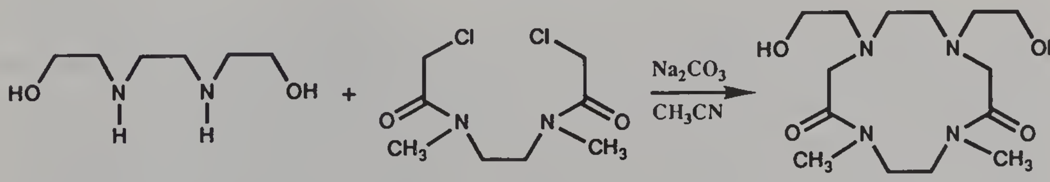


Reaction of the crab-like starting material with a bis-secondary amine gave a 1:1 cycloadduct where each terminal amine reacted with the alkyl chloride function on the ends of the crab-like reactant. In one case, a tris secondary amine was reacted to give a peraza-crown with a secondary amine substituent (Krakowiak et al., 1989b). The functional group also can be attached to a ring carbon atom. *N*,*N*′-Dibenzyl-2-hydroxy-1,3-propanediamine was reacted with the bis-α-chloroamide to give hydroxy-substituted tetrazacrowns in excellent yields (Bradshaw et al., 1989a). Aza-crowns with two hydroxyethyl groups attached to ring nitrogen atoms have also been prepared by the crab-like cyclization reaction (Bradshaw et al., 1990b; Krakowiak et al., 1990b). Again, using a carbonate base ensures that the amine nitrogen atoms react as nucleophiles and not the hydroxy oxygen atoms. In each case, the crab-like cyclization reaction produced the cyclic diamides, which can be easily reduced to the cyclic polyamines.

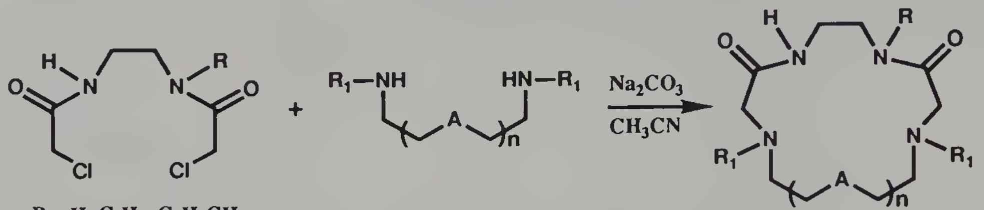




n = 2, R = C_6H_5
n = 0, R = CH_3

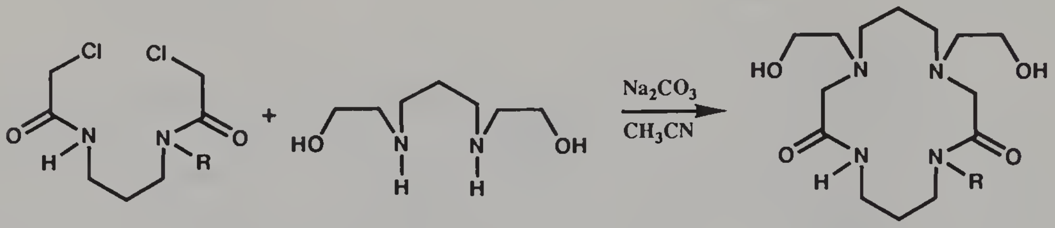


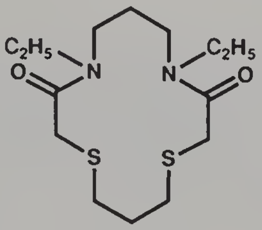
The crab-like cyclization reaction was used to prepare polyaza-crowns with one or two unsubstituted ring nitrogen atoms (Bradshaw et al., 1989a, 1990b; Krakowiak et al., 1990b). The amide nitrogen atoms are not effective nucleophiles, so reaction takes place via the amine nucleophiles. This alleviates the need for protecting groups on the amide nitrogen atoms.

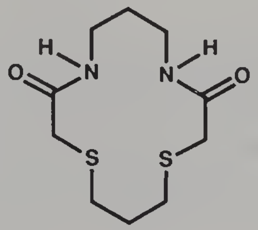


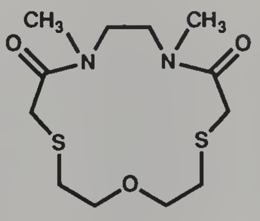
$R = H, C_2H_5, C_6H_5CH_2$
$R_1 = C_2H_5$
$A = O, N\text{-}C_2H_5$
$n = 1,2$

The crab-like cyclization reaction makes possible a one- or two-step, high-yield synthesis of the much studied [14]N_4 (cyclam) compounds. For example, *N*,*N*′-bis(2-hydroxyethyl)-substituted [14]N_4 recently was prepared (Bradshaw et al., 1990b). This dihydroxy-substituted cyclam could be used to make cage-like compounds. Similar macrocycles containing two sulfur ring atoms have also been prepared using the crab-like reactant and a dimercaptan with sodium or cesium carbonate as the base (Krakowiak et al., 1990a, 1990b).



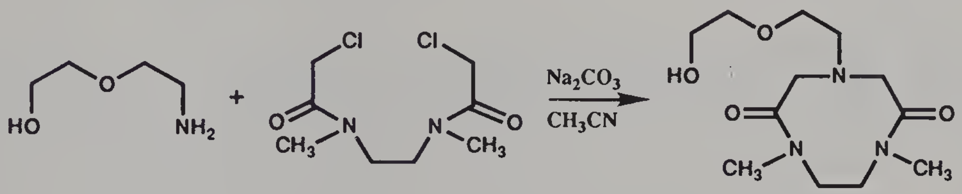




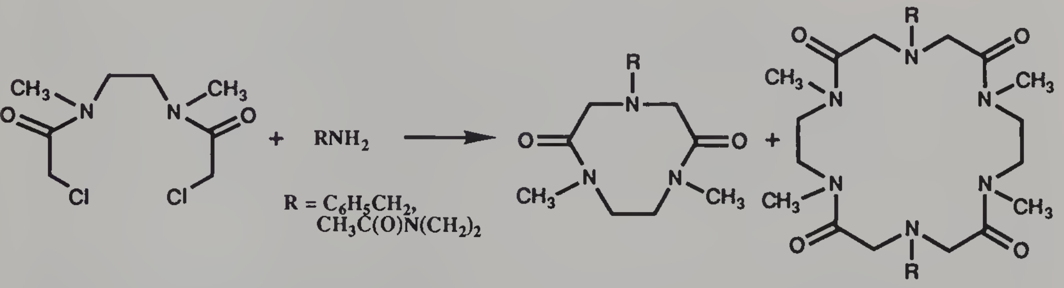


The yields for the crab-like cyclizations to prepare 12- to 15-membered rings were 50% or higher. The preparation of the [14]N_4 macrocycles was particularly favorable with yields of ≤70%. A careful addition of the two reactants in high dilution using syringe pumps gave the [14]N_4 compounds in yields of 80%. Other reaction conditions (reaction times, stirring speed, degree of dilution, base concentration, etc.) were not optimized because of the already high yields for the preparation of the cyclams (Bradshaw et al., 1990b).

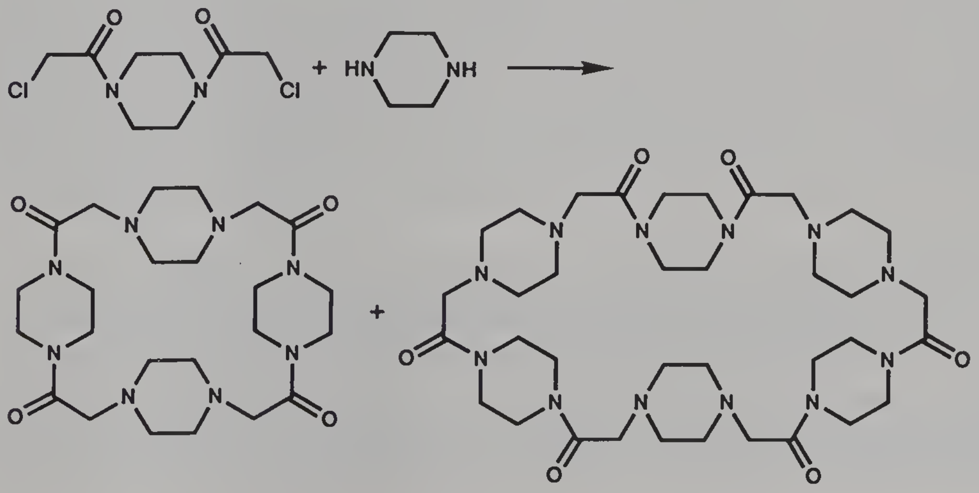
A 2:2 cyclocondensation process was a by-product when the crab-like cyclization was used to form the nine-membered macrocycles. Thus, $[18]N_6$ accompanied the desired $[9]N_3$ when the crab-like starting material was reacted with a primary amine. An exception to this general process was observed for the cyclization reaction using the monoamine derivative of diethylene glycol where only the $[9]N_3$ formed (Krakowiak et al., 1990b). Presumably,



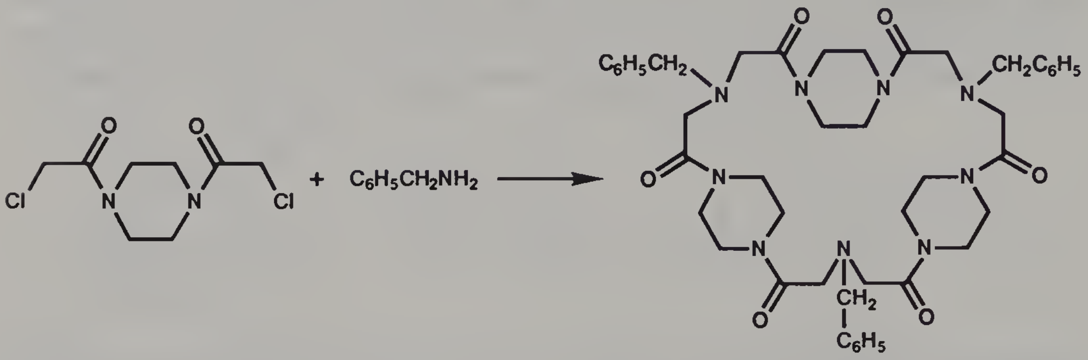
the oxygen on the side chain of the amine and the carbonyl oxygens of the bis-α-chloroamide formed a complex with the sodium ion so that only the 1:1 cyclization product was possible. When benzylamine or *N*-acetylethylenediamine reacted with the crab-like reactant, both 1:1 and 2:2 cyclizations were observed (Krakowiak et al., 1990b).



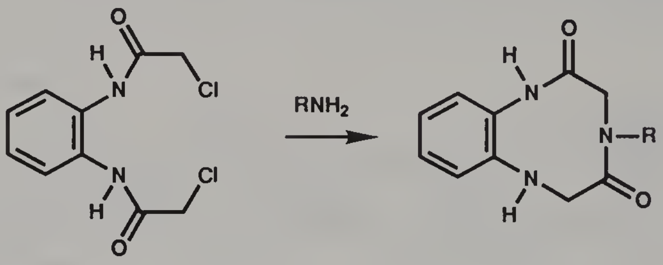
Rigid starting materials can cause 2:2 and 3:3 cyclizations to take place. A bis-α-chloroamide was prepared from piperazine. When this material was treated with piperazine, 2:2 and 3:3 cyclocondensations to form piperazine-containing belt-like compounds occured (Krakowiak et al., 1991). No 1:1



cyclization product was observed in this reaction. A similar reaction of the piperazino-crab and benzylamine gave only the 3:3 cyclization product in a 20% yield.



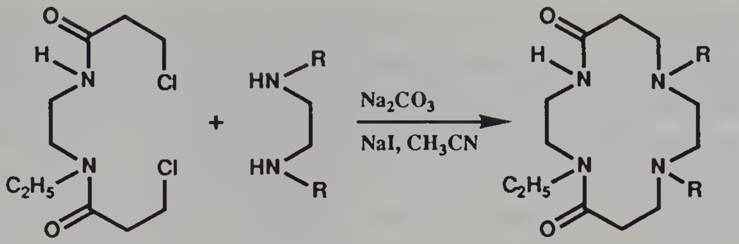
Recently, a crab-like material prepared from *o*-phenylenediamine was reacted with various primary amines to form diamide-containing triaza-9-crown-3 ligands (Mikiciuk-Olasik, 1990). The rearranged structure was proved by



^{1}H and ^{13}C NMR spectroscopy. No rearrangement was observed for the formation of the belt-like compounds shown in the preceding paragraph as proved by an X-ray structure analysis (Krakowiak et al., 1991).

The best solvent for the crab-like cyclization reaction was found to be refluxing acetonitrile. Reactions carried out at low temperatures and for long reaction times gave poor results. Generally the reactants were mixed at room temperature and the solution was immediately heated to reflux temperature (Bradshaw et al., 1989a; Krakowiak et al., 1990b). When high-dilution techniques were used, the reactants were slowly added to refluxing acetonitrile. A mixture of acetonitrile and DMF was used in a few cases where one of the reactants was not soluble in pure acetonitrile. Although a complete study of solvent systems has not been done, the yields were better in acetonitrile than in ethanol.

In contrast to the facile reaction and high product yields when using the bis-α-chloroamides, the bis-β-chloroamides were not reactive in refluxing acetonitrile unless sodium iodide was added to in situ convert the dichloride to the more reactive diiodide. Even with this improvement, yields of only about 20% were obtained for this cyclization (Bradshaw et al., 1990b; Krakowiak et al., 1990b).

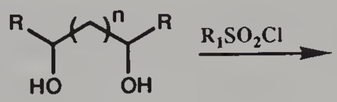


The cyclic diamide products of the crab-like cyclization reaction were reduced using borane–THF or in one case, borane-dimethyl sulfide. The use of lithium alumminum hydride gave only poor yields of the aza-crowns. Reduction with borane is straightforward, but some precautions must be taken. Reduction must be done under argon on cyclic polyamides that do not have impurities. The chromatographed cyclic polyamides are generally pure enough, but the elution solvent must be removed completely. The borane must be fresh and used in a large excess. The resulting macrocycle-BH$_3$ complex was decomposed by an overnight treatment with 18% aqueous hydrochloric acid at room temperature and then 15 min at reflux temperature. Extended refluxing in hydrochloric acid could decompose some of the macrocycle. Base must be added to the resulting solution to a pH value of 12 or higher. The polyaza-crown can be extracted into purified methylene chloride (no acid or phosgene) or other chlorinated hydrocarbons (Krakowiak et al., 1990b). Usually, the base should be sodium or potassium hydroxide, especially when there are secondary amine groups in the macroring (Bradshaw et al., 1989a). Often, the product is pure after extraction. If not pure, the macrocycles are purified on short silica gel columns using methanol/30% aqueous ammonia (5/1 to 10/1) or by reverse-phase chromatography. The product, especially one that contains tertiary amine functions, is difficult to remove from silica gel; hence the use of a short column. The product after column chromatography often needs to be dissolved in toluene or chloroform and filtered to remove precipitated inorganic material.

From these comments, it is evident that the crab-like cyclization reaction is a convenient method for preparation of a great variety of aza-crowns in good yields. Some of the polyaza products included *N*-pivot lariat polyaza-crowns, polyaza-crowns and cyclams with one or two unsubstituted ring nitrogen atoms, peraza-cage compounds, and polyaza-crowns containing sulfur atoms. This new method could become the method of choice for preparation of the functionalized polyaza- and peraza-crowns.

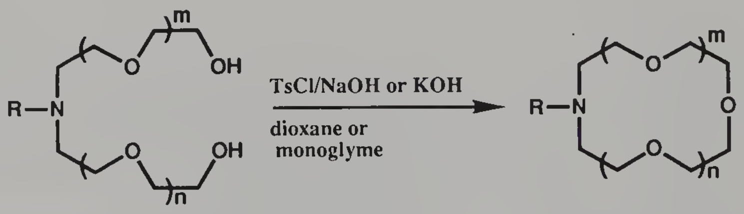
F. INTRAMOLECULAR RING CLOSURE OF α,ω-DIOLS USING ORGANIC SULFONYL CHLORIDES (THE OKAHARA RING-CLOSURE REACTION)

The first example of ring closure by treating two alcohols with one sulfonyl chloride to form a cyclic ether was reported in 1950 (Reynolds and Kenyon, 1950a, 1950b). The ethers were formed by an intramolecular reaction of the hydroxy groups of polyvinyl alcohol and suitably situated alkyl- or arylsulfonyl groups on vinyl sulfonate copolymer units. The same authors prepared a series of cyclic ethers in yields of 3–86% by slowly adding one mole of an arylsulfonyl chloride to one mole of the glycol in refluxing solvent in the presence of a tertiary amine (Reynolds and Kenyon, 1950a, 1950b). Some by-products of this reaction included the chloroalcohols and unsaturated alcohols. Various tetrahydropyranes were prepared in a similar manner but with better yields from various 1,5-diols. The reaction was carried out in hexamethylene phosphotriamide (Picard et al., 1975). A monotosylated diol and even the ditosylated diol using water as a catalyst were also used to prepare the cyclic ether.



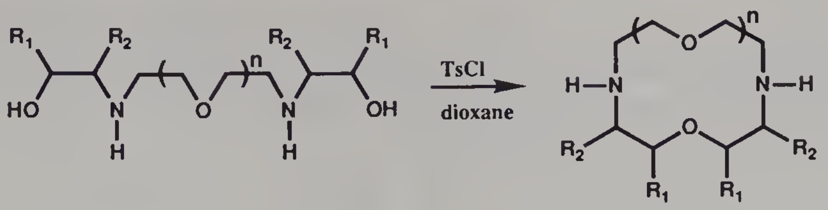
R = alkyl
$R_1 = CH_3, C_6H_5, CH_3C_6H_4$

Okahara and coworkers used the diol plus arylsulfonyl chloride procedure to prepare the crown ethers (Kuo et al., 1978). This method is convenient for preparing the *N*-alkyl-substituted monoaza-crowns as shown in the following reaction.

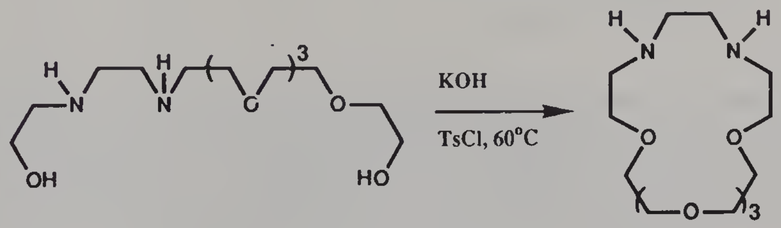


The *N*-alkyl-substituted azadiol was treated with an equimolar amount of tosyl chloride and excess alkali metal hydroxide in an aprotic solvent (powdered NaOH, dioxane, room temperature, 3 hr) to give a 60% yield of the monoaza-crown (Kuo et al., 1978). Template effects are important in this cyclization reaction, so sodium hydroxide was used for aza-15-crown-5 and potassium hydroxide for aza-18-crown-6. The intramolecular ring-closure process is the result of the initial formation of a tosylate by the reaction of one alkoxide anion with tosyl chloride followed by displacement of the tosylate leaving group by the second alkoxide anion. The pure monoaza-crowns were isolated from their metal ion complexes by thermolysis under reduced pressure (Kuo et al., 1980).

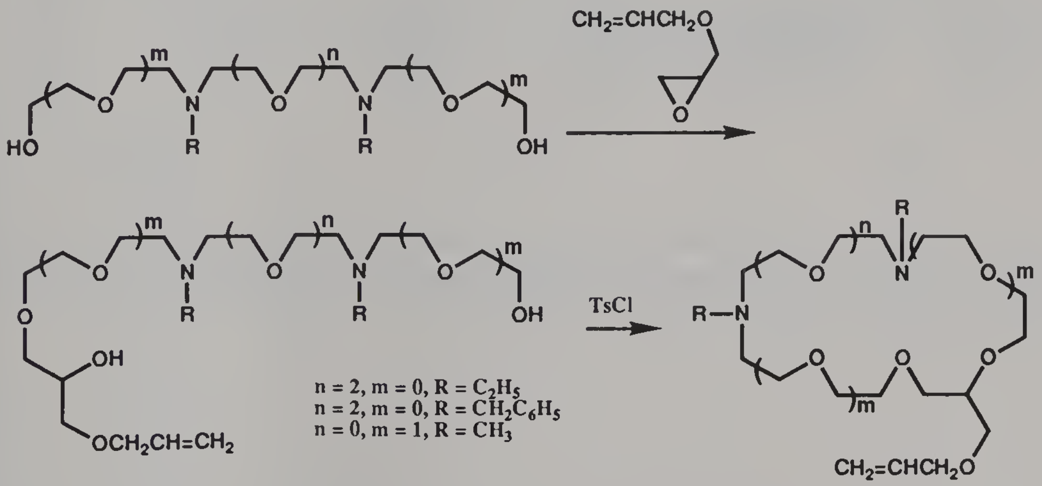
Diaza-crowns were prepared in 11–26% yields in a like manner from the reaction of one mole of the diazadiol with one mole of tosyl chloride using powdered alkali metal hydroxide in dioxane at 60°C (Maeda et al., 1983).



Some aziridine (or bis-aziridine) by-product, formed by a 1,3-displacement of the tosylate by the amine group, was observed in the NMR spectrum, but it was not separated. Other diaza-crowns, including those from unsymmetric starting diazadiols, have been prepared with yields of up to 30% (Ajinomoto, 1983). Many other examples of the formation of aza-crowns by this method were provided in the cited publications. The best solvents were dioxane and diglyme at 20–80°C. Tosyl chloride or benzenesulfonyl chloride was used with sodium or potassium hydroxide as the base.

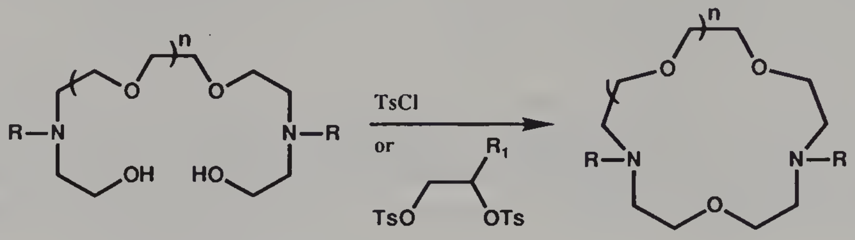


A series of nonsymmetric diazadiols containing an allyloxymethyl substituent was reacted with tosyl chloride to prepare diaza-crowns that could be attached to silica gel (Bradshaw et al., 1988a, 1989b, 1989c). These authors found that cyclization of the diol also occurred with the use of ditosylate esters of ethylene glycol or allyloxymethyl-substituted ethylene glycol (Bradshaw and Krakowiak, 1988, Bradshaw et al., 1988a). The reaction with ethylene glycol derivatives was carried out in *t*-butyl alcohol with sodium or potassium



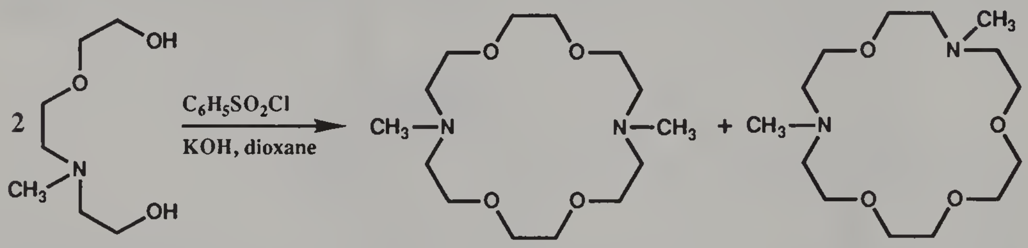
$n = 2, m = 0, R = C_2H_5$
$n = 2, m = 0, R = CH_2C_6H_5$
$n = 0, m = 1, R = CH_3$

metal or sodium hydride in THF or DMF with the desire to obtain a 1:1 cyclization product, but the reaction resulted in an intramolecular ring closure as shown. The ethylene glycol ditosylate eliminated to form an alkene, and during this process transferred a tosyl group to the diazadiol. Others have also observed that the ditosylate and dihalide derivatives of ethylene glycol do not undergo 1:1 cyclizations in strong base to form crown compounds (Chenevert and Plante, 1983; Dale and Kristiansen, 1972; de Jong et al., 1983). These authors did not report an internal ring-closure reaction.



$R = C_2H_5; C_6H_{13}$
$R_1 = H, CH_2OCH_2CH{=}CH_2$

One intermolecular 1:1 cyclization of an azadiol to give two isomeric diaza-18-crown-6 compounds was reported (Kuo et al., 1978). 3-Methyl-5-oxa-3-aza-1,8-octanediol reacted with tosyl chloride to give two isomers of the *N,N'*-dimethyldiaza-18-crown-6, depending on the orientation of the two reacting diols. No aza-9-crown-3 was formed in this reaction.



The Okahara ring-closure method is useful for the preparation of aza- and diaza-crowns in good yields and could be useful for the preparation of other polyaza-crowns (Nakatsuji et al., 1988; Son et al., 1984).

G. DETOSYLATION PROCESSES

TABLE 4.1. DETOSYLATION PROCESSES

Method	Compound	Yield (%)	References
H_2SO_4 Reactions			
70% H_2SO_4	[9]N_2O	<20	Reinen et al., 1987
conc H_2SO_4	[9]N_2O	low	Thöm et al., 1986
96% H_2SO_4	[9]N_3	87	Briellmann et al., 1987
96% H_2SO_4	[9]N_3		Buttafava et al., 1986
98% H_2SO_4	[9]N_3	90	Searle and Geue, 1984
conc H_2SO_4	[9]N_3		McAuley et al., 1984
conc H_2SO_4	([9]N_3)$_2$	80	Wieghardt et al., 1985
conc H_2SO_4	[9]N_3-Me	59	McAuley and Xu, 1988
96% H_2SO_4	[10]N_3	56	Briellmann et al., 1987
96% H_2SO_4	[10]N_3		Buttafava et al., 1986
96% H_2SO_4	[11]N_3	78,83	Briellmann et al., 1987
96% H_2SO_4	[11]N_3		Buttafava et al., 1986

TABLE 4.1. (*Continued*)

Method	Compound	Yield (%)	References
conc H_2SO_4	$[12]N_2O_2$	41	Rasshofer and Vögtle, 1977; Buhleier et al., 1977
96% H_2SO_4	$[12]N_3$	34,46,58	Briellmann et al., 1987
conc H_2SO_4	$[12]N_3O$	61	Rasshofer et al., 1976; Rasshofer and Vögtle, 1977; Buhleier et al., 1977
96% H_2SO_4	$[13]N_3$	50	Briellmann et al., 1987
conc H_2SO_4	$[14]N_4$		Hediger and Kaden, 1983
96% H_2SO_4	$[14]N_4$	72	Leugger et al., 1978
conc H_2SO_4	$[14]N_4$-3Ts	90	Ciampolini et al., 1986
conc H_2SO_4	$[14]N_4$-isocyclam-3Ts	55	Ciampolini et al., 1986
conc H_2SO_4	$[15]N_3O_2$	19	Rasshofer and Vögtle, 1977; Buhleier et al., 1977
96% H_2SO_4	$[15]N_4$	58	Leugger et al., 1978
conc H_2SO_4	$[15]N_4O$	64	Rasshofer and Vögtle, 1977; Buhleier et al., 1977
96% H_2SO_4	$[15]N_5$		Bencini et al., 1981
98% H_2SO_4	$[16]N_4$	60	Smith et al., 1978

96% H_2SO_4	[16]N_5		Bencini et al., 1981
conc H_2SO_4	[18]N_4O_2	74	Rasshofer and Vögtle, 1977 Buhleier et al., 1977
97% H_2SO_4	[18]N_6	50	Atkins et al., 1978
conc H_2SO_4	[20]N_3O_3	35	Rasshofer and Vögtle, 1977 Buhleier et al., 1977
70% H_2SO_4	[20]N_4	56	Stetter and Roos, 1954
70% H_2SO_4	[20]N_4		Suet and Handel, 1984
70% H_2SO_4	[20]N_4	60	Bianchi et al., 1988
conc H_2SO_4	[21]N_7	87	Micheloni et al., 1985
96% H_2SO_4	[22]N_6	70	Briellmann et al., 1987
96% H_2SO_4	[24]N_6	83	Briellmann et al., 1987
96% H_2SO_4	[24]N_8	63	Bianchi et al., 1985
96% H_2SO_4	[27]N_9	86	Bencini et al., 1987b
conc H_2SO_4	[30]N_{10}	85	Bencini et al., 1987b
conc H_2SO_4	[33]N_{11}	81	Bencini et al., 1988
conc H_2SO_4	[36]N_{12}	76	Bencini et al., 1988
96% H_2SO_4	([12]N_4)$_2$	53	Alfheim et al., 1986
conc H_2SO_4	([14]N_4)$_2$	74	Schneider et al., 1985
90% H_2SO_4	cyclophane N_4	90	Stetter and Roos, 1954
90% H_2SO_4	pyridinophane N_2		Bottino et al., 1988

TABLE 4.1. (*Continued*)

Method	Compound	Yield (%)	References
HBr Reactions			
30% HBr/CH_3CO_2H	$[9]N_2O$	92	Thöm et al., 1986
47% HBr/CH_3CO_2H	(sealed tube)	80	Graham and Weatherburn, 1981
47% HBr/CH_3CO_2	$H[9]N_3$-Me	10	Mason and Peacock, 1976
40% HBr/CH_3CO_2H	$[9]N_3$-Me		Graham and Weatherburn, 1981
30% HBr/CH_3CO_2H, phenol	$[10]N_3$	62	Searle and Geue, 1984
45% HBr/CH_3CO_2H	$[10]N_3$-Me		Graham and Weatherburn, 1981
HBr/phenol	$[12]N_3O$	67	Buhleier et al., 1977
HBr/CH_3CO_2H, phenol	$([12]N_3O)_2$	71	Alfheim et al., 1986
30% HBr/CH_3CO_2H	$[13]N_3O$		Thöm et al., 1986
HBr/CH_3CO_2H	$[13]N_3O$		Thöm and Hancock, 1983
40% HBr/CH_3CO_2H	$[14]N_4$	68	Osvath et al., 1987
48% HBr/CH_3CO_2H	$[14]N_4$-isocyclam	60	Sabatini and Fabbrizzi, 1979

33% HBr/CH_3CO_2H,	[14]N_4-$(CH_2)_2CONH_2$	66	Benabdallah and Guglielmetti, 1988
40% HBr/CH_3COH, phenol	[14]N_4-$(CH_2)_2CONH_2$	66	Hediger and Kaden, 1983
40% HBr/CH_3CO_2H, phenol	[14]N_4-CH_2CONH_2	37	Hediger and Kaden, 1983
33% HBr/CH_3CO_2H, phenol	[14]N_4-$(CH_2)_4OH$	66	Benabdallah and Guglielmetti, 1988
33% HBr/CH_3CO_2H, phenol	[14]N_4-$(CH_2)_4SCH_3$	69	Benabdallah and Guglielmetti, 1988
conc HBr/CH_3CO_2H	[15]N_3O_2	34	Hancock et al., 1989
40% HBr/CH_3CO_2H, phenol	[15]N_5 (sealed tube)	61	Osvath et al., 1987
33% HBr/CH_3CO_2H, phenol	[16]N_4-$(CH_2)_2CONH_2$	63	Benabdallah and Guglielmetti, 1988
40% HBr/CH_3CO_2H, phenol	[16]N_5 (sealed tube)	85	Osvath et al., 1987
33% HBr/CH_3CO_2H, phenol	[17]N_4-$(CH_2)_2CONH_2$	67	Benabdallah and Guglielmetti, 1988
40% HBr/CH_3CO_2H, phenol	[17]N_5 (sealed tube)	94,95	Osvath et al., 1987
conc HBr/CH_3CO_2H	[18]N_4O_2	48	Hancock et al., 1989
40% HBr/CH_3CO_2H, phenol	[18]N_5 (sealed tube)	93,95	Osvath et al., 1987
40% HBr/CH_3CO_2H, phenol	[19]N_5 (sealed tube)	94	Osvath et al., 1987

TABLE 4.1. (*Continued*)

Method	Compound	Yield (%)	References
40% HBr/CH_3CO_2H, phenol	$[20]N_5$	90	Osvath et al., 1987
48% HBr	$([21]N_3)_2$	80	Schmidtchen, 1980
33% HBr/CH_3CO_2H, phenol	$[26]N_4O_4$	25	Sun et al., 1986
48% HBr	$([27]N_3)_2$	85	Schmidtchen, 1980
33% HBr/CH_3CO_2H, phenol	$[27]N_3O_6$	90	Dietrich et al., 1983
33% HBr/CH_3CO_2H, phenol	$[32]N_6$	90,92	Hosseini and Lehn, 1986
48% HBr/CH_3CO_2H, phenol	$[32]N_8$	80	Dietrich et al., 1983
33% HBr/CH_3CO_2H, phenol	$[38]N_6$	33	Hosseini and Lehn, 1986
48% HBr/CH_3CO_2H, phenol	cyclophane N_4	90,93	Stetter and Roos, 1955
48% HBr/CH_3CO_2H	benzophane N_5	28	Kimura et al., 1990b

$LiAlH_4$ Reactions			
$LiAlH_4$/THF	[10]N_2	51	Naemura et al., 1989
$LiAlH_4$/THF	[12]N_2O_2	10	Alfheim et al., 1986
$LiAlH_4$/THF	[12]N_3O	35	Buhleier et al., 1977
$LiAlH_4$/THF	[12]N_4	40	Stetter and Mayer, 1961
$LiAlH_4$/THF	[13]N_4	50	Stetter and Mayer, 1961
$LiAlH_4$/THF	[14]N_4	50	Stetter and Mayer, 1961
$LiAlH_4$/THF	[14]N_4-Me	30,35	Buxtorf and Kaden, 1974
$LiAlH_4$/THF	[17]N_4	75	Stetter and Mayer, 1961
$LiAlH_4$/THF	[18]N_2O_4	85	Pietraszkiewicz and Jurczak, 1984
$LiAlH_4$/THF	[18]N_3O_3	75	Graf and Lehn, 1981
$LiAlH_4$/THF	([18]N_3O_3)$_2$	85	Graf and Lehn, 1981
$LiAlH_4$/THF	[18]N_4O_2	95	Buhleier et al., 1977
$LiAlH_4$/THF	[20]N_4	55	Naemura et al., 1989
$LiAlH_4$/THF	[32]N_4	65	Stetter and Mayer, 1961
$LiAlH_4$/THF	macrotricyclic	44	Saigo et al., 1990

TABLE 4.1. (*Continued*)

Method	Compound	Yield (%)	References
Na/liqNH_3, Li/liqNH_3, or Na/other Reactions			
Na/1-butanol and di-n-butyl ether	[9]N_2O	55	Reinen et al., 1987
Na/anth/DME	[12]NS_2O	20-60	Youinou et al., 1986
Na/liqNH_3	[12]N_2O_2	80	Ostaszewski et al., 1988
$NaAlH_2$-$(OCH_2CH_2OCH_3)_2$	[12]N_2O_2	37	Buhleier et al., 1977
$NaAlH_2$-$(OCH_2CH_2OCH_3)_2$	[12]N_3O	17	Buhleier et al., 1977
Na/liqNH_3	[15]N_2O_3	60	Ostaszewski et al., 1988
Na/liqNH_3	[15]N_2O_3-phenyl	65	Ostaszewski et al., 1988
sodium amalgam in Na_2HPO_4/CH_3OH	[18]N_2	90	Vriesema et al., 1984
Li/liqNH_3	[18]N_2O_4	70	Ostaszewski et al., 1988
Na/liqNH_3	[18]N_2O_4-diphenyl	50,55	Ostaszewski et al., 1988
Na/liqNH_3	[18]N_4O_2	96	Lehn and Montavon, 1976

sodium/naphtalenide	[18]N_2O_4		Desreux et al., 1977
Li/liqNH_3/ n-propylamine	([21]N_3)$_2$	94	Schmidtchen, 1980
sodium amalgam in Na_2HPO_4/CH_3OH	[24]N_4O_4	88	Sessler et al., 1989
Li/liqNH_3/ n-propylamine	([27]N_3)$_2$	85	Schmidtchen, 1980
Na/liqNH_3	cyclophane	78-90	Bottino et al., 1988
Li/liqNH_3/ether	cryptand-Ts	86	Lehn and Montavon, 1976
Li/liqNH_3/ether	cryptand-Ts_4	88	Lehn and Montavon, 1976
Electrochemical Reactions			
electrochem	[12]N_3O	26	Kossai et al., 1979
electrochem	[12]N_4	52	Kossai et al., 1979
electrochem	[14]N_4	85	Kossai et al., 1979
electrochem	[14]N_4-CH_2CONH_2	51	Hediger and Kaden, 1983
electrochem	[15]N_3O_2	43	Kossai et al., 1979
electrochem	[15]N_2O_2-dibenzo	92	Kossai et al., 1979

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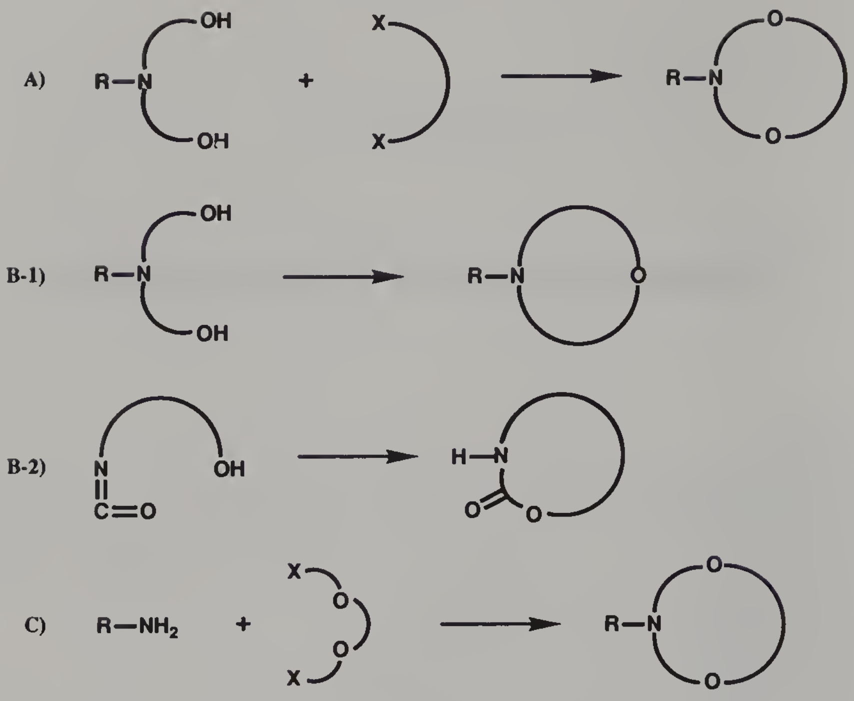
CHAPTER V

Monoaza-crown Macrocycles

A. INTRODUCTION

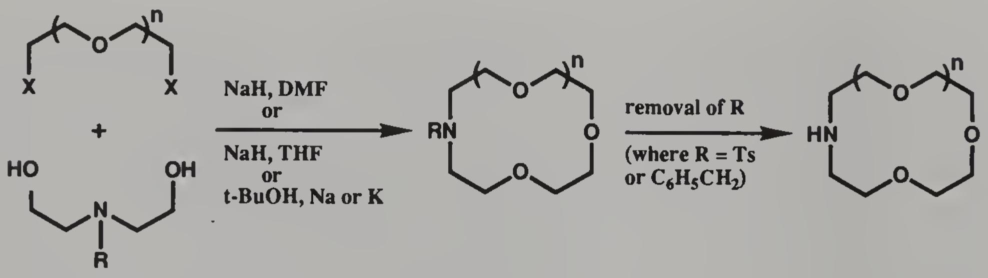
The monoaza-crowns can be prepared by three types of ring-closure reactions: (A) ring closure to form two C—O—C or C(O)—O—C linkages from two different starting materials (see next page), (B) intramolecular ring closure to form a C—O—C linkage from an α,ω-diol or intramolecular formation of a urethane from an ω-hydroxyisocyanate molecule, or (C) ring closure to form a C—N—C linkage from an amine and an α,ω-difunctional compound. The choice of method to prepare a monoaza-crown depends on the availability or ease of preparation of the starting materials. All three of these methods have given good results, especially in the presence of an appropriate template metal ion.



B. RING CLOSURE TO FORM TWO C—O—C OR C(O)—O—C LINKAGES

The monoaza-crown macrocycles were first prepared by reacting the appropriate diethanolamine with an oligoethylene glycol ditosylate, dimesylate, or dihalide (method A-1) (Dix and Vögtle, 1980; Gokel and Garcia, 1977; Greene, 1972; Johnson et al., 1979, 1985; Nakatsuji et al., 1989; Schultz et al., 1982a, 1985). This method is convenient because the two starting materials

Method A-1



X = OTs, OMs, Cl, I
n = 1-4

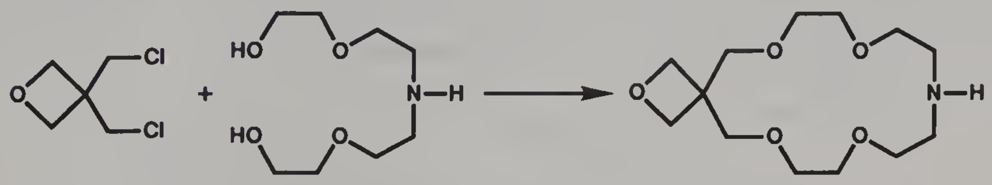
are readily available. Aza-crowns with no substituent on the nitrogen atom can be prepared when the R group is replaceable, such as when R is a benzyl, trityl, or tosyl moiety. Removal of the protecting group can be achieved by acid cleavage or reduction (Johnson et al., 1979, 1985). The cyclization step was accomplished by using sodium hydride in DMF or in THF or in *t*-butyl alcohol with sodium or potassium metal. The yields were moderate, depending on the size of the macroring.

The 1:1 cyclization product was the usual product isolated in method A-1, however, in some cases, both 1:1 and 2:2 cyclization products were observed. In the synthesis of aza-12-crown-4 where $n = 1$, the 2:2 cycloaddition product (diaza-24-crown-8) was isolated in a 10% yield while the yield of the 1:1 adduct was only 6% (Johnson et al., 1985). When a lithium template ion was used, aza-12-crown-4 was isolated in a 40–50% yield and very little of the 2:2 cycloadduct was observed (Miyazaki et al., 1982; Nakatsuji et al., 1989). Other researchers improved this yield to 63% (Pacey and Sasaki, 1987). If one of the reactants was rigid, such as being part of an aromatic system, 2:2 cyclization was preferred and generally no 1:1 cycloadduct was isolated (Johnson et al., 1985).

It is important to note that strong basic conditions, such as sodium hydride or potassium *t*-butoxide, favor the reaction between the hydroxy group and an alkyl halide or tosylate over alkylation by the amine (Bradshaw et al., 1989). Weak bases, such as sodium or potassium carbonate, favor the alkylation of amines over ether formation. Thus, a compound containing both alcohol and amine functions can undergo amine alkylation to give a product with a free substituent alcohol.

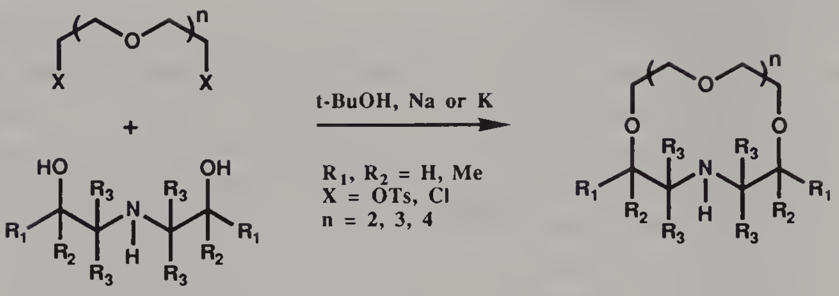
It is possible to manipulate reaction conditions to have ring closure of an aminodiol without the need for an *N*-protecting group. The first example of this type of ring closure (method A-2) was reported in 1975 (Krespan, 1975, 1976). The cyclization reaction gave yields of 35–40% depending on the size of the ring and on the metal ion used as a template. The spirooxetane shown in method A-2 could be opened by aqueous ammonia to give an aza-crown with both amino and hydroxy pendant groups or by aqueous acid to provide an aza-crown with two hydroxymethyl substituents (Krespan, 1975, 1980).

Method A-2



Okahara and coworkers reported a similar reaction to produce unsubstituted aza-crowns (Maeda et al, 1983a). They treated unprotected diethanolamines, some of which contained methyl substituents on carbon atoms, with various ditosylate or dichloride derivatives of an oligoethylene glycol to obtain the macrocycle (method A-3). They also detected a small amount of a smaller crown formed by ring closure through the internal amine group and one of the hydroxy functions. Changes in the reaction temperature did not affect the yields in this cyclization reaction. For the formation of monoaza-15-crown-

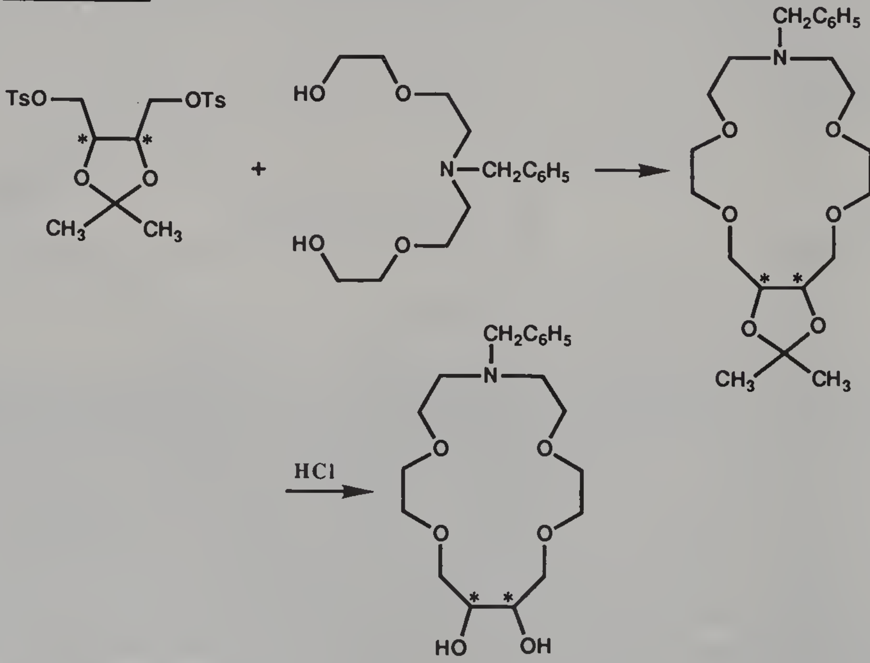
Method A-3



5, sodium ion was a superior template as compared to potassium ion. When 2 mol of the diethanolamine were used for the preparation of aza-15-crown-5, the yield increased to 77%. Use of excess base and the ditosylate derivative of triethylene glycol caused an increase in the yield of 1,8-di-*t*-butoxy-3,6-dioxaoctane, the di-*t*-butyl ether by-product, with a resulting decrease in the cycloadduct. Others obtained monoaza-15-crown-5 in a 46% yield using method A-3 but with barium oxide as a catalyst (Bogatskii et al., 1985b). Lai also modified method A-3 to prepare similar monoaza-crowns in higher yields (Lai, 1985). Sosnovsky and Lukszo (1985) prepared spin-labeled *N*-oxide-containing aza-crowns by this process.

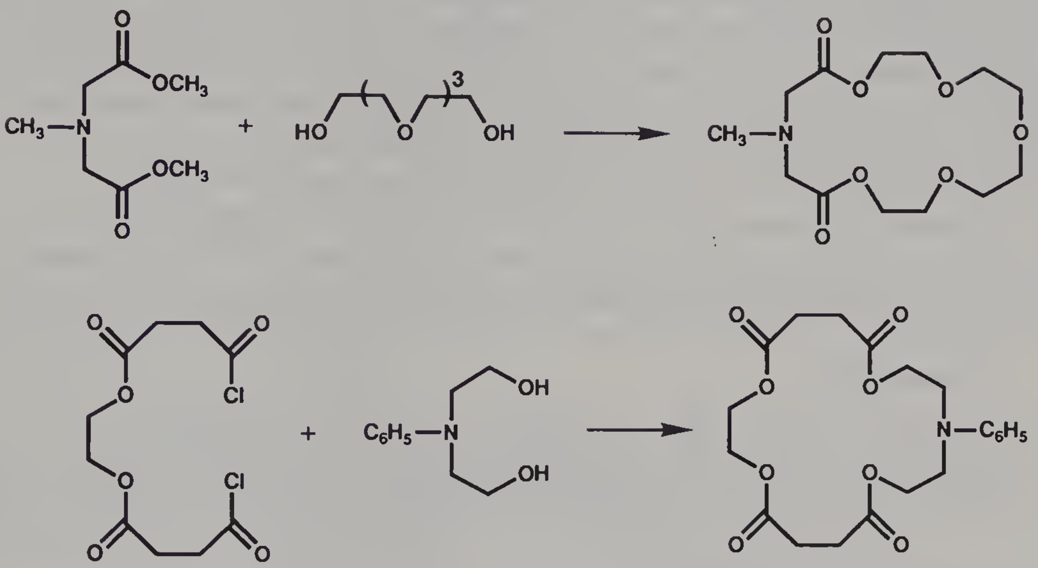
A monoaza-crown with a butylene bridge and containing two hydroxy groups on chiral ring carbon atoms was prepared by a similar process (method A-4) (Lukyanenko et al., 1988).

Method A-4



Monoazadiester-crowns were prepared from amine-containing diesters or glycols (method A-5) (Asay et al., 1977; Bradshaw et al., 1983). The yields

Method A-5

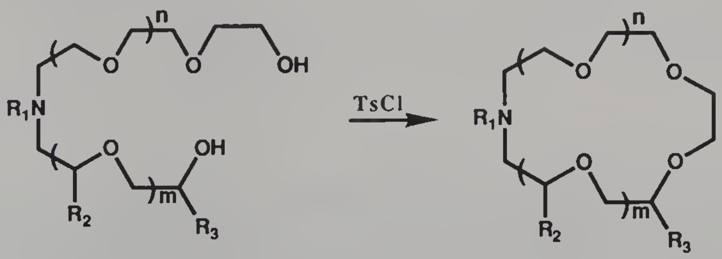


of these reactions were not high but were improved to as much as 41% by adding dibutyltin oxide to the glycol (Ninagawa et al., 1984). The glycol was probably converted to the more reactive dibutyltin derivative.

C. INTRAMOLECULAR RING CLOSURE TO FORM A C—O—C LINKAGE FROM AN *α,ω*-DIOL OR AN *ω*-HYDROXYISOCYANATE

The Okahara ring-closure reaction used for the preparation of all types of macrocycles (Kuo et al., 1978, 1980; Maeda et al., 1983b) has been used to prepare many aza-crown compounds (method B-1). The yields of these reactions were 50–80% depending on ring size and the substituent on the nitrogen atom. One equivalent of tosyl chloride or benzenesulfonyl chloride was used for the ring-closure reaction carried out in dioxane and in the presence of sodium or potassium hydroxide. The reaction of an amine-con-

Method B-1

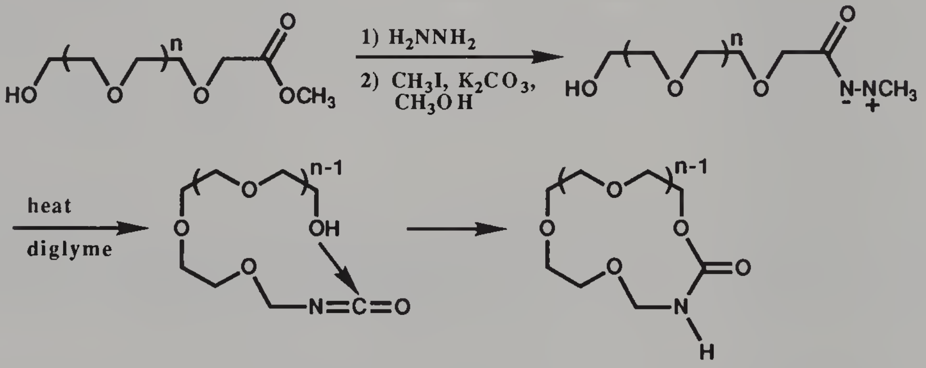


R_3 = H_2; O =

taining triethylene glycol gave diaza-18-crown-6 (the 2:2 adduct) rather than aza-9-crown-3. (This reaction will be discussed in Chapter VI.) The Okahara ring-closure reaction can work in the presence of other functional groups such as a bromomethyl or a pendant aminoalkyl substituent (Nakatsuji et al., 1988b). A similar process was carried out using the reaction of an alcohol in one arm with an acid in the other (R_3 = double-bonded O) to produce a monoazaester-crown in yields of 9–16% (Matsushima et al., 1986).

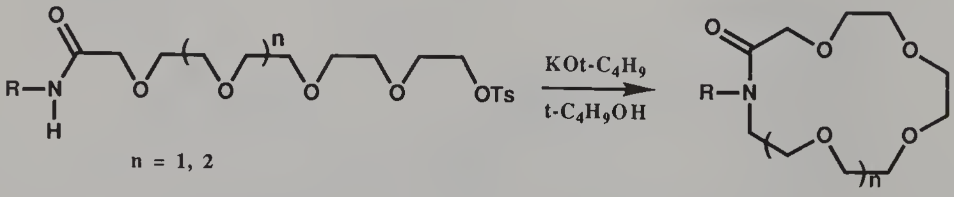
Urethane-containing crown compounds have been prepared (method B-2). These crowns are similar to the amide-containing crowns (Masuyama et al., 1985). The reaction proceeds by a thermal rearrangement of an amino amide to an isocyanate as shown. The ω-hydroxy group then adds to the isocyanate.

Method B-2



Some macrocyclic monoamides were prepared in yields of 7–12% by cyclizing the tosylate derivative of an ω-hydroxyamide (method B-3) (Nakatsuji et al., 1982). This method has not been developed by using other solvent or base conditions.

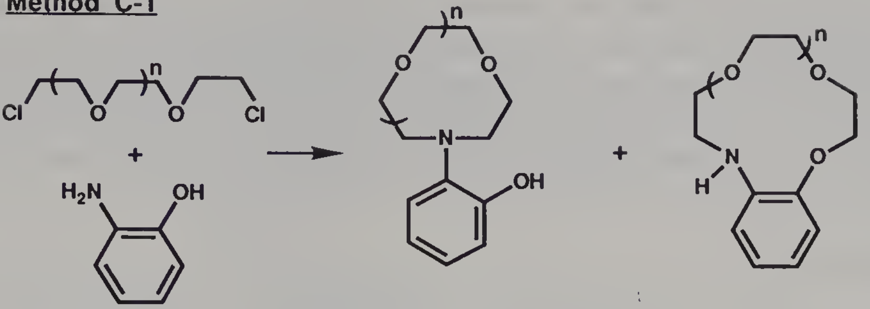
Method B-3



D. RING CLOSURE TO FORM A C—N—C LINKAGE FROM THE REACTION OF A PRIMARY AMINE OR AMIDE AND A DIHALIDE OR DITOSYLATE

Lockhart and coworkers prepared both *N*-phenyl-substituted and benzoaza-crowns by reacting 2-aminophenol with various dihalides (method C-1) (Lockhart and Thompson, 1977; Lockhart et al., 1973). When the reaction

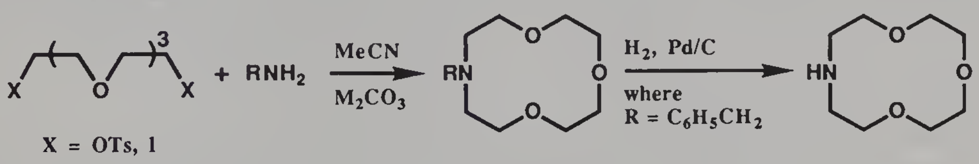
Method C-1



was carried out in water and $n = 2$, only the *N*-phenyl-substituted aza-crown was formed. In other solvents, such as DMF, and where $n > 2$, only the benzoaza-crown was formed.

Calverley and Dale (1981, 1982) treated various aliphatic and aromatic amines with the diiodide derivative of tetraethylene glycol to prepare *N*-alkyl(aryl)-substituted aza-12-crown-4 compounds (method C-2). The diiodide was prepared from the dichloride and sodium iodide in acetone.

Method C-2

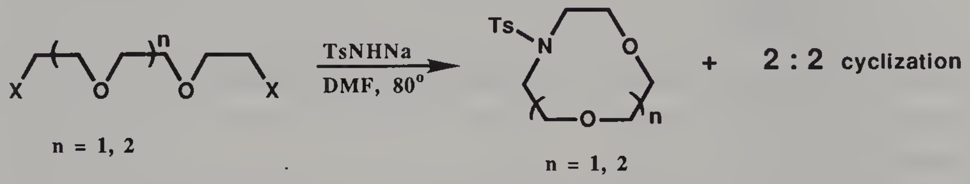


Recently, additional aza-12-crown-4 ligands have been prepared by the method C-2 process (Arnold et al., 1988; Sakamoto et al., 1986). Both aliphatic and aromatic amines were successful reactants with yields of 26–60%. Gokel and coworkers made some interesting observations concerning the formation of aza-12-crown-4 ligands. Product yields for the aza-12-crown-4 appeared to be subject to steric constraints. 4-Methoxyaniline reacted to give a 40% yield of the aza-12-crown-4, while 2-methoxyaniline gave only a 26% yield. It was also interesting that 2-methoxybenzylamine reacted to give nearly twice the yield of the substituted aza-12-crown-4 than did 2-methoxyaniline. Thus, the amine with a higher nucleophilicity apparently reacts the best (Arnold et al., 1988). It is important to note that aza-crowns with no substituent on the nitrogen atom can be alkylated to form the *N*-alkyl-substituted aza-crowns (Arnold et al., 1988; Sakamoto et al., 1986).

Diiodide derivatives of the larger oligoethylene glycols are more reactive in the formation of larger aza-crowns than the dichlorides (Sakamoto et al., 1986). The larger dichloro precursors needed to make the diiodides by the sodium iodide/acetone process are generally not available. On the other hand, the ditosylate derivatives of the available tetra- and pentaethylene glycols can be produced and reacted directly with the amine to form the aza-15-crown-5 and aza-18-crown-6 ligands. The ditosylates also can be converted to the more reactive diiodides by reaction with sodium iodide in acetone or acetonitrile.

p-Toluenesulfonamide can react with the dihalogen compounds to form *N*-tosylaza-crowns. A one-pot nucleophilic condensation in DMF of the dihalide and 2 eq of the sodium salt of tosylamide, acting both as nitrogen nucleophile and as the base, offers an inexpensive and practical route to the monoaza- and diaza-crowns (method C-3) (Bottino et al., 1988; Pappalardo et al., 1985).

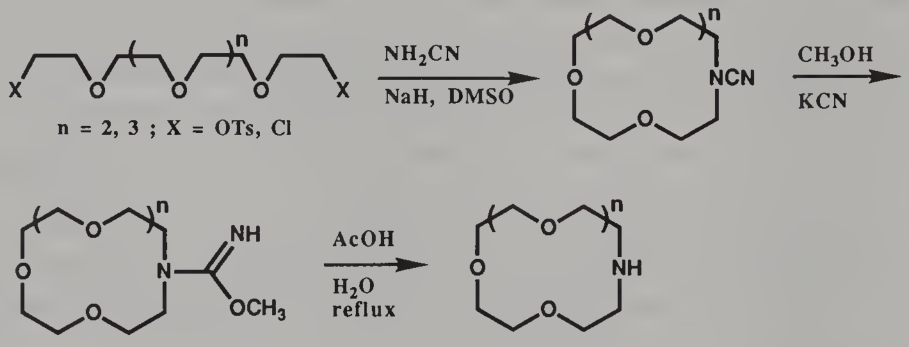
Method C-3



Treatment of 1,2-bis(2-iodoethoxy)ethane with the sodium salt of tosylamide gave the *N*-tosylaza-9-crown-3 (1:1 cyclization) and *N*,*N*′-ditosyldiaza-18-crown-6 (2:2 cyclization) in 25% and 5% yields, respectively. Using the corresponding dichloro starting material, yields of 32% (9-crown-3) and 15% (18-crown-6) were realized. Rasshofer and Vögtle (1978) isolated only the diaza-18-crown-6 cycloadduct. Bis[2-(2-bromoethoxy)ethyl]ether gave only the *N*-tosylaza-12-crown-4 (1:1 cyclization) product.

Okahara and coworkers used cyanamide instead of tosylamide to prepare some aza-crowns (method C-4) (Maeda et al., 1981a). The *N*-cyano group was converted to an imino ester that hydrolyzed to the unsubstituted aza-crown when treated with aqueous acetic acid.

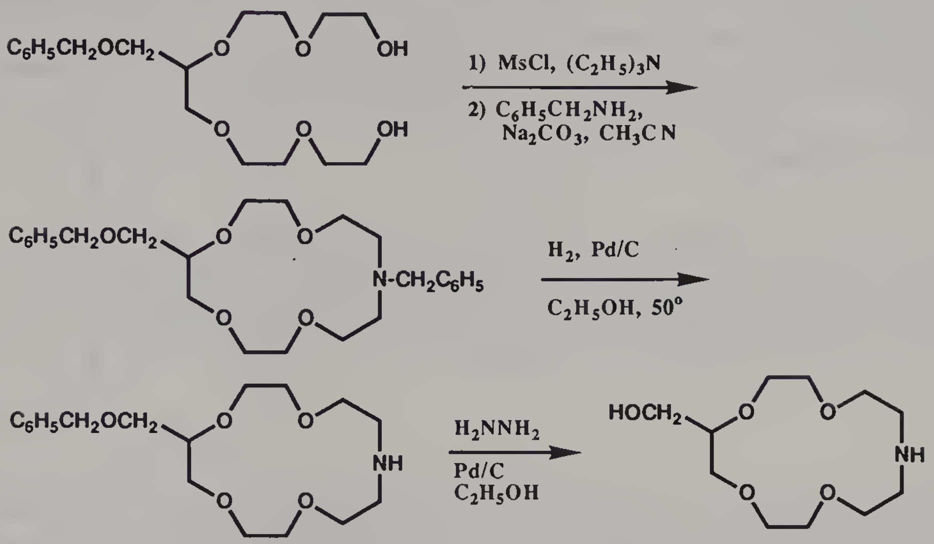
Method C-4



A more complicated diol was used by Bartsch and coworkers to prepare monoaza crowns with no substituent on the ring nitrogen atom and with a hydroxymethyl substituent on a macroring carbon atom (method C-5) (Son et al., 1984, 1985).

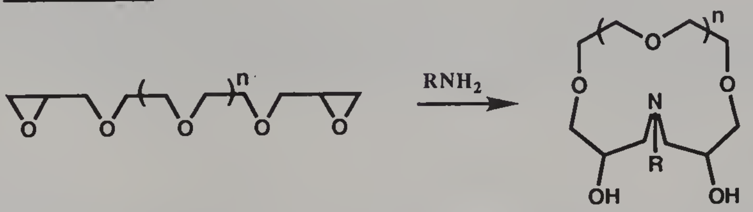
Functionalized monoaza-crown ethers are important intermediates for further transformations. The dihydroxyaza-crowns, where the hydroxy groups are attached to ring carbon atoms, were prepared by reacting a primary amine

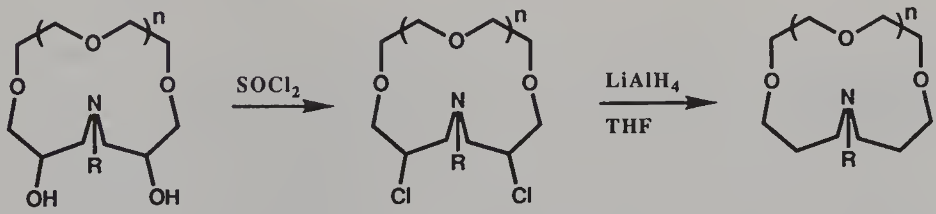
Method C-5



with an oligoethylene diglycidyl ether in protic solvents such as water or methanol (method C-6) (Kikui et al., 1984; Nippon Oils, 1984). These dihydroxy-substituted aza-crowns were reacted with thionyl chloride followed by lithium aluminum hydride to give the fully reduced aza-crowns (Nakatsuji et al., 1989). This is a viable process to prepare the aza-crowns containing propylene bridges between heteroatoms because amino glycols with propylene bridges are not readily available.

Method C-6

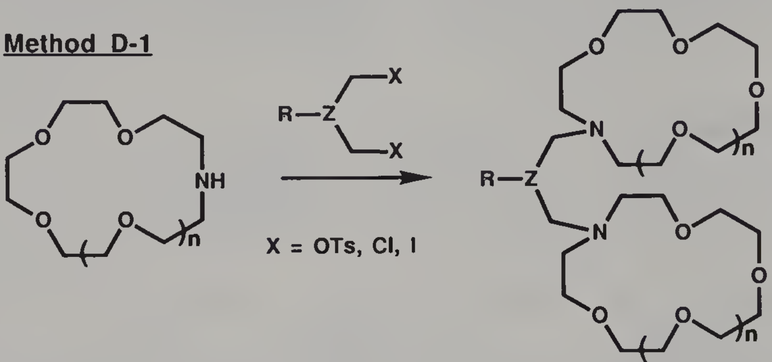




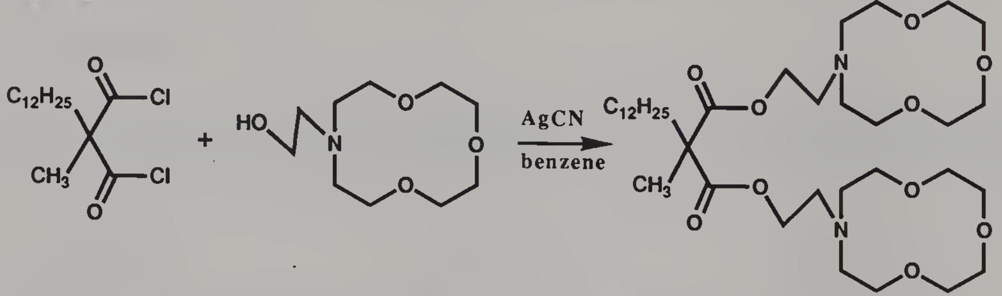
E. PREPARATION OF BIS(MONOAZA-CROWN) MACROCYCLES

Ligands containing two connected crown ethers can have higher cation-binding properties than the single macrocycles. These materials are usually prepared from the separate aza-crowns. Dihalide or ditosylate compounds have been used to bridge two monoaza-crowns to form these bis-crown ligands (method D-1) (Calverley and Dale, 1981; Sakamoto et al., 1986). In cases where the bridge between the two crowns is short (C_2H_4 or C_3H_6), the connection is carried out using the diacid dichloride followed by reduction with $LiAlH_4$ (Johnson et al., 1980). Bridged monoaza-crowns also were prepared by reacting a diacid dichloride with an *N*-(2-hydroxyethyl)aza-crown (method D-2) (Sakamoto et al., 1986, 1987), by the reaction of a monoaza-crown with formaldehyde in methanol followed by treatment with a cyclic urea derivative (method D-3) (Bogatskii et al., 1983), and by the biscyclization of *N*,*N*,*N'N'*-tetrakis(2-hydroxyethyl)ethylenediamine with 2 mol of triethylene glycol ditosylate (method D-4) (de Jong et al., 1983).

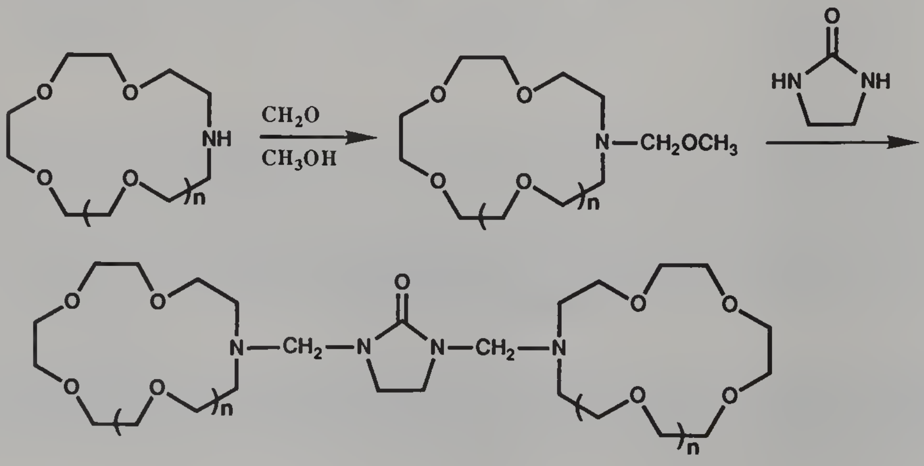
Method D-1



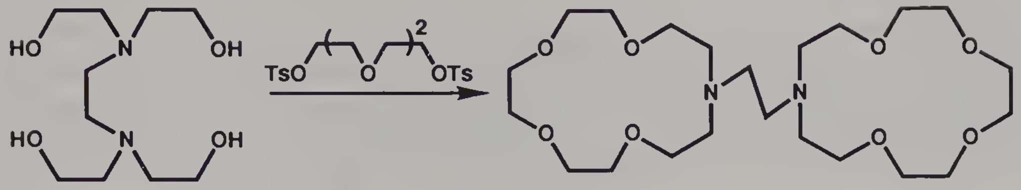
Method D-2



Method D-3

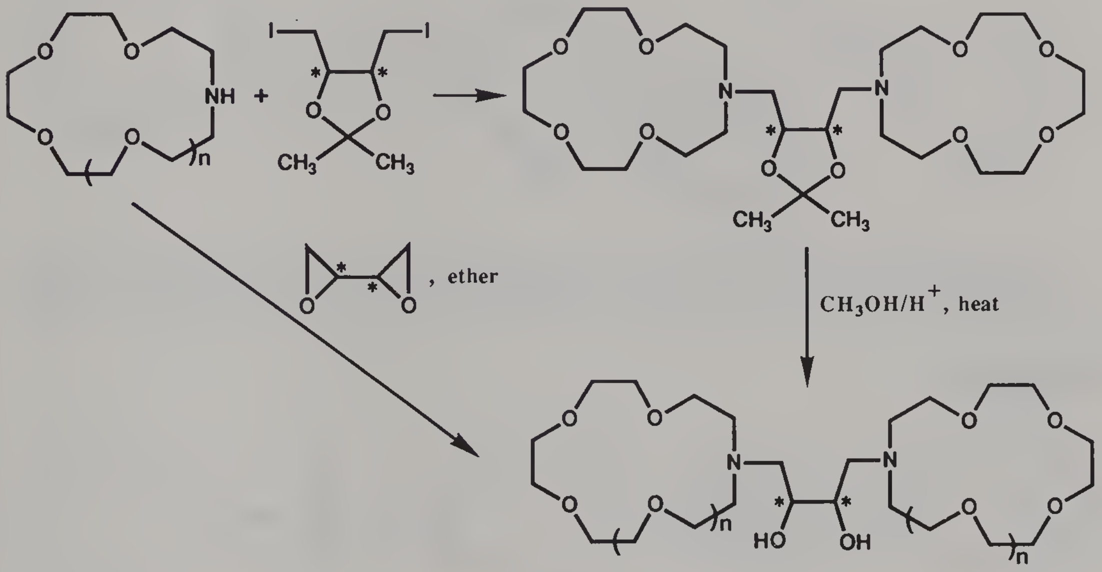


Method D-4



Interesting bis(aza-crown)-substituted chiral crown compounds have been prepared (Lukyanenko et al., 1986). The precursor bis(aza-crown)-substituted chiral diol was prepared by two pathways (method D-5). In the first pathway, two monoaza-crowns were connected by treatment with the isopropylidene-blocked chiral 1,4-diiodo-2,3-butanediol. The dioxolane was hydrolyzed by acidified methanol. In the second pathway, two aza-crown molecules were reacted with chiral 1,2-3,4-diepoxybutane to give the 1,4-bis(aza-crown)-substituted chiral 2,3-butanediol. The best results were obtained in the second pathway. This chiral diol was then reacted with the ditosylate derivatives of the appropriate oligoethylene glycol to give the bis(aza-crown)-substituted chiral crown compound.

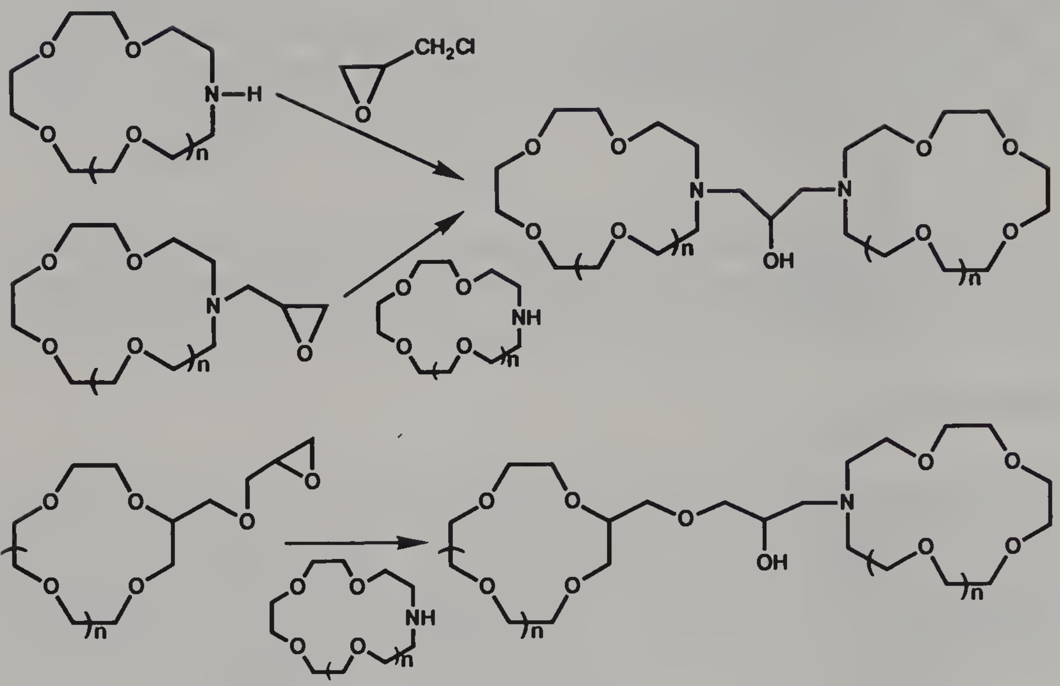
Method D-5



n = 1, 2

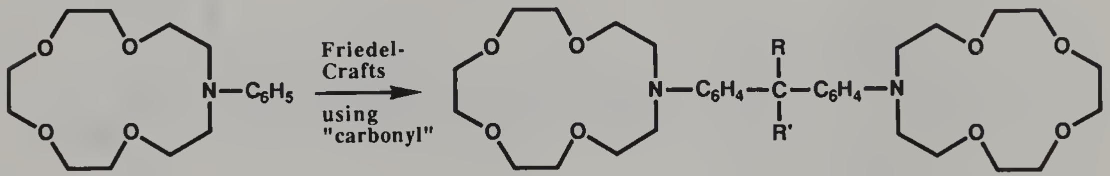
Epichlorohydrin, when treated with an excess of monoaza-crown, formed the bis(aza-crown) (method D-6) (Belohradsky et al., 1987b). The same bis macrocycle was prepared in a two-step process via an epoxymethyl-substituted aza-crown as shown. Crown-substituted aza-crowns containing an ether linkage were also prepared from the glycidyloxymethyl-substituted crown ethers (see method D-6).

Method D-6



N-Phenylaza-15-crown-5 was dimerized by a Friedel–Crafts type reaction using various carbonyl compounds (method D-7) (Dix and Vögtle, 1978).

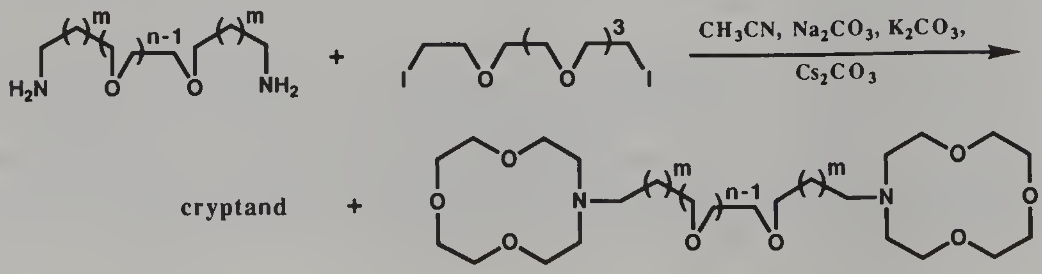
Method D-7



This process was also used to prepare tris(aza-crown)s.

Krakowiak and Bradshaw (1991) have observed that the reaction of certain diamines with the diiodide derivative of tetraethylene glycol gave the bis(aza-12-crown-4)s as by-products in the one-step synthesis of cryptands (method D-8). More work needs to be done on this interesting new one-step synthesis

Method D-8

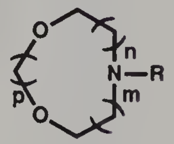


of the cryptands and bis(aza-12-crown-4)s before a mechanism can be determined.

Extensive tables of the monoaza-crown compounds follow. The tables are organized in order of increasing ring size and complexity of the substituent(s). Where possible, the preparative method is indicated so that one can see how the crown was made. References and yields are given for each compound.

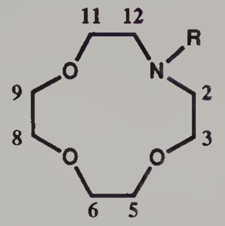
F. TABLES OF COMPOUNDS

TABLE 5.1. AZA-9,10 AND 13-CROWN-3 MACROCYCLES



R	m	n	p	Other Substituents	Methods (or from R = H)	Yield (%)	References
H	1	1	2		C-2		Sakamoto et al., 1986
Ts	1	1	2		C-3	25	Bottino et al., 1988
					C-3	25	Pappalardo et al., 1985
2-HO-5-NO_2-$C_6H_3CH_2$-	1	1	2		(H)	57	Katayama et al., 1985
$C_6H_5CH_2$-	1	1	2		C-2	31	Sakamoto et al., 1986
4-$CH_3OC_6H_4$-	1	1	2		C-2	13	Gatto and Gokel, 1984
					C-2	13	Gokel and Gatto, 1986
Ts	2	1	1		A-1	42	Krakowiak et al., 1988
Ts	2	2	1		A-1	32	Krakowiak et al., 1988
CH_3	1	1	6	5,10-$(O)_2$	A-5	41	Ninagawa et al., 1984

TABLE 5.2. AZA-12-CROWN-4 MACROCYCLES



R		Other Substituents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
H	H		C-2	95	Arnold et al., 1988
			C-2	85	Calverley and Dale, 1981, 1982
			C-2	85	Dale and Calverley, 1982
			A-1	42	Johnson et al., 1985
			A-3	3	Maeda et al., 1983a
			A-1	60	Pacey and Sasaki, 1987
			C-2	89	Sakamoto et al., 1986
			C-2	95	Schultz et al., 1985
			C-2	95	White et al., 1985a, 1987a
H	H	2,2,12,12-$(CH_3)_4$	A-3	7	Lai, 1985
H	H	3-C_8F_{17}	A-3	20	Okahara et al., 1982

TABLE 5.2. *(Continued)*

R		Other Substituents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
CH_3	CH_3		$(C_7H_5O_2)$	74	Calverley and Dale, 1982
			$(C_7H_5O_2)$	74	Dale and Calverley, 1982
			(H)	92	Johnson et al., 1985
C_2H_4Cl	$Cl(CH_2)_2$-		(C_2H_5O,a)	83 (salt)	Carroy et al., 1986
C_2H_4NO	$H_2NC(O)CH_2$-		C-2	24	Calverley and Dale, 1982
			C-2	24	Dale and Calverley, 1982
C_2H_5O,a	$HO(CH_2)_2$-		C-2	48	Calverley and Dale, 1982
			C-2	48	Dale and Calverley, 1982
			(H)	43	Maeda et al., 1983a
			C-2	32	Sakamoto et al., 1986
C_2H_5O,b	CH_3OCH_2-				Lukyanenko et al., 1990
C_3H_5O	glycidyl		(H)	78	Belohradsky et al., 1987a
$C_3H_5O_2$	$CH_3O_2CCH_2$-		C-2	22	Kataky et al., 1990

C_3H_6NO	$(CH_3)_2NC(O)$-	(H)	72	Kataky et al., 1990
C_3H_7O	$CH_3O(CH_2)_2$-	C-2	51	Calverley and Dale, 1982
		C-2	51	Dale and Calverley, 1982
		C-2	60	Schultz et al., 1985
C_3H_7O	$HO(CH_2)_3$-	C-2	56	Schultz et al., 1985
		C-2	56	White et al., 1985a
C_3H_7O	$CH_3CH(OH)CH_2$-	(H)	90	Zavada et al., 1989
$C_4H_7O_2$	$C_2H_5O_2CCH_2$-	C-2	30	Calverley and Dale, 1981, 1982
		C-2	30	Dale and Calverley, 1982
$C_4H_{10}N$	$(CH_3)_2N(CH_2)_2$-	C-2	21	Gokel, 1984
		C-2	21	Schultz et al., 1985
		C-2	21	White et al., 1985a
$C_5H_{11}O_2$	$CH_3(OCH_2CH_2)_2$-	(H)	66	Schultz et al., 1985
C_6H_5	C_6H_5	C-2	51	Calverley and Dale, 1982
		C-2	51	Calverley and Dale, 1981, 1982
C_6H_5O	2-HOC_6H_4-	C-1		Blackborow et al., 1975
		C-1		Lockhart et al., 1973
$C_7H_5O_2$	$C_6H_5O_2C$-	(C_7H_7)		Calverley and Dale, 1981, 1982
$C_7H_6NO_2$	2-$NO_2C_6H_4CH_2$-	(H)	41	Katayama et al., 1986a

TABLE 5.2. *(Continued)*

R					
Formula	Structure	Other Substituents	Methods (or from R = formula)	Yield (%)	References
			(H)	86	Schultz et al., 1985
			(H)	86	White et al., 1985a
$C_7H_6NO_3$	2-HO-5-$NO_2C_6H_3CH_2$-		(H)	71	Katayama et al., 1985, 1986a, 1986b
			(H)	93	Pacey and Sasaki, 1987
C_7H_7	$C_6H_5CH_2$-		C-2	54	Arnold et al., 1988
			C-2	54	Calverley and Dale, 1982
			C-2	54	Dale and Calverley, 1982
			A-1	63	Pacey and Sasaki, 1987
			C-2	40	Sakamoto et al., 1986
			C-2	53	Schultz et al., 1985
			C-2	53,54	White et al., 1985a, 1987a
C_7H_7O	2-$CH_3OC_6H_4$-		C-2	29	Gokel, 1984
			C-2	26	Schultz et al., 1985
			C-2	26	White et al., 1985a
C_7H_7O	4-$CH_3OC_6H_4$-		C-2	40	Schultz et al., 1985

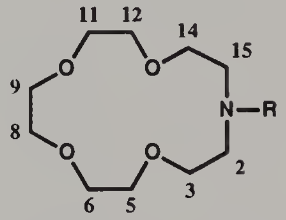
			C-2	40	White et al., 1985a
$C_7H_7O_2S$	Ts		C-3	35	Bottino et al., 1988
			A-1	6	Johnson et al., 1985
			C-2	31	Pappalardo et al., 1985
$C_7H_7O_2S$	Ts	$3,11\text{-}(O)_2$	I-2	7	Qin and Hu, 1984
C_7H_8N	$2\text{-}NH_2C_6H_4CH_2\text{-}$		$(C_7H_6NO_2)$	94	Katayama et al., 1986a
$C_7H_{14}NO_2$	4-morpholinyl- $CH_2CH(OH)CH_2\text{-}$		(H)	93	Belohradsky et al., 1987b
$C_7H_{15}O_3$	$CH_3(OCH_2CH_2)_3\text{-}$		(H)	52	Schultz et al., 1985
			(H)	52	White et al., 1985a, 1985b
C_8H_9O	$2\text{-}CH_3OC_6H_4CH_2\text{-}$		C-2	32	Gokel, 1984
			C-2	47	Schultz et al., 1985
			C-2	47	White et al., 1985a
$C_8H_{10}N_5O$	adenin-3-yl$CH_2CH(OH)CH_2\text{-}$		(C_3H_5O)		Holy et al., 1987
$C_8H_{10}N_5O$	adenin-7-yl$CH_2CH(OH)CH_2\text{-}$		(C_3H_5O)		Holy et al., 1987
$C_8H_{10}N_5O$	adenin-9-yl$CH_2CH(OH)CH_2\text{-}$		(C_3H_5O)	72	Holy et al., 1987
C_8H_{17}	C_8H_{17}		A-1	38	Nakatsuji et al., 1989
$C_9H_{19}O_4$	$CH_3(OCH_2CH_2)_4\text{-}$		(H)	54	Schultz et al., 1985
$C_{10}H_{21}O$	$C_8H_{17}O(CH_2)_2\text{-}$		A-1	43	Nakatsuji et al., 1989

TABLE 5.2. (*Continued*)

R		Other Substituents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
$C_{11}H_9O_3$	3-CH_3-7-HO-coumarin-8-CH_2-		(H)	43	Katayama et al., 1985
$C_{11}H_{21}O_4$	allyl(OCH_2CH_2)$_4$-		(H)	50	Schultz et al., 1985
			(H)	50	White et al., 1985a
$C_{11}H_{23}O$	$C_8H_{17}O(CH_2)_3$-		A-1	51	Nakatsuji et al., 1989
$C_{11}H_{23}O_5$	$CH_3(OCH_2CH_2)_5$-		(H)	69	Arnold et al., 1988
$C_{12}H_8N_3O_2$	4-(4-$NO_2C_6H_4N{=}N$)C_6H_4-		(C_6H_5)	51	Calverley and Dale, 1982
			(C_6H_5)	51	Dale and Calverley, 1982
$C_{12}H_{10}P$	$(C_6H_5)_2P$-		(H)	99	McLain, 1986
$C_{12}H_{23}O_6$	2-(12-crown-4-)- $CH_2OCH_2CH(OH)CH_2$-		D-6b	91	Belohradsky et al., 1987b

$C_{12}H_{25}$	$C_{12}H_{25}$	C-2	50	Sakamoto et al., 1986
$C_{13}H_9N_4O_6$	2,4,6-$(NO_2)_3C_6H_2$-2-$NHC_6H_4CH_2$-	(C_7H_8N)	53	Katayama et al., 1986a
$C_{13}H_{23}N_2$	3,5-$(C_3H_7)_2$-4-C_2H_5-pyrazol-2$(CH_2)_2$-	A-1		Ivanov et al., 1990
$C_{14}H_{14}P$	$(C_6H_5)_2P(CH_2)_2$-	(H)	41	Carroy et al., 1986
$C_{14}H_{27}O_7$	2-(15-crown-5)-$CH_2OCH_2CH(OH)CH_2$-	D-6	97	Belohradsky et al., 1987b
$C_{16}H_{31}O_8$	2-(18-crown-6)-$CH_2OCH_2CH(OH)CH_2$-	D-6	74	Belohradsky et al., 1987b
$C_{17}H_{35}O_8$	$CH_3(OCH_2CH_2)_8$-	(H)	69	Arnold et al., 1988
$C_{15}H_{27}N_2$	3,5-$(CH_3)_2$-4-C_8H_{17}pyrazolyl-2-$(CH_2)_2$-	A-1		Ivanov et al., 1990
$C_{18}H_{35}O_9$	2-(21-crown-7)-$CH_2OCH_2CH(OH)CH_2$-	D-6	74	Belohradsky et al., 1987b
$C_{20}H_{39}O_{10}$	2-(24-crown-8)-$CH_2OCH_2CH(OH)CH_2$-	D-6	79	Belohradsky et al., 1987b

TABLE 5.3. AZA-15-CROWN-5 MACROCYCLES



R		Other	Method	Yield	References
Formula	Structure	Substituents	(or from R = formula)	(%)	
H	H		A-3	46	Bogatskii et al., 1985b
			A-1	76 (salt)	Dix and Vögtle, 1981
			A-1	98	Gokel et al., 1987
			($C_7H_7O_2S$)	92	Johnson et al., 1979
			C-4	100	Maeda et al., 1981a
			A-3	37, 1-77	Maeda et al., 1981b, 1983a
			A-3	37	Okahara et al., 1982
			C-2	88	Sakamoto et al., 1986
			C-2	98	Schultz et al., 1985
H	H	3-CH_3	A-3	26	Maeda et al., 1983a

H	H	3,14-$(CH_3)_2$	A-3	33,26	Maeda et al., 1981b, 1983a
			A-3	33	Okahara et al., 1982
H	H	2,2,15,15-$(CH_3)_4$	A-3	60	Lai, 1985
			A-3	47	Sosnovsky and Lukszo, 1985
H	H	2-C_2H_5	A-3	46	Maeda et al., 1983a
H	H	2,2,15-$(CH_3)_3$; 15-C_2H_5	A-3	55	Lai, 1985
H	H	2,2-$(CH_3)_2$; 15,15-$(CH_2)_5$	A-3	49	Lai, 1985
H	H	9-CH_2OH	C-5	66	Son et al., 1984
H	H	8,9-$(OH)_2$(chiral)	A-4	86	Lukyanenko et al., 1988
H	H	8-CH_3,8-CH_2Br	A-3	37	Wakita et al., 1990
H	H	2,3-cyclohexano	A-3	52	Maeda et al., 1983a
H	H	3-C_6H_5	A-3	33	Maeda et al., 1983a
H	H	3,14-$(C_6H_5)_2$	A-3	32	Okahara et al., 1982
H	H	8-$CH_2OCH_2C_6H_5$	C-5	76	Son et al., 1984
H	H	3,14-$(C_8H_{17})_2$	A-3		Okahara et al., 1982
H	H	3-$C_{10}H_{21}$	A-3	41	Okahara et al., 1982
O	O	2,2,15,15-$(CH_3)_4$	(H)		Sosnovsky and Lukszo, 1985
			(H)	31	Sosnovsky et al., 1987

TABLE 5.3. (*Continued*)

R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
COCl	ClC(O)-		(H)	78	Bogatskii et al., 1985a
CN	CN		C-4	34	Maeda et al., 1981a
			C-4	33	Ajinomoto, 1983
$CNaS_2$	NaSC(S)-		(H)	68	Granell et al., 1990
CH_3,a	CH_3		B-1	45	Kuo et al., 1978
			(H)	92	Johnson et al., 1979
			(H)	37	Schultz et al., 1982a, 1982b, 1985
CH_3	CH_3	8-CH_3,8-CH_2Br	A-1	30	Wakita et al., 1990
CH_4O_3P	$(HO)_2P(O)CH_2$-		(H)		Tazaki et al., 1982
C_2H_2ClO	$ClCH_2C(O)$-		(H)	98	McLain, 1986
			(H)	90	Newkome and Marston, 1985
C_2H_3O	$CH_3C(O)$-		(H)	84	Johnson et al., 1979
C_2H_4Cl	$Cl(CH_2)_2$-		(C_2H_5O,a)		Newkome and Marston, 1985
C_2H_4NO,a	$CH_3OC(NH)$-		C-4	95	Maeda et al., 1981a
C_2H_4NO,b	$CH_3NHC(O)$-		(CClO)	90	Bogatskii et al., 1985a

C_2H_4NO,c	$NH_2CH_2C(O)$-	($C_{10}H_{10}NO_3$)	81	Voronina et al., 1988
		($C_{10}H_{10}NO_3$)	100	Zinic et al., 1990
C_2H_4NO,d	$HC(O)NHCH_2$-	(C_2H_5O,b)	96	Lukyanenko and Pastushok, 1989
C_2H_5	C_2H_5	B-1	75	Kuo et al., 1978
		(C_2H_3O)	77	Johnson et al., 1979
C_2H_5O,a	$HO(CH_2)_2$-	(H)	41	Maeda et al.,1983a
		(H)		Masuyama et al., 1981
		(H)	40	Newkome and Marston, 1985
		($C_7H_{13}O_2$)	94	Newkome and Marston, 1985
		C-2	19	Sakamato et al., 1986
C_2H_5O,b	CH_3OCH_2-	(H)	98	Bogatskii et al., 1983
				Lukyanenko and Pastushok, 1989
C_3H_4ClO	$Cl(CH_2)_2C(O)$-	(H)	99	McLain, 1986
C_3H_5	allyl	A-1		Chen et al., 1989
		B-1	48	Kuo et al., 1978
		A-1	61	Schultz et al., 1981, 1985
C_3H_5O	glycidyl	(H)	75	Belohradsky et al., 1987a
C_3H_6N	aziridinyl-CH_2-	(C_2H_5O,b)	94	Bogatskii et al., 1983
C_3H_6NO,a	$H_2NCH(CH_3)C(O)$-	($C_8H_{14}NO_3$)	90	Chadwick et al., 1984

TABLE 5.3. (*Continued*)

R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
C_3H_6NO	$H_2N(CH_2)_2C(O)$-		($C_{11}H_{12}NO_3$,a)	97 (salt)	Voronina et al., 1988
C_3H_6NO	$CH_3C(O)NHCH_2$-		(C_2H_5O,b)	98	Lukyanenko and Pastushok, 1989
C_3H_7O	$CH_3O(CH_2)_2$-		A-1	69	Gokel, 1984
			A-1	55	Schultz et al., 1982a, 1985
C_3H_7O	$CH_3CH(OH)CH_2$-		(H)	88	Zavada et al., 1989
C_3H_7S	$CH_3S(CH_2)_2$-		(H)	40	Hanlon et al., 1989
C_3H_7OS	$CH_3S(O)(CH_2)_2$-		(C_3H_7S)	56	Hanlon et al., 1989
C_3H_8N	$H_2NCH(CH_3)CH_2$-		(C_3H_6NO,a)	98	Chadwick et al., 1984
C_4H_6NO	CH_2=$CHC(O)NHCH_2$-		(C_2H_5O,b)	93	Lukyanenko and Pastushok, 1989
C_4H_8NO	$H_2N(CH_2)_3C(O)$-				Karaseva et al., 1990
			($C_{12}H_{14}NO_3$,b)	86	Voronina et al., 1988
$C_4H_8NO_2$	$O_2NC(CH_3)_2CH_2$-		(C_2H_5O,b)	89	Bogatskii et al., 1983
			B-1	58	Kuo et al., 1978
C_4H_9	n-C_4H_9		A-1	65	Schultz et al., 1981, 1985
C_4H_9	t-C_4H_9		A-1	28	Schultz et al., 1985

$C_4H_9O_2$, a	$H(OCH_2CH_2)_2$-		(H)		Masuyama et al., 1981
$C_4H_9O_2$	$H(OCH_2CH_2)_2$-	8-CH_2OH	($C_{11}H_{15}O_2$)	93	Son et al., 1985
$C_4H_{10}N$	$CH_3NHCH(CH_3)CH_2$-		($C_{11}H_{12}NO_3$, b)	60	Chadwick et al., 1984
			($C_6H_{10}NO_3$)	87	Chadwick et al., 1984
$C_5H_{10}NO$	$CH_3C(O)NHCH(CH_3)CH_2$-		(C_3H_8N)	84	Chadwick et al., 1984
$C_5H_{11}O_2$	$CH_3(OCH_2CH_2)_2$-		A-1	47	Schultz et al., 1981, 1982a, 1985
			A-1	47	Gokel, 1984
C_6H_4NO	4-NOC_6H_4-		(C_6H_5)	83	Dix and Vögtle, 1978, 1980
C_6H_5	C_6H_5		A-1	16	Dix and Vögtle, 1978, 1980
C_6H_5	C_6H_5	3-(O)	B-1	9	Matsushima et al., 1986
C_6H_6N	4-$NH_2C_6H_4$-		(C_6H_4NO)	87	Dix and Vögtle, 1978, 1980
$C_6H_6NO_2S$	4-$NH_2C_6H_4SO_2$-		(H)	64	Bogatskii et al., 1986
$C_6H_{10}NO_3$	$C_2H_5O_2CNHCH(CH_3)C(O)$-		(H)	76	Chadwick et al., 1984
$C_6H_{11}O$	$C_5H_{11}C(O)$-		(H)	70	Nakatsuji et al., 1982
$C_6H_{11}O_2$	t-$C_4H_9O_2CCH_2$-		(H)	66	Schultz et al., 1985
$C_6H_{11}N_2O_2$	$H_2N(CH_2)_3C(O)NHCH_2C(O)$-		($C_{14}H_{13}N_2O_4$)	81 (salt)	Voronina et al., 1988
C_6H_{13}	C_6H_{13}		B-1	75	Kuo et al., 1980
C_6H_{13}	C_6H_{13}	2-(O)	B-3	10	Nakatsuji et al., 1982
C_6H_{13}	C_6H_{13}	3-(O)	B-1	12	Matsushima et al., 1986

TABLE 5.3. *(Continued)*

R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
$C_6H_{13}O_3$	$H(OCH_2CH_2)_3$-		(H)		Masuyama et al., 1981
C_7H_5O	4-$HC(O)C_6H_4$-		(C_6H_5)	75	Dix and Vögtle, 1978, 1980
$C_7H_5N_2O_6$	2,6-$(NO_2)_2$-4-$CH_3C_6H_2$-		(H)	77	Ivanov and Fedorova, 1986
C_7H_6Cl	2-$ClC_6H_4CH_2$-		(H)	72	Gustowski et al., 1987
C_7H_6Cl	4-$ClC_6H_4CH_2$-		(H)	80	Gustowski et al., 1987
$C_7H_6NO_2$,a	2-$NO_2C_6H_4CH_2$-		(H)	35,96	Gustowski et al.,1984, 1987
			(H)	98	Katayama et al., 1986c
			(H)	35	Schultz et al., 1985
$C_7H_6NO_2$	4-$NO_2C_6H_4CH_2$-		(H)	22,85	Gustowski et al., 1984, 1987
			(C_2H_5O,b)		Lukyanenko et al., 1990
			(H)	22	Schultz et al., 1985
$C_7H_6NO_3$	2-HO-5-$NO_2C_6H_3CH_2$-		(H)	91	Katayama et al., 1985
			(H)	91	Nakamura et al., 1981
C_7H_7	$C_6H_5CH_2$-		A-1	46	Gokel et al., 1987
			A-1	46	Hanlon et al., 1989

			(H)		Johnson et al., 1979
			C-2		Sakamoto et al., 1986
			A-1	38,46	Schultz et al., 1981, 1985
C_7H_7	$C_6H_5CH_2$-	8-$CH_2OCH_2C_6H_5$	C-5	51	Son et al., 1984
C_7H_7	2-$CH_3OC_6H_4$-		A-1	38	Schultz et al., 1985
C_7H_7O,a	4-$CH_3OC_6H_4$-		A-1	30	Schultz et al., 1985
C_7H_7O,b	2-$HOC_6H_4CH_2$-		($C_9H_9O_2$,a)	55	Dix and Vögtle, 1981
			(C_2H_5O,b)		Lukyanenko et al., 1990
$C_7H_7O_2S$	Ts		A-1	44	Johnson et al., 1979
$C_7H_7O_2S$	Ts	3,14-$(O)_2$	I-2	30	Qin and Hu, 1984
C_7H_8N	2-$NH_2C_6H_4CH_2$-		($C_7H_6NO_2$,a)	95	Katayama et al., 1986c
$C_7H_{13}O_2$	THP-O-$(CH_2)_2$-		A-1	44	Newkome and Marston, 1985
			(H)	62	Newkome and Marston, 1985
$C_7H_{14}NO_2$	4-morpholinyl- $CH_2CH(OH)CH_2$-		(H)	96	Belohradsky et al., 1987b
$C_7H_{15}O_3$	$CH_3(OCH_2CH_2)_3$-		(H)	34	Gokel, 1984
			A-1		Schultz et al., 1982a
			(H)	34	Schultz et al., 1985
C_8H_6N	2-$CNC_6H_4CH_2$-		(H)	82	Gustowski et al., 1987
C_8H_6N	4-$CNC_6H_4CH_2$-		(H)	82	Gustowski et al., 1987

TABLE 5.3. (*Continued*)

R Formula	Structure	Other Substituents	Method (or from R = formula)	Yield (%)	References
$C_8H_7NO_2$	2-HO-5-HC(O)$C_6H_3CH_2$-		(C_2H_5O,b)		Lukyanenko et al., 1990
C_8H_8NO	$C_6H_5CH_2NHC(O)$-		(COCl)	90	Bogatskii et al., 1985a
C_8H_8NO	$C_6H_5C(O)NHCH_2$-		(C_2H_5O,b)	85	Lukyanenko and Pastushok, 1989
C_8H_9O	2-$CH_3OC_6H_4CH_2$-		A-1	40	Gustowski et al., 1987
			A-1	40	Shultz et al., 1985
C_8H_9O	4-$CH_3OC_6H_4CH_2$-		(H)	83	Gustowski et al., 1987
C_8H_9O	2-HO-5-$CH_3C_6H_3CH_2$-		(C_2H_5O,b)		Lukyanenko et al., 1990
C_8H_9S	$C_6H_5S(CH_2)_2$-		(H)	36	Hanlon et al., 1989
$C_8H_{10}N_5O$	adenin-3-yl-$CH_2CH(OH)CH_2$-		(C_3H_5O)		Holy et al., 1987
$C_8H_{10}N_5O$	adenin-7-yl-$CH_2CH(OH)CH_2$-		(C_3H_5O)		Holy et al., 1987
$C_8H_{10}N_5O$	adenin-9-yl-$CH_2CH(OH)CH_2$-		(C_3H_5O)	54	Holy et al., 1987
$C_8H_{14}NO_3$	t-$C_4H_9O_2CNHCH(CH_3)C(O)$-		(H)	80	Chadwick et al., 1984
C_8H_{17}	C_8H_{17}		B-1	90	Kuo et al., 1980
C_8H_{17}	C_8H_{17}	8-CH_3,8-CH_2Br	(H)		Masuyama et al., 1981
			(H)		Wakita et al., 1990

$C_8H_{17}O$	$C_6H_{13}CH(OH)CH_2$-	(H)	86	Inokuma et al., 1988b
$C_9H_5N_4O_2S$	5-NO_2-2-thiazalyl-4-N=NC_6H_4-	(C_6H_5)	21	Dix and Vögtle, 1980
$C_9H_9O_2$,a	2-$CH_3CO_2C_6H_4CH_2$-	(H)		Dix and Vögtle, 1981
$C_9H_9O_2$,b	2-$HOC_6H_4(CH_2)_2C(O)$-	(H)	84	Katayama et al., 1986a
$C_9H_{10}NO$	$C_6H_5CH(CH_3)NHC(O)$-	(COCl)	87	Bogatskii et al., 1985a
$C_9H_{10}NO$	$CH_3C(O)N(C_6H_5)CH_2$-	(C_2H_5O,b)	47	Lukyanenko and Pastushok, 1989
$C_9H_{11}O$,a	2-$HOC_6H_4(CH_2)_3$-	($C_9H_9O_2$,b)	62	Katayama et al., 1986a
$C_9H_{11}O$,b	3,5-$(CH_3)_2$-4-$HOC_6H_2CH_2$-	(C_2H_5O,b)	97	Bogatskii et al., 1983
$C_9H_{17}NO$	4[N(O)-2,2,6,6-$(CH_3)_4$]-piperdinyl-	A-3		Sosnovsky and Lukszo, 1985
		A-3	45	Sosnovsky et al., 1987
$C_9H_{19}O_2$	$C_6H_{13}OCH_2CH(OH)CH_2$-	(H)	85	Inokuma et al., 1988b
$C_9H_{19}O_4$	$CH_3(OCH_2CH_2)_4$-	(H)	55	Gokel, 1984
		(H)	55	Schultz et al., 1982b, 1985
$C_9H_{21}O_3Si$	$(C_2H_5O)_3Si(CH_2)_3$-	(C_3H_5)		Chen et al., 1989
$C_{10}H_5O_2$	1,4-naphthoquinonyl	(H)	42	Dix and Vögtle, 1981
$C_{10}H_{10}NO_3$	$C_6H_5CH_2O_2CNHCH_2C(O)$-	(H)		Voronina et al., 1988
$C_{10}H_{13}O_2$	$C_6H_5(OCH_2CH_2)_2$-	($C_4H_9O_2$,a)	30	He et al., 1986
$C_{10}H_{21}$	$C_{10}H_{21}$	B-1	82	Kuo et al., 1980
$C_{10}H_{21}O$,a	$C_8H_{17}O(CH_2)_2$-	(H)	71	Masuyama et al., 1983

TABLE 5.3. (*Continued*)

R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
$C_{10}H_{21}O$,b	$C_8H_{17}CH(OH)CH_2$-		(H)	86	Inokuma et al., 1988b
$C_{10}H_{21}O$	$C_8H_{17}O(CH_2)_2$-	8-CH_3;8-CH_2Br	(H)	67	Wakita et al., 1990
$C_{11}H_9O_3$	3-CH_3-7-HO-coumarin-8-CH_2-		(H)	47	Katayama et al., 1985
			(H)		Nishida et al., 1982
$C_{11}H_{10}NO_4$	$CH_3O_2CCH_2NHC(O)C_6H_4C(O)$-		(H)	45	Ganin, et al., 1987
$C_{11}H_{12}NO_3$,a	$C_6H_5CH_2O_2CNH(CH_2)_2C(O)$-		(H)		Voronina et al., 1988
$C_{11}H_{12}NO_3$,b	$C_6H_5CH_2O_2CNHCH(CH_3)C(O)$-		(H)	99	Chadwick et al., 1984
$C_{11}H_{12}NO_3$	$CH_3O_2CCH(C_6H_5)NHCH_2C(O)$-		(C_2H_2ClO)	55	Zinic et al., 1990
$C_{11}H_{15}O_2$	$C_6H_5CH_2$- $(OCH_2CH_2)_2$-	8-$CH_2OCH_2C_6H_5$	(H)	76	Son et al., 1985
$C_{11}H_{21}$	CH_2=$CH(CH_2)_9$-		A-1	34	Chen et al., 1989
$C_{11}H_{23}O$	$CH_3OCH(C_8H_{17})CH_2$-		($C_{10}H_{21}O$,b)	68	Inokuma et al., 1988a
$C_{11}H_{23}O_2$	$C_8H_{17}OCH_2CH(OH)CH_2$-		(H)	87	Inokuma et al., 1988b
$C_{11}H_{23}O_5$	$CH_3(OCH_2CH_2)_5$-		(H)	78	Shultz et al., 1982b, 1985
			(H)	26	Yoo et al., 1989

$C_{12}H_8NO$	$4\text{-}[4\text{-}O{=}C_6H_4{=}N]C_6H_4\text{-}$	(C_6H_6N)	91	Dix and Vögtle, 1980
$C_{12}H_8N_2O_3SNa$	$4\text{-}NaO_3SC_6H_4N{=}NC_6H_4\text{-}$	(C_6H_5)		Dix and Vögtle, 1978
$C_{12}H_8N_3O_2$	$3\text{-}NO_2C_6H_4N{=}NC_6H_4\text{-}$	(C_6H_5)		Dix and Vögtle, 1978
$C_{12}H_8N_3O_2$	$4\text{-}NO_2C_6H_4N{=}NC_6H_4\text{-}$	(C_6H_5)		Dix and Vögtle, 1978
$C_{12}H_9N_2$	$C_6H_5N{=}NC_6H_4\text{-}$	(C_6H_5)		Dix and Vögtle, 1978
$C_{12}H_{10}P$	$(C_6H_5)_2P\text{-}$	(H)	98	McLain, 1986
$C_{12}H_{12}NO_4$	$(D,L)\text{-}CH_3O_2CCH(CH_3)NHC(O)$ $C_6H_4C(O)\text{-}$	(H)	47	Ganin et al., 1987
$C_{12}H_{14}NO$	piperidinyl-4-$C(O)C_6H_4$-	$(C_{13}H_8NO_4)$		Dix et al., 1980
$C_{12}H_{14}NO_3$, a	$C_2H_5OC_2H_4NHC(O)C_6H_4C(O)\text{-}$	(H)	58	Ganin et al., 1987
$C_{12}H_{14}NO_3$, b	$C_6H_5CH_2O_2CNH(CH_2)_3C(O)\text{-}$	(H)		Voronina et al., 1988
$C_{12}H_{23}O_6$	2-(12-crown-4)- $CH_2OCH_2CH(OH)CH_2$-	D-6b	92	Belohradsky et al., 1987b
$C_{12}H_{25}$	$C_{12}H_{25}$	B-1	67	Kuo et al., 1980
		C-2	54	Sakamoto et al., 1986
$C_{12}H_{25}O$	$C_{10}H_{21}CH(OH)CH_2\text{-}$	(H)	87	Inokuma et al., 1988b
$C_{12}H_{25}O$	$C_{12}H_{25}O$	(H)	62	Devinsky et al., 1990
$C_{12}H_{25}O_2$	$C_8H_{17}(OCH_2CH_2)_2\text{-}$	(H)	60	Masuyama et al., 1983
$C_{12}H_{25}O_2$	$C_8H_{17}(OCH_2CH_2)_2\text{-}$ 8-CH_3;8-CH_2Br	(H)	47	Wakita et al., 1990
$C_{13}H_6N_2O_5$	$2,4\text{-}(NO_2)_2\text{-}6\text{-}C_6H_2C(O)C_6H_4\text{-}$	(H)	84	Ivanov and Fedorova, 1986

TABLE 5.3. *(Continued)*

R					
Formula	Structure	Other Substituents	Method (or from R = formula)	Yield (%)	References
$C_{13}H_7N_4O_2S$	3-NO_2-5-benzoisothiazolyl-4-N=NC_6H_4-		(C_6H_5)	15	Dix and Vögtle, 1980
$C_{13}H_8NO_4$	4-$NO_2C_6H_4OC(O)C_6H_4$-				Dix et al., 1980
$C_{13}H_8N_2O_2Na$	2-$NaO_2CC_6H_4N$=NC_6H_4-		(C_6H_5)		Dix and Vögtle, 1978
$C_{13}H_9N_4O_6$	2,4,6-$(NO_2)_3C_6H_2NHC_6H_4CH_2$-		(C_7H_8N)	48	Katayama et al., 1986c
$C_{13}H_{12}P$	$(C_6H_5)_2PCH_2$-		(H)	98	McLain, 1986
$C_{13}H_{14}NO$	2,2,3-trimethylindolenine		(H)		Inouye et al., 1990
$C_{13}H_{23}N_2$	3,5-$(C_3H_7)_2$-4-C_2H_5-pyrazol-2-$(CH_2)_2$-		A-1		Ivanov et al., 1990
$C_{13}H_{27}O_2$	$CH_3O(CH_2)_2OCH(C_8H_{17})CH_2$-		($C_{10}H_{21}O$,b)	73	Inokuma et al., 1988a
$C_{13}H_{28}$	CH_3, $C_{12}H_{25}$		(CH_3,a)		Devinsky et al., 1990
$C_{14}H_6ClO_2$	8-chloroanthraquinonyl		(H)	12	Dix and Vögtle, 1980
$C_{14}H_9NO_2Br$	4-$BrC_6H_4NHC(O)C_6H_4C(O)$-		(H)	55	Ganin et al., 1987
$C_{14}H_9NO_2Cl$	4-$ClC_6H_4NHC(O)C_6H_4C(O)$-		(H)	62	Ganin et al., 1987
$C_{14}H_9N_2O_4$	2,4-$(NO_2)_2C_6H_3$-4-CH=CHC_6H_4-		(C_7H_5O)	46	Dix and Vögtle, 1980
$C_{14}H_9N_4S$	3-C_6H_5-1,2,4-(thiazadiazol-5-yl)N=N-C_6H_4-		(C_6H_5)	71	Dix and Vögtle, 1980

$C_{14}H_9O_2$	2-$C_6H_5C(O)C_6H_4C(O)$-			Malinovski et al., 1990
$C_{14}H_{10}NO_2$	$C_6H_5NHC(O)C_6H_4C(O)$-	(H)	74	Ganin et al., 1987
$C_{14}H_{12}PO$	$(C_6H_5)_2PCH_2C(O)$-	(C_2H_2ClO)	60	McLain, 1986
$C_{14}H_{13}N$	N-CH_3-4-pyridinyl-4-CH=CHC_6H_4-	(C_7H_5O)	78 (salt)	Dix and Vögtle, 1980
$C_{14}H_{13}N_2O_4$	phthalimidyl-$(CH_2)_3C(O)NHCH_2C(O)$-	(C_2H_4NO,c)	99	Voronina et al., 1988
$C_{14}H_{14}P$	$(C_6H_5)_2P(CH_2)_2$-	($C_{14}H_{12}PO$)	98	McLain, 1986
$C_{14}H_{17}O_5$	2-[CH_3-4,6-O-C_6H_5CH-2-deoxy-L,D-altropyranosidyl]		32	Toth et al., 1987
$C_{14}H_{17}O_5$	3-[CH_3-4,6-O-C_6H_5CH-3-deoxy-L,D-glycopyranosidyl]		27	Toth et al., 1987
$C_{14}H_{27}O_7$	2-(15-crown-5)-$CH_2OCH_2CH(OH)CH_2$-	D-6b	81	Belohradsky et al., 1987b
$C_{14}H_{29}O$	$C_{12}H_{25}O(CH_2)_2$-	(H)	60	Masuyama et al., 1983
$C_{14}H_{29}O_3$	$C_8H_{17}(OCH_2CH_2)_3$-	(H)	61	Masuyama et al., 1983
$C_{14}H_{29}O_3$	$C_8H_{17}(OCH_2CH_2)_3$- 8-CH_3;8-CH_2Br	(H)	42	Wakita et al., 1990
$C_{15}H_9O_4$	2,3-$(HO)_2$anthraquinonyl-CH_2-		35	Katayama et al., 1985
$C_{15}H_{11}$	9-anthraceneCH_2-	(H)		Silva and Silva, 1986
$C_{15}H_{13}N_2O_2$	4-$C_2H_5O_2CC_6H_4N$=NC_6H_4-			Dix and Vögtle, 1978
$C_{15}H_{14}N_3O_3$	4-$NO_2C_6H_4N$=N-2-$HOC_6H_3(CH_2)_3$-	($C_9H_{11}O$,a)	49	Katayama et al., 1986a

TABLE 5.3. (*Continued*)

R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
$C_{15}H_{14}PO$	$(C_6H_5)_2P(CH_2)_2C(O)$-		(C_3H_4ClO)	34	McLain, 1986
$C_{15}H_{15}N_2O$	4-$(CH_3)_2NC_6H_4N{=}NC_6H_3$-4-(O)-3-$CH_2$-		(C_7H_7O,b)	36	Dix and Vögtle, 1981
$C_{15}H_{16}P$	$(C_6H_5)_2P(CH_2)_3$-		$(C_{15}H_{14}PO)$	98	McLain, 1986
$C_{15}H_{18}NO_4$	(D,L)-$CH_3O_2CCH(i\text{-}C_4H_9)NHC(O)C_6H_4C(O)$-			39	Ganin et al., 1987
$C_{15}H_{27}N_2$	3,5-$(CH_3)_2$-4-C_8H_{17}pyrazolyl-2-$(CH_2)_2$-		A-1		Ivanov et al., 1990
$C_{15}H_{31}O_2$	$C_{12}H_{25}OCH_2CH(OH)CH_2$-		(H)	81	Inokuma et al., 1988b
$C_{15}H_{31}O_3$	$CH_3(OCH_2CH_2)_2OCH(C_8H_{17})CH_2$-		$(C_{10}H_{21}O,b)$	57	Inokuma et al., 1988a
$C_{16}H_{10}NO$	4-naphthalinon-4-NHC_6H_4-		(C_6H_6N)	65	Dix and Vögtle, 1980
$C_{16}H_{10}NO_2$	naphthaquinonyl-4-NHC_6H_4-		(C_6H_6N)	56	Dix and Vögtle, 1981
$C_{16}H_{13}O_3$	2-[4-$C_2H_5OC_6H_4C(O)]C_6H_4C(O)$-				Malinovski et al., 1990
$C_{16}H_{13}Fe$	4-ferroceneC_6H_4-		(H)	25	Beer et al., 1988, 1990b
$C_{16}H_{14}NO_2$	(-)$C_6H_5CH(CH_3)NHC(O)C_6H_4C(O)$-		(H)	68	Ganin et al., 1987
$C_{16}H_{14}NO_2$	(+)$C_6H_5CH(CH_3)NHC(O)C_6H_4C(O)$-		(H)	55	Ganin et al., 1987

$C_{16}H_{14}NO_3$	$4\text{-}C_2H_5OC_6H_4NHC(O)C_6H_4C(O)\text{-}$	(H)	48	Ganin et al., 1987
$C_{16}H_{14}NO_3$	$C_6H_5OC_2H_4NHC(O)C_6H_4C(O)\text{-}$	(H)	54	Ganin et al., 1987
$C_{16}H_{22}NO_2$	$C_8H_{17}NHC(O)C_6H_4C(O)\text{-}$	(H)	72	Ganin et al., 1987
$C_{16}H_{31}O_7$	$(2\text{-}CH_3\text{-}15\text{-crown-}5)CH_2(OCH_2CH_2)_2\text{-}$	$(C_4H_9O_2, a)$		Nakatsuji et al., 1988a
$C_{16}H_{31}O_8$	$(18\text{-crown-}6)CH_2OCH_2CH(OH)CH_2\text{-}$	D-6	79	Belohradsky et al., 1987b
$C_{16}H_{33}$	$C_{16}H_{33}$	(H)	70	Anelli and Quici, 1988
$C_{16}H_{33}O_2$	$C_{12}H_{25}(OCH_2CH_2)_2\text{-}$	(H)	63	Masuyama et al., 1983
$C_{16}H_{33}O_2$	$HO(CH_2)_2OCH\text{-}$ $(C_{12}H_{25})CH_2\text{-}$ $8\text{-}CH_2OCH_2C_6H_5$	$(C_{23}H_{39}O_2)$	58	Son et al., 1985
$C_{17}H_8NO_2$	1,3-$(O)_2$-2-indanyliden-$C(CN)C_6H_4\text{-}$	$(C_{18}H_9N_2O_2)$	53	Junek et al., 1990
$C_{17}H_{11}N_2O$	$4\text{-}(CN)_2C\text{-}2\text{-}CH_3C_5H_2O\text{-}6\text{-}CH{=}CHC_6H_4\text{-}$			Bourson et al., 1988
$C_{17}H_{11}N_4O$	$(3\text{-}NH_2$-4,5-dihydro-5-(O)-1-C_6H_5-4-pyrazolyliden)$C(CN)C_6H_4\text{-}$	$(C_{18}H_{12}N_5O)$	97	Junek et al., 1990
$C_{17}H_{14}NO_4$	$4\text{-}C_2H_5O_2CC_6H_4NHC(O)C_6H_4C(O)\text{-}$		42	Ganin et al., 1987
$C_{17}H_{19}N_2O$	$4\text{-}C_2H_5C_6H_4N{=}NC_6H_4O(CH_2)_3\text{-}$	(H)	91	Shinkai et al., 1987
$C_{17}H_{35}O_8$	$CH_3(OCH_2CH_2)_8\text{-}$	A-1	49	Schultz et al., 1985
		(H)		Schultz et al., 1982a

TABLE 5.3. (*Continued*)

R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
$C_{17}H_{37}O_3Si$	$(C_2H_5O)_3Si(CH_2)_{11}$-		$(C_{11}H_{21})$	75	Chen et al., 1989
$C_{18}H_9N_2O_2$	1,3-$(O)_2$-2-indanyl-4-$C(CN)_2C_6H_4$-		(C_6H_5)	40	Junek et al., 1990
$C_{18}H_{12}N_3O$	4,5-dihydro-3-CH_3-5-(O)-1-C_6H_5-4-pyrazolylidenC(CN)C_6H_4-		$(C_{19}H_{13}N_4O)$	96	Junek et al., 1990
$C_{18}H_{12}N_5O$	3-NH_2-4,5-dihydro-5-(O)-1-C_6H_5-4-pyrazolylC$(CN)_2C_6H_4$-		(C_6H_5)	88	Junek et al., 1990
$C_{18}H_{15}N_2O_2$	$(CH_3)_2$N-benzoxazine-2-(O)-CH=CHC_6H_4-		(C_7H_5O)		Fery-Forgues et al., 1988
$C_{18}H_{15}Fe$	4-(ferrocenyl-CH=CH)C_6H_4-		(C_7H_5O)		Andrews et al., 1987
					Beer et al., 1990c
$C_{18}H_{17}N_2O_4$	$C_6H_5CH_2O_2CNHCH(C_6H_5)CONHCH_2C(O)$-		(C_2H_4NO,c)	50	Zinic et al., 1990
$C_{18}H_{17}Fe$	4-[ferrocenyl-$(CH_2)_2$]C_6H_4-		$(C_{18}H_{15}Fe)$		Andrews et al., 1987
			$(C_{18}H_{15}Fe)$	89	Beer et al., 1990c
$C_{18}H_{21}N_2O$	4-$C_2H_5C_6H_4N$=$NC_6H_4O(CH_2)_4$-		(H)	81	Shinkai et al., 1987
$C_{18}H_{27}O_7$	3-(benzo-15-crown-5)$(OCH_2CH_2)_2$-		$(C_4H_9O_2,a)$	17	He et al., 1986
$C_{18}H_{35}O_9$	2-(21-crown-8)$CH_2OCH_2CH(OH)CH_2$-		D-6b	81	Belohradsky et al., 1987b

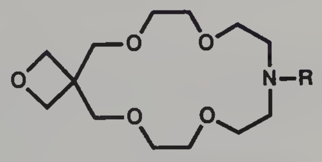
$C_{19}H_{12}N_3O_3$	$[1-(4-CO_2C_6H_4)-4,5$-dihydro-3- CH_3-5-(O)-4-pyrazolylidenC(CN)]C_6H_4-	$(C_{20}H_{13}N_4O_3)$	87	Junek et al., 1990
$C_{19}H_{13}N_4O$	[4,5-dihydro-3-CH_3-5-(O)-1- C_6H_5-4-pyrazolylC$(CN)_2$]C_6H_4-	(C_6H_5)		Junek et al., 1990
$C_{19}H_{14}NFe$	4-Ferrocenyl-C(CN)=CHC_6H_4-	(C_7H_5O)		Andrews et al., 1987
$C_{19}H_{15}N_4O_5S$	2-(3-CH_3Opyrazine)NH$SO_2C_6H_4$- NHC(O)C_6H_4C(O)-	(H)	25	Ganin et al., 1987
$C_{19}H_{15}N_4O_5S$	3-(6-CH_3Opyrazine)NH$SO_2C_6H_4$- NHC(O)C_6H_4C(O)-	(H)	22	Ganin et al., 1987
$C_{19}H_{19}N_2O_4$	CH_3OCH_2-5-oxazolinyl-3-C_6H_5- 5-pyridinyl-6-CH_2OCH_2C(O)-	(C_2H_2ClO)	87	Newkome and Marston, 1985
$C_{19}H_{21}N_2O_3$	CH_3OCH_2-5-oxazolinyl-3-C_6H_5- 5-pyridinyl-6-$CH_2O(CH_2)_2$-	(C_2H_4Cl)		Newkome and Marston, 1985
$C_{19}H_{23}N_2O$	4-$C_4H_9C_6H_4N$=N$C_6H_4O(CH_2)_3$-	(H)	82	Shinkai et al., 1987
$C_{20}H_{13}N_4O_3$	$[1-(4-CO_2C_6H_4)-4,5$-dihydro-3- CH_3-5-(O)-4-pyrazolylC$(CN)_2$]C_6H_4-	(C_6H_5)	92	Junek et al., 1990
$C_{20}H_{14}N_3O_2$	4-C_6H_5N=NC_6H_4NHC(O)C_6H_4C(O)-	(H)	65	Ganin et al., 1987
$C_{20}H_{15}N$	10-methylacridine-9-C_6H_4-	(H)	42	Jonker et al., 1989
$C_{20}H_{16}N_3O$	[4,5-dihydro-5-(O)-1-C_6H_5-3- C_3H_7-4-pyrazolylidenC(CN)]C_6H_4-	$(C_{21}H_{17}N_4O)$	92	Junek et al., 1990

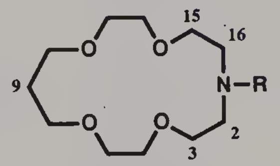
TABLE 5.3. (*Continued*)

R					
Formula	Structure	Other Substituents	Method (or from R = formula)	Yield (%)	References
$C_{20}H_{17}N_2O_4$	Spiropyrane		$(C_{13}H_{14}NO)$		Inouye et al., 1990
$C_{20}H_{17}N_4O_6S$	4-[2,6-$(CH_3O)_2$-pyrimidine]-$NHSO_2C_6H_4NHC(O)C_6H_5C(O)$-		(H)	18	Ganin et al., 1987
$C_{20}H_{22}N_2O_4$	CH_3OCH_2-5-oxazolinyl-3-C_6H_5-5-pyridinyl-4-CH_3-6-$CH_2OCH_2C(O)$-		$(C_{19}H_{19}N_2O_4)$	55,26	Newkome and Marston, 1985
$C_{20}H_{23}N_2O_5$	3-(benzo-15-crown-5)$N{=}NC_6H_4$-		(C_6H_5)	13	Shinkai et al., 1981
$C_{20}H_{25}N_2O$	4-$C_4H_9C_6H_4N{=}NC_6H_4O(CH_2)_4$-		(H)	80	Shinkai et al., 1987
$C_{20}H_{30}NO_2$	$C_{12}H_{25}NHC(O)C_6H_4C(O)$-		(H)	70	Ganin et al., 1987
$C_{20}H_{31}O_8$	3-(benzo-18-crown-6)$(OCH_2CH_2)_2$-		$(C_4H_9O_2$,a)	22	He et al., 1986
$C_{20}H_{39}O_{10}$	2-(24-crown-8)$CH_2OCH_2CH(OH)CH_2$-		D-6	81	Belohradsky et al., 1987b
$C_{21}H_{13}O$	9-anthracenon-CHC_6H_4-		(C_7H_5O)	40	Dix and Vögtle, 1980

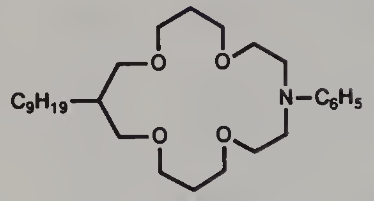
$C_{21}H_{17}N_4O$	[4,5-dihydro-5-(O)-1-C_6H_5- 3-C_6H_7-4-pyrazolylC(CN)$_2$]C_6H_4-	(C_6H_5)	52	Junek et al., 1990
$C_{22}H_{25}N_2O_6$	CH_3OCH_2-5-oxazolinyl-3-C_6H_5- 5-pyridinyl-4-CH_3-NCO_2CH_3- 6-$CH_2OCH_2C(O)$-	($C_{19}H_{19}N_2O_4$)	43	Newkome and Marston, 1985
$C_{23}H_{14}N_3O$	[4,5-dihydro-1,3-(C_6H_5)$_2$-5-(O)- 4-pyrazolylidenC(CN)]C_6H_4-	($C_{21}H_{17}N_4O$)	94	Junek et al., 1990
$C_{23}H_{25}N_2$	[$(CH_3)_2NC_6H_4$]$_2CHC_6H_4$-	(C_6H_5)		Dix and Vögtle, 1978
$C_{23}H_{39}O_2$	$C_6H_5CH_2O(CH_2)_2O$- 8-$CH_2OCH_2C_6H_5$ $CH(C_{12}H_{25})CH_2$-	(H)	30	Son et al., 1985
$C_{24}H_{15}N_4O$	[4,5-dihydro-5-(O)-1,3-(C_6H_5)$_2$- 4-pyrazolylC(CN)$_2$]C_6H_4-	(C_6H_5)	30	Junek et al., 1990
$C_{28}H_{45}O_2$	cholesteryl-C(O)-	(H)	34	Gokel et al,. 1987
$C_{29}H_{25}N_2O_2Cl_4$	[$(CH_3)_2NC_6H_4$]$_2C(C_6HCl_4O_2)C_6H_4$-	(C_6H_5)		Dix and Vögtle, 1978
$C_{29}H_{47}O_2$	cholesteryl-C(O)CH_2-	(H)	68	Gokel et al., 1987
$C_{29}H_{49}O_2$	cholestanyl-C(O)CH_2	(H)	67	Gokel et al., 1987

TABLE 5.4. AZA-16,17,19 AND 22-CROWN MACROCYCLES


5.4 A



5.4 B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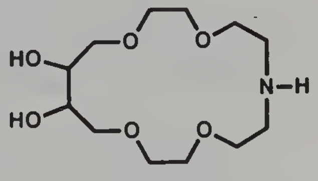
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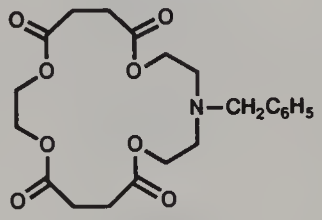
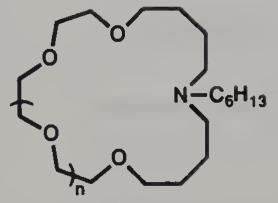

5.4 E

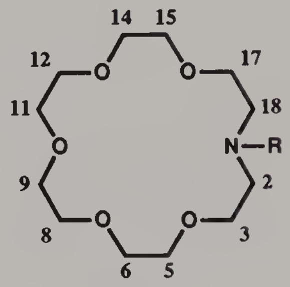


5.4 F

Structure	R or n	Other Substituents	Methods (or from R = formula)	Yield (%)	References
5.4 A	H,a		A-2	67	Krespan, 1976
			A-2	67	Krespan, 1975
	$HO(CH_2)_2$-		(H,a)	87	Krespan, 1976
				87	Krespan, 1975

5.4 B	H	9-CH_2OH;9-CH_2NH_2	(H,a)	52	Krespan, 1976
	H	9-CH_2OH; 9-$O(CH_2)_2Cl$	(H,a)	29	Krespan, 1976
5.4 C			A-1	26	Bradshaw et al., 1987
5.4 D			A-4	86	Lukyanenko et al., 1988
5.4 E			A-5		Asay et al., 1977
5.4 F	1		B-3	7	Nakatsuji et al., 1982
	2		B-3	7	Nakatsuji et al., 1982

TABLE 5.5. AZA-18-CROWN-6 MACROCYCLES



R Formula	R Structure	Other Substituents	Methods (or from R = formula)	Yield (%)	References
H	H		A-3	25	Bogatskii et al., 1985b
H	H		A-1		Gokel and Garcia, 1977
			A-1	98	Gokel et al., 1987
			($C_7H_7O_2S$)	83	Johnson et al., 1979
			A-3	27-35,61	Maeda et al., 1981b, 1983a
			A-3	58-78 (GC)	Maeda et al., 1983a
			A-3	35,61	Okahara et al., 1982
			C-2	47	Sakamoto et al., 1986
			A-1	98	Schultz et al., 1985

H	H	3-CH_3	A-3	39	Maeda et al., 1983a
H	H	3,17-$(CH_3)_2$	A-3	28,34	Maeda et al., 1981b, 1983a
			A-3	34	Okahara et al., 1982
H	H	2,2,18,18-$(CH_3)_4$	A-3	41	Lai, 1985
			A-3	46	Sosnovsky and Lukszo, 1985
H	H	2-C_2H_5	A-3	41	Maeda et al., 1983a
H	H	2,3-cyclohexano	A-3	43	Maeda et al., 1983a
H	H	3-C_6H_5	A-3	33	Maeda et al., 1983a
O	O	2,2,18,18-$(CH_3)_4$	(H)		Sosnovsky and Lukszo, 1985
CN	CN		C-4		Ajinomoto et al., 1983
			C-4	17	Maeda et al., 1981a
CH_3	CH_3		B-1	55	Kuo et al., 1978
			(H)		Johnson et al., 1979
			(H)	29	Schultz et al., 1982a, 1982b
CH_3	CH_3	3,17-$(O)_2$	A-5	77	Bradshaw et al., 1983
CH_4O_3P	$(HO)_2P(O)CH_2$-		(H)	74	Tazaki et al., 1982
C_2H_2ClO	$ClCH_2C(O)$-		(H)	93	Newkome and Marston, 1985
C_2H_3O	$CH_3C(O)$-		(H)	86	Johnson et al., 1979

TABLE 5.5. (*Continued*)

R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
C_2H_4Cl	$Cl(CH_2)_2$-		(C_2H_5O,a)	92	Newkome and Marston, 1985
			(C_2H_3O)	78	Johnson et al., 1979
C_2H_5	C_2H_5		B-1	60	Kuo et al., 1978
C_2H_5O,a	$HO(CH_2)_2$-		C-2	14	Sakamoto et al., 1986
C_2H_5O,b	CH_3OCH_2-				Lukyanenko et al., 1990
			(H)	52	Maeda et al., 1983a
			(H)		Masuyama et al., 1981
			($C_7H_{13}O_2$)	87	Newkome and Marston, 1985
			(H)	40	Newkome and Marston, 1985
C_3H_5	allyl		A-1	34	Chen et al., 1989
			A-1	38	Gokel, 1984
			B-1	40	Kuo et al., 1978
			A-1		Schultz et al., 1981
C_3H_5O	glycidyl		(H)	79	Belohradsky et al., 1987a
C_3H_7	C_3H_7			19	White et al., 1987b

C_3H_7O	$CH_3CH(OH)CH_2$-		(C_3H_5)	100	Gokel, 1984
			(H)	87	Zavada et al., 1989
C_3H_7O	$CH_3O(CH_2)_2$-		A-1	53	Gokel, 1984
			A-1	53	Schultz et al., 1981,1982a,1985
$C_4H_7O_2$	$C_2H_5O_2CCH_2$-		(H)	79	White et al., 1987b, 1989
C_4H_9	C_4H_9		B-1	67	Kuo et al., 1978
$C_4H_9O_2$	$H(OCH_2CH_2)_2$-		(H)		Masuyama et al., 1981
$C_4H_8NO_3$	$CH_3O_2CCH_2NHC(O)CH_2$-		(H)	51	White et al., 1987b, 1989
$C_5H_{11}O_2$	$CH_3(OCH_2CH_2)_2$-		A-1	50	Gokel, 1984
			A-1	50	Schultz et al., 1982a, 1985
C_6H_5	C_6H_5	3-(O)	A-1	13	Dix and Vögtle, 1978, 1980
			B-3	16	Matsushima et al., 1986
$C_6H_6NO_2S$	$4-NH_2C_6H_4SO_2$-		(H)	66	Bogatskii et al., 1986
$C_6H_{11}O$	$C_5H_{11}C(O)$-		(H)	73	Nakatsuji et al., 1982
C_6H_{13}	C_6H_{13}		B-1	58	Kuo et al., 1980
C_6H_{13}	C_6H_{13}	2-(O)	B-3	10	Nakatsuji et al., 1982
$C_6H_{13}O_3$	$H(OCH_2CH_2)_3$		(H)		Masuyama et al., 1981
C_7H_5O	$4-HC(O)C_6H_4$-		(C_6H_5)	65	Dix and Vögtle, 1980

TABLE 5.5. (*Continued*)

R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
$C_7H_6NO_3$	2-HO-5-$NO_2C_6H_3CH_2$-		(H)	54	Katayama et al., 1985
			(H)		Nakamura et al., 1981
C_7H_7	$C_6H_5CH_2$-		A-1	25	Gokel and Garcia, 1977
			A-1	40	Gokel et al., 1987
			(H)	83	Johnson et al., 1979
			C-2	47	Sakamoto et al., 1986
			A-1	40	Schultz et al., 1985
C_7H_7O, a	2-$HOC_6H_4CH_2$-		($C_9H_9O_2$)	55	Dix and Vögtle, 1981
C_7H_7O	2-$CH_3OC_6H_4$-		A-1	41	Schultz et al., 1985
$C_7H_7O_2S$	Ts		(H)	46	Gokel and Garcia, 1977
			A-1	46	Johnson et al., 1979
$C_7H_7O_2S$	Ts	3,17-$(O)_2$	I-2	37	Qin and Hu, 1984
$C_7H_{13}O_2$	THP-O-$(CH_2)_2$-		A-1	57	Newkome and Marston, 1985
$C_7H_{14}NO_2$	4-morpholinyl$CH_2CH(OH)CH_2$-		(H)	94	Belohradsky et al., 1987b
$C_7H_{15}O_3$	$CH_3(OCH_2CH_2)_3$-		(H)	16	Gokel, 1984
			(H)		Masuyama et al., 1981
			A-1		Schultz et al., 1982a

		(H)	46	Schultz et al., 1985
$C_8H_8NO_3S$	$4\text{-}CH_3C(O)NHC_6H_4S(O)_2\text{-}$	(H)	66	Malinovski et al., 1989
$C_8H_{10}N_5O$	3-adeninyl$CH_2CH(OH)CH_2$-	(C_3H_5O)		Holy et al., 1987
$C_8H_{10}N_5O$	7-adeninyl$CH_2CH(OH)CH_2$-	(C_3H_5O)		Holy et al., 1987
$C_8H_{10}N_5O$	9-adeninyl$CH_2CH(OH)CH_2$-	(C_3H_5O)	58	Holy et al., 1987
$C_8H_{14}NO_3$	$CH_3OC(O)CH(i\text{-}C_3H_7)NHC(O)CH_2\text{-}$	(H)	56	White et al., 1987b, 1989
C_8H_{17}	C_8H_{17}	(H)	88	Kuo et al., 1980
$C_9H_9O_2$	$2\text{-}CH_3CO_2C_6H_4CH_2\text{-}$	(H)		Dix and Vögtle, 1981
$C_9H_{16}NO_3$	$CH_3O_2CCH(s\text{-}C_4H_9)NHC(O)CH_2\text{-}$	(H)	50	White et al., 1987b, 1989
$C_9H_{17}NO$	4-[N(O),2,2,6,6-$(CH_3)_4$]piperdine	A-3		Sosnovsky and Lukszo, 1985
$C_9H_{19}O_2$	$C_6H_{13}OCH_2CH(OH)CH_2\text{-}$	(H)	18	Gokel, 1984
		(H)	90	Inokuma et al., 1988b
		(H)		Schultz et al., 1982a
$C_9H_{19}O_4$	$CH_3(OCH_2CH_2)_4\text{-}$	(H)	18	Schultz et al., 1985
$C_9H_{21}O_3Si$	$(C_2H_5O)_3Si(CH_2)_3\text{-}$	(C_3H_5)	65	Chen et al., 1989
$C_{11}H_{23}O_2$	$C_8H_{17}OCH_2CH(OH)CH_2\text{-}$	(H)	81	Inokuma et al., 1988b
$C_{10}H_{17}$	azulenyl	(H)	54	Lohr and Vögtle, 1985
$C_{10}H_{13}O_2$	$C_6H_5(OCH_2CH_2)_2\text{-}$			He et al., 1986
$C_{10}H_{21}$	$C_{10}H_{21}$	B-1	70	Kuo et al., 1980
$C_{10}H_{21}O$,a	$C_8H_{17}O(CH_2)_2$	(H)	68	Masuyama et al., 1983

TABLE 5.5. (*Continued*)

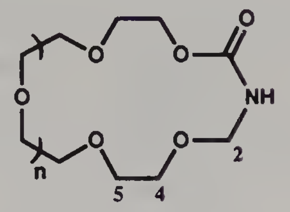
R		Other.	Method	Yield	References
Formula	Structure	Substituents	(or from R = formula)	(%)	
$C_{10}H_{21}O$,b	$C_8H_{17}CH(OH)CH_2$-		(H)	80	Inokuma et al., 1988b
$C_{11}H_9O_3$	3-CH_3-7-HO-coumarin-8-CH_2-		(H)	62	Katayama et al., 1985
			(H)		Nishida et al., 1982
$C_{11}H_{21}$	CH_2=CH(CH_2)$_9$-		A-1	30	Chen et al., 1989
$C_{11}H_{23}O$	$CH_3OCH(C_8H_{17})CH_2$-		($C_{10}H_{21}O$,b)	65	Inokuma et al,. 1988a
$C_{11}H_{23}O_5$	$CH_3(OCH_2CH_2)_5$-		(H)	15	Schultz et al., 1982a, 1985
$C_{12}H_8N_3O_2$	4-$NO_2C_6H_4N$=NC_6H_4-		(C_6H_5)	56	Dix and Vögtle, 1978, 1980
$C_{12}H_{14}NO$	piperidinyl-4-C(O)C_6H_4-		($C_{13}H_8NO_4$)		Dix et al., 1980
$C_{12}H_{23}O_6$	2-(12-crown-4)$CH_2OCH_2CH(OH)CH_2$-		D-6	75	Belohradsky et al., 1987b
$C_{12}H_{25}$	$C_{12}H_{25}$			94	Kuo et al., 1980
			C-2	35	Sakamoto et al., 1986
$C_{12}H_{25}O$	$C_{10}H_{21}CH(OH)CH_2$-		(H)	84	Inokuma et al., 1988b
$C_{12}H_{25}O_2$	$C_8H_{17}(OCH_2CH_2)_2$-		(H)	52	Masuyama et al., 1983
$C_{13}H_8NO_4$	4-$NO_2C_6H_4OC(O)C_6H_4$-				Dix et al., 1980
$C_{13}H_{14}NO$	2,2,3-trimethylindolenine		(H)		Inouye et al., 1990
$C_{13}H_{23}N_2$	3,5-$(C_3H_7)_2$-4-C_2H_5pyrazol-2-$(CH_2)_2$-		A-1		Ivanov et al., 1990

$C_{13}H_{27}O_2$	$CH_3O(CH_2)_2OCH(C_8H_{17})CH_2$-	($C_{10}H_{21}O$,b)	58	Inokuma et al., 1988a
$C_{13}H_{27}O_2$	$C_{10}H_{21}OCH_2CH(OH)CH_2$-	(H)		Inokuma et al., 1988b
$C_{14}H_9N_2O_4$	2,4-$(NO_2)_2C_6H_3CH{=}CHC_6H_4$-	(C_7H_5O)	39	Dix and Vögtle, 1980
$C_{14}H_{13}N$	$N(CH_3)$pyridinyl$CH{=}CHC_6H_4$-	(C_7H_5O)	58 (salt)	Dix and Vögtle, 1980
$C_{14}H_{27}O_7$	2-(15-crown-5)$CH_2OCH_2CH(OH)CH_2$-	D-6b	67	Belohradsky et al., 1987b
$C_{14}H_{29}O$	$C_{12}H_{25}CH(OH)CH_2$-	(H)	80	Inokuma et al., 1988b
$C_{14}H_{29}O$	$C_{12}H_{25}O(CH_2)_2$-	(H)	55	Masuyama et al., 1983
$C_{14}H_{29}O_3$	$C_8H_{17}(OCH_2CH_2)_3$-	(H)	62	Masuyama et al., 1983
$C_{15}H_9O_4$	2,3-$(HO)_2$anthraquinonylCH_2-	(H)	38	Katayama et al., 1985
$C_{15}H_{11}$	9-anthracenylCH_2-	(H)		Silva and Silva, 1986
$C_{15}H_{15}N_2O$	4-$(CH_3)_2NC_6H_4N{=}C_6H_3(O)CH_2$-	(C_7H_7O,a)	36	Dix and Vögtle, 1981
$C_{15}H_{27}N_2$	3,5-$(CH_3)_2$-4-(C_8H_{17})pyrazolyl- 2-$(CH_2)_2$-	A-1		Ivanov et al., 1990
$C_{15}H_{31}O$	$C_{12}H_{25}OCH_2CH(OH)CH_2$-	(H)	76	Inokuma et al., 1988b
$C_{15}H_{31}O_3$	$CH_3(OCH_2CH_2)_2OCH(C_8H_{17})CH_2$-	($C_{10}H_{21}O$,b)	60	Inokuma et al., 1988a
$C_{16}H_{12}NO_2$	anthraquinonyl-$NH(CH_2)_2$	(H)		Ossowski and Schneider,1990
$C_{16}H_{22}NO_2$	$C_8H_{17}NHC(O)C_6H_4C(O)$-	(H)	70	Ganin et al., 1987
$C_{16}H_{31}O_7$	(2-CH_3-15-crown-5)$CH_2(OCH_2CH_2)_2$-	($C_4H_9O_2$)		Nakatsuji et al., 1988a
$C_{16}H_{31}O_8$	(18-crown-6)$CH_2OCH_2CH(OH)CH_2$-	D-6b	50	Belohradsky et al., 1987b
$C_{16}H_{33}$	$C_{16}H_{33}$	(H)	55	Anelli and Quici, 1988

TABLE 5.5. *(Continued)*

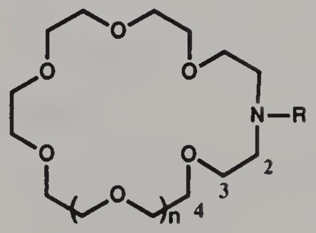
R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
$C_{16}H_{33}O$	$C_{14}H_{29}CH(OH)CH_2$-		(H)	75	Inouye et al., 1988b
$C_{16}H_{33}O_2$	$C_{12}H_{25}(OCH_2CH_2)_2$-			63	Masuyama et al., 1983
$C_{17}H_{35}O_8$	$CH_3(OCH_2CH_2)_8$-		(H)	60	Schultz et al., 1982a, 1985
$C_{17}H_{37}O_3Si$	$(C_2H_5O)_3Si(CH_2)_{11}$-		$(C_{11}H_{21})$	77	Chen et al., 1989
$C_{18}H_{27}O_7$	3-(benzo-15-crown-5)$(OCH_2CH_2)_2$-		$(C_4H_9O_2)$	29	He et al., 1986
$C_{18}H_{35}O_9$	(21-crown-7)$CH_2OCH_2CH(OH)CH_2$-		D-6b	57	Belohradsky et al., 1987b
$C_{19}H_{19}N_2O_4$	CH_3OCH_2-5-oxazolinyl-3-C_6H_5- 5-pyridine-6-$CH_2OCH_2C(O)$-		(C_2H_2ClO)	8	Newkome and Marston, 1985
$C_{19}H_{21}N_2O_3$	CH_3OCH_2-5-oxazolinyl-3-C_6H_5- 5-pyridine-6-$CH_2OCH_2CH_2$-		(C_2H_4Cl)	5	Newkome and Marston, 1985
$C_{20}H_{14}N_3O_2$	4-$C_6H_5N{=}NC_6H_4NHC(O)C_6H_4C(O)$-		(H)	57	Ganin et al., 1987
$C_{20}H_{17}N_2O_4$	spiropyrane		$(C_{13}H_{14}NO)$		Inouye et al., 1990
$C_{20}H_{30}NO_2$	$C_{12}H_{25}NHC(O)C_6H_4C(O)$-		(H)	63	Ganin et al., 1987
$C_{20}H_{31}O_8$	3-(Benzo-18-crown-6)$(OCH_2CH_2)_2$-		$(C_4H_9O_2)$	37	He et al., 1986
$C_{20}H_{39}O_{10}$	2-(24-crown-8)$CH_2OCH_2CH(OH)CH_2$-		D-6b	50	Belohradsky et al., 1987b
$C_{28}H_{45}O_2$	cholesteryl-C(O)-		(H)	52	Gokel et al., 1987
$C_{29}H_{47}O_2$	cholesteryl-$C(O)CH_2$-		(H)	63	Gokel et al., 1987
$C_{29}H_{49}O_2$	cholestanyl-$C(O)CH_2$-		(H)	65	Gokel et al., 1987

TABLE 5.6. AZA-16-CROWN-6 AND AZA-19-CROWN-7 MACROCYCLES



n	Methods	Yield (%)	References
1	B-2	49	Masuyama et al., 1985
2	B-2	58	Masuyama et al., 1985

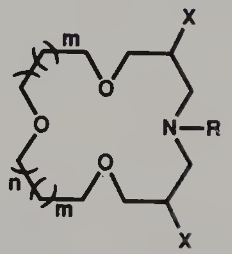
TABLE 5.7. AZA-21-CROWN-7 AND AZA-24-CROWN-8 MACROCYCLES



R		n	Other Substituents	Methods	Yield (%)	References
Formula	Structure					
H	H	1		A-1	77	Johnson et al., 1985
				A-3	35,33	Maeda et al., 1981b, 1983b
				A-3	35	Okahara et al., 1982
H	H	2		A-1	66	Johnson et al., 1985
H	H	1	3-$C_{10}H_{21}$	A-3		Okahara et al., 1982
CH_3	CH_3	1		(H)		Johnson et al., 1985

CH_3	CH_3	2	(H)	93	Johnson et al., 1985
C_6H_5	C_6H_5	1			Dix and Vögtle, 1978
C_6H_{13}	C_6H_{13}	1	B-1	79	Kuo et al., 1980
$C_7H_7O_2S$	Ts	1	A-1	23	Johnson et al., 1985
$C_7H_7O_2S$	Ts	2	A-1	17	Johnson et al., 1985
C_8H_{17}	C_8H_{17}	1	B-1	78	Kuo et al., 1980
$C_{10}H_{21}$	$C_{10}H_{21}$	1	B-1	61	Kuo et al., 1980
$C_{12}H_8N_3O_2$	4-$NO_2C_6H_4N$= NC_6H_4-	1	(C_6H_5)		Dix and Vögtle, 1978
$C_{13}H_{14}NO$,a	2,2,3-trimethylindolenine	1	(H)		Inouye et al., 1990
$C_{13}H_{14}NO$,b	2,2,3-trimethylindolenine	2	(H)		Inouye et al., 1990
$C_{20}H_{17}N_2O_4$	spiropyrane	1	($C_{13}H_{14}NO$,a)		Inouye et al., 1990
$C_{20}H_{17}N_2O_4$	spiropyrane	2	($C_{13}H_{14}NO$,b)		Inouye et al., 1990

TABLE 5.8. AZA-CROWN MACROCYCLES WITH PROPYLENE BRIDGES



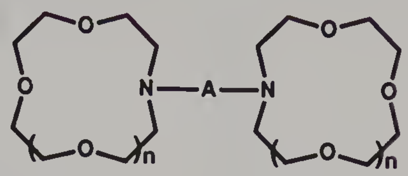
R		X	m	n	Methods	Yield (%)	References
Formula	Structure						
H	H	OH	0	1	C-6	31	Kikui et al., 1984
					C-6		Nippon Oils, 1984
C_2H_5	C_2H_5	OH	0	1	C-6	38	Kikui et al., 1984
					C-6		Nippon Oils, 1984
C_2H_5	C_2H_5	OH	0	2	C-6	35	Kikui et al., 1984
					C-6		Nippon Oils, 1984
C_2H_5	C_2H_5	OH	0	3	C-6	24	Kikui et al., 1984
					C-6		Nippon Oils, 1984
C_2H_5	C_2H_5	OH	2	1	C-6		Nippon Oils, 1984
C_2H_5O	$HO(CH_2)_2$-	OH	0	1	C-6	34	Kikui et al., 1984
					C-6		Nippon Oils, 1984

C_4H_9	i-C_4H_9	OH	0	1	C-6	49	Kikui et al., 1984
					C-6		Nippon Oils, 1984
C_4H_9	i-C_4H_9	OH	0	2	C-6	50	Kikui et al., 1984
C_6H_5	C_6H_5	OH	0	1	C-6	48	Kikui et al., 1984
					C-6		Nippon Oils, 1984
C_8H_{17}	C_8H_{17}	H	0	1	C-6	72	Nakatsuji et al., 1989
C_8H_{17}	C_8H_{17}	Cl	0	1	C-6	87	Nakatsuji et al., 1989
$C_8H_{17}O_2$	n-$C_4H_9(OCH_2CH_2)_2$-	OH	0	1	C-6		Nakatsuji et al., 1986
$C_{10}H_{21}$	$C_{10}H_{21}$	OH	0	1	C-6	45	Ikeda et al., 1987
					C-6	50	Kikui et al., 1984
					C-6		Nippon Oils, 1984
$C_{10}H_{21}$	$C_{10}H_{21}$	OH	0	2	C-6	43	Ikeda et al., 1987
					C-6		Nakatsuji et al., 1986
$C_{10}H_{21}$	$C_{10}H_{21}$	OH	0	3	C-6	43	Ikeda et al., 1987
$C_{10}H_{21}O$	$C_8H_{17}O(CH_2)_2$-	H	0	1	C-6	73	Nakatsuji et al., 1989
$C_{10}H_{21}O$	$C_8H_{17}O(CH_2)_2$-	Cl	0	1	C-6	92	Nakatsuji et al., 1989
$C_{11}H_{23}O$	$C_8H_{17}O(CH_2)_3$-	H	0	1	C-6	63	Nakatsuji et al., 1989
$C_{11}H_{23}O$	$C_8H_{17}O(CH_2)_3$-	Cl	0	1	C-6	59	Nakatsuji et al., 1989

TABLE 5.8. *(Continued)*

R		X	m	n	Methods (or from R = H)	Yield (%)	References
Formula	Structure						
$C_{12}H_{25}$	$C_{12}H_{25}$	OH	0	1	C-6	40	Ikeda et al., 1987
$C_{12}H_{25}$	$C_{12}H_{25}$	OH	0	2	C-6	44	Ikeda et al., 1987
$C_{12}H_{25}$	$C_{12}H_{25}$	OH	0	3	C-6	38	Ikeda et al., 1987
$C_{12}H_{25}O_2$	$C_8H_{17}(OCH_2CH_2)_2$-	H	0	1	C-6	73	Nakatsuji et al., 1989
$C_{12}H_{25}O_2$	$C_8H_{17}(OCH_2CH_2)_2$-	Cl	0	1	C-6	72	Nakatsuji et al., 1989

TABLE 5.9. BIS(MONOAZA-CROWN) MACROCYCLES



A Formula	A Structure	n	m	Methods (or from R = formula in appropriate table)	Yield (%)	References
C_2O_2	$-[C(O)]_2-$	1	1			Calverley and Dale, 1981
						Dale and Calverley, 1982
C_2S_4	$-C(S)S_2C(S)-$	2	2		55	Granell et al., 1990
$C_2H_2N_2O_2$	$-(CNOH)_2-$	1	1			Ashen et al., 1990
C_2H_4	$-(CH_2)_2-$	0	0	D-8	4	Alfheim et al., 1986
C_2H_4	$-(CH_2)_2-$	1	1	(C_2O_2)	85	Calverley and Dale, 1981
				D-1	85,84	Dale and Calverley, 1982
C_2H_4	$-(CH_2)_2-$	2	2	D-4	36	deJong et al., 1983
C_3H_6	$-(CH_2)_3-$	1	1	D-1	84	Calverley and Dale,1981
				D-1	84	Dale and Calverley, 1982
				D-1	98	Zavada et al., 1989

TABLE 5.9. *(Continued)*

A		n	m	Methods (or from R = formula in appropriate table)	Yield (%)	References
Formula	Structure					
C_3H_6	$-(CH_2)_3-$	2	2	D-1	60	Zavada et al., 1989
C_3H_6	$-(CH_2)_3-$	3	3	D-1	77	Zavada et al., 1989
C_3H_6O,a	$-CH_2CH(OH)CH_2-$	1	1	D-6	81,91	Belohradsky et al., 1987b
C_3H_6O	$-CH_2CH(OH)CH_2-$	1	2	D-6	77	Belohradsky et al., 1987b
C_3H_6O	$-CH_2CH(OH)CH_2-$	1	3	D-6	64	Belohradsky et al., 1987b
C_3H_6O,b	$-CH_2CH(OH)CH_2-$	2	2	D-6	57,67	Belohradsky et al., 1987b
C_3H_6O	$-CH_2CH(OH)CH_2-$	2	3	D-6	71	Belohradsky et al., 1987b
C_3H_6O,c	$-CH_2CH(OH)CH_2-$	3	3	D-6	55,73	Belohradsky et al., 1987b
$C_4H_4O_2$	$-C(O)(CH_2)_2C(O)-$	2	2	D-1	97	Johnson et al., 1980
$C_4H_4O_2$	$-C(O)(CH_2)_2C(O)-$	3	3	D-1	87	Johnson et al., 1980
$C_4H_4O_3$	$-C(O)CH_2OCH_2C(O)-$	2	2	D-1		He et al., 1988
$C_4H_4O_3$	$-C(O)CH_2OCH_2C(O)-$	3	3	D-1		He et al., 1988
C_4H_8	$-(CH_2)_4-$	2	2	D-1		Johnson et al., 1980
C_4H_8	$-(CH_2)_4-$	3	3	D-1		Johnson et al., 1980

C_4H_8O	$-(CH_2)_2O(CH_2)_2-$	2	2	D-1		He et al., 1988
C_4H_8O	$-(CH_2)_2O(CH_2)_2-$	3	3	D-1		He et al., 1988
C_4H_8O	$-CH_2CH(OCH_3)CH_2-$	1	1	D-1	59	Zavada et al., 1989
C_4H_8O	$-CH_2CH(OCH_3)CH_2-$	2	2	D-1	58	Zavada et al., 1989
C_4H_8O	$-CH_2CH(OCH_3)CH_2-$	3	3	D-1	52	Zavada et al., 1989
$C_4H_8O_2$,a	$-CH_2(CHOH)_2CH_2-$	2	2	D-5	88	Lukyanenko et al., 1986
$C_4H_8O_2$,b	$-CH_2(CHOH)_2CH_2-$	3	3	D-5	62	Lukyanenko et al., 1986
$C_5H_6O_2$	$-C(O)(CH_2)_3C(O)-$	2	2	D-1		He et al., 1988
				D-1	100	Johnson et al., 1980
$C_5H_6O_2$	$-C(O)(CH_2)_3C(O)-$	3	3	D-1		He et al., 1988
				D-1	95	Johnson et al., 1980
$C_5H_8N_2O$	2-oxotetrahydroimidazol-1,3-$(CH_2)_2-$	1	1	D-3	95	Bogatskii et al., 1983
C_5H_{10}	$-(CH_2)_5-$	2	2	D-1		He et al., 1988
				D-1		Johnson et al., 1980
C_5H_{10}	$-(CH_2)_5-$	3	3	D-1		He et al., 1988
				D-1		Johnson et al., 1980
$C_6H_8O_2$	$-C(O)(CH_2)_4C(O)-$	2	2	D-1	94	Johnson et al., 1980
$C_6H_8O_2$	$-C(O)(CH_2)_4C(O)-$	3	3	D-1	94	Johnson et al., 1980

TABLE 5.9. (*Continued*)

A		n	m	Methods (or from R = formula in appropriate table)	Yield (%)	References
Formula	Structure					
$C_6H_{10}N_2OS_2$	$-C(S)NH(CH_2)_2O(CH_2)_2NHC(S)-$	2	2		98	Lukyanenko et al., 1987
C_6H_{12}	$-(CH_2)_6-$	2	2	D-1		Johnson et al., 1979, 1980
C_6H_{12}	$-(CH_2)_6-$	3	3	D-1		Johnson et al., 1980
$C_6H_{12}O_2$	$-(CH_2)_2O(CH_2)_2O(CH_2)_2-$	1	1	D-8	17	Krakowiak and Bradshaw, 1991
$C_7H_{10}O_2$	$-C(O)(CH_2)_5C(O)-$	2	2	D-1	71	Johnson et al., 1979, 1980
$C_7H_{10}O_2$	$-C(O)(CH_2)_5C(O)-$	3	3	D-1	85	Johnson et al., 1980
C_7H_{14}	$-(CH_2)_7-$	2	2	D-1		Johnson et al., 1980
C_7H_{14}	$-(CH_2)_7-$	3	3	D-1		Johnson et al., 1980
$C_7H_{14}O_2$	2,2-$(CH_3)_2$-1,3-dioxolan-4,5-$(CH_2)_2$-	2	2	D-5	34	Lukyanenko et al., 1986
$C_8H_9NO_2$	$-CH_2$-1,3-(2-NO_2)$C_6H_3CH_2$-	2	2	D-1	97	Johnson et al., 1980
$C_8H_9NO_3$	$-CH_2$-1,3-(2-HO-5-NO_2)$C_6H_2CH_2$-	1	1	(C_2H_5O,b;T 5.2)		Lukyanenko et al., 1990
$C_8H_9NO_3$	$-CH_2$-1,3-(2-HO-5-NO_2)$C_6H_2CH_2$-	2	2	(C_2H_5O,b;T 5.3)		Lukyanenko et al., 1990
$C_8H_9NO_3$	$-CH_2$-1,3-(2-HO-5-NO_2)$C_6H_2CH_2$-	3	3	(C_2H_5O,b;T 5.5)		Lukyanenko et al., 1990

C_8H_8	$-CH_2-1,3-C_6H_4CH_2-$	2	2	D-1	88	Johnson et al., 1980
C_8H_8	$-CH_2-1,3-C_6H_4CH_2-$	3	3	D-1	98	Johnson et al., 1980
C_8H_8	$-CH_2-1,4-C_6H_4CH_2-$	2	2	D-1	89	Johnson et al., 1980
C_8H_8	$-CH_2-1,4-C_6H_4CH_2-$	3	3	D-1	97	Johnson et al., 1980
C_8H_8O	$-CH_2-1,3-(2-HO)C_6H_3CH_2-$	2	2	$(C_{10}H_{10}O_2)$		Kitazawa et al., 1983
$C_8H_{16}O_2$	$-(CH_2)_3O(CH_2)_2O(CH_2)_3-$	1	1	D-8	16	Krakowiak and Bradshaw, 1991
$C_9H_8O_2$	$-CH_2-1,3-(2-HO-5-CHO)C_6H_2CH_2-$	1	1	$(C_2H_5O,b;T\ 5.2)$		Lukyanenko et al., 1990
$C_9H_8O_2$	$-CH_2-1,3-(2-HO-5-CHO)C_6H_2CH_2-$	2	2	$(C_2H_5O,b;T\ 5.3)$		Lukyanenko et al., 1990
$C_9H_8O_2$	$-CH_2-1,3-(2-HO-5-CHO)C_6H_2CH_2-$	3	3	$(C_2H_5O,b;T\ 5.5)$		Lukyanenko et al., 1990
$C_9H_{10}O$	$-CH_2-1,3-(2-HO-5-CH_3)C_6H_2CH_2-$	1	1	$(C_2H_5O,b;T\ 5.2)$		Lukyanenko et al., 1990
$C_9H_{10}O$	$-CH_2-1,3-(2-HO-5-CH_3)C_6H_2CH_2-$	2	2	$(C_2H_5O,b;T\ 5.3)$		Lukyanenko et al., 1990
$C_9H_{10}O$	$-CH_2-1,3-(2-HO-5-CH_3)C_6H_2CH_2-$	3	3	$(C_2H_5O,b;T\ 5.5)$		Lukyanenko et al., 1990
$C_{10}H_{10}O_2$	$-CH_2-1,3-(2-CH_3CO_2)C_6H_3CH_2-$	2	2			Kitazawa et al., 1983
$C_{10}H_{12}O$	$-CH_2CH(OCH_2C_6H_5)CH_2-$	1	1	(C_3H_6O,a)	93	Zavada et al., 1989
$C_{10}H_{12}O$	$-CH_2CH(OCH_2C_6H_5)CH_2-$	2	2	(C_3H_6O,b)	71	Zavada et al., 1989
$C_{10}H_{12}O$	$-CH_2CH(OCH_2C_6H_5)CH_2-$	3	3	(C_3H_6O,c)	76	Zavada et al., 1989
$C_{10}H_{18}N_2O_3S_2$	$-C(S)NHCH_2(CH_2OCH_2)_3-CH_2NHC(S)-$	2	2		98	Lukyanenko et al., 1987
$C_{10}H_{20}O_3$	$-(CH_2)_2(CH_2OCH_2)_3(CH_2)_2-$	1	1	D-8	8	Krakowiak and Bradshaw, 1991

TABLE 5.9. (*Continued*)

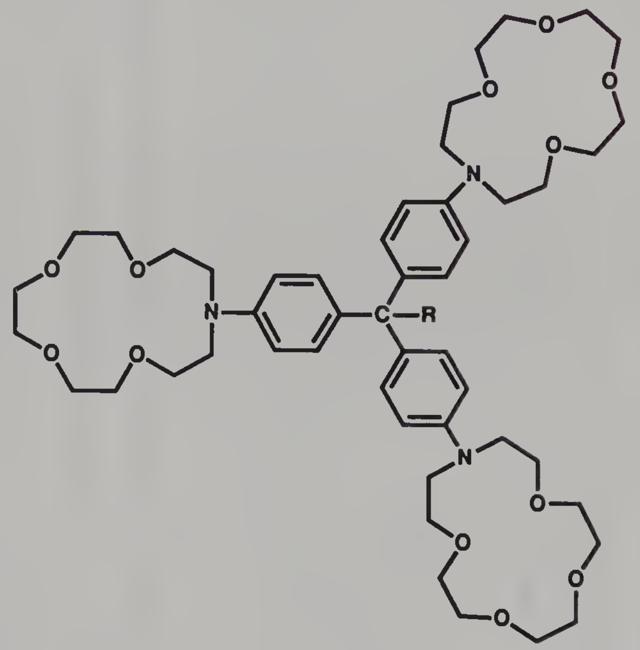
A		n	m	Methods (or from R = formula in appropriate table)	Yield (%)	References
Formula	Structure					
$C_{12}H_8N_2O$	-4-C_6H_4N(O)=N-4-C_6H_4-	2	2	(C_6H_4NO;T 5.3)	65	Dix and Vogtle, 1978, 1980
$C_{12}H_8O_2Fe$	-C(O)ferroceneC(O)-	2	2	D-1	85	Beer, 1985
						Beer et al., 1990a
$C_{12}H_8O_2Fe$	-C(O)ferroceneC(O)-	3	3	D-1	80	Beer, 1985
				D-1		Beer et al., 1990a
$C_{12}H_8O_2Ru$	-C(O)ruthenoceneC(O)-	2	2	D-1		Beer and Keefe, 1986
					80	Beer et al., 1990a
$C_{12}H_8O_2Ru$	-C(O)ruthenoceneC(O)-	3	3	D-1		Beer and Keefe, 1986
					75	Beer et al., 1990a
$C_{12}H_{10}$	-CH_2-2,7-naphthaleneCH_2-	2	2	D-1	99	Johnson et al., 1980
$C_{12}H_{22}O_5$	-2-CH_2(15-crown-5)3-CH_2-	2	2	($C_4H_8O_2$,a)	23	Lukyanenko et al., 1986
$C_{12}H_{22}N_2O_4S_2$	-C(S)NHCH_2(CH_2OCH_2)$_4$-CH_2NHC(S)-	2	2		98	Lukyanenko et al., 1987
$C_{13}H_{10}$	4-$C_6H_4CH_2$-4-C_6H_4-	2	2	D-7		Dix and Vögtle, 1978
$C_{14}H_8N_2O_2$	C(O)C_6H_4N=NC_6H_4C(O)-	2	2		72	Shinkai et al., 1981

$C_{14}H_{12}N_2$	$CH_2C_6H_4N{=}NC_6H_4CH_2$-	2	2		36	Shinkai et al., 1981
$C_{14}H_{26}O_6$	-2-CH_2(18-crown-6)3-CH_2-	3	3	($C_4H_8O_2$,b)	21	Lukyanenko et al., 1986
$C_{15}H_{10}O_4$	-$C_6H_4CH(C_2O_4H)C_6H_4$-	2	2	D-7		Dix and Vögtle, 1978
$C_{15}H_{30}$	-$CH_2CH(C_{12}H_{25})CH_2$-	0	0	D-1	12	Sakamoto et al., 1986
				D-1		Kimura et al., 1985
$C_{15}H_{30}$	-$CH_2CH(C_{12}H_{25})CH_2$-	1	1	D-1	28	Sakamoto et al., 1986
				D-1		Kimura et al., 1985
$C_{15}H_{30}$	-$CH_2CH(C_{12}H_{25})CH_2$-	2	2	D-1	22	Sakamoto et al., 1986
				D-1		Kimura et al., 1985
$C_{15}H_{30}$	-$CH_2CH(C_{12}H_{25})CH_2$-	3	3	D-1	19	Sakamoto et al., 1986
$C_{16}H_{17}N_3O_3$	-CH_2-1,3-[2-HO-5($N{=}NC_6H_4$)-4-$SO_2N(CH_3)_2$]-$C_6H_2CH_2$-	2	2	(C_8H_8O)		Kitazawa et al., 1983
$C_{17}H_{15}N_2$	-C_6H_4-4-$NH(CH)_5$-4-NHC_6H_4-	2	2	(C_6H_6N;T 5.3)	89	Dix and Vögtle, 1980
$C_{19}H_{14}$	-$C_6H_4CH(C_6H_5)C_6H_4$-	2	2	D-7		Dix and Vögtle, 1978
$C_{19}H_{36}$	-$CH_2(CH_2)_{16}CH_2$-	2	2	D-1	72	Anelli and Quici, 1988
$C_{19}H_{36}$	-$CH_2(CH_2)_{16}CH_2$-	3	3	D-1	59	Anelli and Quici, 1988
$C_{19}H_{38}O_2$	-$CH(C_{12}H_{25})[CH_2O(CH_2)_2]_2$-	0	0	D-1	31	Sakamoto et al., 1986
$C_{19}H_{38}O_2$	-$CH(C_{12}H_{25})[CH_2O(CH_2)_2]_2$-	1	1	D-1	36	Sakamoto et al., 1986
$C_{19}H_{38}O_2$	-$CH(C_{12}H_{25})[CH_2O(CH_2)_2]_2$-	2	2	D-1	30	Sakamoto et al., 1986

TABLE 5.9. (*Continued*)

A		n	m	Methods (or from R = formula in appropriate table)	Yield (%)	References
Formula	Structure					
$C_{19}H_{38}O_2$	$-CH(C_{12}H_{25})[CH_2O(CH_2)_2]_2-$	3	3	D-1	23	Sakamoto et al., 1986
$C_{20}H_{36}O_4$	$-C(C_{12}H_{25})(CH_3)[CO_2(CH_2)_2]_2-$	1	1	D-2	20	Sakamoto et al., 1986
$C_{20}H_{36}O_4$	$-C(C_{12}H_{25})(CH_3)[CO_2(CH_2)_2]_2-$	2	2	D-2	21	Sakamoto et al., 1986
$C_{20}H_{36}O_4$	$-C(C_{12}H_{25})(CH_3)[CO_2(CH_2)_2]_2-$	3	3	D-2	18	Sakamoto et al., 1986
$C_{21}H_{19}N$	$-C_6H_4CH[(CH_3)_2NC_6H_4]C_6H_4-$	2	2			Dix and Vögtle, 1978
$C_{25}H_{14}O_2Cl_4$	$-C_6H_4C(C_6H_5)(C_6HCl_4O_2)C_6H_4-$	2	2			Dix and Vögtle, 1978

TABLE 5.10. TRIS(MONOAZA-15-CROWN-5) MACROCYCLES



R	Method	References
H	D-7	Dix and Vögtle, 1978
$C_6HCl_4O_2$	D-7	Dix and Vögtle, 1978

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CHAPTER VI

Diaza-crown Macrocycles

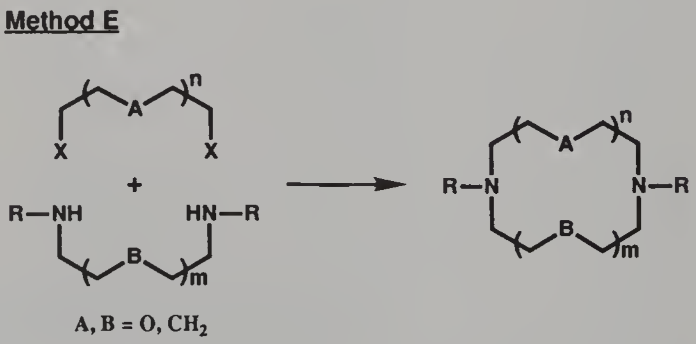
A. INTRODUCTION

The diaza-crowns are important because they are key intermediates in the synthesis of cryptands and other *N*-substituted ligands (Dietrich et al., 1969, 1973; Lehn, 1973, 1978). The diaza-crowns also have complexing properties that are similar to those of certain biological compounds (Hosseini et al., 1987). Diaza-crowns that have no substituents on nitrogen or that have functional groups substituted on nitrogen are also useful for the synthesis of macrotricyclic ligands (Graf and Lehn, 1981; Lehn, 1978; Sutherland, 1986). In addition, functionalized cryptands that are formed from diaza-crowns can be attached to synthetic polymers (Kakiuchi and Tomoi, 1981; Montanari and Tundo, 1981, 1982; Tomoi et al., 1979). Diaza-crowns have also been attached to silica gel (Bradshaw et al., 1988a, 1988b, 1989a).

Ring closure to form a diaza-crown can be done by forming either C—O or C—N bonds. In general, there are either two or four bonds formed in the cyclization process (1:1 or 2:2 cyclizations). The various methods to form diaza-crowns are as follows.

Method E.

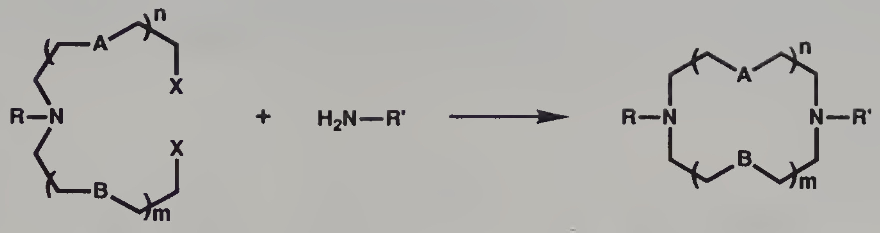
The formation of two C—N bonds by a 1:1 cyclization process. This 1:1 cyclization has been the most common method for preparation of the diaza-crowns, but high-dilution techniques are needed to obtain the best results where diacid dichlorides react with diamines.



Method F.

The formation of two C—N bonds by a 1:1 cyclization of a primary amine and an α,ω-dihalide or ditosylate.

Method F

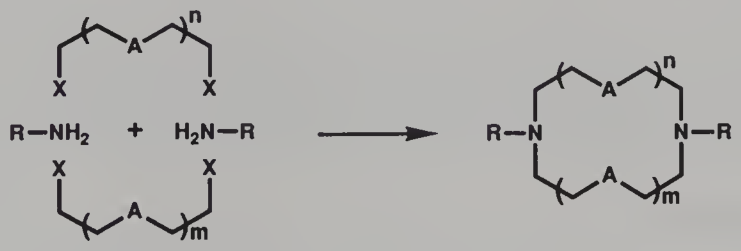


A, B = O, CH_2

Method G.

The formation of four C—N bonds by a 2:2 cyclization of two primary amines and two alkyl dihalides. This method usually gives lower yields of the diaza-crowns than in method E because of the need to form four C—N bonds.

Method G

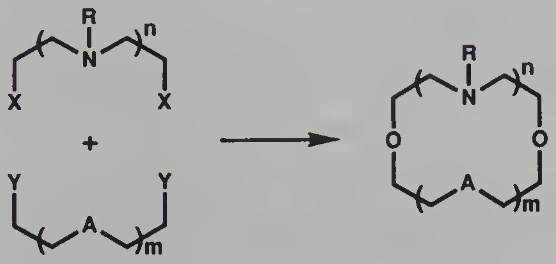


A = O, CH_2

Method H.

The formation of two C—O bonds by a 1:1 cyclization.

Method H

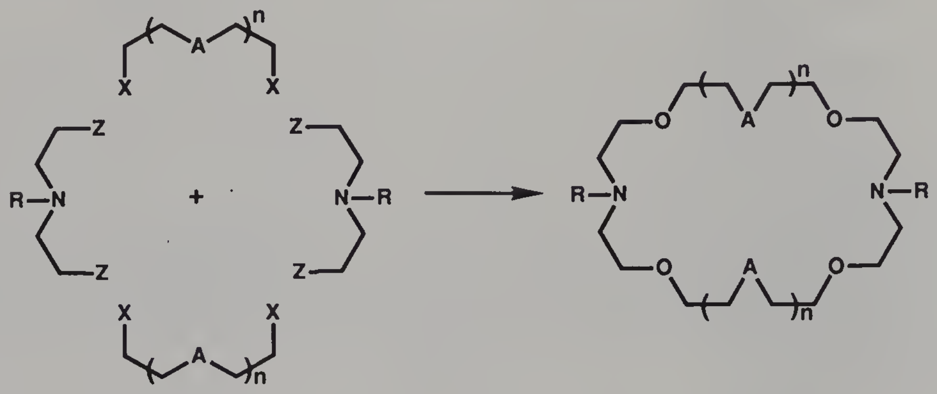


A = NR, O, CH_2
X or Y = OH
the opposite = halogen or OTs

Method I.

The formation of four C—O bonds by a 2:2 cyclization. Again, the yields for method I are somewhat lower than for method H because of the need to form four C—O bonds.

Method I

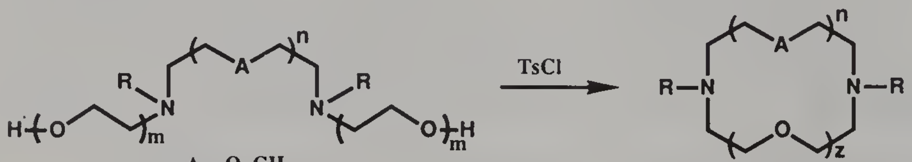


$X = OH$ or OTs
$Z = Cl$ or OH

Method J.

The formation of one C—O bond by an internal cyclization process involving a diaza-α,ω-diol. This intramolecular cyclization (the so-called Okahara cyclization) has been a popular method in recent years.

Method J



$A = O, CH_2$

Method K.

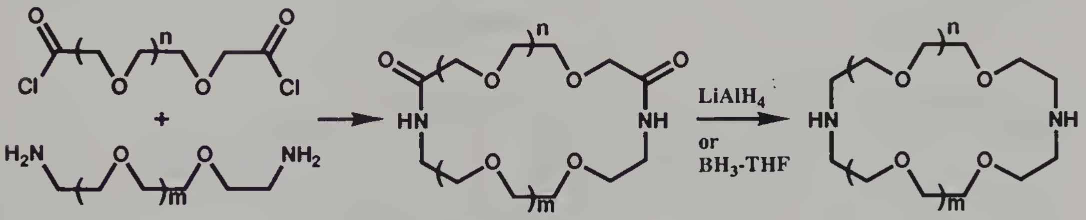
Special reactions.

B. RING CLOSURE TO FORM TWO C—N BONDS BY A 1:1 CYCLIZATION OF A DIAMINE WITH A DIHALIDE OR DITOSYLATE

1. The Reaction of a Dicarboxylyl Dichloride and a Diamine

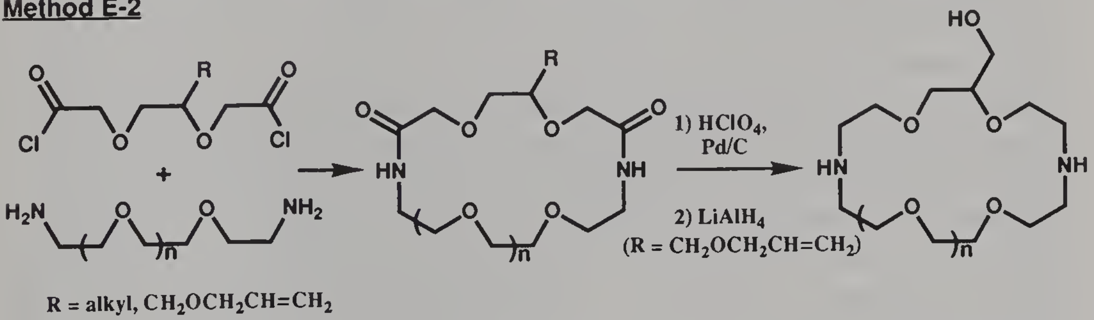
The reaction between a diacid dichloride and a diamine to form a cyclic diamide is the oldest and perhaps most used method to prepare the diaza macrocycles (method E-1) (Dietrich et al., 1973; Simons and Parker, 1967; Stetter and Marx, 1957). This method requires high dilution in benzene, toluene, or THF using a tertiary amine or the starting diamine in excess as the hydrochloric acid scavenger. Using an excess of the starting diamine is preferred if it is inexpensive. The starting materials are each simultaneously dripped into the stirred solvent at 0–25 °C. After the reaction is completed, the reaction mixture is filtered (hot or cold) to remove the hydrochloride salt. The macrocyclic diamide (sometimes called a *dilactam*) is usually purified using silica gel chromatography. Often if the dilution is not high enough (by adding the reactants too fast or by not having enough solvent), a 2:2 cyclization occurs, giving the cyclic tetraamide as a by-product. This by-product can be separated from the desired cyclic diamide by the silica gel chromatography step. The macrocyclic diamide was reduced by $LiAlH_4$ in THF or the borane–THF complex as shown (Dietrich et al., 1969, 1973; Petranek and Ryba, 1980).

Method E-1



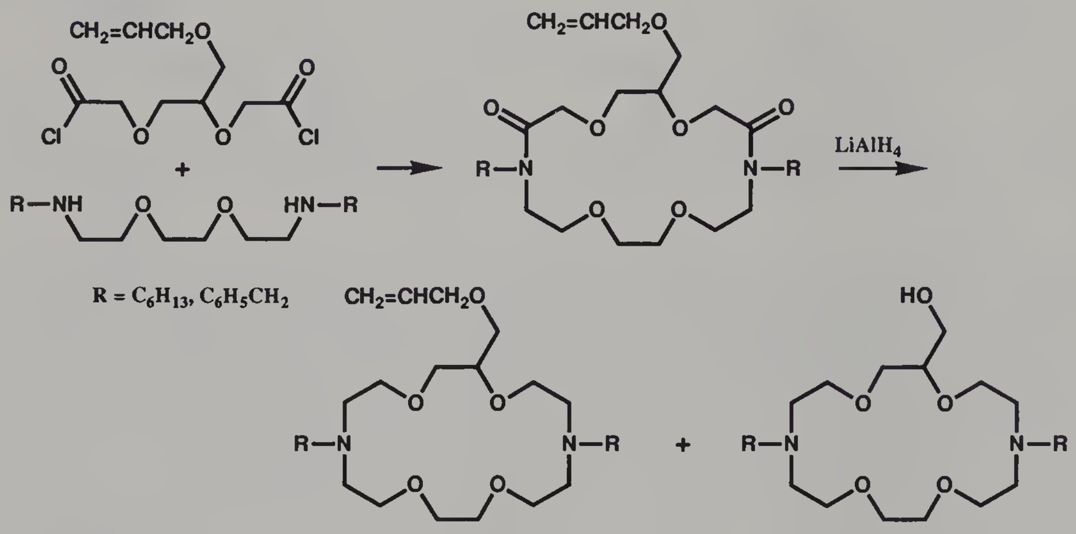
Three hydroxymethyl-substituted diaza-crown compounds were prepared by Bartsch and coworkers using method E-2 but with an (allyloxy)methyl substituent on the diacid dichloride reactant (Babb et al., 1986). The starting (allyloxy)methyl-substituted diacid dichloride was prepared in three steps. Purification of the diacid was difficult because it polymerized during distillation. The cyclization step also required high-dilution techniques. Cinquini and Tundo (1976) used method E-2 to prepare diaza-crowns containing long-chain lipophilic substituents on both a ring carbon and the two ring nitrogen atoms.

Method E-2



A similar method (E-3) was used to prepare allyloxymethyl-substituted *N*,*N*′-dialkyldiaza-18-crown-6, except using a bis secondary amine starting material rather than the bis primary amine (Bradshaw et al., 1988a). Some of the allyl groups were removed during the reduction process to yield the hydroxymethyl-substituted diaza-crown as shown. This hydroxymethyl material was converted back to the allyloxymethyl-substituted macrocycle using allyl bromide. Some of the diaza-crowns prepared using methods E-2 and E-3 can be attached to a solid support (Bradshaw et al., 1988b).

Method E-3

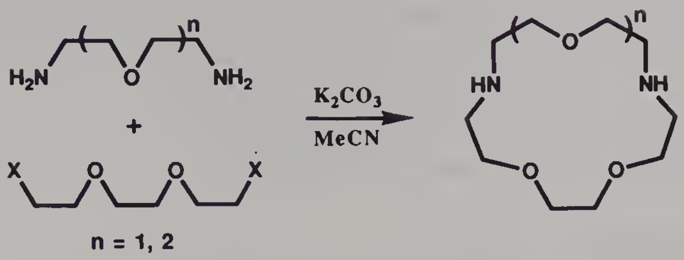


2. The Reaction of a Dihalide or Ditosylate and a Diamine

The cyclization reaction of dihalogen or ditosylate compounds with bis primary or bis secondary amines is similar to the diacid dichloride reaction except that the diaza-crown is obtained in a single step. This is a convenient procedure particularly since the dihalide is usually readily available and inexpensive. This cyclization process does not need high-dilution techniques because of template effects by metal ions. It is important to note that when using a bis primary amine and a dihalide, many side products such as the cryptands and bis-crown ethers can be formed (Alfa et al., 1988; Krakowiak and Bradshaw, 1991).

Kulstad and Malmsten reported that the diaza-crowns could be prepared by reacting a bis primary amine-containing ether and a diiodo ether with sodium or potassium carbonate as the base (method E-4) (Kulstad and Malmsten, 1979, 1980a). The yield was 17% for the preparation of diaza-15-crown-

Method E-4



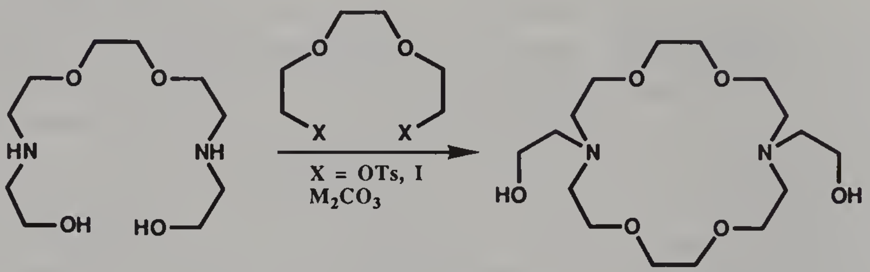
5 but 44% for diaza-18-crown-6. The best yields were obtained when the cation size matched the cavity size (Kulstad and Malmsten, 1980b). The diiodides were the most reactive for ring closure followed by the dibromides. The dichlorides are not reactive in refluxing acetonitrile, so reactions with dichlorides must be carried out in a higher-boiling solvent.

Secondary diamines react with dihalides to give the diaza-crowns in 60–85% yields in acetonitrile in the presence of sodium carbonate (for diaza-15-crown-5) or potassium carbonate (for diaza-18-crown-6) (method E-5). Gokel and coworkers found that the reaction gave higher yields when a 25% excess of the diiodide was used in the presence of 0.5 eq. of sodium iodide (Gatto et al., 1986a, 1986b). Sodium carbonate has a low solubility in acetonitrile while sodium iodide is quite soluble. In the initial stages, the sodium iodide could act as the template for the cyclization reaction. One problem with using sodium iodide in these reactions is that after sitting around for a few days, the diaza-crowns partially decompose even after alumina chromatography. This decomposition could be caused by traces of iodine. Decomposition was absent when dichloro starting materials were used, but product yields were lower (Krakowiak et al, 1989). On the other hand, commercially available ditosylate starting materials can be used in place of the diiodide compounds to give the macrocycles in good yields. The E-5 method was used to prepare *N,N′*-dibenzyldiaza-15-crown-5 and *N,N′*-dibenzyldiaza-18-crown-6. The benzyl groups can be removed by hydrogenation to form the unsubstituted diaza-crowns (Bradshaw et al., 1988a; Gatto et al., 1986b, 1989). The unsubstituted diaza-crowns can be realkylated to form more complicated *N,N′*-dialkyldiaza-crowns.

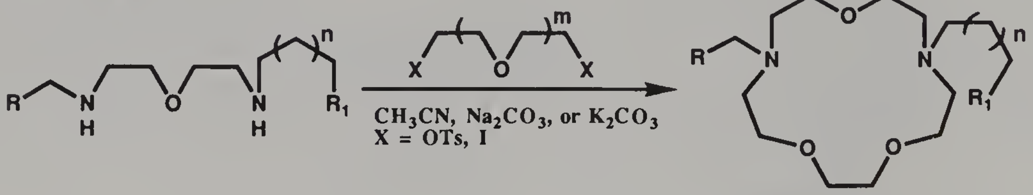
Method E-5

Method E-5 is useful for the preparation of functionalized diaza-crown ethers. As mentioned in previous chapters, alkylation of secondary amine groups in the presence of hydroxy groups is possible when weak bases are used in the reaction. A bis(2-hydroxyethyl)-substituted diaza-18-crown-6 was prepared by this procedure (method E-6) (Bradshaw et al., 1990b; Krakowiak et al., 1990). This procedure also allows the preparation of diaza-crowns with two different groups on the ring nitrogen atoms (method E-7) (Bradshaw et al., 1990a). Some of the alkyl groups contained hydroxy functions. Another interesting approach to the preparation of functionalized diaza-crowns was published recently by Mikiciuk-Olasik and Kotelko (1987) (method E-8).

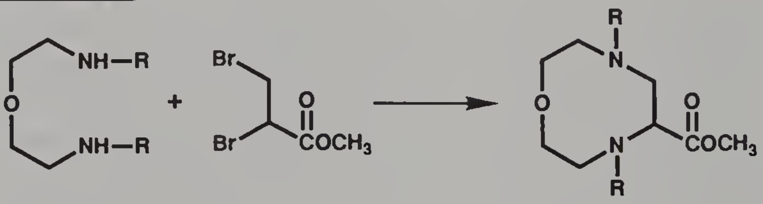
Method E-6



Method E-7



Method E-8

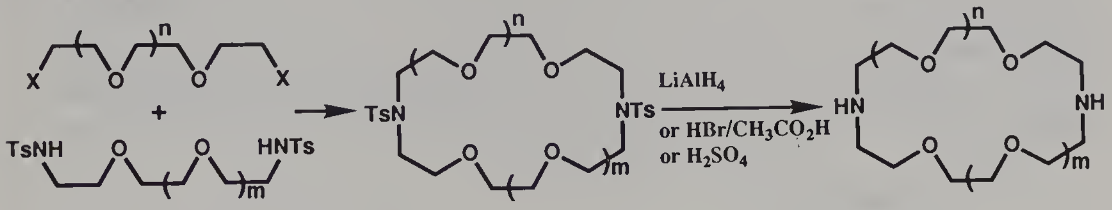


3. The Reaction of a Dihalide or Ditosylate and an *N*,*N*′-Bistosylamide or Biscarboxamide

The *N*,*N*′-bis(*p*-toluenesulfonamide) derivative of diaza-18-crown-6 was prepared by treating the ditosylate ester of triethylene glycol with the *N*,*N*′-bis(*p*-toluenesulfonamide) derivative of a diamino ether in base (method

E-9) (Richman and Atkins, 1974, 1978; Ostaszewski et al., 1988). This method was also successful for the preparation of small diaza macrocycles in good yields (Krakowiak and Kotelko, 1982; Rasshofer et al., 1976). Removal of the *N*-tosyl groups by reduction with lithium aluminum hydride gave the unsubstituted diaza-crowns (Buhleier et al., 1977; Graf and Lehn, 1981; Hosseini et al., 1987). The best cyclization results were realized when ditosylate, dibenzenesulfonate, or dimesylate esters were used as the reactant. Lower yields were realized when using a dichloride or diiodide. It is interesting that at low temperatures, the dibromides gave nearly the same yields as did the ditosylates (Chavez and Sherry, 1989; Krakowiak and Kotelko, 1983). This process was described in great detail in Chapter IV.

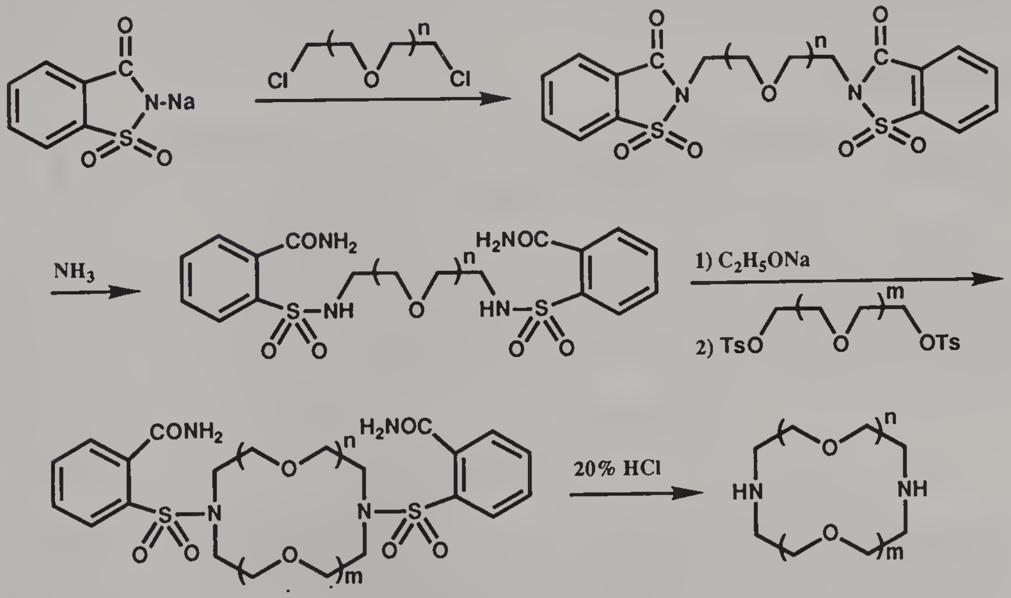
Method E-9



X = OTs, OMs, Cl, Br, I

A similar method uses the *o*-carbamoylbenzenesulfonyl group, derived from saccharin, as the nitrogen atom protecting group rather than the *p*-toluenesulfonyl moiety (method E-10) (Wang et al., 1989). The advantages of this new method are (1) the dichloro derivatives of the polyethylene glycols are inexpensive and readily available as compared to the diamines used in

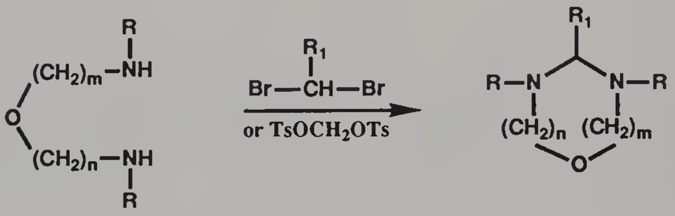
Method E-10



method E-9 and (2) the *o*-carbamoylbenzenesulfonyl protecting groups can be removed more easily than the corresponding *p*-toluenesulfonyl groups. More information about this method is given in Chapter IV.

Small diaza-9-crown-3 and 10-crown-3 compounds with methylene, ethylene, and propylene chains between heteroatoms were prepared by Krakowiak and Kotelko (1982, 1983). These materials were prepared using the *N*-tosyl or *N*-benzenesulfonyl protecting groups on the amine nitrogen atoms (method E-11). The yields were greater than 50%. Unfortunately, methylenediamine compounds are not stable, and when the tosyl groups were removed, the macrocycle cleaved to form an open chain compound.

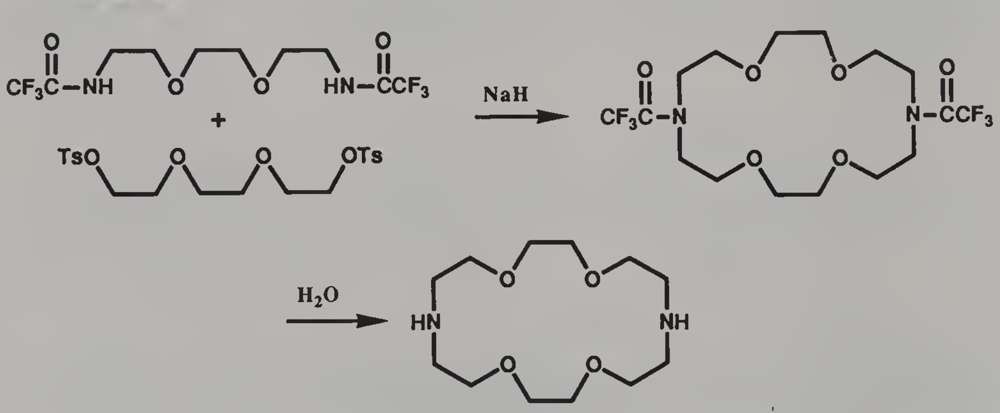
Method E-11



R = Ts, Bs
$R_1 = C_6H_5$, H
m, n = 2, 3

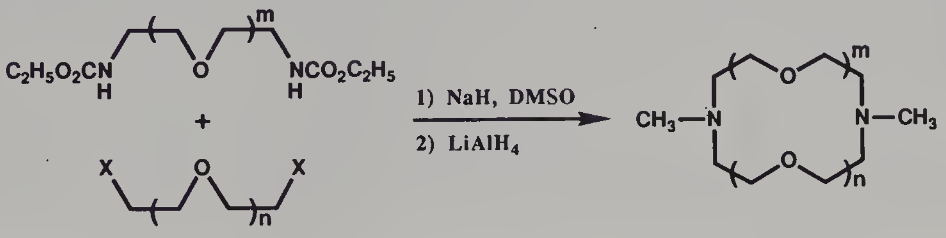
Other amide derivatives have been used to prepare macrocycles. King and Krespan, for example, used the bis(trifluoroacetamide) derivatives rather than the bis(*p*-toluenesulfonamides) for the preparation of diaza-crowns (method E-12) (King and Krespan, 1974). Removal of the trifluoroacetyl group was accomplished by a simple hydrolysis step rather than the more difficult reduction process needed to remove the tosyl protecting groups in method E-9. Even with this modification, the overall yield for method E-12 was only 3% since the cyclization yield was very low.

Method E-12



Sutherland and coworkers used ethyl carboxylate protecting groups when they reacted an oligo(ethyleneoxy)bis(carbamate) with a ditosylate or dihalide to form an *N,N′*-bis(ethoxycarbonyl)-substituted diaza-18-crown-6. The ethoxycarbonyl groups were reduced to form the dimethyl-substituted diaza-crowns (method E-13) (Hodgkinson et al., 1979; Leigh and Sutherland, 1975).

Method E-13



m, n = 1, 2, 3
X = Br, OTs

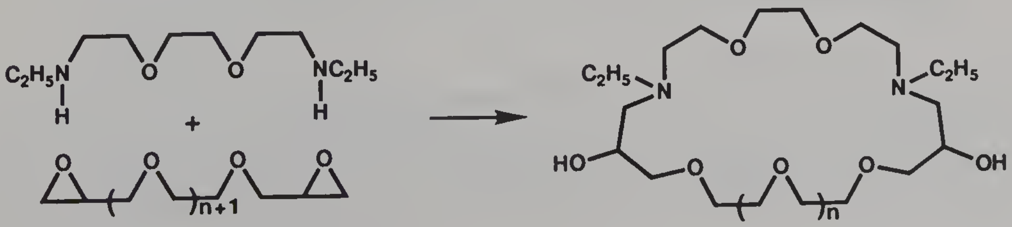
Yields of the macrocycles produced in this reaction were from moderate to good (Pietraszkiewicz and Jurczak, 1984).

Method E-5 is a useful route to the substituted diaza-crowns. However, method E-5 cannot be used to prepare diaza-crowns using bis(2-bromo- or 2-chloroethyl) ether because these starting materials form morpholine derivatives when treated with primary or secondary amines in polar solvents rather than the diaza-crown (Gatto et al., 1986a). Thus, method E-13 could be useful to form the diaza-crowns using bis(2-bromo- or 2-chloroethyl) ether. Method E-9 is useful to form the *N,N′*-unsubstituted diaza-crowns where bis(2-bromo- or 2-chloroethyl) ether is used as a starting material (Lukyanenko et al., 1988a; Richman and Atkins, 1974). Introduction of the diethylene oxide group between nitrogen atoms would also be possible using methods E-1 and E-2, except that diglycolyl dichloride must be used and the product diamide must be reduced (Dietrich et al., 1973).

4. Miscellaneous Ring-Closure Reactions to Form Two C—N Bonds from a Diamine

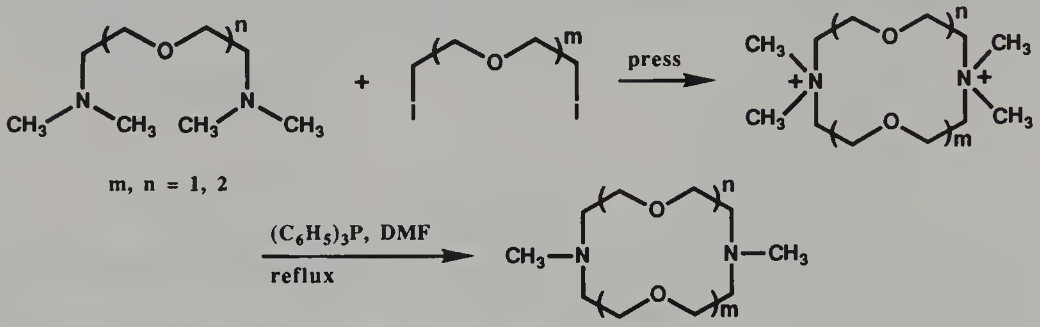
Some miscellaneous reactions have been used to form diaza-crowns from diamines. Okahara and coworkers prepared some diaza-crowns containing two hydroxy functions by reacting a diamine with a bisepoxide (method E-14) (Kikui et al., 1984).

Method E-14



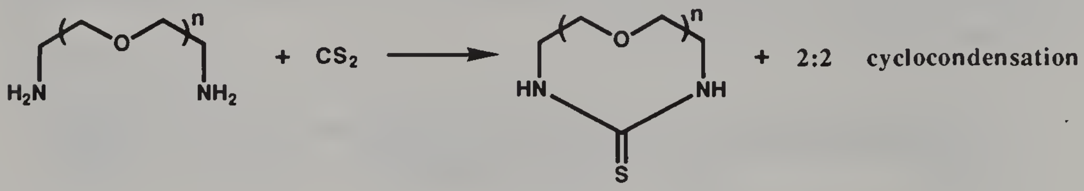
The high-pressure reaction of α,ω-tertiary diamines with α,ω-diiodo compounds gave an almost quantitative yield of the macrocyclic bis quaternary ammonium salts (method E-15) (Jurczak and Pietraszkiewicz, 1985; Jurczak et al., 1989). The macrocyclic bis quaternary ammonium salt was demethylated with triphenylphosphine to give the *N*,*N'*-dimethyldiaza-crowns in good yields. The method looks simple but one needs 10 kbar of pressure, which can be obtained only in a piston cylinder. These authors have prepared other cyclic compounds using this high-pressure method (Jurczak and Pietraszkiewicz, 1985).

Method E-15



Bogatskii and coworkers have formed new diaza-crowns by reacting a bis primary amine with carbon disulfide to form a macrcycle containing the thiourea function (method E-16) (Bogatskii et al., 1980b, 1982b, 1982c, 1984b, 1984c, 1985b). The authors isolated both 1:1 and 2:2 cyclization products.

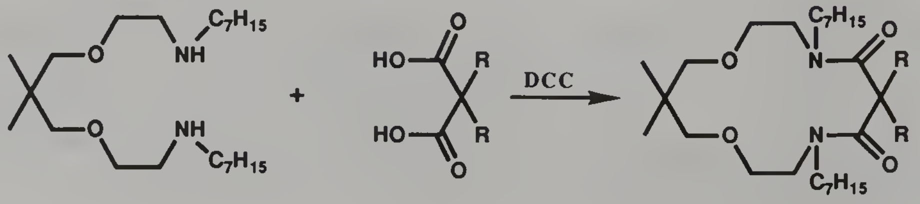
Method E-16



The thiourea unit could be converted to the urea function.

Peptide formation from amino acids is common. The peptide-forming reaction often uses coupling reagents such as *N*,*N'*-dicyclohexylcarbodiimide (DCC). This type of reaction has been used to prepare certain diaza-crowns (method E-17) (Attiyat et al., 1990).

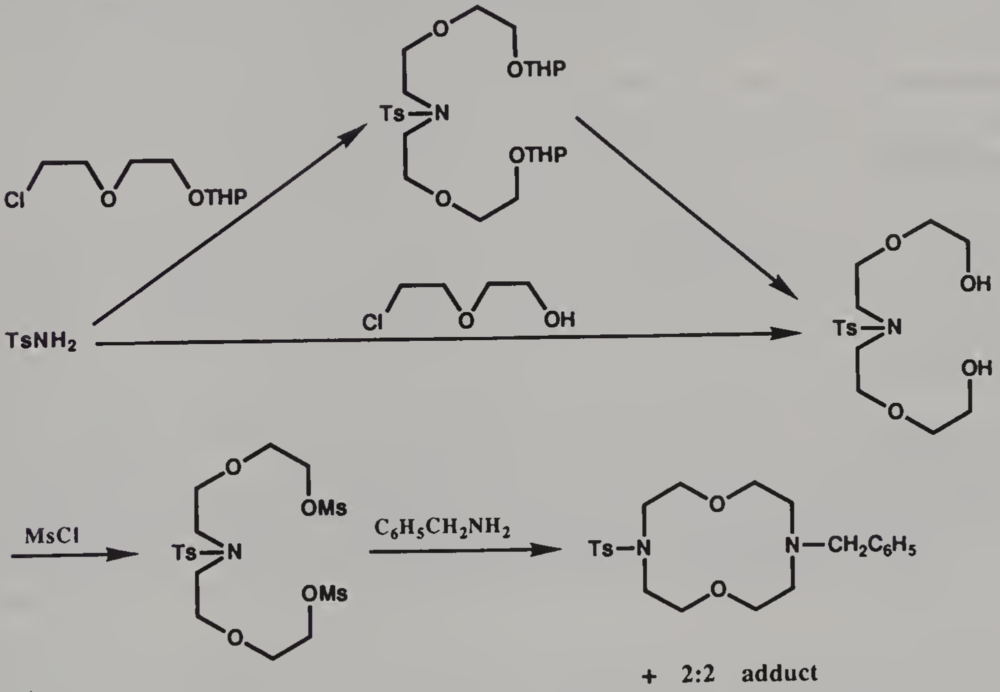
Method E-17



C. RING CLOSURE TO FORM TWO C—N BONDS BY A 1:1 CYCLIZATION OF A PRIMARY AMINE OR AMIDE WITH A DIHALIDE OR DITOSYLATE

The syntheses of diaza-crowns by ring closure reactions to form two C—N bonds with the same nitrogen atom are rare. The cyclization of an *N*-tosylamidodimesylate with benzylamine gave more than a 50% yield of the *N*-benzyl-*N*′-tosyldiaza-12-crown-4 (method F-1) (Calverley and Dale, 1981; Anelli et al., 1988). Anelli and coworkers also isolated the 2:2 adduct, tetraaza-24-crown-8, in a 5% yield. The tosylamidodiol was first prepared from THP-protected 2-(2-chloroethoxy)ethanol (Calverley and Dale, 1981; Dale and Calverley, 1982). Later it was found that the THP protecting group was not necessary (Anelli et al., 1988).

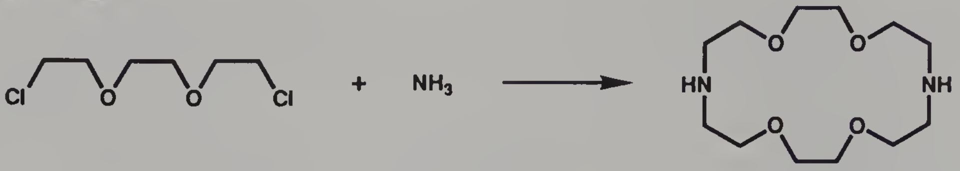
Method F-1



D. RING CLOSURE TO FORM FOUR C—N BONDS BY A 2:2 CYCLIZATION OF A PRIMARY AMINE OR AMIDE WITH A DIHALIDE OR DITOSYLATE

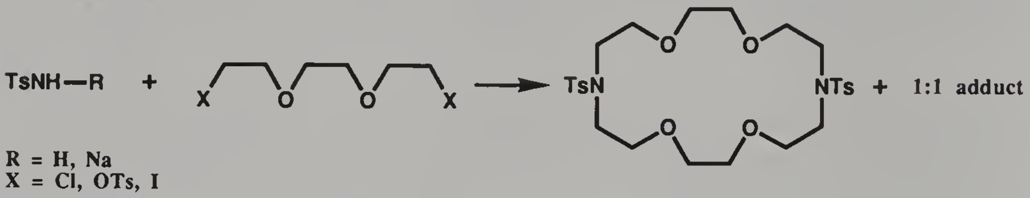
The simultaneous formation of four C—N bonds to form a diaza-crown is much more difficult, and the yields are lower than where cyclization takes place by formation of two C—N bonds. In the first example, diaza-18-crown-6 was isolated as a by-product in the formation of linear polyoxaamines in the reaction of the dichloro derivative of triethylene glycol with ammonia (method G-1) (King and Krespan, 1974). It was later determined that the diiodide derivative of triethylene glycol gave higher cyclization yields (Kulstad and Malmsten, 1979).

Method G-1



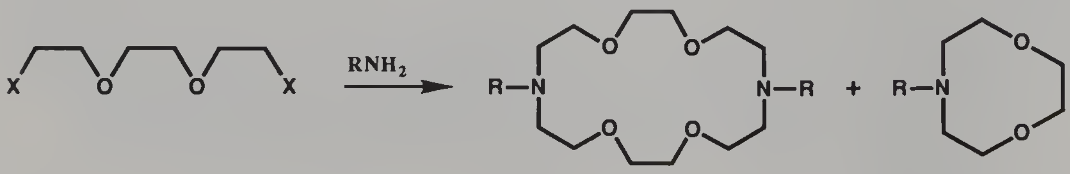
The reaction of sodium tosylamide (or tosylamide in the presence of base) with the ditosylate ester of triethylene glycol gave *N*,*N*′-ditosyldiaza-18-crown-6 in 9% or 77% yields depending on reaction conditions, while the dichloro starting material gave a 15% yield of the diaza-crown (method G-2) (Rasshofer and Vögtle, 1978; Ostaszewski et al., 1988). Reaction with the diiodo starting material gave a 5% yield of the macrocycle and 25% of *N*-tosylaza-9-crown-3, the 1:1 cycloadduct (Bottino et al., 1988; Pappalardo et al., 1985). It should be mentioned that nearly the same conditions and starting materials can give linear *N*,*N*′-ditosylpolyoxadiamines (Lukyanenko et al., 1988a).

Method G-2



Gokel and coworkers prepared a series of *N*,*N*′-di-substituted diaza-18-crown-6 ligands by a 2:2 cyclization of a primary amine with triethylene glycol dihalide (method G-3) (Gatto and Gokel, 1984; Gatto et al., 1986a, 1986b).

Method G-3

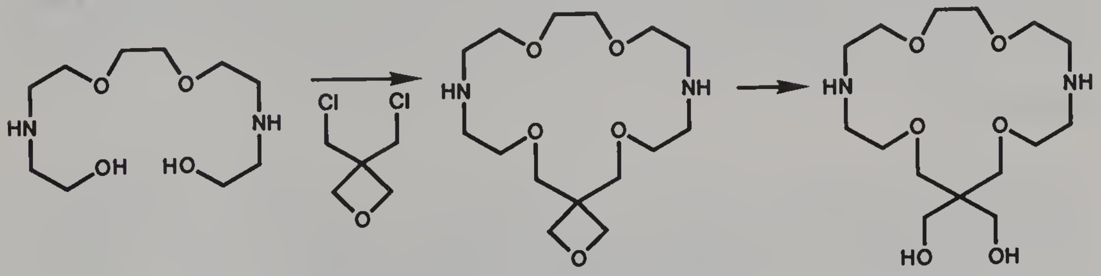


Only the diaza-18-crown-6 was observed when R was a benzylic or aliphatic group. When R was a 4-substituted phenyl (e.g., 4-OCH_3), only the 1:1 adduct, aza-9-crown-3, was isolated. The authors suggested that since the aniline nitrogen atom is less nucleophilic than an aliphatic amine nitrogen atom, it reacted more slowly with the iodide and therefore cyclization to the nine-membered ring was preferred. The reaction gave a 25–30% yield of the products (1:1 with substituted aniline or 2:2 with aliphatic amines) in refluxing acetonitrile. Some of the *N*,*N*′-dialkyldiaza-crowns were prepared by method E-5 with twice the yields as in G-3. The product is more difficult to isolate in the one-step G-3 method because of the many by-products that are formed but the starting materials are inexpensive and there are less steps in the overall process.

E. RING CLOSURE TO FORM TWO C—O BONDS BY A 1:1 CYCLIZATION OF A DIOL WITH A DIHALIDE, DITOSYLATE, OR EPICHLOROHYDRIN

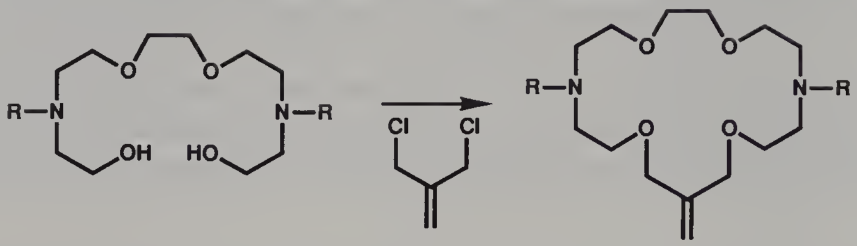
As mentioned previously, crown ethers containing functional substituents, such as a hydroxymethyl or vinyl group, are important synthetic intermediates used to immobilize the crown onto silica gel (Bradshaw et al., 1988b, 1989a, 1989b; Izatt et al., 1988) and to prepare more complex compounds such as the lariat crown ethers (Gatto et al., 1986a). The easiest method to attach a functional group is through one of the ring nitrogen atoms by alkylation or acylation reactions. Functionalized diaza-crowns containing the functional group attached to a ring carbon atom also have been synthesized. These latter functionalized diaza-crowns have been prepared by the reaction of a diol and a dihalide (ditosylate) or epichlorohydrine. Krespan was one of the first to prepare a functionalized diaza-crown when he synthesized a bis(hydroxymethyl)diaza-19-crown-6 by treating a diazadiol with 3,3-bis(chloromethyl)oxetane (method H-1) (Krespan, 1975, 1980).

Method H-1



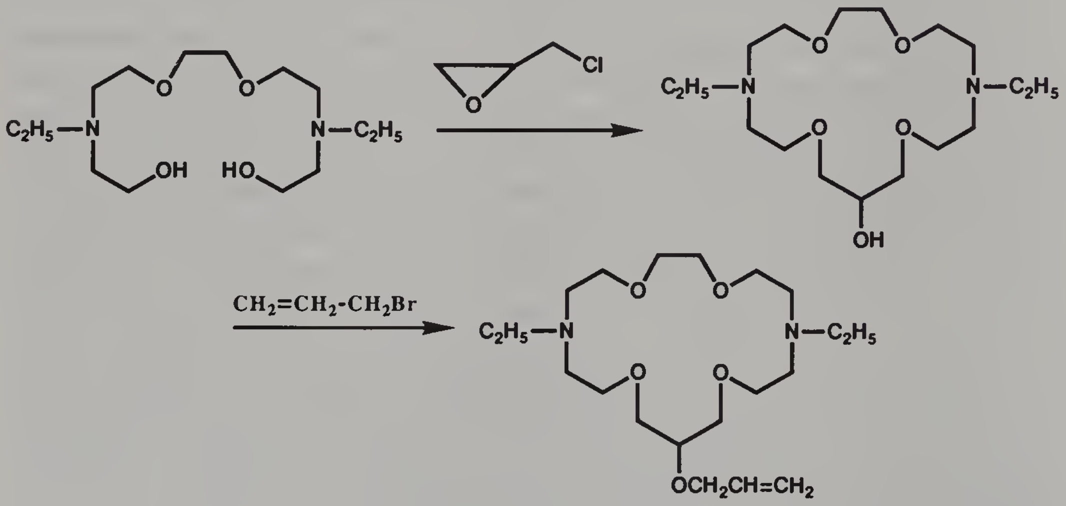
Tomoi and coworkers and, more recently, Bradshaw and coworkers, have prepared similar diaza-crowns but containing an exocyclic methylene group (method H-2) (Bradshaw et al., 1989c; Kakiuchi and Tomoi, 1981; Kakiuchi et al., 1980; Tomoi et al., 1978, 1979). The methylene group can be converted into a hydroxymethyl substituent by hydroboration (Tomoi et al., 1978). The hydroxy group can also be introduced by a one-step reaction of epichloro-

Method H-2



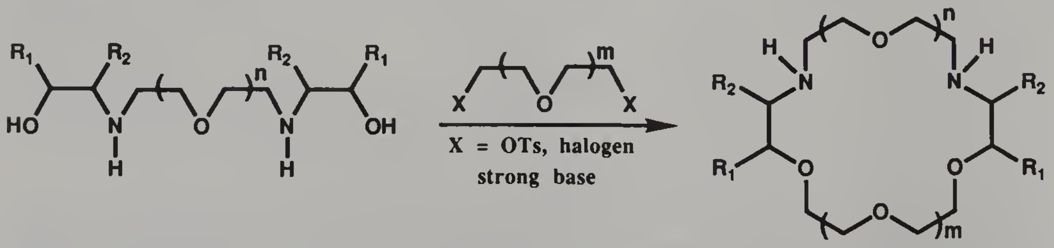
hydrin with a glycol (Bartsch et al., 1983). This procedure was applied to the preparation of hydroxy-substituted diaza-crowns (method H-3) (Bradshaw et al., 1989c).

Method H-3



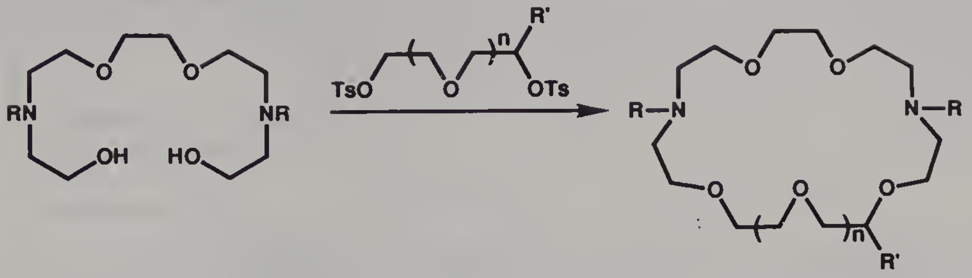
Okahara and coworkers prepared a number of diaza-crown compounds with substituents on the macroring carbon atoms. They used the reaction of a diazaoligoethylene glycol with a ditosylate to close the ring (method H-4) (Maeda et al., 1983). They used a strong base that favored reaction by the alkoxy nucleophile over an amine nucleophile.

Method H-4



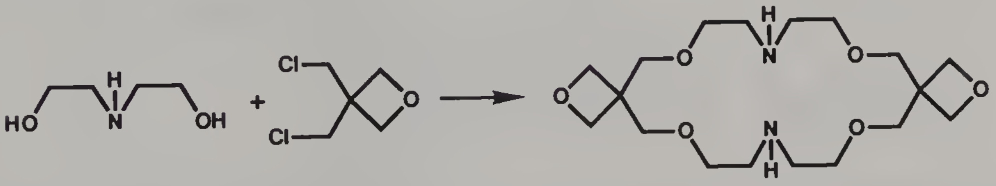
Bradshaw and Krakowiak (1988) prepared *N,N′*-dialkyldiaza-15-crown-5, -18-crown-6, and -21-crown-7 compounds by similar reactions except that the nitrogen atoms contained alkyl substituents (method H-5). They obtained excellent yields of the diaza-crowns.

Method H-5



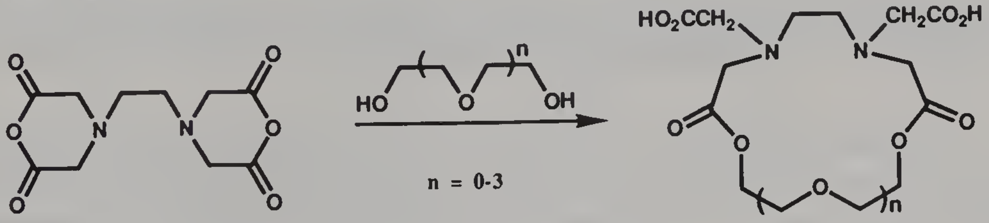
The reaction of diethanolamine and 3,3-bis(chloromethyl)oxetane produced a dioxetanodiaza-20-crown-6 by a 2:2 cyclization process (method H-6) (Krespan, 1975).

Method H-6



EDTA dianhydride when treated with various oligoethylene glycols formed the *N*,*N*′-dicarboxymethyldiazadiester-crown ethers (method H-7) (Qin, 1984).

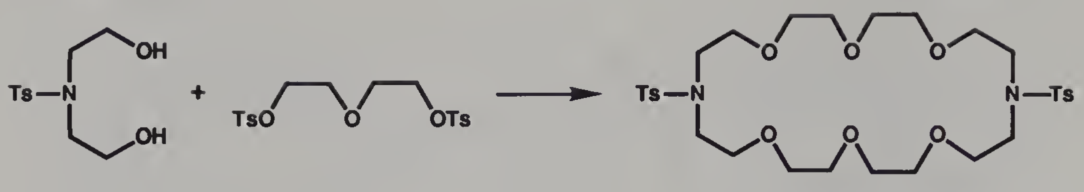
Method H-7



F. RING CLOSURE TO FORM FOUR C—O BONDS BY A 2:2 CYCLIZATION OF A DIOL WITH A DIHALIDE OR DITOSYLATE

While 1:1 cyclization reactions are generally preferred, 2:2 cyclizations to form four C—O bonds will occur where the 1:1 cyclization would produce a 9- or 10-membered ring or where one of the reactants contains a rigid aromatic ring. More often, 2:2 cyclization occurs with concomitant formation of the 1:1 cyclization product. An example of 2:2 cyclization is shown in method I-1 (Johnson et al., 1985). The yield of diaza-24-crown-8 was only 10% and

Method I-1

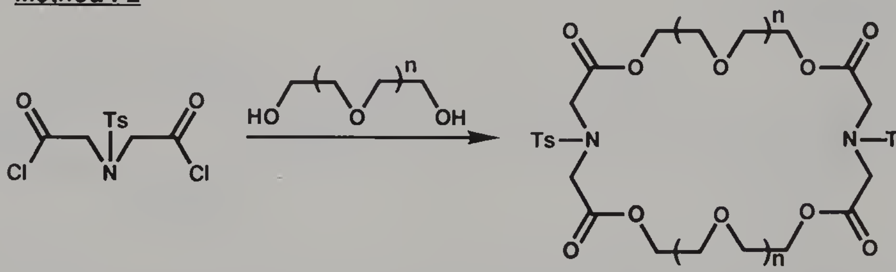


+ **1:1 cycloadduct**

6% of monoaza-12-crown-4, the 1:1 adduct was isolated.

The reaction of a diacid dichloride with an oligoethylene glycol likewise can give both the 1:1 cyclic diester and the 2:2 cyclic tetraester (method I-2) (Qin and Hu, 1984). It is interesting to note that the 2:2 adduct was favored for the formation of 24-crown-8 over 12-crown-4 ligands; however,

Method I-2



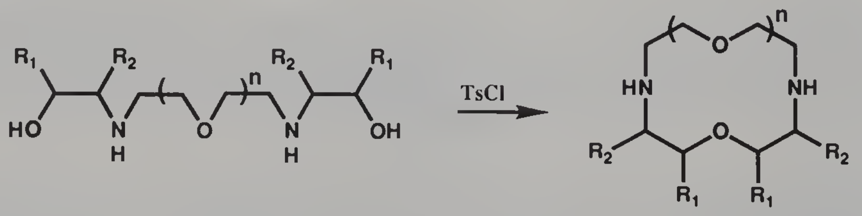
+ **1 : 1 cycloadduct**

the 1:1 cycloadducts were favored where 15- or 18-membered rings could be formed.

G. RING CLOSURE TO FORM ONE C—O BOND BY AN INTERNAL CYCLIZATION PROCESS OF AN α,ω-DIOL

The Okahara ring-closure reaction of an oligoethylene glycol discussed previously has also been used with good results for the preparation of diazacrowns from diazaglycols (method J-1). The final crown has one oxygen less

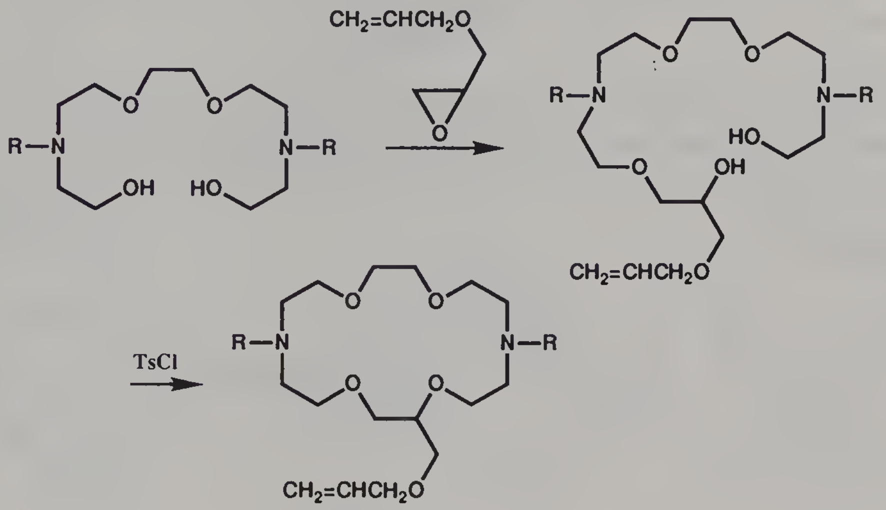
Method J-1



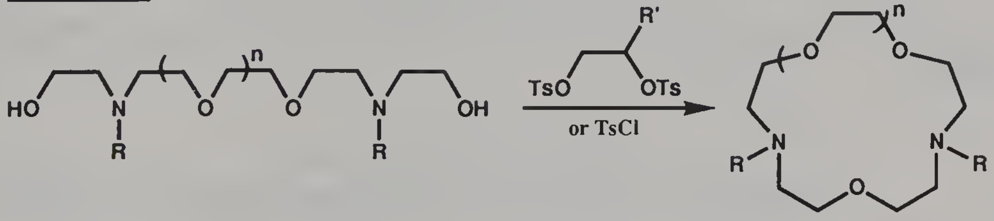
than the starting diazaglycol (Ajinomoto Inc., 1983b; deJong et al., 1983; Maeda et al., 1983). The reaction can be carried out in a *t*-butyl alcohol/dioxane mixture with sodium or potassium hydroxide as the base.

Bradshaw and coworkers reported a more convenient method to prepare the (allyloxy)methyl-substituted diaza-crown compounds (method J-2) (Bradshaw et al., 1988a). Their method, using the Okahara ring-closure procedure, gave a good overall yield of *N*,*N*′-dialkyl-substituted (allyloxy)methyldiaza-18-crown-6. It is interesting that the ditosylate derivative of ethylene glycol also reacted with a diazaoligoethylene glycol to give the Okahara-type ring-closure reaction and not the 1:1 cyclic adduct that was expected (method J-3) (Bradshaw and Krakowiak, 1988; Bradshaw et al., 1988a). The ditosylate eliminated presumably to substitute a tosyl group on the glycol. Some of the same glycols were ring-closed using tosyl chloride.

Method J-2



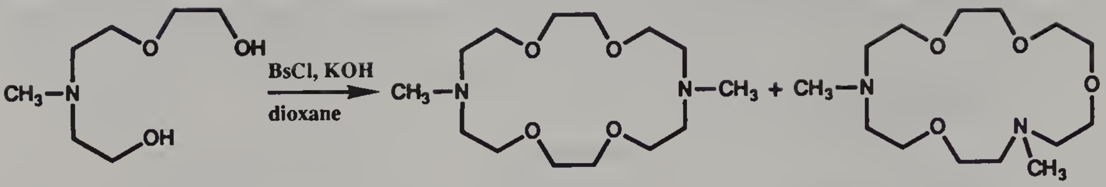
Method J-3



H. MISCELLANEOUS RING-CLOSURE REACTIONS TO FORM DIAZA-CROWN MACROCYCLES

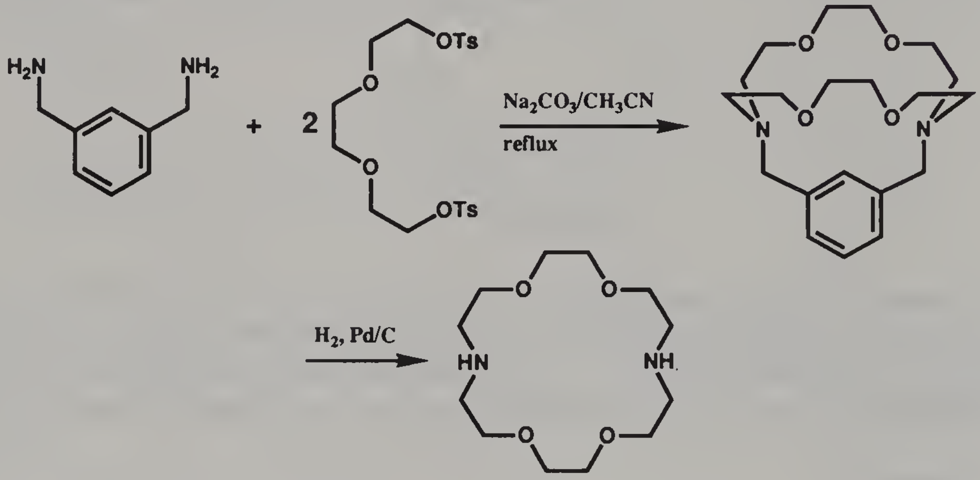
Two miscellaneous methods for preparing the diaza-crowns are presented here. Okahara and coworkers, in an attempt to prepare aza-9-crown-3, reacted an azatriethylene glycol with benzenesulfonyl chloride. The small crown was not obtained, but rather two diaza-18-crown-6 compounds resulting from different orientations of reactants in the dimerization pathway (method K-1) (Kuo et al., 1978).

Method K-1



An unusual method for preparation of 4,13-diaza-18-crown-6 was recently published by Pietraszkiewicz and coworkers (1989) (method K-2). They first formed a 1,3-benzocryptand by reacting 2 mol of triethylene glycol ditosylate with bis-1,3-(aminomethyl)benzene followed by the reductive removal of *m*-xylene.

Method K-2

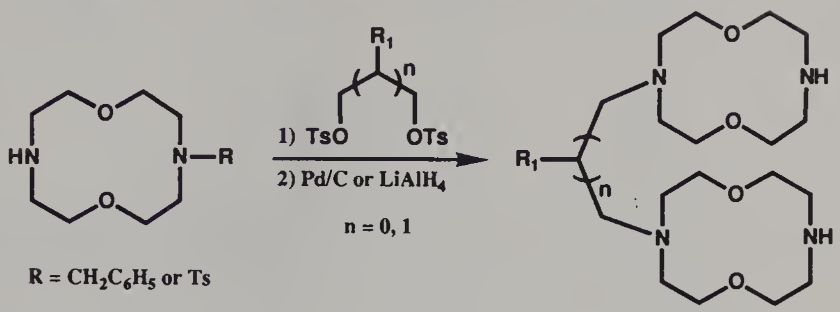


I. PREPARATION OF BIS(DIAZA-CROWN) MACROCYCLES

The bis(diaza-crown ether)s are excellent complexing agents and are starting materials for preparing tricyclic host compounds. Methods to connect two diaza-crowns use a mono *N*-protected diaza-crown as the starting material. The two rings are then connected and the protecting groups removed. The mono-protected diaza-crowns were prepared by two methods. (1) the diaza-crown was prepared with two different *N*-protecting groups and one of the protecting groups was removed selectively (see method F-1 for example) and (2) an excess of an unsubstituted diaza-crown was reacted with the protecting group to form a mono-protected diaza-crown that can be separated from the starting unsubstituted crown. Methods L-1 (Anelli et al., 1985, 1988; Calverley and Dale, 1981; Dale and Calverley, 1982), L-2 (Kumar et al., 1986), L-3 (Lehn et al., 1977), and L-4 (Lukyanenko et al., 1986a) are given below.

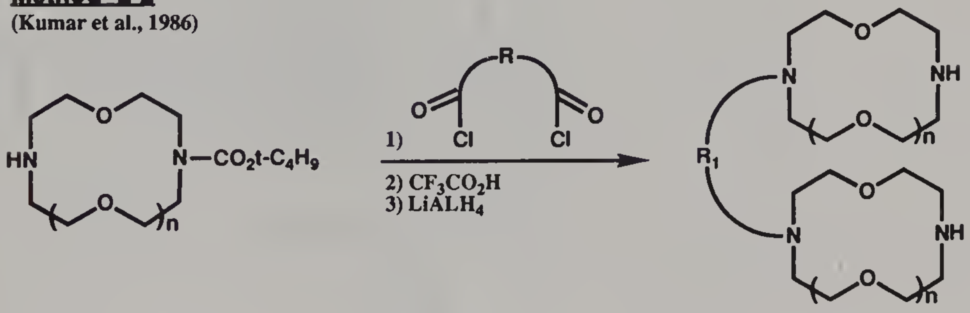
Method L-1

(Anelli et al., 1985, 1988; Calverly and Dale, 1981; Dale and Calverly, 1982)



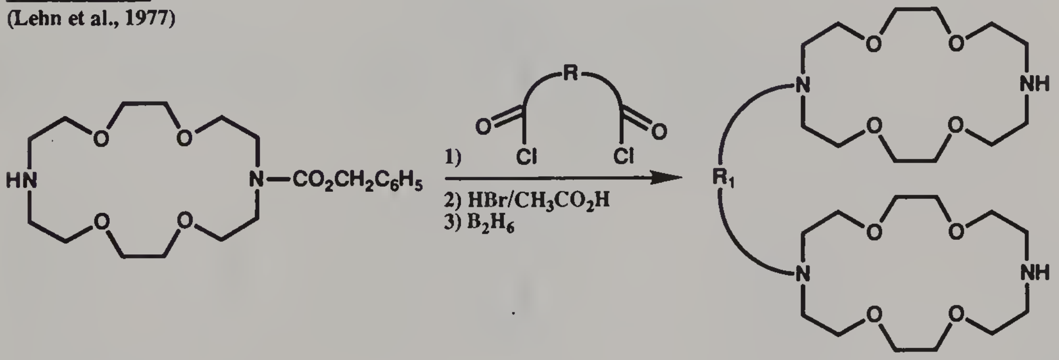
Method L-2

(Kumar et al., 1986)



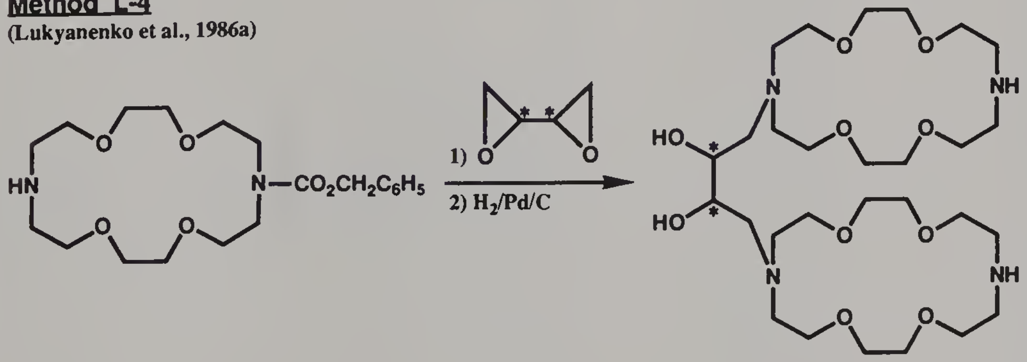
Method L-3

(Lehn et al., 1977)



Method L-4

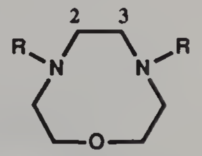
(Lukyanenko et al., 1986a)



Extensive tables containing listings of diaza-crown macrocycles follow. The tables are organized in order of increasing ring size and complexity of the substituent(s). Where possible, the preparative method is indicated along with the yields and references.

J. TABLES OF COMPOUNDS

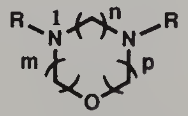
TABLE 6.1. DIAZA-9-CROWN-3 MACROCYCLES



R		Other Substituents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
H	H		E-9	71	Cabral et al., 1990
				59	Ewin and Hill, 1985
			E-9		Hancock and Thöm, 1982
			E-9	55	Reinen et al., 1987
			E-9	92 (salt)	Thöm et al., 1986
H	H	2,3-$(C_6H_5)_2$	E-4	43	Mikiciuk-Olasik et al.,1977
CH_3	CH_3		(H)		Cabral et al., 1990

CH_3	CH_3	$2,3\text{-}(C_6H_5)_2$	(H)	70	Mikiciuk-Olasik et al.,1977
$C_2H_3O_2$	$HO_2CCH_2\text{-}$		(H)		Cabral et al., 1990
				53	Ewin and Hill, 1985
			$(C_4H_7O_2)$	salt	Neves et al., 1988
C_3H_7	C_3H_7	$3\text{-}CO_2CH_3$	E-8	49	Mikiciuk-Olasik and Kotelko, 1987
$C_4H_7O_2$	$C_2H_5O_2CCH_2\text{-}$		(H)	80	Neves et al., 1988
C_4H_9	C_4H_9	$3\text{-}CO_2CH_3$	E-8	51	Mikiciuk-Olasik and Kotelko, 1987
$C_4H_{10}N$	$(CH_3)_2N(CH_2)_2\text{-}$		E-5	16	Mikiciuk-Olasik et al., 1983
$C_5H_{12}N$	$(CH_3)_2N(CH_2)_3\text{-}$		E-5	24	Mikiciuk-Olasik et al., 1983
$C_6H_{14}N$	$(C_2H_5)_2N(CH_2)_2\text{-}$		E-5	41	Mikiciuk-Olasik et al., 1983
$C_7H_7O_2S$	Ts		E-9	41	Craig et al., 1990
				79	Ewin and Hill, 1985
			E-9	41	Hancock and Thöm, 1982
			E-9	41	Rasshofer and Vögtle, 1978
			E-9	32	Rasshofer et al., 1976

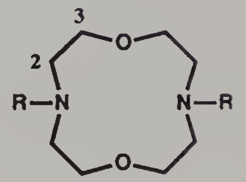
TABLE 6.2. DIAZA-9,10-CROWN-3 MACROCYCLES



R	n	m	p	Other Substituents	Methods (or from R = formula)	Yield (%)	References
H	3	2	2				Cabral et al., 1990
						72	Ewin and Hill, 1985
					E-9	64	Hancock et al., 1990
CH_3SO_2-	2	2	3		E-9	35	Krakowiak and Kotelko, 1982
HO_2CCH_2-	3	2	2			45	Ewin and Hill, 1985
$C_6H_5SO_2$-	1	2	3		E-11	49	Krakowiak and Kotelko, 1983
$C_6H_5SO_2$-	2	2	3		E-9	29	Krakowiak and Kotelko, 1982

$C_6H_5SO_2$-	1	3	3		E-11	29	Krakowiak and Kotelko, 1982
$C_6H_5SO_2$-	4	1	1		E-9	35	Krakowiak et al., 1984
$C_6H_5SO_2$-	5	1	1		E-9	32	Krakowiak et al., 1984
Ts	1	3	3		E-11	32	Krakowiak and Kotelko, 1982
Ts	2	2	3		E-9	32	Krakowiak and Kotelko, 1982
Ts	1	2	3		E-11	53,68	Krakowiak and Kotelko, 1983
Ts	4	1	1		E-9	46	Krakowiak et al., 1984
Ts	5	1	1		E-9	32	Krakowiak et al., 1984
Ts	3	2	2		E-9	47	Ewin and Hill, 1985
					E-9	66	Rasshofer et al., 1976
Ts	2	2	3	2 or 3-CH_3	E-9	28	Krakowiak and Kotelko, 1982
Ts	1	2	3	2-C_6H_5	E-11	38	Krakowiak and Kotelko, 1983
Ts	1	3	3	2-C_6H_5	E-11	23	Krakowiak and Kotelko, 1982

TABLE 6.3. 1,7-DIAZA-12-CROWN-4 MACROCYCLES



R		Other Substituents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
H	H		E-9	88	Amble and Dale, 1979
					Amorim et al., 1990
			E-9	68	Bogatskii et al., 1984d
			E-1		Cowie and Wu, 1988
			E-1	93	Cram et al., 1986
			E-1	55	Dietrich et al., 1973
			E-9	76	Lukyanenko et al., 1988a, 1988b
			E-9		Sheng et al., 1982, 1983
			E-10	46	Wang et al., 1989
H	H	2,6-$(O)_2$	E-1		Cowie and Wu, 1988
			E-1	60	Cram et al., 1986

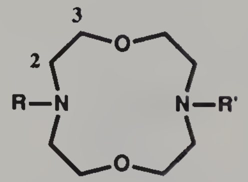
		E-1	65	Dietrich et al., 1973
CH_3	CH_3	(H)	95	Jurczak and Ostaszewski, 1988
		E-15	81	Jurczak and Ostaszewski, 1989
		E-15	81	Jurczak et al., 1989
		(H)	61	Metcalfe et al., 1977
		(H)	82	Ostaszewski et al., 1988
$C_2H_3O_2$	HO_2CCH_2-			Amorim et al., 1990
		(H)		Kolinski and Mrozinski, 1983
C_2H_4Cl	$Cl(CH_2)_2$-	(C_2H_5O)	91	Boyce et al., 1984
		(C_2H_5O)	90	Carroy et al., 1986
C_2H_5O	$HO(CH_2)_2$-	(H)	41	Amble and Dale, 1979
		(H)	94	Boyce et al., 1984
		(H)		Carroy et al., 1986
C_3H_6NO	$(CH_3)_2NC(O)$-	(H)	85	Kataky et al., 1990
C_3H_7O	$CH_3O(CH_2)_2$-	(H)	64	Sheng et al., 1982, 1983
C_2H_6	$(CH_3)_2$-	E-15	99	Jurczak et al., 1989
$C_4H_5O_4$	$HO_2CCH_2OCH_2C(O)$-	(H)	90	Boyce et al., 1984
		(H)	90	Carroy and Lehn, 1986
		(H)		Carroy et al., 1986

TABLE 6.3. (*Continued*)

R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
C_4H_8ClO	$Cl(CH_2)_2O(CH_2)_2$-		($C_4H_9O_2$)	90	Boyce et al., 1984
			($C_4H_9O_2$)	90	Carroy and Lehn, 1986
			($C_4H_9O_2$)	90	Carroy et al., 1986
C_4H_8NO	$(CH_3)_2NC(O)CH_2$-		(H)		Kataky et al., 1990
			(H)	90	Matthes et al., 1987
$C_4H_9O_2$	$HO(CH_2)_2O(CH_2)_2$-		($C_4H_5O_4$)	92	Boyce et al., 1984
			($C_4H_5O_4$)	85	Carroy and Lehn, 1986
			($C_4H_5O_4$)	91	Carroy et al., 1986
$C_5H_9O_2$	t-$C_4H_9OC(O)$-		(H)	87	Kumar et al., 1986
$C_5H_{10}NO$	$(CH_3)_2NCO(CH_2)_2$-		(H)	86	Matthes et al., 1987
$C_5H_{11}O_2$	$CH_3(OCH_2CH_2)_2$-		(H)	65	Sheng et al., 1982, 1983
$C_7H_6NO_3S$	2-$H_2NC(O)C_6H_4SO_2$-		E-10	75	Wang et al., 1989

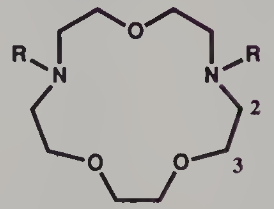
$C_7H_7O_2S$	Ts	E-9		Amble and Dale, 1979
		E-9	82,58	Bogatskii et al., 1984d
			28	Krakowiak et al., 1983
		E-9	90	Lukyanenko et al., 1988a
		E-9	71	Ostaszewski et al., 1988
		E-9	80	Richman and Atkins, 1974
		E-9		Sheng et al., 1982, 1983
$C_7H_{15}O_3$	$CH_3(OCH_2CH_2)_3$-	(H)		Sheng et al., 1982
$C_8H_{17}O_2$	$C_4H_9(OCH_2CH_2)_2$-	(H)	48	Sheng et al., 1982, 1983
$C_9H_7O_3$	2-$CH_3CO_2C_6H_4CH_2$-	(H)	81	Elben et al., 1979
$C_9H_7O_3$	4-$CH_3O_2CC_6H_4C(O)$-	(H)		Sutherland, 1989
$C_9H_{12}NO_2S$	$TsNH(CH_2)_2$-	(H)	91	Lukyanenko et al., 1988a, 1988c
$C_{14}H_{14}P$	$(C_6H_5)_2P(CH_2)_2$-	(C_2H_4Cl)	45	Boyce et al., 1984
		(C_2H_4Cl)	44	Carroy et al., 1986
$C_{16}H_{18}OP$	$(C_6H_5)_2P(CH_2)_2O(CH_2)_2$-	(C_4H_8ClO)	45	Boyce et al., 1984
		(C_4H_8ClO)	45	Carroy et al., 1986

TABLE 6.4. 1.7-DIAZA-12-CROWN-4 MACROCYCLES (R AND R′ DIFFERENT)



R	R'	Methods (or from R, R' = formulas)	Yield (%)	References
H	$C_4H_9OC(O)$-	[$C_4H_9OC(O)$,$C_4H_9OC(O)$]	68	Kumar et al., 1986
H	$C_6H_5CH_2$-	($C_6H_5CH_2$,Ts)	91	Calverley and Dale, 1981
		($C_6H_5CH_2$,Ts)	91	Dale and Calverley, 1982
H	Ts	($C_2H_5OC(O)$,Ts)	80	Anelli et al., 1985, 1988
		($C_6H_5CH_2$,Ts)	89	Anelli et al., 1988
$C_2H_5OC(O)$-	Ts	($C_6H_5CH_2$,Ts)	90	Anelli et al., 1985, 1988
$C_6H_5CH_2$-	Ts	F-1	51	Anelli et al., 1988
		F-1	58	Calverley and Dale, 1981
		F-1	60	Dale and Calverley, 1982

TABLE 6.5. 1,10-DIAZA-15-CROWN-5 MACROCYCLES



R		Other Substituents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
H	H		J-1	37	Ajinomoto Co., 1983b
			E-9	58	Bogatskii et al., 1984d
			E-9	97	Cheng et al., 1983
			E-1	90	Dietrich et al., 1973
			E-1	85	Gansow et al,. 1981
			(C_7H_7)	85,91	Gatto et al., 1986a, 1986b
			E-4	17	Kulstad and Malmsten, 1979
			E-9	88	Lukyanenko et al., 1988a, 1988b
			J-1	26	Maeda et al., 1983
			E-10	71	Wang et al., 1989

TABLE 6.5. (*Continued*)

R		Other Substitutents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
H	H	$12,14\text{-}(CH_3)_2$	J-1	17	Maeda et al., 1983
H	H	$11,15\text{-}(C_2H_5)_2$	J-1	12	Maeda et al., 1983
H	H	$11,15\text{-}(O)_2$	E-1	75	Dietrich et al., 1973
			E-1	60	Gansow et al., 1981
H	H	$2,6,9\text{-}(O)_3$	E-1	40	Lukyanenko et al., 1980
H	H	$5\text{-}CH_2OH$	E-2	78	Babb et al., 1986
H	H	$2,9\text{-}(O)_2;5\text{-}CH_2OH$	E-2	74	Babb et al., 1986
H	H	$2,9\text{-}(O)_2;$ $5\text{-}CH_2O\text{-}$allyl	E-2	43	Babb et al., 1986
H	H	$2,6,9\text{-}(O)_3;$ $8\text{-}CH_2C_6H_5$	E-1	55	Lukyanenko et al., 1980
H	H	$3,8,11,15\text{-}(O)_4;$ $2,9\text{-}(C_6H_5)_2$	H-4	20	Zinic and Skaric, 1988
CHO_2	$HO_2C\text{-}$		(H)		Delgado et al., 1987
CH_3	CH_3		E-13	58	Johnson et al., 1985
			(H)	60	Jurczak and Ostaszewski, 1988

			E-15	48,42 overall	Jurczak and Ostaszewski, 1989
			E-15	77	Jurczak et al., 1989
			(H)	62	Ostaszewski et al., 1988
			E-5	48	Pietraszkiewicz, 1984
CH_3	CH_3	2,6,9-$(O)_3$	E-3	35	Bogatskii et al., 1984a
CH_3	CH_3	2,6,9-$(O)_3$ 8-$CH_2C_6H_5$	E-3	34	Bogatskii et al., 1984a
$C_2H_3O_2$	HO_2CCH_2-		(H)		Kolinski and Mrozinski, 1983
$C_2H_3O_2$	CH_3CO_2-		(H)	62	Gatto et al., 1986a
C_2H_4NO	$H_2NC(O)CH_2$-				Lukyanenko et al., 1990
C_2H_5O	$HO(CH_2)_2$-		(H)	80	Gramain and Frere, 1979
C_2H_6	$(CH_3)_2$-		E-15	99 (salt)	Jurczak et al., 1989
C_2H_6N	$H_2N(CH_2)_2$-		$(C_{10}H_8NO_2)$	45	Cho and Chang, 1981a
C_3H_4N	$CN(CH_2)_2$-		(H)	93	Kyte et al., 1987
C_3H_6NO	$H_2NCH(CH_3)C(O)$-		$(C_8H_{14}NO_3)$	95	Chadwick et al., 1984
C_3H_7O	$CH_3CH(OH)CH_2$-		(H)	68	Hancock et al., 1986
C_3H_7O	$CH_3O(CH_2)_2$-		(H)		Cheng et al., 1983
			E-5	38	Gatto et al., 1986a, 1986b

TABLE 6.5. *(Continued)*

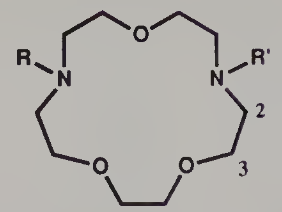
R		Other Substitutents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
C_3H_8N	$H_2N(CH_2)_3$-		($C_{11}H_{10}NO_2$,a)	46,75	Cho and Chang, 1981a, 1981b
			(C_3H_4N)		Kyte et al., 1987
$C_4H_5O_4$	$HO_2CCH_2OCH_2C(O)$-		(H)		Carroy and Lehn, 1986
C_4H_8ClO	$Cl(CH_2)_2O(CH_2)_2$-		($C_4H_9O_2$)	90	Carroy and Lehn, 1986
$C_4H_9O_2$	$H(OCH_2CH_2)_2$-		($C_4H_5O_4$)	85	Carroy and Lehn, 1986
$C_5H_3O_2$	2-furanyl-C(O)-		(H)		Tsukube et al., 1984
C_5H_5O	2-furanyl-CH_2-		E-5	67	Gatto et al., 1986a, 1986b
			($C_5H_3O_2$)		Tsukube et al., 1984
$C_5H_9O_2$	t-$C_4H_9OC(O)$-		(H)	45	Kumar et al., 1986
$C_5H_{10}NO_2$	$HOCH_2CH(CH_3)NHC(O)CH_2$-		(H)	72	Chadwick et al., 1984
$C_5H_{11}O_2$	$CH_3(OCH_2CH_2)_2$-		(H)		Cheng et al., 1983
$C_5H_{12}N$	$H_2N(CH_2)_5$-		($C_{13}H_{14}NO_2$)	39	Cho and Chang, 1981a
$C_6H_4NO_2$	2-$NO_2C_6H_4$-		(H)	50	Gatto et al., 1986a
C_6H_5	C_6H_5	5,6-$(CH_3)_2$;2,9-$(O)_2$	E-3	66	Petranek and Ryba, 1980
C_6H_7N	2-pyridinyl-CH_2-		(H)		Tsukube et al., 1988

$C_6H_{13}O$	$C_4H_9O(CH_2)_2$-		(H)		Cheng et al., 1983
$C_7H_6NO_2$	2-$NO_2C_6H_4CH_2$-		(H)	74	Katayama et al., 1986
$C_7H_6NO_3$	2-HO-5-$NO_2C_6H_3CH_2$-		(H)	59	Shiga et al., 1983
			(H)		Ueno, 1982
$C_7H_6NO_3S$	2-$H_2NC(O)C_6H_4SO_2$-		E-10	46	Wang et al., 1989
C_7H_7	$C_6H_5CH_2$-		J-3	73,78	Bradshaw and Krakowiak, 1988
			J-3	65	Bradshaw et al., 1988a
			E-5	72	Gatto et al., 1986a, 1986b
			(H)	65	Tsukube, 1984c
C_7H_7	$C_6H_5CH_2$-	5-CH_2O-allyl	E-5	72	Bradshaw et al., 1989c
C_7H_7	$C_6H_5CH_2$-	5,6-$(CH_3)_2$; 2,9-$(O)_2$	E-3	48	Petranek and Ryba, 1977, 1980
C_7H_7O	2-$HOC_6H_4CH_2$-		(H)	64	Shiga et al., 1983
$C_7H_7O_2S$	Ts		E-9	77	Bogatskii et al., 1984d
			E-9	47	Cheng et al., 1983
			E-9	80	Lukyanenko et al., 1988a
			E-9	75	Ostaszewski et al., 1988
C_7H_8N	2-$NH_2C_6H_4CH_2$-		($C_7H_6NO_2$)	96	Katayama et al., 1986
C_8H_9O	2-$CH_3OC_6H_4CH_2$-		E-5	52	Gatto et al., 1986a, 1986b

TABLE 6.5. *(Continued)*

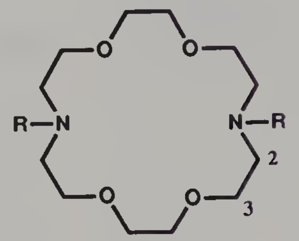
R		Other Substitutents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
$C_8H_{14}NO_3$	$C_4H_9O_2CNHCH(CH_3)C(O)$-		(H)	77,95	Chadwick et al., 1984
$C_8H_{17}O_2$	$C_4H_9(OCH_2CH_2)_2$-		(H)		Cheng et al., 1983
C_9H_7O	$C_6H_5(CH_2)_2C(O)$-		(H)	64	Elben et al., 1979
$C_9H_7O_3$	2-$CH_3CO_2C_6H_4C(O)$-		(H)	88	Elben et al., 1979
$C_9H_7O_3$	4-$CH_3O_2CC_6H_4C(O)$-		(H)		Sutherland, 1989
$C_9H_9O_2$	2-$HOC_6H_4C(O)(CH_2)_2$-		(H)	93	Katayama et al., 1988
$C_9H_{11}O$	2-$HOC_6H_4(CH_2)_3$-		($C_9H_9O_2$)	68	Katayama et al., 1988
$C_9H_{12}NO_2S$	$TsNH(CH_2)_2$-		(H)	64	Dragomiretskaya et al., 1987
			(H)	75,96	Lukyanenko et al., 1988a, 1988c
$C_{10}H_8NO_2$	phthalimidyl-$(CH_2)_2$-		(H)		Cho and Chang, 1981a
$C_{10}H_{12}NO_2$	$HOCH_2CH(C_6H_5)NHC(O)CH_2$-		(H)	46	Chadwick et al., 1984
$C_{11}H_{10}NO_2$, a	phthalimidyl-$(CH_2)_3$-		(H)	64	Cho and Chang, 1981a, 1981b
$C_{11}H_{14}NO_2$	$HOCH_2CH(CH_2C_6H_5)NHC(O)CH_2$-		(H)	44	Chadwick et al., 1984
$C_{13}H_9N_4O_6$	2,4,6-$(NO_2)_3C_6H_2NHC_6H_4CH_2$-		(C_7H_8N)	30	Katayama et al., 1986
$C_{13}H_{10}N_3O_3$	5-(4-$NO_2C_6H_4N{=}N$)-2-$HOC_6H_3CH_2$-		(C_7H_7O)	12	Shiga et al., 1983
$C_{13}H_{14}NO_2$	phthalimidyl-$(CH_2)_5$-		(H)		Cho and Chang, 1981a
$C_{15}H_{14}N_3O_3$	5-(4-$NO_2C_6H_4N{=}N$)-2-$HOC_6H_3(CH_2)_3$-		($C_9H_{11}O$)	53	Katayama et al., 1988

TABLE 6.6. 1,10-DIAZA-15-CROWN-5 MACROCYCLES (R AND R′ DIFFERENT)



R	R′	Methods (or from R = formula)	Yield (%)	References
H	$C_4H_9OC(O)$-		59	Kumar et al., 1986
H	$\underline{t}$-$C_4H_9OC(O)$-	(H)		Jones et al., 1981
CH_2=CH-	$\underline{t}$-$C_4H_9CH_2MgO(CH_2)_2$-			Squiller et al., 1985
C_2H_5	$HO(CH_2)_2$-	E-7	52	Bradshaw et al., 1990a
C_2H_5	$HO(CH_2)_2O(CH_2)_2$-	E-7	81	Bradshaw et al., 1990a
C_2H_5	$(CH_3)_2N(CH_2)_2$-	E-7	49	Bradshaw et al., 1990a
C_2H_5	morpholinyl-$(CH_2)_2$-	E-7	67	Bradshaw et al., 1990a
C_2H_5	$(CH_3)_2N(CH_2)_3$-	E-7	21	Bradshaw et al., 1990a
C_2H_5	$(C_2H_5)_2N(CH_2)_2$-	E-7	71	Bradshaw et al., 1990a
C_2H_5	$C_6H_5CH_2$-	E-7	62	Bradshaw et al., 1990a
C_2H_5	$(C_2H_5)_2N(CH_2)_3$-	E-7	72	Bradshaw et al., 1990a
$C_6H_5CH_2$-	$(C_2H_5)_2N(CH_2)_3$-	E-7	80	Bradshaw et al., 1990a

TABLE 6.7. 1,10-DIAZA-18-CROWN-6 MACROCYCLES



R		Other Substituents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
H	H		E-9	63	Bogatskii et al., 1984d
			E-1	49	deJong et al., 1983
			($C_7H_7O_2S$,a)		Desreaux et al., 1977
			E-1	75	Dietrich et al., 1969, 1970, 1973
			(C_7H_7,a)	92	Gatto and Gokel, 1984
			G-3	27 overall	Gatto et al., 1986b
			(C_7H_7,a)	63,92	Gatto et al., 1986a, 1986b, 1989
			E-4	30	Gatto et al., 1986a
			(C_7H_7,a)	92	Gokel and Gatto, 1986
			G-1	4	King and Krespan, 1974

			E-12	3	King and Krespan, 1974
			E-4	44 (salt)	Kulstad and Malmsten, 1979, 1980a, 1980b
			E-4	23	Li et al., 1985
			E-4	30	Lukyanenko et al., 1984a
			E-9	94	Lukyanenko et al., 1988a, 1988b
			E-9		Rasshofer and Vögtle, 1978
			E-4		Sheng et al., 1983
			E-10	81	Wang et al., 1989
H	H	$5-CH_2OH$	E-2	75	Babb et al., 1986
H	H	$2,9-(O)_2$	E-1		deJong et al., 1983
			E-1	75,80	Dietrich et al., 1969, 1970, 1973
			E-1	70	Dye et al., 1973
			E-1	37 overall	Rasshofer and Vögtle, 1978
H	H	$2,6,9-(O)_3$	E-1	40	Lukyanenko et al., 1980
H	H	$2,9-(O)_2;5-CH_2OH$	E-2	77	Babb et al., 1986
H	H	$5,6-(CO_2H)_2$		77	Anantanarayan and Fyles, 1990
H	H	$5,6-(CO_2H_2)_2;$ $14',15'-(CO_2H)_2$		74	Anantanarayan and Fyles, 1990

TABLE 6.7. (*Continued*)

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
H	H	5,6-$[C(O)N(CH_3)_2]_2$	$(C_7H_7O_2S$,d)	58	Anantanarayan and Fyles, 1990
H	H	5,6,14,15-$[C(O)N(CH_3)_2]_4$	$(C_7H_7O_2S$,e)	60	Anantanarayan and Fyles, 1990
H	H	2,9-$(O)_2$;5-CH_2O-allyl	E-2	51	Babb et al., 1986
H	H	2,6,9-$(O)_3$;8-$CH_2C_6H_5$	E-1	45	Lukyanenko et al., 1980
H	H	5-undecyl	E-2		Cinquini et al., 1977
H	H	5-tetradecyl	E-2		Cinquini et al., 1977
H	H	5-eicosyl	E-2		Cinquini et al., 1977
H	H	2,9-$(O)_2$;5-undecyl	E-2		Cinquini et al., 1977
H	H	2,9-$(O)_2$;5-tetradecyl	E-2		Cinquini et al., 1977
H	H	2,9-$(O)_2$;5-eicosyl	E-2		Cinquini et al., 1977
H	H	6-$C_{14}H_{29}$	E-2	90	Cinquini and Tundo, 1976
H	H	2,9-$(O)_2$;6-$C_{14}H_{29}$	E-2	67	Cinquini and Tundo, 1976
H,a	H	5,6-$(CH_2OCH_2C_6H_5)_2$	E-2	23	Ando et al., 1978
H,b	H	2,9-$(O)_2$;5,6-$(CH_2OCH_2C_6H_5)_2$	E-2	90	Ando et al., 1978

CClO	ClC(O)-		(H)	69	Bogatskii et al., 1985a
CS_2	S_2C-		(H)	93 (salt)	Lukyanenko et al., 1984b
CHO	HC(O)-			49	Elben et al., 1979
CH_3	CH_3		($C_3H_5O_2$,a)	91	deJong et al., 1983
			E-13	97	Hodgkinson et al., 1979
			(H)	95	Jurczak and Ostaszewski, 1988
			E-15	38	Jurczak and Ostaszewski, 1989
			E-15	59	Jurczak et al., 1989
			K-1		Kuo et al., 1978
			(H)	77	Ostaszewski et al., 1988
			E-5	55	Pietraszkiewicz, 1984
CH_3	CH_3	5,6-$CH_2OCH_2C_6H_5$	(H,a)	98	Ando et al., 1980
CH_3	CH_3	5,6,14,15-1,3-dioxolan-2,2-$(CH_3)_2$-4-yl-	E-13	86	Laidler and Stoddart, 1976
CH_3O_3S	HO_3SCH_2-		(H)	50 (salt)	deJong et al., 1983
CH_4O_2P	$H_2O_2PCH_2$-		(H)	74	deJong et al., 1983
CH_4O_3P	$H_2O_3PCH_2$-		(H)	84	deJong et al., 1983
			(H)		Tazaki et al., 1982
C_2OF_3	$F_3CC(O)$-		E-12		King and Krespan, 1974

TABLE 6.7. *(Continued)*

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
C_2H_2N	$CNCH_2$-		(H)	75	Arnold et al., 1988
C_2H_3O	$CH_3C(O)$-		(H)	90	Fages et al., 1989
$C_2H_3O_2$	HO_2CCH_2-		(H)	47	Kulstad and Malmsten, 1979
			(H)	38	Chang and Rowland, 1983
			(H)	55	deJong et al., 1983
			($C_4H_7O_2$,a)	81	Gatto and Gokel, 1984
			(H)		Kolinski and Mrozinski, 1983
$C_2H_3O_2$	HO_2CCH_2-	5,6-CO_2H		60	Anantanarayan and Fyles, 1990
$C_2H_3O_2$	HO_2CCH_2-	5,6,14,15-CO_2H		51	Anantanarayan and Fyles, 1990
C_2H_4Cl	$Cl(CH_2)_2$-		(C_2H_5O,b)	69	deJong et al., 1983
C_2H_4NO,a	$CH_3NHC(O)$-		(H)	88	Bogatskii et al., 1985a
C_2H_4NO,b	$H_2NC(O)CH_2$-		(H)	61	Kulstad and Malmsten, 1979
C_2H_4NO,c	$H_2NCH_2C(O)$-		($C_{10}H_{10}NO_3$,b)	92	Lukyanenko et al., 1984a
			($C_{10}H_{10}NO_3$,b)		Zinic et al., 1990
C_2H_5	C_2H_5	5-CH_2O-allyl	J-2	63	Bradshaw et al., 1988a, 1989b

		(C_2H_3O)	87	Fages et al., 1989
C_2H_5O,a	CH_3OCH_2-	(H)	82	Bogatskii et al., 1982a, 1983
C_2H_5O,b	$HO(CH_2)_2$-	(H)	62	Buoen et al., 1984
		(H)	52	Cho and Chang, 1980
		(H)	84	deJong et al., 1983
		G-3	28	Gatto & Gokel, 1984; Gokel & Gatto, 1986
		(H)	60	Gramain and Frere, 1979
		(H)	90	Gramain et al., 1980
		E-6	51	Krakowiak et al., 1990
		G-3	24	Krakowiak et al., 1990
		(H)	58	Kulstad and Malmsten, 1979
		(H)	89	Nabeshima et al., 1990
$C_2H_5O_3S$	$HO_3S(CH_2)_2$-	(C_2H_4Cl)	91	deJong et al., 1983
$C_2H_5O_4S$	$HO_3SO(CH_2)_2$-	(C_2H_5O,b)	79	deJong et al., 1983
C_2H_6	$(CH_3)_2$	E-15	97	Jurczak et al., 1989
C_2H_6N	$H_2N(CH_2)_2$-	($C_{10}H_8NO_2$)	52	Cho and Chang, 1980, 1981a
		($C_{10}H_8NO_2$)	91	deJong et al., 1983
		($C_9H_{12}NO_2S$,a)	80	Gramain et al., 1980
$C_2H_6O_3P$	$H_2O_3P(CH_2)_2$-	(C_2H_4Cl)	74	deJong et al., 1983

TABLE 6.7. *(Continued)*

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
$C_2H_6O_4P$	$H_2O_3PO(CH_2)_2$-		($C_{14}H_{14}O_4P$)	74	deJong et al., 1983
C_3H_2NS	thiazolyl		(H)	51	Matsumoto et al., 1990
C_3H_3	propargyl		G-3	22	Arnold et al., 1988
			G-3	22	Gatto et al., 1986a
$C_3H_3O_4$	$(HO_2C)_2CH$-		($C_5H_7O_4$)	65	deJong et al., 1983
C_3H_4ClO	$ClC(O)(CH_2)_2$-		($C_3H_5O_2$,c)		Hamilton and Kazanjian, 1985
C_3H_4N	$NC(CH_2)_2$-		(H)	100	Chang, 1977
			(H)	99	deJong et al., 1983
			(H)		Hamilton and Kazanjian, 1985
			(H)	100	Takagi et al., 1978
C_3H_5	allyl		G-3	26,25	Gatto & Gokel, 1984; Gokel & Gatto, 1986
			G-3	26	Gatto et al., 1986a
C_3H_5O	$C_2H_5C(O)$-		(H)	100	Gatto et al., 1986a
$C_3H_5O_2$,a	$C_2H_5OC(O)$-		(H)	76	deJong et al., 1983
			E-13	35	Hodgkinson et al., 1979

			(H)	86	Vögtle and Elben, 1978
$C_3H_5O_2$,b	$C_2H_5OC(O)$-	5,6,14,15-1,3-dioxolan-2,2-$(CH_3)_2$-4-yl	E-13	33	Laidler and Stoddart, 1976
$C_3H_5O_2$,c	$HO_2C(CH_2)_2$-		(C_3H_4N)	79	deJong et al., 1983
			($C_4H_7O_2$,c)		Hamilton and Kazanjian, 1985
			(C_3H_4N)	65	Takagi et al., 1978
			(H)	82	Tsuchida, 1981
					Gatto and Gokel, 1984
$C_3H_5O_2$,d	$CH_3OCH_2C(O)$-		(H)	80	Gokel and Gatto, 1986
$C_3H_5O_2$,e	$HO_2CCH(CH_3)$-		(H)		Kolinski and Mrozinski, 1983
C_3H_6N	aziridinyl-CH_2-		(H)	92	Bogatskii et al., 1982a
			(C_2H_5O,a)	94	Bogatskii et al., 1982a
$C_3H_7NO_3PS$	$(CH_3O)_2P(S)NHC(O)$-		(H)	74	Zabirov et al., 1990b
C_3H_6Cl	$Cl(CH_2)_3$-		(C_3H_7O,a)	88	Carroy et al., 1986
C_3H_6NO	$H_2NC(O)(CH_2)_2$-		($C_4H_7O_2$,c)	58	deJong et al., 1983
C_3H_6NO	$H_2N(CH_2)_2C(O)$-		($C_{11}H_{12}NO_3$,b)		Karaseva et al., 1990
			($C_{11}H_{12}NO_3$,b)	92	Lukyanenko et al., 1984a
C_3H_6NO	$H_2NCH(CH_3)C(O)$-		($C_{11}H_{12}NO_3$,a)	97	Lukyanenko et al., 1984a
C_3H_7	C_3H_7		(H)	70	Cho and Chang, 1980, 1981a

TABLE 6.7. *(Continued)*

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
			(C_3H_5O)	78	Gatto et al., 1986a
C_3H_7O,a	$HO(CH_2)_3$-		($C_4H_7O_2$,c)	81	Carroy et al., 1986
			(H)	54	Cho and Chang, 1981a
			($C_5H_9O_2$)	98	deJong et al., 1983
C_3H_7O,b	$CH_3O(CH_2)_2$-		($C_3H_5O_2$,d)	97	Gatto and Gokel, 1984
			E-5	43	Gatto et al., 1986a, 1986b
			($C_3H_5O_2$,d)	97	Gokel and Gatto, 1986
			(H)	29	Kulstad and Malmsten, 1979
			(H)	54	Sheng et al., 1982, 1983
$C_3H_7O_4S$	$HO_3SO(CH_2)_3$-		(C_3H_7O,a)	40	deJong et al., 1983
C_3H_8N	$H_2N(CH_2)_3$-		(H)		Beer et al., 1989
			(C_3H_4N)		Chang, 1977
			($C_{11}H_{10}NO_2$)	45,70	Cho and Chang, 1980, 1981a, 1981b
$C_3H_8NO_2$	$(CH_3O)_2NCH_2$-		(C_2H_5O,a)	100	Rubchenko et al., 1986
C_4ClO_2	chlorocyclobutenedione		(H)	55	Vögtle and Dix, 1977

$C_4H_2N_2Cl$	3-Cl-6-pyridazinyl	(H)	81	Matsumoto et al., 1990
$C_4H_3N_2$	2-piperidinyl	(H)	100	Matsumoto et al., 1990
$C_4H_3N_2$	2-piperazinyl	(H)	86	Matsumoto et al., 1990
$C_4H_3O_3$	$HO_2CCH{=}CHC(O)$-	(H)	55	deJong et al., 1983
$C_4H_5N_2$	imidazolyl-CH_2-	(C_2H_5O,a)	96	Bogatskii et al., 1983
$C_4H_5O_3$	$HO_2C(CH_2)_2C(O)$-	(H)	83	deJong et al., 1983
$C_4H_5O_4$,a	$HO_2CCH_2CH(CO_2H)$-	(H)	5	deJong et al., 1983
$C_4H_5O_4$,b	$HO_2CCH_2OCH_2C(O)$-	(H)	95	Beer et al., 1986
		(H)	90	Carroy and Lehn, 1986
$C_4H_5NCl_3O$	$CH_3C(O)NHCH(CCl_3)$-	(H)	83	Zabirov et al., 1990b
$C_4H_7O_2$,a	$C_2H_5O_2CCH_2$-	(H)	92	Gatto and Gokel, 1984
		(H)	92	Gokel and Gatto, 1986
		(H)	71	Kulstad and Malmsten, 1979
		(H)	92	White et al., 1987
$C_4H_7O_2$,b	$HO_2C(CH_2)_3$-	(H)		Tsuchida, 1981
$C_4H_7O_2$,c	$CH_3O_2C(CH_2)_2$-	(H)	67	Carroy et al., 1986
		(H)	78	deJong et al., 1983
		(C_3H_4N)		Hamilton and Kazanjian, 1985
$C_4H_7O_2$,d	$CH_3C(O)O(CH_2)_2$-	(C_2H_5O,b)	81	Gramain et al., 1980

TABLE 6.7. (*Continued*)

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
C_4H_8ClO	$Cl(CH_2)_2O(CH_2)_2$-		($C_4H_9O_2$)	90	Carroy and Lehn, 1986
C_4H_8NO	$H_2NCH(C_2H_5)C(O)$-		($C_{12}H_{14}NO_3$,b)	97	Lukyanenko et al., 1984a
C_4H_8NO	$CH_3C(O)NH(CH_2)_2$-		(C_2H_6N)	80	Gramain et al., 1980
C_4H_8NO	$H_2N(CH_2)_3C(O)$-				Karaseva et al., 1990
			($C_{12}H_{14}NO_3$,a)	91	Lukyanenko et al., 1984a
C_4H_8NO	$H_2NCH(CH_3)CH_2C(O)$-		($C_{12}H_{14}NO_3$,c)	97,94	Lukyanenko et al., 1985
$C_4H_8NO_2$	$O_2NC(CH_3)_2CH_2$-		(C_2H_5O,a)	93	Bogatskii et al., 1982a
C_4H_9	C_4H_9		E-5	77	Gatto et al., 1986a, 1986b
$C_4H_9O_2$	$H(OCH_2CH_2)_2$-		($C_4H_5O_4$,b)	92	Beer et al., 1986
			($C_4H_5O_4$,b)	85	Carroy and Lehn, 1986
			E-6	7J	Hancock et al., 1989
			(H)	51	Nabeshima et al., 1990
$C_4H_{10}NO$	$NH_2(CH_2)_2O(CH_2)_2$-				Kirichenko et al., 1990
$C_4H_{10}O_2PS$	$(C_2H_5O)_2P(S)$-		(H)	83	Zabirov et al., 1990a
$C_4H_{10}NO_6S_2$	$(HO_3SCH_2)_2N(CH_2)_2$-		(C_2H_6N)	46	deJong et al., 1983

$C_5H_3N_2O_2$	3-NO_2pyridin-5-yl	(H)	77	Matsumoto et al., 1990
C_5H_3OS	2-thiophenyl-C(O)-	(H)		Tsukube, 1984a
		(H)		Tsukube et al., 1984, 1986
$C_5H_3O_2$	2-furanyl-C(O)-	(H)		Tsukube, 1984a, 1984b
		(H)		Tsukube et al., 1984, 1986
C_5H_5O	2-furanyl-CH_2-	G-3	27	Gatto and Gokel, 1984
		G-3	27	Gatto et al., 1986b
		E-5	62	Gatto et al., 1986a, 1986b
		G-3	27	Gokel and Gatto, 1986
		($C_5H_3O_2$)		Tsukube, 1984a, 1984b
		($C_5H_3O_2$)		Tsukube et al., 1984, 1986
C_5H_5S	2-thiophenyl-CH_2-	(C_5H_3OS)	60	Tsukube, 1984a
			60	Tsukube et al., 1984, 1986
$C_5H_6NO_2$	succinimide-CH_2-	(C_2H_5O,a)	90	Bogatskii et al., 1983
		(C_2H_5O,a)	90	Lukyanenko et al., 1985
$C_5H_6NO_3$	morpholinyl-2,6-dione-CH_2-	(C_2H_5O,a)	86	Bogatskii et al., 1983
$C_5H_7O_4$	$(CH_3O_2C)_2CH$-	(H)	23	deJong et al., 1983
C_5H_8NO	2-pyrolidinone-CH_2-	(C_2H_5O,a)	95	Lukyanenko et al., 1985

TABLE 6.7. *(Continued)*

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
C_5H_8NO	2-pyrolidinyl-C(O)-			95	Lukyanenko et al., 1990a
$C_5H_8NO_3$	$CH_3O_2CCH_2NHC(O)CH_2$-		(H)	58	White et al., 1987, 1989
$C_5H_9O_2$	$C_2H_5O_2C(CH_2)_2$-		(H)	98	deJong et al., 1983
$C_5H_{10}NO$	$H_2NCH(\underline{i}C_3H_7)C(O)$-		($C_{13}H_{16}NO_3$)	93	Lukyanenko et al., 1984a
C_5H_{11}	$(CH_3)_3CCH_2$-			82	Wester and Vögtle, 1978
$C_5H_{11}NO_3PS$	$(C_2H_5O)_2P(S)NHC(O)$-		(H)	86	Zabirov et al., 1990b
$C_5H_{11}NO_3PS$	$(C_2H_5O)_2P(O)NHC(S)$-		(H)	86	Zabirov et al., 1990b
$C_5H_{11}NO_4P$	$(C_2H_5O)_2P(O)NHC(O)$-		(H)	82	Zabirov et al., 1990b
$C_5H_{11}O_2$	$CH_3(OCH_2CH_2)_2$-		(H)	36	Sheng et al., 1982, 1983
$C_5H_{12}N$	$H_2N(CH_2)_5$-		($C_{13}H_{14}NO_2$)	41	Cho and Chang, 1980, 1981a
$C_6H_3F_3$	3-CF_3-5-pyridinyl-		(H)	85	Matsumoto et al., 1990
$C_6H_4NO_4S$	4-$NO_2C_6H_4SO_2$-		(H)	86	Vögtle and Elben, 1978
C_6H_5,a	C_6H_5		(C_6H_5,b)	71,80	Sonveaux, 1982, 1984
C_6H_5,b	C_6H_5	1,9-$(O)_2$	E-3	73,75	Sonveaux, 1982, 1984
C_6H_6N,a	2-$NH_2C_6H_4$-		($C_{13}H_{12}NO_2S$,a)	70	Sonveaux, 1982, 1984

C_6H_6N,b	2-picolinyl		G-3	22	Gatto and Gokel, 1984
			G-3	22	Gokel and Gatto, 1986
			(H)		Tsukube et al., 1988, 1989
C_6H_6N,c	4-picolinyl		(H)		Tsukube et al., 1988
$C_6H_6NO_2S$	4-$NH_2C_6H_4SO_2$-		(H)	50	Bogatskii et al., 1986
$C_6H_8NO_2$	glutarimidyl-CH_2-		(C_2H_5O,a)	99	Bogatskii et al., 1983
$C_6H_{10}NO_3$	$CH_3O_2CCH(CH_3)NHC(O)CH_2$-		(H)	50	White et al., 1987, 1989
$C_6H_{10}NO_4$	$(HO_2CCH_2)_2N(CH_2)_2$-		(C_2H_6N)	65	deJong et al., 1983
$C_6H_{11}N_2O_2$	$NH_2(CH_2)_3C(O)NHCH_2C(O)$-				Karaseva et al., 1990
$C_6H_{12}Cl$	$Cl(CH_2)_6$-				Gokel et al., 1989
$C_6H_{12}NO$	$H_2NCH(\underline{i}\text{-}C_4H_9)C(O)$-		($C_{14}H_{18}NO_3$)	95	Lukyanenko et al., 1984a
C_6H_{13},a	C_6H_{13}		E-5	32	Gatto et al., 1986a, 1986b
			G-3	7	Gatto et al., 1986a, 1986b
			(H)	50	Gatto et al., 1986a
C_6H_{13},b	C_6H_{13}	5-CH_2OH	E-3	50	Bradshaw et al., 1988a, 1989b
C_6H_{13},c	C_6H_{13}	5-CH_2O-allyl	E-3	35	Bradshaw et al., 1988a, 1989b
C_6H_{13},d	C_6H_{13}	2,9-$(O)_2$;5-CH_2O-allyl	E-3	42	Bradshaw et al., 1988a, 1989b
$C_6H_{14}NO_2$	$H_2NCH_2(CH_2OCH_2)_2CH_2$-				Kirichenko et al., 1990
$C_6H_{14}O_2PS$	$(i\text{-}C_3H_7O)_2P(S)$-		(H)	54	Zabirov et al., 1990a

TABLE 6.7. *(Continued)*

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
$C_6H_{14}O_3P$	$(i\text{-}C_3H_7O)_2P(O)$-		(H)	43	Zabirov et al., 1990a
$C_7H_3NO_2F_3$	2-NO_2-4-$CF_3C_6H_3$-		(H)	79	Matsumoto et al., 1990
$C_7H_3N_2O_6$	2,6-$(NO_2)_2$-4-$(HO_2C)C_6H_2$-		(H)	80	Ivanov and Federova, 1986
C_7H_4FO	4-$FC_6H_4C(O)$-		(H)	86	Elben et al., 1979
C_7H_4NO	benzoxazolyl		(H)	64	Matsumoto et al., 1990
$C_7H_4NO_3$	4-$NO_2C_6H_4C(O)$-		(H)	82	Elben et al., 1979
$C_7H_4NO_4$	2-HO-5-$NO_2C_6H_3C(O)$-		(H)	38	Yamashita et al., 1980
C_7H_4NS	benzothiazolyl		(H)	51	Matsumoto et al., 1990
C_7H_5O	$C_6H_5C(O)$-		(H)	78	Keana et al., 1983
			(H)		Tsukube, 1984a
					Tsukube et al., 1984
$C_7H_5O_2$	2-$HOC_6H_4C(O)$-		(H)	36	Yamashita et al., 1980
C_7H_6Cl	2-$ClC_6H_4CH_2$-		(H)	82	Gustowski et al., 1987
C_7H_6Cl	4-$ClC_6H_4CH_2$-		(H)	75	Gustowski et al., 1987
C_7H_6NO	4-$NH_2C_6H_4C(O)$-		$(C_7H_4NO_3)$	72	Elben et al., 1979

$C_7H_6NO_2$, a	$2-NO_2C_6H_4CH_2-$	(H)	90	Gatto et al., 1986a
		(H)	90	Gustowski et al., 1987
		(H)	96	Katayama et al., 1986
$C_7H_6NO_2$, b	$3-NO_2C_6H_4CH_2-$	(H)	95	Gatto et al., 1986a
$C_7H_6NO_2$, c	$4-NO_2C_6H_4CH_2-$	(H)	70	Gatto et al., 1986a
		(H)	90	Gustowski et al., 1987
$C_7H_6NO_3$	$2-HO-5-NO_2C_6H_3CH_2-$	(H)		Sakai et al., 1986
		(H)	75	Shiga et al., 1983
		(H)	90	Ueno, 1982
$C_7H_6NO_3S$	$2-H_2NC(O)C_6H_4SO_2-$	E-10	56	Wang et al., 1989
C_7H_6NS	$C_6H_5NHC(S)-$	(H)	98	Zabirov et al., 1990b
C_7H_7, a	$C_6H_5CH_2-$	G-3	29	Gatto et al., 1986a, 1986b
		E-5	66-71	Gatto et al., 1986a, 1986b, 1989
		G-3	29	Gatto and Gokel, 1984
		G-3	29	Gokel and Gatto, 1986
		E-5	66	Gustowski et al., 1987
		(C_7H_5O)	92	Keana et al., 1983
		(C_7H_5O)		Tsukube, 1984a
		(C_7H_5O)		Tsukube et al., 1984

TABLE 6.7. (*Continued*)

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
			(H)	60,80	Tsukube 1983, 1984c
					Tsukube et al., 1986
				75	Wester and Vögtle, 1978
C_7H_7,b	$C_6H_5CH_2$-	5-CH_2OH	E-3	60	Bradshaw et al., 1988a, 1989b
			E-5	20	Bradshaw et al., 1989b
C_7H_7,c	$C_6H_5CH_2$-	5-CH_2O-allyl	E-3	15	Bradshaw et al., 1988a, 1989b
			J-2	30,62	Bradshaw et al., 1988a
			(C_7H_7,b)	90	Bradshaw et al., 1988a
			E-5	80	Bradshaw et al., 1988a, 1989b
C_7H_7,d	$C_6H_5CH_2$-	5,6-$(CH_3)_2$;2,9-$(O)_2$	E-3	50	Petranek and Ryba, 1977, 1980
C_7H_7,e	$C_6H_5CH_2$-	5-CH_2Oallyl;2,9-$(O)_2$	E-3	40	Bradshaw et al., 1988a, 1989b
C_7H_7,f	$C_6H_5CH_2$-	5,6-$(CH_2OCH_2C_6H_5)_2$	(H,a)	64	Ando et al., 1980
C_7H_7O	2-$HOC_6H_4CH_2$-		(H)	54	Shiga et al., 1983
			($C_9H_9O_2$,c)	85	Gatto and Gokel, 1984
			($C_9H_9O_2$,c)	85	Gokel and Gatto, 1986

$C_7H_7O_2S$,a	Ts		E-9	70	Anantanarayan and Fyles, 1990
			E-9	80	Bogatskii et al., 1984d
			G-2	5	Bottino et al., 1988
			E-9	70	Anantanarayan and Fyles, 1990
			E-9	82	Desreaux et al., 1977
			E-9	79	Lukyaneko et al., 1988a, 1988b
			G-2	77	Ostaszewski et al., 1988
			E-9	76	Ostaszewski et al., 1988
			G-2	5	Pappalardo et al., 1985
			E-9	13 overall	Rasshofer and Vögtle, 1978
			G-2	15	Rasshofer and Vögtle, 1978
			E-9	80	Richman and Atkins, 1974
$C_7H_7O_2S$,b	Ts	3,8,12,17-$(O)_4$	T-2	12	Qin and Hu, 1984
$C_7H_7O_2S$,c	Ts	5,6,14,15-$(CO_2H)_4$	($C_7H_7O_2S$,e)	71	Anantanarayan and Fyles, 1990
$C_7H_7O_2S$,d	Ts	5,6-$[C(O)N(CH_3)_2]_2$	E-9	81	Anantanarayan and Fyles, 1990
$C_7H_7O_2S$,e	Ts	5,6,14,15-$[(C(O)N(CH_3)_2]_4$-	E-9	79	Anantanarayan and Fyles, 1990
C_7H_8N	2-$NH_2C_6H_4CH_2$-		($C_7H_6NO_2$,a)		Katayama et al., 1986
C_7H_9N	pyridinyl-$(CH_2)_2$-		(C_2H_5O,b)	72	deJong et al., 1983

TABLE 6.7. (*Continued*)

R Formula	R Structure	Other Substituents	Method	Yield (%)	References
$C_7H_{15}NO_2PS_2$	$(i\text{-}C_3H_7O)_2P(S)NHC(S)\text{-}$		(H)		Chekhlov et al., 1987
			(H)	84	Zabirov et al., 1990b
$C_7H_{15}NO_3PS$	$(i\text{-}C_3H_7O)_2P(O)NHC(S)\text{-}$		(H)	92	Zabirov et al., 1990b
$C_7H_{15}O_3$	$CH_3(OCH_2CH_2)_3\text{-}$		(H)	30	Sheng et al., 1982, 1983
$C_8H_5N_2O_6$	$2,6\text{-}(NO_2)_2\text{-}4\text{-}CH_3CO_2C_6H_2\text{-}$		(H)	92	Ivanov and Fedorova, 1986
$C_8H_5N_2O_6$	$2,4\text{-}(NO_2)_2\text{-}6\text{-}CH_3CO_2C_6H_2\text{-}$		(H)	88	Ivanov and Fedorova, 1986
C_8H_6N	$2\text{-}CNC_6H_4CH_2\text{-}$		(H)	90	Gatto et al., 1986a
C_8H_6N	$4\text{-}CNC_6H_4CH_2\text{-}$		(H)	91	Gustowski et al., 1987
$C_8H_7O_2$	$C_6H_5CH_2OC(O)\text{-}$		(H)	50	Lehn et al., 1977
$C_8H_7O_2S$	$2\text{-}HSC_6H_4OCH_2C(O)\text{-}$				Shinkai et al., 1983a
C_8H_8NO	$H_2NCH(C_6H_5)C(O)\text{-}$		$(C_{16}H_{14}NO_3, c)$	93	Lukyanenko et al., 1984a
C_8H_8NO	$C_6H_5CH_2NHC(O)\text{-}$		(H)	94	Bogatskii et al., 1985a
C_8H_9	$C_6H_5(CH_2)_2\text{-}$		(H)		Nishimura et al., 1981
C_8H_9O	$2\text{-}HO\text{-}5\text{-}CH_3C_6H_3CH_2\text{-}$				Lukyanenko et al., 1990a

C_8H_9O	$2\text{-}CH_3OC_6H_4CH_2\text{-}$	G-3	30	Gatto and Gokel, 1984
		G-3	30	Gatto et al., 1986b
		G-3	30	Gokel and Gatto, 1986
C_8H_9O	$4\text{-}CH_3OC_6H_4CH_2\text{-}$	(H)	91	Gustowski et al., 1987
			78	Wester and Vögtle, 1978
$C_8H_{10}N_5$	adeninyl-$(CH_2)_3$-	(H)	24	Kim and Gokel, 1987
$C_8H_{11}N_2O_2$	thyminyl-$(CH_2)_3$-	(H)	58	Kim and Gokel, 1987
$C_8H_{12}ClO_2$	$ClC(O)(CH_2)_6C(O)\text{-}$	$(C_8H_{13}O_3)$		Kotzyba-Hibert et al., 1980
$C_8H_{13}O_3$	$HO_2C(CH_2)_6C(O)\text{-}$	$(C_9H_{15}O_3)$	58	Kotzyba-Hibert et al., 1980
$C_8H_{14}NO_3$	$CH_3O_2CCH(\underline{i}C_3H_7)NHC(O)CH_2\text{-}$	(H)	59	White et al., 1987, 1989
$C_8H_{15}O$	$C_7H_{15}C(O)\text{-}$	(H)	71	Gatto et al., 1986a
C_8H_{17}	C_8H_{17}	$(C_8H_{15}O)$	63	Gatto et al., 1986a
$C_8H_{17}O_2$	$n\text{-}C_4H_9(OCH_2CH_2)_2\text{-}$ (H)		42	Sheng et al., 1982, 1983
$C_9H_6NO_2$	phthalimidyl-CH_2-	(C_2H_5O,a)	87	Bogatskii et al., 1983
C_9H_7O	$C_6H_5CH{=}CHC(O)\text{-}$	(H)	72	Vögtle and Elben, 1978
$C_9H_7O_3$	$2\text{-}CH_3CO_2C_6H_4C(O)\text{-}$ (H)		73	Elben et al., 1979
$C_9H_7O_3$	$4\text{-}CH_3O_2CC_6H_4C(O)\text{-}$ (H)			Sutherland, 1989
$C_9H_8NO_4$	$2\text{-}HO\text{-}5\text{-}NO_2C_6H_3(CH_2)_2C(O)\text{-}$	(H)	48	Yamashita et al., 1980
C_9H_9O	$C_6H_5(CH_2)_2C(O)\text{-}$	(C_9H_7O)	94	Vögtle and Elben, 1978

TABLE 6.7. (*Continued*)

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
$C_9H_9O_2$, a	2-$HOC_6H_4(CH_2)_2C(O)$-		(H)	80	Yamashita et al., 1980
$C_9H_9O_2$, b	2-$HOC_6H_4C(O)(CH_2)_2$-		(H)	92	Katayama et al., 1988
$C_9H_9O_2$, c	$CH_3O_2CC_6H_4CH_2$-		(H)		Gatto and Gokel, 1984
			(H)		Gokel and Gatto, 1986
$C_9H_{10}NO$	$H_2NCH(CH_2C_6H_5)C(O)$-		($C_{17}H_{16}NO_3$)	96	Lukyanenko et al., 1984a
$C_9H_{10}NO$	$C_6H_5CH(CH_3)NHC(O)$-		(H)	89	Bogatskii et al., 1985a
$C_9H_{10}NO_2$	1,2,5,6,-H_4-phthalimidyl-CH_2-		(C_2H_5O, a)	99	Bogatskii et al., 1983
$C_9H_{10}NO_3S$	$TsNHCH_2C(O)$-		(H)	90	Gramain et al., 1980
$C_9H_{11}O$	2-$HOC_6H_4(CH_2)_3$-		($C_9H_9O_2$, b)	67	Katayama et al., 1988
$C_9H_{12}NO_2$	$C_6H_5CH_2ON(OCH_3)CH_2$-		(C_2H_5O, a)	92	Rubchenko et al., 1986
$C_9H_{12}NO_2S$, a	$TsNH(CH_2)_2$-		(H)	68	Dragomiretskaya et al., 1987
			($C_9H_{10}NO_3S$)	95	Gramain et al., 1980
			(H)	99,98	Lukyanenko et al., 1987, 1988a, 1988c
$C_9H_{12}NO_2S$, b	$CH_3N(Ts)CH_2$-		(C_2H_5O, a)	98	Lukyanenko et al., 1986b
$C_9H_{15}O_3$	$CH_3O_2C(CH_2)_6C(O)$-(H)		97		Kotzyba-Hibert et al., 1980

$C_9H_{16}NO_3$	$CH_3O_2CCH(s\text{-}C_4H_9)NHC(O)CH_2$-		(H)	60	White et al., 1987, 1989
$C_9H_{16}NO_3$	$CH_3O_2CCH(\underline{i}\text{-}C_4H_9)NHC(O)CH_2$-		(H)	51	White et al., 1987, 1989
$C_9H_{17}O$	$C_8H_{17}C(O)$-		(H)	71	Gatto et al., 1986a
C_9H_{19}	C_9H_{19}		$(C_9H_{17}O)$	48	Gatto et al., 1986a
			G-3	11	Gatto et al., 1986a, 1986b
			(H)	45	Gatto et al., 1986a
					Tsukube et al., 1986
$C_{10}H_7$	azulenyl		(H)	4	Löhr and Vögtle, 1985
$C_{10}H_8N$	2-quinolinyl-CH_2-		(H)	60	Pietraszkiewicz et al., 1990
			(H)		Tsukube et al., 1988
$C_{10}H_8NO$	2-quinolinyl-N-oxide-CH_2-		(H)	65	Pietraszkiewicz et al., 1990
$C_{10}H_8NO_2$	phthalimidyl-$(CH_2)_2$-		(H)		Cho and Chang, 1980, 1981a
			(C_2H_4Cl)	76	deJong et al., 1983
$C_{10}H_{10}NO_3$, a	2-$[HO_2C(CH_2)_2C(O)NH]C_6H_4$-		(C_6H_6N, a)	50	Sonveaux, 1984
$C_{10}H_{10}NO_3$, b	$C_6H_5CH_2O_2CNHCH_2C(O)$-		(H)		Lukyanenko et al., 1984a
			(H)		Zinic et al., 1990
$C_{10}H_{12}Cl$	4-$ClC_6H_4CH(\underline{i}\text{-}C_3H_7)$-		E-3	40	Wang and Hu, 1989
$C_{10}J_{12}Cl$	4-$ClC_6H_4CH(i\text{-}C_3H_7)$-	2,9-$(O)_2$	E-3	74	Wang and Hu, 1989
$C_{10}H_{19}O$	$C_9H_{19}C(O)$-		(H)	100	Gatto et al., 1986a

TABLE 6.7. *(Continued)*

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
$C_{10}H_{21}$	$C_{10}H_{21}$		$(C_{10}H_{19}O)$	96	Gatto et al., 1986a
$C_{11}H_9O_3$	4-CH_3-8-HO-coumarinyl-9-CH_2-		(H)		Nishida et al., 1982
$C_{11}H_{10}NO_2$	phthalimidyl-$(CH_2)_3$-		(H)	64	Cho and Chang, 1980, 1981a, 1981b
$C_{11}H_{10}NO_4$	$CH_3O_2CCH_2NHC(O)C_6H_4C(O)$-			40	Ganin et al., 1987
$C_{11}H_{11}N_2O$	H_2NCH(indolyl-CH_2)$C(O)$-		$(C_{19}H_{17}N_2O_3)$	98	Lukyanenko et al., 1984a
$C_{11}H_{11}O_3$	$C_6H_5CH_2O_2C(CH_2)_2C(O)$-				Basok, 1984
$C_{11}H_{11}O_3S_2$	2-$[C_2H_5OC(S)S]C_6H_4OCH_2C(O)$-		(H)		Shinkai et al., 1983a
$C_{11}H_{12}NO_3$,a	$C_6H_5CH_2O_2CNHCH(CH_3)C(O)$-		(H)	90,92,94	Lukyanenko et al., 1984a
$C_{11}H_{12}NO_3$,b	$C_6H_5CH_2O_2CNH(CH_2)_2C(O)$-		(H)	89	Lukyanenko et al., 1984a
$C_{11}H_{12}NO_3$,c	$CH_3O_2CCH(C_6H_5)NHC(O)CH_2$-		(H)		Zinic et al., 1990
$C_{11}H_{16}NO_2$	a bornanedione		$(C_2H_5O$,a)	92	Bogatskii et al., 1983
$C_{11}H_{22}NO_4$	aza-12-crown-4-$CH_2CH(OH)CH_2$-		(H)	12	Belohradsky et al., 1987
$C_{12}H_{12}NO_4$	2-$[CH_3O_2CCH(CH_3)NHC(O)]C_6H_4C(O)$-		(H)	37	Ganin et al., 1987
$C_{12}H_{13}O_4$	3,4,5-$(CH_3O)_3C_6H_2CH{=}CH_2C(O)$-		(H)	83	Elben et al., 1979
$C_{12}H_{14}NO_3$,a	$C_6H_5CH_2O_2CNH(CH_2)_3C(O)$-		(H)	87	Lukyanenko et al., 1984a

$C_{12}H_{14}NO_3$,b	$C_6H_5CH_2O_2CNHCH(C_2H_5)C(O)$-	(H)	91	Lukyanenko et al., 1984a
$C_{12}H_{14}NO_3$,c	$C_6H_5CH_2O_2CNHCH(CH_3)CH_2C(O)$-	(H)	94	Lukyanenko et al., 1985
$C_{12}H_{14}NO_3$	2-$[C_2H_5O(CH_2)_2NHC(O)]C_6H_4C(O)$-	(H)	56	Ganin et al., 1987
$C_{12}H_{16}NO_4S$	$C_2H_5O_2CCH_2N(Ts)CH_2$-	(C_2H_5O,a)	87	Lukyanenko et al., 1986b
$C_{12}H_{20}NO_3S$	camphoryl-$SO_2N(CH_3)CH_2$-	(C_2H_5O,a)	87	Lukyanenko et al., 1986b
$C_{12}H_{22}O_2$	menthyl-$CH_2C(O)$-	(H)	72	Ando et al., 1980
$C_{12}H_{23}O$	$C_{11}H_{23}C(O)$-	(H)	87	Gatto et al., 1986a
$C_{12}H_{23}O_6$	12-crown-4-$CH_2OCH_2CH(OH)CH_2$-	(H)	28	Belohradsky et al., 1987
$C_{12}H_{24}O$	menthyl-$(CH_2)_2$-	($C_{12}H_{22}O_2$)	53	Ando et al., 1980
$C_{12}H_{25}$	$C_{12}H_{25}$	($C_{12}H_{23}O$)	45	Gatto et al., 1986a
		G-3	11	Gatto et al., 1986a
$C_{13}H_7ClNOS$	2-chlorophenothiazinyl	(H)	80	Elben et al., 1979
$C_{13}H_7N_2O_5$	2,4-$(NO_2)_2$-6-$[C_6H_5C(O)]C_6H_2$-	(H)	76	Ivanov and Fedorova, 1986
$C_{13}H_8NOS$	phenothiazinyl	(H)	77	Elben et al., 1979
$C_{13}H_9N_4O_5$	4-$[2,4$-$(NO_2)_2C_6H_3N{=}N]$-2-$HOC_6H_3CH_2$-	(C_7H_7O)		Shiga et al., 1983
$C_{13}H_9N_4O_6$	2,4,6-$(NO_2)_3C_6H_2NHC_6H_4CH_2$-	(C_7H_8N)	32	Katayama et al., 1986
$C_{13}H_{10}N_3O_3$	4-$[2$-$NO_2C_6H_4N{=}N]$-2-$HOC_6H_3CH_2$-	(C_7H_7O)		Shiga et al., 1983
$C_{13}H_{11}$	$(C_6H_5)_2CH$-	(H)	86	Vögtle and Elben, 1978
$C_{13}H_{12}NO_2S$,a	2-$TsNHC_6H_4$-	($C_{13}H_{12}NO_2S$,b)	50,61	Sonveaux, 1982, 1984

TABLE 6.7. (*Continued*)

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
$C_{13}H_{12}NO_2S$,b	2-TsNHC_6H_4-	2,9-$(O)_2$	E-3	50,62	Sonveaux, 1982, 1984
$C_{13}H_{12}P$	$(C_6H_5)_2PCH_2$-		(H)		Balch and Rowley, 1990
$C_{13}H_{14}NO_2$	phthalimidyl-$(CH_2)_5$-		(H)		Cho and Chang, 1980, 1981a
$C_{13}H_{16}NO_3$	$C_6H_5CH_2O_2CNHCH$($\underline{i}$-C_3H_7)C(O)-		(H)	93	Lukyanenko et al., 1984a
$C_{13}H_{26}NO_5$	aza-15-crown-5-$CH_2CH(OH)CH_2$-		(H)	20	Belohradsky et al., 1987
$C_{14}H_9BrNO_2$	2-[4-BrC_6H_4NHC(O)]C_6H_4C(O)-		(H)	52	Ganin et al., 1987
$C_{14}H_9ClNO_2$	2-[4-ClC_6H_5NHC(O)]C_6H_4C(O)-		(H)	50	Ganin et al., 1987
$C_{14}H_{10}NO_2$	2-[C_6H_5NHC(O)]C_6H_4C(O)-		(H)	56	Ganin et al., 1987
$C_{14}H_{14}O_4P$	$(C_6H_5)_2O_3PO(CH_2)_2$-		(C_2H_5O,b)	93	deJong et al., 1983
$C_{14}H_{16}NO$	ferrocenyl-C(O)NH$(CH_2)_3$-		(C_3H_8N)		Beer et al., 1989
$C_{14}H_{17}O_3$	$C_6H_5CH_2O_2CCH$($\underline{i}$-C_3H_7)CH_2C(O)-				Basok, 1984
$C_{14}H_{18}NO_3$	$C_6H_5CH_2O_2CNHCH$($\underline{i}$-C_4H_9)C(O)-		(H)	89,91	Lukyanenko et al., 1984a
$C_{14}H_{27}O$	$C_{13}H_{27}$C(O)-		(H)	78	Gatto et al., 1986a
$C_{14}H_{27}O_7$	15-crown-5-$CH_2OCH_2CH(OH)CH_2$-		(H)	34	Belohradsky et al., 1987

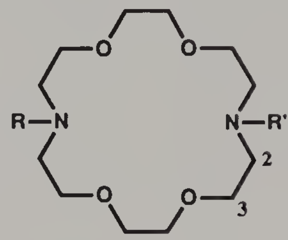
$C_{14}H_{28}NO_3$	aza-12-crown-4-$(CH_2)_6$-	$(C_6H_{12}Cl)$	58	Gokel et al., 1989
$C_{14}H_{29}$	$C_{14}H_{29}$	$(C_{14}H_{27}O)$	67	Gatto et al., 1986a
$C_{15}H_9O_2$	4-anthraquinonyl-CH_2-	(H)		Ossowski and Schneider, 1990
$C_{15}H_{10}NO$	dibenzoazacycloheptatrienyl-C(O)-	(H)	45	Vögtle and Elben, 1978
$C_{15}H_{12}N_3O_4$	5-(4-$NO_2C_6H_4N{=}N$)-2-$HOC_6H_3(CH_2)_2C(O)$-	$(C_9H_9O_2$, a)	49	Yamashita et al., 1980
$C_{15}H_{13}O_2$	3-anthraquinonyl-CH_2-			Ossowski and Schneider, 1990
$C_{15}H_{14}N_3O_3$	5-(4-$NO_2C_6H_4N{=}N$)-2-$HOC_6H_3(CH_2)_3$-	$(C_9H_{11}O)$	30	Katayama et al., 1988
$C_{15}H_{16}NO_2S$	$C_6H_5CH_2N(Ts)CH_2$-	$(C_2H_5O$, a)	95	Lukyanenko et al., 1986b
$C_{15}H_{16}P$	$(C_6H_5)_2P(CH_2)_3$-	(C_3H_6Cl)	45	Carroy et al., 1986
$C_{15}H_{18}NO_4$	2-$[CH_3O_2C(CH_2CH(CH_3)_2)CHNHC(O)]$-$C_6H_4C(O)$-	(H)	35	Ganin et al., 1987
$C_{15}H_{30}NO_6$	aza-18-crown-6-$CH_2CH(OH)CH_2$-	(H)	8	Belohradsky et al., 1987
$C_{16}H_{12}NO_2$	4-anthraqinonyl$NH(CH_2)_2$-	(H)		Ossowski and Schneider, 1990
$C_{16}H_{14}NO_2$	2-$[C_6H_5CH(CH_3)NHC(O)]C_6H_4C(O)$-	(H)	57,53	Ganin et al., 1987
$C_{16}H_{14}NO_3$, a	2-$[C_6H_5O(CH_2)_2NHC(O)]C_6H_4C(O)$-	(H)	50	Ganin et al., 1987
$C_{16}H_{14}NO_3$, b	2-[(4-$C_2H_5O)C_6H_4NHC(O)]C_6H_4C(O)$-	(H)	43	Ganin et al., 1987
$C_{16}H_{14}NO_3$, c	$C_6H_5CH_2O_2CNHCH(C_6H_5)C(O)$-	(H)	85	Lukyanenko et al., 1984a
$C_{16}H_{22}NO_2$	2-$[C_8H_{17}NHC(O)]C_6H_4C(O)$-	(H)	53	Ganin et al., 1987
$C_{16}H_{31}O$	$C_{15}H_{31}C(O)$-	(H)	95	Cinquini and Tundo, 1976

TABLE 6.7. (*Continued*)

R		Other Substituents	Method	Yield (%)	References
Formula	Structure				
$C_{16}H_{31}O_8$	18-crown-6-$CH_2OCH_2CH(OH)CH_2$-		(H)	16	Belohradsky et al., 1987
$C_{16}H_{32}NO_4$	aza-15-crown-5-$(CH_2)_6$-		($C_6H_{12}Cl$)	61	Gokel et al., 1989
$C_{16}H_{33}$	$C_{16}H_{33}$		($C_{16}H_{31}$,O)	94	Cinquini and Tundo, 1976
			(H)	25	Gatto et al., 1986a
$C_{17}H_{14}NO_4$	2-[4-$C_2H_5O_2CC_6H_4NHC(O)]C_6H_4C(O)$-		(H)	40	Ganin et al., 1987
$C_{17}H_{16}NO_3$	$C_6H_5CH_2O_2CNHCH(CH_2C_6H_5)C(O)$-		(H)	86	Lukyanenko et al., 1984a
$C_8H_{17}O_4N_2$	$C_6H_5CH_2(O)CONHCH(C_6H_5)C(O)NHCH_2C(O)$-		(C_2H_4NO,c)	50	Zinic et al., 1990
$C_{18}H_{34}NO_5$	aza-18-crown-6-$(CH_2)_6$-		($C_6H_{12}Cl$)	67	Gokel et al., 1989
$C_{18}H_{35}O$	$C_{17}H_{35}C(O)$-		(H)	100	Gatto et al., 1986a
$C_{18}H_{37}$	$C_{18}H_{37}$		($C_{18}H_{35}O$)	60	Gatto et al., 1986a

$C_{19}H_{15}N_2O_2$	2-HO-5-naphthylN=N$C_6H_3(CH_2)_2C(O)$-	($C_9H_9O_2$,a)	43	Yamashita et al., 1980
$C_{19}H_{17}N_2O_3$	$C_6H_5CH_2O_2CNHCH$(idolyl-CH_2)C(O)-	(H)	88,92	Lukyanenko et al., 1984a
$C_{20}H_{14}N_3O_2$	2-[C_6H_5N=N-4-$C_6H_4NHC(O)$]$C_6H_4C(O)$-	(H)	45	Ganin et al., 1987
$C_{20}H_{23}O$	4-$C_7H_{15}C_6H_4$-4-$C_6H_4C(O)$-	(H)	76	He et al., 1990
$C_{20}H_{25}$	4-$C_7H_{15}C_6H_4$-4-$C_6H_4CH_2$-	($C_{20}H_{23}O$)	70	He et al., 1990
$C_{20}H_{30}NO_2$	2-[$C_{12}H_{25}NHC(O)$]$C_6H_4C(O)$	(H)	48	Ganin et al., 1987
$C_{21}H_{15}N_6O_6$	2,5-(4-$NO_2C_6H_4N$=N$)_2$-2-HOC_6H_2- $(CH_2)_2C(O)$-	($C_9H_9O_2$,a)	14	Yamashita et al., 1980
$C_{21}H_{25}O_2$	4-$C_8H_{17}OC_6H_4$-4-$C_6H_4C(O)$-	(H)	65	He et al., 1990
$C_{21}H_{27}O$	4-$C_8H_{17}OC_6H_4$-4-$C_6H_4CH_2$-	($C_{21}H_{25}O_2$)	69	He et al., 1990
$C_{28}H_{23}N_2O$	6-[6'-CH_3-4,4'-$(C_6H_5)_2$-2,2'-$(C_6H_2N)_2$]- $CH_2O(CH_2)_2$-	(H)	9	Nabeshima et al., 1990
$C_{30}H_{27}N_2O_2$	6[6'-CH_3-4,4'-$(C_6H_5)_2$-2,2'-$(C_6H_2N)_2$]- $CH_2O(CH_2)_2O(CH_2)$-	(H)	22	Nabeshima et al., 1990

TABLE 6.8. 1,10-DIAZA-18-CROWN-6 MACROCYCLES (R AND R′ DIFFERENT)



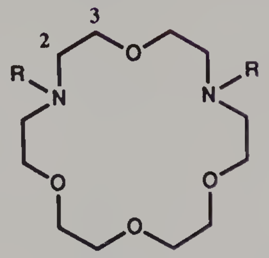
R	R'	Method (or from R,R'=)	Yield (%)	References
H	HO_2CCH_2-	(H,H)	70	Kasprzyk and Wilkins, 1988
		(H,H)	85	Shinkai et al., 1982, 1983b
H	$HO_3S(CH_2)_2$-	(H,H)	85	Shinkai et al., 1987
H	$HOCH_2(CH_2OCH_2)_2CH_2$-	(H,H)	78	Nabeshima et al., 1990
H	2-$HO_2CC_6H_4C(O)$-	(H,H)	65	Vögtle and Elben, 1978
H	2-NO_2-3-HO-4-$CH_3C_6H_2C(O)$-		60	Elben and Vögtle, 1978
H	$C_6H_5CH_2OC(O)$-	(H,H)	50	Lehn et al., 1973, 1977
		(H,H)		Lukyanenko et al., 1986a
H	2-NH_2-3-HO-4-$CH_3C_6H_2C(O)$-			Elben and Vögtle, 1978
H	$C_6H_5(CH_2)_2$-	(H,H)		Nishimura et al., 1981

H	4-$NO_2C_6H_4CO_2(CH_2)_2$-	(H,H)	24	Vögtle and Elben, 1978
H	4-$NH_2C_6H_4CO_2(CH_2)_2$-	[H,4-$NO_2C_6H_4CO_2$-$(CH_2)_2$]	60	Vögtle and Elben, 1978
H	12-crown-4-$CH_2OCH_2CH(OH)CH_2$-	(H,H)	26	Belohradsky et al., 1987
H	aza-12-crown-4-$CH_2CH(OH)CH_2$-	(H,H)-	46	Belohradsky et al., 1987
H	$C_{12}H_{25}$	(H,H)		Nakano et al., 1990
H	$(C_6H_5)_2CH$-	(H,H)	22	Vögtle and Elben, 1978
H	aza-15-crown-5-$CH_2CH(OH)CH_2$-	(H,H)	21	Belohradsky et al., 1987
H	15-crown-5-$CH_2OCH_2CH(OH)CH_2$-	(H,H)	25	Belohradsky et al., 1987
H	aza-18-crown-6-$CH_2CH(OH)CH_2$-	(H,H)	27	Belohradsky et al., 1987
H	4-anthraquinonyl-$NH(CH_2)_2$-	(H,H)		Ossowski and Schneider, 1990
H	18-crown-6-$CH_2OCH_2CH(OH)CH_2$-	(H,H)	38	Belohradsky et al., 1987
$CH_3C(O)$-	9-C_2H_5anthracenyl-10-CH_2-	[H,$CH_3C(O)$]	84	Fages et al., 1989
$CH_3C(O)$-	9-C_2H_5anthracenyl-10-$(CH_2)_3$-	[H,$CH_3C(O)$]	83	Fages et al., 1989
HO_2CCH_2-	$C_{11}H_{23}C(O)$-	(H,HO_2CCH_2)	17	Shinkai et al., 1982, 1983b
		(H,HO_2CCH_2)		Sugai Co., 1983
HO_2CCH_2-	$C_{17}H_{35}C(O)$-	(H,HO_2CCH_2)	20	Shinkai et al., 1987
HO_2CCH_2-	$(C_{16}H_{33}OCH_2)_2CHOCH_2C(O)$-	(H,HO_2CCH_2)	27	Shinkai et al., 1987
C_2H_5	9-C_2H_5anthracenyl-10-$(CH_2)_2$-	(H,$CH_3C(O)$)	92	Fages et al., 1989

TABLE 6.8. (*Continued*)

R	R'	Method (or from R,R'=)	Yield (%)	References
C_2H_5	9-C_2H_5anthracenyl-10-$(CH_2)_3$-	$(H,CH_3C(O))$	88	Fages et al., 1989
$HO_3S(CH_2)_2$-	$C_{11}H_{23}C(O)$-	$[H,HO_3S(CH_2)_2]$	27	Shinkai et al., 1987
$HO_3S(CH_2)_2$-	$(C_{16}H_{33}OCH_2)_2CHOCH_2C(O)$-	$[H,HO_3S(CH_2)_2]$	14	Shinkai et al., 1987
$HO_2C(CH_2)_2$-	$C_{11}H_{23}C(O)$-	$[H,HO_2C(CH_2)_2]$	18	Sugai Co., 1983
$C_6H_5CH_2OC(O)$-,a	2-NO_2-3-$C_6H_5CH_2O$-4-$CH_3C_6H_2C(O)$-	$[H,C_6H_5CH_2OC(O)]$	92	Elben and Vögtle, 1978
$C_6H_5CH_2OC(O)$-	2-NH_2-3-HO-4-$CH_3C_6H_2C(O)$-	$[C_6H_5CH_2OC(O),a]$		Elben and Vögtle, 1978
$C_6H_5CH_2OC(O)$-	3,4,5-$(CH_3O)_3C_6H_2CH_2C(O)$-	$[H,C_6H_5CH_2OC(O)]$	34	Elben et al., 1979
$(C_6H_5)_2CH$-	$C_6H_5CH{=}CHCH_2$-	$[H,(C_6H_5)_2CH]$	87	Vögtle and Elben, 1978
$C_{12}H_{24}Br$	$C_{12}H_{25}$	$(H,C_{12}H_{25})$		Nakano et al., 1990
6-[6'-CH_3-4,4'-$(C_6H_5)_2$-2,2'-$(C_6H_5N)_2$]CH_2-	6-[6'-CH_3-4,4'-$(C_6H_5)_2$-2,2'-$(C_6H_5N)_2$]$CH_2OCH_2(CH_2OCH_2)_2CH_2$	(H,H)	10	Nabeshima et al., 1990

TABLE 6.9. 1,7-DIAZA-18-CROWN-6 MACROCYCLES



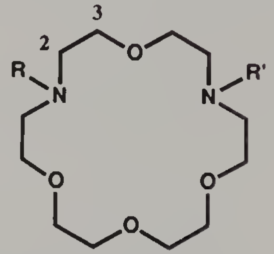
R	Other Substituents	Method (or from R = formula)	Yield (%)	References
H,a		H-4		Ajinomoto Co., 1983a
		J-1	45	Ajinomoto Co., 1983b
		(H,b)		Biernat and Luboch, 1984
		(Ts)	68	Lukyanenko et al., 1988a
		E-9	68	Lukyanenko et al., 1986b
		J-1	11	Maeda et al., 1983
H,b	$2,6\text{-}(O)_2$			Biernat and Luboch, 1984
H	$8,18\text{-}(\underline{i}\text{-}C_3H_7)_2$	E-1	27	Chadwick et al., 1984
H	$8,18\text{-}(\underline{i}\text{-}C_3H_7)_2;2,6\text{-}(O)_2$	E-1	22	Chadwick et al., 1984
H	$8,18\text{-}(C_6H_5)_2$	E-1	97	Chadwick et al., 1984

TABLE 6.9. (*Continued*)

R	Other Substituents	Method (or from R = formula)	Yield (%)	References
H	8,18-$(C_6H_5)_2$;2,6-$(O)_2$	E-1	18	Chadwick et al., 1984
H	8,18-$(C_6H_5)_2$; 2,6,9,17-$(O)_4$	H-4	32	Zinic and Skaric, 1988
H	8,18-$(CH_2C_6H_5)_2$	E-1	99	Chadwick et al., 1984
H	8,18-$(CH_2C_6H_5)_2$;2,6-$(O)_2$	E-1	30	Chadwick et al., 1984
		E-13	80	Hodgkinson et al., 1979
CH_3		K-1		Kuo et al., 1978
CH_3	8,18-$(i\text{-}C_3H_7)_2$	(H)	92	Chadwick et al., 1984
CH_3	8,18-$(C_6H_5)_2$	(H)	82	Chadwick et al., 1984

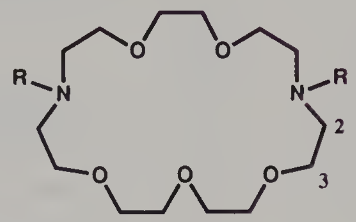
CH_3	8,18-$(CH_2C_6H_5)_2$	(H)	99	Chadwick et al., 1984
		E-5	63	Gatto et al., 1986a
$(CH_3)_2CH$-	8,18-$(CH_2C_6H_5)_2$	(H)		Chadwick et al., 1981
$CH_3CH(OH)CH_2$-			68	Hancock et al., 1986
$C_2H_5OC(O)$-		E-13	25	Hodgkinson et al., 1979
$C_6H_5CH_2$-		J-3	68	Bradshaw and Krakowiak, 1988
		E-5	63	Gatto et al., 1986a
$C_6H_5CH_2$-	8,18-$(i\text{-}C_3H_7)_2$	(H)		Chadwick et al., 1984
$C_6H_5CH_2$-	8,18-$(C_6H_5)_2$	(H)	77	Chadwick et al., 1984
$C_6H_5CH_2$-	8,18-$(CH_2C_6H_5)_2$	(H)	91	Chadwick et al., 1981, 1984
Ts		E-9	69	Atkins et al., 1978
		E-9	86	Lukyanenko et al., 1988a, 1988b

TABLE 6.10. 1,7-DIAZA-18-CROWN-6 MACROCYCLES (R AND R′ DIFFERENT)



R	R'	Method	Yield (%)	References
C_2H_5	$HO(CH_2)_2$-	E-7	62	Bradshaw et al., 1990a
C_2H_5	$HO(CH_2)_2O(CH_2)_2$-	E-7	73	Bradshaw et al., 1990a
C_2H_5	$(CH_3)_2N(CH_2)_2$-	E-7	47	Bradshaw et al., 1990a
C_2H_5	$(CH_3)_2N(CH_2)_3$-	E-7	33	Bradshaw et al., 1990a
C_2H_5	$(C_2H_5)_2N(CH_2)_2$-	E-7	44	Bradshaw et al., 1990a
C_2H_5	$(C_2H_5)_2N(CH_2)_3$-	E-7	33	Bradshaw et al., 1990a
C_2H_5	morpholine-$(CH_2)_2$-	E-7	55	Bradshaw et al., 1990a
C_2H_5	$C_6H_5CH_2$-	E-7	72	Bradshaw et al., 1990a
$C_6H_5CH_2$-	$(C_2H_5)_2N(CH_2)_3$-	E-7	68	Bradshaw et al., 1990a

TABLE 6.11. 1,13-DIAZA-21-CROWN-7 MACROCYCLES



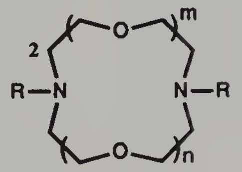
R		Other Substituents	Methods (or from R = formula)	Yield (%)	References
Formula	Structure				
H	H		H-4	20	Ajinomoto Co., 1983a
			J-1		Ajinomoto Co., 1983b
			H-4	85	deJong et al., 1983
			E-1	85	Dietrich et al., 1973
			(Ts)	45	Lukyanenko et al., 1988a
			E-9	45	Lukyanenko et al., 1988b
			H-4	38	Maeda et al., 1983
			H-4	38	Shinkai et al., 1983b
H	H	17-CH_2OH	E-2	73	Babb et al., 1986
H	H	14,21-$(O)_2$	E-1	75	Dietrich et al., 1973

TABLE 6.11. *(Continued)*

R		Other Substituents	Method (or from R = formula)	Yield (%)	References
Formula	Structure				
H	H	17-CH_2OH; 14,21-$(O)_2$	E-2	81	Babb et al., 1986
H	H	17-CH_2Oallyl; 14,21-$(O)_2$	E-2	54	Babb et al., 1986
H	H	14,18,21-$(O)_3$	E-1	35	Lukyanenko et al., 1981
H	H	14,18,21-$(O)_3$; 20-$CH_2C_6H_5$	E-1	28	Lukyanenko et al., 1981
CH_3	CH_3		E-13	58	Johnson et al., 1985
CH_3	CH_3	14,18,21-$(O)_3$; 20-$CH_2C_6H_5$	E-3	30	Bogatskii et al., 1984a
$C_2H_3O_2$	HO_2CCH_2-		(H)	10	deJong et al., 1983
C_2H_5O	$HO(CH_2)_2$-	14,21-$(O)_2$; 17,18-$(CH_3)_2$	E-1		Kimura et al., 1984
$C_5H_3O_2$	2-furanyl-C(O)-		(H)		Tsukube et al., 1984

C_5H_5O	2-furanyl-CH_2-		($C_5H_3O_2$)		Tsukube et al., 1984
C_6H_6N	2-pyridinyl-CH_2-				Tsukube et al., 1988
C_7H_7	$C_6H_5CH_2$-		J-3	54	Bradshaw and Krakowiak, 1988
			(H)	58	Tsukube, 1984c
C_7H_7	$C_6H_5CH_2$-	5-CH_2Oallyl	H-5	31	Bradshaw et al., 1989c
C_7H_7	$C_6H_5CH_2$-	14,21-$(O)_2$	E-3	63	Petranek and Ryba, 1980
C_7H_7	$C_6H_5CH_2$-	14,21-$(O)_2$; 17,18-$(CH_3)_2$	E-1	59	Petranek and Ryba, 1977, 1980
C_7H_7	$C_6H_5CH_2$-	14,21-$(O)_2$; 17-C_4H_8-18	E-1	55	Petranek and Ryba, 1983
$C_7H_7O_2S$	Ts		E-9	82	Lukyanenko et al., 1988a, 1988b
$C_8H_7O_2$	$C_6H_5CH_2OC(O)$-		E-13	34	Johnson et al., 1985
C_8H_{17}	C_8H_{17}	17,18-$(CH_3)_2$	E-1	52	Petranek and Ryba, 1983
C_8H_{17}	C_8H_{17}	17,17,18,18-$(CH_3)_4$	E-1	43	Petranek and Ryba, 1983
$C_{10}H_{19}O_2$	$CH_3(CH_2)_6CO_2(CH_2)$-	14,21-$(O)_2$; 17,18-$(CH_3)_2$	(C_2H_5O)		Kimura et al., 1984

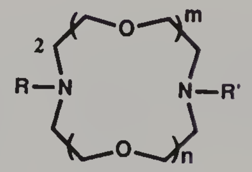
TABLE 6.12. 1,7-DIAZA-21-CROWN-7; 1,7-DIAZA-24-CROWN-8; 1,10-DIAZA-24-CROWN-8; 1,13-DIAZA-24-CROWN-8; 1,10-DIAZA-27-CROWN-9; 1,13-DIAZA-27-CROWN-9; 1,10-DIAZA-30-CROWN-10; 1,16-DIAZA-30-CROWN-10; AND 1,13-DIAZA-36-CROWN-12 MACROCYCLES



R	m	n	Other Substituents	Methods (or from R = formula)	Yield (%)	References
H	1	4		H-4		Ajinomoto Co., 1983a
				J-1	11	Maeda et al., 1983
H	1	4	2,6-$(O)_2$	E-1	25	Lukyanenko et al., 1981
H	1	4	2,6,9,20-$(O)_4$; 8,21-$(C_6H_5)_2$	H-4	48	Zinic and Skaric, 1988
H	1	5	8,12,20,24-$(O)_4$	E-1	11	Lukyanenko et al., 1981
H	1	5	2,6,9,23-$(O)_4$; 8,24-$(C_6H_5)_2$	H-4		Ajinomoto Co., 1983a
				H-4	28	Zinic and Skaric, 1988

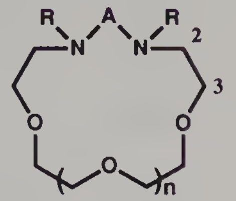
H	2	4	2,9,12,23-$(O)_4$; 11,24-$(C_6H_5)_2$	H-4	42	Zinic and Skaric, 1988
H	2	4	2,6,9,-$(O)_3$	E-1	20	Lukyanenko et al., 1981
H	3	3		E-1		Cowie and Wu, 1988
				E-1	90	Dietrich et al., 1973
				(Ts)	42	Johnson et al., 1985
				E-9	47	Lukyanenko et al., 1988a, 1988b
H	3	3	2,12-$(O)_2$	E-1	68	Dietrich et al., 1973
H	3	3	2,11-$(O)_2$	E-1		Cowie and Wu, 1988
CH_3	3	3		(H)	92	Johnson et al., 1985
2-HO-5-$NO_2C_6H_3CH_2$-	3	3		(H)	81	Katayama et al., 1988
Ts	3	3		I-1	10	Johnson et al., 1985
				E-9	50	Lukyanenko et al., 1988a, 1988b
Ts	3	3	3,11,15,23-$(O)_4$	I-2	12	Qin et al., 1984
H	2	6	11,15,26,30-$(O)_4$	E-1	17	Lukyanenko et al., 1981
Ts	4	4	3,14,18,29-$(O)_4$	I-2	11	Qin et al., 1984
H	3	7	14,18,32,36-$(O)_4$	E-1	19	Lukyanenko et al., 1981

TABLE 6.13. DIAZA-CROWN MACROCYCLES (R AND R′ DIFFERENT)



R	R'	m	n	Method (or from R = formula)	Yield (%)	References
HO_2CCH_2-	H	2	4	(H,H)		Sugai Co., 1983
HO_2CCH_2-	H	3	4	(H,H)		Sugai Co., 1983
HO_2CCH_2-	H	2	5	(H,H)		Sugai Co., 1983
$HO_2C(CH_2)_2$-	H	3	3	(H,H)		Sugai Co., 1983
$HO_2C(CH_2)_3$-	H	4	4	(H,H)		Sugai Co., 1983
HO_2CCH_2-	$C_6H_{13}CH(CH_3)C(O)$-	3	4	(H,HO_2CH_2)	12	Sugai Co., 1983
HO_2CCH_2-	$C_{11}H_{23}C(O)$-	2	5	(H,HO_2CH_2)	10	Sugai Co., 1983
$HO_2C(CH_2)_3$-	$C_{14}H_{29}C(O)$-	4	4	$[H,HO_2C(CH_2)_3]$	16	Sugai Co., 1983
$C_{11}H_{23}C(O)$-	HO_2CCH_2-	2	4	(H,HO_2CCH_2)	11	Sugai Co., 1983
$C_{11}H_{23}C(O)$-	$HO_2C(CH_2)_2$-	3	3	$[H,HO_2C(CH_2)_2]$	14	Sugai Co., 1983

TABLE 6.14. DIAZA-CROWN MACROCYCLES WITH ONE MISCELLANEOUS BRIDGE



A	R	n	Other Substituents	Method (or from R = formula)	Yield (%)	References
nothing	$CH_3C(O)$-	1				Bradshaw et al., 1988c
nothing	C_2H_5	1			35 overall	Bradshaw et al., 1988c
C=S,a	H	0		E-16	27	Bogatskii et al., 1980a, 1980b
C=S,b	H	1		E-16	34	Bogatskii et al., 1980a
C=S,c	H	2		E-16	29	Bogatskii et al., 1982b
C=S	CH_3	0		(C=S,a)	55,79	Bogatskii et al., 1984c, 1985b
C=S	CH_3	1		(C=S,b)	49,74	Bogatskii et al., 1984c, 1985b
C=S	CH_3	2		(C=S,c)	86,67	Bogatskii et al., 1983, 1985b
C=O	CH_3	0		(C=S,a)	86	Bogatskii et al., 1984b
C=O	CH_3	1		(C=S,b)	85	Bogatskii et al., 1982c, 1984b

TABLE 6.14. (*Continued*)

A	R	n	Other Substituents	Methods (or from R = formula)	Yield (%)	References
C=O	CH_3	2		(C=S,c)	87	Bogatskii et al., 1984b
$-(CH_2)_2-$,a	H	0		E-4	10	Alfheim et al., 1986
				E-9	41	Rasshofer and Vögtle, 1977
				E-9	65	Lukyanenko et al., 1988b
$-(CH_2)_2-$,b	H	1		$[(CH_2)_2$,c]	50	Biernat and Luboch, 1984
				H-4	32	Maeda et al., 1983
$-(CH_2)_2-$,c	H	1	2,12-$(O)_2$		60	Biernat and Luboch, 1984
$-(CH_2)_2-$	H	1	2,3;11,12-(cyclohexano)$_2$	H-4	42	Maeda et al., 1983
$-(CH_2)_2-$	H	2		H-4	39	Maeda et al., 1983
$-(CH_2)_2-$	H	2	2,3;14,15-(cyclohexano)$_2$	H-4	42	Maeda et al., 1983
$-(CH_2)_2-$	H	3		H-4		Ajinomoto Co., 1983a
				J-1		Ajinomoto Co., 1983b
$-(CH_2)_2-$	CH_3	2	8-CH_2O-allyl	J-2	62	Bradshaw et al., 1989c
$-(CH_2)_2-$	HO_2CCH_2-	0	3,8-$(O)_2$	H-7	15	Qin, 1984

$-(CH_2)_2-$	HO_2CCH_2-	1	3,11-$(O)_2$	H-7	20	Qin, 1984
$-(CH_2)_2-$	HO_2CCH_2-	2	3,14-$(O)_2$	H-7	22	Qin, 1984
$-(CH_2)_2-$	HO_2CCH_2-	3	3,17-$(O)_2$	H-7	25	Qin, 1984
$-(CH_2)_2-$	C_2H_5	2	8-CH_2O-allyl	H-5	21	Bradshaw et al., 1989c
$-(CH_2)_2-$	$HO(CH_2)_2-$	0		E-6	71	Bradshaw et al., 1990b
$-(CH_2)_2-$	$HO(CH_2)_2-$	1		E-6	70-79	Bradshaw et al., 1990b
$-(CH_2)_2-$	$HO(CH_2)_2-$	2		E-6	66	Bradshaw et al., 1990b
$-(CH_2)_2-$	C_6H_5	0	2,9-$(O)_2$		80	Leyque et al., 1987
$-(CH_2)_2-$	$C_6H_5CH_2-$	0	2,9-$(O)_2$		73,80	Leyque et al., 1988
$-(CH_2)_2-$	$C_6H_5CH_2-$	2	8-CH_2O-allyl	H-5	21	Bradshaw et al., 1989c
$-(CH_2)_2-$	Ts	0		E-9	67	Lukyanenko et al., 1988b
				E-9	52	Rasshofer et al., 1976
				E-9	43	Rasshofer and Vögtle, 1978
$-(CH_2)_2-$	Ts	1		E-9	23	Rasshofer et al., 1976
$-(CH_2)_2-$	2-HO-5-$NO_2C_6H_3CH_2-$	1		(H)	50	Katayama et al., 1988
$-(CH_2)_2-$	2-HO-5-$NO_2C_6H_3CH_2-$	2		(H)	54	Katayama et al., 1988
$-(CH_2)_2-$	2-HO-5-$NO_2C_6H_3CH_2-$	3		(H)	71	Katayama et al., 1988
-C(O)C(O)-	H	0	3,8-$(O)_2$; 2,9$(C_6H_5)_2$	E-3	84,92	Zinic et al., 1980

TABLE 6.14. *(Continued)*

A	R	n	Other Substituents	Methods (or from R = formula)	Yield (%)	References
-C(O)C(O)-	H	1	3,11-$(O)_2$; 2,12-$(C_6H_5)_2$	E-3	84,86	Zinic et al., 1980
-C(O)C(O)-	H	2	3,14-$(O)_2$; 2,15-$(C_6H_5)_2$	E-3	70	Zinic et al., 1980
-$(CH_2)_3$-	CH_3	0		E-13		Hodgkinson et al., 1976
-$(CH_2)_3$-	HO_2CCH_2-	0			25	Ewin and Hill, 1985
-$(CH_2)_3$-	$C_2H_5O_2C$-	0		E-13		Hodgkinson et al., 1976
-$(CH_2)_3$-	Ts	0		E-9	77	Ewin and Hill, 1985
				E-9	16,28	Rasshofer et al., 1976
-$(CH_2)_2$-	Ts	1		E-9	7	Rasshofer et al., 1976
-$(CH_2)_4$-	CH_3	0		E-13		Hodgkinson et al., 1976
-$(CH_2)_5$-	$C_2H_5O_2C$-	0		E-13		Hodgkinson et al., 1976
-C(O)$(CH_2)_2$C(O)-	$C_6H_5CH_2$-	1		E-3	11	Petranek and Ryba, 1980
-$(CH_2)_5$-	CH_3	0		E-13		Hodgkinson et al., 1976
-$(CH_2)_2$-	$C_2H_5O_2C$-	0		E-13		Hodgkinson et al., 1976
-$(CH_2)_5$-	Ts	0		E-9	76	Vriesema et al., 1984

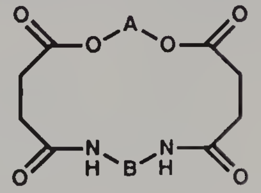
$-(CH_2)_5-$	Ts	1		E-9	66	Vriesema et al., 1984
$-(CH_2)_6-$	CH_3	0		E-13		Hodgkinson et al., 1976
$-(CH_2)_6-$	$C_2H_5O_2C-$	0		E-13		Hodgkinson et al., 1976
$-(CH_2)_6-$	$4-CH_3O_2CCH_2C_6H_4-$	0	$2,9-(O)_2;$ $5,5,6,6-(CH_3)_4$	E-3	61	Hruska and Petranek, 1988
$-C(O)(CH_2)_4C(O)-$	$C_6H_5CH_2-$	1		E-3	25	Petranek and Ryba, 1980
$-(CH_2)_7-$	CH_3	0		E-13		Hodgkinson et al., 1976
$-(CH_2)_7-$	$C_2H_5O_2C-$	0		E-13		Hodgkinson et al., 1976
$-(CH_2)_8-$	H	0		E-13		Hodgkinson et al., 1976
$-(CH_2)_8-$	CH_3	0		E-13		Hodgkinson et al., 1976
$-(CH_2)_8)-$	$C_2H_5O_2C-$	0		E-13		Hodgkinson et al., 1976
$-(CH_2)_{10}-$	C_6H_{13}	0	$2,9-(O)_2$			Leyque et al., 1987
$-(CH_2)_{10}-$	Ts	1		E-9	50	Vriesema et al., 1984
$-(CH_2)_{10}-$	$4-CH_3O_2CCH_2C_6H_4-$	0	$2,9-(O)_2;$ $5,5,6,6-(CH_3)_4$	E-1	85	Hruska and Petranek, 1988
$-(CH_2)_{12}-$	H	0		E-1	49	Rossa and Vögtle, 1981
$-(CH_2)_{12}-$	H	0	$2,9-(O)_2$	E-1	90	Rossa and Vögtle, 1981
$-(CH_2)_{12}-$	cyclohexyl	0	$2,9-(O)_2;$ $5,5,6,6-(CH_3)_4$	E-1	22	Hruska and Petranek, 1987
$-(CH_2)_{12}-$	$C_6H_5CH_2-$	0	$2,9-(O)_2;$ $5,6-(CH_3)_2$	E-1	55	Petranek and Ryba, 1980

TABLE 6.14. (*Continued*)

A	R	n	Other Substituents	Methods (or from R = formula)	Yield (%)	References
$-(CH_2)_{12}-$	$C_6H_5CH_2-$	0	$2,9-(O)_2;$ $5,5,6,6-(CH_3)_4$	E-1	48	Hruska and Petranek, 1987
$-(CH_2)_{12}-$	$4-CH_3O_2CCH_2C_6H_4-$	0	$6,6-(CH_3)_2;$ $2,9-(O)_2$	E-1	58	Hruska and Petranek, 1988
$-(CH_2)_{12}-$	$4-CH_3O_2CCH_2C_6H_4-$	0	$2,9-(O)_2;$ $5,5,6,6-(CH_3)_4;$	E-1	74	Hruska and Petranek, 1987
$-(CH_2)_{14}-$	$4-CH_3)_2CCH_2C_6H_4-$	0	$2,9-(O)_2;$ $5,5,6,6-(CH_3)_2$		73	Hruska and Petranek, 1988
$-CH_2CH(CH_2OCH_2)CH_2-$	H	1		E-4	17	Krespan, 1976
$-(CH_2)_2OCH_2-$ $CH(OH)CH_2O(CH_2)_2-$	C_2H_5	0		H-3	34	Bradshaw et al., 1989c
$-(CH_2)_2OCH_2-$ $C(=CH_2)CH_2O(CH_2)_2-$	H	0		H-2	35	Kakiuchi and Tomoi, 1981

			H-2	35	Tomoi et al., 1978
$-(CH_2)_2OCH_2-$ $C(=CH_2)CH_2O(CH_2)_2-$	C_2H_5	0	H-3	67	Bradshaw et al., 1989c
$-(CH_2)_2OCH_2-$ $C(=CH_2)CH_2O(CH_2)_2-$	$C_6H_5CH_2-$	0	H-2	63	Bradshaw et al., 1989c
$-(CH_2)_2OCH_2CH-$ $(Oallyl)CH_2O(CH_2)_2-$	C_2H_5	0	H-3	81	Bradshaw et al., 1989c
$-C(O)CH_2OCH_2-$ $C(CH_3)_2CH_2OCH_2C(O)-$	$C_6H_5CH_2-$	0	E-1	43	Petranek and Ryba, 1983
$-(CH_2)_2OCH_2CH-$ $CH_2OCH_2CH_2O(CH_2)_2-$	H	0	H-1	71	Krespan, 1975
$-C(O)CH_2O(CH_2)_3-$ $OCH_2C(O)-$	$C_6H_5CH_2-$	1	E-1	52	Petranek and Ryba, 1983
$-C(O)CH_2O(CH_2)_4-$ $OCH_2C(O)-$	$C_6H_5CH_2-$	1	E-1	60	Petranek and Ryba, 1983
$-(CH_2)_2OCH_2C-$ $(CH_2OH)CH_2O(CH_2)_2-$	H	0	H-1		Krespan, 1980

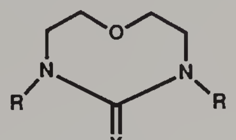
TABLE 6.15. DIAZA-CROWN MACROCYCLES WITH BUTYLENE BRIDGES

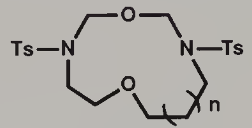


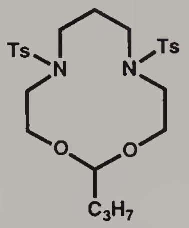
A	B	Method	Yield (%)	References
$-(CH_2)_2-$	$-(CH_2)_2-$	E-1	46	Asay et al., 1977
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2-$	E-1	8	Asay et al., 1977
$-CH_2(CH_2OCH_2)_2CH_2-$	$-(CH_2)_2-$	E-1	10	Asay et al., 1977
$-(CH_2)_3-$	$-(CH_2)_4-$	E-1	21	Lukyanenko et al., 1981

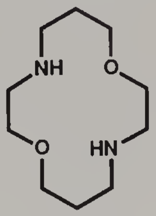
$-CH_2C(CH_3)_2CH_2-$	$-(CH_2)_4-$	E-1	22	Lukyanenko et al., 1981
$-(CH_2)_3-$	$-(CH_2)_6-$	E-1	25	Lukyanenko et al., 1981
$-CH_2C(CH_3)_2CH_2-$	$-(CH_2)_6-$	E-1	23	Lukyanenko et al., 1981
$-(CH_2)_3-$	$-(CH_2)_8-$	E-1	20	Lukyanenko et al., 1981
$-CH_2C(CH_3)_2CH_2-$	$-(CH_2)_8-$	E-1	16	Lukyanenko et al., 1981
$-(CH_2)_3-$	$-(CH_2)_2O(CH_2)_2-$	E-1	26	Lukyanenko et al., 1981
$-CH_2C(CH_3)_2CH_2-$	$-(CH_2)_2O(CH_2)_2-$	E-1	19	Lukyanenko et al., 1981
$-CH_2C(CH_3)_2CH_2-$	$-CH_2(CH_2OCH_2)_2CH_2-$	E-1	17	Lukyanenko et al., 1981
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	E-1	31	Lukyanenko et al., 1981
$-CH_2(CH_2OCH_2)_2CH_2-$	$-CH_2(CH_2OCH_2)_2CH_2-$	E-1	9	Lukyanenko et al., 1981
$-CH_2(CH_2OCH_2)_3CH_2-$	$-CH_2(CH_2OCH_2)_3CH_2-$	E-1	12	Lukyanenko et al., 1981

TABLE 6.16. MISCELLANEOUS DIAZA-CROWN MACROCYCLES


6.16 A


6.16 B


6.16 C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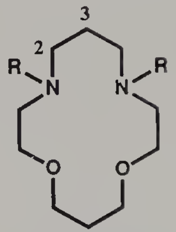
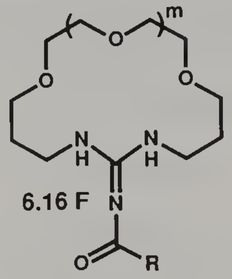
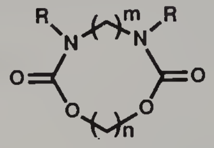
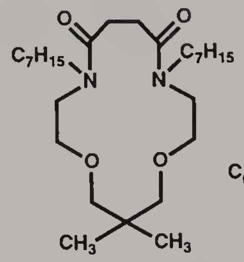

6.16 E


6.16 F


6.16 G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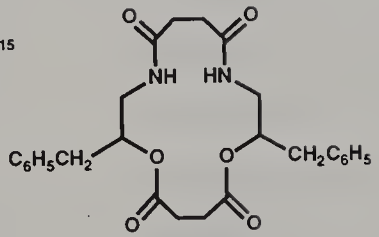
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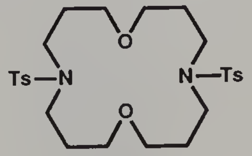
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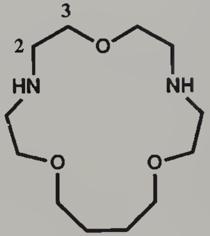
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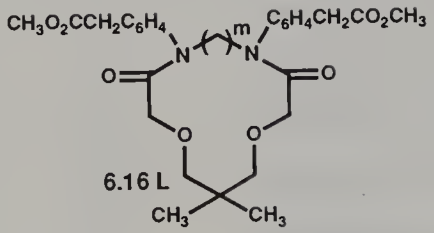
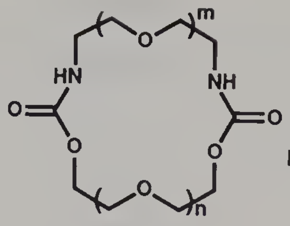
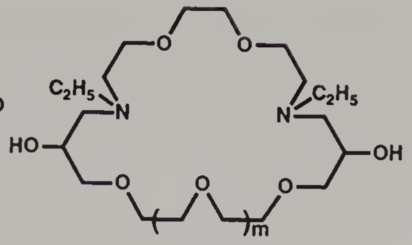
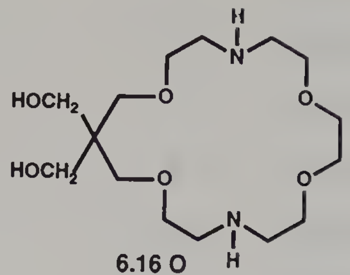

6.16 L



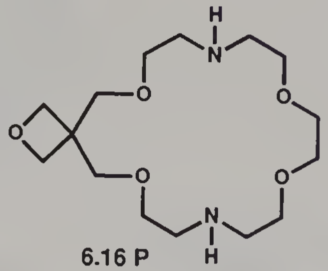
6.16 M



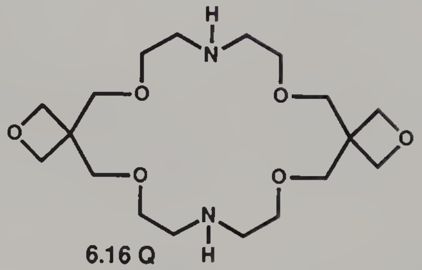
6.16 N



6.16 O



6.16 P



6.16 Q

Structure	R	X or Other Substituents	m	n	Method	Yield (%)	References
6.16 A	H	S			E-16	41	Bogatskii et al., 1980a
	CH_3	O					Bogatskii et al., 1982c
	C_2H_5	O					Bogatskii et al., 1982c
6.16 B				0	E-9	28	Krakowiak et al., 1984
					E-9	24	Krakowiak et al., 1984

TABLE 6.16. (*Continued*)

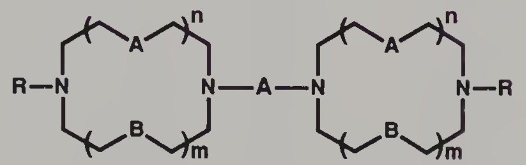
Structure	R	X or other Substituents	m	n	Methods	Yield (%)	References
6.16 C					E-9	60	Krakowiak et al., 1988
6.16 D							Formanovskii, 1990
6.16 E	C_7H_{15}	$10,10\text{-}(CH_3)_2;2,4\text{-}(O)_2$			E-17		Attiyat et al., 1990
	C_7H_{15}	$3,3,10,10\text{-}(CH_3)_4;2,4\text{-}(O)_2$			E-17		Attiyat et al., 1990
	C_7H_{15}	$3,3\text{-}CH_2C_6H_5;$ $2,4\text{-}(O)_2;10,10\text{-}(CH_3)_2$			E-17		Attiyat et al., 1990
6.16 F	C_6H_5		0			25	Fukada et al., 1990
	$2\text{-}ClC_6H_4\text{-}$		0			59	Fukada et al., 1990
	$4\text{-}ClC_6H_4\text{-}$		0			65	Fukada et al., 1990
	$2\text{-}O_2NC_6H_4\text{-}$		0			73	Fukada et al., 1990
	$4\text{-}CH_3C_6H_4\text{-}$		0			80	Fukada et al., 1990
	C_6H_5		1			24	Fukada et al., 1990
	$2\text{-}ClC_6H_4\text{-}$		1			18	Fukada et al., 1990
	$4\text{-}ClC_6H_4\text{-}$		1			16	Fukada et al., 1990

	$2\text{-}O_2NC_6H_4\text{-}$		1			43	Fukada et al., 1990
	$4\text{-}CH_3C_6H_4\text{-}$		1			73	Fukada et al., 1990
6.16 G	H		5	2			Shanzer et al., 1980
	H		6	2		35	Shanzer et al., 1980
						35	Yeda, 1985
	H		6	6			Yeda, 1985
	C_2H_5		6	2			Yeda, 1985
6.16 H					E-17		Attiyat et al., 1987
6.16 I					E-1	40	Lukyanenko et al., 1980
6.16 J						2	Krakowiak et al., 1983
6.16 K		$2,6,9,16\text{-}(O)_4;8,17\text{-}(C_6H_5)_2$			H-4	53	Zinic and Skaric, 1988
		$8,11,14,17\text{-}(O)_4;$ $9,16\text{-}(CH_2C_6H_5)_2$			E-1	35	Lukyanenko et al., 1980
6.16 L			10			62	Hruska and Petranek, 1988
			12			58	Hruska and Petranek, 1988

TABLE 6.16. (*Continued*)

Structure	R	X or Other Substituents	m	n	Method	Yield (%)	References
6.16 M			1	0	E-1	37	Buhleier et al., 1978
			2	0	E-1	84	Buhleier et al., 1978
			3	0	E-1	84	Buhleier et al., 1978
			1	1	E-1	89	Buhleier et al., 1978
			2	1	E-1	77	Buhleier et al., 1978
			3	1	E-1	90	Buhleier et al., 1978
6.16 N			0		E-14	30	Kikui et al., 1984
			1		E-14	22	Kikui et al., 1984
6.16 O							Krespan, 1976
6.16 P					H-1		Krespan, 1976
6.16 Q					H-1	17	Krespan, 1976
					H-6	17	Krespan, 1976

TABLE 6.17. BIS(DIAZA-CROWN) MACROCYCLES



A	R	n	m	Method	Yield (%)	References
$-(CH_2)_2-$	H	1	1	L-1	85	Calverley and Dale, 1981
		1	1	L-1	85	Dale and Calverley, 1982
$-(CH_2)_2-$	$C_6H_5CH_2-$	1	1	L-1		Calverley and Dale, 1981
		1	1	L-1		Dale and Calverely, 1982
$-C(O)(CH_2)_7C(O)-$	H	1	1	L-2	86	Kumar et al., 1986
$-C(O)(CH_2)_7C(O)-$	$t-C_4H_9O_2C-$	1	1	L-2	74	Kumar et al., 1986
$-CH_2CH(CH_2C_6H_5)CH_2-$	H	1	1	L-1	95	Anelli et al., 1985, 1988
$-CH_2CH(CH_2C_6H_5)CH_2-$	Ts	1	1	L-1	78,93	Anelli et al., 1985, 1988
$-CH_2-4-C_6H_4-4-C_6H_4CH_2-$	H	1	1	L-2	94	Kumar et al., 1986
$-CH_2-4-C_6H_4-4-C_6H_4CH_2-$	$t-C_4H_9O_2C-$	1	1	L-2	23	Kumar et al., 1986

TABLE 6.17. (*Continued*)

A	R	n	m	Method	Yield (%)	References
$-CH_2CH(C_{16}H_{33})CH_2-$	H	1	1	L-1	96	Anelli et al., 1985, 1988
$-CH_2CH(C_{16}H_{33})CH_2-$	Ts	1	1	L-1	72,75	Anelli et al., 1985, 1988
$-CH_2(CH_2OCH_2)_2CH_2-$	H	2	1	L-2		Jones et al., 1981
				L-2	66	Kumar et al., 1986
$-C(O)CH_2O(CH_2)_2OCH_2C(O)-$	H	2	1	L-2		Jones et al., 1981
				L-2	84	Kumar et al., 1986
$-C(O)CH_2O(CH_2)_2OCH_2C(O)-$	$t-C_4H_9O_2C-$	2	1	L-2		Jones et al., 1981
				L-2	74	Kumar et al., 1986
$-C(O)CH_2OCH_2C(O)-$	H	2	2	L-3	90	Lehn et al., 1973, 1977
$-C(O)(CH_2)_3C(O)-$	$C_6H_5CH_2O_2C-$	2	2	L-3		Lehn et al., 1973

$-C(O)(CH_2)_3C(O)-$	H	2	2	L-3		Lehn et al., 1973
$-C(O)CH_2OCH_2C(O)-$	$C_6H_5CH_2O_2C-$	2	2	L-3		Lehn et al., 1973, 1977
$-C(O)CH_2N(Ts)CH_2C(O)-$	H	2	2	L-3	85	Lehn et al., 1973, 1977
$-C(O)CH_2N(Ts)CH_2C(O)-$	$C_6H_5CH_2O_2C-$	2	2	L-3		Lehn et al., 1973, 1977
$-CH_2[CH(OH)]_2CH_2-$	H	2	2	L-4	60	Lukyanenko et al., 1986a
$-CH_2[CH(OH)]_2CH_2-$	$C_6H_5CH_2O_2C-$	2	2	L-4	60	Lukyanenko et al., 1986a
$-C(O)(CH_2)_3C(O)-$	H	2	2		80	Lehn et al., 1977
$-C(O)(CH_2)_3C(O)-$	$C_6H_5CH_2O_2C-$	2	2			Lehn et al., 1977
$-C(O)CH_2-2-C_6H_4CH_2C(O)-$	H	2	2		70	Lehn et al., 1977
$-C(O)CH_2-2-C_6H_4CH_2C(O)-$	$C_6H_5CH_2O_2C-$	2	2			Lehn et al., 1977
actinocinyl	H	2	2		17	Elben and Vögtle, 1978
actinocinyl	$C_6H_5CH_2O_2C-$	2	2		20	Elben and Vögtle, 1978
$-(CH_2)_2O_2C(CH_2)_5CO_2(CH_2)_2-$	$CH_3(CH_2)_6CO_2-$ $CH_2-2,9-(O)_2;$ $5,6-(CH_3)_2$	2	3		30	Kimura et al., 1984

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CHAPTER VII

Polyaza-crown Macrocycles

A. INTRODUCTION

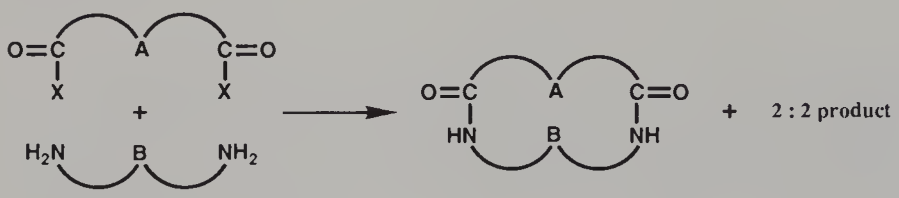
Preparation of the polyaza-crowns (macrocycles containing many nitrogen atoms and at least one oxygen atom) more often involves cyclization reactions of the nitrogen rather than oxygen atoms. Cyclizations to nitrogen can be carried out using weak bases such as triethylamine or an alkali metal carbonate. The polyaza-crowns, especially the larger ones, are important from a biological point of view because they have multiple complexation sites and can fit a multiplicity of guest molecules.

From a synthetic standpoint, routes to the polyaza-crowns are similar to those mentioned for the monoaza- and diaza-crowns in Chapters V and VI.

Thus, 1:1 and 2:2 cyclization reactions prevail for ring closure to form the polyaza-crowns. Specific methods are as follows.

Method M.

Formation of two amide bonds by a 1:1 cyclization of a bisprimary amine and a diacid dichloride or a diester. Generally, high-dilution conditions must be used for reactions with the very reactive diacid dichlorides. Reactions with the less reactive diesters are not generally done under high dilution. By-products resulting from a 2:2 cyclization are formed at higher concentrations of the reactants; however, the yields for these by-products are never very high except where the 1:1 cyclization reaction would give 8- to 10-membered rings.

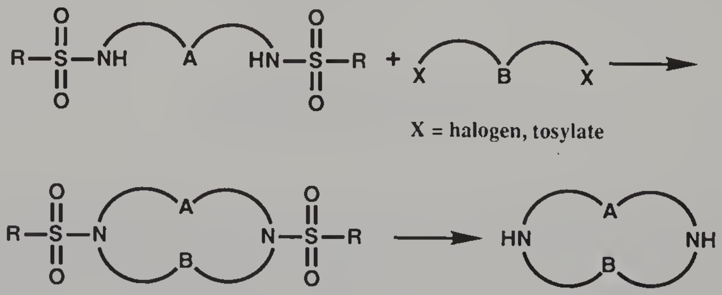


Method M

A, B contain N and/or O atoms
X = Cl, OR

Method N.

Formation of two C—N bonds by a 1:1 cyclization of a bissulfonamide with a dihalide or a ditosylate. The sulfonamide groups include *p*-toluenesulfonamide (tosyl), benzenesulfonamide, methanesulfonamide (mesyl), or the 2-carboxyamidobenzenesulfonamide. These sulfonamide groups serve both as activators for the amide nitrogen and as



Method N

X = halogen, tosylate

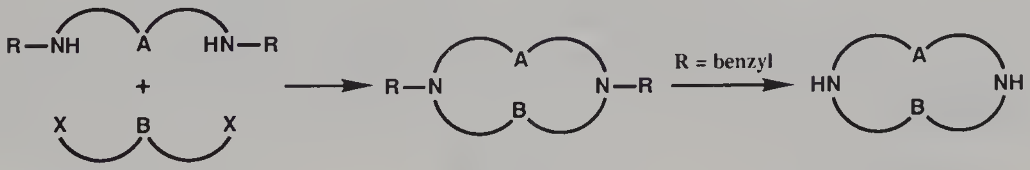
A, B contain N and/or O atoms
R = tolyl, phenyl, methyl, substituted phenyl

protecting groups for the N—H function. The sodium or potassium salts of the sulfonamides are much more reactive than the sulfonamide. Removal of the sulfonyl portion of the cyclized diamide by acid or base or under reductive conditions introduces a proton on the ring nitrogen atoms. Sulfonamide groups in the starting materials cause the open chain molecules to cyclize rather than polymerize because rotation of bulky sulfonamide groups is restricted. Thus, the loss in internal energy on cyclization is small (Shaw, 1975). Often, especially where a 1:1 cyclization produces a 9-crown-3, 2:2 cyclization is the preferred process.

Method O.

Formation of two C—N bonds by a 1:1 cyclization reaction of a bis secondary amine and a dihalide or a ditosylate. The *N*,*N*′-dialkyl-substituted macrocyclic product can be used for complexation purposes, or, in some cases, the alkyl group can be removed to give the unsubstituted polyaza-crown. The benzyl group is most used because it can be reductively cleaved. Recently, it has been reported that a methyl group can be removed without using drastic *N*-dealkylation conditions, which would rupture the macroring (Cooley and Evain, 1989). Up to now, this *N*-demethylation process has not been used for the preparation of aza-crowns (Santamaria et al., 1989a, 1989b).

Method O

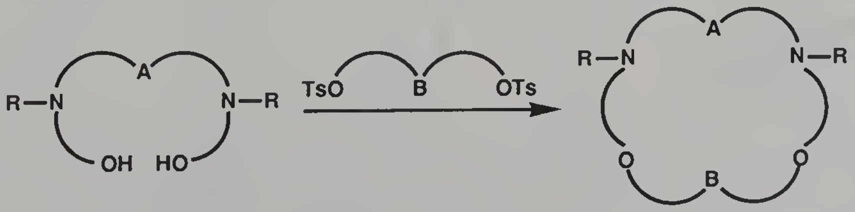


A, B contain O and/or N atoms
X = halogen, tosylate

Method P.

Formation of two C—O bonds by a 1:1 cyclization of a diol and a ditosylate. Although it should be possible to use the Okahara ring-closure reaction

Method P



A, B = contain N and/or O atoms

of a diol with one mole of tosyl chloride to prepare the polyaza-crowns (method B-1, Chapter V), this internal cyclization process has not been used. The 1:1 cyclization of a diol and a ditosylate has been used to prepare polyaza macrocycles containing three or more nitrogen atoms.

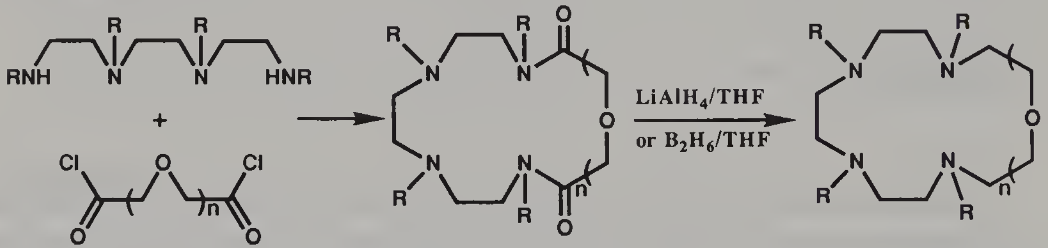
Method R.

Miscellaneous cyclizations to form the polyaza-crowns (see methods R-1 and R-2).

B. RING CLOSURE TO FORM TWO C—N BONDS BY A 1:1 CYCLIZATION OF A DIACID DICHLORIDE OR DIESTER WITH A BIS PRIMARY AMINE

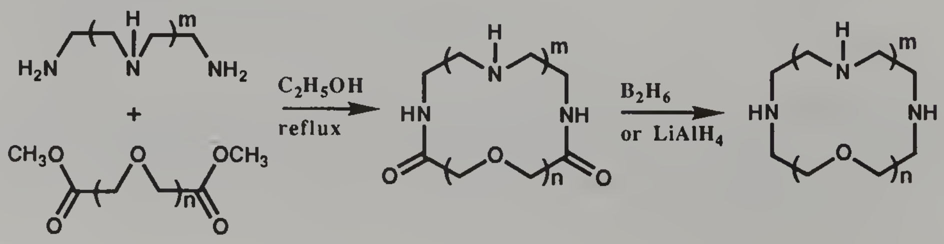
Pelissard and Louis (1972) prepared *N*,*N*′,*N*″,*N*‴-tetramethyltetraaza-15-crown-5 (and its tetraethyl analog) by treating the tetramethyltriethylenetetraamine (or its tetraethyl analog) with diglycolyl dichloride followed by reduction (method M-1). High dilution conditions are necessary for this cyclization reaction. This procedure is more direct than that using *N*-tosyl starting materials. The high-molecular-weight tosyl groups are avoided and do not need to be removed from the macrocyclic products. The final polyaza-crowns contain *N*-alkyl substituents, but for many applications, the *N*-alkyl groups are not detrimental. For example, complexation of metal and organic ammonium cations by the *N*-alkyl-substituted aza-crowns is about the same as complexation by the unsubstituted aza-crowns (Izatt et al., 1985, 1991).

Method M-1



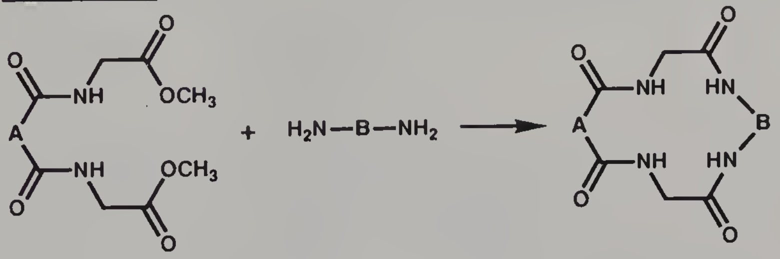
Tabushi and coworkers reported a general synthetic procedure to prepare the polyaza-crown compounds by treating a polyamine with the dimethyl ester of an oligoglycolic acid followed by reduction of the resulting cyclic diamide (method M-2) (Tabushi et al., 1976, 1977a, 1977b). This method uses readily

Method M-2



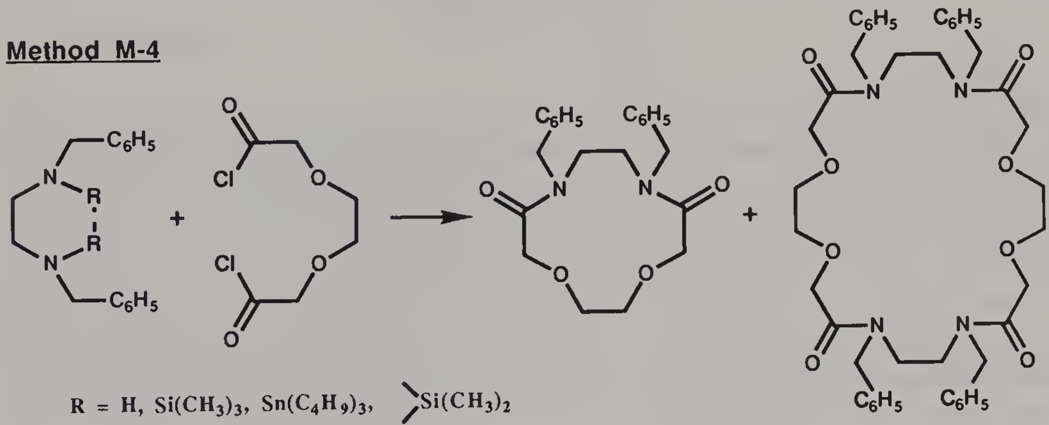
available starting materials and does not require high-dilution conditions. The reaction requires a high temperature for several days because of the low reactivity of the diester functions. The reaction is usually carried out in an alcohol; however, Bradshaw and coworkers have recently prepared a triazacrown in good yields in diglyme using dimethyl 2,6-pyridinedicarboxylate (Huszthy et al., 1992). A similar approach to these compounds was made by Lukyanenko and coworkers (method M-3), although they did not reduce the cyclic bisamide (Lukyanenko et al., 1979, 1981). Generally, the yield of their condensation was low (10–45%).

Method M-3

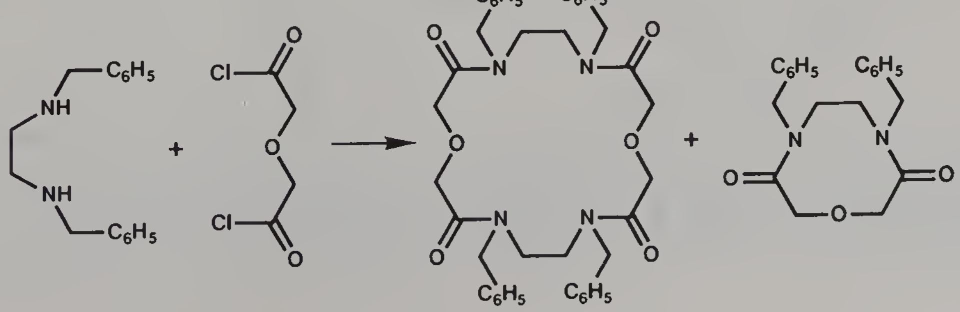


Leygue and coworkers have reacted 1,4-diamino compounds with triglycolyl dichloride to form a tetraaza macrocycle (method M-4) (Leygue et al., 1987, 1988). Unfortunately, 1:1 cyclization was the major process and the yields for the 2:2 cyclization reaction were low even when modified diamines [R = Si(CH$_3$)$_3$ or Sn(C$_4$H$_9$)$_3$] were used or where the diamine was in the form of a cyclic diazasilicone. On the other hand, the smaller diglycolyldichloride gave the tetraaza macrocycle as the major product (method M-5).

Method M-4

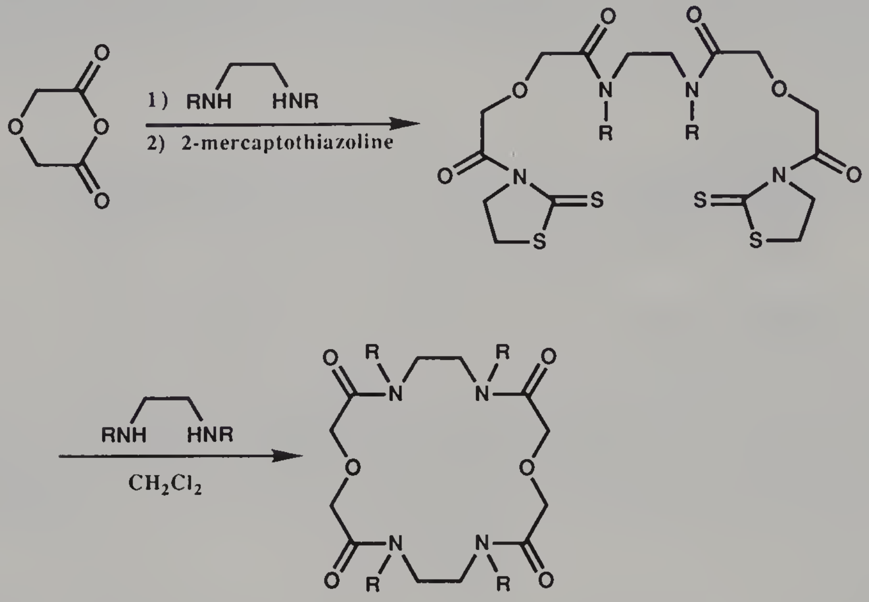


Method M-5



Similar results were observed using the *N*-acyl thiazolidinethione derivative of a bis(diglycolic) acid (method M-6) (Cazaux et al., 1989). Again, as in the method M-5 process, 2:2 cyclization to form an 18-membered ring was the major process since 1:1 cyclization would form a 9-membered ring.

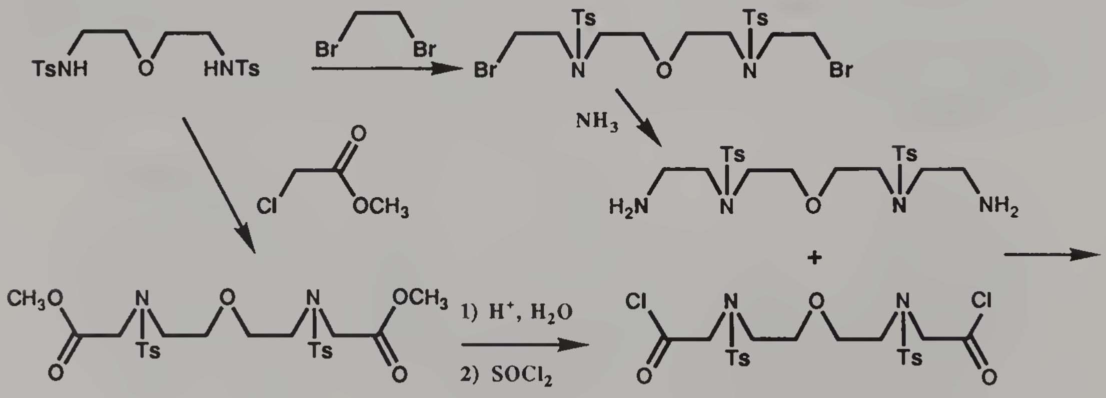
Method M-6

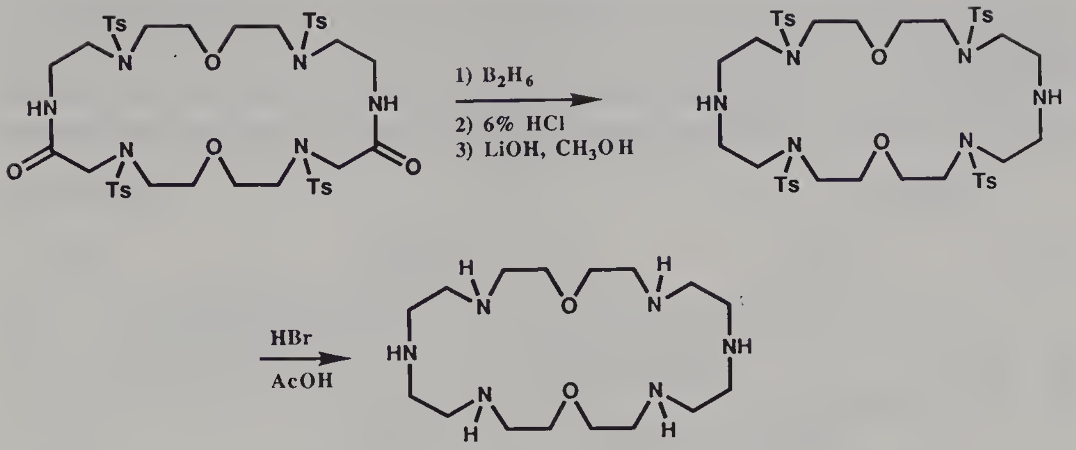


Recently, many new coupling agents have been used to improve the yields of amide formation from acids and amines. However, these coupling agents are expensive and only a few of them have found application in macrocyclic chemistry. For example, diphenylphosphenyl azide was used to prepare a macrocyclic diamide with higher yields than other methods (Qian et al., 1990).

Lehn and coworkers used a number of methods to prepare some interesting polyoxaaza macrocycles. These authors used many steps to elaborate a bis(*p*-toluenesulfonamide) derivative of a diamino ether to form $[24]N_6O_2$ macrocycles (method M-7) (Lehn et al., 1977). In the process, the reaction of a

Method M-7

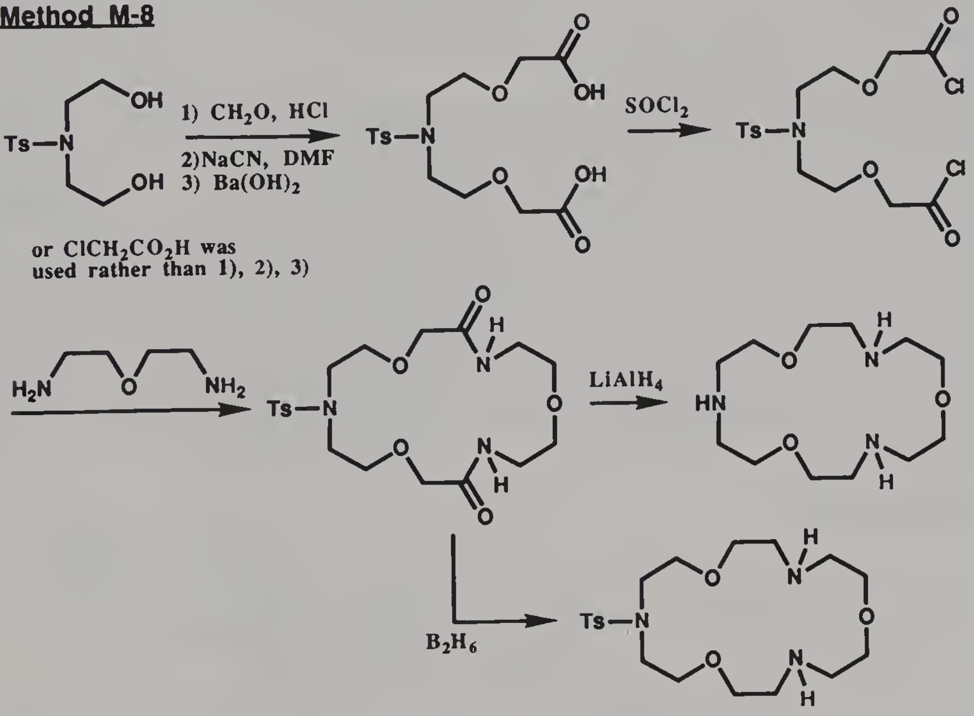




diacid dichloride and a diamine was used to close the ring, followed by reduction and detosylation. Althought the yield for each step was reasonable, the use of many steps greatly reduced the overall yield of the polyaza-crown. This procedure allows the preparation of polyaza-crowns with some of the ring nitrogen atoms protected.

A different procedure was used by Graf and Lehn (1975, 1981) to prepare the triaza-18-crown-6 compounds (method M-8). This method uses the *p*-toluenesulfonamide derivative of diethanolamine as a starting material. Recently, Gokel and coworkers used a similar pathway to prepare $[18]N_3O_3$ using chloroacetic acid instead of formaldehyde, sodium cyanide, and barium hydroxide as shown in method M-8 (Miller et al., 1989). Free ligand $[18]N_3O_3$

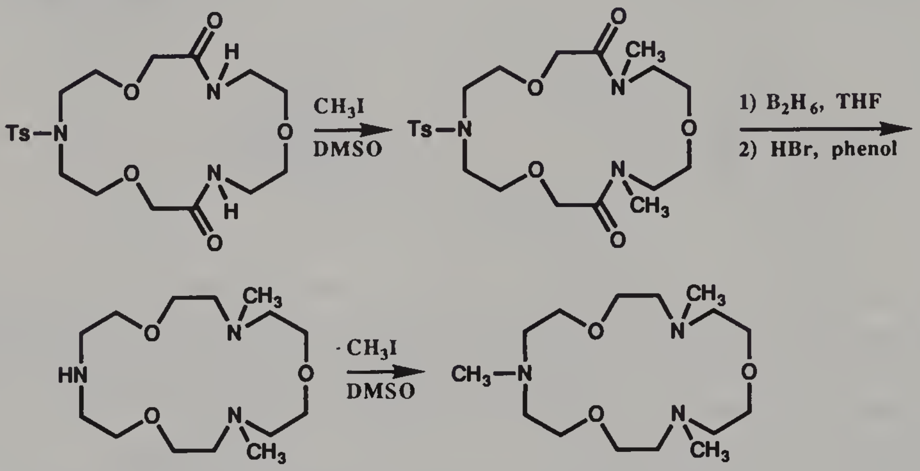
Method M-8



was obtained in a 75% yield after reducing the diamide, which also reductively removed the *N*-tosyl group.

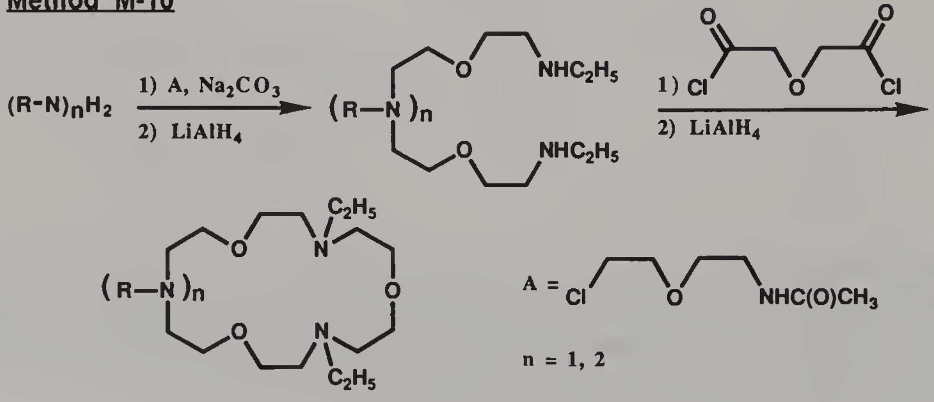
The dimethyl and trimethyl derivatives of [18]N_3O_3 were obtained from the above cyclic *N*-tosyldiamide macrocycle (method M-9). The methylation and reduction-detosylation steps shown in the middle of the sequence can be reversed (Graf and Lehn, 1975, 1981). Schmidtchen reported the synthesis of the [18]N_3O_3 crowns in 12 steps (Schmidtchen, 1986). *N*-Alkyl-substituted derivatives of [18]N_3O_3 can be prepared from the unsubstituted [18]N_3O_3 ligand (Lehn and Vierling, 1980).

Method M-9



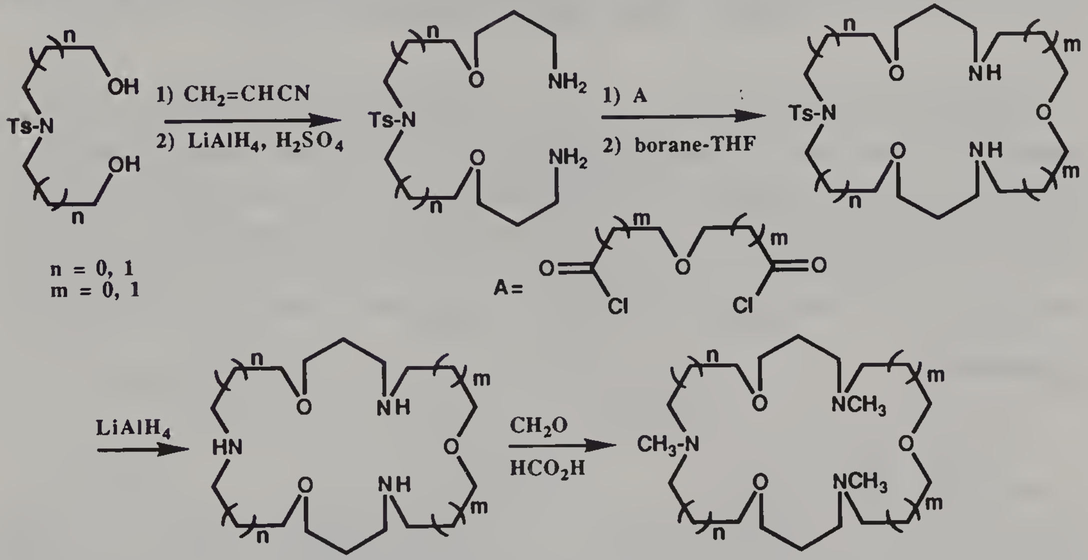
Methods M-7, M-8, and M-9 show that the usual procedures on preparation of the functionalized polyaza-crowns require many steps. More recently a new method has been developed to prepare alkyl-substituted [18]N_3O_3 derivatives from simple and inexpensive starting materials and in only a few steps (Krakowiak et al., 1988, 1989a). *N*-[2-(2-Chloroethoxy)ethyl]acetamide is the key reactant in the new method (Krakowiak and Bradshaw, 1991). Method M-10 shows that 2 mol of the key reactant can be added to a primary amine (n = 1) followed by a diacid dichloride and reduction to form the symmetric trialkyl-substituted triaza-18-crown-6 in four steps from compound A.

Method M-10



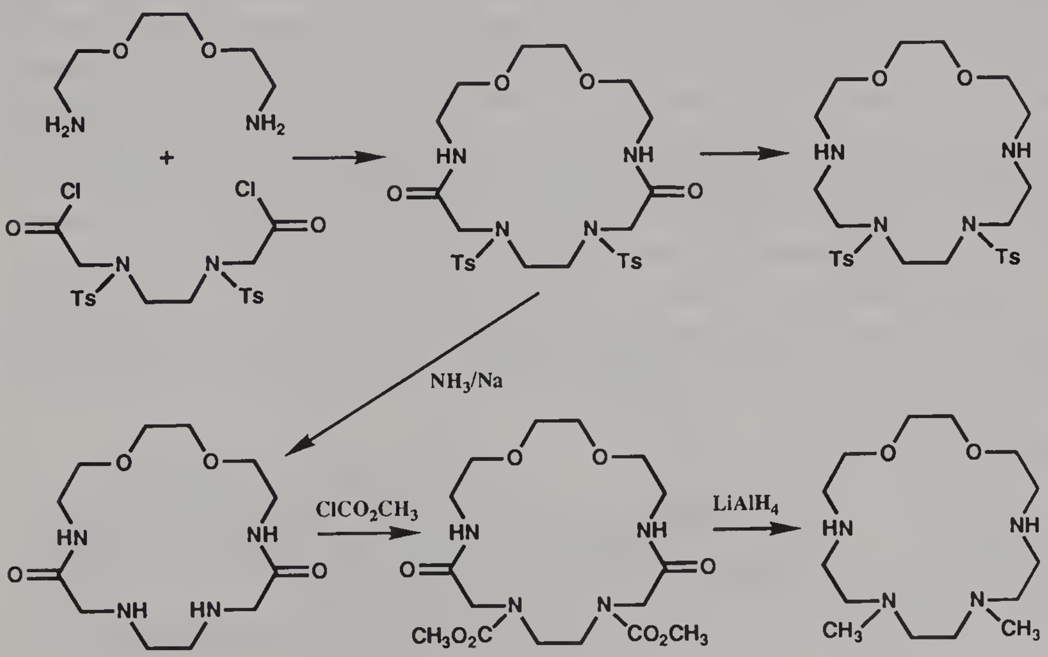
Sutherland and coworkers prepared symmetric crown ethers with trimethylene or mixed trimethylene and ethylene bridges (Pratt et al., 1988). The *N*-tosylamino glycol was reacted with acrylonitrile followed by reduction to give a triamine that was used to build the crown ethers (method M-11). A triaza-crown containing both ethylene and trimethylene bridges was prepared in a similar manner by using (*N*-tosyl)diethanolamine rather than the (*N*-tosylamino)dipropanol.

Method M-11



Lehn and Montavon (1976) prepared tetraaza-crowns using similar tech-

Method M-12

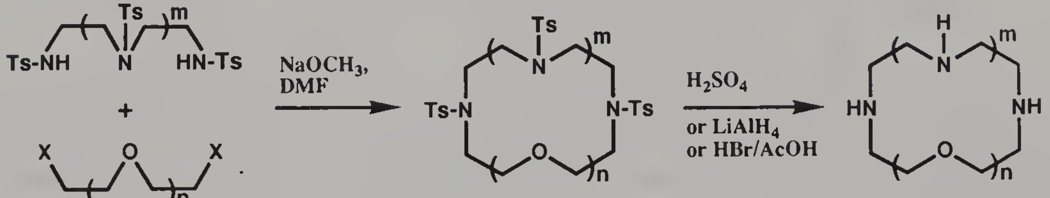


niques (method M-12). The final tetraaza-crown was used as starting material for the preparation of cryptands with two nitrogen atoms in one of the bridges.

C. RING CLOSURE TO FORM TWO C—N BONDS BY A 1:1 CYCLIZATION OF A BIS-SULFONAMIDE WITH A DIHALIDE OR DITOSYLATE

Richman and Atkins (1974, 1978), as well as Vögtle and coworkers, have prepared a number of polyaza-crowns by treating the appropriate per-*p*-toluenesulfonamide derivative of a polyamine with the ditosylate (dimesylate or dihalide) derivative of an oligoethylene glycol (method N-1) (Buhleier et al., 1977; Rasshofer and Vögtle, 1977; Rasshofer et al., 1976). They were able to prepare polyaza-crowns with different ring sizes and numbers of oxygen and nitrogen atoms. Different methods to remove the *N*-tosyl protecting groups were tried, including HBr/phenol, H_2SO_4, $LiAlH_4$/THF, and $NaAlH_2(OCH_2CH_2OCH_3)_2$ (see Chapter IV). Product yields from this last step varied as a function of the number of tosyl groups and with the size of the macrocycle. With a triaza-12-crown-4, it was found that HBr/phenol was the best detosylating reagent followed by H_2SO_4 and $LiAlH_4$ (Buhleier et al., 1977). Bogatskii and coworkers modified this cyclization process by using a phase-transfer catalyst. They obtained polyaza-crowns using benzene or toluene and aqueous alkali metal hydroxide with tetra-*n*-butylammonium iodide as the phase-transfer catalyst (Bogatskii et al., 1984b).

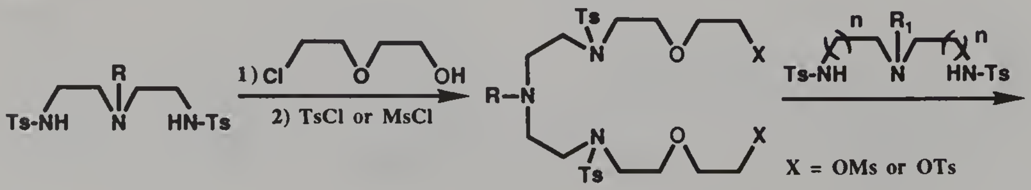
Method N-1



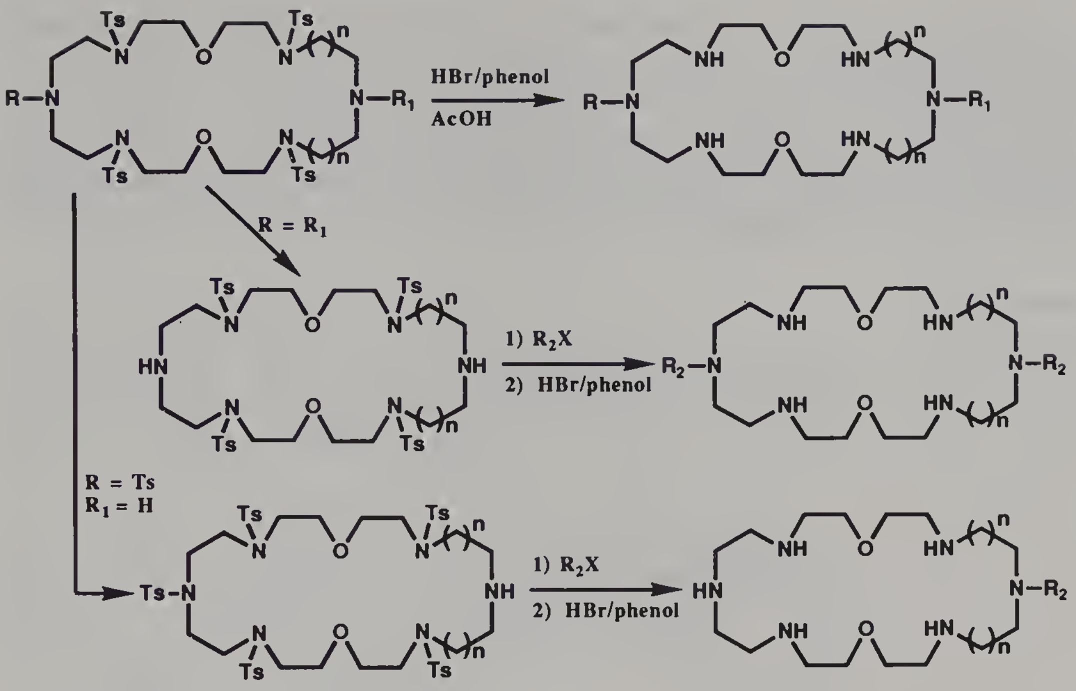
m, n = 0-3
X = OTs, OMs, Br, I

A similar sequence was used to form the same hexaaza-24-crown-8 as in method M-7 but by a shorter route (method N-2) (Comarmond et al., 1982; Hosseini et al., 1987). This method does not require the cyclic diamide for-

Method N-2

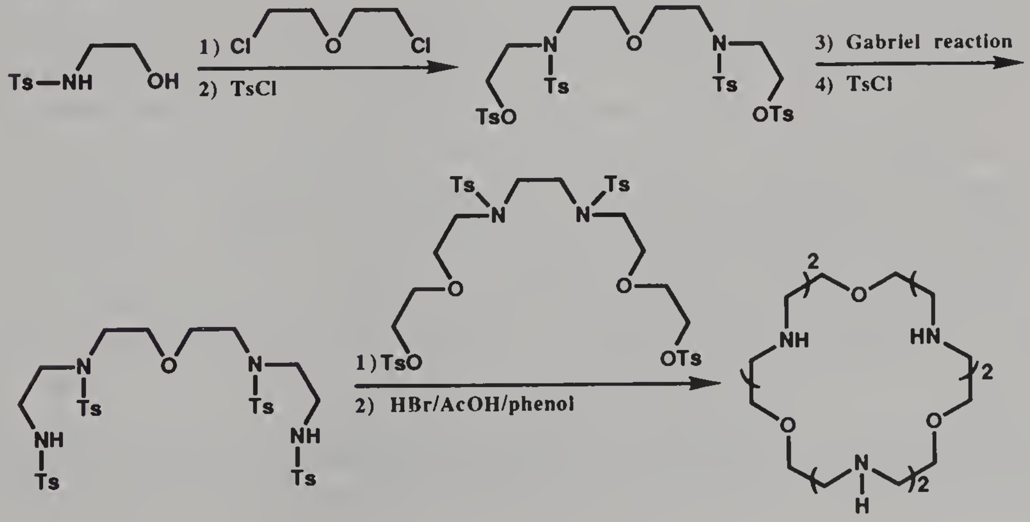


X = OMs or OTs



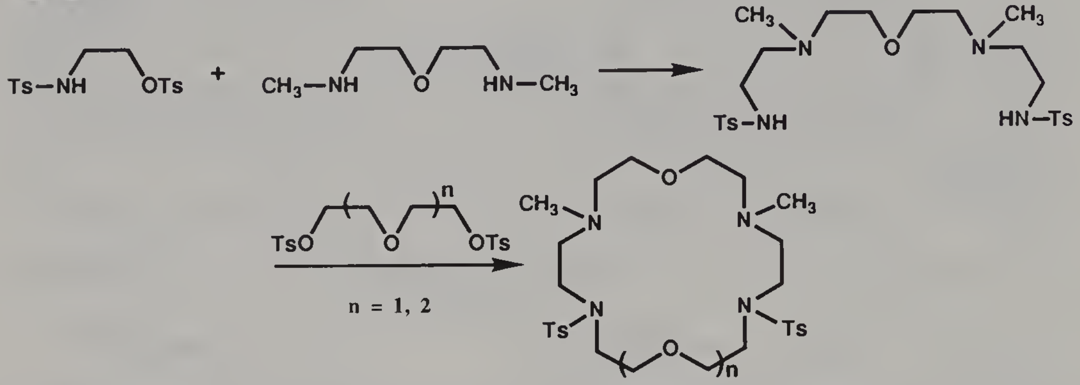
mation and reduction process of method M-7 but does require a detosylation step to form the $[24]N_6O_2$ macrocycles. Where R = R_1 = Ts, the formation of an unexpected side product ($[12]N_3O$) during the ring-closure step decreased the yield of the main product. The tosyl groups greatly add to the molecular weight of the starting materials and intermediates so that large quantities (by weight) of these materials must be used to obtain reasonable amounts of the final products. A more selective protection of nitrogen atoms was achieved by using *N*,*N*″-ditosyl-*N*′-benzoyldiethylenetriamine (R = R_1 = C_6H_5CO) (Hosseini et al., 1987; Martin et al., 1982). A reaction sequence using *N*-tosyl protecting groups was used to prepare a $[27]N_6O_3$ (method N-3) (Dietrich et al., 1983).

Method N-3

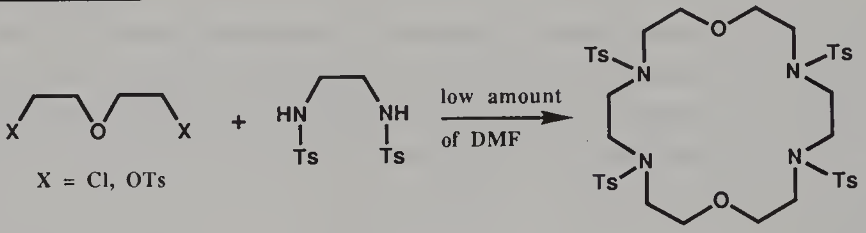


There are a number of methods for preparation of polyaza-crowns with interesting sequences of nitrogen atoms in the ring and with varying substituents on the ring nitrogen atoms. Tetraaza-18-crown-6 and 21-crown-7 with two *N*-methyl and two *N*-tosyl substituents were easily prepared in a few steps (method N-4) (Dragomiretskaya et al., 1987). The tetra-*N*-tosyl-substituted tetraaza-18-crown-6 was prepared in a 40% yield by a 2:2 cyclization of *N*,*N*′-ditosylethylenediamine with 2-chloroethyl ether (Biernat and Luboch, 1984) or with diethylene glycol ditosylate (Craig et al., 1989) in DMF in the presence of potassium or cesium carbonate (method N-5). In the first reaction, 1:1 cyclization would give the hard-to-form diaza-9-crown-3; therefore, the 18-crown-6 was the favored product without using high-dilution conditions. Only a 10% yield of product was obtained in the presence of sodium carbonate. In the second reaction, only $[18]N_4O_2$ was isolated in a 20% yield in the presence of cesium carbonate. On the other hand, $[9]N_2O$ (the 1:1 cyclization product) was obtained in high-dilution conditions (Vejimelka, 1977). *N*,*N*′-Ditosyldiaza-10-crown-3, the 1:1 cyclization product, also was obtained when *N*,*N*′-ditosyl-1,3-propanediamine was treated with 2-chloroethyl ether in the presence of potassium *t*-butoxide in dilute solution (Krakowiak and Kotelko, 1983).

Method N-4

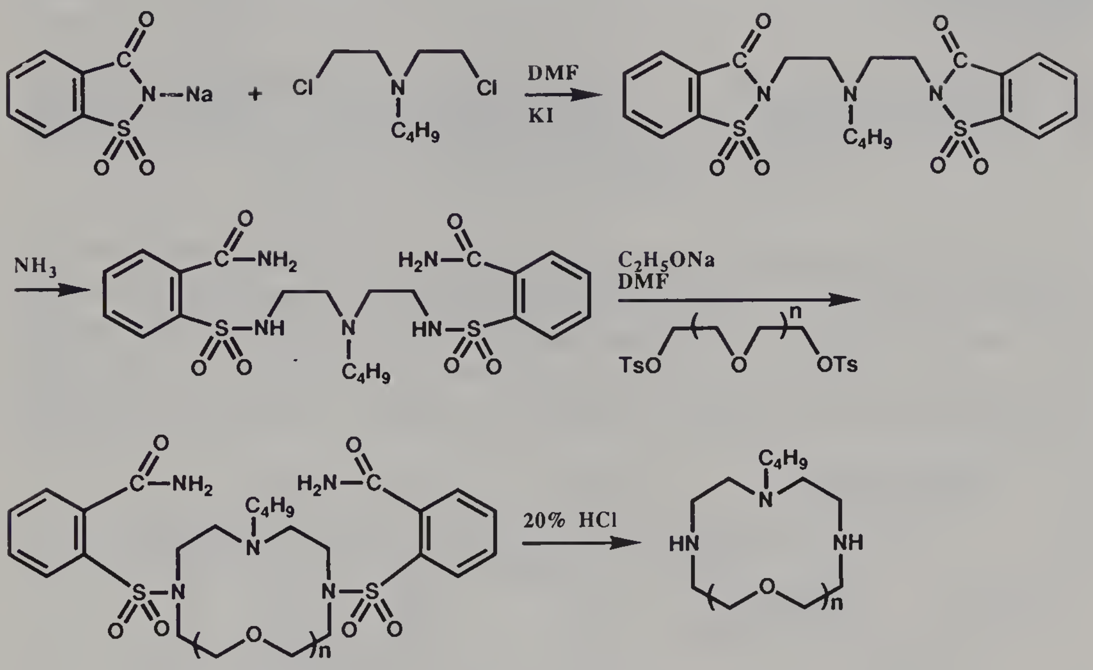


Method N-5



Recently, certain polyaza-crowns have been prepared using a nitrogen protecting group that is easier to remove than the tosyl moiety (method N-6) (Wang et al., 1989). Two equivalents of saccharin were first alkylated

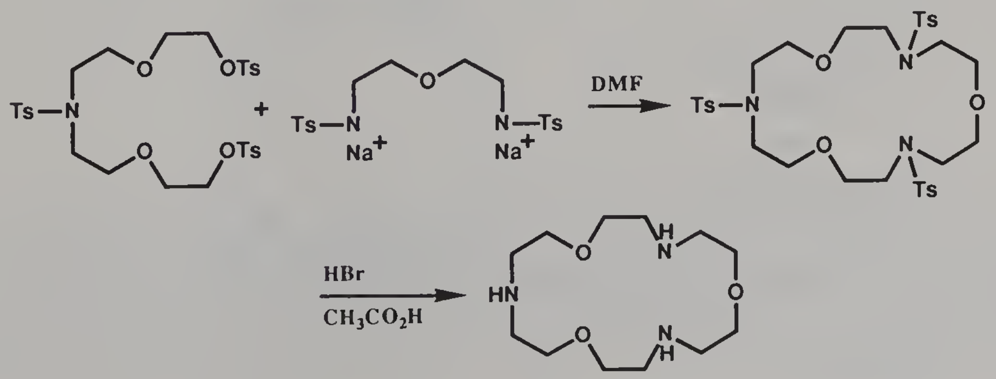
Method N-6



with *N*,*N*-bis(2-chloroethyl)butylamine in DMF in the presence of a small amount of potassium iodide. The bis-saccharin intermediate was treated with ammonia to give the *N*,*N*′-bis(amidocarbonylbenzene)sulfonamide compound, which was cyclized with a ditosylate. The protecting groups were readily removed using 20% aqueous hydrochloric acid. Saccharin has been used to prepare secondary amines from alkyl halides, but the process has not been as common as the Gabriel phthalimide method (Abe, 1955; Eckenroth and Koeppermann, 1896, 1897).

As shown above (methods M-8, M-9, and M-10), [18]N_3O_3 crowns were obtained using three different routes by cyclization of diacid dichlorides with the appropriate diamines or triamines. Recently, a new method was introduced using the *N*,*N*′-ditosyl-3-oxa-1,5-pentanediamine (method N-7) (Chen

Method N-7

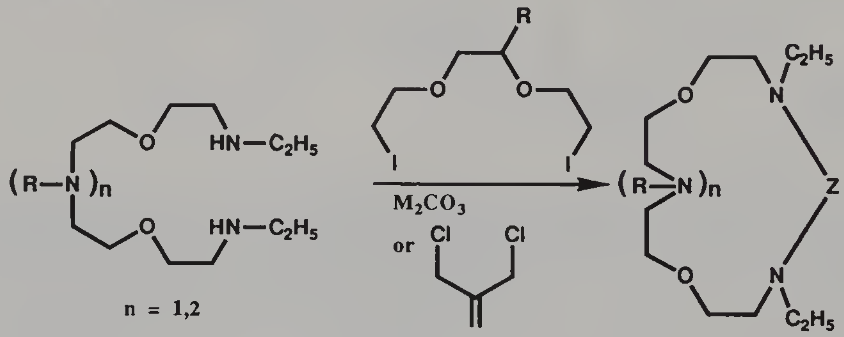


et al., 1990). The starting material was derived from expensive 3-oxa-1,5-pentanediamine.

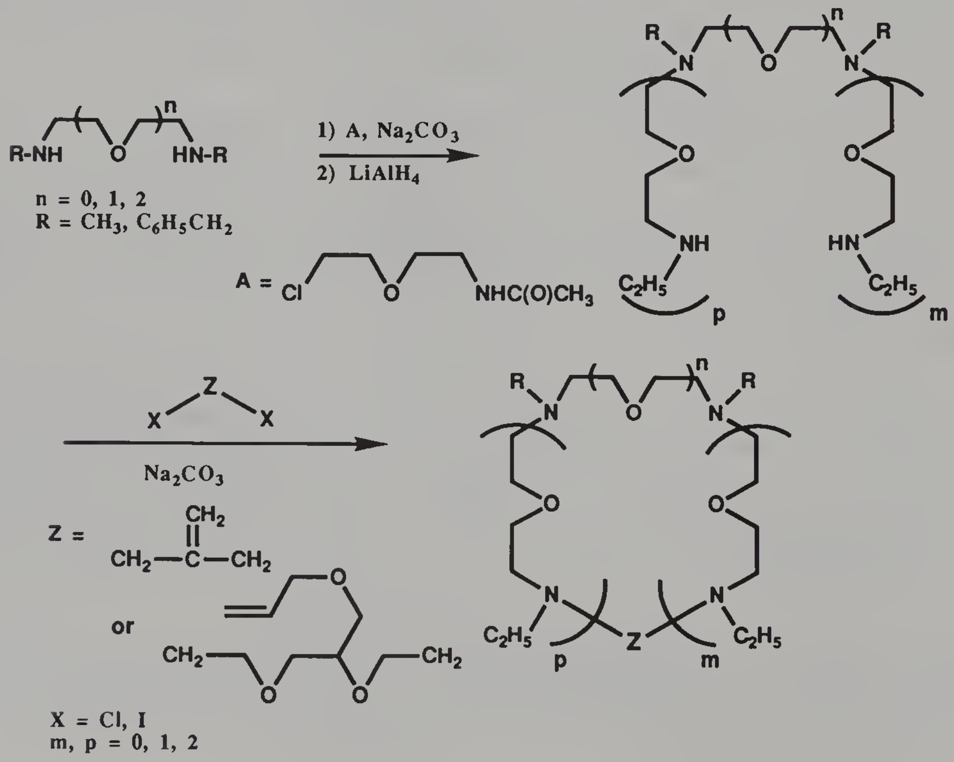
D. RING CLOSURE TO FORM TWO C—N BONDS BY A 1:1 CYCLIZATION OF A BIS SECONDARY AMINE WITH A DIHALIDE OR DITOSYLATE

Terminal bis secondary amines can be cyclized with dihaloalkanes. There could be some template affect by alkali metal cations in the cyclization step even though the log *K* for the association of the alkali metal ions (except lithium) with a cyclic amine is low. In the "building-block" method to form the polyaza-crowns (methods O-1 and O-2), sodium, or potassium carbonate

Method O-1



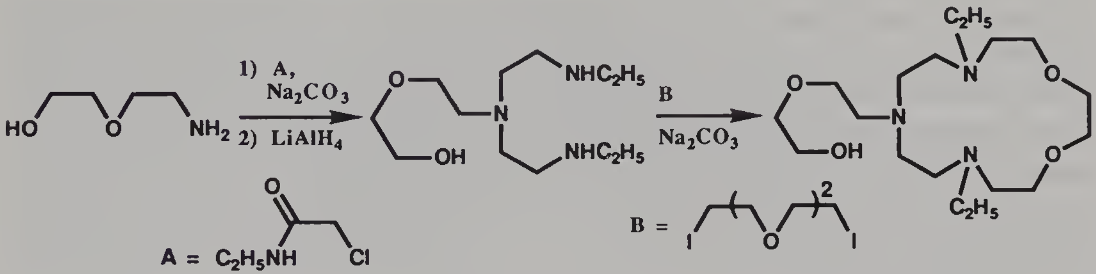
Method O-2



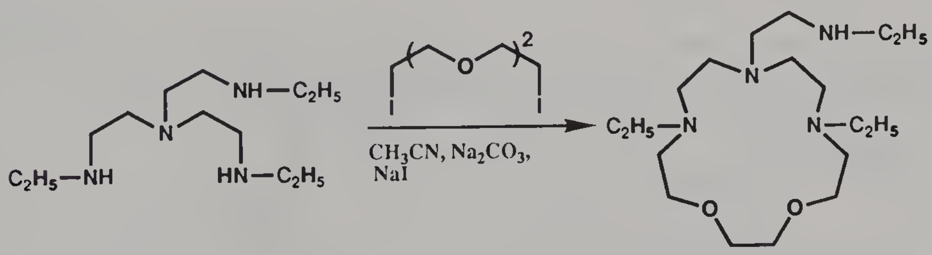
was used to scavenge the hydrogen halide by-product but the cations also seemed to increase the yield in the cyclization step. Thus, a template effect is possible in these systems. This building-block method allows the synthesis of tri-and tetraaza-crowns in a few steps with good overall yields (30–40%). The polyaza macrocycles can also have a variety of functional groups on the ring (Krakowiak et al., 1988, 1989a; Krakowiak and Bradshaw, 1991).

As discussed previously, mono-functionalized aza-crowns are important intermediates for bonding the aza-crowns to solid supports. A new method for preparation of *N*-(hydroxyalkyl)polyaza-crowns and cyclams has been developed (method O-3) (Bradshaw et al., 1989a). The pendant hydroxy groups are not ionized by the sodium carbonate base, so the reaction takes place on the amine nitrogen atoms. A similar functionalized triaza-crown but with a pendant secondary amine was prepared from tris[2-(*N*-ethylamino)ethyl]amine. The triamine and the diiodide were reacted in a 1:1 ratio in acetonitrile in the presence of sodium carbonate (method O-4) (Krakowiak et al., 1989b).

Method O-3

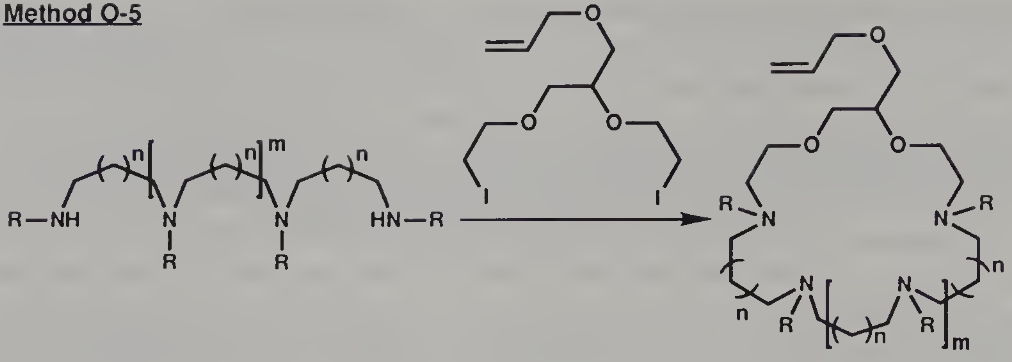


Method O-4



Using the same techniques as reported above (sodium or potassium carbonate base and acetonitrile solvent), diiodo compounds can react with other commercially available amines to form polyaza-crowns of differing sizes and numbers of ring nitrogen atoms (method O-5) (Krakowiak et al., 1989c). The polyamine starting materials need to have tertiary internal amines with sec-

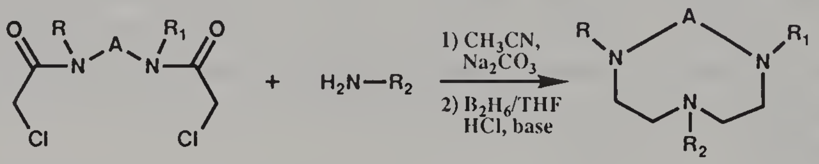
Method O-5



ondary amine functions at the ends. The yields are generally good but decrease as the size of the ring increases.

A useful "crab-like" cyclization has been used to synthesize a variety of polyaza- and peraza-crowns. The crab-like reactants are bis-α-chloroamides, which are more reactive than a regular alkyl chloride but are not as dangerous as the nitrogen mustards. The starting bis-α-chloroamide was reacted with a primary amine in acetonitrile in the presence of sodium carbonate followed by reduction of the cyclic diamide to form the polyaza-crown (method O-6) (Bradshaw et al., 1989b; Krakowiak et al., 1989b). Good yields of the cyclic diamides were observed.

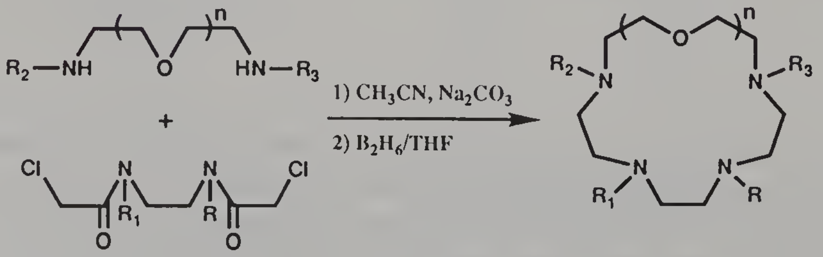
Method O-6



A = $CH_2(CH_2OCH_2)_nCH_2$,
$CH_2CH_2(CH_2OCH_2)_3CH_2CH_2$
n = 2, 3
R, R_1 = H, alkyl
R_2 = alkyl, $CH_2CH_2NHCOCH_3$

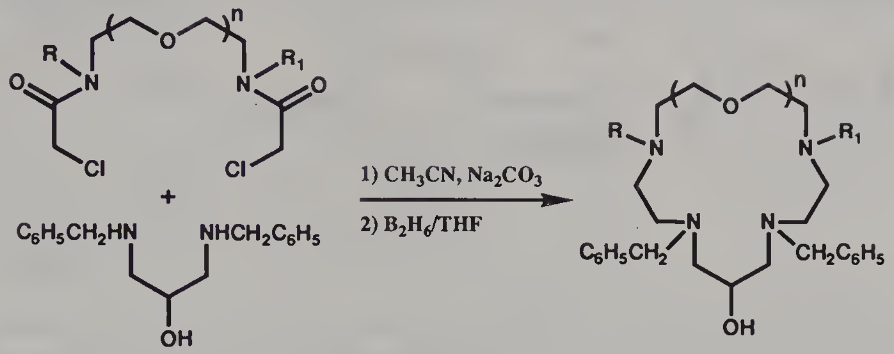
Other polyaza-crowns have been prepared by reacting the crab-like bis-α-chloroamides with bis secondary amines. As shown in methods O-7 and

Method O-7



R, R_1 = H, alkyl
R_2, R_3 = alkyl or side chain with heteroatoms

Method O-8

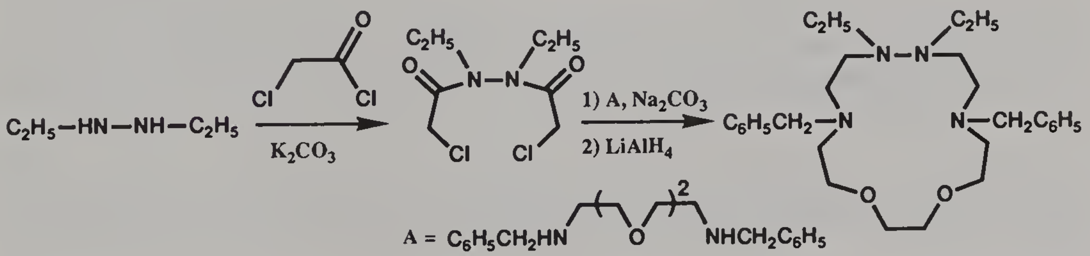


O-8, many different combinations of the bis-α-chloroamides can be used with the diamines to produce a variety of macrocycles (Bradshaw et al., 1989b; Krakowiak et al., 1990). The bis-α-chloroamides were prepared by reacting chloroacetyl chloride with the appropriate diamine. It is important to note that R and R_1 can be hydrogen atoms, which means that nitrogen protecting groups are not necessary to form the polyaza-crowns with one or two secondary amine units in the ring. .

Methods O-6, O-7, and O-8 are simple procedures for preparing the polyaza macrocycles with reactive secondary amine groups in the ring or on pendant alkyl groups or a hydroxy group on a ring carbon atom. These reactive functional groups allow these macrocycles to be further reacted to add other species or to be attached to a solid support.

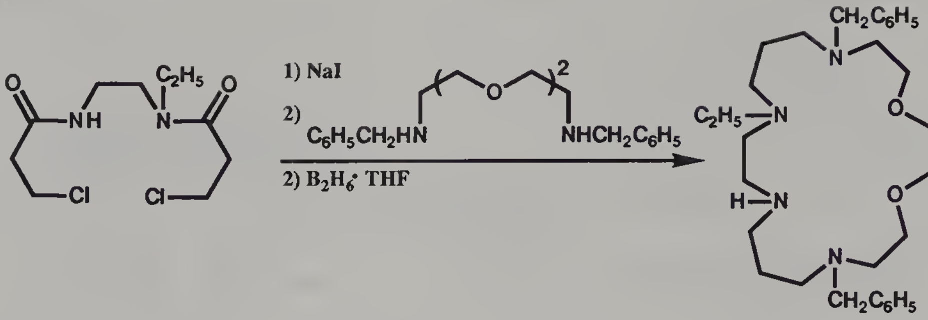
New polyaza-crowns containing the hydrazine moiety also have been prepared by the crab-like method, except a hydrazine starting material was used rather than an amine (Bradshaw et al., 1988). 1,2-Diethylhydrazine was reacted with chloroacetyl chloride, followed by a diamine and reduction to prepare the new hydrazino-crowns (method O-9).

Method O-9



In contrast to the easy reaction of the bis-α-chloroamides, the bis-β-chloroamides are not very reactive under the same reaction conditions. In this case, sodium iodide was added in acetonitrile to in situ convert the chloride to the more reactive iodide (method O-10) (Krakowiak et al., 1990). The

Method O-10

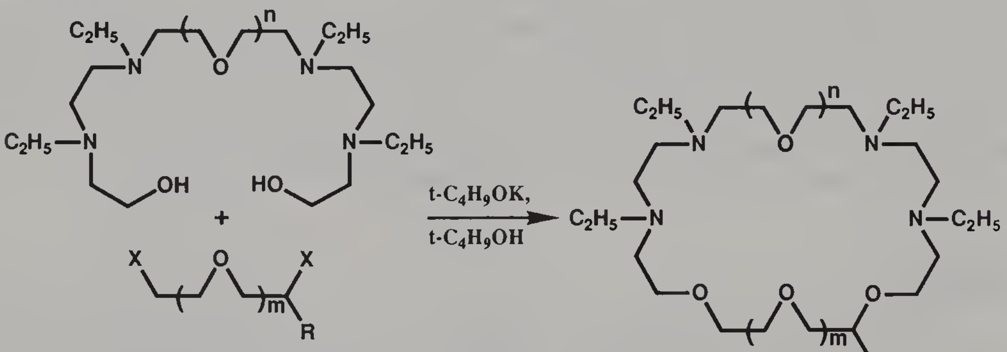


trimethylene bridge between nitrogen atoms is more readily introduced into the polyaza-crown by a bis-α-chloroamide prepared from 1,3-diaminopropane (method O-6) than with the bis-β-chloroamide.

E. RING CLOSURE TO FORM TWO C—O BONDS BY A 1:1 CYCLIZATION OF A DIOL WITH A DITOSYLATE

Ring-closure reactions by the formation of two C—O bonds are not common for the preparation of the polyaza-crowns because preparation of the starting diols is often difficult. Tetraaza-24-crown-8 and 27-crown-9 ligands were prepared by the reaction of tetraazadiols and ditosylates or dimesylates (method P-1) (Krakowiak et al., 1989c). The cyclization reaction gave yields of only about 20% possibly because the potassium ion was too small to match the size of the macrocycle cavity. Cesium ion was not used in this reaction.

Method P-1

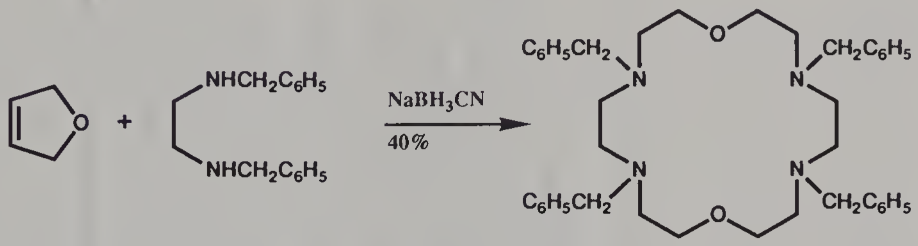


X = OTs, OMs
R = H, CH_2OCH_2-CH=CH_2
m = 1, 2; n = 0, 2

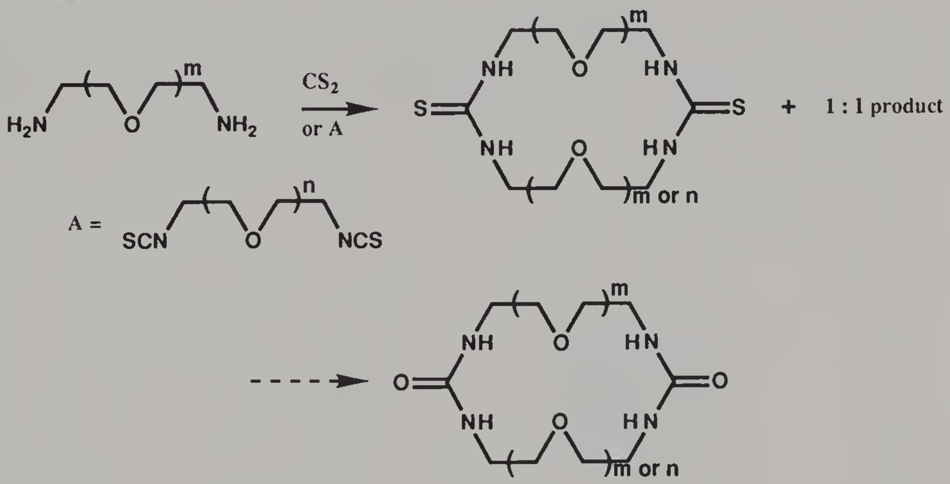
F. MISCELLANEOUS RING CLOSURE REACTIONS TO FORM POLYAZA-CROWN MACROCYCLES

Two miscellaneous reactions were used to prepare some polyaza-crowns. Kawaguchi and Ohashi (1985) reported a one-step procedure to prepare a symmetric tetraaza-18-crown-6 compound (method R-1). This method is useful for the preparation of polyaza-crowns containing the diethyleneoxy unit because other diethyleneoxy-containing starting materials, such as 2-chloroethyl ether, cannot be used since they react with amines to give a morpholine derivative. Tetraaza-crown ethers were obtained by Bogatskii and coworkers starting from derivatives of a diamine and carbon disulfide or an isothiocyanate (method R-2) (Bogatskii et al., 1980a, Lukyanenko et al., 1987).

Method R-1



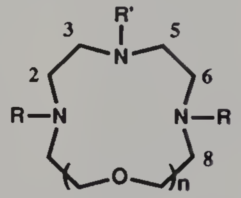
Method R-2



Tables of polyaza-crown compounds follow. Each table is organized in order of increasing ring size and/or complexity of substituents. Information on yields and methods of preparation is given along with relevant references.

G. TABLES OF COMPOUNDS

TABLE 7.1. 1,4,7-TRIAZA-CROWN MACROCYCLES



R	R'	Other Substituents	n	Method (or from R,R' =)	Yield (%)	References
H	H		1	(Ts,Ts)	82	Amorim et al., 1988
				N-1	67,11	Buhleier et al., 1977
				N-1		Buoen et al., 1984
				N-1	96	Kossai et al., 1979
				N-1	62	Lukyanenko et al., 1988a, 1988b
				N-1	61	Rasshofer and Vögtle, 1977
				N-1	100 (salt)	Rasshofer et al., 1976
				N-1	70	Thöm et al., 1986
H	n-C_4H_9		1	N-6	19	Wang et al., 1989

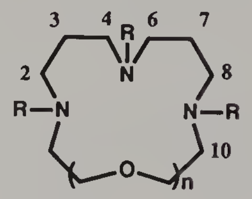
H	H		2	N-1	34 (overall)	Hancock et al., 1989
				N-1	94	Kossai et al., 1979
				N-1	62	Lukyanenko et al., 1988a, 1988b
						Tabushi et al., 1977
H	H		2	N-1	19	Rasshofer and Vögtle, 1977
				M-2		Tabushi et al., 1976
H	H	8,15-$(O)_2$	2			Tabushi et al., 1977a
				M-2	32	Tabushi et al., 1976
H	n-C_4H_9		2	N-6	22	Wang et al., 1989
H	H		3	N-1	50	Lukyanenko et al., 1988b
H	H	8,9;17,18-(cyclohexano)$_2$	3		27	Maeda et al., 1983
H	H	8,9;20,21-(cyclohexano)$_2$	4		21	Maeda et al., 1983
CH_3	CH_3		1	(H,H)		Amorim et al., 1990
HO_2CCH_2-	H		1	(H,H)	25	Amorim et al., 1990
HO_2CCH_2-	HO_2CCH_2-		1	(H,H)		Tweedle et al., 1987
				(H,H)	70	Amorim et al., 1988
C_2H_5	C_2H_5	9-CH_2O-allyl	2	O-5	65	Krakowiak et al., 1989c

TABLE 7.1. (*Continued*)

R	R'	Other Substituents	n	Method (or from R,R' =)	Yield (%)	References
C_2H_5	$H(OCH_2CH_2)_2$-		2	O-3	68	Bradshaw et al., 1989a
C_2H_5	$C_2H_5HN(CH_2)_2$-		1	O-6	26 (overall)	Krakowiak et al., 1989b
C_2H_5	$C_2H_5HN(CH_2)_2$-		2	O-6	35 (overall)	Krakowiak et al., 1989b
C_2H_5	morpholine-$(CH_2)_2$-		2	O-6	26	Krakowiak et al., 1990
C_2H_5	$CH_3C(O)NH(CH_2)_2$-	2,6-$(O)_2$	1	O-6		Krakowiak et al., 1989b
		2,6-$(O)_2$	2	O-6		Krakowiak et al., 1989b
C_2H_5	$(C_2H_5)_2N(CH_2)_3$-		2	O-6	34	Krakowiak et al., 1990
$HO(CH_2)_2$-	$HO(CH_2)_2$		1	(H,H)	88	Buoen et al., 1984
$CH_3O(CH_2)_2$-	$CH_3O(CH_2)_2$-		1	[$HO(CH_2)_2$, $HO(CH_2)_2$]	86	Buoen and Dale, 1986

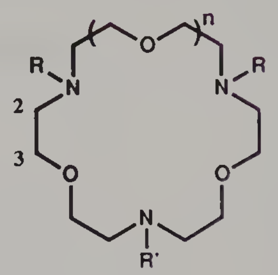
$CH_3CH(OH)CH_2$-	$CH_3CH(OH)CH_2$-	1	(H,H)		Hancock et al., 1988
		2	(H,H)	48	Hancock et al., 1989
2-$H_2NC(O)C_6H_4S(O_2)$-	n-C_4H_9	1	N-6	9	Wang et al., 1989
		2	N-6	13	Wang et al., 1989
$C_6H_5CH_2$-	$C_2H_5NH(CH_2)_2$-	2	O-6	43	Krakowiak et al., 1990
		3	O-6	31	Krakowiak et al., 1990
Ts	Ts	1	N-1	52	Amorim et al., 1988
				65-83	Bogatskii et al., 1984b
					Comarmond et al., 1982
			N-1	90	Lukyanenko et al., 1988a, 1988b
			N-1	63	Rasshofer et al., 1976
Ts	Ts	2		80	Bogatskii et al., 1984b
			N-1	90	Lukyanenko et al., 1988a, 1988b
			N-1	71	Atkins et al., 1978
Ts	Ts		N-1	14	Rasshofer et al., 1976

TABLE 7.2. 1,5,9-TRIAZA-CROWN MACROCYCLES



R = R'	R'	Other Substituents	n	Method	Yield (%)	References
H			1	N-1	65	Lukyanenko et al., 1988a, 1988b
H			2	N-1	30	Lukyanenko et al., 1988a, 1988b
H			3	N-1	25	Lukyanenko et al., 1988a, 1988b
H				N-1	35	Rasshofer and Vögtle, 1977
C_2H_5		11-CH_2Oallyl	2	O-5	66	Krakowiak et al., 1989c
Ts			1	N-1		Atkins et al., 1978
				N-1	86	Lukyanenko et al., 1988a, 1988b
Ts			2	N-1	96	Lukyanenko et al., 1988a, 1988b
				N-1	85	Rasshofer et al., 1976
Ts			3	N-1	54	Lukyanenko et al., 1988a, 1988b
				N-1	83	Rasshofer et al., 1976

TABLE 7.3. TRIAZA-18-CROWN-6 AND TRIAZA-21-CROWN-7 MACROCYCLES



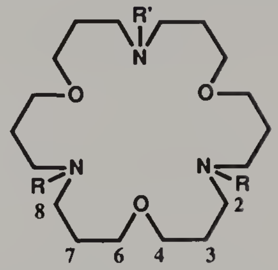
R	R'	Other Substituents	n	Method (or from R,R' =)	Yield (%)	References
H	H		1	N-7	80	Chen et al., 1990
			1	M-8	75,78	Graf and Lehn, 1975, 1981
				M-8	65	Miller et al., 1989
H	Ts		1	M-8	98	Graf and Lehn, 1975, 1981
				M-8	90	Schmidtchen, 1984, 1986
H	Ts	2,12-$(O)_2$	1	M-8	63,70	Graf and Lehn, 1975, 1981
				M-8		Miller et al., 1989
CH_3	H		1	M-9	85,90	Schmidtchen, 1984, 1986
CH_3	CH_3		1	(H,H)		Lehn and Vierling, 1980

TABLE 7.3. (*Continued*)

R	R^1	Other Substituents	n	Method (or from R,R' =)	Yield (%)	References
CH_3	Ts		1	M-9	85,90	Schmidtchen, 1984, 1986
CH_3	Ts	2,12-$(O)_2$	1	M-9	80,78	Schmidtchen, 1984, 1986
CH_3	$(C_2H_5)_3N^+CH_2C_6H_4CH_2$-		1	[CH_3,$(C_2H_5)_3N^+$ $CH_2C_6H_4C(O)$]	15 (salt)	Schmidtchen, 1986
CH_3	$(C_2H_5)_3N^+CH_2C_6H_4C(O)$-		1	(CH_3,H)	50	Schmidtchen, 1986
CH_3	4-(tetrazac-CH_2)$C_6H_4CH_2$-		1	[CH_3,4-tetrazac-CH_2-$C_6H_4C(O)$]	70	Schmidtchen, 1986
CH_3	4-(tetrazac-CH_2)$C_6H_4C(O)$-		1	(CH_3,H)	35	Schmidtchen, 1984, 1986
NaO_2CCH_2-	NaO_2CCH_2-		1	(H,H)	80	Chen et al., 1990
HO_2CCH_2-	Ts	3,11-$(O)_2$	1		30	Qin, 1986

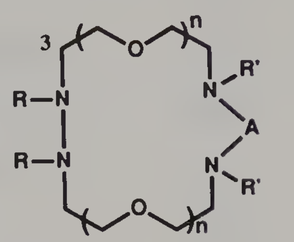
C_2H_5	$HO(CH_2)_2O(CH_2)_2$-		2	O-1	45	Bradshaw et al., 1989a
				O-1	58	Krakowiak et al., 1989a
C_2H_5	$HO(CH_2)_2O(CH_2)_2$-	17-CH_2O-allyl	2	O-1	42	Bradshaw et al., 1989a
				O-1	56	Krakowiak et al., 1989a
C_2H_5	$C_6H_5CH_2$-		1	M-10	73,74	Krakowiak et al.,1988,1989a
C_2H_5	$C_6H_5CH_2$-	17-CH_2O-allyl	2	O-1	72	Krakowiak et al.,1988,1989a
C_2H_5	$C_6H_5CH_2$-	14,18-$(O)_2$	1	M-10	62	Krakowiak et al., 1988
C_2H_5	allyl-$O(CH_2)_2O(CH_2)_2$-		2	[C_2H_5, $HO(CH_2)_2O(CH_2)_2$]	81	Krakowiak et al., 1989a
$NH_2(CH_2)_3$-	$NH_2(CH_2)_3$-		1			Beer et al., 1989
ferrocenylC(O)$NH(CH_2)_3$-						Beer et al., 1989
$C_6H_5CH_2$-	C_2H_5-	17 or 18-CH_2O-allyl	2	O-2	51	Krakowiak et al., 1989a
$C_6H_5CH_2$-	$C_6H_5CH_2$-		2	O-1	49	Krakowiak et al., 1989a
Ts	Ts		1	N-7	80	Chen et al., 1990

TABLE 7.4. TRIAZA-CROWN MACROCYCLES WITH TRIMETHYLENE BRIDGES



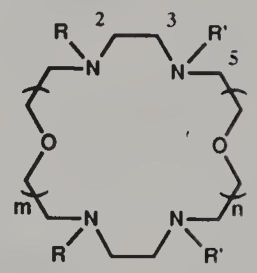
R	R'	Other Substituent	Method (or from R,R' =)	Yield (%)	References
H	H		M-11	46 (HCl)	Pratt et al., 1988
CH_3	CH_3		M-11	42	Pratt et al., 1988
H	Ts		M-11	96	Pratt et al., 1988
H	Ts	2,8-$(O)_2$	M-11	27	Pratt et al., 1988
4-$HO_2CC_6H_4C(O)$-	Ts		(4-$CH_3O_2CC_6H_4C(O)_2$,Ts)	100	Pratt et al., 1988
4-$CH_3O_2CC_6H_4C(O)$-	Ts		(H,Ts)	84	Pratt et al., 1988
4-$ClC(O)C_6H_4C(O)$-	Ts		(4-$HO_2CC_6H_4C(O)$,Ts)		Pratt et al., 1988
4-$HO_2CC_6H_4C(O)$-	4-$HO_2CC_6H_4C(O)$-		([4-$CH_3O_2CC_6H_4C(O)]_2$)	100	Pratt et al., 1988
4-$CH_3O_2CC_6H_4C(O)$-	4-$CH_3O_2CC_6H_4C(O)$-		(H,H)	87	Pratt et al., 1988
4-$ClC(O)C_6H_4C(O)$-	4-$ClC(O)C_6H_4C(O)$-		([4-$HO_2CC_6H_4C(O)]_2$)		Pratt et al., 1988

TABLE 7.5. TRIAZA-CROWN MACROCYCLES CONTAINING THE HYDRAZINE MOIETY



R	R'	A	Other Substituents	n	Method	Yield (%)	References
$CH_3C(O)$-	$CH_3(O)$-	nothing		3			Bradshaw et al., 1988
C_2H_5	C_2H_5	nothing		3		8	Bradshaw et al., 1988
C_2H_5	C_2H_5	$-C(O)CH_2OCH_2C(O)-$		1	M-10	65	Bradshaw et al., 1988
C_2H_5	C_2H_5	$-(CH_2)_2O(CH_2)_2-$		1	M-10	71	Bradshaw et al., 1988
C_2H_5	C_2H_5	$-CH_2C(=CH_2)CH_2-$		1	O-1	48	Bradshaw et al., 1988
$C_6H_5CH_2$-	C_2H_5	$-CH_2C(=CH_2)CH_2-$		1	O-9	50	Dalley et al., 1990
C_2H_5	$C_6H_5CH_2$-	$-CH_2(CH_2OCH_2)_2CH_2-$		0	O-9	45	Bradshaw et al., 1988
C_2H_5	$C_6H_5CH_2$-	$-CH_2(CH_2OCH_2)_2CH_2-$	3,16-$(O)_2$	0	O-9		Bradshaw et al., 1988
C_2H_5	C_2H_5	$-(CH_2)_2OCH(CH_2O\text{-allyl})CH_2O(CH_2)_2-$		1	O-9	50	Bradshaw et al., 1988

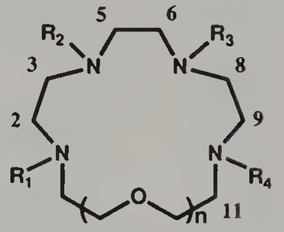
TABLE 7.6. TETRAAZA-CROWN MACROCYCLES



R	R'	m	n	Other Substituents	Method (or from R,R' =)	Yield (%)	References
H	H	1	1		N-5	25	Biernat and Luboch, 1984
					N-5	25	Craig et al., 1989, 1990
					N-5	11	Hancock et al., 1989
H	H	1	1	5,9,14,18-$(O)_4$	M-6	32	Cazaux et al., 1989
H	H	1	1	3,11,14,18-$(O)_4$	M-3	8	Lukyanenko et al., 1981
H	H	1	1	2,3,11,12-$(O)_4$	M-2	75	Vögtle and Dix, 1977
CH_3	CH_3	1	1			80	Craig et al., 1990
$HO(CH_2)_2$-	$HO(CH_2)_2$-	1	1		(H,H)	80	Hancock et al., 1989

$CH_3CH(OH)CH_2$-	$CH_3CH(OH)CH_2$-	1	1		(H,H)	100	Hancock et al., 1989
$C_6H_5CH_2$-	$C_6H_5CH_2$-	1	1		R-1	41	Kawaguchi and Ohashi, 1985
$C_6H_5CH_2$-	$C_6H_5CH_2$-	1	1	5,9,14,18-$(O)_4$	M-5	31	Cazaux et al., 1989
					M-6	69	Cazaux et al., 1989
						58	Qian et al., 1990
CH_3	Ts	1	1		N-1	52	Dragomiretskaya et al., 1987
Ts	Ts	1	1		N-5	30-40	Biernat and Luboch, 1984
					N-5	20	Craig et al., 1989, 1990
					N-5	100	Hancock et al., 1989
H	H	2	1	3,11,14,21-$(O)_2$	M-3	9	Lukyanenko et al., 1981
CH_3	Ts	1	2		N-1	40	Dragomiretskaya et al., 1987
H	H	2	2	2,15,17,24-$(O)_4$	M-3	10	Lukyanenko et al., 1981
					M-1		Ostrovskaya and Lyakonova, 1987
H	H	2	2	2,3,14,15-$(O)_4$	M-2	60	Vögtle and Dix, 1977
$C_6H_5CH_2$-	$C_6H_5CH_2$-	2	2	5,12,17,24-$(O)_4$	M-4	4-10	Leygue et al., 1987, 1988
C_2H_5	C_2H_5	2	3		O-5	16	Krakowiak et al., 1989c
H	H	3	3	5,15,20,30-$(O)_4$	M-1		Ostrovskaya and Lyakonova, 1987

TABLE 7.7. 1,4,7,10-TETRAAZA-15-CROWN-5; -18-CROWN-6; -21-CROWN-7; -24-CROWN-8; -27-CROWN-9; AND -30-CROWN-10 MACROCYCLES



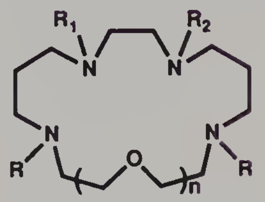
R_1	R_2	R_3	R_4	n	Other Substituents	Method (or from R_1,R_2,R_3,R_4 =)	Yield (%)	References
H	H	H	H	1		N-1	67	Hancock et al., 1990
						N-1	64	Rasshofer and Vögtle, 1977
						M-2		Tabushi et al., 1976
H	H	H	H	1	11,15-$(O)_2$	M-2		Tabushi et al., 1976
CH_3	CH_3	CH_3	CH_3	1		M-1		Pelissard and Louis, 1972
CH_3	CH_3	CH_3	CH_3	1	11,15-$(O)_2$	M-1	59	Pelissard and Louis, 1972
Ts	Ts	Ts	Ts	1		N-1	52	Rasshofer et al., 1976
morpholine$(CH_2)_2$-	H	H	C_2H_5	1		O-7	22	Krakowiak et al., 1990

morpholine$(CH_2)_2$-	CH_3	CH_3	C_2H_5	1		O-7	40	Krakowiak et al., 1990
$(C_2H_5)_2N(CH_2)_3$-	H or C_2H_5	H or C_2H_5	C_2H_5	1		O-7	16	Krakowiak et al., 1990
C_2H_5	H or $C_6H_5CH_2$-	H or $C_6H_5CH_2$-	$HO(CH_2)_2$-$O(CH_2)_2$-	1		O-7	18	Krakowiak et al., 1990
H	H	H	H	2		N-1	48	Hancock et al., 1989
						N-1	74	Rasshofer and Vögtle, 1977
						M-2		Tabushi et al., 1976, 1977
H	H	H	H	2	11,18-$(O)_2$	M-2	67	Tabushi et al., 1976, 1977
H	H	H	H	2	2,9-$(O)_2$	M-13	96	Lehn and Montavon, 1976
H	H	H	H	2	2,5,6,9-$(O)_4$	M-3	8	Lukyanenko et al., 1981
H	CH_3	CH_3	H	2		M-13	85	Lehn and Montavon, 1976
H	CH_3O_2CC-	CH_3O_2CC-	H	2	2,9-$(O)_2$	M-13	89	Lehn and Montavon, 1976
H	Ts	Ts	H	2		M-13	98	Lehn and Montavon, 1976
H	Ts	Ts	H	2	2,9-$(O)_2$	M-13	71	Lehn and Montavon, 1972, 1976
C_2H_5	C_2H_5	C_2H_5	C_2H_5	2	14-CH_2O-allyl	O-5	58	Krakowiak et al., 1989c
Ts	Ts	Ts	Ts	2		N-1	25	Rasshofer et al., 1976
								Richman and Atkins, 1974
$(C_2H_5)_2N(CH_2)_2$-	H	C_2H_5	$(C_2H_5)_2N$-$(CH_2)_2$-	2		O-7	23	Krakowiak et al., 1990

TABLE 7.7. (*Continued*)

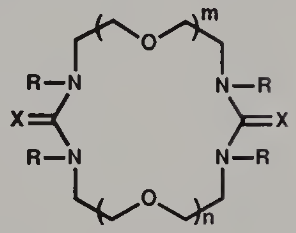
R^1	R_2	R_3	R_4	n	Other Substituents	Method (or from R_1,R_2,R_3,R_4 =)	Yield (%)	References
H	H	H	H	3		N-1	82	Sink et al., 1990
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	3		(H)	50	Sink et al., 1990
Ts	Ts	Ts	Ts	3		N-1	35	Rasshofer et al., 1976
						N-1	75	Sink et al., 1990
H	H	H	H	4		N-1	88	Sessler et al., 1989
						N-1	82	Sink et al., 1990
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	4		(H)	56	Sink et al., 1990
C_2H_5	CH_3	CH_3	C_2H_5	4	17-CH_2OH		55	Krakowiak et al., 1989c
Ts	Ts	Ts	Ts	4		N-1	54	Sessler et al., 1989
						N-1	70	Sink et al., 1990
H	H	H	H	5		N-1	82	Sink et al., 1990
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	5		(H)	60	Sink et al., 1990
Ts	Ts	Ts	Ts	5		N-1	12	Sink et al., 1990
						N-1	60	Sink et al., 1990
H	H	H	H	6		N-1	82	Sink et al., 1990
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	6		(H)	62	Sink et al., 1990
Ts	Ts	Ts	Ts	6		N-1	30	Sink et al., 1990

TABLE 7.8. TETRAAZA-CROWN MACROCYCLES WITH TWO TRIMETHYLENE BRIDGES



R	R_1	R_2	n	Method	Yield (%)	References
H	H	H	1	N-1	45	Lukyanenko et al., 1988a, 1988b
Ts	Ts	Ts	1	N-1	94	Lukyanenko et al., 1988a, 1988b
H	H	H	2	N-1	37	Lukyanenko et al., 1988a, 1988b
$C_6H_5CH_2$-	H	C_2H_5	2	O-10	26	Krakowiak et al., 1990
Ts	Ts	Ts	2	N-1	88	Lukyanenko et al., 1988a, 1988b
H	H	H	3	N-1	35	Lukyanenko et al., 1988a, 1988b
Ts	Ts	Ts	3	N-1	54	Lukyanenko et al., 1988a, 1988b

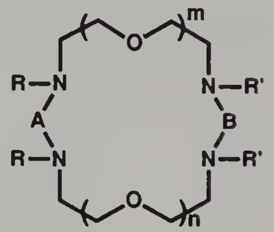
TABLE 7.9. TETRAAZA-CROWN MACROCYCLES WITH UREA OR THIOUREA BRIDGES



R	X	m	n	Method	Yield (%)	References
H	O	1	1		87	Lukyanenko et al., 1986
H	O	2	2		93	Lukyanenko et al., 1986
CH_3	O	1	1	R-2	82	Bogatskii et al., 1984c
CH_3	O	2	2			Bogatskii et al., 1982
				R-2	81	Bogatskii et al., 1984c
H	S	0	1	R-2	86	Lukyanenko et al., 1987
H	S	0	2	R-2	80	Lukyanenko et al., 1987
H	S	0	3	R-2	75	Lukyanenko et al., 1987

H	S	0	4	R-2	65	Lukyanenko et al., 1987
H	S	1	1	R-2	75	Lukyanenko et al., 1987
				R-2	18	Bogatskii et al., 1980a, 1980b
H	S	1	2	R-2	75	Lukyanenko et al., 1987
H	S	1	3	R-2	68	Lukyanenko et al., 1987
H	S	1	4	R-2	70	Lukyanenko et al., 1987
H	S	2	2	R-2	66	Lukyanenko et al., 1987
				R-2	8	Bogatskii et al., 1980a, 1980b
H	S	2	3	R-2	69	Lukyanenko et al., 1987
H	S	2	4	R-2	57	Lukyanenko et al., 1987
H	S	3	3	R-2	49	Lukyanenko et al., 1987
					5	Bogatskii et al., 1980b
H	S	3	4	R-2	55	Lukyanenko et al., 1987
H	S	4	4	R-2	40	Lukyanenko et al., 1987
CH_3	S	2	2		54	Bogatskii et al., 1984a

TABLE 7.10. TETRAAZA-CROWN MACROCYCLES WITH MISCELLANEOUS BRIDGES



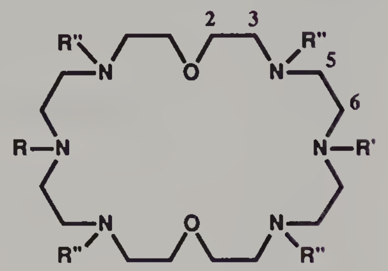
R	R'	A	B	Other Substituents	m	n	Method (or from R,R' =)	Yield (%)	References
H	H	$-(CH_2)_3-$	$-(CH_2)_2O(CH_2)_2-$		0	0	N-1	59 (salt)	Hancock et al., 1990
							N-1		Kodama and Kimura, 1980
H	H	$-C(O)(CH_2)_2C(O)-$	$-(CH_2)_2O(CH_2)_2-$	$3,14-(O)_2$	0	0	M-3	16	Lukyanenko et al., 1981
H	H	$-C(O)(CH_2)_2C(O)-$	$-CH_2(CH_2OCH_2)_2CH_2-$	$3,14-(O)_2$	0	0	M-3	12	Lukyanenko et al., 1979, 1981
H	H	$-C(O)(CH_2)_4C(O)-$	$-(CH_2)_2O(CH_2)_2-$	$3,14-(O)_2$	0	0	M-3	14	Lukyanenko et al., 1981
H	H	$-C(O)(CH_2)_4C(O)-$	$-CH_2(CH_2OCH_2)_2CH_2-$	$3,14-(O)_2$	0	0	M-3	12	Lukyanenko et al., 1981
H	H	$-(CH_2)_3OCH_2C(CH_3)_2-$ $CH_2O(CH_2)_3-$	$-(CH_2)_3OCH_2C(CH_3)_2$ $CH_2O(CH_2)_3-$	$2,3,17,18-(O)_4$	0	0	M-3	63	Vögtle and Dix, 1977

CH_3	C_2H_5	$-(CH_2)_2-$	$-CH_2CH(OH)CH_2-$		1	1	O-2	3	Krakowiak et al., 1989a
CH_3	C_2H_5	$-(CH_2)_2-$	$-CH_2CH(=CH_2)CH_2-$		1	1	O-2	36	Krakowiak et al., 1989a
C_2H_5	C_2H_5	$-(CH_2)_2-$	$-CH_2CH(=CH_2)CH_2-$		1	1	O-2	55	Krakowiak et al., 1989a
C_2H_5	C_2H_5	$-(CH_2)_2-$	$-CH_2CH(OCH_2CH=CH_2)CH_2-$		1	1	O-2	20	Krakowiak et al., 1989a
H	H	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	2,6,9,14,18, 23-$(O)_6$;8,12, 20,24-$(s\text{-}C_4H_9)_4$	1	1		24	Katagi and Kuriyama, 1982
H	H	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	2,6,9,14,18, 23-$(O)_6$;8,12, 20,24-$(CH_2C_6H_5)_4$	1	1		9	Katagi and Kuriyama, 1982
CH_3	C_2H_5	$-(CH_2)_2-$	$-(CH_2)_2OCH_2CH-$ $(CH_2O\text{-allyl})O(CH_2)_2-$		1	1	O-2	48	Krakowiak et al., 1988, 1989a
C_4H_9	C_2H_5	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2OCH_2CH-$ $(CH_2O\text{-allyl})O(CH_2)_2-$		1	1	O-2	20	Krakowiak et al., 1988, 1989a
$C_6H_5CH_2-$	C_2H_5	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2OCH_2CH-$ $(CH_2O\text{-allyl})O(CH_2)_2-$		1	1	O-2	26	Krakowiak et al., 1988, 1989a
$C_6H_5CH_2-$	C_2H_5	$-CH_2(CH_2OCH_2)_2CH_2-$	$-(CH_2)_2OCH_2CH-$ $(CH_2O\text{-allyl})O(CH_2)_2-$		1	1	O-2	27	Krakowiak et al., 1988, 1989a
H	H	$-C(O)C(O)-$	$-CH_2(CH_2OCH_2)_3CH_2-$	3,14-$(O)_2$	0	2	M-3	8	Lukyanenko et al., 1981
C_2H_5	C_2H_5	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2-$	11 or 12-CH_2 O-allyl	0	2	O-2	56	Krakowiak et al., 1989a
OH	H	$-(CH_2)_2C(O)-$	$-C(O)(CH_2)_2-$		2	2	$(C_6H_5\text{-}CH_2O,Ts)$	25	Sun et al., 1985

TABLE 7.10. (*Continued*)

R	R'	A	B	Other Substituents	m	n	Method (or from R,R' =)	Yield (%)	References
H	Ts	$-(CH_2)_2C(O)-$	$-C(O)(CH_2)_2-$		2	2	M-1	56	Sun et al., 1985
OH	Ts	$-(CH_2)_2C(O)-$	$-C(O)(CH_2)_2-$		2	2	[Si-$(CH_3)_3$,Ts]	6	Sun et al., 1985
OH	HO_2CCH_2	$-(CH_2)_2C(O)-$	$-C(O)(CH_2)_2-$		2	2	(OH,H)	28	Sun et al., 1985
$Si(CH_3)_3$-	Ts	$-(CH_2)_2C(O)-$	$-C(O)(CH_2)_2-$		2	2	(H,Ts)		Sun et al., 1985
$C_6H_5CH_2O$-	Ts	$-(CH_2)_2C(O)-$	$-C(O)(CH_2)_2-$		2	2	M-1	26	Sun et al., 1985

TABLE 7.11. HEXAAZA-24-CROWN-8 MACROCYCLES



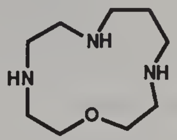
R	R'	R''	Other Substituents	Method (or from R,R',R'' =)	Yield (%)	References
H	H	H		M-7	75	Comarmond et al., 1982
				N-2	90	Comarmond et al., 1982
				(H,H,Ts)		Coughlin et al., 1979
CH_3	CH_3	CH_3		(H)	71	Hosseini and Lehn, 1987
Ts	Ts	Ts		N-2		Comarmond et al., 1982
$4\text{-}C_{12}H_{25}OC_6H_4C(O)\text{-}$	$4\text{-}C_{12}H_{25}OC_6H_4C(O)\text{-}$	$4\text{-}C_{12}H_{25}OC_6H_4C(O)\text{-}$				Lehn et al., 1985
HC(O)-	H	H		(H)	39	Johansouz et al., 1989
						Jiang et al., 1989
$H_2O_3P\text{-}$	H	H		(H)		Hosseini and Lehn, 1985
$HO(CH_2)_2\text{-}$	H	H		N-2	64	Hosseini et al., 1987

TABLE 7.11. (*Continued*)

R	R'	R''	Other Substituents	Method (or from R,R',R'' =)	Yield (%)	References
$HS(CH_2)_2$-	H	H		N-2	65	Hosseini et al., 1987
$H_2N(CH_2)_2$-	H	H		N-2	71	Hosseini et al., 1987
9-acridine$NH(CH_2)_3$-	H	H			90	Hosseini et al., 1988
H	Ts	Ts		N-2	82	Hosseini et al., 1987
$HO(CH_2)_2$-	Ts	Ts		N-2	57	Hosseini et al., 1987
$CN(CH_2)_2$-	Ts	Ts		N-2	94	Hosseini et al., 1988
$HS(CH_2)_2$-	Ts	Ts		N-2	68	Hosseini et al., 1987
$H_2N(CH_2)_3$-	Ts	Ts		N-1	61	Hosseini et al., 1988
$C_6H_5C(O)$-	Ts	Ts		N-2	55	Hosseini et al., 1987
$TsNH(CH_2)_2$-	Ts	Ts		N-2	98	Hosseini et al., 1987
9-acridine$NH(CH_2)_3$-	Ts	Ts		[$NH_2(CH_2)_3$, Ts,Ts]	44	Hosseini et al., 1988

H	H	Ts		M-7	75	Comarmond et al.,1982
				M-7	98	Lehn et al., 1977
				N-2	56	Hosseini et al., 1987
H	H	Ts	8,18-$(O)_2$	M-7	30	Lehn et al., 1977
$HO(CH_2)_2$-	$HO(CH_2)_2$-	H		N-2	61	Hosseini et al., 1987
$HO(CH_2)_2$-	$HO(CH_2)_2$-	Ts		N-2	77	Hosseini et al., 1987
$HS(CH_2)_2$-	$HS(CH_2)_2$-	Ts		N-2	70	Hosseini et al., 1987
$H_2N(CH_2)_2$-	$H_2N(CH_2)_2$-	Ts		N-2	72	Hosseini et al., 1987
$C_6H_5C(O)$-	$C_6H_5C(O)$-	Ts		N-2	53	Hosseini et al., 1987
$TsNH(CH_2)_2$-	$TsNH(CH_2)_2$-	Ts		N-2	88	Hosseini et al., 1987
H	9-acridine$NH(CH_2)_3$-	H				Hosseini et al., 1990
Ts	$CN(CH_2)_2$-	Ts				Hosseini et al., 1990
Ts	$NH_2(CH_2)_3$-	Ts				Hosseini et al., 1990
Ts	9-acridine$NH(CH_2)_3$-	Ts				Hosseini et al., 1990
$TsNH(CH_2)_2$-	$TsNH(CH_2)_2$-	$TsNH(CH_2)_2$-		(H)		Hosseini and Lehn, 1987
$NH_2(CH_2)_2$-	$NH_2(CH_2)_2$-	$H_2N(CH_2)_2$-		[$TsNH(CH_2)_2$]		Hosseini and Lehn, 1987

TABLE 7.12. MISCELLANEOUS POLYAZA-CROWN MACROCYCLES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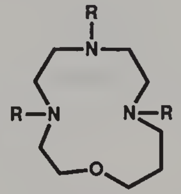
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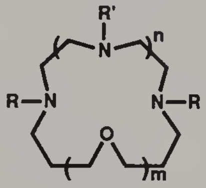
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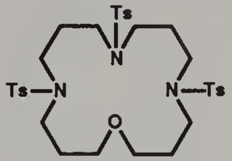
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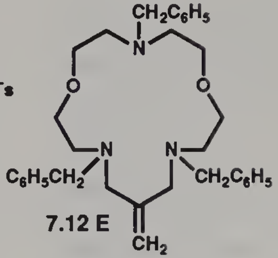
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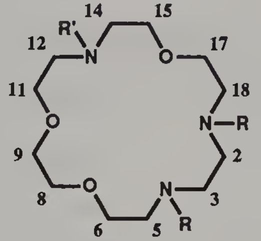
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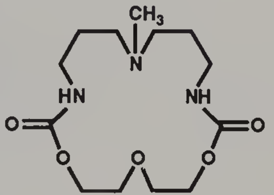
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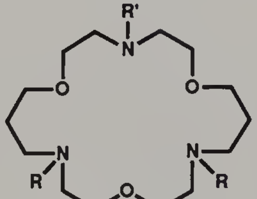
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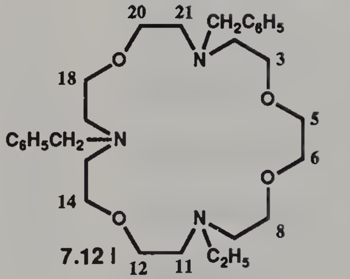
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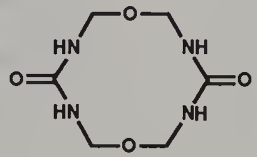
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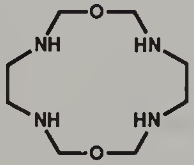
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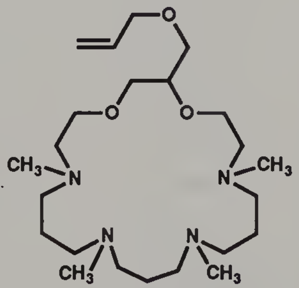
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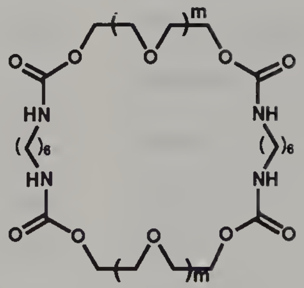
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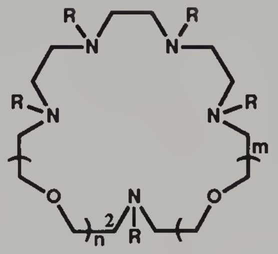
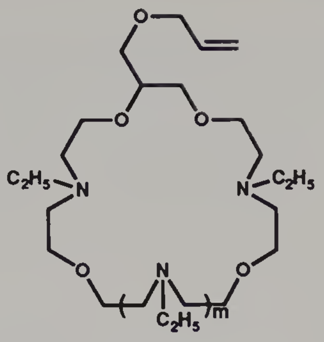
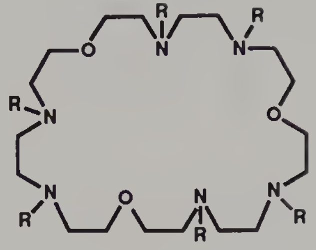


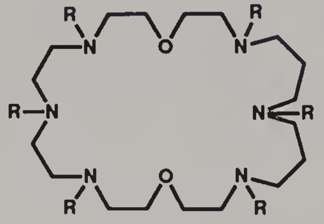
7.12 N



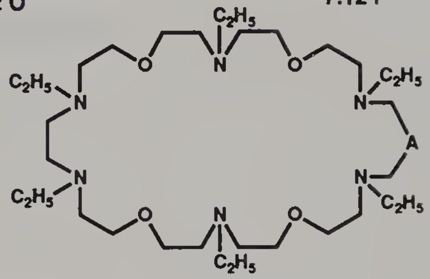
7.12 O



7.12 P



7.12 Q



7.12 R

Structure	R	R'	Other Substituents or:			Method	Yield (%)	References
				m	n			
7.12 A						N-1		Thöm and Hancock, 1985
7.12 B	H					N-1		Thöm and Hancock, 1983
	Ts							Rasshofer et al., 1976
						N-1		Thöm and Hancock, 1983

TABLE 7.12. *(Continued)*

Structure	R	R'	Other Substituents or:			Method	Yield	References
				m	n		(%)	
7.12 C	Ts	Ts		1	1	N-1	29	Rasshofer et al., 1976
	Ts	Ts		1	2	N-1	44	Rasshofer et al., 1976
	$C_6H_5CH_2$-	$C_2H_5NH(CH_2)_2$-		3	1	O-6	22	Krakowiak et al., 1990
	$C_6H_5CH_2$-	morpholine$(CH_2)_2$-		3	1	O-6	25	Krakowiak et al., 1990
7.12 D						N-1	69	Rasshofer et al., 1976
7.12 E						O-1	63	Krakowiak et al., 1989a
7.12 F	CH_3	C_2H_5	8 or 9-CH_2Oallyl			O-2	66	Krakowiak et al., 1989a
7.12 G						M-1	62	Buhleier et al., 1978
7.12 H	H	H				M-11	55	Pratt et al., 1988
	CH_3	CH_3				M-11	57	Pratt et al., 1988
	H	Ts				M-11	94	Pratt et al., 1988

	H	Ts	2,6-(O)$_2$			M-11	45	Pratt et al., 1988
7.12 I			5 or 6-CH$_2$Oallyl			O-1	51	Krakowiak et al., 1989a
7.12 J								Ostrovskaya and Lyakonova, 1987
								Popov et al., 1980
7.12 K							(as CO complex)	Geue et al., 1976
7.12 L						O-5	45	Krakowiak et al., 1989c
7.12 M				3				Lipatova et al., 1983
				4				Lipatova et al., 1983
7.12 N	H			1	0	N-1	50	Lukyanenko et al., 1988a
						M-2		Tabushi et al., 1976
	H	14,18-(O)$_2$		1	0	M-2	12	Tabushi et al., 1976
	C$_2$H$_5$	20 or 21-CH$_2$O-allyl		2	1	O-2	56	Krakowiak et al., 1989a
		Ts		1	0	N-1	60	Lukyanenko et al., 1988a

TABLE 7.12. (*Continued*)

		Other Substituents or:				Yield	
Structure	R	R'	m	n	Method	(%)	References
7.12 O			3		O-2	37	Krakowiak et al., 1989a
			4		O-2	36	Krakowiak et al., 1989a
7.12 P	H				N-3	90	Dietrich et al., 1981, 1983
							Lehn et al., 1985
		Ts			N-3	65	Dietrich et al., 1981, 1983
		4-$C_{12}H_{25}OC_6H_4C(O)$–					Lehn et al., 1985
7.12 Q	H				N-2	95 (HCl)	Hosseini and Lehn, 1987
	Ts				N-2	44	Hosseini and Lehn, 1987
7.12 R		A = C = CH_2			O-2	8	Krakowiak et al., 1989a
		A = $(CH_2OCH_2)_2$			O-2	11	Krakowiak et al., 1989a

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CHAPTER VIII

Benzoaza-crown Macrocycles

A. INTRODUCTION

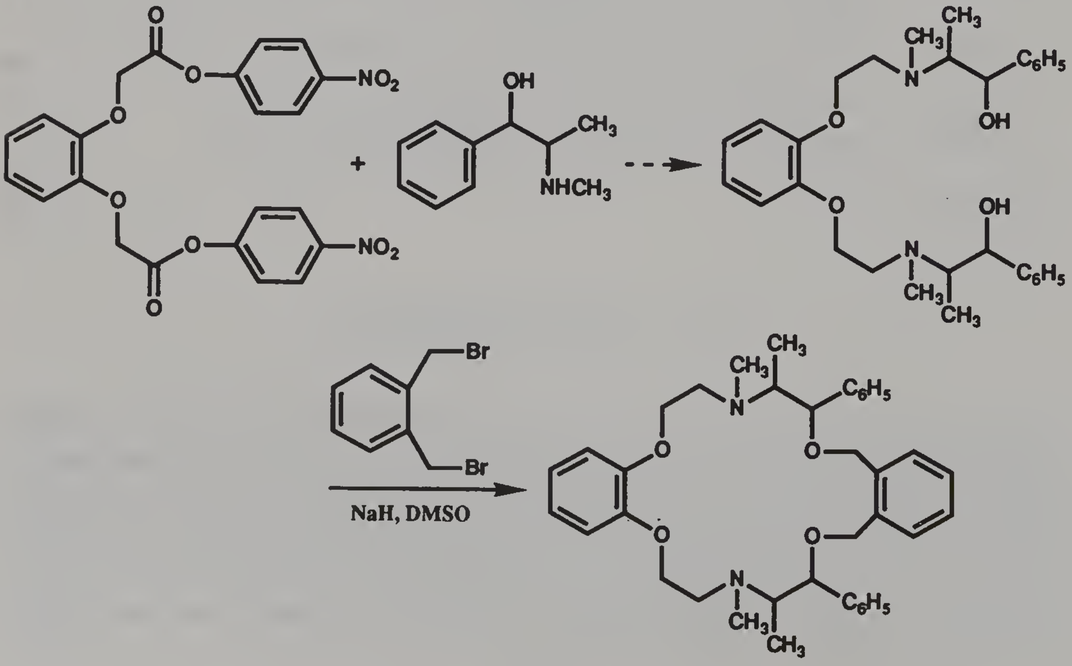
Many benzoaza-crowns have been prepared. This chapter presents specific methods for the synthesis of aza-crowns with one and more benzo groups. Benzoaza-crowns with one nitrogen atom in the ring were first reported in the early 1970s (Lockhart et al., 1973; Pedersen and Bromels, 1974; Wudl and Gaeta, 1972). The hydroxy group of phenol is much more reactive than an aliphatic alcohol. Aromatic amines, on the other hand, are less reactive than their aliphatic amine counterparts. These reactivity differences make possible many synthetic methods for the preparation of the benzoaza-crowns. Thus, ring-closure methods used to prepare these macrocycles utilize all four reactive groups: phenol, alcohol, aromatic amine, and aliphatic amine.

The most popular ring closure methods to prepare the benzoaza-crowns are (1) ring closure to form two aliphatic C—O bonds (ester or ether) by a 1:1 cyclization reaction (method S); (2) ring closure to form two phenolic O—C bonds by a 1:1 cyclization of a bis-phenol and an aliphatic dihalide or ditosylate ester (method T); (3) ring closure to form two aliphatic N—C bonds by a 1:1 cyclization of a diamine (or primary amine) and a dihalide or ditosylate ester (method U); (4) ring closure to form two anilinic N—C bonds by a 1:1 cyclization of a diaminobenzene derivative and a dihalide, ditosylate ester, or bis-carboxylyl dichloride (method V); (5) ring closure to form one phenolic O—C bond and one anilinic N—C bond by a 1:1 cyclization of *o*-hydroxyaniline with a dihalide or ditosylate ester (method W); and (6) ring closure to form a dibenzoaza-crown containing any combination of four phenolic O—C and anilinic N—C bonds by a 2:2 cyclization of *o*-disubstituted (hydroxy and/or amino) benzene with a dihalide or ditosylate ester (method X).

B. RING CLOSURE TO FORM TWO ALIPHATIC C—O BONDS BY A 1:1 CYCLIZATION REACTION

One of the earliest methods for preparation of a benzoaza-crown used a bis-*p*-nitrophenyl ester for the preparation of an intermediate benzodiazadiol (method S-1) (Wudl and Gaeta, 1972). The resulting diol intermediate was

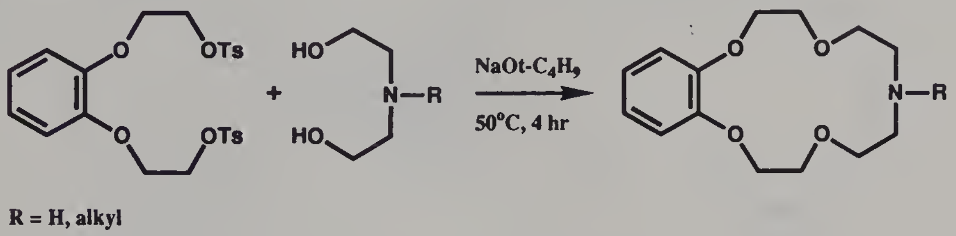
Method S-1



reacted with α,α′-dibromo-o-xylene to form a dibenzodiaza-crown containing two phenyl substituents.

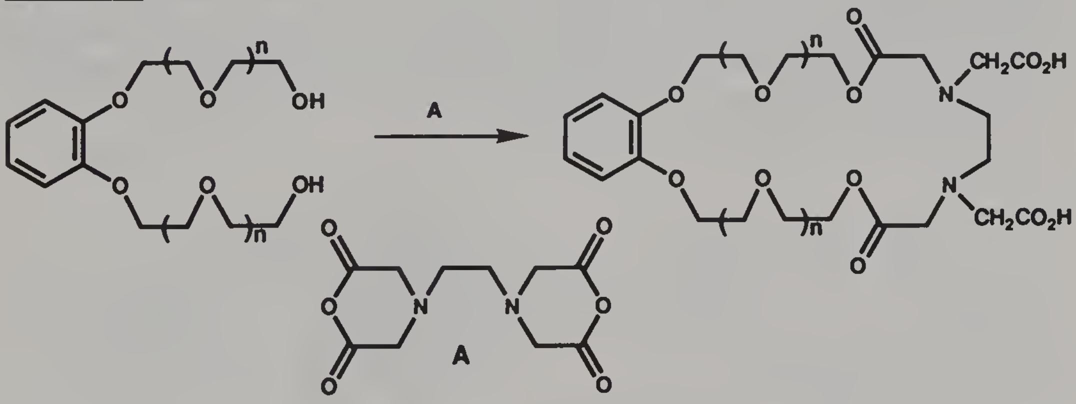
An improvement of the Högberg and Cram (1975) procedure to prepare benzomonoaza-crowns using tosylate leaving groups was reported in 1985 and 1986 (Lu and Wu, 1985; Wu and Lu, 1986) (method S-2). The reaction of 1,2-bis(2-tosyloxyethoxyl)benzene with diethanolamine (R = H) in *t*-butyl alcohol using sodium *t*-butoxide as the base gave a 37% yield of the benzoaza-crown. McLain (1986) prepared a similar macrocycle in a 21% yield after recrystallization from toluene. The condensation reaction of diethanolamine (R = H) takes place in strong base, which allows the deprotonated alcohols to act as nucleophiles rather than the amine group. This reaction with a 2,2′-bis(tosyloxyethoxy)-substituted 1,1′-binaphthyl and substituted diethanolamine (N = R) gave a binaphthoaza-crown compound (Cram, 1977).

Method S-2



Benzodiaza-crowns containing *N*-acetic acid substituents have been reported (Qin, 1986). The synthetic procedure involved the use of ethylenediamine–tetraacetic dianhydride. Macrocyclic diesters have been prepared with yields in the 21–24% range (method S-3).

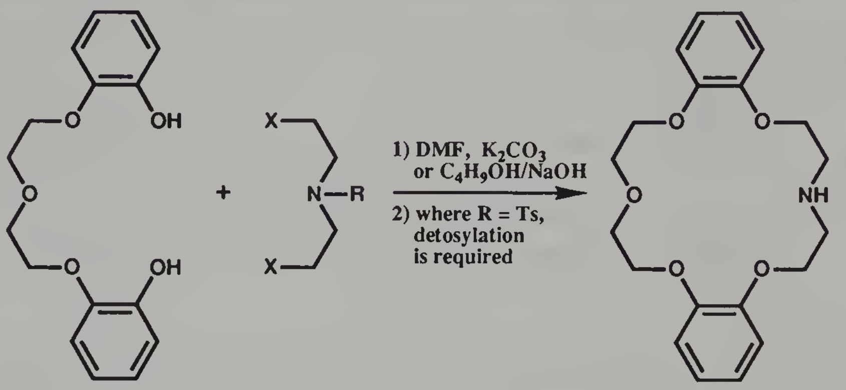
Method S-3



C. RING CLOSURE TO FORM TWO PHENOLIC O—C BONDS BY A 1:1 CYCLIZATION OF A BIS-PHENOL AND A DIHALIDE OR DITOSYLATE ESTER

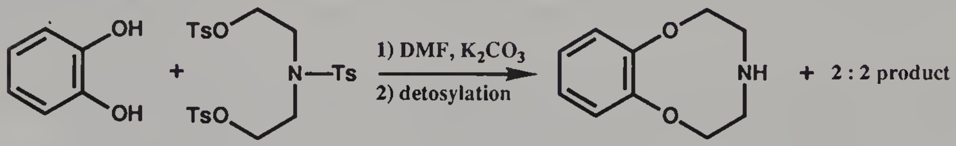
Ring closure using the phenoxide ion can be achieved using sodium or potassium carbonate and the corresponding phenol in contrast to the alcohols, which require a much stronger base to form the alkoxide. This method was used to produce macrocycles by treatment of either a bisphenol (method T-1) or catechol (method T-2) with the ditosylate ester of *N*-tosyldiethanolamine. Cyclic condensations of a bisphenol with bis(2-chloroethyl)amine (*CAUTION: blistering agent*) in refluxing *t*-butyl alcohol using a strong base (method T-1) gave the dibenzoaza-crowns in 20–30% yields (Pedersen and Bromels, 1974, 1977; Wu and Song, 1986). The yield of the 1:1 product in method T-2 was about 35% (Högberg and Cram, 1975). A similar condensation was used to give both 1:1 (49%) and 2:2 (20%) cyclic condensations using 2,2′-dihydroxy-1,1′-binaphthyl (method T-3) (Cram, 1977). Larger macrocycles were obtained by a similar method as that used in methods T-1, T-2, and T-3 (method T-4) (Anelli et al., 1988).

Method T-1

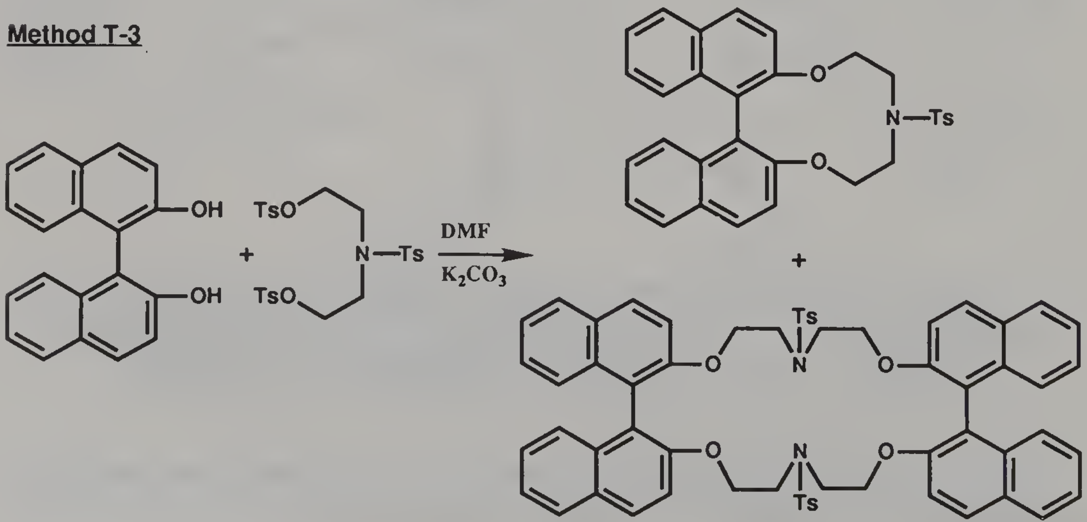


X = Cl, Br, OTs

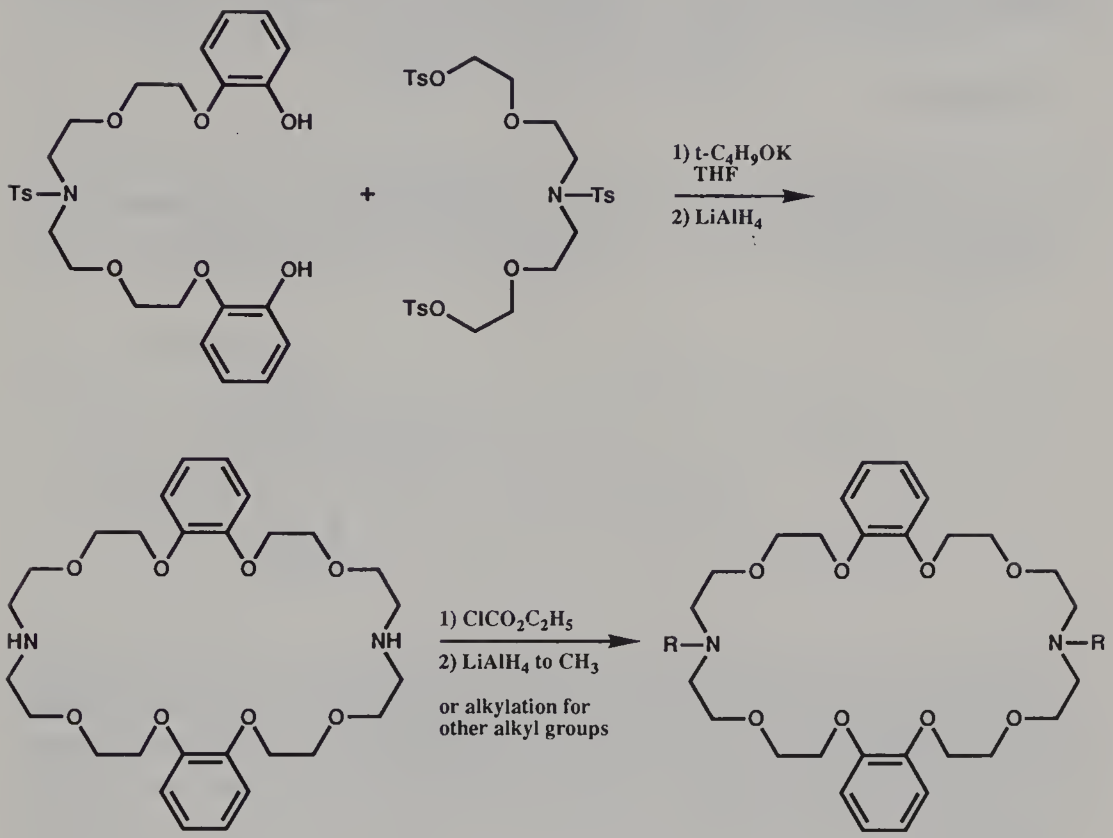
Method T-2



Method T-3

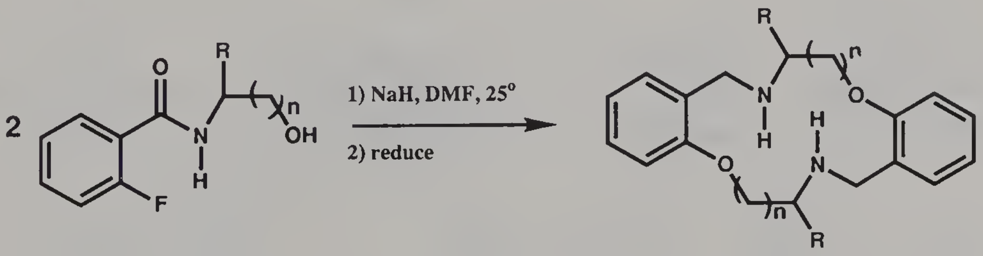


Method T-4



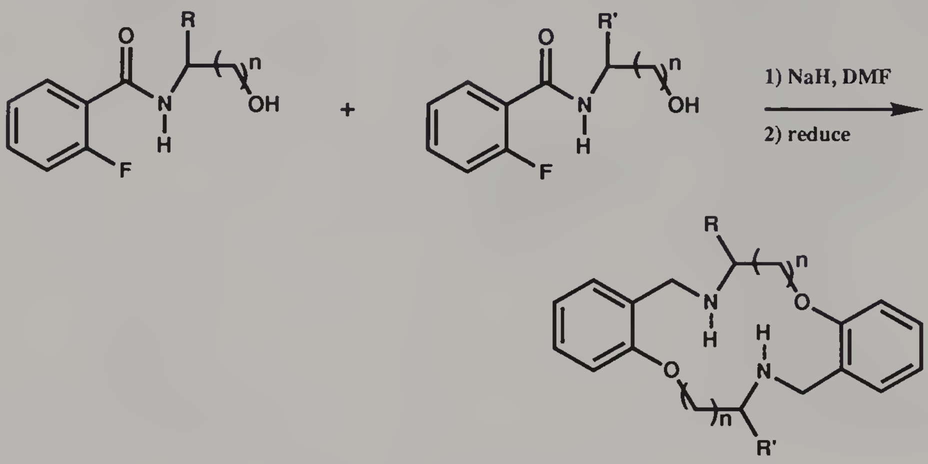
Ring closure to form a phenolic O—C bond can be achieved by reacting an alcohol and a fluoroaromatic compound in strong base (Schultz et al., 1988). A bimolecular cyclic self-condensation of an *N*-hydroxyalkyl-*o*-fluorobenzamide gave the dibenzodiaza-crowns in yields of 60–70% (method T-5). The amide nitrogen must be secondary for this reaction. A tertiary amide reactant cyclized intramolecularly to give the benzooxazepinone in 60–90% yields. This oxazepinone product was observed in yields of only 2–6% when a secondary amide was used (as in method T-5). The alkyl group on the tertiary amide probably disrupts the template that leads to forming a 14-membered ring. No macrocyclic product was observed when the fluorine atom was replaced by a bromine atom. The same type of macrocycle was prepared

Method T-5



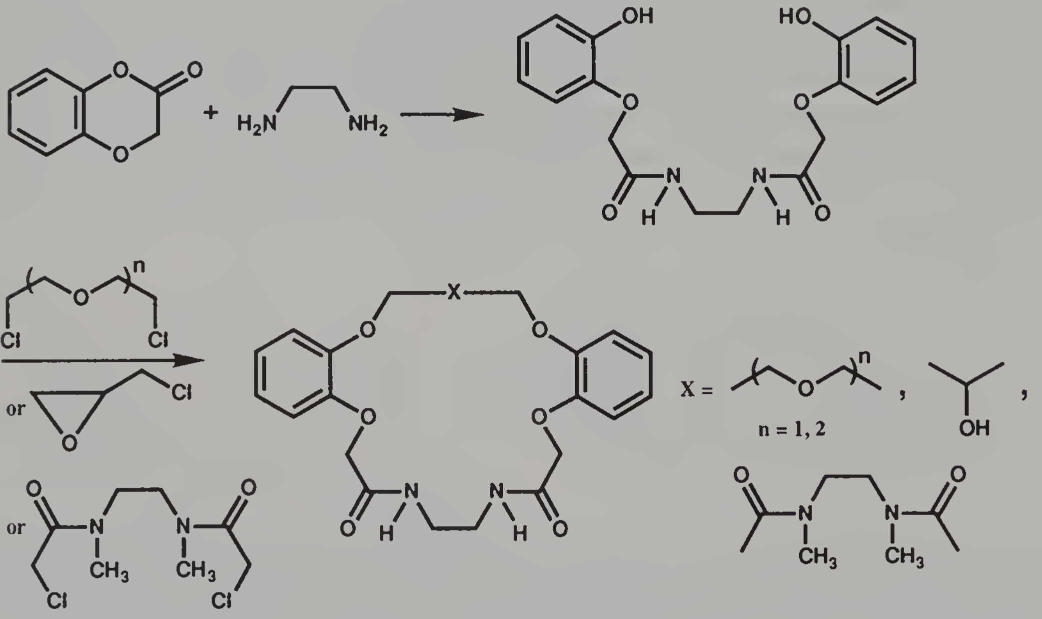
by these authors by the cyclocondensation of two different hydroxyfluorobenzamides as shown (method T-6) (Schultz et al., 1988).

Method T-6



A macrocyclic dibenzobisamide system has also been studied. A bisamide-containing bis-phenol was first prepared quantitatively from a benzolactone and ethylenediamine. This bis-phenol was cyclized in 12–16% yields with either a glycol dichloride or a chlorohydrin (method T-7) (Ashby et al., 1974).

Method T-7

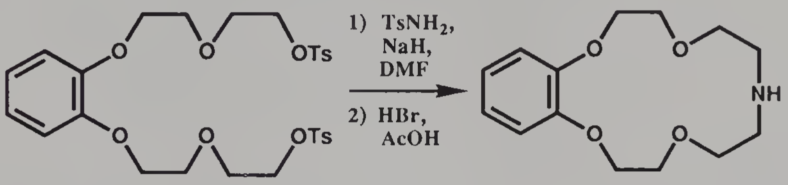


The low yields for this cyclization may be a result of cleavage of the bisamide product in the strong base.

D. RING CLOSURE TO FORM TWO ALIPHATIC N—C BONDS BY A 1:1 CYCLIZATION OF A DIAMINE (OR PRIMARY AMINE) AND A DIHALIDE OR DITOSYLATE ESTER

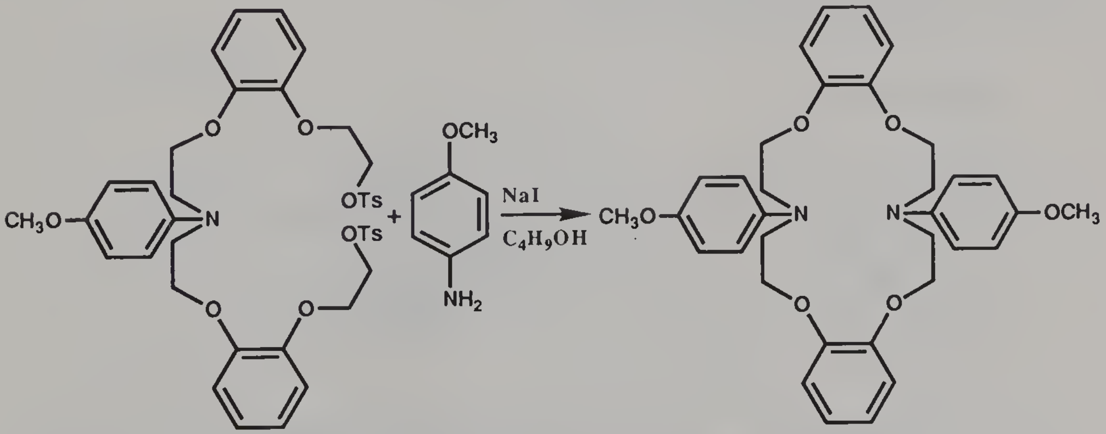
p-Toluenesulfonamide has been treated with the ditosylate derivative of a benzoglycol to form a benzoaza-crown where two N—C bonds were formed (method U-1) (Högberg and Cram, 1975). Methanesulfonamide gave higher yields of the *N*-mesyl-protected product, but the mesyl group was more difficult to remove.

Method U-1



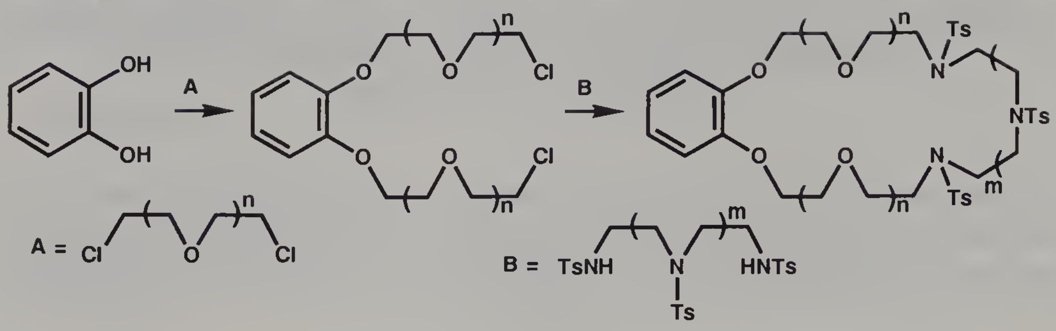
Degutis and Medekshene (1982) used *p*-methoxyaniline to prepare similar compounds. They treated a dibenzo-containing ditosylate ester with *p*-methoxyaniline in the presence of sodium iodide, which in situ converted the ditosylate to the diodide, to give a 57% yield of the crown (method U-2).

Method U-2



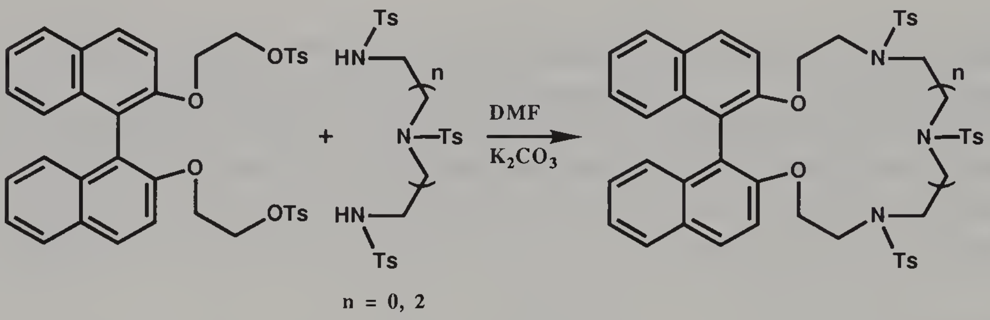
A similar sequence was reported by He and Wu (1984) for the preparation of benzopolyaza-crowns, except they used the tris- or tetrakis(*p*-toluenesulfonyl) derivative of diethylenetriamine or triethylenetetraamine (method

Method U-3

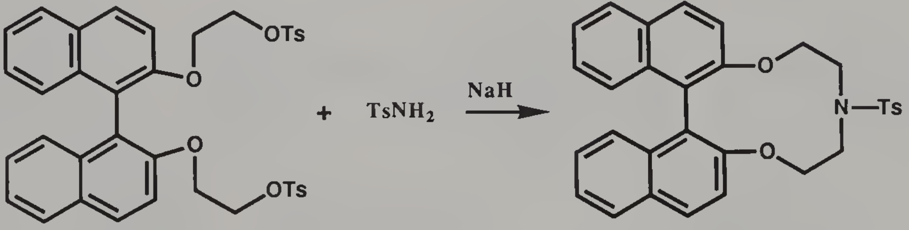


U-3). These authors did not report their method for removing the tosyl groups. Similar macrocycles were prepared in yields of 11–20% from 2,2′-bis(2-tosyloxyethoxy)-1,1′-binaphthyl and the per-*N*-tosylated oligoethylene polyamine (method U-4) (Cram, 1977). Surprisingly, a much higher yield was obtained when *p*-toluenesulfonamide was used rather than the pertosylated polyamine (method U-5) (Cram, 1977).

Method U-4

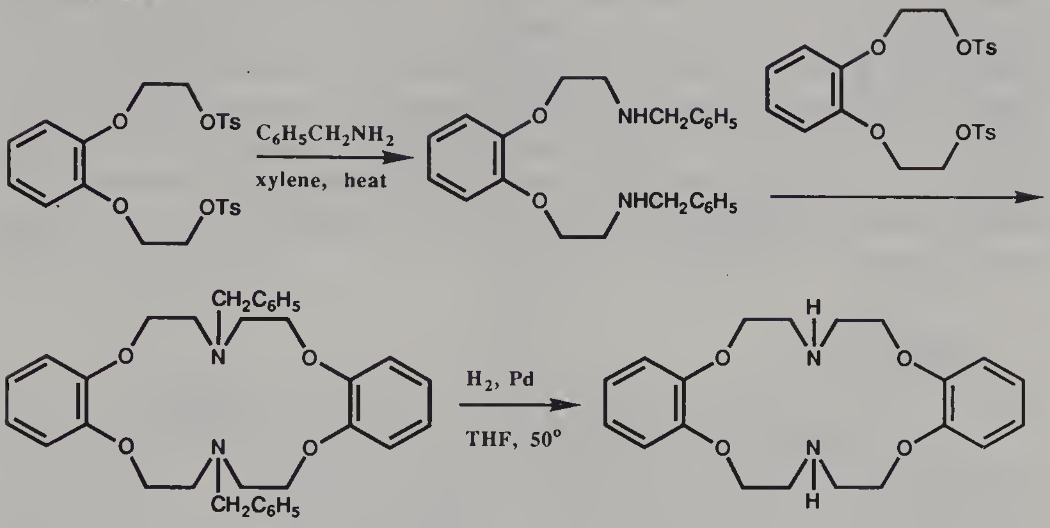


Method U-5



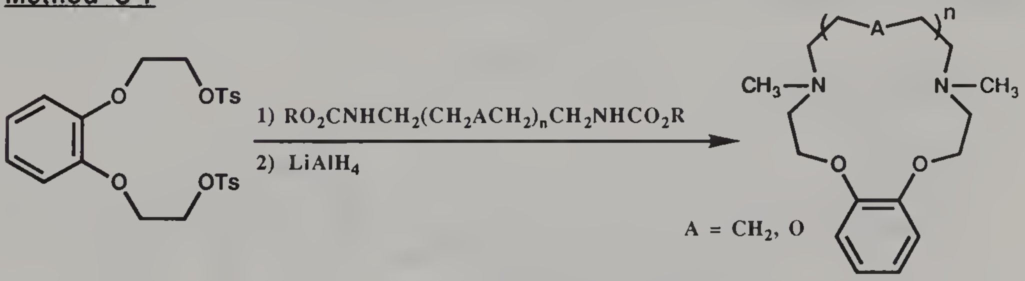
Alkyl- or aryl-substituted amines also have been used to prepare the benzoaza-crowns. Pedersen and Bromels (1974, 1977) prepared a dibenzodiazacrown by reacting a benzobis secondary amine with 1,2-bis(2-tosyloxyethoxy)benzene followed by reductive removal of the benzyl groups (method U-6).

Method U-6

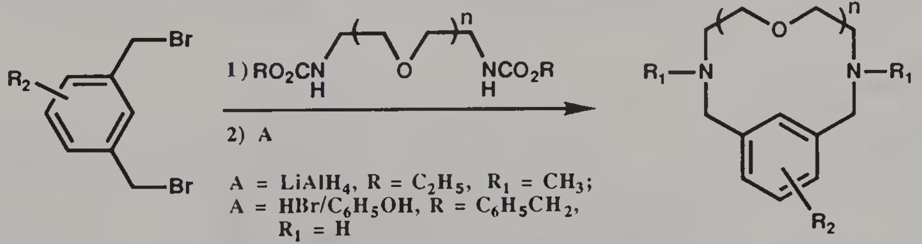


Sutherland and coworkers used several procedures to prepare a series of *o*-, *m*-, and *p*-benzodiaza-crown ligands. Three of the methods using bis-urethane functions are shown here (methods U-7, U-8, and U-9) (Hodgkinson and Sutherland, 1979; Hodgkinson et al., 1976a, 1976b, 1979; Leigh and Sutherland, 1975, 1979). The 1,3-benzodiaza-crowns were prepared as shown

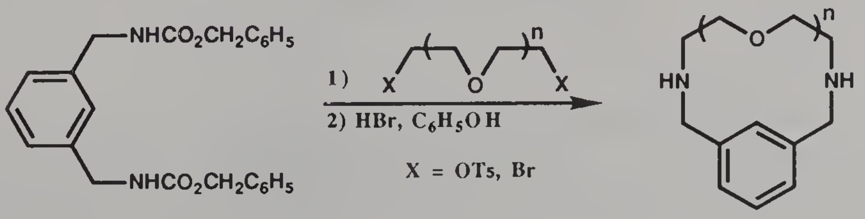
Method U-7



Method U-8

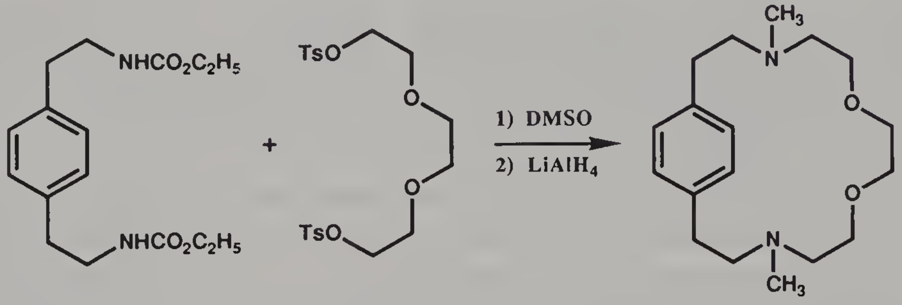


Method U-9



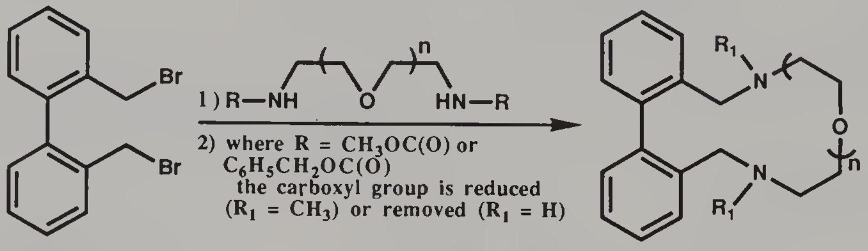
in method U-8 from the corresponding α,α′-dibromo-*m*-xylene. The ring-closure step for each of these methods gave yields of up to 40%. The alkoxycarboxamide group in the product of method U-8 can be reduced to an *N*-methyl function by lithium aluminum hydride or removed altogether with acid as shown. Method U-9 shows that it is possible to reverse the functional groups in the starting materials of method U-8. Stoddart and coworkers used a similar reaction sequence to prepare a 1,4-benzodiaza-crown ether (method U-10) (Beckford et al., 1978).

Method U-10

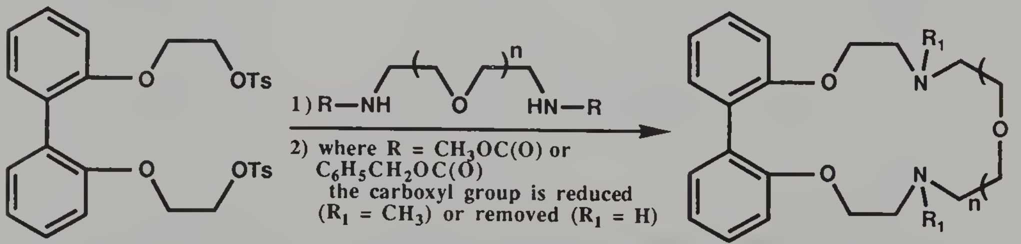


Sutherland and coworkers have prepared some interesting biphenyl-containing diaza-crowns (methods U-11 and U-12) (Pearson et al., 1979). A mixed

Method U-11

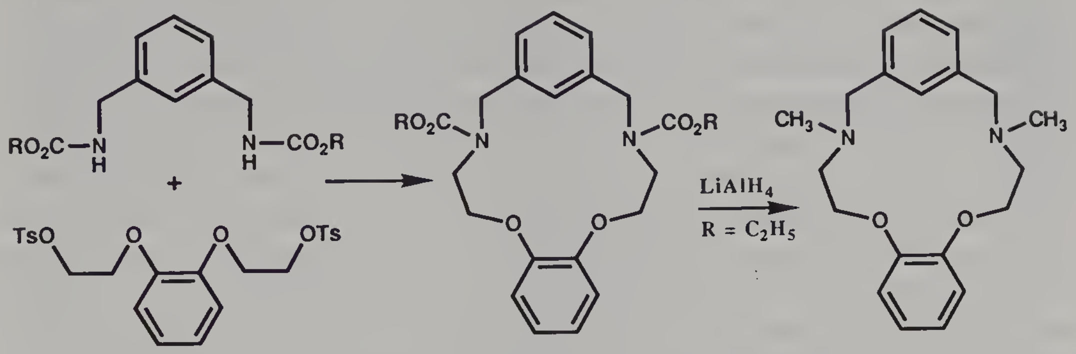


Method U-12



1,2-benzo- and 1,3-benzodiaza-crown system was prepared by the same researchers (method U-13) (Hodgkinson and Sutherland, 1979). In another paper, these authors reported the preparation of bis(1,2-benzodiaza-crown)s using this same method (Hodgkinson et al., 1979). Preparation of these mac-

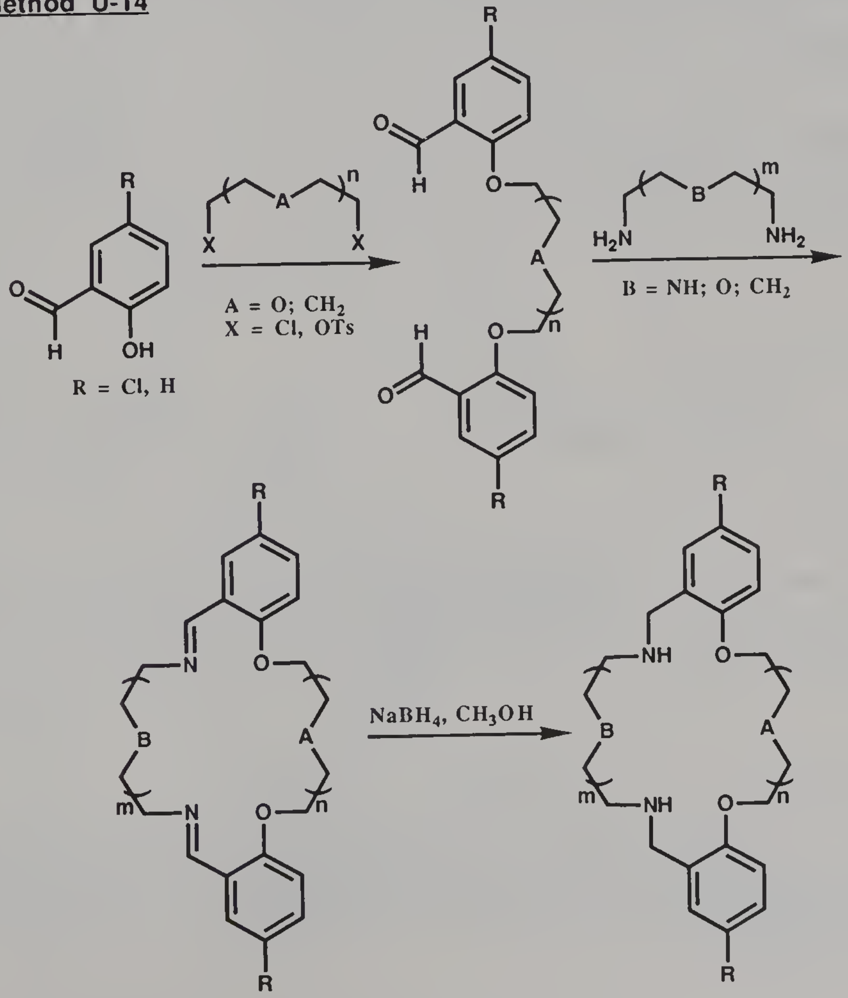
Method U-13



rocyclic bis-alkoxycarboxamides (methods U-7 through U-13) could be done in hot DMSO but isolation of the products was more difficult.

The synthesis of a variety of dibenzodiaza-crowns from salicylaldehyde or its derivatives has been reported by Lindoy and coworkers (Adam et al., 1981a, 1981b; Armstrong and Lindoy, 1975; Armstrong et al., 1977; Baldwin et al., 1987; Grimsley et al., 1977). The macrocycles were obtained via the corresponding diimines (Schiff bases), which were obtained by condensations of the appropriate dialdehydes and diamines as shown (method U-14). It was

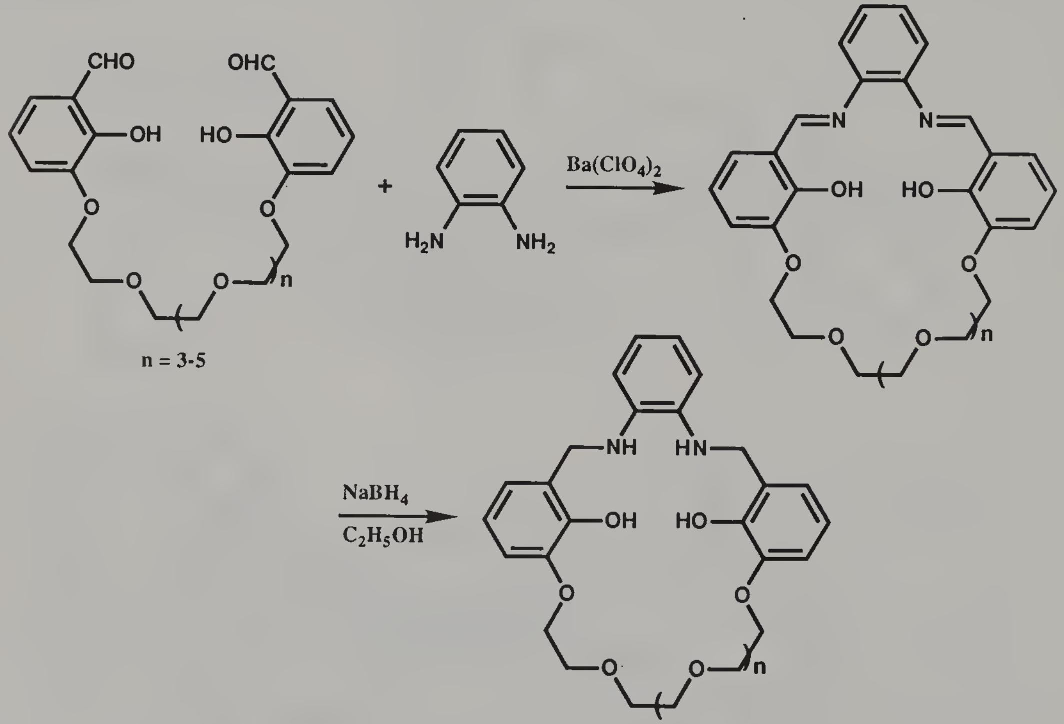
Method U-14



not necessary to isolate the cyclic diimine prior to the reduction process. The reduction was carried out by slowly adding sodium borohydride to the crude Schiff base. Purification of the product was accomplished by a variety of procedures (Baldwin et al., 1987). In a typical reaction procedure, salicylaldehyde was first reacted with the dihalide, followed by condensation with a diamine to form the diimine, which was reduced as shown (method U-14). When using a polyamine for the ring-closure step, the aldehyde could react with two nitrogen atoms of the polyamine to give a macrocycle containing diazacyclopentane or diazacyclohexane units. These small diaza rings would open during the reduction step to form the desired macrocycle. These authors also reversed the process by first reacting the salicylaldehyde with the diamine followed by the dihalide. Kodera and coworkers used the same method to prepare a series of diamino-crowns, except they used $LiAlH_4$ in the reduction step (Kodera et al., 1985). More complicated macrocycles containing four benzo groups were obtained by a method similar toU-14 but without reducing the Schiff base (Armstrong et al., 1977).

A tribenzodiaza-crown containing two intraannular phenolic functions was prepared as the barium perchlorate complex by reacting 1,2-diaminobenzene with the appropriate dihydroxydialdehyde (method U-15) (Staveren et al., 1988). The uncomplexed Schiff-base-containing macrocycles were not stable

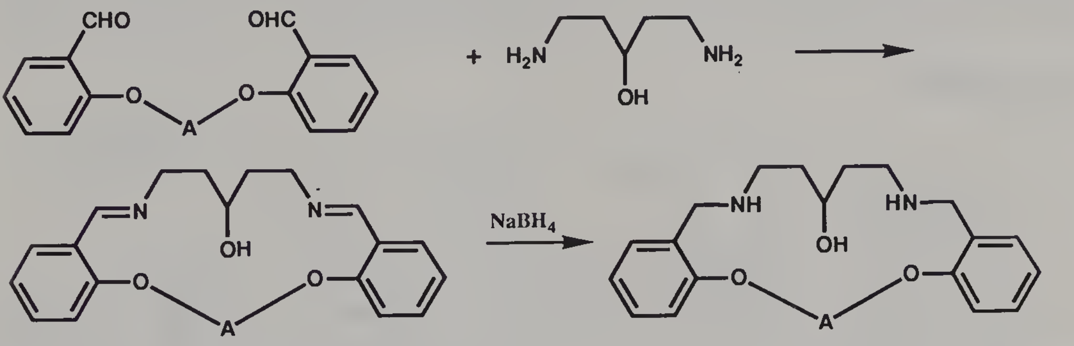
Method U-15



and slowly hydrolyzed to the diamine and dialdehyde. The unsaturated macrocycles were reduced to the stable diaza-crowns with sodium borohydride in yields of 63–71%.

A series of dibenzooxaaza macrocycles have been prepared by a nontemplate cyclization of 1,5-diamino-3-pentanol and various bis-benzaldehyde compounds. The resulting cyclic bis Schiff base was reduced with sodium borohydride to give the dibenzodiaza-crowns in overall yields of 10–20% (method U-16) (Bailey et al., 1989, 1990). They also recovered the 2:2 cyclic products using HPLC, but no additional data were given.

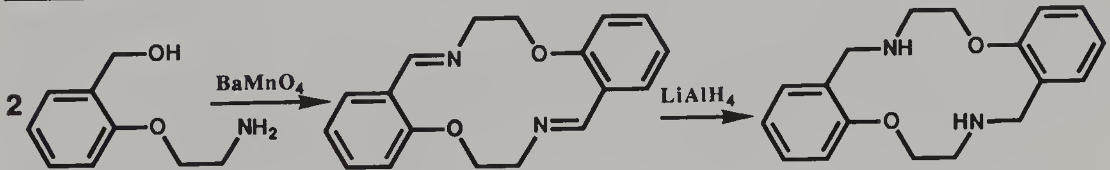
Method U-16



A = $(CH_2)_n$, n = 2-6; $(CH_2)_2NH(CH_2)_2$; m-C_6H_4

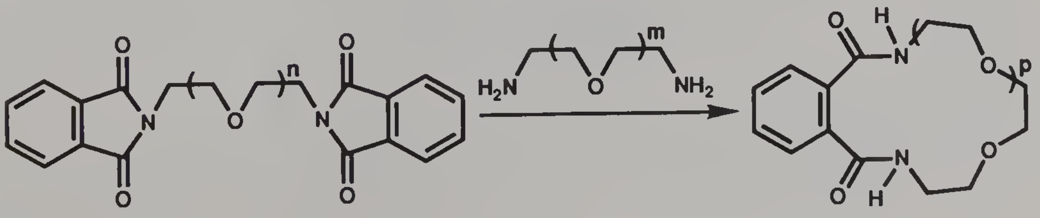
A spontaneous self-condensation of an amine-substituted benzaldehyde takes place in high yield, at room temperature, and without regard to concentration or any other precautions that usually apply to macrocyclic condensation reactions (Martin et al., 1985). The hydroxymethyl substituent of the starting material was first oxidized to the aldehyde, which condensed with the primary amine of another molecule of starting material (method U-17). The resulting bis Schiff base was reduced to form the final dibenzodiaza-crown.

Method U-17



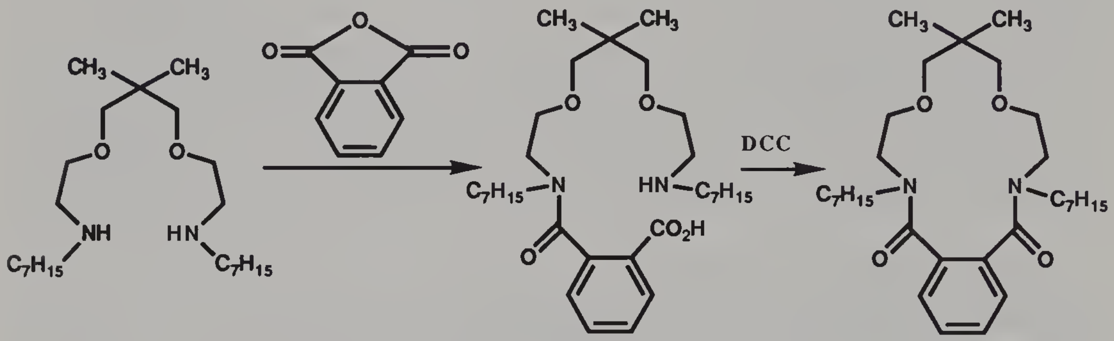
Using the bis(phthalimide) derivatives of the oligoethylene glycols, Komalov and coworkers prepared crown ethers containing a phthalamide moiety (method U-18) (Ganin et al., 1981; Anikin et al., 1982). The starting bis(phthalimide) and diamine were reacted in a water-methanol mixture, and

Method U-18



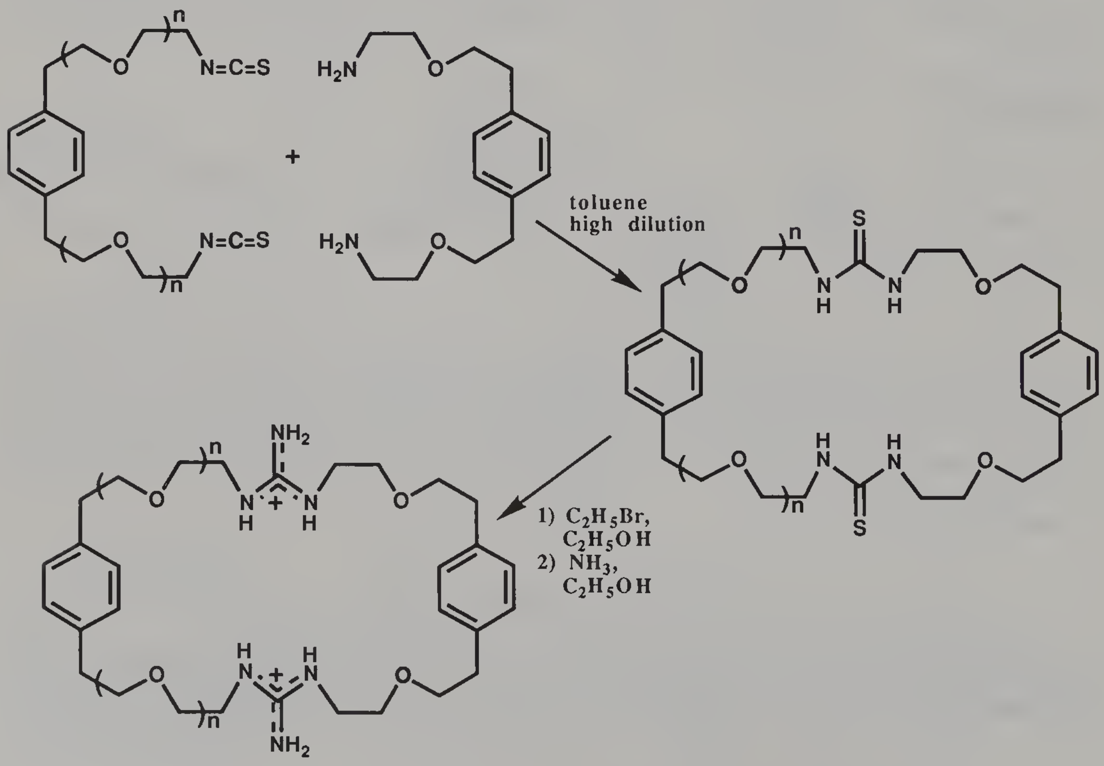
the product was isolated by chromatography in yields of 7–31%. Another procedure to form a macrocycle containing a phthalamide unit has been reported (Attiyat et al., 1987). *N*,*N*′-Diheptyl-5,5-dimethyl-3,7-dioxa-1,9-nonanediamine was reacted with phthalic anhydride to give an aminoamido benzoic acid intermediate that was cyclized using *N*,*N*′-dicyclohexylcarbodimide (DCC) (method U-19).

Method U-19



Lehn and coworkers prepared some dibenzo macrocycles that incorporated two guanidinium units into the macroring (method U-20) (Dietrich et al.,

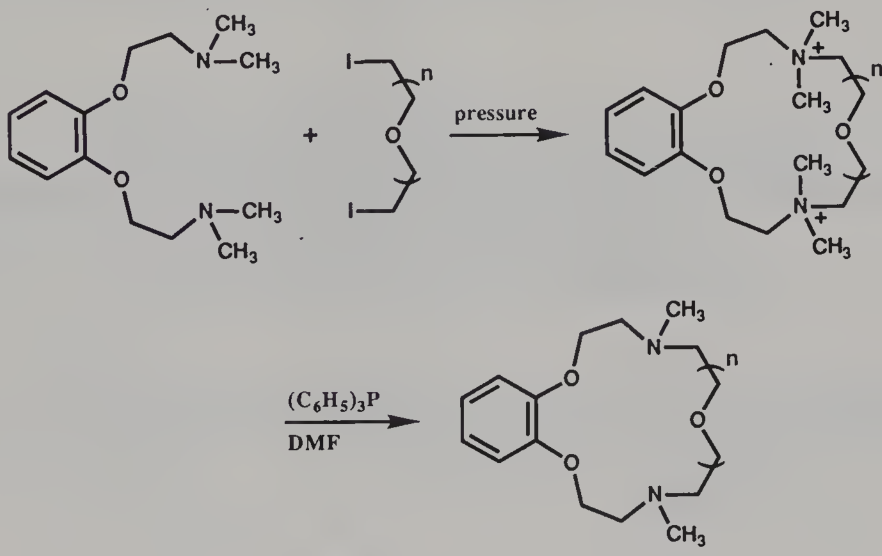
Method U-20



1978). A bis(isothiocyanate) was treated with a diamine in the ring-closure step. The resulting cyclic bis(thiourea) was converted into the bis(guanidinium)-containing macrocycle.

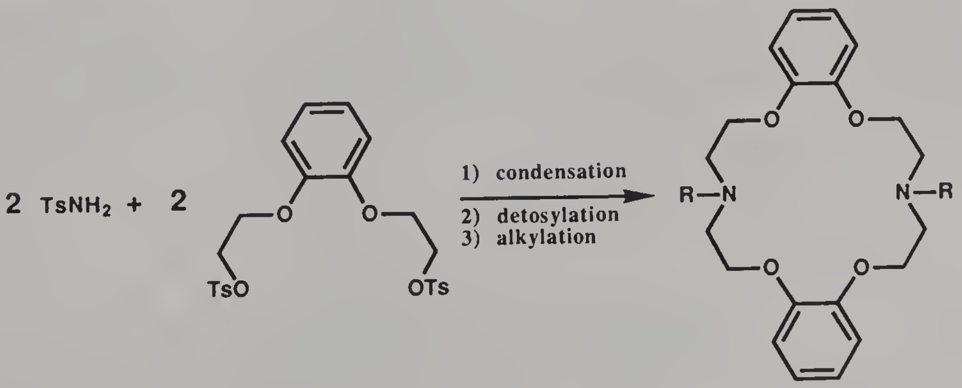
Tertiary amines have been cyclized with diiodides under high pressure (10 kbar) to produce a macrocyclic bis quaternary ammonium salt (method U-21) (Jurczak et al., 1989). The methyl groups were removed using triphenylphosphine. The cyclization reaction gave high yields even when using bis(2-iodoethyl)ether, which usually cyclizes with amines (including secondary amines) to give a morpholine derivative (Boon, 1949).

Method U-21

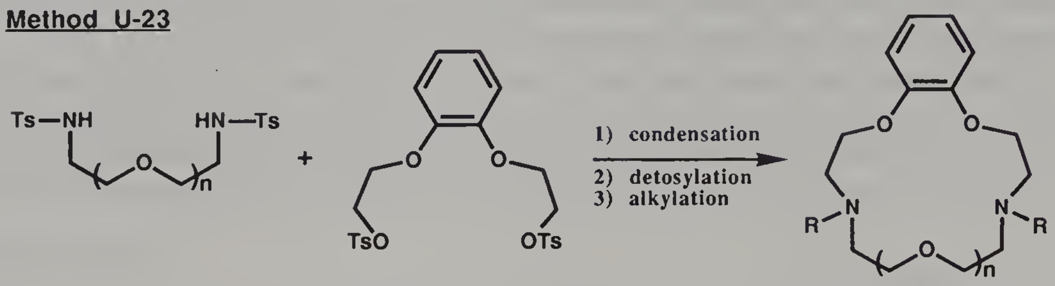


p-Toluenesulfonamide and 1,2-bis(2-tosyloxyethoxy)benzene cyclocondensed in a ratio of 2:2 to form a dibenzodiaza-18-crown-6 in a 76% yield (method U-22) (Ostaszewski et al., 1988). The 1,2-bis(2-tosyloxyethoxy)benzene also reacted with a bistosylamide to form a benzodiaza-crown

Method U-22

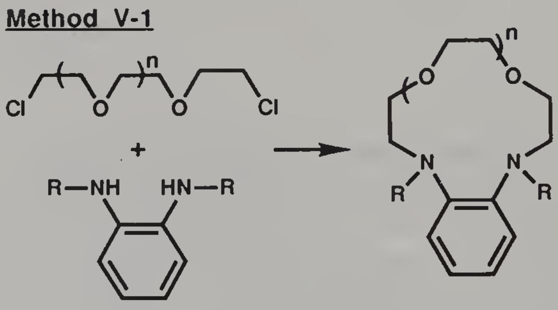


(method U-23) (Ostaszewski et al., 1988). This reaction was carried out using potassium carbonate and a catalytic amount of tetrabutylammonium chloride in DMF at 80°C.



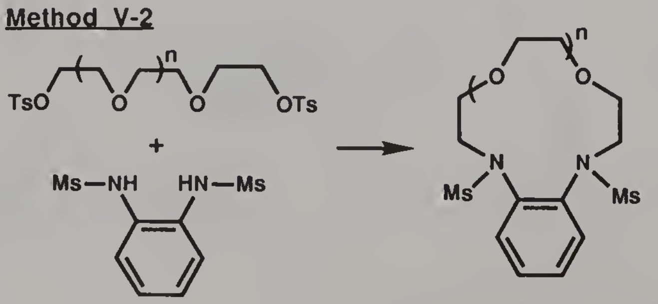
E. RING CLOSURE TO FORM TWO ANILINIC N—C BONDS BY A 1:1 CYCLIZATION OF A DIAMINOBENZENE DERIVATIVE AND A DIHALIDE, A DITOSYLATE ESTER, OR A BIS-CARBOXYLYL DICHLORIDE

Lockhart and coworkers reacted *o*-diaminobenzene with a series of dihalides to give benzodiaza-crowns (method V-1) (Lockhart and Thompson, 1977; Lockhart et al., 1973). Others reacted the tosyl or acetyl derivatives of *o*-diaminobenzene with bis(2-chloroethyl) ether to give the dibenzodiaza-9-crown-3 ligands (Mikiciuk-Olasik and Kotelko, 1984a).



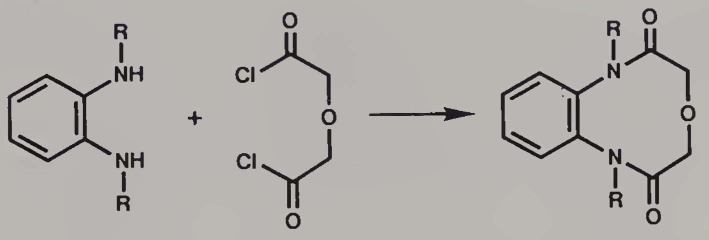
R = Ts, $CH_3C(O)$, H, alkyl

Högberg and Cram (1975) prepared some benzoaza- and benzodiaza-crowns from the methanesulfonamide derivative of 1,2-diaminobenzene (method V-2). The diaza-crown was formed in only a 5% yield.



Aromatic diamines have been used to prepare small macrocycles such as the benzodiaza-9-crown-3 ligands (method V-3) (Glinka et al., 1977; Mikiciuk-Olasik and Kotelko, 1984b). The macrocycles were prepared from various 1,2-diaminobenzene derivatives and diglycolyl dichloride. A high product yield was reported and, for most reactions, no 2:2 cyclization products (dibenzotetraaza-18-crown-6) were isolated. The yield for the macrocyclic bisacetamide [where R = C(O)CH_3] was only 15%.

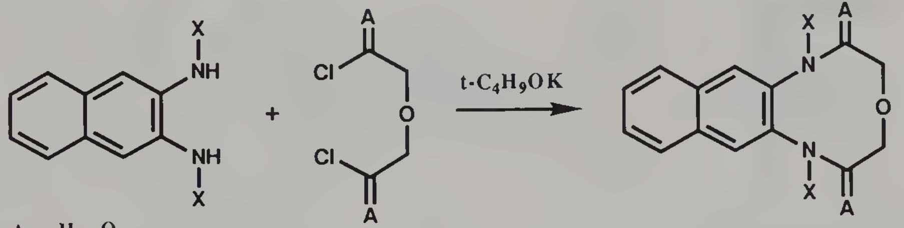
Method V-3



R = alkyl, H, Ts, $CH_3C(O)$

Similar reactions were observed using 2,3-diaminonaphthalene and its *N*,*N*′-ditosylamide derivative (method V-4) (Mikiciuk-Olasik and Kotelko, 1984a). Again, good yields of the 1:1 cyclization product were reported with no 2:2 cyclization.

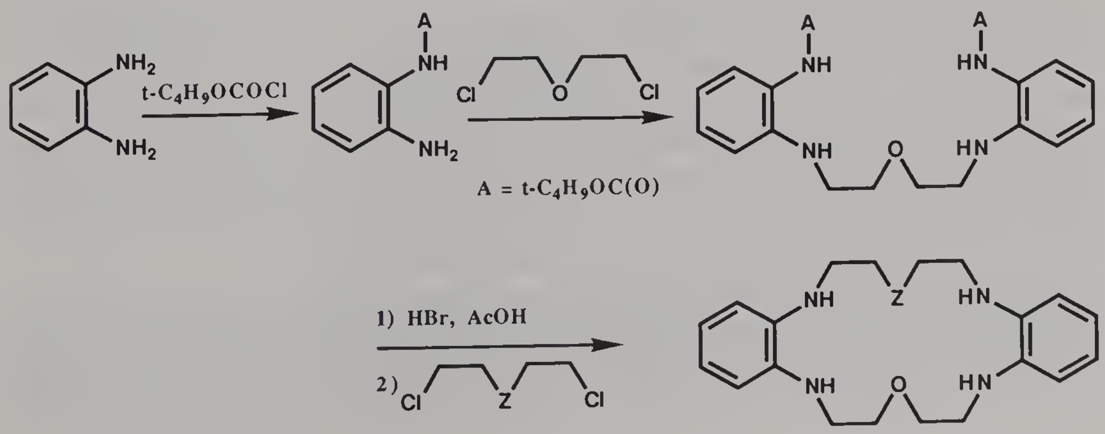
Method V-4



A = H_2, O
X = Ts, H

1,2-Diaminobenzene also has been used to prepare dibenzotetraaza-crowns (method V-5) (Pedersen and Bromels, 1974, 1977). One of the amine nitrogen atoms was blocked using *tert*-butoxycarbonyl chloride, which was readily re-

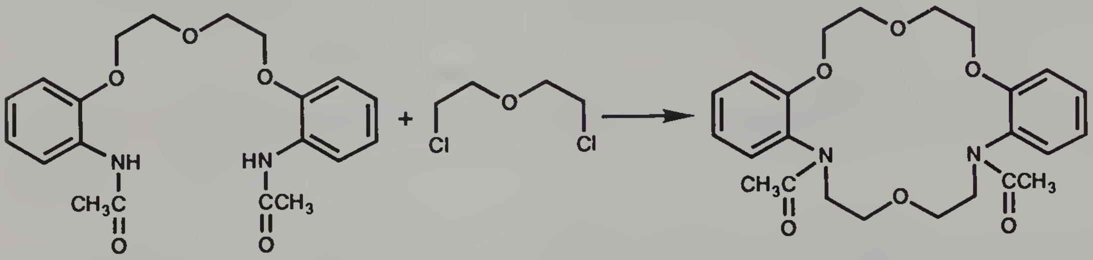
Method V-5



A = t-$C_4H_9OC(O)$

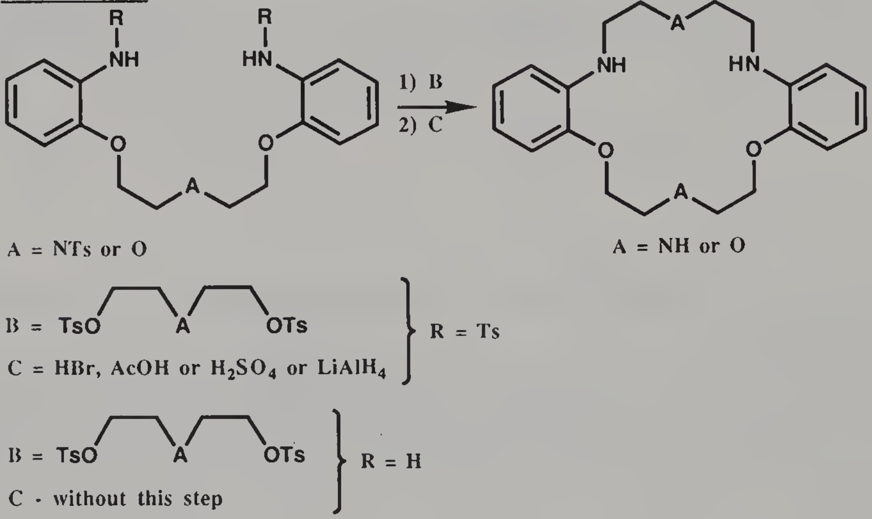
moved in a later step. Unfortunately, the experimental procedure was not fully described in the patent. Biernat and coworkers reported the use of *N*-acetyl protecting groups on *o*-aminophenol but obtained the dibenzodiaza-crown in only a 15% yield (method V-6) (Biernat et al., 1979).

Method V-6



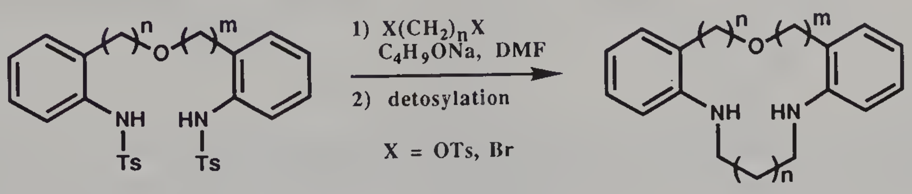
Högberg and Cram (1975) and Biernat and Luboch (1984) prepared some dibenzodiaza-, triaza-, and tetraaza-crowns from a bis-tosylanilide derivative prepared from *o*-nitrophenol (method V-7). This procedure allows the synthesis of dibenzo-crowns containing from two to four nitrogen atoms depending on the nature of A in the starting materials. The *N*-tosyl groups were best removed using a mixture of glacial acetic acid and hydrobromic acid. A small amount of a by-product containing bromine on one or more benzene rings was also isolated in this reaction. This product was converted to the desired dibenzo-crown by debromination with hydrazine and palladium on carbon (Högberg and Cram, 1975). The process using aniline compounds (R = H) gave lower yields (Biernat and Luboch, 1984).

Method V-7

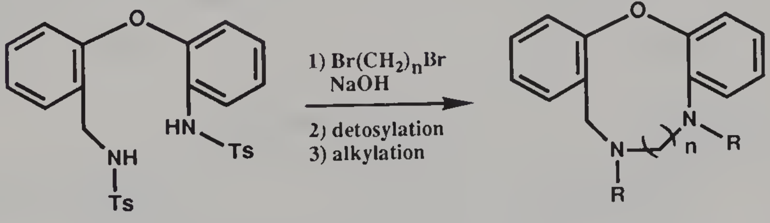


Some aromatic bis-*N*-tosylamides have been used to prepare certain dibenzodiaza-crowns. The bis(2-*N*-tosylaminophenyl)alkyl ethers were reacted with an α,ω-dibromide or ditosylate to form 10- to 13-membered heterocyclic systems (method V-8) (Glinka and Walczynski, 1986; Glinka et al., 1985). The yields were more than 90% when a ditosylate ester was used. Condensation of the sodium salt 2-tosylaminophenyl 2-(tosylaminomethyl)phenyl ether with dibromomethane ($n = 1$) gave a dibenzodiaza-9-crown-3 ligand (method V-9) (Glinka, 1982). The *N*,*N*′-ditosylated product (R = Ts) was isolated in an 80% yield, but the detosylated macrocycle could not be isolated (92% sulfuric acid at 80–90°C). Similar reactions of *N*,*N*′-trifluoromethanesulfonyl-2,2′-diamino-1,1′-binaphthyl with the ditosylate ester of pentaethylene glycol gave the binaphthyl-containing diaza-crown compounds (method V-10) (Cram, 1977).

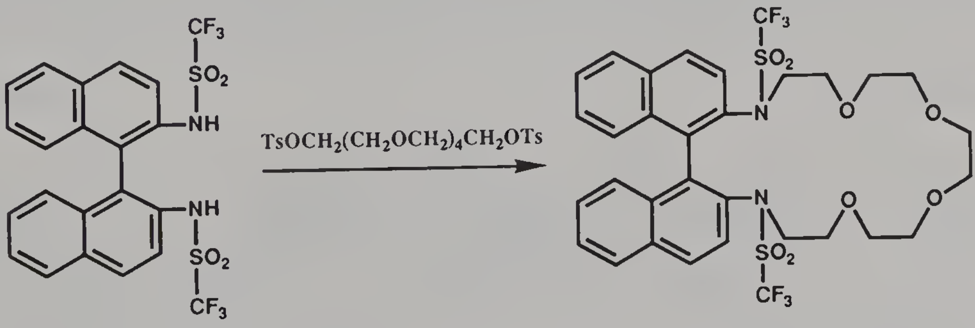
Method V-8



Method V-9

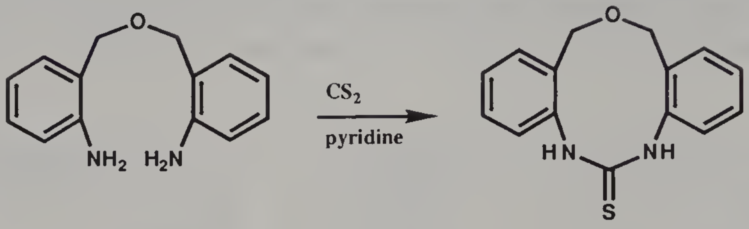


Method V-10



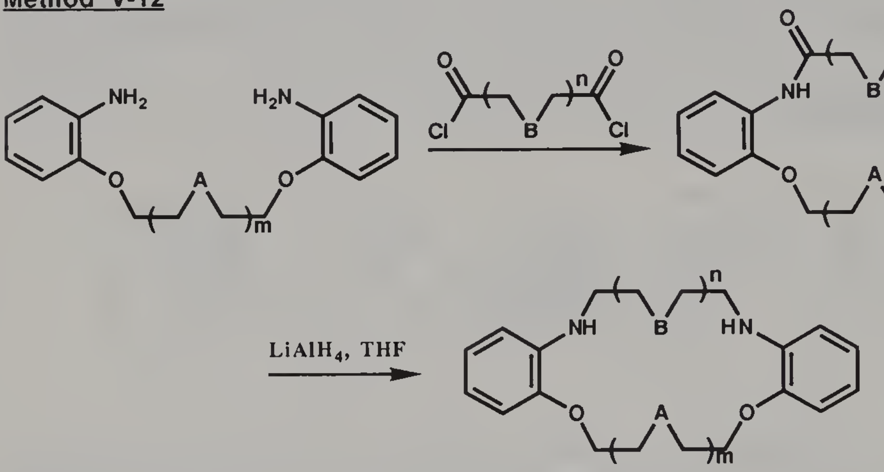
A thiourea-containing dibenzodiaza-crown was prepared by treating 2,2′-diaminobenzyl ether with carbon disulfide using iodine as the catalyst (method V-11) (Glinka and Piatkowska, 1984).

Method V-11



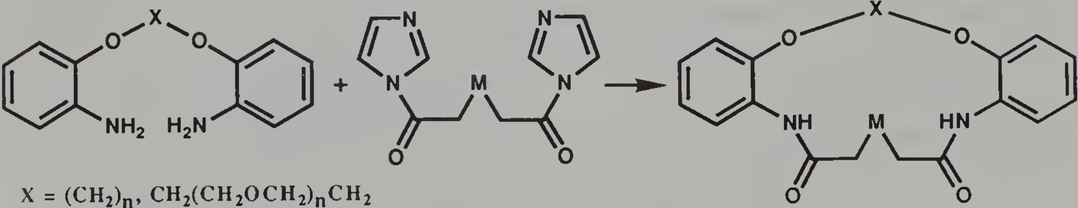
Lockhart and Thompson (1977) prepared a dibenzodiaza-crown by treating triglycolyl dichloride ($n = 2$) with a bis(aromatic amine) followed by reduction (method V-12). This method, using the Stetter bis-amide synthesis for ring closure, has been used by others for the preparation of dibenzodiaza-crowns (Formanovskii and Murakhovskaya, 1985; Formanovskii et al., 1988, 1989; Markovich et al., 1983). Biernat and coworkers have prepared a series of dibenzodiaza-crowns by methods V-12 (above) and V-13 (below), except that some of their macrocycles contained propylene bridges and they used dichlorides as well as activated diacid derivatives as starting materials (Biernat and Luboch, 1984; Biernat et al., 1979). The bis-imidazolides shown in method V-13 are reactive acylating agents. They were prepared from the acids, imidazole, and phenyldichlorophosphate.

Method V-12



A = O, CH_2, NTs
B = O, CH_2

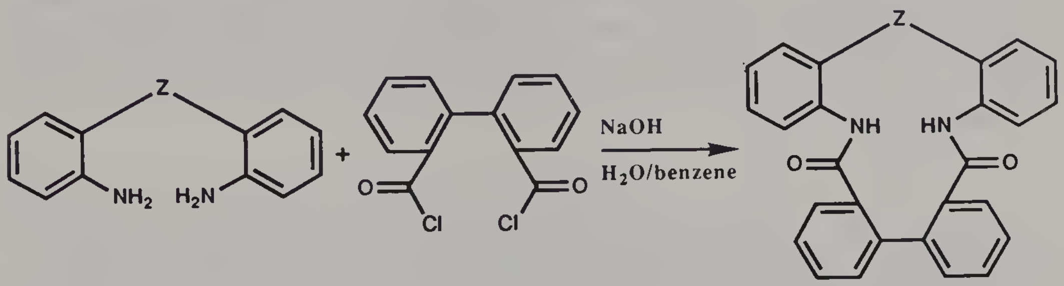
Method V-13



X = $(CH_2)_n$, $CH_2(CH_2OCH_2)_nCH_2$
M = O, NCH_3

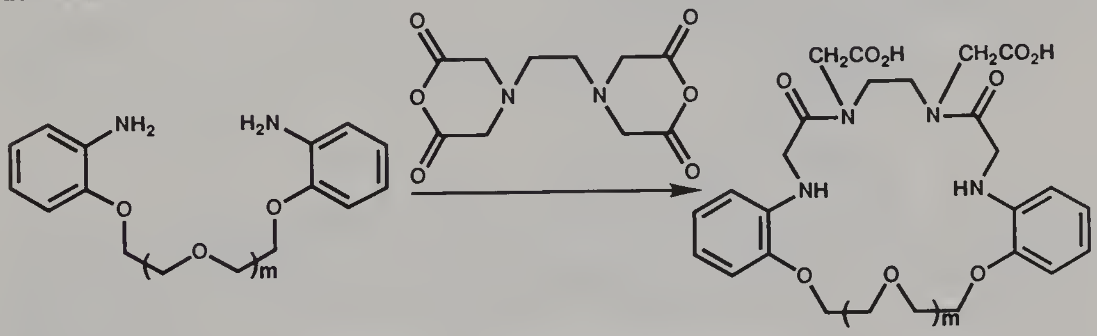
Tetrabenzodiaza-crowns were prepared by the reaction of a bis-aniline with 2,2′-biphenyldicarboxylyl dichloride in a two-phase water–benzene mixture (method V-14) (Glinka et al., 1988). The cyclic diamides could be reduced with lithium aluminum hydride to the diaza-crown.

Method V-14



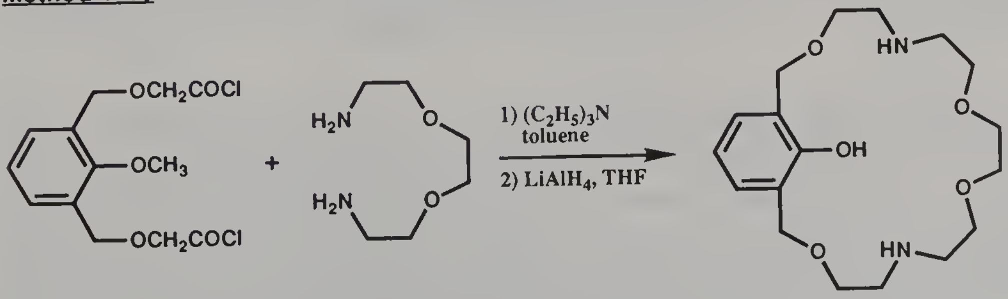
Dibenzotetraaza-crowns containing *N*-acetic acid substituents have been prepared using ethylenediaminetetraacetic dianhydride as a starting material (method V-15) (Qin, 1986). The cyclic diamides were formed in yields of about 50%.

Method V-15



The reaction of an anisole-containing diacid dichloride with a diamine produced a methoxy-substituted macrocyclic bis-amide (method V-16) (Czech et al., 1988). The amide functions were reduced by $LiAlH_4$ and, surprisingly,

Method V-16

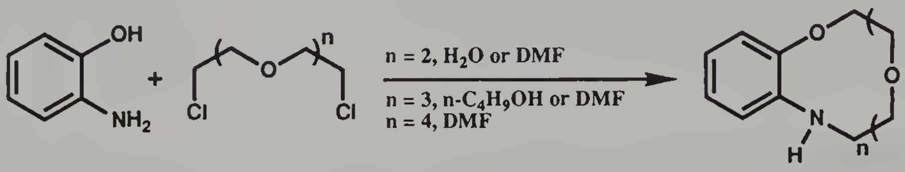


the methoxy group was hydrolyzed in the same step as shown.

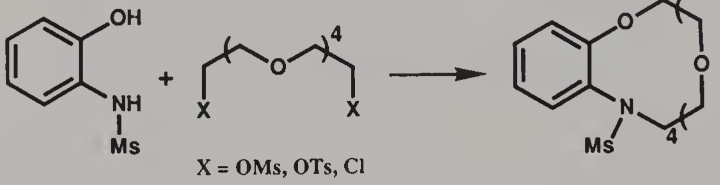
F. RING CLOSURE TO FORM ONE PHENOLIC O—C BOND AND ONE ANILINIC N—C BOND BY A 1:1 CYCLIZATION OF *o*-HYDROXYANILINE WITH A DIHALIDE OR DITOSYLATE ESTER

A few benzoaza-crowns have been prepared by reacting *o*-hydroxyaniline with a dichloroether (method W-1) (Lockhart et al., 1973; Pedersen and Bromels, 1974, 1977). This reaction required DMF as a solvent for the preparation of all macrocycles (n = 2, 3 or 4), although water or 1-butanol could be used in some cases. Only *N*-(2-hydroxyphenyl)aza-12-crown-4 was obtained in water where n = 3. Högberg and Cram (1975) obtained a similar macrocyclic product in a 32% yield when treating *N*-mesyl-*o*-hydroxyaniline with a dichloroether (method W-2).

Method W-1



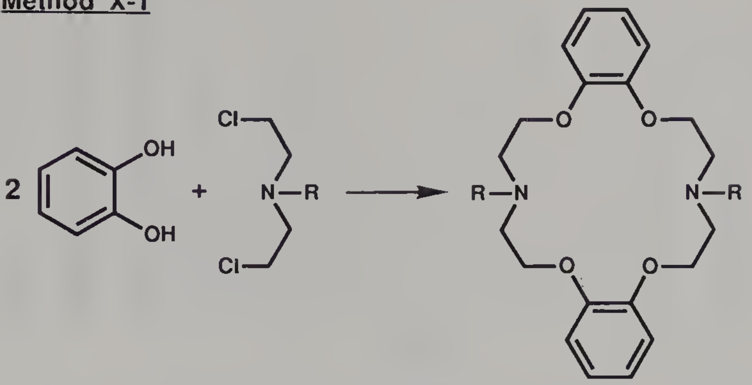
Method W-2



G. RING CLOSURE TO FORM A DIBENZOAZA-CROWN CONTAINING ANY COMBINATION OF FOUR PHENOLIC O—C AND ANILINIC N—C BONDS BY A 2:2 CYCLIZATION OF *o*-DISUBSTITUTED (HYDROXY AND/OR AMINO) BENZENE WITH A DIHALIDE OR DITOSYLATE ESTER

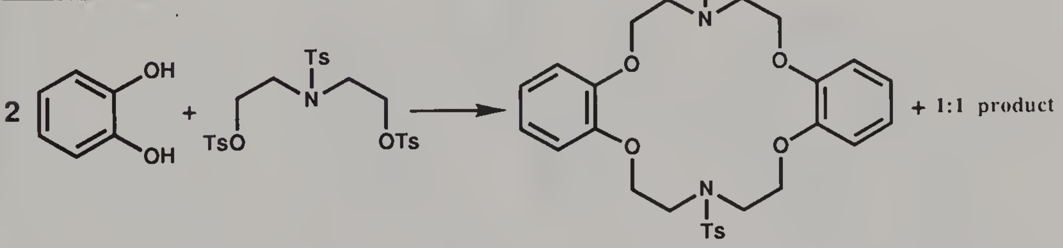
In general, rigid building blocks cause 2:2, 3:3, and higher-order cyclizations. This is especially true with *m*- and *p*-disubstituted aromatic compounds. *o*-Disubstituted benzene, on the other hand, can give 1:1 cyclizations as shown in methods W-1 and W-2 above. Catechol, in contrast to *o*-hydroxyaniline, gave mainly the 2:2 cyclization products when treated with various *N*-substituted bis(2-chloroethyl)amines (method X-1) (Degutis and Medekshene, 1982; Wu and Song, 1986). This is an example of preparing a

Method X-1



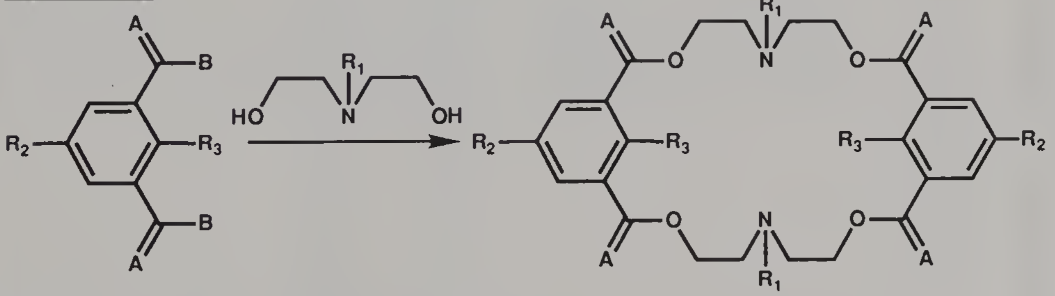
dibenzodiaza-crown by the formation of four C—O bonds. The yields of these 2:2 cyclization reactions were 10–36%. No benzoaza-9-crown-3 ligands, the 1:1 cyclization products, were observed. Other derivatives of the dibenzodiaza-crowns were produced by the method X-1 pathway (Wu and Song, 1986). Högberg and Cram (1975) observed some 1:1 cyclization products when they prepared similar dibenzodiaza-crowns using the ditosylate derivative of *N*-tosyldiethanolamine (method X-2).

Method X-2



Both isophthaloyl dichloride and α,α′-dibromo-*m*-xylene gave only dibenzodiaza-crowns, the 2:2 cyclization products, when treated with *N*-substituted diethanolamine (method X-3) (He et al., 1986; Johnson et al., 1985; Zhang et al., 1983).

Method X-3

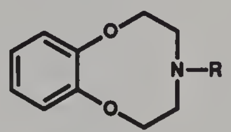


A = O, H_2; B = Cl, Br;
R_1 = alkyl, Ts; R_2 = H, Cl, CH_3; R_3 = H, OCH_3

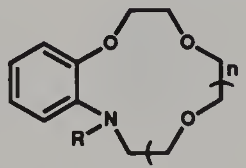
A listing of benzoaza-crown macrocycles follows. The tables are organized by monobenzo units (Tables 8.1–8.3), dibenzo units (Tables 8.4–8.10), polybenzo or naphtho units (Table 8.11), ring size (each table) and number of ring nitrogen atoms (each table).

H. TABLES OF COMPOUNDS

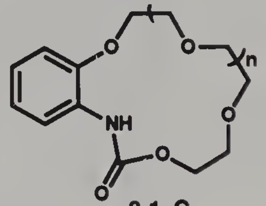
TABLE 8.1. BENZOMONOAZA-CROWN MACROCYCLES



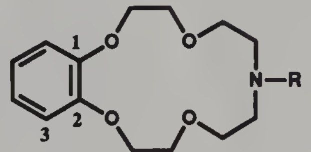
8.1 A



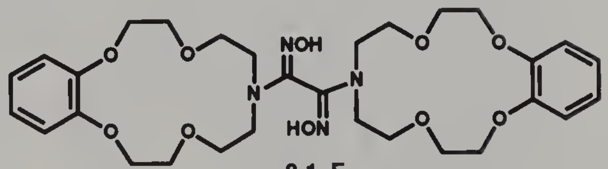
8.1 B



8.1 C



8.1 D



8.1 E

Structure	R	n	Other Substituents	Method (from R,n)	Yield (%)	References
8.1 A	H			T-2	50	Högberg and Cram, 1975
	Ts			T-2	35	Högberg and Cram, 1975
8.1 B	H	1		W-1		Blackborow et al., 1975
				W-1		Lockhart et al., 1973
	H	1	2-($N{=}NC_6H_4$-4-NO_2)		38	Markovich et al., 1983

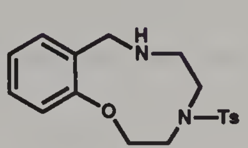
H	2		W-1		Blackborow et al., 1975
			W-1		Lockhart et al., 1973
			W-1		Pedersen and Bromels, 1974
H	2	1 or 2 - NO	(H)		Pedersen and Bromels, 1974
C_3H_7	2		(H,2)		Lockhart and Thompson, 1977
$Br(CH_2)_3$-	2		(H,2)		Lockhart and Thompson, 1977
$C_2H_5O(CH_2)_3$-	2		(H,2)		Lockhart and Thompson, 1977
$HO_2C(CH_2)_2C(O)$-	2		(H,2)		Lockhart and Thompson, 1977
$Br(CH_2)_2C(O)$-	2		(H,2)		Lockhart and Thompson, 1977
H	3		W-1		Blackborow et al., 1975
			W-1		Lockhart and Thompson,1977
H	3		W-1		Pedersen and Bromels, 1974
Ms	3		W-2	32	Högberg and Cram, 1975
H	4		W-1		Blackborow et al., 1975
			W-1		Lockhart and Thompson, 1977
H	5		W-1		Blackborow et al., 1975
			W-1		Lockhart and Thompson, 1977
H	6		W-1		Blackborow et al., 1975

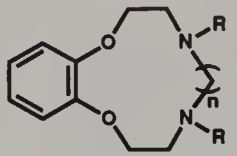
TABLE 8.1. (*Continued*)

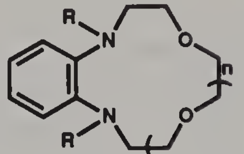
Structure	R	n	Other Substituents	Method (from R,n)	Yield (%)	References
8.1 C		1			35	Masuyama et al., 1985
		2			50	Masuyama et al., 1985
8.1 D	H			S-2		Högberg and Cram, 1975
				U-1	5	Lu and Wu, 1985
				S-2	21	McLain, 1986
				S-2	36	Wu and Lu, 1986
	CH_2=CHC(O)-			(H)		Zeng et al., 1988
	allyl			[CH_2=CHC(O)]		Wu and Lu, 1990 Zeng et al., 1988
	$CH_3O(CH_2)_2$-			(H)		Wu and Lu, 1986, 1990
	n-C_4H_9					Wu and Lu, 1990
	$C_2H_5O(CH_2)_2$-					Wu and Lu, 1990
	i-C_4H_9C(O)-			(H)		Zeng et al., 1988
	i-$C_4H_9CH_2$-			[i-C_4H_9C(O)]		Wu and Lu, 1990 Zeng et al., 1988
	$C_4H_9O(CH_2)_2$-			(H)		Wu and Lu, 1986, 1990

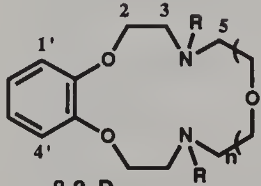
	$CH_3(OCH_2CH_2)_2$-		(H)		Wu and Lu, 1986, 1990
	$C_2H_5(OCH_2CH_2)_2$				Wu and Lu, 1990
	$C_6H_5C(O)$-		(H)		Zeng et al., 1988
	$C_6H_5CH_2$-		$[C_6H_5C(O)]$		Wu and Lu, 1990
					Zeng et al., 1988
	$C_6H_5CH_2$-	5-HC(O)			Zhilina et al., 1989
	Ts		U-1	36	Högberg and Cram, 1975
	Ts	5-HC(O)			Zhilina et al., 1989
	n-C_7H_{15}				Wu and Lu, 1990
	2-HO-3-$HOCH_2$-5-$BrC_6H_2CH_2$-		(H)	50	Chen et al., 1988
	n-$C_4H_9(OCH_2CH_2)_2$-				Wu and Lu, 1990
	2-HO-3-$HOCH_2$-5-$CH_3C_6H_2CH_2$-		(H)		Chen et al., 1988
	$(C_6H_5)_2PCH_2$-		(H)	92	McLain, 1986
	ZProLeuGlyAhx				Kulikov et al., 1990
	Boc-L-Pro-D-Leu				Lukyanenko et al., 1990
		4,5-$(Br)_2$			Ahsen et al., 1989
8.1 E		4,5-$(Br)_2$			Musluoglu et al., 1990

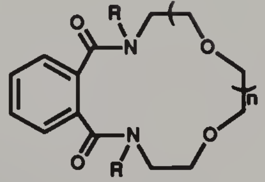
TABLE 8.2. BENZODIAZA-CROWN MACROCYCLES

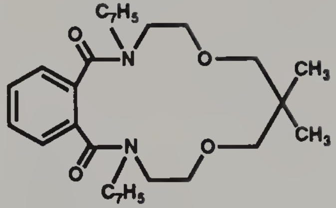

8.2 A

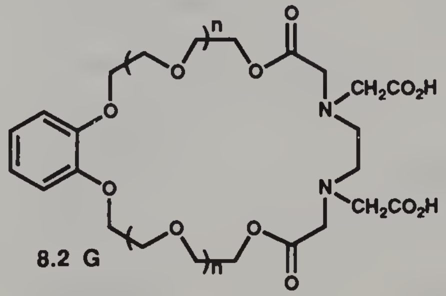

8.2 B

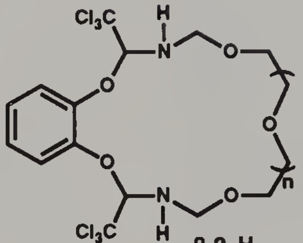

8.2 C

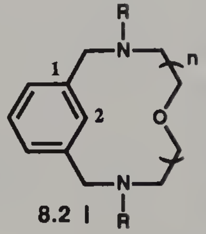

8.2 D

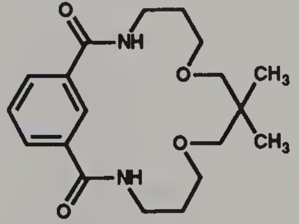

8.2 E

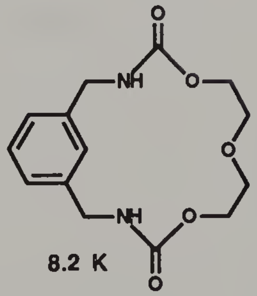

8.2 F

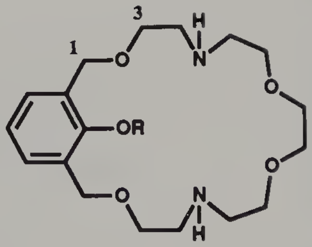

8.2 G

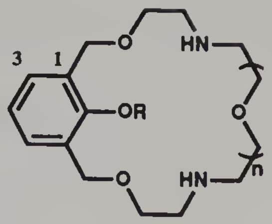

8.2 H


8.2 I

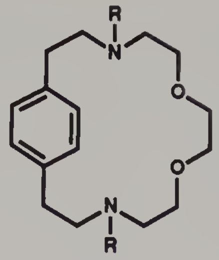

8.2 J


8.2 K

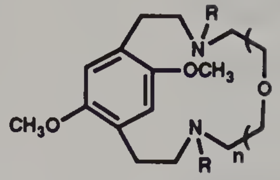

8.2 L



8.2 M



8.2 N



8.2 O

Structure	R	n	Other Substituents	Method (or from R,n)	Yield (%)	References
8.2 A					23	Mikiciuk-Olasik, 1989
8.2 B	CH_3	4		U-7		Hodgkinson et al., 1976b
	$C_2H_5O_2C$-	4		U-7		Hodgkinson et al., 1976b
	CH_3	5		U-7		Hodgkinson et al., 1976b
	$C_2H_5O_2C$-	5		U-7		Hodgkinson et al., 1976b
	CH_3	6		U-7		Hodgkinson et al., 1976b
	$C_2H_5O_2C$-	6		U-7		Hodgkinson et al., 1976b
	CH_3	7		U-7		Hodgkinson et al., 1976b
	$C_2H_5O_2C$-	7		U-7		Hodgkinson et al., 1976b

TABLE 8.2. (*Continued*)

Structure	R	n	Other Substituents	Method (or from R,n)	Yield (%)	References
	CH_3	8		U-7		Hodgkinson et al., 1976b
	$C_2H_5O_2C$-	8		U-7		Hodgkinson et al., 1976b
8.2 C	H	0		V-1	48	Mikiciuk-Olasik and Kotelko, 1984b
	H	0	8,12-$(O)_2$	V-3	62	Mikiciuk-Olasik and Kotelko, 1984b
	CH_3	0		V-1	23	Glinka et al., 1977
	CH_3O_2C-	0		(H)	25	Mikiciuk-Olasik and Kotelko, 1984b
				V-1	15	Mikiciuk-Olasik and Kotelko, 1984b
	C_2H_5	0		V-1	32	Glinka et al., 1977
	Ts	0		V-1	95	Mikiciuk-Olasik and Kotelko, 1984b
	H	1		V-1		Blackborow et al., 1975
				V-1		Lockhart et al., 1973
	Ts	1		V-1	41	Mikiciuk-Olasik and Kotelko, 1984b
	H	2		V-1		Blackborow et al., 1975
				V-1		Lockhart et al., 1973

	H	2	3-CH_3	V-1		Blackborow et al., 1975
				(H,2)		Lockhart and Thompson, 1977
	Ms	3		V-2	5	Högberg and Cram, 1975
8.2 D	CH_3	1			95	Jurczak and Ostaszewski, 1988
				U-7	77	Hodgkinson and Sutherland, 1979
				V-7		Hodgkinson et al., 1976a
				U-23	69	Ostaszewski et al., 1988
	$(CH_3)_2$-	1		U-21	68 (overall)	Jurczak et al., 1989
	$C_2H_5O_2C$-	1		U-7	55	Hodgkinson and Sutherland, 1979
				U-7		Hodgkinson et al., 1976a
		2		U-7	50	Hodgkinson et al., 1979
	$C_6H_5CH_2O_2C$-	1		U-7	55	Hodgkinson and Sutherland, 1979
	Ts	1		U-23	89	Ostaszewski et al., 1988
	H	2				Blasius and Maurer, 1977
						Iwachido et al., 1977
	H	2	3,14-$(O)_2$			Blasius and Maurer, 1977
	H	2	2,3-Br_2			Kalinin and Timoshenko, 1990
	H	2	2,3-$(NO_2)_2$			Kalinin and Timoshenko, 1990

TABLE 8.2. (*Continued*)

Structure	R	n	Other Substituents	Method (or from R,n)	Yield (%)	References
	H	2	2,3-$(NH_2)_2$			Kalinin and Timoshenko, 1990
	CH_3	2		U-23	58	Ostaszewski et al., 1988
				U-7	96	Hodgkinson et al., 1979
	$(CH_3)_2$-			U-21	63 (overall)	Jurczak et al., 1989
	$CH_3O(CH_2)_2$-	2			45	Tsukube et al., 1989
	$C_2H_5O_2CCH_2$-	2			80	Tsukube et al., 1989
	$C_2H_5O_2C(CH_2)_2$-	2			60	Tsukube et al., 1989
	$C_2H_5O_2C(CH_2)_3$-	2			60	Tsukube et al., 1989
	$(C_2H_5)_2NC(O)CH_2$-	2			60	Tsukube et al., 1989
	Ts	2		U-23	72	Ostaszewski et al., 1988
8.2 E	H	0		U-18	10	Anikin et al., 1982
				U-18	10	Ganin et al., 1981
	H	1		U-18	38	Anikin et al., 1982
				U-18	38	Ganin et al., 1981

	H	2	U-18	7	Anikin et al., 1982
			U-18	7	Ganin et al., 1981
	CH_3	2		37	Petranek and Ryba, 1980
	H	3	U-18	9	Anikin et al., 1982
			U-18	9	Ganin et al., 1981
8.2 F	C_7H_{15}		U-19	57	Attiyat et al., 1987
8.2 G		0	S-3	24	Qin, 1986
		1	S-3	22	Qin, 1986
8.2 H		1		15	Kudrya et al., 1979
		2		11	Kudrya et al., 1979
		3		3	Kudrya et al., 1979
8.2 I	CH_3	1	U-8	81	Leigh and Sutherland, 1979
	$C_2H_5O_2C$-	1	U-8	54	Leigh and Sutherland, 1979
	H	2	U-9	100	Hodgkinson et al., 1976b Leigh and Sutherland, 1979

TABLE 8.2. (*Continued*)

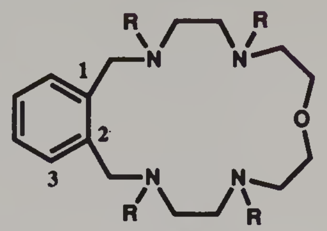
Structure	R	n	Other Substituents	Method (or from R,n)	Yield (%)	References
	CH_3	2		U-8	93	Leigh and Sutherland, 1979
	$ClCH_2C(O)$-	2		(H)	59	Leigh and Sutherland, 1979
	$HO(CH_2)_2$-	2		(H)	96	Hodgkinson et al., 1976b
				(H)		Leigh and Sutherland, 1979
	$HO(CH_2)_2$-	2	5-Cl			Wu et al., 1988
	$HO(CH_2)_2$-	2	5-CH_3			Wu et al., 1988
	$C_2H_5O_2C$-	2		U-8	41	Leigh and Sutherland, 1979
	$CH_3NHC(O)CH_2$-	2		(H)	97	Leigh and Sutherland, 1979
	$C_2H_5O_2CCH_2$-	2		(H)	85	Leigh and Sutherland, 1979
	$(CH_3)_2NC(O)CH_2$-	2		(H)	58	Hodgkinson et al., 1976b
				(H)		Leigh and Sutherland, 1979
	2-pyridinyl-CH_2	2		(H)	55	Hodgkinson et al., 1976b
				(H)		Leigh and Sutherland, 1979
	$C_6H_5CH_2O_2C$-	2		U-8	31	Leigh and Sutherland, 1979
				U-9	32	Leigh and Sutherland, 1979

	$CH_3O_2CCH(i\text{-}C_3H_7)\text{-}NHC(O)CH_2\text{-}$	2		(H)	80	Leigh and Sutherland, 1979
	$CH_3(CH_2)_7CO\text{-}$	2		(H)	92	Leigh and Sutherland, 1979
	$CH_3(CH_2)_8\text{-}$	2		$[CH_3(CH_2)_7\text{-}C(O)]$	84	Leigh and Sutherland, 1979
	phthalimido$CH_2C(O)$-	2		(H)	57	Leigh and Sutherland, 1979
	phthalimidoethyl	2			69	Leigh and Sutherland, 1979
	CH_3	3		U-8	77	Leigh and Sutherland, 1979
	$C_2H_5O_2C\text{-}$	3		U-8	29	Leigh and Sutherland, 1979
	Ts	4			46	Vriesema et al., 1984
8.2 J					91	Nagao et al., 1981
8.2 K					66	Buhleier et al., 1978
8.2 L	H			V-16	79	Czech et al., 1988
	CH_3		$4,15\text{-}(O)_2$	V-16	40	Czech et al., 1988
8.2 M	H	1	5-Cl			Wu et al., 1988
	H	1	$5\text{-}CH_3$			Wu et al., 1988

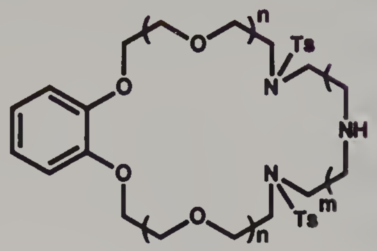
TABLE 8.2. (*Continued*)

Structure	R	n	Other Substituents	Method (or from R,n)	Yield (%)	References
	CH_3	0	5-Cl			Wu et al., 1988
	CH_3	0	5-CH_3			Wu et al., 1988
	CH_3	1	5-Cl			Wu et al., 1988
	CH_3	1	5-CH_3			Wu et al., 1988
	CH_3	2	5-Cl			Wu et al., 1988
	CH_3	2	5-CH_3			Wu et al., 1988
8.2 N	CH_3			U-10	94	Beckford et al., 1978
	$C_2H_5O_2C$-			U-10	20	Beckford et al., 1978
8.2 O	CH_3	2		U-8	99	Pearson et al., 1979
	$C_2H_5O_2C$-	2		U-8		Pearson et al., 1979
	CH_3	3		U-8	99	Pearson et al., 1979
	$C_2H_5O_2C$-	3		U-8		Pearson et al., 1979

TABLE 8.3. BENZOTRIAZA-(OR TETRAAZA)-CROWN MACROCYCLES



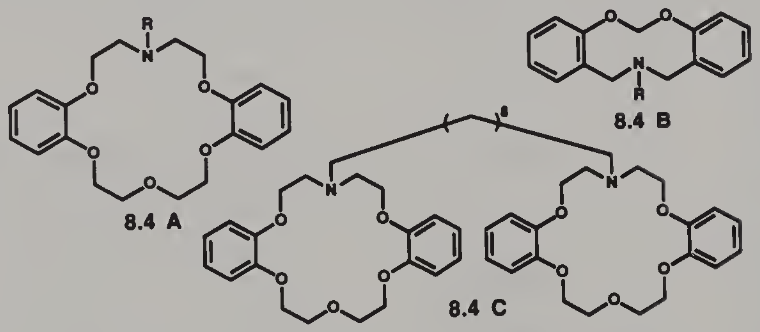
8.3 A



8.3 B

Structure	R	Other Substituents	n	m	Method (R =)	Yield (%)	References
8.3 A	H	5-NO_2			(Ts,5-NO_2)		Parker and Millican, 1987
	H	5-NH_2			(H, 5-NO_2)		Parker and Millican, 1987
	Ts	5-NO_2					Parker and Millican, 1987
	HO_2CCH_2-	5-NH_2			(H, 5-NH_2)		Parker and Millican, 1987
8.3 B			1	1	U-3	75	He and Wu, 1984
			2	1	U-3	71	He and Wu, 1984
			3	1	U-3	65	He and Wu, 1984
			1	2	U-3	64	He and Wu, 1984
			2	2	U-3	55	He and Wu, 1984
			3	2	U-3	46	He and Wu, 1984

TABLE 8.4. DIBENZOMONOAZA-CROWN MACROCYCLES


8.4 A

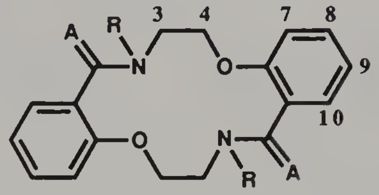
8.4 B

8.4 C

R Formula Index	 Structure	Method (R =)	Yield (%)	References
Macrocycle 8.4 A				
H	H	T-1	22	Pedersen and Bromels, 1974
		T-1	35	Högberg and Cram, 1975
CH_3	CH_3	T-1	2	Weber and Vögtle, 1976
C_2H_3O	$CH_3C(O)$-	(H)		Pedersen and Bromels, 1974
C_2H_5	C_2H_5	(H)		Pedersen and Bromels, 1974

C_3H_5	allyl	T-1	25	Wu and Song, 1986
C_3H_7O	$CH_3O(CH_2)_2$-	T-1	25	Wu and Song, 1986
C_4H_9	n-C_4H_9	T-1	25	Wu and Song, 1986
C_4H_9O	$C_2H_5O(CH_2)_2$-	T-1	25	Wu and Song, 1986
C_5H_{11}	C_5H_{11}	T-1	25	Wu and Song, 1986
$C_5H_{11}O_2$	$CH_3(OCH_2CH_2)_2$-	T-1	25	Wu and Song, 1986
$C_6H_{13}O$	$C_4H_9O(CH_2)_2$-	T-1	25	Wu and Song, 1986
C_7H_7	$C_6H_5CH_2$-	T-1	25	Wu and Song, 1986
$C_7H_7O_2S$	Ts	T-1	34	Högberg and Cram, 1975
C_8H_{17}	C_8H_{17}	(H)	34	Pedersen and Bromels, 1974
$C_8H_{17}O_2$	$C_4H_9(OCH_2CH_2)_2$-	T-1	25	Wu and Song, 1986
Macrocycle 8.4 B				
CH_3	CH_3			Ollis et al., 1974
C_7H_7	$C_6H_5CH_2$-			Ollis et al., 1974
Macrocycle 8.4 C				Pedersen and Bromels, 1974

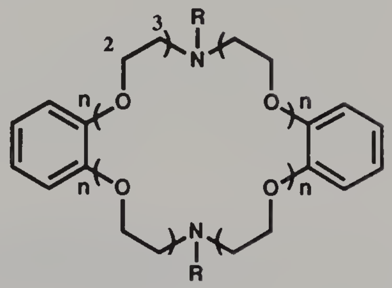
TABLE 8.5. DIBENZODIAZA-14-CROWN-4 MACROCYCLES



R	A	Other Substituents	Method	Yield (%)	References
H	H_2		V-17	65	Martin et al., 1985
			T-6	82-84	Schultz et al., 1988
H	H_2	$3,14\text{-}(CH_3)_2$	T-5	75	Schultz et al., 1988
H	H_2	$3,14\text{-}(\underline{i}C_3H_7)_2$	T-5	70	Schultz et al., 1988
CH_3	H_2	$3,14\text{-}(\underline{i}C_3H_4)_2$		40	Schultz et al., 1988

$CH_3C(O)$-	H_2			70	Schultz et al., 1988
H	O		T-5	62	Schultz et al., 1988
H	O	$3,14-(CH_3)_2$	T-5	69	Schultz et al., 1988
H	O	$3-\underline{i}-C_3H_7$	T-6	40	Schultz et al., 1988
H	O	$3-\underline{i}-C_3H_7;14-CH_3$	T-6	41	Schultz et al., 1988
H	O	$3,14-(\underline{i}-C_3H_7)_2$	T-5	72	Schultz et al., 1988
H	O	$3,14-(s-C_4H_9)_2$	T-5	60	Schultz et al., 1988
H	O	$3-(CH_2)_2SCH_3$	T-6	45	Schultz et al., 1988
H	O	$3,14-[(CH_2)_2SCH_3]_2$	T-5	57	Schultz et al., 1988
H	O	$3,14-(CH_2SCH_2C_6H_5)_2$	T-5	70	Schultz et al., 1988
H	O	$3-CH_3;4-C_6H_5$	T-6	45	Schultz et al., 1988
H	O	$3,14-(CH_3)_2;4,15-(C_6H_5)_2$	T-6	62	Schultz et al., 1988

TABLE 8.6. DIBENZODIAZA-18-CROWN-6 OR -30-CROWN-10 MACROCYCLES



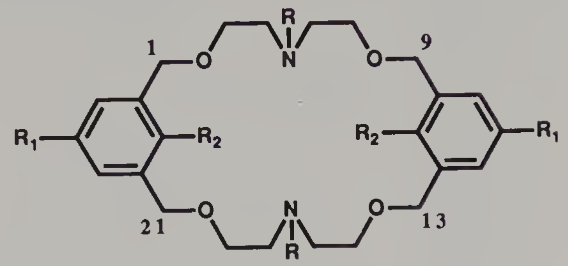
R		Other		Method	Yield	References
Formula Index	Structure	Substituents	n	(R)	(%)	
H	H		1	U-6		Hodgkinson et al., 1979
				X-2	45	Högberg and Cram, 1975
				($C_8H_7O_2$)	90	Pedersen and Bromels, 1977
				U-6	80	Pedersen and Bromels, 1977
H	H		2	T-4	66	Anelli et al., 1988
CH_3	CH_3		1		92	Hodgkinson et al., 1979
				(H)	50	Jurczak and Ostaszewski, 1988
				U-22	51	Ostaszewski et al., 1988
CH_3	CH_3		2	T-4	76	Anelli et al., 1988

C_3H_5	allyl	1	X-1	10	Wu and Song, 1986
$C_3H_5O_2$	$C_2H_5O_2C$-	2	T-4	65	Anelli et al., 1988
C_3H_7O	$CH_3O(CH_2)_2$-	1	X-1	10	Wu and Song, 1986
$C_4H_7O_2$	$C_2H_5O_2CCH_2$-	2	T-4	60	Anelli et al., 1988
C_4H_9	n-C_4H_9	1	X-1	10	Wu and Song, 1986
C_4H_9O	$C_2H_5O(CH_2)_2$-	1	X-1	10	Wu and Song, 1986
C_5H_{11}	C_5H_{11}	1	X-1	10	Wu and Song, 1986
$C_5H_{11}O_2$	$CH_3(OCH_2CH_2)_2$-	1	X-1	10	Wu and Song, 1986
C_6H_5	C_6H_5	1	X-1	10	Degutis and Medekshene, 1982
$C_6H_{13}O$	$C_4H_9O(CH_2)_2$-	1	X-1	10	Wu and Song, 1986
C_7H_7	$C_6H_5CH_2$-	1		34	Degutis and Medekshene, 1982
			U-6		Pedersen and Bromels, 1974
			U-6		Pedersen and Bromels, 1977
C_7H_7	$C_6H_5CH_2$-	2	T-4	64	Anelli et al., 1988
C_7H_7O	4-$CH_3OC_6H_4$-	1	U-2	64	Degutis and Medekshene, 1982
			X-1	36	Degutis and Medekshene, 1982
$C_7H_7O_2S$	Ts	1	X-2	10	Högberg and Cram, 1975

TABLE 8.6. (*Continued*)

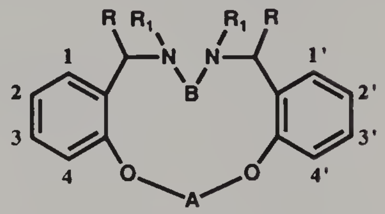
R		Other		Method	Yield	References
Formula Index	Structure	Substituents	n	(R)	(%)	
				U-22	62	Ostaszewski et al., 1988
$C_7H_7O_2S$	Ts		2	T-4	23	Anelli et al., 1988
$C_8H_7O_2$	$C_6H_5CH_2O_2C$-		1	U-13	50	Hodgkinson et al., 1979
C_8H_9O	4-$CH_3OC_6H_4CH_2$-		2	T-4	71	Anelli et al., 1988
$C_8H_{17}O_2$	$C_4H_9(OCH_2CH_2)_2$-		1	X-1	10	Wu and Song, 1986

TABLE 8.7. DIBENZODIAZA-CROWN MACROCYCLES WITH *m*-BENZO GROUPS



R	R_1	R_2	Other Substituents	Method	Yield (%)	References
CH_3	H	H		X-3	11	Johnson et al., 1985
CH_3	CH_3	CH_3O		X-3		He et al., 1986
C_2H_5	Cl	CH_3O		X-3	7	He et al., 1986
n-C_4H_9	CH_3	CH_3O		X-3	3	He et al., 1986
n-C_4H_9	Cl	CH_3O		X-3	6	He et al., 1986
C_8H_{17}	CH_3	CH_3O		X-3	8	He et al., 1986
C_8H_{17}	Cl	CH_3O		X-3	7	He et al., 1986
Ts	H	CH_3O	1,9,13,21-$(O)_4$	X-3	4	Zhang et al., 1983
Ts	CH_3	CH_3O		X-3	8	He et al., 1986
Ts	Cl	CH_3O		X-3		He et al., 1986

TABLE 8.8. DIBENZOTRIAZA-CROWN MACROCYCLES WITH AZA GROUPS TWO ATOMS REMOVED FROM THE BENZO UNITS



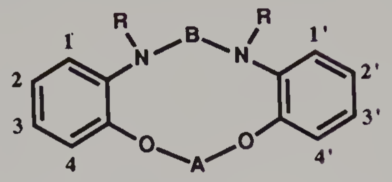
A	B	R	R_1	Other Substituents	Method	Yield (%)	References
$-CH_2-$	$-(CH_2)_2O(CH_2)_2-$	H	H		U-14	10	Baldwin et al., 1987
$-CH_2-$	$-(CH_2)_2NH(CH_2)_2-$	H	H			45	Baldwin et al., 1987
$-(CH_2)_2-$	$-(CH_2)_2-$	H	H		U-14	30	Grimsley et al., 1977
						9	Morosanova et al., 1984
$-(CH_2)_2-$	$-CH_2CH(CH_3)-$	H	H		U-14		Ekstrom et al., 1980
$-(CH_2)_2-$	$-(CH_2)_3-$	H	H		U-14	90	Grimsley et al., 1977
$-(CH_2)_2-$	$-(CH_2)_3-$	H	H	$2,2'-(Br)_2$	U-14		Armstrong et al., 1978
$-(CH_2)_2-$	$-(CH_2)_3-$	H	H	$2,2'-(Cl)_2$	U-14	75	Grimsley et al., 1977
$-(CH_2)_2-$	$-(CH_2)_3-$	H	H	$4,4'-(OCH_3)_2$	U-14		Armstrong et al., 1978
$-(CH_2)_2-$	$-(CH_2)_3-$	H	CH_3		U-14		Armstrong et al., 1978
$-(CH_2)_2-$	$-(CH_2)_3-$	H	HO_2C-			70 (K complex)	Jide et al., 1990

$-(CH_2)_3-$	$-(CH_2)_2-$	H	H	U-14	46	Grimsley et al., 1977
$-(CH_2)_3-$	$-(CH_2)_3-$	H	H	U-14	40	Grimsley et al., 1977
$-(CH_2)_4-$	$-(CH_2)_3-$	H	H	U-14		Anderegg et al., 1980
$-(CH_2)_2-$	$-CH_2CHOHCH_2-$	H	H	U-14		Anderegg et al., 1980
$-(CH_2)_2-$	$-CH_2CHOHCH_2-$	H	CH_3	U-14		Armstrong et al., 1978
$-(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	H	H	U-14	60	Baldwin et al., 1987
				U-14		Adam et al., 1987b
$-(CH_2)_2-$	$-(CH_2)_2NH(CH_2)_2-$	H	H	U-14	40	Adam et al., 1981a, 1987b
				U-14		Chang et al., 1986
				U-14		Cho et al., 1989
$-(CH_2)_2-$	$-(CH_2)_2CHOH(CH_2)_2-$	H	H	U-16	20	Bailey et al., 1990
$-(CH_2)_2-$	$-(CH_2)_2N(CH_3)(CH_2)_2-$	H	CH_3			Adam et al., 1983
$-(CH_2)_2-$	$-(CH_2)_2NH(CH_2)_3-$	H	H	U-14	55	Adam et al., 1981a, 1983
$-(CH_2)_2-$	$-(CH_2)_2N(CH_2CO_2H)(CH_2)_2-$	H	HO_2C-		65 (salt)	Jide et al., 1990
$-(CH_2)_2-$	$-(CH_2)_2N(CH_2C_6H_5)(CH_2)_2-$	H	H			Lindoy, 1989
$-(CH_2)_2-$	$-(CH_2)_3NH(CH_2)_3-$	H	H	U-14		Adam et al., 1983
$-(CH_2)_2-$	$-(CH_2)_3N(CH_3)(CH_2)_3-$	H	H	U-14		Adam et al., 1983
$-(CH_2)_2-$	$-CH(CH_3)CH_2NHCH(CH_3)CH_2-$	H	H	U-14		Adam et al., 1987a
$-(CH_2)_2-$	$-CH(CH_3)CH_2NHCH_2CH(CH_3)-$	H	H	U-14	50	Adam et al., 1981a

TABLE 8.8. (*Continued*)

A	B	R	R_1	Other Substituents	Method	Yield (%)	References
$-(CH_2)_2-$	$-(CH_2)_2NH(CH_2)_4-$	H	H		U-14		Adam et al., 1983
$-(CH_2)_3-$	$-(CH_2)_2CHOH(CH_2)_2-$	H	H		U-16	10	Bailey et al., 1990
$-(CH_2)_4-$	$-(CH_2)_2CHOH(CH_2)_2-$	H	H		U-16	20	Bailey et al., 1990
$-(CH_2)_4-$	$-(CH_2)_2O(CH_2)_2-$	H	H		U-14	80	Baldwin et al., 1987
$-(CH_2)_4-$	$-(CH_2)_2NH(CH_2)_2-$	H	H		U-14	50	Baldwin et al., 1987
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2-$	H	H		U-14	58	Kodera et al., 1985
					U-14		Adam et al., 1983
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2-$	CH_3	H		U-14	96	Kodera et al., 1985
$-(CH_2)_2O(CH_2)_2-$	-C(=NOH)C(=NOH)-	H	H			47	ZongUr and Bekaroglu, 1984
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_3-$	H	H		U-14		Adam et al., 1983
					U-14	75	Kodera et al., 1985
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_3-$	CH_3	H		U-14	90	Kodera et al., 1985
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_3-$	H	HO_2C-			65 (salt)	Jide et al., 1990
$-CH_2(CH_2OCH_2)_2CH_2-$	$-(CH_2)_2-$	H	H		U-14		Kodera et al., 1985
$-CH_2(CH_2OCH_2)_2CH_2-$	$-(CH_2)_3-$	H	H		U-14		Kodera et al., 1985

TABLE 8.9. DIBENZO(DI-, TRI-, OR TETRA)AZA-CROWN MACROCYCLES WITH AZA GROUPS NEXT TO THE BENZO UNITS



A	B	R	Other Substituents	Method	Yield (%)	References
$-(CH_2)_2-$	$-(CH_2)_2-$	H		V-7	3,6	Biernat and Luboch, 1984
$-(CH_2)_2-$	$-(CH_2)_3-$	H		V-7	9	Biernat and Luboch, 1984
					96	Kossai et al., 1979
$-(CH_2)_2-$	$-(CH_2)_5-$	H		V-12	70	Formanovskii and Murakhovskaya, 1985
$-(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	H		V-12	84	Formanovskii and Murakhovskaya, 1985
$-(CH_2)_2-$	$-C(O)CH_2OCH_2C(O)-$	H		V-12	87	Formanovskii and Murakhovskaya, 1985
$-(CH_2)_2-$	$-C(O)(CH_2)_3C(O)-$	H		V-12	50	Formanovskii and Murakhovskaya, 1985
$-(CH_2)_3-$	$-(CH_2)_2-$	H		V-7	1,7	Biernat and Luboch, 1984
$-(CH_2)_3-$	$-(CH_2)_3-$	H			86	Behr and Breitmaier, 1978
				V-7	4	Biernat and Luboch, 1984

TABLE 8.9. (*Continued*)

A	B	R	Other Substituents	Method	Yield (%)	References
$-(CH_2)_3-$	$-CH_2CH(CH_3)CH_2-$	H			84	Adam et al., 1990
$-(CH_2)_3-$	$-(CH_2)_5-$	H		V-12	53	Formanovskii and Mikhura, 1990
$-(CH_2)_3-$	$-(CH_2)_2O(CH_2)_2-$	H		V-12	54	Formanovskii and Mikhura, 1990
$-(CH_2)_3-$	$-C(O)CH_2OCH_2C(O)-$	H		V-12	89	Formanovskii and Mikhura, 1990
$-(CH_2)_3-$	$-C(O)(CH_2)_3C(O)-$	H		V-12	68	Formanovskii and Mikhura, 1990
$(CH_2)_3-$	$-(CH_2)_2N(Ts)(CH_2)_2-$	H		V-12	28	Formanovskii and Mikhura, 1990
$-(CH_2)_3-$	$-C(O)CH_2N(Ts)CH_2C(O)-$	H		V-12	20	Formanovskii and Mikhura, 1990
$-(CH_2)_4-$	$-(CH_2)_5-$	H		V-12	50	Formanovskii and Mikhura, 1990
						Mikhura et al., 1990
$-(CH_2)_4-$	$-(CH_2)_2O(CH_2)_2-$	H		V-12	72	Formanovskii and Mikhura, 1990
						Mikhura et al., 1990
$-(CH_2)_4-$	$-C(O)CH_2OCH_2C(O)-$	H		V-12	81	Formanovskii and Mikhura, 1990

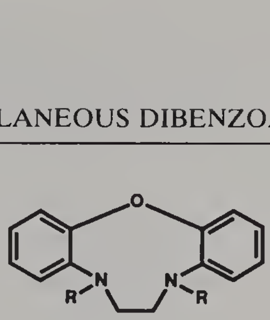
						Mikhura et al., 1990
$-(CH_2)_4-$	$-C(O)(CH_2)_3C(O)-$	H		V-12	84	Formanovskii and Mikhura, 1990
						Mikhura et al., 1990
$-(CH_2)_4-$	$-(CH_2)_2N(Ts)(CH_2)_2-$	H		V-12	78	Formanovskii and Mikhura, 1990
$-(CH_2)_4-$	$-C(O)CH_2N(Ts)CH_2C(O)-$	H		V-12	25	Formanovskii and Mikhura, 1990
$-(CH_2)_5-$	$-(CH_2)_5-$	H		V-12	77	Formanovskii et al., 1988
$-(CH_2)_5-$	$-(CH_2)_2O(CH_2)_2-$	H		V-12	74	Formanovskii et al., 1988
$-(CH_2)_5-$	$-C(O)CH_2OCH_2C(O)-$	H		V-12	88	Formanovskii et al., 1988
$-(CH_2)_5-$	$-C(O)(CH_2)_3C(O)-$	H		V-12	83	Formanovskii et al., 1988
$-(CH_2)_5-$	$-(CH_2)_2NH(CH_2)_2-$	H		V-12	71	Formanovskii et al., 1988
$-(CH_2)_5-$	$-(CH_2)_2N(Ts)(CH_2)_2-$	H		V-12	85	Formanovskii et al., 1988
$-(CH_2)_5-$	$-C(O)CH_2N(Ts)CH_2C(O)-$	H		V-12	92	Formanovskii et al., 1988
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2-$	H		V-7	8	Biernat and Luboch, 1984
				V-12	77	Markovich et al., 1983
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2-$	H	$3,3'-(4-NO_2C_6H_4N{=}N)_2$	V-12	11	Markovich et al., 1983
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_5-$	H		V-12	88	Formanovskii et al., 1988
$-(CH_2)_2O(CH_2)_2-$	$-C(O)C(O)-$	H		V-12	54	Markovich et al., 1983
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	H		V-7	6	Biernat and Luboch, 1984

TABLE 8.9. (*Continued*)

A	B	R	Other Substituents	Method	Yield (%)	References
				V-12		Formanovskii et al., 1988
				V-7	71	Högberg and Cram, 1975
				V-12	71	Markovich et al., 1983
						Pedersen and Bromels, 1977
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	H	$3,3'-(4-NO_2C_6H_4N{=}N)_2$	V-12	32	Markovich et al., 1983
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	$CH_3C(O)-$		V-6	10	Biernat et al., 1979
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	Ms		V-7	40	Högberg and Cram, 1975
$-(CH_2)_2O(CH_2)_2-$	$-C(O)(CH_2)_3C(O)-$	H		V-12	88	Formanovskii et al., 1988
$-(CH_2)_2O(CH_2)_2-$	$-C(O)CH_2OCH_2C(O)-$	H		V-13	41	Biernat et al., 1979
				V-12		Formanovskii et al., 1988
				V-12	40	Markovich et al., 1983
$-(CH_2)_2O(CH_2)_2-$	$-CH_2(CH_2OCH_2)_2CH_2-$	H		V-7	12	Biernat and Luboch, 1984
				V-12		Lockhart & Thompson, 1977
$-(CH_2)_2O(CH_2)_2-$	$-C(O)(CH_2OCH_2)_2C(O)-$	H		V-12	88	Lockhart & Thompson, 1977
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2NH(CH_2)_2-$	H				Cho et al., 1989
				V-12	67	Formanovskii et al., 1988
$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2N(Ts)(CH_2)_2-$	H		V-12	90	Formanovskii et al., 1988
-(CH)O(CH)-	-C(O)CH N(CH)CH C(O)-	H		V-13	10	Biernat et al., 1979

$-(CH_2)_2O(CH_2)_2-$	$-C(O)CH_2N(Ts)CH_2C(O)-$	H	V-12	78	Formanovskii et al., 1988
$-(CH_2)_2O(CH_2)_2-$	$-[C(O)CH_2N(CH_2CO_2H)CH_2]_2-$	H	V-15	55	Qin, 1986
$-CH_2(CH_2OCH_2)_2CH_2-$	$-(CH_2)_2-$	H	V-7	8	Biernat and Luboch, 1984
$-CH_2(CH_2OCH_2)_2CH_2-$	$-C(O)CH_2OCH_2C(O)-$	H	V-13	14	Biernat et al., 1979
$-CH_2(CH_2OCH_2)_2CH_2-$	$-[C(O)CH_2N(CH_2CO_2H)CH_2]_2-$	H	V-15	42	Qin, 1986
$-(CH_2)_2NH(CH_2)_2-$	$-(CH_2)_5-$	H	V-12	60	Formanovskii et al., 1988
$-(CH_2)_2NH(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	H	V-12	60	Formanovskii et al.,1988
			V-7	82	Högberg and Cram, 1975
$-(CH_2)_2NH(CH_2)_2-$	$-(CH_2)_2NH(CH_2)_2-$	H	V-12		Formanovskii et al., 1988
			V-7	30	Högberg and Cram, 1975
$-(CH_2)_2N(Ts)(CH_2)_2-$	$-(CH_2)_5-$	H	V-12	95	Formanovskii et al., 1988
$-(CH_2)_2N(Ts)(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	Ts	V-12	86	Formanovskii et al., 1988
			V-7	54	Högberg and Cram, 1975
$-(CH_2)_2N(Ts)(CH_2)_2-$	$-C(O)(CH_2)_3C(O)-$	H	V-12	90	Formanovskii et al., 1988
$-(CH_2)_2)N(Ts)(CH_2)_2-$	$-C(O)CH_2OCH_2C(O)-$	H	V-12	94	Formanovskii et al., 1988
$-(CH_2)_2N(Ts)(CH_2)_2-$	$-(CH_2)_2N(Ts)(CH_2)_2-$	Ts	V-12	77	Formanovskii et al., 1988
			V-7	20	Högberg and Cram, 1975
$-(CH_2)_2N(Ts)(CH_2)_2-$	$-C(O)CH_2N(Ts)C(O)-$	H	V-12	87	Formanovskii et al., 1988

TABLE 8.10. MISCELLANEOUS DIBENZOAZA-CROWN MACROCYCLES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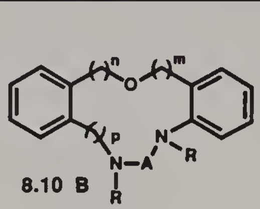
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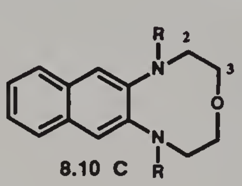
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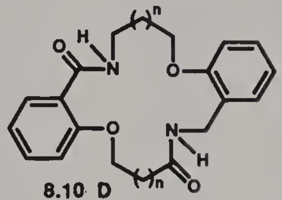
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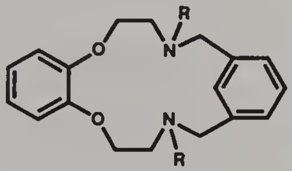
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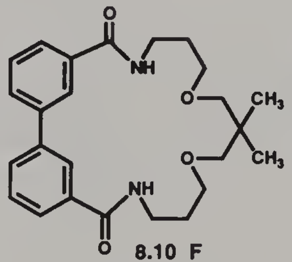
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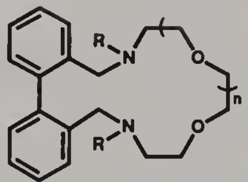
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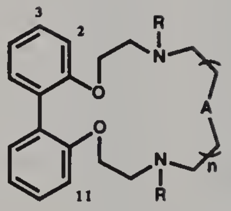
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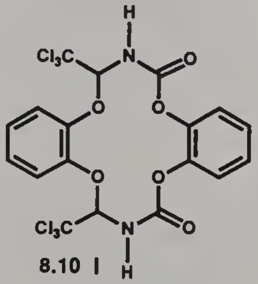
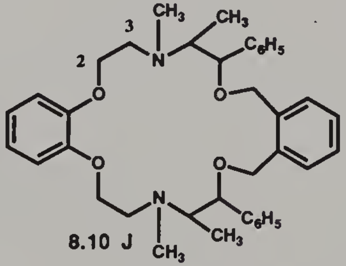

8.10 I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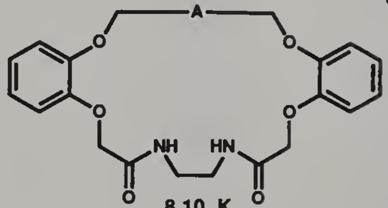
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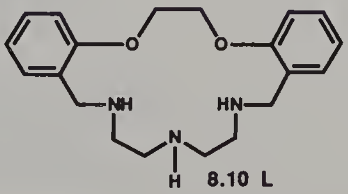
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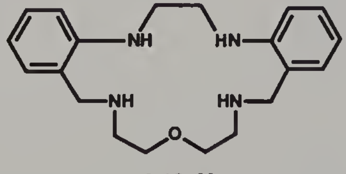
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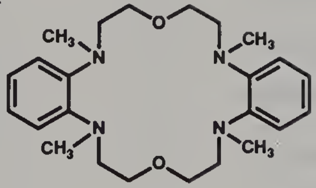
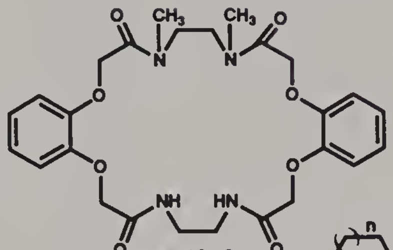
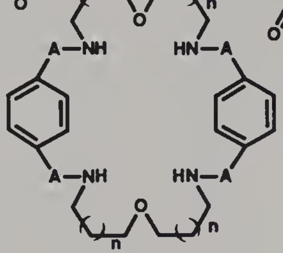
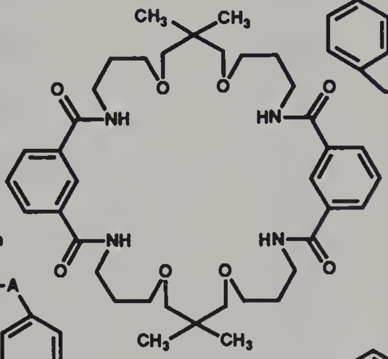

8.10 N



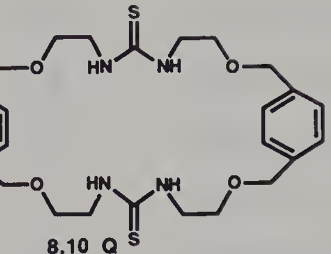
8.10 O



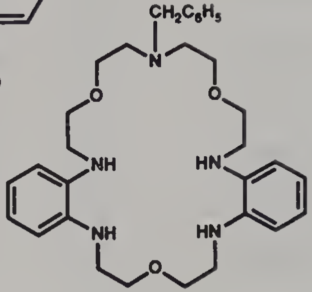
8.10 R



8.10 P



8.10 Q



8.10 S

Structure	R	P	m	n	A or Other Substituents	Method (or from R =)	Yield (%)	References
8.10 A	H					V-9	88	Glinka, 1980
	CH$_3$					V-9	55	Glinka, 1980
	C$_2$H$_5$					V-9	62	Glinka, 1980
	Ts					V-9	54	Glinka, 1980

TABLE 8.10. (*Continued*)

Structure	R	P	m	n	A or Other Substituents	Method (or from R =)	Yield (%)	References
8.10 B	H	1	0	0	CS	V-11	84	Glinka and Piatkowska, 1984
	H	0	0	1	CS	V-11	88	Glinka and Piatkowska, 1984
	H	0	1	1	CS	V-11	85	Glinka and Piatkowska, 1984
	H	0	0	1	CO		56	Brzezinska and Glinka, 1986
	H	0	0	1	C=NH		42,57	Brzezinska and Glinka, 1986
	H	0	0	1	$C=NCH_2C_6H_5$		31	Brzezinska and Glinka, 1986
	H	0	0	1	$(CH_2)_4$	V-8	23	Glinka et al., 1985
	Ts	1	0	0	CH_2	V-9	80	Glinka, 1982
	Ts	0	0	1	$(CH_2)_3$	V-8	37	Glinka et al., 1985
	Ts	0	0	0	$(CH_2)_4$	V-8	31	Glinka et al., 1985
	Ts	0	1	1	CH_2	V-8	94	Glinka and Walczynski, 1986
	Ts	0	1	1	$(CH_2)_2$	V-8	96	Glinka and Walczynski, 1986
	Ts	0	1	1	$(CH_2)_3$	V-8	93	Glinka and Walczynski, 1986

	Ts	0	0	0	$(CH_2)_3$	V-8	26	Glinka et al., 1985
	Ts	0	1	1	$(CH_2)_4$	V-8	95	Glinka and Walczynski, 1986
	Ts	0	0	1	$(CH_2)_4$	V-8	35	Glinka et al., 1985
8.10 C	H				2,6-$(O)_2$	V-4	31	Mikiciuk-Olasik & Kotelko, 1984a
	Ts					V-1	59	Mikiciuk-Olasik & Kotelko, 1984a
8.10 D				1		T-5	45	Schultz et al., 1988
				2		T-5	38	Schultz et al., 1988
8.10 E	H					$(C_6H_5CH_2O_2C)$	100	Hodgkinson and Sutherland, 1979
								Hodgkinson et al., 1976b
	CH_3					U-13	96	Hodgkinson and Sutherland, 1979
						$(C_2H_5O_2C)$		Hodgkinson et al., 1976a
	$HO(CH_2)_2$-					(H)	60	Hodgkinson and Sutherland, 1979
						(H)		Hodgkinson et al., 1976b
	$C_2H_5O_2C$-					U-13	33	Hodgkinson and Sutherland, 1979

TABLE 8.10. (*Continued*)

Structure	R	P	m	n	A or Other Substituents	Method (or from R =)	Yield (%)	References
						(H)		Hodgkinson et al., 1976a
	$CH_3NHC(O)CH_2$-					(H)	65	Hodgkinson and Sutherland, 1979
	$(CH_3)_2NC(O)CH_2$-					(H)	50	Hodgkinson and Sutherland, 1979
						(H)		Hodgkinson et al., 1976b
	$C_6H_5CH_2O_2C$-					U-13	45	Hodgkinson and Sutherland, 1979
8.10 F							76	Nagao et al., 1981
8.10 G	CH_3			1		U-11	99	Pearson et al., 1979
	$C_2H_5O_2C$-			1		U-11	40	Pearson et al., 1979
	CH_3			2		U-11	99	Pearson et al., 1979
	$C_2H_5O_2C$-			2		U-11	36	Pearson et al., 1979

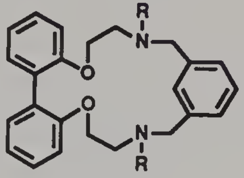
8.10 H	CH_3	1	CH_2	U-12	55	Pearson et al., 1979
	$C_6H_5CH_2O_2C$-	1	CH_2	U-12	39	Pearson et al., 1979
	H	1	O	U-12	91	Pearson et al., 1979
	CH_3	1	O	U-12	66	Pearson et al., 1979
	CH_3	1	O; 2,11-$(CH_2CH_2CH_3)_2$	U-12		Pearson et al., 1979
	CH_3	1	O; 2,11-$(CH{=}CHCH_3)_2$	U-12	93	Pearson et al., 1979
	CH_3	1	O; 2,11-$(CH_2OH)_2$	U-12	85	Pearson et al., 1979
	$HO(CH_2)_2$-	1	O	U-12	47	Pearson et al., 1979
	$C_2H_5O_2C$-	1	O	U-12	43	Pearson et al., 1979
	$C_2H_5O_2C$-	1	O; 2,11-$(CH_3)_2$	U-12	56	Pearson et al., 1979
	$C_2H_5O_2C$-	1	O; 2,11-$(CH{=}CHCH_3)_2$	U-12	43	Pearson et al., 1979
	$C_2H_5O_2C$-	1	O; 2,11-$(CH_2OH)_2$	U-12	42	Pearson et al., 1979
	$C_6H_5CH_2O_2C$-	1	O	U-12	48	Pearson et al., 1979
	CH_3	2	O	U-12	84	Pearson et al., 1979
	$C_6H_5CH_2O_2C$-	2	O	U-12	40	Pearson et al., 1979
8.10 I						Kudrya et al., 1979

TABLE 8.10. (*Continued*)

Structure	R	P	m	n	A or Other Substituents	Method (or from R =)	Yield (%)	References
8.10 J						S-1	40 (overall)	Wudl and Gaeta, 1972
8.10 K					$-CH_2OCH_2-$	T-7	15	Ashby et al., 1974
					-CH(OH)-	T-7	12	Ashby et al., 1974
					$-(CH_2OCH_2)_2-$	T-7	16	Ashby et al., 1974
8.10 L						U-14		Adam et al,. 1987b
8.10 M						U-14		Adam et al., 1987b

8.10 N				40	Kawaguchi et al., 1985
8.10 O			T-7	46	Bradshaw et al., 1990
8.10 P				6	Nagao et al., 1981
8.10 Q			V-20	80	Dietrich et al., 1978
8.10 R	0	$-CH_2-$			Krassig and Greber, 1956
	1	$-CH_2-$			Krassig and Greber, 1956
	1	$-CH(CN)-$			Krassig and Greber, 1956
8.10 S			V-5		Pedersen and Bromels, 1977

TABLE 8.11. MISCELLANEOUS POLYBENZOAZA- AND BINAPHTHALENOAZA-CROWN MACROCYCLES



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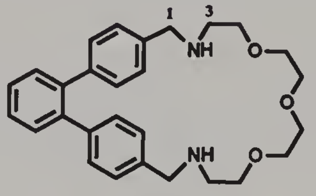

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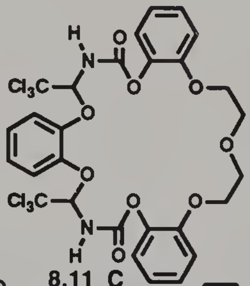

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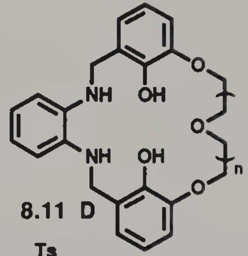

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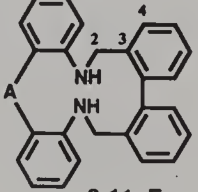

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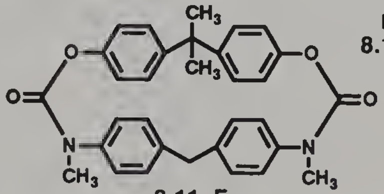
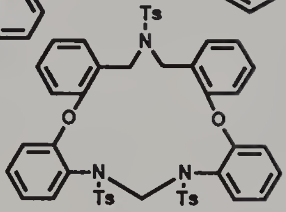


8.11 F



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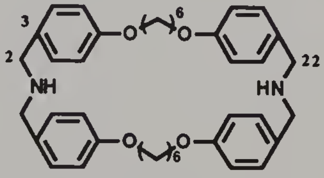

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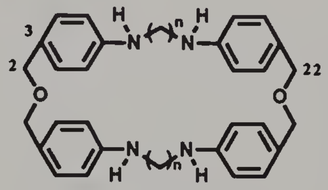

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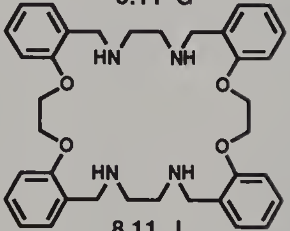
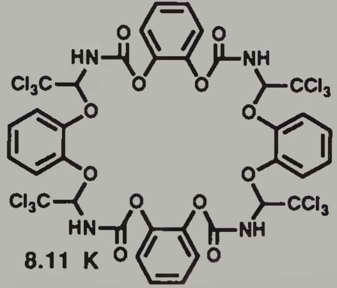


8.11 J



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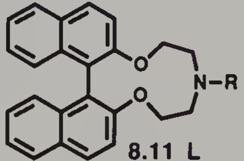

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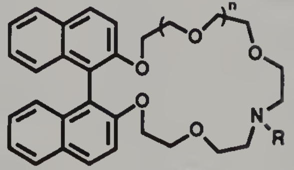

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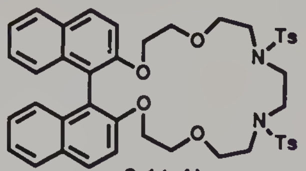

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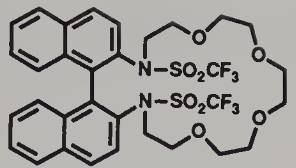

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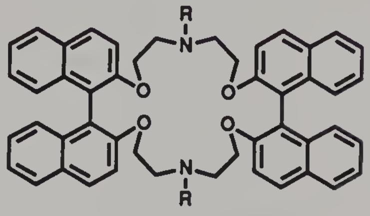

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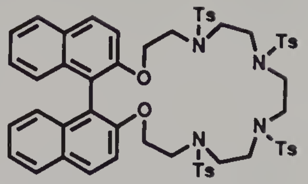

8.11 P

Structure	R	n	A or Other Substituents	Method	Yield (%)	References
8.11 A	CH_3			U-12	69	Pearson et al., 1979
	$C_6H_5CH_2O_2C$-			U-12	25	Pearson et al., 1979
8.11 B					32	Rossa and Vögtle, 1981
			1,15-$(O)_2$		80	Rossa and Vögtle, 1981
8.11 C					9	Kudrya et al., 1979
8.11 D		4		U-15	70	Staveren et al., 1988

TABLE 8.11. (*Continued*)

Structure	R	n	A or other Substituents	Method	Yield (%)	References
		5		U-15	63	Staveren et al., 1988
		6		U-15	71	Staveren et al., 1988
8.11 E			O	V-14	52	Glinka et al., 1988
			CH_2O	V-14	45	Glinka et al., 1988
			$O;2,15\text{-}(O)_2$	V-14	83	Glinka et al., 1988
			$CH_2O;2,15\text{-}(O)_2$	V-14	43	Glinka et al., 1988
8.11 F						Foti et al., 1981
8.11 G					31	Glinka, 1982
8.11 H					45	Wester and Vögtle, 1980
			$2,22\text{-}(O)_2$		26	Wester and Vögtle, 1980

8.11 I		3			Chun et al., 1988
		4			Chun et al., 1988
		5			Chun et al., 1988
		6			Chun et al., 1988
8.11 J				30	Adam et al., 1981b
				25	Morosanova et al., 1984
8.11 K				12	Kudrya et al., 1979
8.11 L	H			50	Cram, 1977
	Ts		V-5	42	Cram, 1977
			T-3		Cram, 1977
8.11 M	H	0	$(C_6H_5CH_2)$	62	Armstrong et al., 1985
	$(CH_3)_3CC(O)$-	0	(H)	78	Armstrong et al., 1985
	$C_6H_5CH_2$-	0		54	Armstrong et al., 1985
	Ts	1		31	Cram, 1977

TABLE 8.11. (*Continued*)

Structure	R	n	A or Other Substituents	Method	Yield (%)	References
8.11 N				U-4	20	Cram, 1977
8.11 O				V-10		Cram, 1977
8.11 P				U-4	11	Cram, 1977
8.11 Q	H				48	Cram, 1977
	Ts			T-3	11	Cram, 1977

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CHAPTER IX

Aza-crown Macrocycles Containing Other Heteroatoms in the Macroring

A. INTRODUCTION

The aza-crowns, in general, have only oxygen and nitrogen atoms in the macroring. There are a number of macrocycles which, in addition to nitrogen atoms, contain sulfur, phosphorous, arsenic, silicon, or tin atoms. Such mixtures of heteroatoms give these materials different ligating properties. This chapter contains information on aza-crowns that contain sulfur atoms in the macroring followed by aza-crowns that contain phosphorous, arsenic, and silicon atoms.

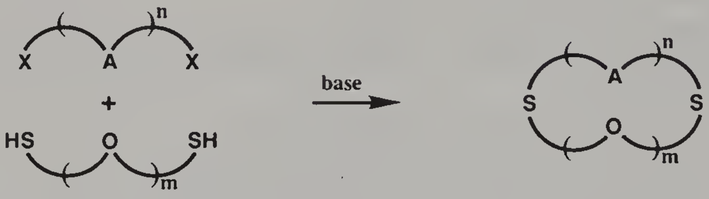
B. AZA-CROWN MACROCYCLES CONTAINING SULFUR ATOMS IN THE MACRORING

In the beginning of the macrocycle chemistry era, thiaaza-crown macrocycles in the form of cyclic bis Schiff bases were prepared by template-assisted ring-closure reactions. In general, the imine double bonds were not reduced and the template metal ions were not removed (Thompson and Busch, 1964; Urbach and Busch, 1973). These macrocyclic imine complexes, which may be used as starting materials for the preparation of thiaaza-crowns, are not listed in the tables at the end of this chapter because this book describes only saturated macrocycles. The two general methods used to prepare the thiaaza-crown macrocycles are listed here.

Method Y.

Ring closure to form two C—S bonds where two mercaptides are the nucleophiles. The yields for ring closure are not high, generally below 50%.

Method Y

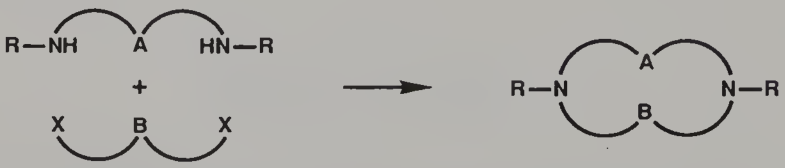


X = halogen atoms or tosylate

Method Z.

Ring closure to form two C—N bonds. The yields for these cyclization reactions are usually higher than those for method Y.

Method Z

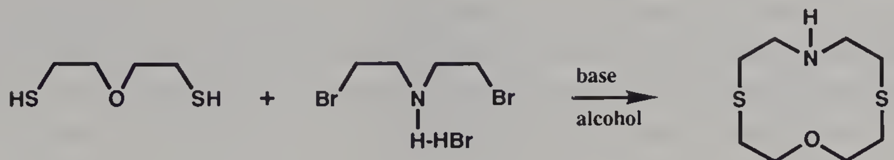


A, B contain N, O and S atoms
X = halogen atoms or aldehyde

1. Ring Closure to Form Two C—S Bonds

One of the first saturated thiaaza-crown macrocycles, the $[12]S_2ON$ macrocycle, was prepared by Black and McLean (1969, 1971) (method Y-1).

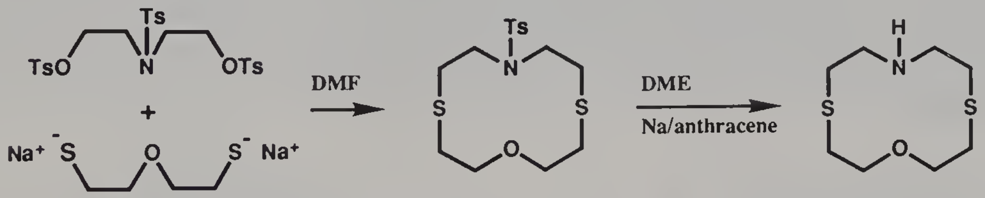
Method Y-1

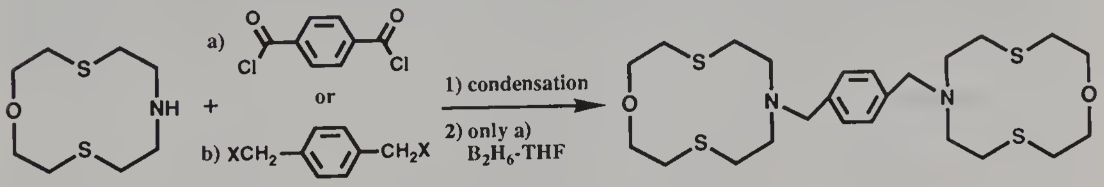


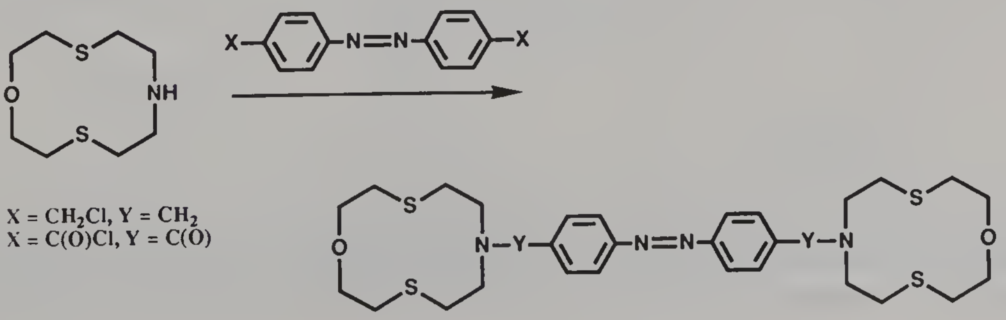
They condensed 3-oxa-1,5-pentanedithiol with 3-aza-1,5-dibromopentane in ethanol and base using high dilution to give [12]S_2ON in an 18% yield. Other authors produced similar crowns in the same manner in yields of up to 32% (Shinkai et al., 1984) and using stronger bases to give yields of up to 38% (Youinou et al., 1986).

Dithiaaza-crown macrocycles have been prepared from *N*-tosyl-protected starting materials to give the *N*-tosyl crowns. These compounds can be detosylated to give macrocycles containing a secondary amine function in an overall yield of 30% (method Y-2) (Youinou et al., 1986). These secondary amine-containing macrocycles can be reacted with compounds containing two functional groups to link two dithiaaza-crowns together. Reactions with terephthaloyl dichloride followed by reduction gave the *p*-xylylyl linked [12]NOS_2 crowns (Bulkowski et al., 1977). Others used α,α′-dibromo-*p*-xylene in acetonitrile to give the same product in a yield of 34% (Shinkai et al., 1984). These latter workers also prepared photoresponsive bis[12]NOS_2 ligands as shown.

Method Y-2



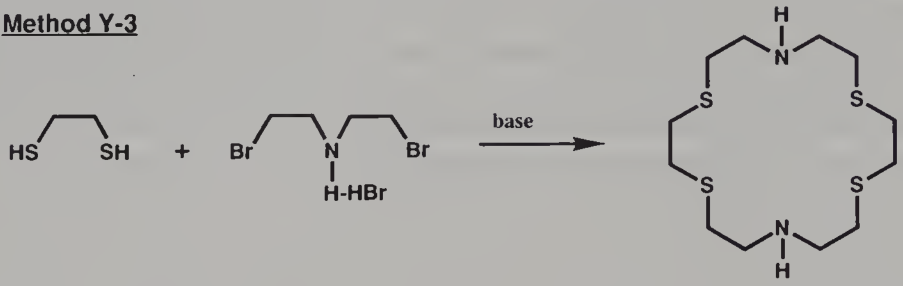




X = CH_2Cl, Y = CH_2
X = C(O)Cl, Y = C(O)

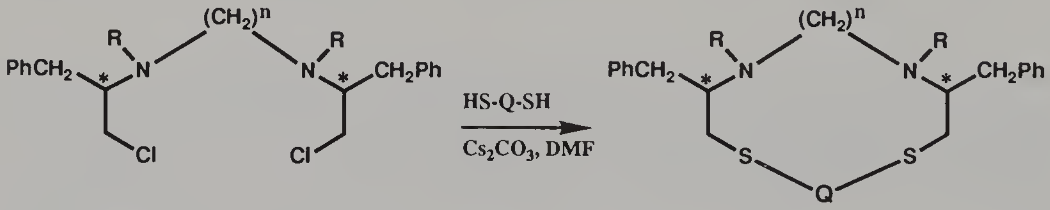
The macrocyclic ligand [18]N_2S_4 was prepared by a 2:2 cyclization reaction of 3-aza-1,5-dibromopentane with the disodium salt of 1,2-ethanedithiol under high-dilution conditions (method Y-3) (Black and McLean, 1969, 1971). The product was separated from polymeric material in a 5% yield by recrystallization from ethanol. No 1:1 cyclization product ([9]NS_2) was isolated, suggesting that formation of an 18-membered ring is preferred in this case even though four C—S bonds were formed.

Method Y-3



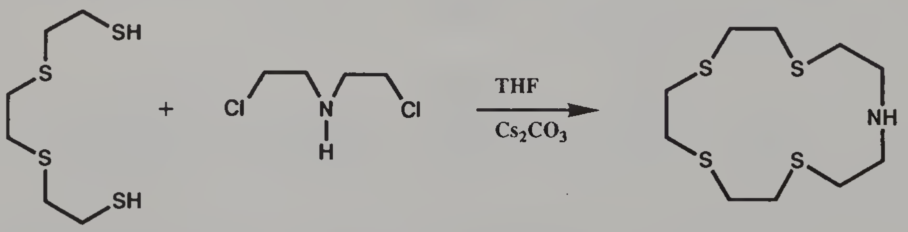
Buter and Kellogg (1987) observed that greater yields of the sulfur-containing macrocycles were obtained when using cesium carbonate as the base. They used this approach to prepare many chiral thia macrocycles, including some containing nitrogen atoms (method Y-4). Kellogg and coworkers obtained thiaaza-crown macrocycles in high yields (Lemaire et al., 1985; Vriesema et al., 1986).

Method Y-4



A 50% yield of [15]NS_4 was observed when dilute THF solutions of 3-aza-1,5-dichloropentane and 3,6-dithia-1,8-octanedithiol were simultaneously dripped into THF containing cesium carbonate (method Y-5) (Pavlishchuk and Strizhak, 1989). Before this latter reaction, the best yields for the thiacrowns were obtained using cesium carbonate in DMF. The above result shows that THF is also an excellent solvent for these cyclization reactions. It is also

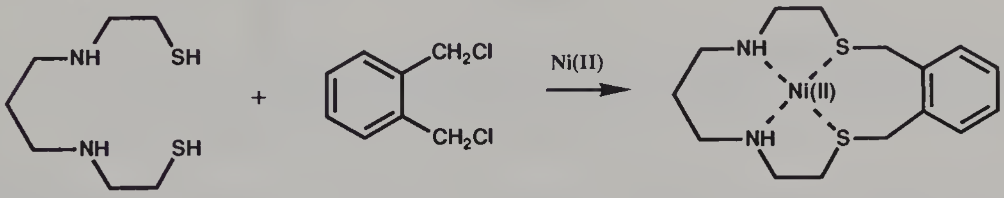
Method Y-5



important to note that these authors did not need to protect the interior amine functions since the mercaptides formed by reacting the thiols with cesium carbonate were more reactive nucleophiles than the amine nitrogen atom.

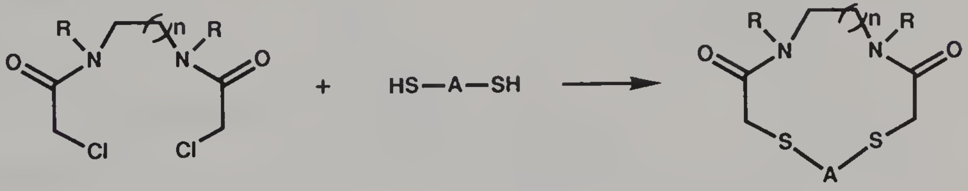
A benzodithiadiaza-crown was prepared by the Ni(II) catalyzed reaction of 3,7-diaza-1,9-nonanedithiol with α,α'-dibromo-o-xylene (method Y-6) (Drew et al., 1980; Hay et al., 1976). The Ni(II) complex of the macrocycle was isolated. The authors did not remove the metal ion from the complex.

Method Y-6



The recently developed crab-like method to prepare aza-crowns has been used to prepare thiaaza macrocycles. A crab-like bis-α-chloroamide was reacted with a dimercaptan in DMF or acetonitrile in the presence of sodium or cesium carbonate to give 30-40% yields of the dithia macrocycle (method Y-7) (Bradshaw et al., 1990; Krakowiak et al., 1990). It is possible that similar crab-like compounds were used for the preparation of thiaaza-crowns with methylene bridges between nitrogen atoms, but no specific details were given (Ishii et al., 1988).

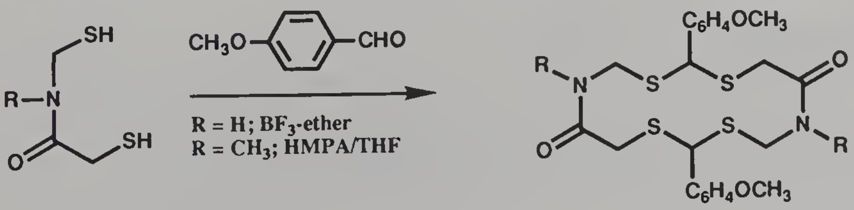
Method Y-7



$n = 0, 1, 2$;
$R = H, CH_3, C_2H_5$;
$A = (CH_2)_3, (CH_2)_2O(CH_2)_2$

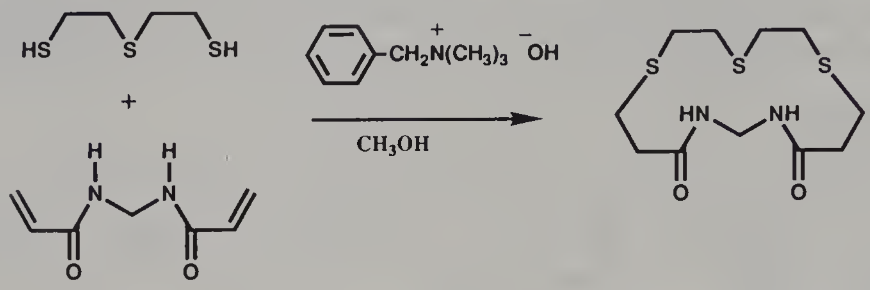
Two additional methods have been used to prepare thiaaza macrocycles by the formation of C—S bonds. Anisaldehyde reacted with dimercaptans in methylene chloride in the presence of boron trifluoride–etherate to give insoluble 2:2 cyclization products (method Y-8) (Cynkier et al., 1979). A second

Method Y-8

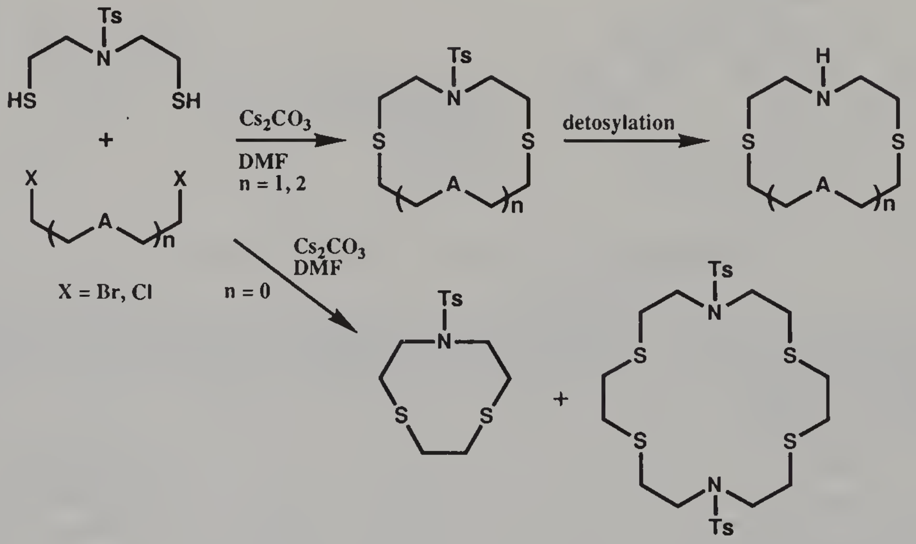


process uses the reaction of a dithiol with an activated diene (method Y-9) (Ishii et al., 1988). No details for this process were included in the patent. A more recent method, similar to methods Y-6 and Y-7 above but with the internal amine nitrogen atom protected by a tosyl group, gave high yields in the cyclization step (method Y-10) (McAuley and Subramanian, 1990).

Method Y-9



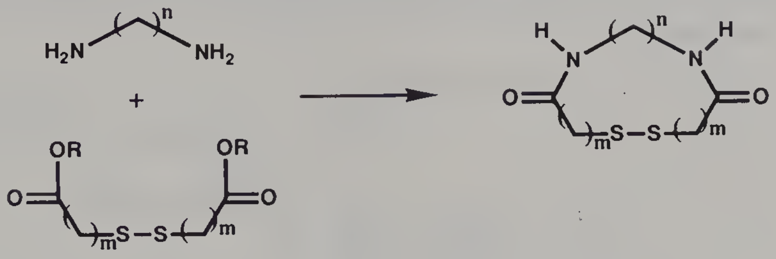
Method Y-10



2. Ring Closure to Form Two C—N Bonds

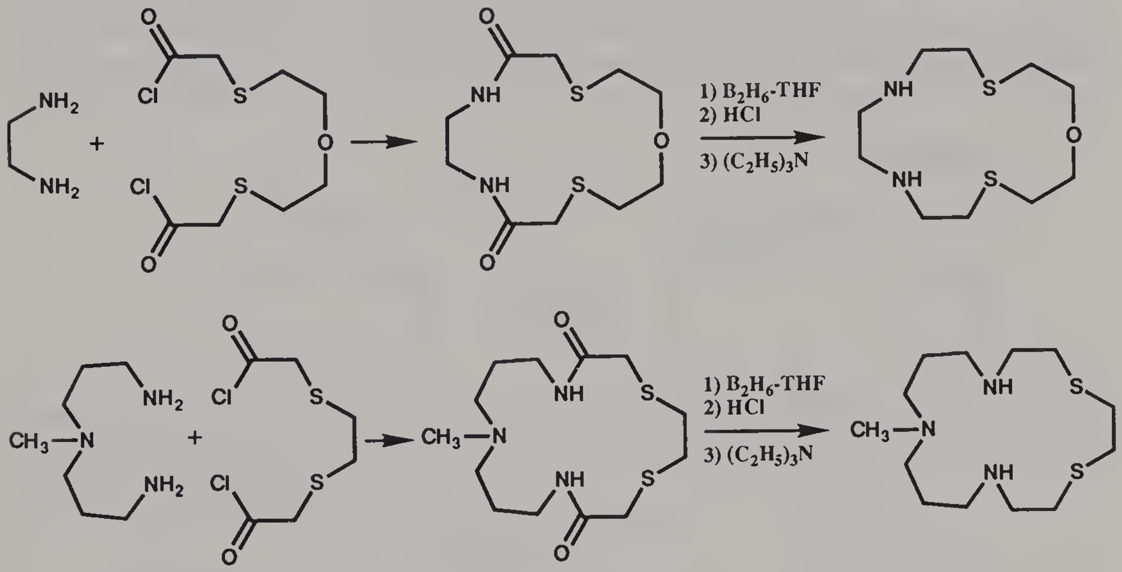
Unsubstituted 10-, 11-, and 13-membered cyclic diazadisulfides were prepared in good yields by the reaction of ethylene- or trimethylenediamine with esters of dithiodiacetic acid or 3,3′-dithiodipropionic acid in the absence of a solvent (method Z-1) (Owen and Fayadh, 1970; Owen et al., 1973). No products were observed when substituted diamines were used.

Method Z-1

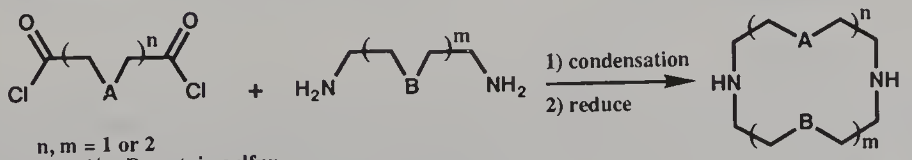


High-dilution reactions of diamines and sulfur-containing diacid dichlorides gave cyclic sulfur-containing diamides that were reduced to the dithiaaza macrocycles (method Z-2) (Pelissard and Louis, 1972). A similar high-dilution reaction between a diacid dichloride and a diamine has been used by Lehn and coworkers to prepare a number of thiaaza-crowns (method Z-3) (Alberts et al., 1977, Dietrich et al., 1970; Lehn et al., 1983). The cyclic diamides were prepared in yields of up to 50%, while reduction was performed in yields

Method Z-2



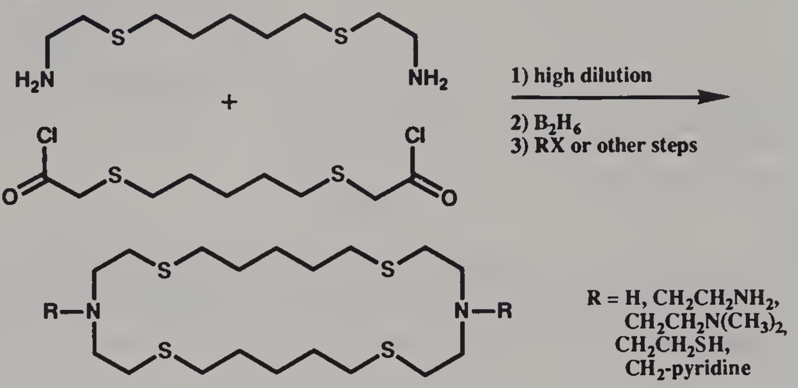
Method Z-3



n, m = 1 or 2
A and/or B contain sulfur

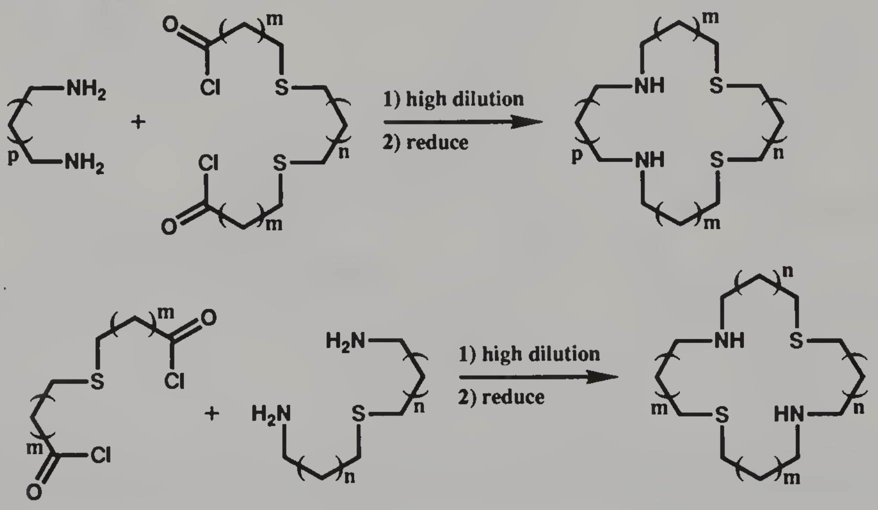
of up to 90%. The same type of process was used to prepare $[24]N_2S_4$ with various types of side chains (method Z-4) (Agnus et al., 1979, 1984). The side chains, in many cases, were attached after the macrocycles were prepared.

Method Z-4

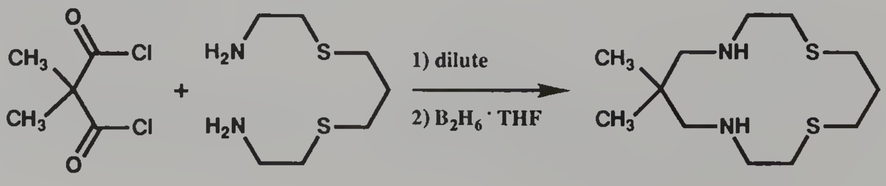


A series of macrocycles containing two sulfur and two nitrogen atoms was prepared in yields of 37–64% from the appropriate diacid dichlorides and diamines (method Z-5) (Siegfried and Kaden, 1984). The cyclic diamides were reduced by borane in yields of 34–64%. The reaction of dimethylmalonyl dichloride with a sulfur-containing diamine in chloroform using cesium carbonate as the base gave a similar dithiadiaza macrocycle (method Z-6) (Kimura et al., 1989).

Method Z-5

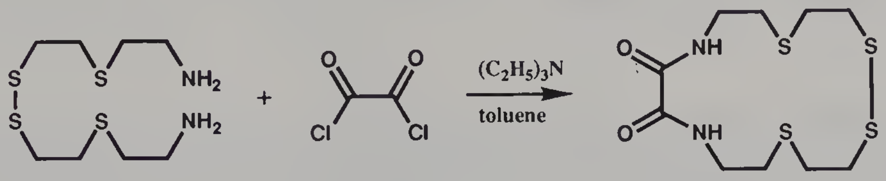


Method Z-6



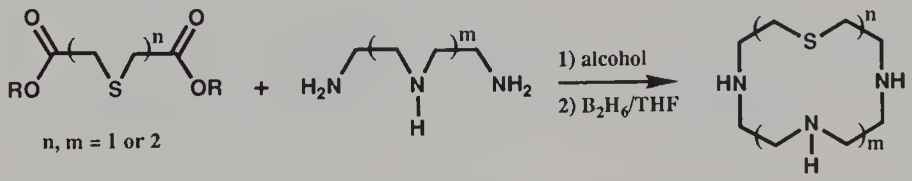
Oxalyl dichloride has been used to prepare a tetrathiadiaza macrocycle. A tetrathiadiamine was reacted with oxalyl dichloride to give the macrocyclic diamide in an 80% yield (method Z-7) (Voronkov et al., 1979).

Method Z-7

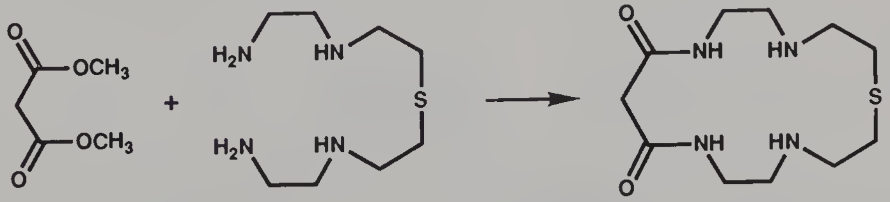


The reaction of a diester with a diamine can also be used to prepare these sulfur-containing macrocycles. Several thiaaza macrocycles were prepared in 15–40% yields from the reaction of sulfur-containing diesters and polyamines (method Z-8) (Kodama et al., 1984; Tabushi et al., 1976). Again, the cyclic diamides were reduced with diborane or lithium aluminum hydride in THF. Dimethyl malonate was used to prepare a monothiatetraaza-crown in a 36% yield (method Z-9) (Kimura et al., 1984).

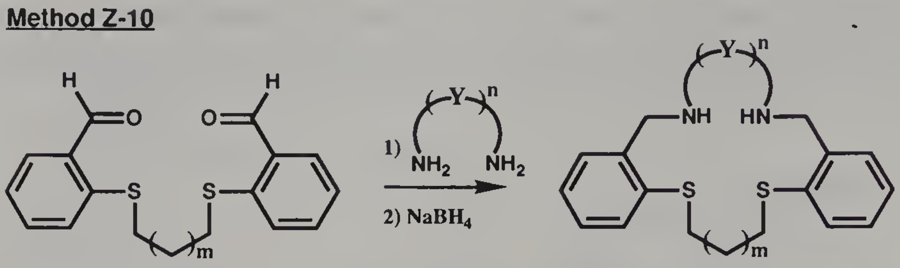
Method Z-8



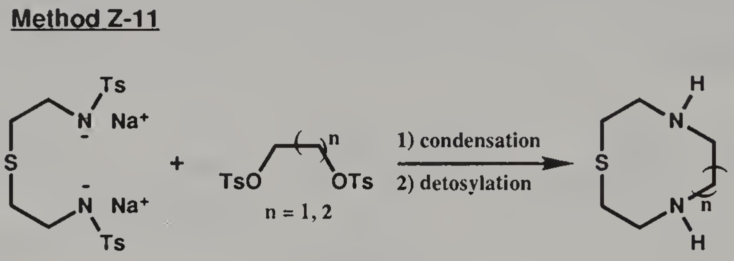
Method Z-9



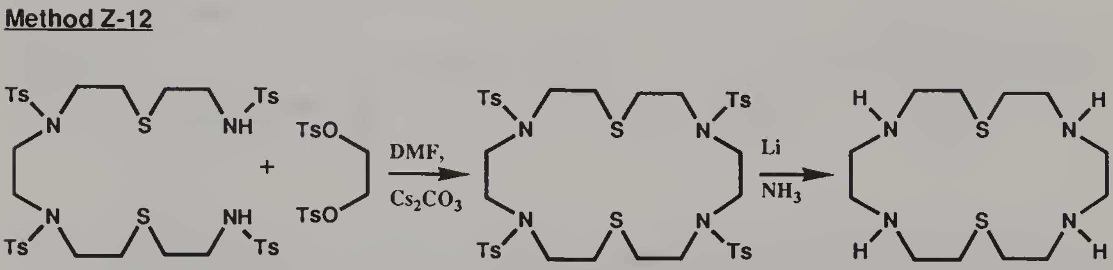
The cyclocondensation of various diamines (some containing internal sulfur atoms) and aromatic dialdehydes is a useful route to the thiaaza-crown macrocycles. The resulting bis Schiff bases were reduced with sodium borohydride in good yields (method Z-10) (Baldwin et al., 1987; Lindoy and Smith, 1981).



Hart and coworkers tried two methods to prepare [9]N_2S compounds. The first method was the reaction of the ditosylate derivative of thiodiethylene glycol with the disodium salt of *N*,*N*′-ditosylethylenediamine. This method did not give [9]N_2S. The second method from *N*,*N*′-ditosylbis(2-aminoethyl)sulfide gave a 10% yield of the macrocycle (method Z-11) (Hart et al., 1983) Others reported the same product but without details (Gahan et al., 1982). A 49% yield of the same product was reported by Boeyens and coworkers using DMF as the solvent (Boeyens et al., 1985). A 27% yield of [10]N_2S was reported for the cyclization reaction using 1,3-propaneditosylate (n = 2) (Wambeke et al., 1989).

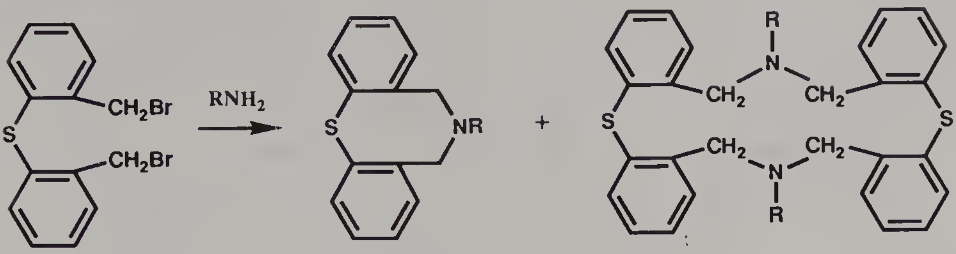


An [18]N_4S_2 macrocycle was prepared in a 62% yield by reacting a per-*N*-tosyldithiatetraamine with 1,2-ethane ditosylate using cesium carbonate in DMF (method Z-12) (Craig et al., 1989). Detosylation was accomplished in a 64% yield by lithium metal in ammonia.



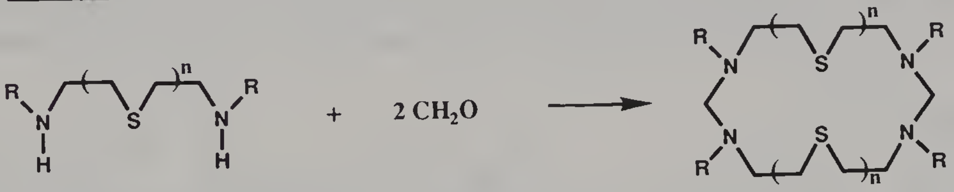
Cyclocondensations to give both 1:1 and 2:2 addition products were observed for the reaction of various primary amines with bis(2-bromomethylphenyl)sulfide (method Z-13) (Tanaka et al., 1973). In a few cases, the te-

Method Z-13



trabenzodithiadiaza-16-crown-4 (the 2:2 cyclization product) was formed in the highest yield but never more than 31%. Macrocycles with methylene bridges between nitrogen atoms were prepared in 60% and 82% yields by reacting formaldehyde with derivatives of 3,6-dithia-1,8-octanediamine and 3-thia-1,5-pentanediamine in methanol (method Z-14) (Voronkov et al., 1988b, 1989).

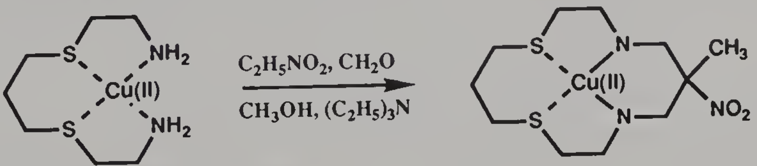
Method Z-14



n = 1 or 2, R = $CH_2CH_2CO_2CH_3$, $CH_2CH_2C_6H_5$, $CH(CO_2CH_3)CH_2CO_2CH_3$

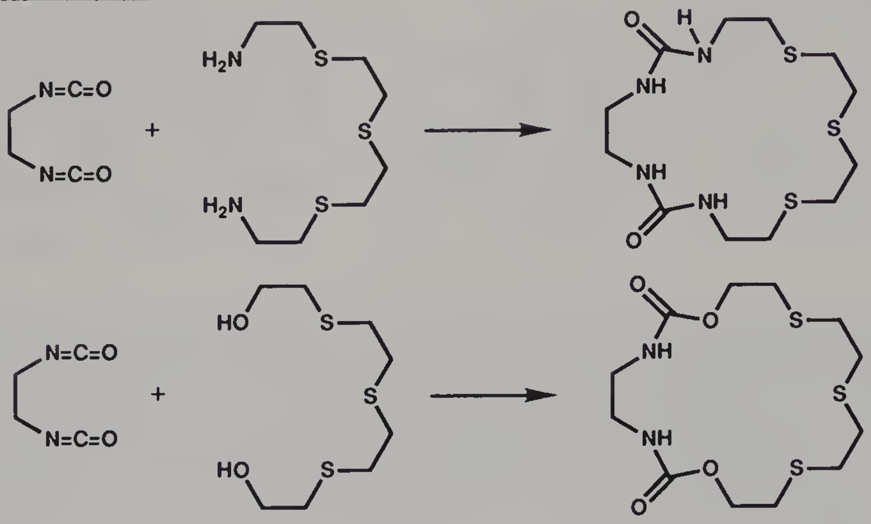
There has been interest in synthetic macrocycles for use as models for biological systems. A macrocycle with the N_2S_2-donor set was prepared in a good yield by the reaction of the 3,7-dithia-1,9-nonanediamine–Cu(II) perchlorate complex with nitroethane and aqueous formaldehyde in the presence of triethylamine in methanol (method Z-15) (Comba et al., 1988). This synthesis of an N_2S_2 macrocycle occured more readily than a similar synthesis of the comparable N_4 macrocycle from the open chain tetraamine–Cu(II) complex (Comba et al., 1988).

Method Z-15



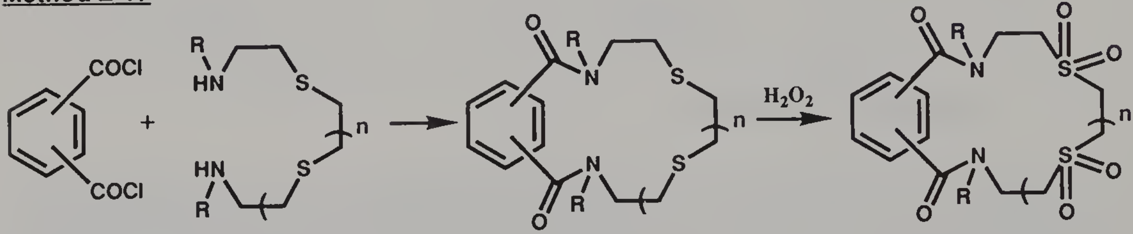
The diisocyanate derivative of ethylenediamine was treated with sulfur-containing diamines or glycols in THF to form macrocycles containing sulfur, nitrogen, and in some cases, oxygen atoms in the ring (method Z-16) (Ishii et al., 1988). No specific details for these reactions were given in the patent.

Method Z-16



Thia- and dithiadiamine derivatives were reacted with phthaloyl or terephthaloyl dichloride to form the benzodithiadiaza-crowns (method Z-17) (Voronkov et al., 1979, 1988a, 1988b). The macrocycle containing the phthalamide moiety was oxidized with 30% hydrogen peroxide to form the cyclic bisulfone derivative in a 60% yield.

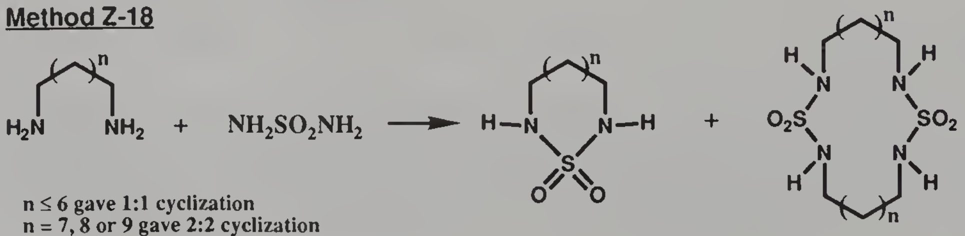
Method Z-17



$R = CH(CO_2CH_3)CH_2CO_2CH_3$

Cyclic sulfonamides were prepared 20 to 25 years ago (Ciaperoni et al., 1965; Knöllmüller, 1970, 1971a, 1971b). These authors reacted 1,6-hexanediamine and 1,10-decanediamine with sulfamide to form the macrocyclic sulfamides. Arya and Shenoy (1976) reported that when the methylene chain between the diamines was less than eight carbon atoms, a 1:1 cyclization took place. A 2:2 cyclization took place when the methylene chain was longer than eight carbon atoms (method Z-18). These authors also reported a 2:2 cycli-

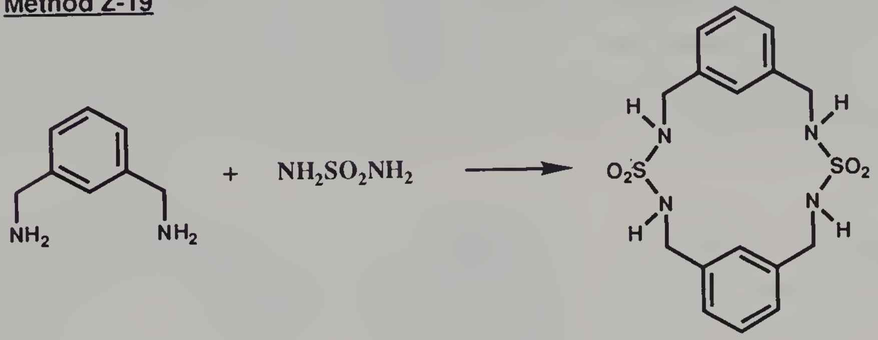
Method Z-18



$n \leq 6$ gave 1:1 cyclization
$n = 7, 8$ or 9 gave 2:2 cyclization

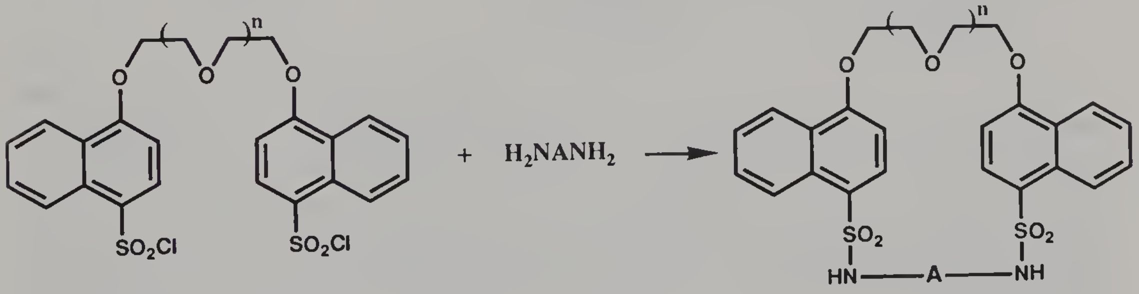
zation from the reaction of *m*-phenylenediamine with sulfamide (method Z-19).

Method Z-19



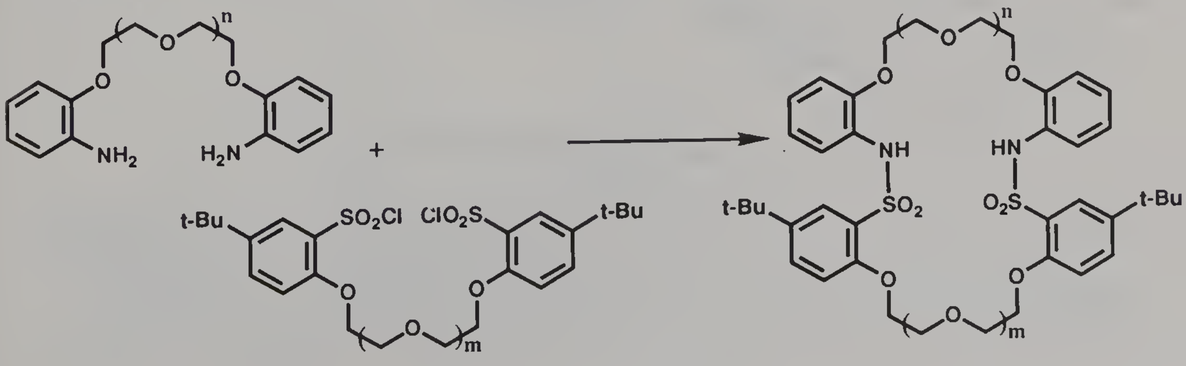
Other macrocyclic bis-sulfonamides were prepared by treating aliphatic diamines and bis-naphthalenesulfonyl dichlorides in THF or diglyme in the presence of sodium or potassium carbonate (method Z-20) (Prajer-Janczewska and Bartosz-Bechowski, 1984, 1987). Bradshaw and Biernat and their coworkers have prepared a number of similar macrocyclic bis-sulfonamides using bis(benzenesulfonyl) dichloride and bis-aniline-type compounds in chloroform at −70°C and using pyridine as the base (method Z-21) (Biernat et al., 1987; Bradshaw et al., 1987).

Method Z-20



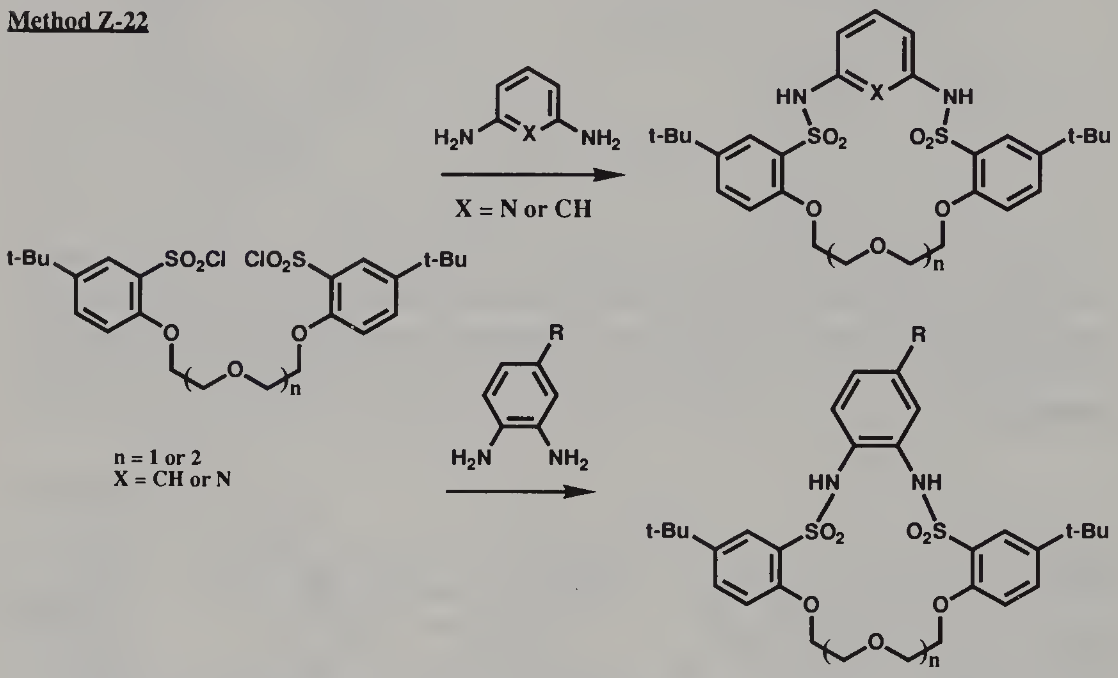
n = 1 or 2, A = $CH_2(CH_2OCH_2)_nCH_2$, $(CH_2)_5$

Method Z-21

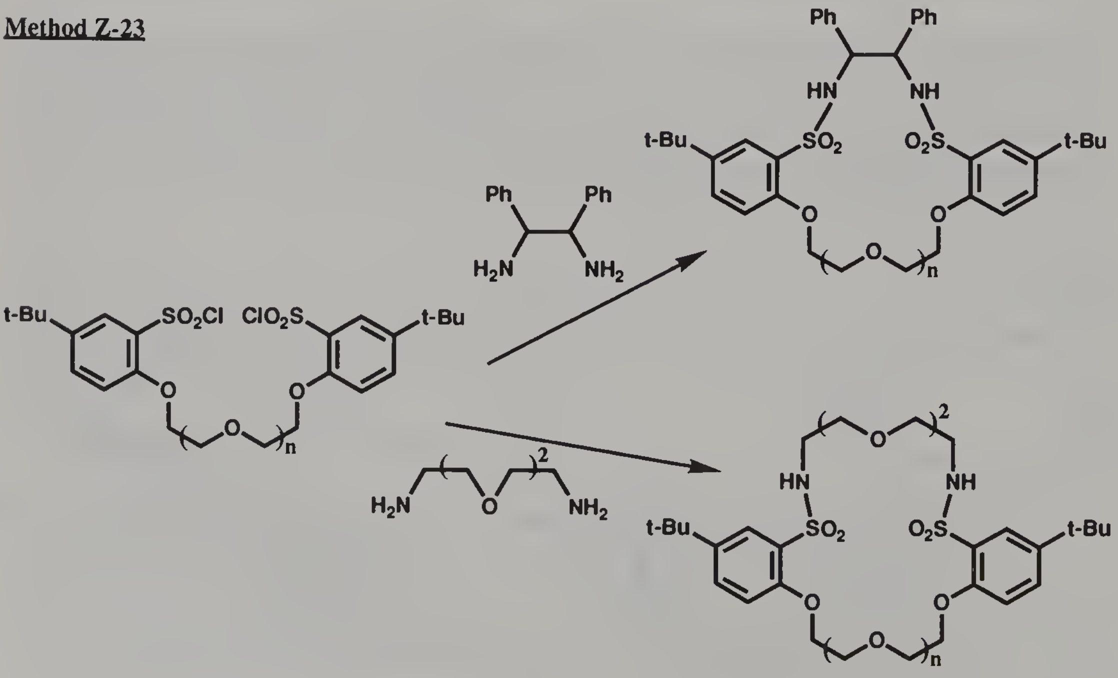


A large family of macrocyclic bis-sulfonamides were prepared by the Bradshaw-Biernat group. The bis(4-*t*-butyl-2-chlorosulfonylphenyl)oligoethyleneoxy ether starting material was reacted with 2,6-diaminopyridine and 1,2- or 1,3-diaminobenzene to form the macrocyclic bis-sulfonamide containing two benzo and a pyridino or three benzo subcyclic units (method Z-22) (Biernat et al., 1986, 1987; Bradshaw et al., 1987). The bis(benzenesulfonyl) dichloride was also reacted with some aliphatic diamines to form other macrocyclic bis-sulfonamides (method Z-23) (Bradshaw et al., 1987).

Method Z-22

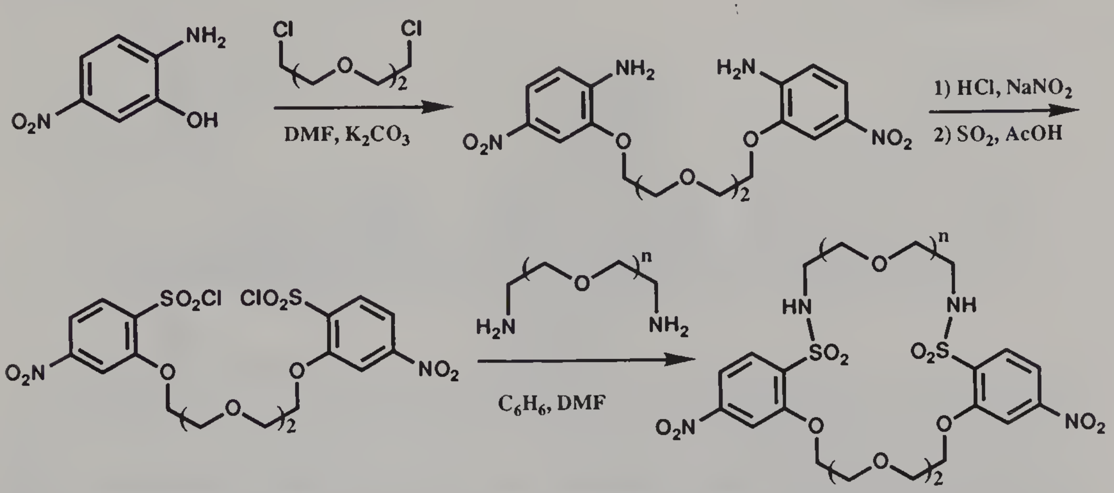


Method Z-23

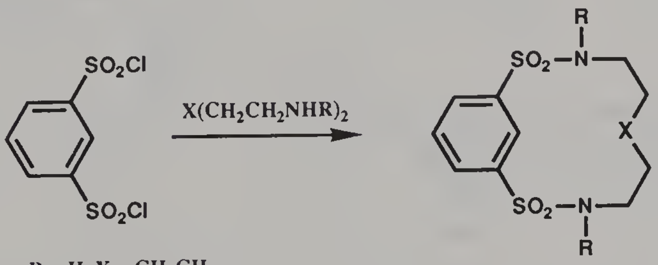


Recently, bis-sulfonamido-crowns have been prepared from 5-nitro-2-aminophenol without the need to protect the amine group in the first step. The aminophenol was reacted with 1,8-dichloro-3,6-dioxaoctane in DMF in the presence of potassium carbonate to form the intermediate diamine (method Z-24) (Dziomko et al., 1989). Here, the phenoxide rather than the amine nitrogen reacted with the alkyl halide. It is interesting to note that the same reactants under different conditions (high temperature) gave a macrocyclic benzoaza-crown (see method W-1, Chapter VIII). In the second step of method Z-24, the amino groups were converted to the sulfonyl chloride moieties through a Sandmeyer-like reaction. The resulting bis(benzenesulfonyl) dichloride was reacted with a diamine to form the macrocyclic bis-sulfonamide in a 20% yield. Two macrocyclic benzobis-sulfonamides were prepared by treating 1,3-benzenedisulfonyl dichloride with two different diamines (method Z-25) (Voronkov et al., 1988b). The new macrocycles were prepared in yields of 65% and 75%, respectively.

Method Z-24



Method Z-25

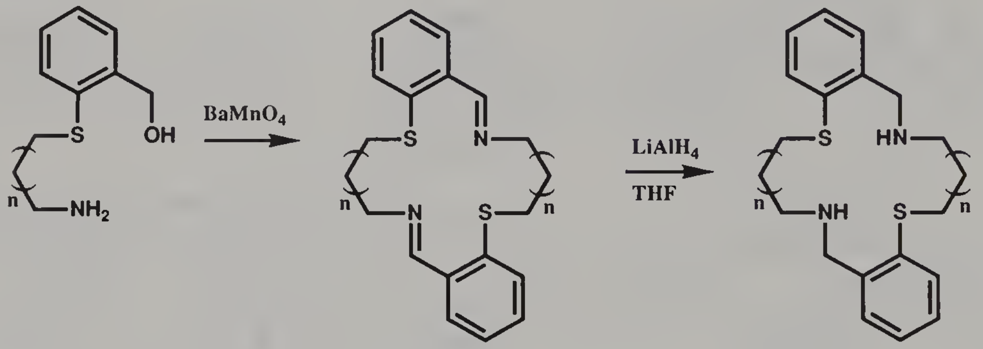


R = H, X = CH_2CH_2
R = $CH_2CH_2CO_2CH_3$, X = SCH_2CH_2S

The spontaneous double condensation of *o*-(3-amino-1-thiapropyl)benzaldehyde or *o*-(4-amino-1-thiabutyl)benzaldehyde gave the [14]N_2S_2 or [16]N_2S_2

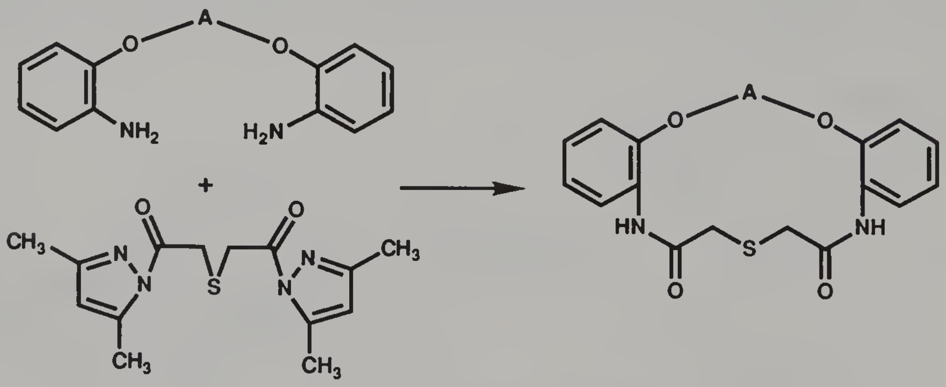
macrocycles (Martin et al., 1985, 1987). The aldehydes were prepared during the course of the reaction by a barium manganate oxidation of their corresponding benzyl alcohol analogs. The two macrocyclic Schiff bases were reduced to the saturated N_2S_2 macrocycles with lithium aluminum hydride in THF (method Z-26).

Method Z-26



Active carboxylic acid compounds are useful acylating agents for ring-closure reactions. For example, dibenzomacrocycles were obtained in yields of about 20% using the dimethylpyrazol activated amides (Biernat and Luboch, 1984) (method Z-27). Acid chlorides have been used instead of active carboxylic acid compounds to obtain the same type of product as in the method

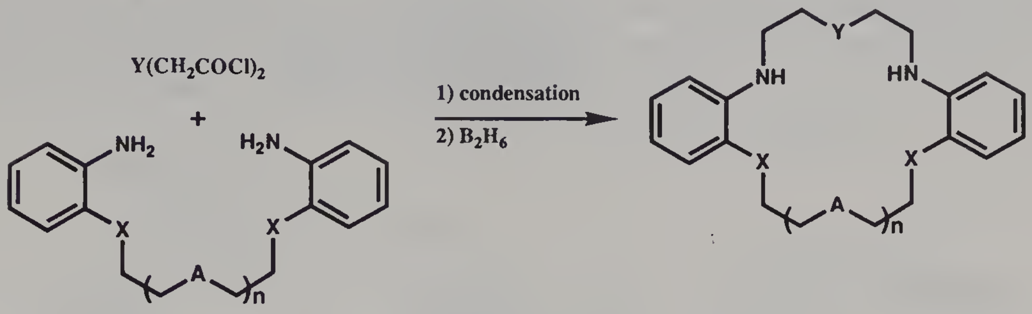
Method Z-27



$A = (CH_2)_3, CH_2(CH_2OCH_2)_{1\ or\ 2}CH_2$

Z-27 process. Because diacid dichlorides are very reactive, high-dilution conditions were required to obtain good yields of the cyclization products (method Z-28) (Formanovskii and Murakhovskaya, 1985).

Method Z-28



X = O, S, N
Y = O, S
A = O, S, N

C. AZA-CROWN MACROCYCLES CONTAINING PHOSPHOROUS ATOMS IN THE MACRORING

Macrocyclic phosphazenes and methylphosphazenes with only phosphorous and nitrogen atoms in the ring (and no carbon atoms) have been known for many years (Gallicano et al., 1977; Oakley et al., 1985; Searle, 1959). Likewise, other inorganic cyclic compounds, including the cyclic forms of sulfur, the metaphosphates, and the siloxanes, are well known (Haiduc, 1970; Rheingold, 1977). Crown ethers, especially the aza-crowns, containing phosphorous have been prepared more recently because they complex well with the transition-metal ions. Closure of the ring to form phosphaaza-crowns mainly concerns reactions at the phosphorous or nitrogen atoms. The three general methods to form these macrocycles are given here.

Method AA.

Ring closure to form two C—P bonds where two phosphides are the nucleophiles.

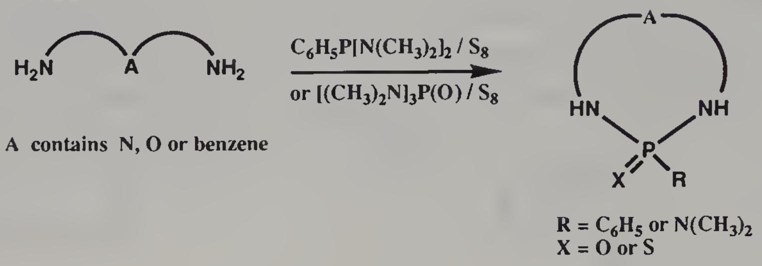
Method AA

A, B contain N, O or benzene
X = halogen atoms

Method AB.

Ring closure to form two P—N bonds where an activated phosphorous compound reacts with a diamine.

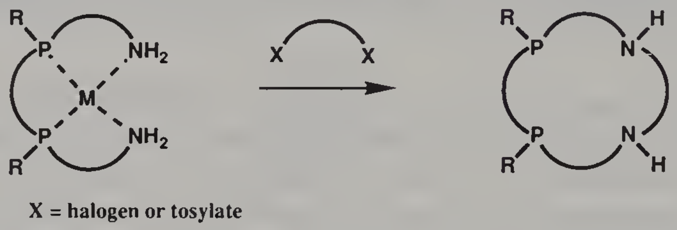
Method AB



Method AC.

Ring closure to form two C—N bonds where one of the reactants contains one or more phosphorous atoms.

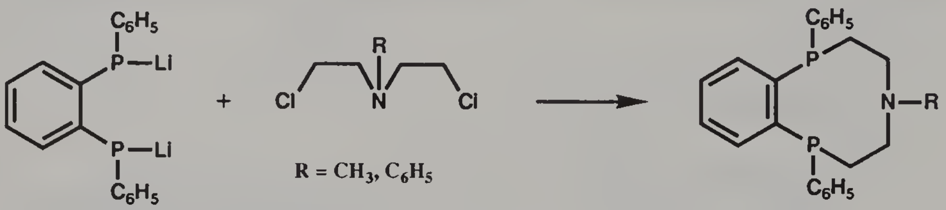
Method AC



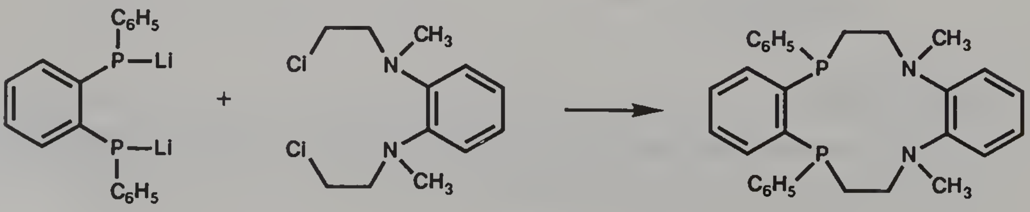
1. Ring Closure to Form Two C—P Bonds

The reaction of the dilithium salt of 1,2-bis(phenylphosphino)benzene with *N*-methyl- or *N*-phenylbis(2-chloroethyl)amine under high-dilution conditions gave a moderate yield of the diphosphinaaza-9-crown-3 (method AA-1) (Kyba et al., 1980a). A similar reaction with a 1,2-bis(*N*-2-chloroethyl-*N*-methylamino)benzene gave a dibenzodiphosphinadiaza-12-crown-4 ligand in an 18% yield (method AA-2) (Kyba et al., 1981).

Method AA-1

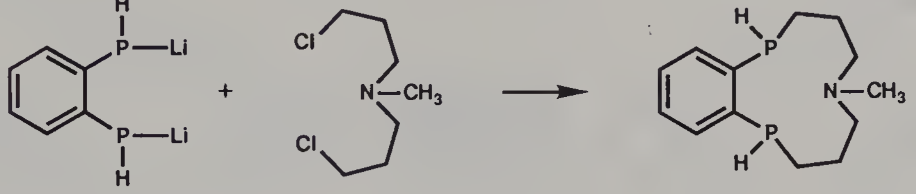


Method AA-2



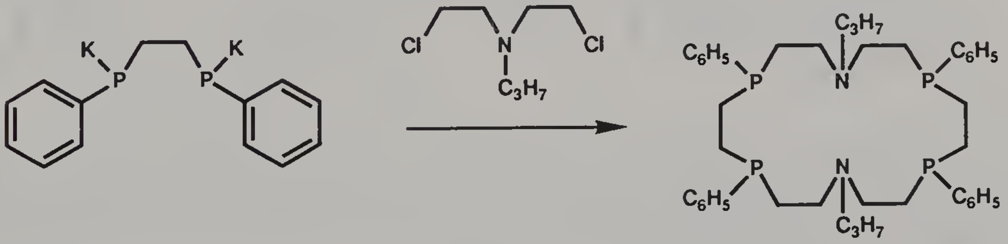
A macrocycle with secondary phosphine ligating sites was prepared in an 80% yield by treating 1,2-bis(phosphino)benzene first with *n*-butyllithium and then with bis(3-aminopropyl)methylamine under high-dilution conditions in THF (method AA-3) (Kyba and Heumuller, 1981).

Method AA-3



The [18]N_2P_4 macrocycle was prepared by a 2:2 cyclic condensation of bis(2-chloroethyl)propylamine and the dipotassium salt of 1,2-bis(phenylphosphino)ethane in THF (method AA-4) (Ciampolini et al., 1983).

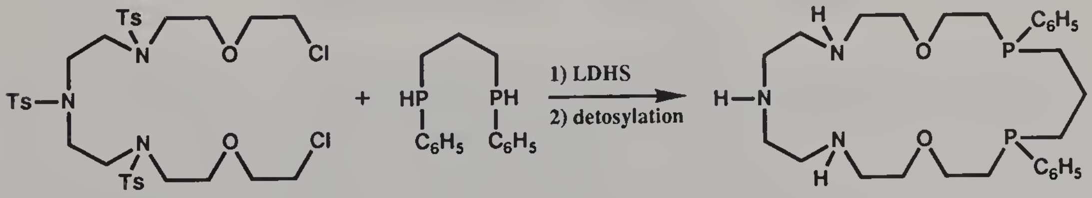
Method AA-4



These authors were able to isolate four diastereoisomers in the pure state.

A similar starting material was used to produce phosphorous-containing macrocycle [22]$N_3O_2P_2$. This ligand was prepared in a 68% yield by a high-dilution reaction of 1,3-bis(phenylphosphino)propane and 1,17-dichloro-6,9,12-tritosyl-3,15-dioxa-6,9,12-triazaheptadecane in THF using lithium hexamethyldisilazane (LDHS) as the base (method AA-5) (Wei et al., 1986, 1990). Two diastereomers of the initial [22]$N_3O_2P_2$-Ts_3 macrocycle were separated as Ni(II) complexes. The Ni(II) ion was removed using cyanide. The tosyl groups were removed without isomerizing the isomers by using sodium naphthalenide in glyme containing *t*-butyl alcohol.

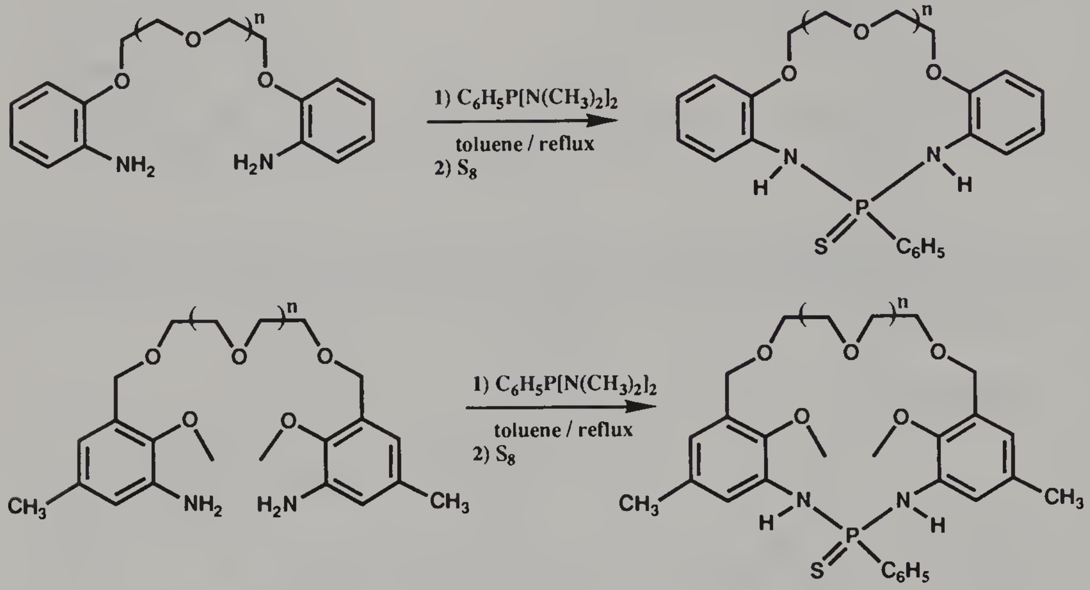
Method AA-5



2. Ring Closure to Form Two P—N Bonds

Bis(*N*,*N*-dimethylamino)phenylphosphine was treated with bis-aniline derivatives in refluxing toluene to give 17- to 21-membered phosphinaaza-crown compounds (method AB-1) (Dutasta and Simon, 1987; Dutasta et al., 1989).

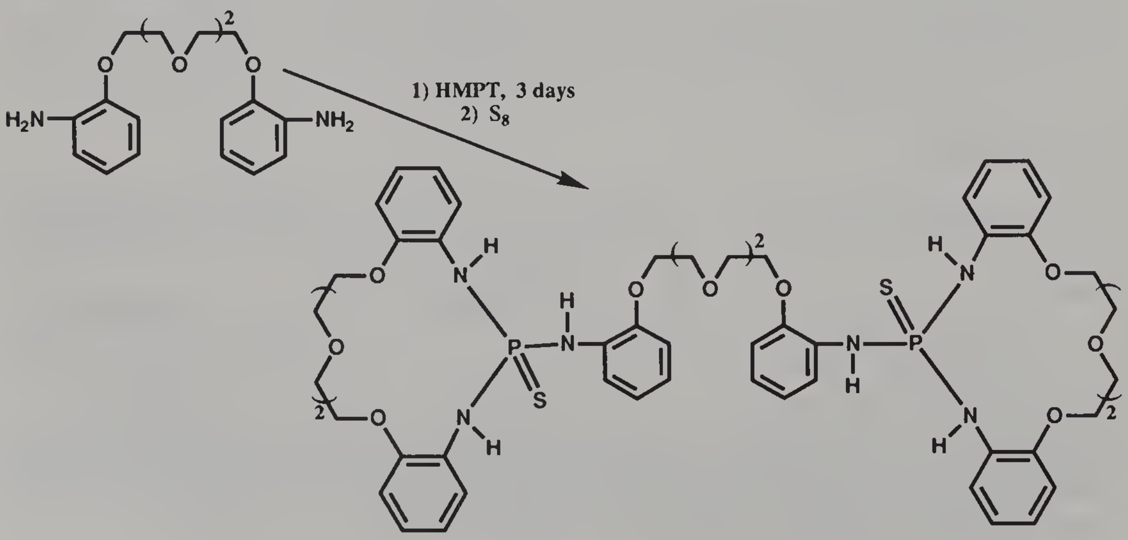
Method AB-1



The cyclization step gave yields of 70–80% even though the reaction was not carried out in high dilution. The initial phosphina-crown intermediates were oxidized to the thiophosphines using sulfur.

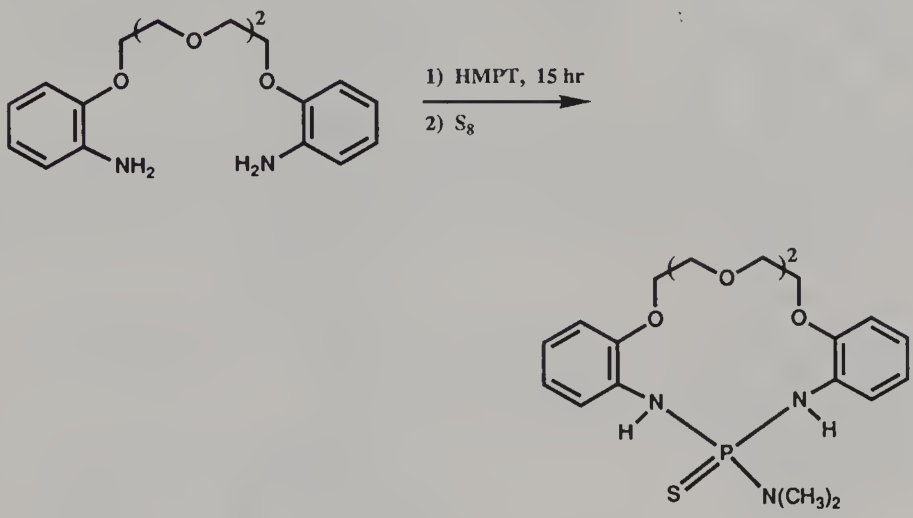
Hexamethylphosphorous triamide (HMPT) reacted with the same bis-aniline derivatives over a period of 3–4 days to form the bis-phosphinadiaza-crowns connected by a bis-anilide moiety (method AB-2) (Dutasta et al.,

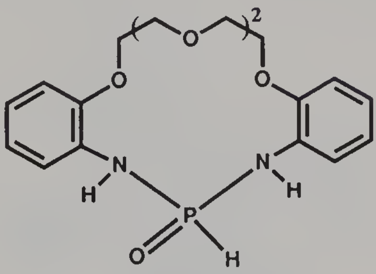
Method AB-2



1989). Sulfur was used to oxidize the initial phosphina-crown intermediate to the thiophosphine. Product yields were low in these reactions. When the cyclization reaction was carried out over a short period of time (15–20 hr), a monocrown was formed in a 36% yield (method AB-3) (Dutasta et al., 1989). The cyclic thiophosphine products are very sensitive to hydrolysis by moisture giving the cyclic phosphine oxide in a 45% yield.

Method AB-3

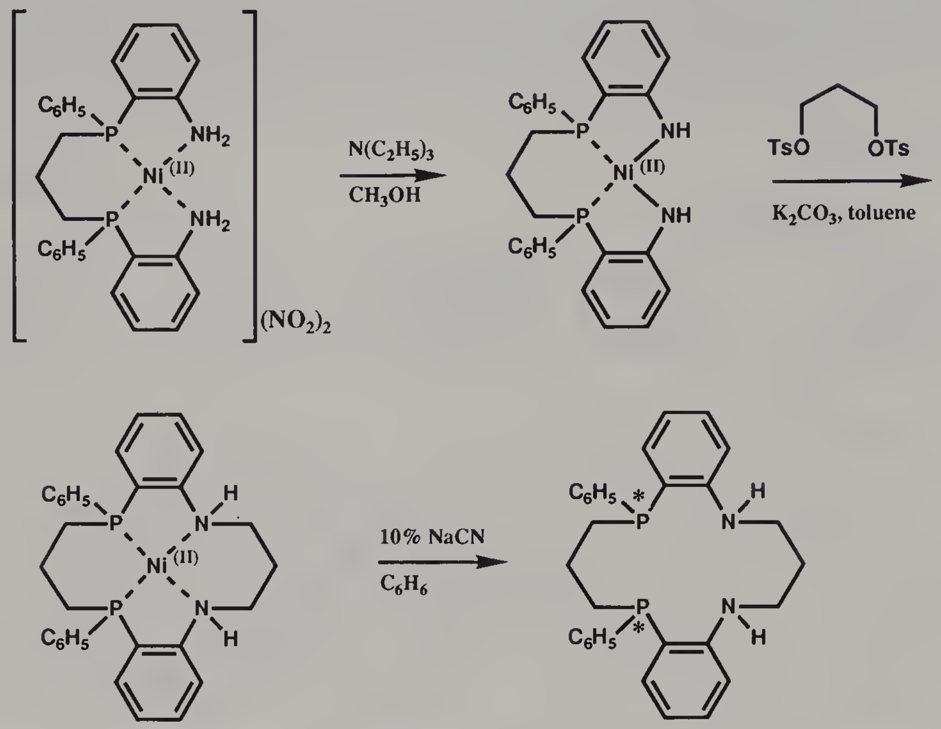




3. Ring Closure to Form Two C—N Bonds

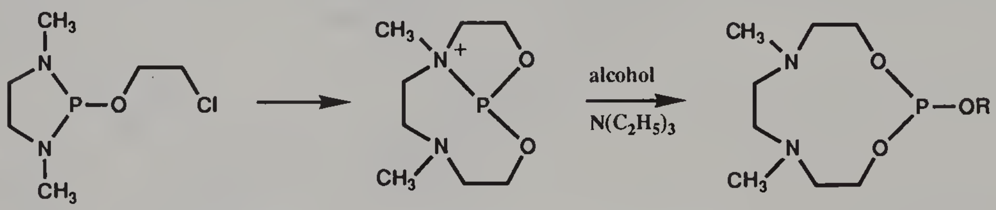
The preparation of macrocyclic ligands by a direct alkylation of metal-coordinated amines using a template effect is rare because the complexed amine is seldom a good nucleophile. The complexed anilines, on the other hand, can be deprotonated, which enhances the nucleophilicity of the nitrogen atom. Such a reaction of a complexed diphosphorous-containing bisaniline with a ditosylate ester gave the complexed macrocyclic ligand (method AC-1) (Ansell et al., 1985).

Method AC-1



An [11]N_2O_2P macrocycle was prepared by the unusual reaction shown below (method AC-2) (Powell et al., 1983; Sliwa and Picavet, 1977; Vaccher et al., 1984). The initial phosphorous complex was reacted with alcohol and base to form the crown.

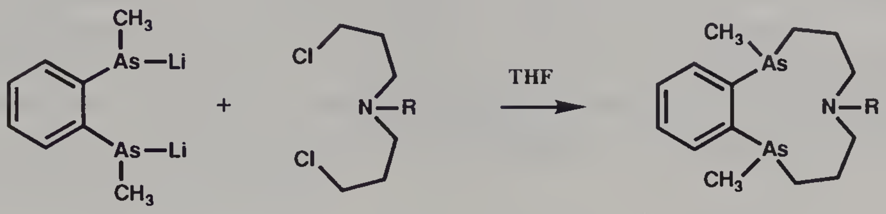
Method AC-2



D. AZA-CROWN MACROCYCLES CONTAINING ARSENIC AND SILICON ATOMS IN THE MACRORING

Only a few examples of an arsenaaza-crown have been reported. 1,2-Bis(dimethylarsino)benzene was treated with bis(3-dichloropropyl)amine in THF under high-dilution conditions to give the benzodiarsenaaza-crown in a yield of 50% (Kyba et al., 1980) (method AD-1).

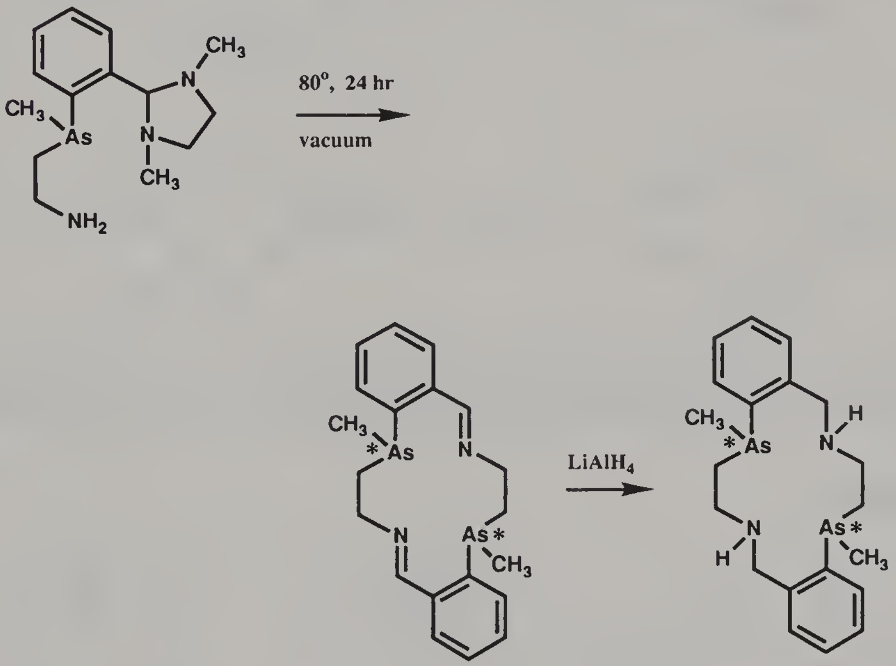
Method AD-1



R = CH_3, C_6H_5

A self-condensation of 2-(2-aminomethylarseno)benzaldehyde (protected by its imidazolidine derivative) gave the diarsenic-containing macrocyclic bis Schiff base as a pure diastereoisomer (method AD-2) (Martin et al., 1988).

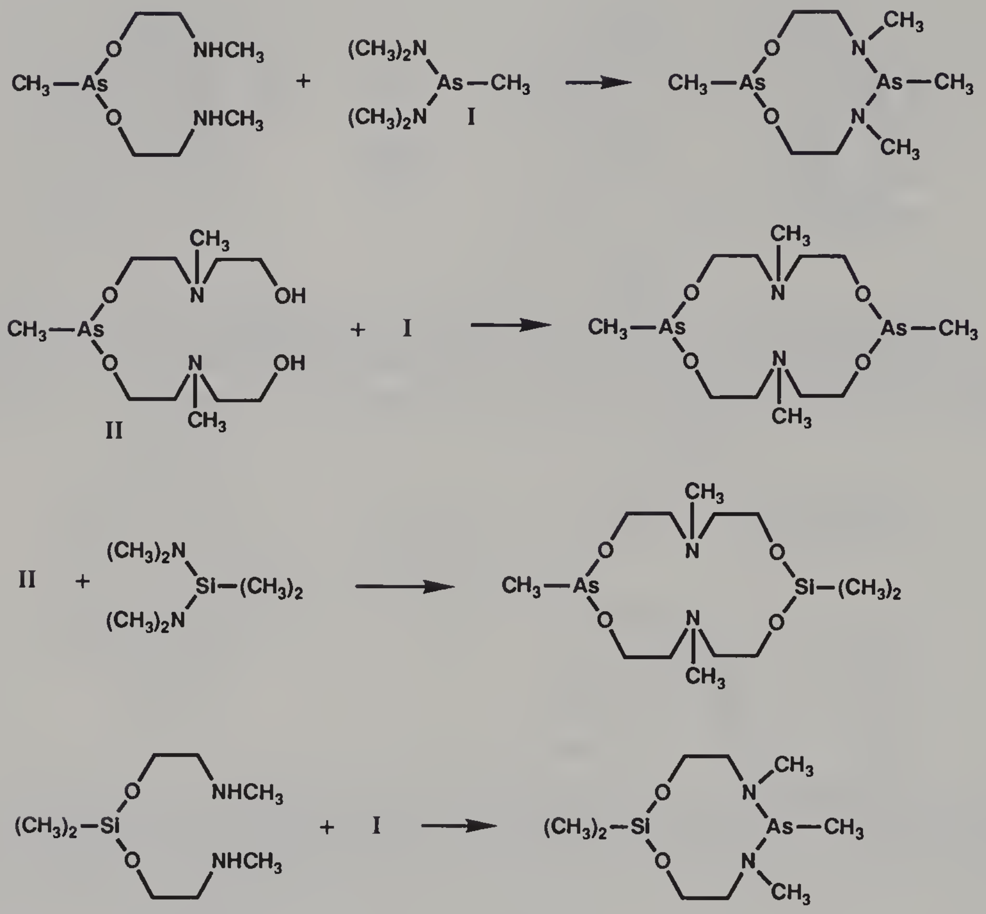
Method AD-2



The reaction was carried out by heating the starting material without high dilution and with no template ion. The bis Schiff base was reduced with lithium aluminum hydride.

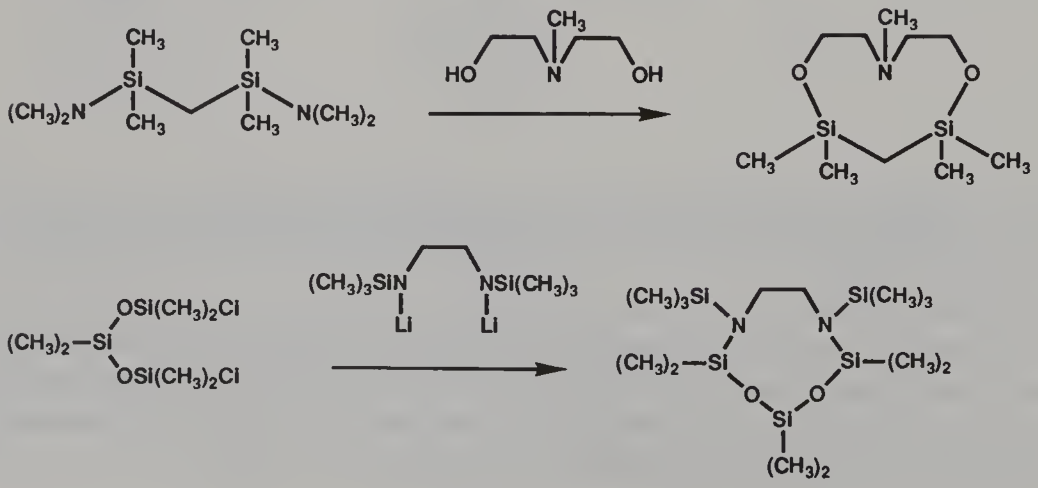
Other examples of arsenic-containing macrocycles have appeared together with synthetic methods to prepare macrocycles containing arsenic and silicon atoms and even tin atoms. The reactions of the aminoarsines with appropriate starting compounds were found to give average yields of various heterocyclicsystems as shown in method AE-1 (Phung et al., 1984).

Method AE-1



Silicon-containing macrocycles have been prepared by a high-dilution condensation of α,ω-difunctionalized silicon derivatives with *N*-methyldiethan-

Method AF-1

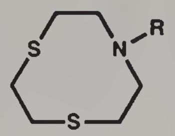


olamine (method AF-1) (Grobe and Voulgarakis, 1983; Wannagat and Eisele, 1978; Voronkov et al., 1982). The same authors have prepared macrocyles with tin, silicon, nitrogen, and oxygen atoms in the same ring.

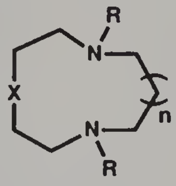
Tables listing the known aza-crown macrocycles containing sulfur, phosphorus, arsenic, and silicon atoms in the macroring are presented hereafter. Insofar as possible, tables are ordered by the number of heteroatoms and complexity of the substituents.

E. TABLES OF COMPOUNDS

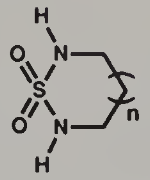
TABLE 9.1. CROWN ETHERS WITH THREE HETEROATOMS



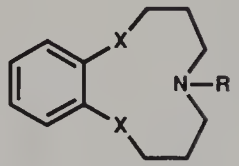
9.1 A



9.1 B



9.1 C

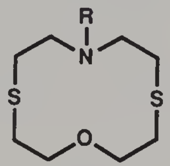


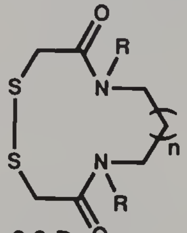
9.1 D

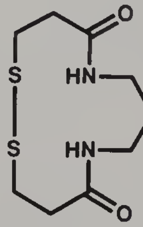
Structure	R	X	n	Method (or from R = formula)	Yield (%)	References
9.1 A	H			Y-10	73	Craig et al., 1990
				Y-10	50	McAuley and Subramanian, 1990
				Y-10	73	Parker et al., 1989
	CH_3			(H)		Craig et al., 1990
	Ts			Y-10	43	Craig et al., 1990
				H-10	59	McAuley and Subramanian, 1990
					43	Parker et al., 1989
9.1 B	H	S	0	Z-11	48	Boeyens et al., 1985
				Z-11		Gahan et al., 1982
				(Ts)		Hart et al., 1983

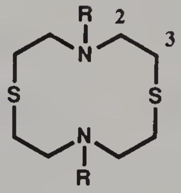
				Z-11	27	Wambeke et al., 1989
	H	S(O)	0	V	24,66 (salt)	Nonoyama and Nonoyama, 1985
	HO_2CCH_2-	S	0	(H)	63	Wambeke et al., 1989
	$H_2N(CH_2)_2$-	S	0	V		Gahan et al., 1982
	$NC(CH_2)_2$-			(H)	100	Fortier and McAuley, 1989
	$N_2N(CH_2)_3$-	S	0	$[CN(CH_2)_2]$		Fortier and McAuley, 1989
	Ts	S	0		10	Hart et al., 1983
				Z-11	30	Wambeke et al., 1989
	H	S	1	Z-11	15	Wambeke et al., 1989
	HO_2CCH_2-	S	1	(H)	56	Wambeke et al., 1989
	Ts	S	1	Z-11	25	Wambeke et al., 1989
9.1 C			5	Z-18	55	Arya and Shenoy, 1976
			6	Z-18	72	Arya and Shenoy, 1976
			7	Z-18	80	Arya and Shenoy, 1976
9.1 D	CH_3	$AsCH_3$		AD-1	41	Kyba and Chou, 1980a
				AD-1		Kyba and Chou, 1980b
	C_6H_5	$AsCH_3$		AD-1		Kyba and Chou, 1980b
	CH_3	PH		AA-3	80	Kyba and Heumuller, 1981
	CH_3	PC_6H_5		AA-1	42	Kyba et al., 1980
	C_6H_5	PC_6H_5		AA-1	56	Kyba et al., 1980

TABLE 9.2. CROWN ETHERS WITH FOUR HETEROATOMS


9.2 A


9.2 B


9.2 C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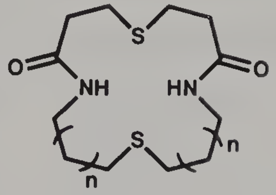
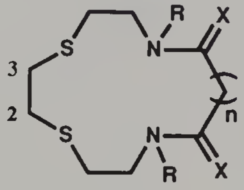
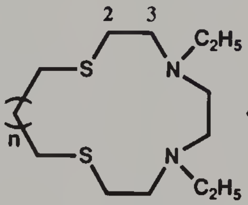
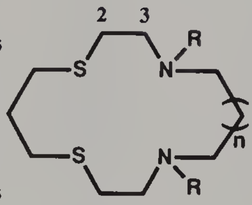
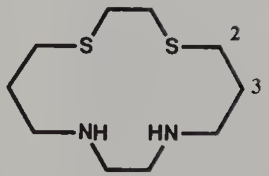
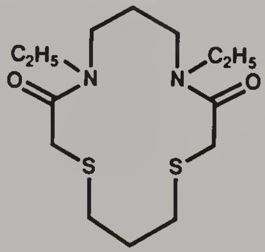

9.2 E


9.2 F


9.2 G


9.2 H


9.2 I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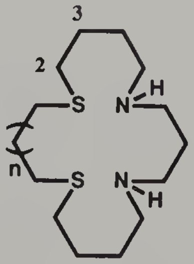
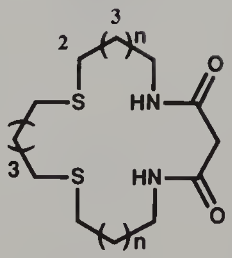
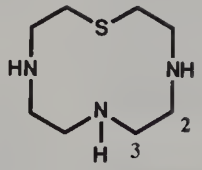

9.2 K


9.2 L


9.2 M

Structure	R	X	n	Other Substituents	Method (or from R = formula)	Yield (%)	References
9.2 A	H				Y-2		Black and McLean, 1969
					Y-1	18	Black and McLean, 1971
					Y-1	32	Shinkai et al., 1984
					Y-1	38	Youinou et al., 1986
					Y-2	65	Youinou et al., 1986
	$4\text{-}NO_2C_6H_4CH_2\text{-}$				(H)	60	Shinkai et al., 1984
	$C_6H_5CH_2\text{-}$				(H)	65	Shinkai et al., 1984
	Ts				Y-2	60	Youinou et al., 1986
9.2 B	H		0		Z-1	83	Owen et al., 1973
	CH_3		0		Z-1	74	Owen et al., 1973
	H		1		Z-1	62	Owen et al., 1973
9.2 C					Z-1	85	Owen et al., 1973

TABLE 9.2. (*Continued*)

Structure	R	X	n	Other Substituents	Method (or from R = formula)	Yield (%)	References
9.2 D	H				Z-3	55,94	Alberts et al., 1977, 1985
						62	Lehn et al., 1983
					Z-5	55	Siegfried and Kaden, 1984
	H			2,6-$(O)_2$	Z-3	76	Alberts et al., 1977, 1985
						58	Lehn et al., 1983
					Z-5	43	Siegfried and Kaden, 1984
	CH_3				(H)	96	Alberts et al., 1977, 1985
	$ClCH_2C(O)$-				(H)	90	Boyce et al., 1984
					(H)	90	Carroy et al., 1986
	$Cl(CH_2)_2$-				[$ClCH_2C(O)$]	63	Boyce et al., 1984
					[$ClCH_2C(O)$]	62	Carroy et al., 1986
	$HO_2CCH_2OCH_2C(O)$-				(H)	70	Alberts et al., 1977
							Carroy et al., 1986
	$Cl(CH_2)_2O(CH_2)_2$-				[$HO(CH_2)_2O$-$(CH_2)_2$]	96	Carroy et al., 1986

	$HO(CH_2)_2O(CH_2)_2$-				$[HO_2CCH_2$- $OCH_2C(O)]$	90	Carroy et al., 1986
	4-$NO_2C_6H_5O_2CCH_2OCH_2C(O)$-				$[HO_2CCH_2OCH_2$- $C(O)]$	85	Alberts et al., 1977
	$(C_6H_5)_2P(CH_2)_2$-				$[Cl(CH_2)_2]$	84	Boyce et al., 1984
					$[Cl(CH_2)_2]$	63	Carroy et al., 1986
	$(C_6H_5)_2P(CH_2)_2O(CH_2)_2$-				$[Cl(CH_2)_2$- $O(CH_2)_2]$	54 overall	Boyce et al., 1984
					$[Cl(CH_2)_2$- $O(CH_2)_2]$	75	Carroy et al., 1986
9.2 E		H_2	0		Z-5	64	Siegfried and Kaden, 1984
		O	0		Z-5	38	Siegfried and Kaden, 1984
		H_2	1		Z-5	37	Siegfried and Kaden, 1984
		O	1		Z-5	64	Siegfried and Kaden, 1984
9.2 F	H	H_2	0		Z-5	46	Siegfried and Kaden, 1984
	H	O	0		Z-5	37	Siegfried and Kaden, 1984
	C_2H_5	H_2	0	6,11-$(CH_2C_6H_5)_2$	Y-4	80	Lemaire et al., 1985
	H	O	4		Z-1	70	Voronkov et al., 1988a
	$NC(CH_2)_2$-	O	4				Voronkov and Knutov, 1990

TABLE 9.2. (*Continued*)

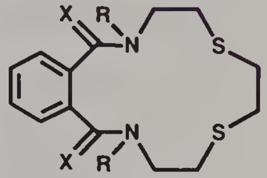
Structure	R	X	n	Other Substituents	Method (or from R = formula)	Yield (%)	References
	$HO(CH_2)_3$-	H_2	4				Voronkov and Knutov, 1990
	$HO_2C(CH_2)_2$-	O	4				Voronkov and Knutov, 1990
	$H_2N(CH_2)_3$-	H_2	4				Voronkov and Knutov, 1990
	$CH_3O_2C(CH_2)_2$-	O	4				Voronkov and Knutov, 1990
	$C_6H_5(CH_2)_2$-	O	4				Voronkov and Knutov, 1990
9.2 G			0	3,8-$(CH_2C_6H_5)_2$	Y-4	20	Vriesema et al., 1986
			1	3,8-$(CH_2C_6H_5)_2$	Y-4	26	Vriesema et al., 1986
			2	3,8-$(CH_2C_6H_5)_2$	Y-4	83	Lemaire et al., 1985
9.2 H	H		1	3,9-$(O)_2$			Bradshaw et al., 1990
	H			6,6-CH_2NO_2	Z-15	as complex	Comba et al., 1988
	H		1	6,6-$(CH_3)_2$	Z-6		Kimura et al., 1989

	H	1	5,7-$(O)_2$; 6,6-$(CH_3)_2$	Z-6		Kimura et al., 1989
	C_2H_5	1	3,9-$(CH_2C_6H_5)_2$	Y-4	88	Lemaire et al., 1985
		1		Y-4	16	Vriesema et al., 1986
	CH_3	2	3,10-$(CH_2C_6H_5)_2$	Y-4	90	Lemaire et al., 1985
	C_2H_5	2	3,10-$(CH_2C_6H_5)_2$	Y-4	83	Lemaire et al., 1985
		2		Y-4	31	Vriesema et al., 1986
9.2 I				Z-5	60	Siegfried and Kaden, 1984
			4,9-$(O)_2$	Z-5	32	Siegfried and Kaden, 1984
9.2 J				Y-7	41	Krakowiak et al., 1990
9.2 K		1	5,11-$(O)_2$	Z-5	44	Siegfried and Kaden, 1984
		3	7,9-$(O)_2$			Tulchinsky et al., 1990
		3	7,9-$(O)_2$;8,8-$(CH_3)_2$			Tulchinsky et al., 1990
		3	7,9-$(O)_2$;8,8-$(C_2H_5)_2$			Tulchinsky et al., 1990

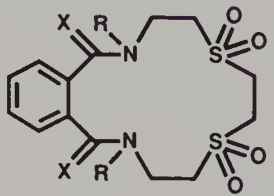
TABLE 9.2. (*Continued*)

Structure	R	X	n	Other Substituents	Method (or from R = formula)	Yield (%)	References
9.2 L			2				Tulchinsky et al., 1990
			2	8,8-$(CH_3)_2$			Tulchinsky et al., 1990
			3	9,9-$(CH_3)_2$			Tulchinsky et al., 1990
			3	9,9-$(C_2H_5)_2$			Tulchinsky et al., 1990
9.2 M					Z-8		Kodama et al., 1984
				8,12-$(O)_2$	Z-8		Kodama et al., 1984

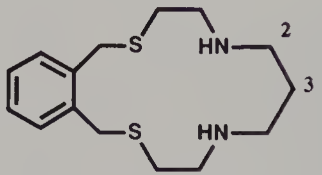
TABLE 9.3. BENZO-CROWN ETHERS WITH FOUR HETEROATOMS



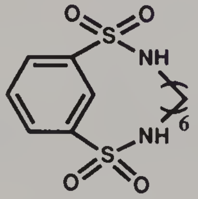
9.3 A



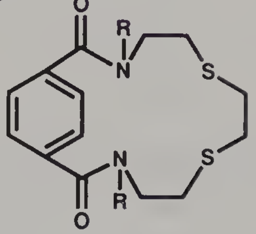
9.3 B



9.3 C



9.3 D



9.3 E

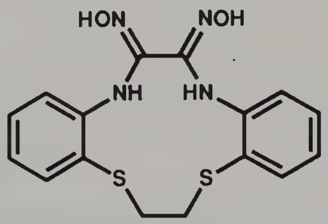
Structure	R	X	m	n	Other Substituents	Method	Yield (%)	References
9.3 A	H	O				Z-17	66	Voronkov et al., 1979, 1984a
	$NC(CH_2)_2$-	O						Voronkov and Knutov, 1990
	$HO_2C(CH_2)_2$-	O						Voronkov and Knutov, 1990

TABLE 9.3. (*Continued*)

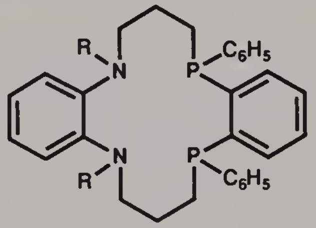
Structure	R	X	m	n	Other Substituents	Method	Yield (%)	References
	$HO(CH_2)_3$-	H_2						Voronkov and Knutov, 1990
	$H_2N(CH_2)_3$-	H_2						Voronkov and Knutov, 1990
	$CH_3O_2C(CH_2)_2$-	O				Z-17	70	Voronkov et al., 1979, 1984a
	$CH_3O_2CCH(CH_2CO_2CH_3)$-					Z-17	57	Voronkov et al., 1988b
	$C_6H_5(CH_2)_2$-	O						Voronkov and Knutov, 1990
	$C_2H_5O_2CCH_2CH(COC_2H_5)$-					Z-17	70	Voronkov et al., 1984b
9.3 B	$CH_3O_2C(CH_2)_2$-					Z-17	50	Voronkov et al., 1988a
	$CH_3O_2CCH(CH_2CO_2CH_3)$-					Z-17	60	Voronkov et al., 1988b

9.3 C		as Ni complex	Y-6		Hay et al., 1976
		as Ni complex	Y-6		Drew et al., 1980
		2-CH_3;4,4-$(CH_3)_2$		42	Kallianou and Kaden, 1979
9.3 D			Z-25	65	Voronkov et al., 1988a
9.3 E	$NC(CH_2)_2$-				Voronkov and Knutov, 1990
	$HO_2C(CH_2)_2$-				Voronkov and Knutov, 1990
	$CH_3O_2C(CH_2)_2$-				Voronkov and Knutov, 1990
			Z-17	70	Voronkov et al., 1988a
	$CH_3O_2CCH(CH_2CO_2CH_3)$-		Z-17	60	Voronkov et al., 1988b
	$C_6H_5(CH_2)_2$-				Voronkov and Knutov, 1990
			Z-17	70	Voronkov et al., 1988a

TABLE 9.4. DIBENZO-CROWN ETHERS WITH FOUR HETEROATOMS



9.4 A



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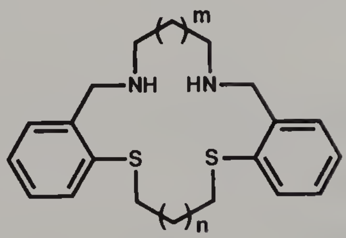

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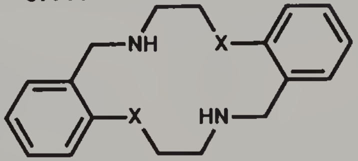

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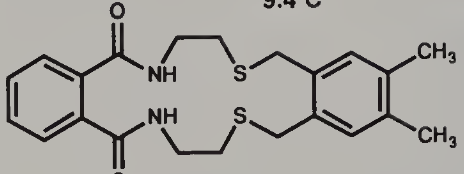
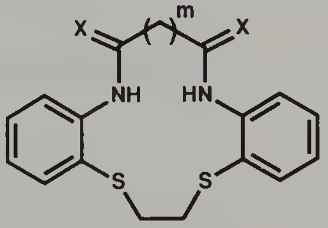
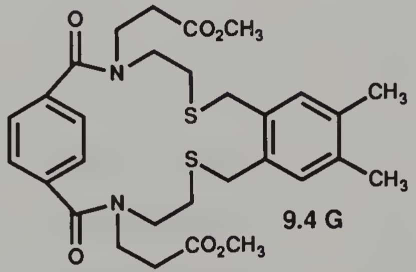


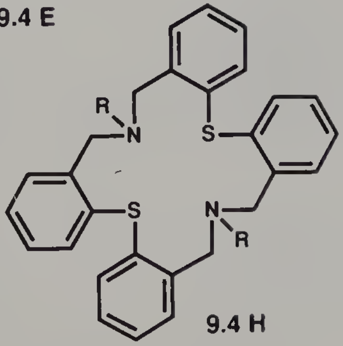
9.4 E



9.4 F



9.4 G



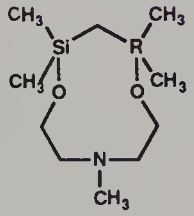
9.4 H

Structure	R	X	m	n	Other Substituents	Method	Yield (%)	References
9.4 A							27	Gok and Demirbag, 1989
9.5 B	H					AC-1		Ansell et al., 1985
	CH_3					AA-2	18	Kyba et al., 1981
9.4 C			0	0		Z-10	40	Lindoy and Smith, 1981
			1	0		Z-10	40	Lindoy and Smith, 1981
			1	1		Z-10	40	Lindoy and Smith, 1981
9.4 D		S				Z-26	85	Martin et al., 1985, 1987
		$AsCH_3$				AD-2		Martin et al., 1988
9.4 E							65	Voronkov et al., 1988a
9.4 F		O	3			Z-28	70	Formanovskii and Murakhovskaya, 1985
		H_2	7			Z-28	78	Formanovskii and Murakhovskaya, 1985

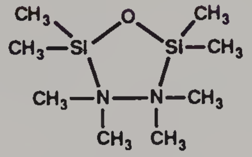
TABLE 9.4. (*Continued*)

Structure	R	X	m	n	Other Substituents	Method	Yield (%)	References
9.4 G							60	Voronkov et al., 1988a
9.4 H	CH_3					Z-13	23	Tanaka et al., 1973
	C_2H_5					Z-13	8	Tanaka et al., 1973
	$HO(CH_2)_2$-					Z-13	4	Tanaka et al., 1973
	CH_2=$CHCH_2$-					Z-13	11	Tanaka et al., 1973
	C_3H_7					Z-13	9	Tanaka et al., 1973
	$HO(CH_2)_3$-					Z-13	4	Tanaka et al., 1973
	$C_6H_5CH_2$-					Z-13	3	Tanaka et al., 1973

TABLE 9.5. CROWN ETHERS WITH FIVE HETEROATOMS



9.5 A



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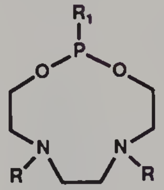

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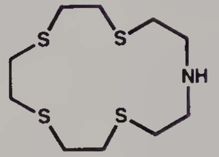

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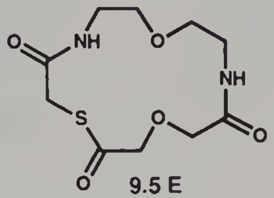

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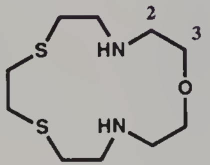
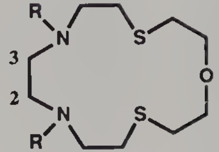
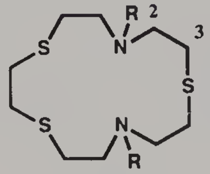


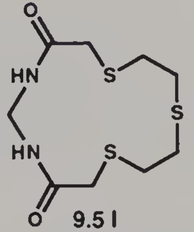
9.5 F



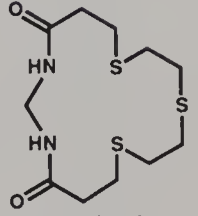
9.5 G



9.5 H



9.5 I



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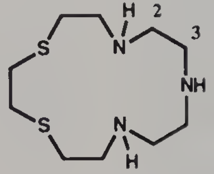
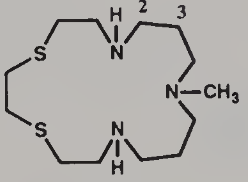
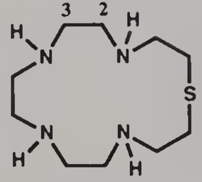


9.5 K



9.5 L



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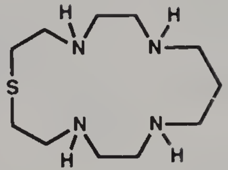


9.5 N

TABLE 9.5. (*Continued*)

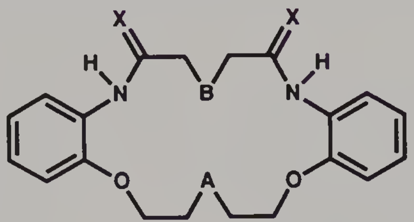
Structure	R	R_1	Other Substituents	Method (or from R = formula)	Yield (%)	References
9.5 A	Si				44	Grobe and Voulgarkis, 1983
	Sn				27	Grobe and Voulgarkis, 1983
9.5 B				AF-1		Voronkov et al., 1982
9.5 C	H	CH_3O-		AC-2	65	Vaccher et al., 1984
	H	C_2H_5O-		AC-2	80	Vaccher et al., 1984
	H	i-C_4H_9O-		AC-2	75	Vaccher et al., 1984
	H	s-C_4H_9O-		AC-2	80	Vaccher et al., 1984
	CH_3	CH_3O-		AC-2		Sliwa and Picavet, 1977
	CH_3	C_2H_5O-		AC-2		Sliwa and Picavet, 1977
9.5 D				Y-5		Pavlishchuk and Strizhak, 1989
						Yatsimirskii et al., 1989

9.5 E			Z-3	35	Lukyanenko et al., 1980
9.5 F			Z-3		Pelissard and Louis, 1972
		2,6-$(O)_2$	Z-3	45	Pelissard and Louis, 1972
9.5 G	H		Z-2		Pelissard and Louis, 1972
	H	5,15-$(O)_2$	Z-2	54	Pelissard and Louis, 1972
	CH_3	5,15-$(O)_2$	Y-7	35	Krakowiak et al., 1990
9.5 H	H		Z-3	93	Alberts et al., 1985
			Z-3		Pelissard and Louis, 1972
	H	6,14-$(O)_2$	Z-3	66	Alberts et al., 1985
	H	2,6-$(O)_2$	Z-3	57	Pelissard and Louis, 1972
	CH_3		(H)		Alberts et al., 1985
	$HO_2CCH_2OCH_2C(O)$-		(H)		Alberts et al., 1985
	4-$NO_2C_6H_4O_2CCH_2OCH_2C(O)$-		[HO_2CCH_2O- $CH_2C(O)$]		Alberts et al.,1985
9.5 I			Y-7		Ishii et al., 1988

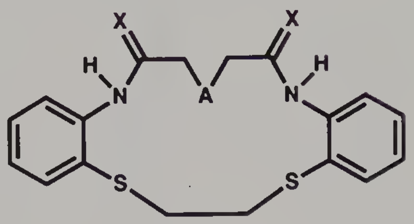
TABLE 9.5. (*Continued*)

Structure	R	R^1	Other Substituents	Method (or from R = formula)	Yield (%)	References
9.5 J				Y-9		Ishii et al., 1988
9.5 K				Z-8	36	Tabushi et al., 1976, 1977
			8,15-$(O)_2$	Z-8	41	Tabushi et al., 1976, 1977
9.5 L				Z-2		Pelissard and Louis, 1972
			10,17-$(O)_2$	Z-2	51	Pelissard and Louis, 1972
9.5 M				Z-8	39	Tabushi et al., 1976, 1977
			11,15-$(O)_2$	Z-8	15,44	Tabushi et al., 1976, 1977
9.5 N				Z-9	36	Kimura et al., 1984
				Z-8		Kodama et al., 1984

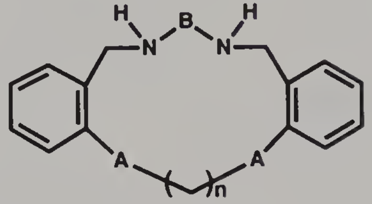
TABLE 9.6. DIBENZO-CROWN ETHERS WITH FIVE HETEROATOMS



9.6 A



9.6 B



9.6 C

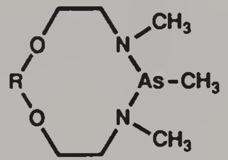
Structure	A	B	X	n	Method	Yield (%)	References
9.6 A	$-(CH_2)_2-$	S	H_2		Z-28	75	Formanovskii and Murakhovskaya, 1985
	$-(CH_2)_2-$	S	O		Z-28	64	Formanovskii and Murakhovskaya, 1985
	$-(CH_2)_3-$	S	H_2				Pasekova et al., 1988
	$-(CH_2)_3-$	S	O		Z-27	4	Biernat et al., 1979
	$-CH_2CH(OH)CH_2-$	S	H_2				Mikhura and Formanovskii, 1990

TABLE 9.6. (*Continued*)

Structure	A	B	X	n	Method	Yield (%)	References
	$-(CH_2)_4-$	S	H_2				Mikhura et al., 1990
							Pasekova et al., 1988
	$-(CH_2)_4-$	S	H_2				Mikhura et al., 1990
	$-(CH_2)_5-$	S	H_2		Z-28	64	Formanovskii et al., 1989
	$-(CH_2)_5-$	S	O		Z-28	80	Formanovskii et al., 1989
	S	CH_2	H_2		Z-28	70	Formanovskii et al., 1989
	S	CH_2	O		Z-28	51	Formanovskii et al., 1989
9.6 B	O		O		Z-28	84	Formanovskii and Murakhovskaya, 1985
	O		H_2		Z-28	95	Formanovskii and Murakhovskaya, 1985
	S		O		Z-28	90	Formanovskii and Murakhovskaya, 1985
	S		H_2		Z-28	89	Formanovskii and Murakhovskaya, 1985

9.6 C	O	$-(CH_2)_2S(CH_2)_2-$	1	Z-10	40	Baldwin et al., 1987
	O	$-(CH_2)_2S(CH_2)_2-$	2	Z-10		Adam et al., 1987
				Z-10	60	Baldwin et al., 1987
	O	$-(CH_2)_3S(CH_2)_3-$	2	Z-10	30	Baldwin et al., 1987
	O	$-(CH_2)_2S(CH_2)_2-$	4	Z-10	20	Baldwin et al., 1987
	S	$-(CH_2)_2S(CH_2)_2-$	1	Z-10	40	Baldwin et al., 1987
	S	$-(CH_2)_2S(CH_2)_2-$	2	Z-10		Adam et al., 1987
				Z-10	40	Baldwin et al., 1987
	S	$-(CH_2)_2S(CH_2)_2-$	3	Z-10	30	Baldwin et al., 1987
	S	$-(CH_2)_2O(CH_2)_2-$	2	Z-10		Adam et al., 1987
					70	Baldwin et al., 1987
	S	$-(CH_2)_2NH(CH_2)_2-$	1	Z-10	70	Baldwin et al., 1987
	S	$-(CH_2)_2NH(CH_2)_2-$	2	Z-10		Adam et al., 1987
				Z-10	40	Baldwin et al., 1987
	S	$-(CH_2)_3NH(CH_2)_3-$	2	Z-10	25	Baldwin et al., 1987
	NH	$-(CH_2)_2S(CH_2)_2-$	2	Z-10		Adam et al., 1987

TABLE 9.7. CROWN ETHERS WITH SIX HETEROATOMS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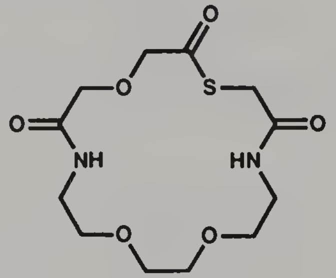
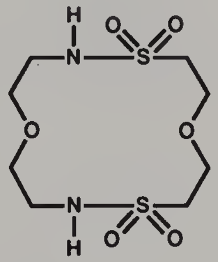

9.7 B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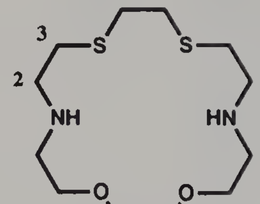
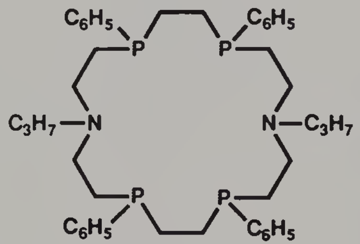
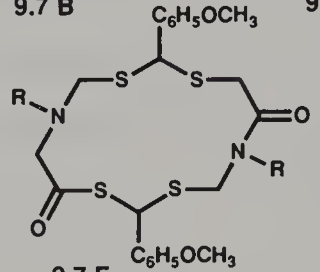

9.7 D


9.7 E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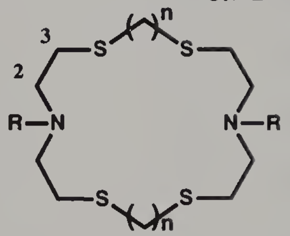
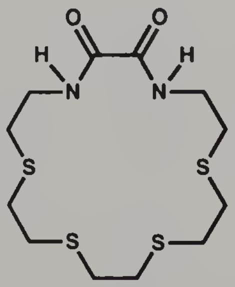

9.7 G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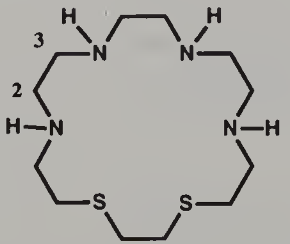
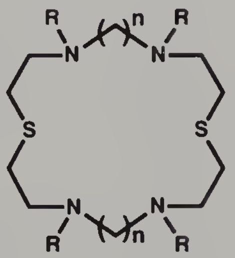

9.7 I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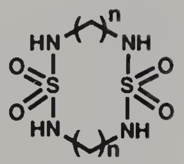

9.7 K

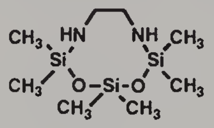
Structure	R	n	Other Substituents	Method	Yield (%)	References
9.7 A	$(CH_3)_2Si$-			AE-1	38	Phung et al., 1984
	CH_3As-			AE-1	35	Phung et al., 1984
9.7 B				Z-3	30	Lukyanenko et al., 1980
9.7 C						Markovich et al., 1990
9.7 D				Z-3	55	Dietrich et al., 1970
				Z-3	70	Lehn, 1975
			11,18-$(O)_2$	Z-3	60	Lehn, 1975
9.7 E				AA-4		Ciampolini et al., 1983
9.7 F	H			Y-8	61	Cynkier et al., 1979
	CH_3			Y-8		Cynkier et al., 1979
9.7 G	H	2		Y-3	8,5	Black and McLean, 1968, 1971
				Z-3	45	Dietrich et al., 1970
				Z-3	50	Lehn, 1975

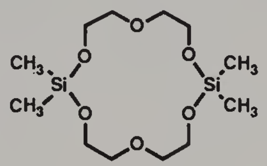
TABLE 9.7. (*Continued*)

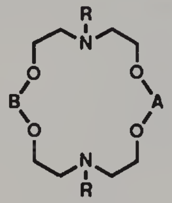
Structure	R	n	Other Substituents	Method	Yield (%)	References
	H	2	2,9-$(O)_2$	Z-3		Dietrich et al., 1970
				Z-3	85	Lehn, 1975
	CH_3	2		(H)		Alberts et al., 1977
	$HO_2CCH_2OCH_2C(O)$-	2		(H)	80	Alberts et al., 1977
	Ts	2		Y-10	10	Craig et al., 1990
	p-nitrophenyl-$O_2CCH_2OCH_2C(O)$-	2		$[H_2OCCH_2O$-$CH_2C(O)]$	70	Alberts et al., 1977
	H	5		Z-4	95	Agnus et al., 1979, 1984
	H	5	2,12-$(O)_2$	Z-4	50	Agnus et al., 1979, 1984
	$HS(CH_2)_2$-	5		Z-4		Agnus et al., 1979
	$H_2N(CH_2)_2$-	5		Z-4	95	Agnus et al., 1979
	$(CH_3)_2N(CH_2)_2$-	5		Z-4		Agnus et al., 1979
	2-pyridinyl-CH_2-	5		Z-4		Agnus et al., 1979
	2-pyridinyl-$CH_2NH(CH_2)_2$-	5		Z-4		Agnus, 1979
	2-$HOC_6H_4CH_2NH(CH_2)_2$-	5		Z-4		Agnus, 1979
	$TsNHCH_2C(O)$-	5		Z-4		Agnus, 1979
	$TsNH(CH_2)_2$-	5		Z-4		Agnus, 1979

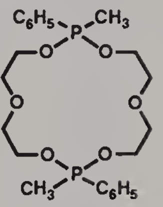
9.7 H				Z-7	80	Voronkov et al., 1979
9.7 I				Z-8		Tabushi et al., 1976, 1977
			11,18-$(O)_2$	Z-8	29	Tabushi et al., 1976, 1977
9.7 J	$NC(CH_2)_2$-	1				Voronkov and Knutov, 1990
	$CH_3O_2C(CH_2)_2$-	1		Z-14	70	Voronkov et al., 1989
						Voronkov and Knutov, 1990
	$C_6H_5(CH_2)_2$-	1		Z-14	68	Voronkov et al., 1989
						Voronkov and Knutov, 1990
	H	2		Z-12	64	Craig et al., 1989, 1990
	CH_3	2		(H)	56,55	Craig et al., 1989, 1990
	Ts	2		Z-12	62	Craig et al., 1989, 1990
9.7 K		6		Z-18	78	Ciaperoni et al., 1965
		9		Z-18	95	Arya and Shenoy, 1976
		10		Z-18	95	Arya and Shenoy, 1976
				Z-18	85	Ciaperoni et al., 1965
		12		Z-18	90	Arya and Shenoy, 1976

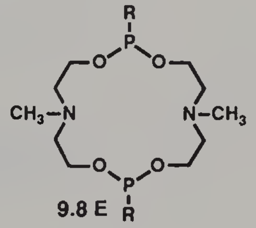
TABLE 9.8. CROWN ETHERS WITH SEVEN AND EIGHT HETEROATOMS

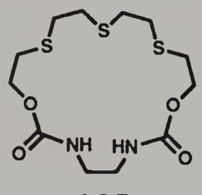

9.8 A

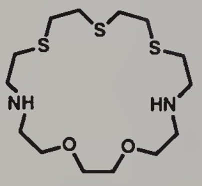

9.8 B

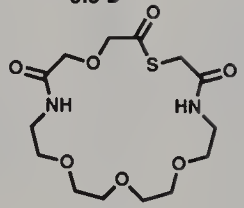

9.8 C

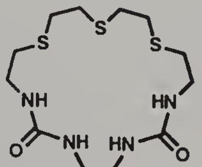

9.8 D

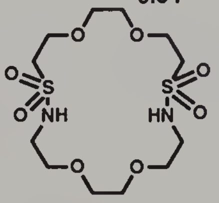

9.8 E

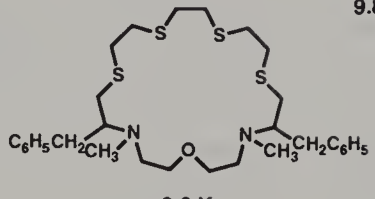

9.8 F

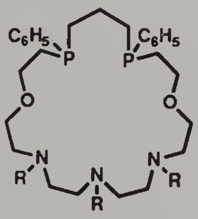

9.8 G

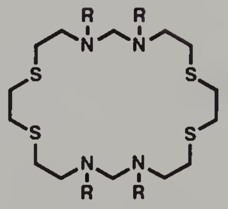

9.8 H

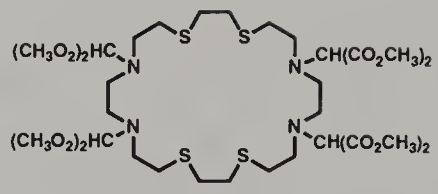

9.8 I


9.8 J


9.8 K


9.8 L


9.8 M


9.8 N

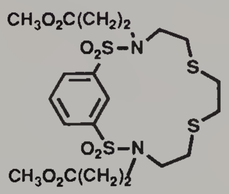
Structure	A	B	R	Method	Yield (%)	References
9.8 A				AF-1		Wannagat and Eisele, 1978
9.8 B						Voronkov et al., 1990
9.8 C	CH_3As	CH_3As	CH_3	AE-1	40	Phung et al., 1984
	$(CH_3)_2Si$	CH_3As	CH_3	AE-1	32	Phung et al., 1984
	$(CH_3)_2Si$	$(CH_3)_2Si$	H			Voronkov et al., 1990
	$C_6H_5(CH_3)Si$	$(CH_3)_2Si$	H			Voronkov et al., 1990
9.8 D						Voronkov et al., 1990
9.8 E			S, CH_3			Dutasta, 1986
			C_6H_5, CH_3			Voronkov et al., 1990
9.8 F				Z-16		Ishii et al., 1988
9.8 G				Z-16		Ishii et al., 1988

TABLE 9.8. (*Continued*)

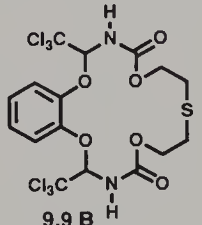
Structure	A	B	R	Method	Yield (%)	References
9.8 H				Z-3	27	Lukyanenko et al., 1981
9.8 I				Z-16		Ishii et al., 1988
9.8 J						Markovich et al., 1990
9.8 K				Y-4	90	Lemaire et al., 1985
				Y-4	21	Vriesema et al., 1986

9.8 L	H		AA-5	86	Wei et al., 1986, 1990
	Ts		AA-5	68	Wei et al., 1986, 1990
9.8 M		$NC(CH_2)_2$-			Voronkov and Knutov, 1990
		$CH_3O_2C(CH_2)_2$-			Voronkov and Knutov, 1990
		$C_6H_5CH_2$-	Z-14		Voronkov et al., 1989
		$C_6H_5(CH_2)_2$-	Z-14		Voronkov et al., 1989
9.8 N			Z-14	65	Voronkov et al., 1988b

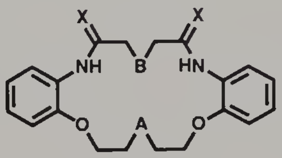
TABLE 9.9. BENZO-CROWN ETHERS WITH SIX TO TEN HETEROATOMS



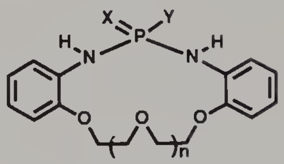
9.9 A



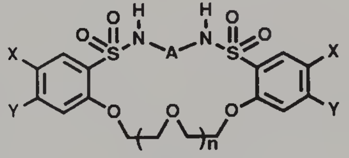
9.9 B



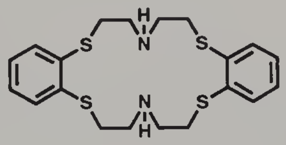
9.9 C



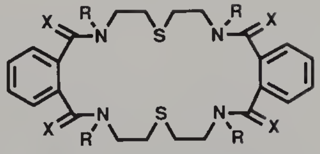
9.9 D



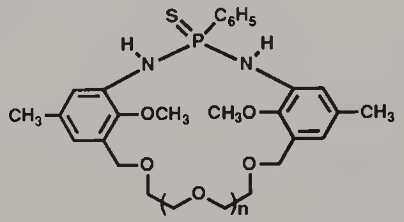
9.9 E



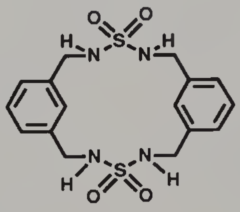
9.9 F



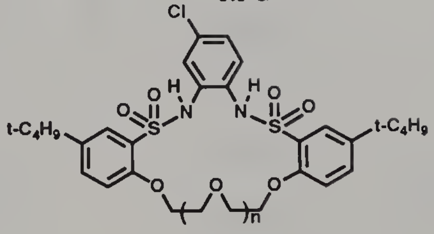
9.9 G



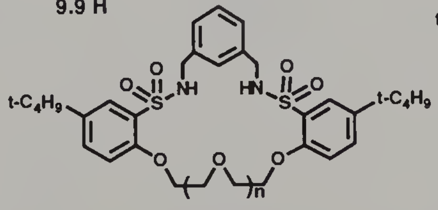
9.9 H



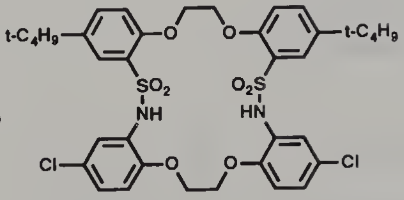
9.9 I



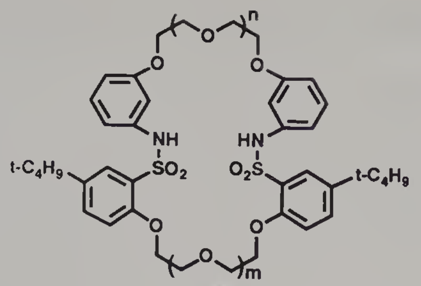
9.9 J



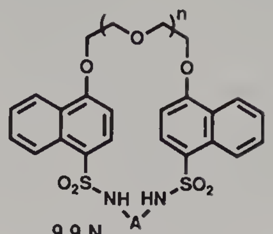
9.9 K



9.9 L



9.9 M



9.9 N

Structure	A	B	R	X	Y	n	m	Method	Yield (%)	References
9.9 A								Z-25	75	Voronkov et al., 1988a
9.9 B								Z-16	13	Kudrya et al., 1979
9.9 C	O	S		H_2				Z-28	77	Formanovskii et al., 1989
										Torocheshnikova et al.,1990
	O	S		O				Z-28	88	Formanovskii et al., 1989
								Z-27		Biernat et al., 1979
	S	O		H_2				Z-28	65	Formanovskii et al., 1989
	S	O		O				Z-28	35	Formanovskii et al., 1989
	S	S		H_2				Z-28	54	Formanovskii et al., 1989

TABLE 9.9. (*Continued*)

Structure	A	B	R	X	Y	n	m	Method	Yield (%)	References
	S	S		O				Z-28	30	Formanovskii et al., 1989
	NTs	S		H_2				Z-28	38	Formanovskii et al., 1989
	NTs	S		O				Z-28	96	Formanovskii et al., 1989
	S	NTs		H_2				Z-28	57	Formanovskii et al., 1989
	S	NTs		O				Z-28	27	Formanovskii et al., 1989
	$-O(CH_2)_2O-$	S		O				Z-27	16	Biernat et al., 1979
9.9 D				O	H	2		AB-3	45	Dutasta et al., 1989
				S	$(CH_2)_3N-$	2		AB-3	36	Dutasta et al. 1989
				S	$C_6H_5CH_2-$	2		AB-1	80	Dutasta and Simon, 1987
				S	$C_6H_5CH_2-$	3		AB-1	70	Dutasta and Simon, 1987

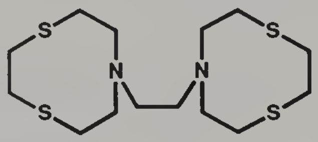
9.9 E	$-CH(C_6H_5)CH(C_6H_5)-$		$t-C_4H_9$	H	1	Z-23	9	Bradshaw et al., 1987
	$-(CH_2)_2O(CH_2)_2-$		CH_3	H	2			Tsirkina et al., 1990
	$-(CH_2)_2O(CH_2)_2-$		H	NO_2	2	Z-24	20	Dziomko et al., 1989
	$-CH_2(CH_2OCH_2)_2CH_2-$		$t-C_4H_9$	H	0	Z-23	72	Bradshaw et al., 1987
	$-CH_2(CH_2OCH_2)_2CH_2-$		CH_3	H	1			Tsirkina et al., 1990
	$-CH_2(CH_2OCH_2)_2CH_2-$		CH_3	H	2			Tsirkina et al., 1990
	$-CH_2(CH_2OCH_2)_2CH_2-$		H	NO_2	2	Z-24	20	Dziomko et al., 1989
9.9 F								Ishii et al., 1988
9.9 G		$NC(CH_2)_2-$	O					Voronkov and Knutov, 1990
		$NO(CH_2)_3-$	H_2					Voronkov and Knutov, 1990
		$CH_3O_2C(CH_2)_2-$	O					Voronkov and Knutov, 1990
		$C_6H_5(CH_2)_2-$	O					Voronkov and Knutov, 1990

TABLE 9.9. *(Continued)*

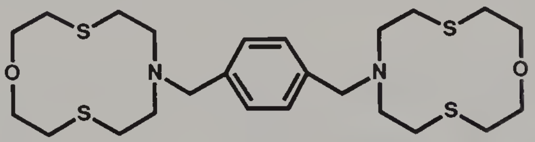
Structure	A	B	R	X	Y	n	m	Method	Yield (%)	References
9.9 H						1		AB-1	10	Dutasta and Simon, 1987
						2		AB-1	20	Dutasta and Simon, 1987
9.9 I								Z-19	80	Arya and Shenoy, 1976
9.9 J						1		Z-22	10	Biernat et al., 1987
						2		Z-22	20	Biernat et al., 1987
9.9 K						1		Z-22	12	Bradshaw et al., 1987
						2		Z-22	17	Bradshaw et al., 1987

9.9 L				Z-21	25	Biernat et al., 1987
9.9 M		0	0	Z-21	70	Bradshaw et al., 1987
		0	1	Z-21	6	Bradshaw et al., 1987
		1	0	Z-21	91	Bradshaw et al., 1987
		1	1	Z-21	10	Bradshaw et al., 1987
9.9 N	$-(CH_2)_2O(CH_2)_2-$	2		Z-20		Prajer-Janczewska and Bartosz-Bechowski, 1987
	$-(CH_2)_5-$	1		Z-20	60	Prajer-Janczewska and Bartosz-Bechowski, 1984, 1987
	$-CH_2(CH_2OCH_2)_2CH_2-$	1		Z-20	64	Prajer-Janczewska and Bartosz-Bechowski, 1984
	$-CH_2(CH_2OCH_2)_2CH_2-$	2		Z-20	38	Prajer-Janczewska and Bartosz-Bechowski, 1984, 1987

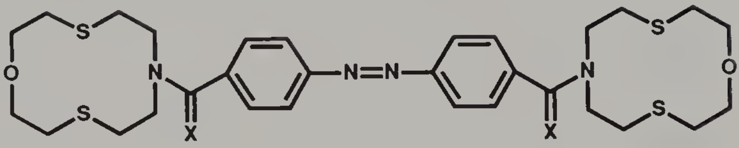
TABLE 9.10. BIS-CROWN ETHERS WITH SULFUR AND PHOSPHOROUS HETEROATOMS



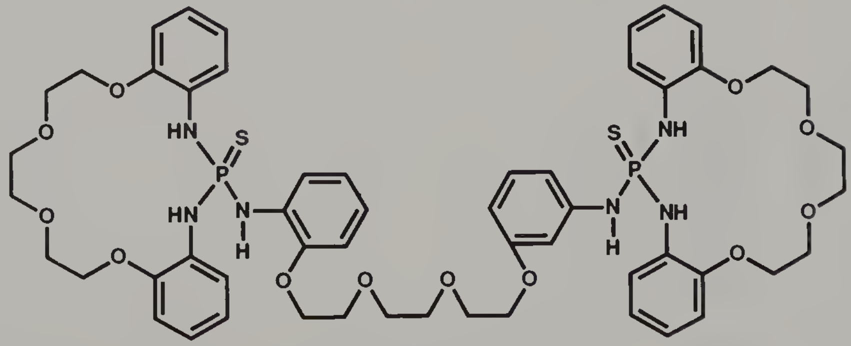
9.10 A



9.10 B



9.10 C



9.10 D

Structure	X		Yield (%)	References
9.10 A			53	Parker et al., 1989
			53	Craig et al., 1990
9.10 B		Y-2		Bulkowski et al., 1977
		Y-2	34	Shinkai et al., 1984
9.10 C	H_2	Y-2	43	Shinkai et al., 1984
	O	Y-2	54	Shinkai et al., 1984
9.10 D		AB-2		Dutasta et al., 1989

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CHAPTER X

Aliphatic Peraza-crown Macrocycles (Cyclams)

A. INTRODUCTION

The peraza-crown macrocycles form the largest group of macrocyclic multidentate compounds. These ligands are most interesting because they provide binding sites for transition-metal and other heavy-metal ions and, in certain cases, for the alkali metal ions, although alkali metal ion complexation is usually weak (Bianchi et al., 1991; Tsukube et al., 1989). The peraza-crowns can complex with one, two, or three metal ions depending on the size of the macrocycle. To be effective, the peraza-crowns should have at least three nitrogen atoms in the ring. Usually the number of nitrogen atoms increases as the size of the ring increases. The methods of preparation of the peraza-crowns are not as diverse as with the other aza-crowns because only nitrogen atoms are in the ring. Attention will be given to the peraza-crowns with different functional groups on the nitrogen and carbon atoms. Additional functional groups can allow these ligands to be attached to antibodies for cancer localization and therapy (Parker, 1990) and to solid supports for selective metal ion removal and separation (Bradshaw et al., 1989c).

The peraza-crowns were the subject of much work even before Pedersen (1967) made his monumental discoveries concerning the crown ethers. Curtis (1968), Busch (1967), Lindoy (1975), and others have prepared a multitude of peraza-crowns. Even after 30 years or more, new methods for preparation of the peraza-crowns are being discovered. This chapter will review the methods to prepare these important macrocycles and give a listing of all reported peraza-crowns.

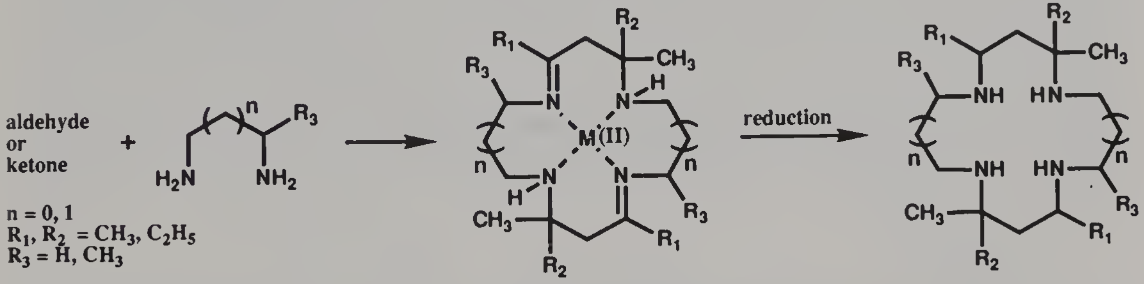
B. RING CLOSURE TO FORM A BIS SCHIFF BASE

The formation of peraza-crown macrocycles containing Schiff base functional groups were among the first syntheses of macrocyclic multidentate compounds (Busch, 1967; Lindoy, 1975). These cyclic reactions between carbonyl and primary amine compounds were the first to use a template cation (Black and Hartshorn, 1972–1973). The unsaturated Schiff bases were then reduced to the peraza-crowns, although this latter process is not trivial because removal of the metal template ion can be difficult.

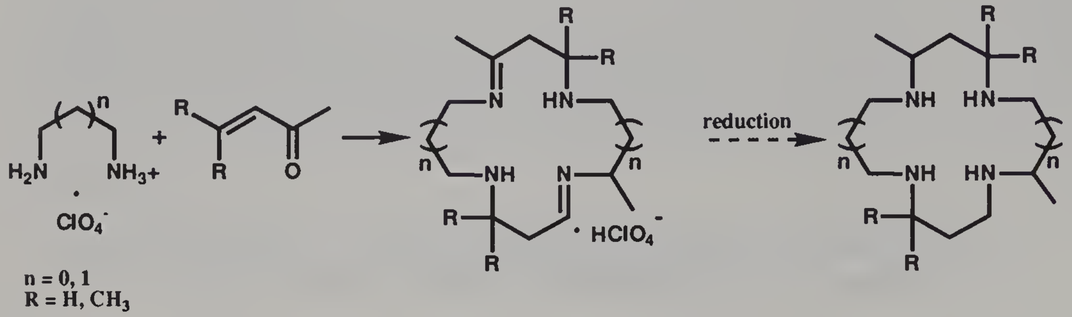
This cyclization process provides a convenient route to complexes of macrocyclic ligands containing three or more nitrogen donor atoms. The template cation is an appropriate metal ion such as Ni(II) or Cu(II). The reactants could be a dicarbonyl compound and an α,ω-bis primary amine to form a cyclic bis Schiff base or an ω-aminocarbonyl compound could be cyclized internally to form a cyclic mono Schiff base (Busch, 1967; Curtis, 1967). In a few cases, more than two Schiff bases were formed in the cyclization step.

1. The Reaction of a Simple Aldehyde, Ketone, or α,β-Unsaturated Carbonyl Compound and a Diamine (Curtis Reaction)

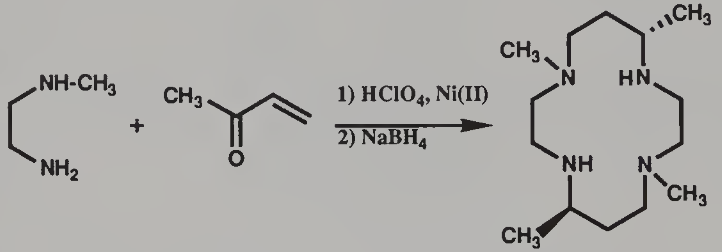
Cyclocondensations of simple carbonyl compounds—such as acetone, methyl ethyl ketone, propionaldehyde, or the butyraldehydes—and simple diamines—such as ethylenediamine and 1,2- or 1,3-propanediamine—were studied by Curtis and coworkers in the 1960s (Curtis, 1968). The resulting complexed cyclic bis Schiff base was reduced to form the tetraaza-crown ligand. The cyclic product is a result of an aldol condensation of the carbonyl compound, followed by ring-closure reactions with the diamine. In 1966, Curtis and others showed that cyclic condensation also was possible in the absence of a metal template ion, but acid was necessary for those reactions. Possibly, the protonated amines formed an internal hydrogen-bonding network that acted as a template. Cyclization was observed in yields of up to 80% (Curtis and Hay, 1966; Kolinski and Korybut-Daszkiewicz, 1969; Tait and Busch, 1978a, 1978b). The isomers of the formed cyclic Schiff bases were difficult to separate. Reduction of the unsaturated macrocycles gave cyclic polyamines with up to six chiral centers and up to 20 diastereomeric isomers (Hay and Piplani, 1977; Kolinski and Korybut-Daszkiewicz, 1969).



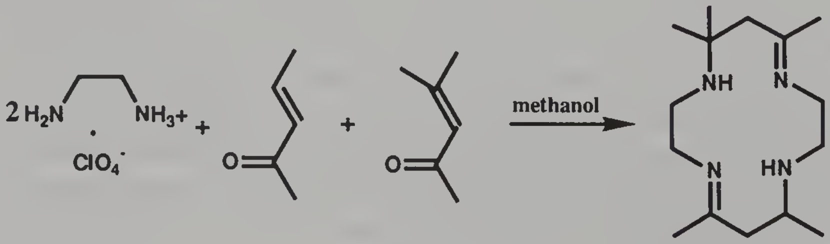
These cyclization reactions were also possible with or without a metal ion template using α,β-unsaturated ketones, such as mesityl oxide or methyl vinyl ketone, or with β-hydroxyketones, such as 4-hydroxy-4-methyl-2-pentanone. The products were the same as when simple carbonyl compounds were used showing that the reaction with the simple carbonyl compounds proceded through the aldol condensation reaction (Curtis and Hay, 1966; MacDermott and Busch, 1967; Hay and Lawrance, 1975; Kolinski and Korybut-Daszkiewicz, 1969, 1975; Kolinski et al., 1982). Different sizes of macrocycles were obtained depending on the size of the diamine and nature of the carbonyl compounds used in this "Curtis" reaction. Thus, imine-containing macrocycles with 13, 14, 15, 16, 18, and 22 ring members were formed and many were reduced to the peraza-crowns (cyclams) (Bembi et al., 1988; Hay and Pujari, 1985; Hay et al., 1977; Kolinski and Korybut-Daszkiewicz, 1975; Korybut-Daszkiewicz, 1985; Yamashita et al., 1983).



N-Methylethylenediamine, a mixed primary and secondary amine, also was used in these reactions. The products were similar except two of the ring nitrogen atoms were substituted by methyl groups (Makino et al., 1979; Miyamura et al., 1986, 1987). The "Curtis" method can produce different optically active isomers depending on the metal template ion (Curtis, 1973; Makino et al., 1979, 1985).

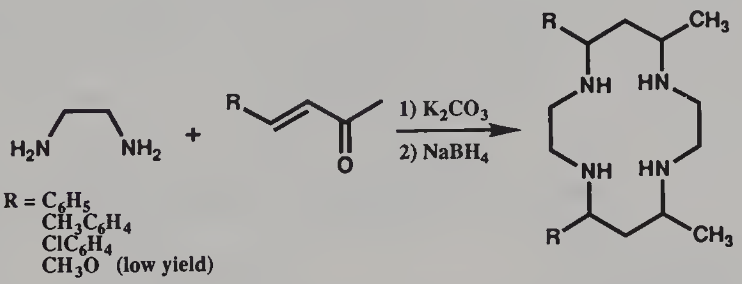


A macrocyclic [14]N$_4$-diene was prepared from two α,β-unsaturated ketones. Ethylenediamine was treated with an equimolar mixture of 3-penten-2-one and mesityl oxide to give [14]N$_4$-diene containing three methyl substituents on one side and two on the other (Hay et al., 1988; Searle et al., 1980). About 5% of the above mixed ligand was isolated when this reaction was

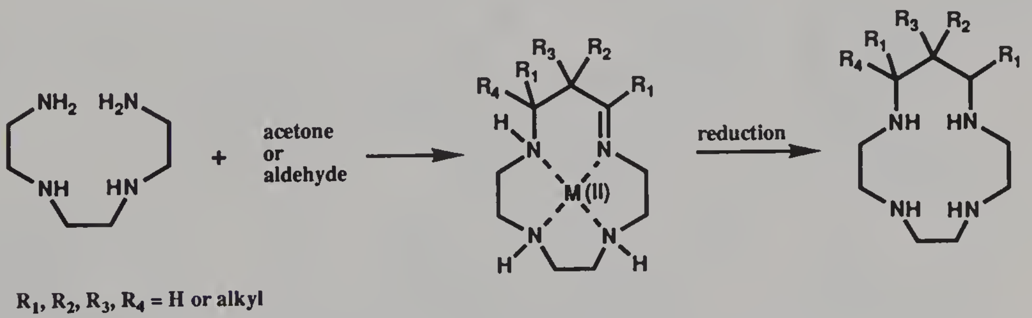


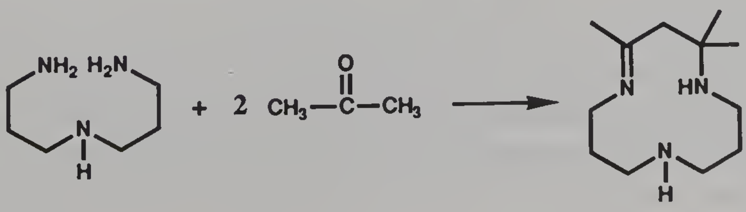
carried out using only mesityl oxide. Probably, the starting mesityl oxide contained 5% of 3-penten-2-one.

An interesting observation was reported for the "Curtis" reaction where no template cation or internal hydrogen-bonding network was used. Using potassium carbonate, mesityl oxide, and ethylenediamine, only a 1:1 cyclocondensation reaction giving the 7-membered tetrahydrodiazepine system was observed (Hideg and Lloyd, 1971). However, the 14-membered tetraazacyclotetradecane derivatives were produced in high yields when ethylenediamine was treated with various arylideneacetones or benzylideneacetophenones rather than with mesityl oxide. 1,3-Propanediamine, on the other hand, reacted with all of the α,β-unsaturated ketones to give the 8-membered hexahydrodiazocine.



Cyclocondensations of one molecule of a polyamine with carbonyl compounds are important methods for the preparation of other unsaturated peraza macrocycles. The reaction of acetone or an aldehyde such as propionaldehyde or a butyraldehyde, with triethylenetetraamine gave a tetraaza macrocycle, [13]N_4, containing one double bond that could be reduced (House and Curtis, 1962, 1964; Busch, 1967). [12]N_3 was prepared in a similar fashion by treating 1,5,9-triazanonane with two molecules of acetone (Martin et al., 1978; House and Curtis, 1965).



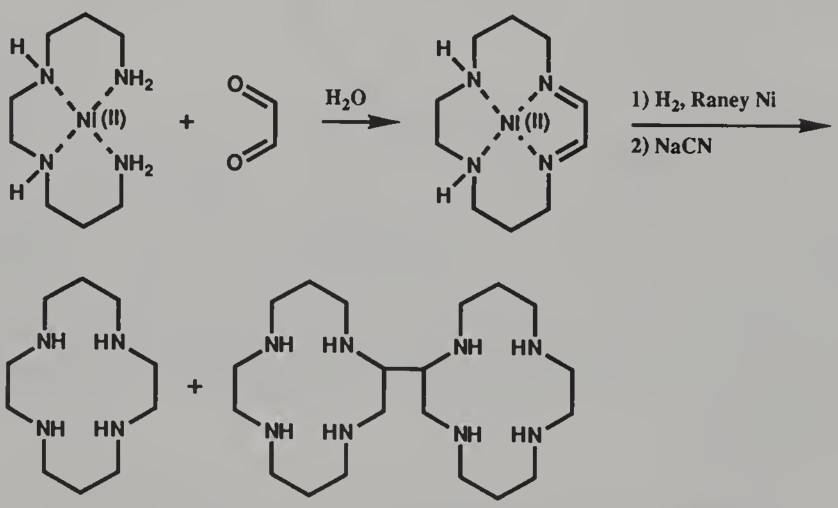


In general, the macrocyclic Schiff-base ligands can be reduced by using hydrogen (platinum), sodium borohydride, nickel–aluminum alloy, or cathodic reduction (Curtis, 1964, 1965, 1967; Hay et al., 1989a; Kolinski and Korybut-Daszkiewicz, 1969; Tait and Busch, 1978b). Usually in the reduction process, the the complexed ion was removed from the reduced ligand by cyanide or by acid (Korybut-Daszkiewicz, 1988). Synthesis of a macrocyclic Schiff base without a template metal ion followed by reduction is one of the most convenient routes to the polyaza macrocycles (Kolinski and Korybut-Daszkiewicz, 1969; Tait and Busch, 1978b).

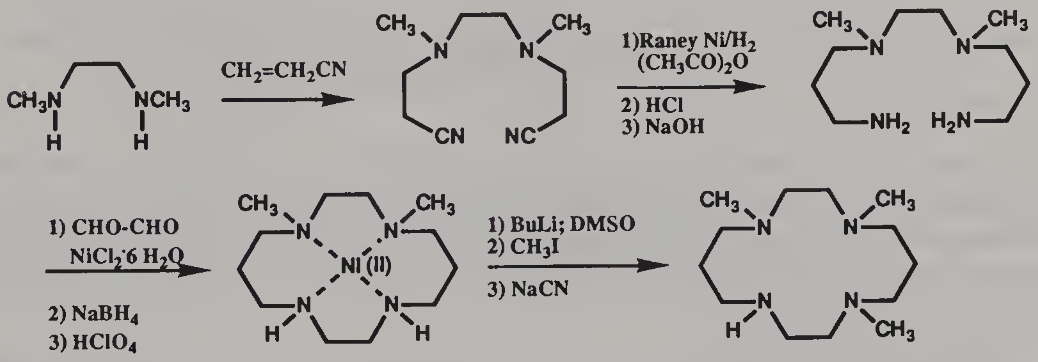
Some macrocyclic Schiff bases are not as useful because they cannot be reduced or the complexed metal ion cannot be removed. Examples of compounds of this type include those derived from biacetyl and 1,3-diaminopropane in the presence of Ni(II) (see Chapter III). In these cases, the metal-free macrocycle could not be isolated (Jackels et al., 1972; Welsh et al., 1977).

2. The Reaction of Glyoxal and a Diamine

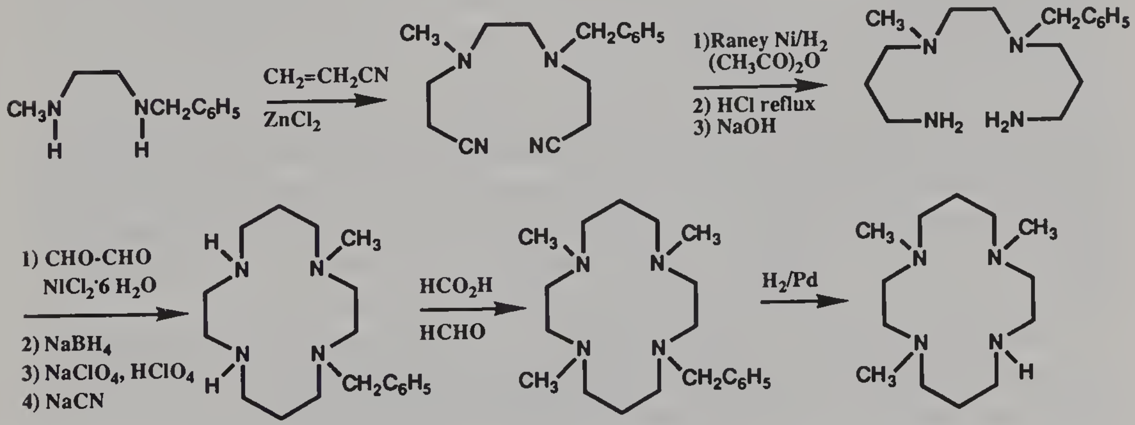
Cyclic condensation processes to form Schiff bases have found application for the preparation of the most common tetraazacyclotetradecanes (the cyclams). For example, the reaction of glyoxal and the Ni(II) complex of 4,7-diaza-1,10-decanediamine gave the cyclic bis Schiff base. This product was reduced using Raney nickel to give cyclam in an overall yield of 20% (Barefield, 1972). The dimeric biscyclam was isolated as a minor product (Barefield et at., 1981). The complexed Ni(II) was removed from the products by sodium cyanide. Yields were improved by using sodium borohydride as the reducing agent, but sodium cyanide was still needed to remove the Ni(II) (Barefield et al., 1976a, 1976b). This above method was used to prepare macrocycles with 13 and 15 ring members with Ni(II), Co(II), and Cu(II) as templates (Barefield and Freeman, 1980; Barefield et al., 1976a, 1976b). The best yields were obtained using Ni(II) as the template ion.



The same type of process as described above was used to produce cyclams with only one secondary amine function in the macroring. This was done in two ways. In the first route, *N*,*N*′-dimethylethylenediamine was treated with acrylonitrile followed by reduction to give a dimethyltetraamine. This material was treated with glyoxal followed by reduction and methylation to give the *N*,*N*′,*N*″-trimethylcyclam in a 50% overall yield (Barefield et al., 1986a). The third methyl group was added by treating the complexed dimethylcyclam with one equivalent of butyl lithium followed by methyl iodide. The second route



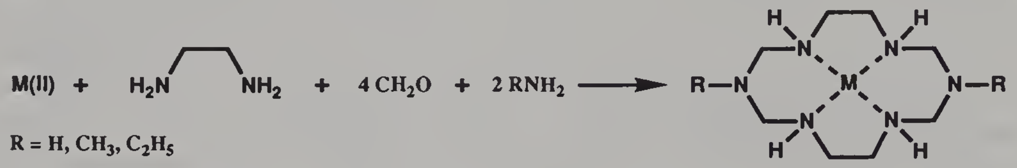
used the *N*-benzyl group to protect one of the ring nitrogen atoms as shown below (Barefield et al., 1986a, 1986b). This process gave a higher overall yield (65%) of the mono-functionalized cyclam, but the starting *N*-benzyl-*N*′-methylethylenediamine is not commercially available. Franz and coworkers prepared similar cyclams but with aminopropyl side arms (Franz et al., 1987).



A new method to prepare these mono-functionalized cyclams using a bis-α-chloroamide has been developed (Bradshaw et al., 1990a). This method works without the need for autoclaves, sealed bottles, perchlorate salts, and sodium cyanide that have been used in the processes described above. The new Krakowiak–Bradshaw procedure is discussed in detail in Chapter IV and later in this chapter (Section D.5).

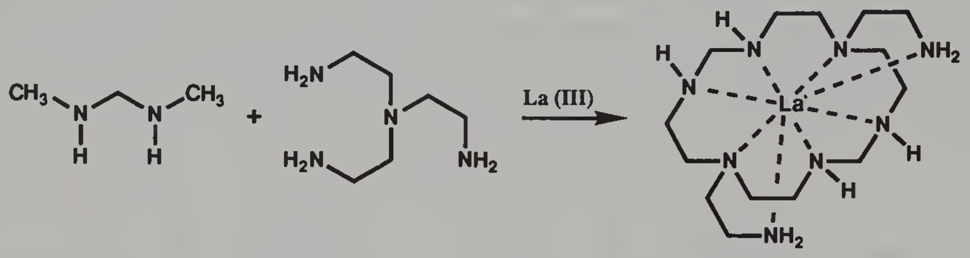
C. CYCLOCONDENSATION OF THREE OR MORE MOLECULES WITHOUT SCHIFF BASE FORMATION

Formaldehyde, ethylenediamine, and ammonia were reacted together in the presence of a divalent metal ion to produce a metal ion–hexaazacyclotetradecane complex as shown below (Naik and Sahoo, 1982; Rout and Sahoo, 1984).

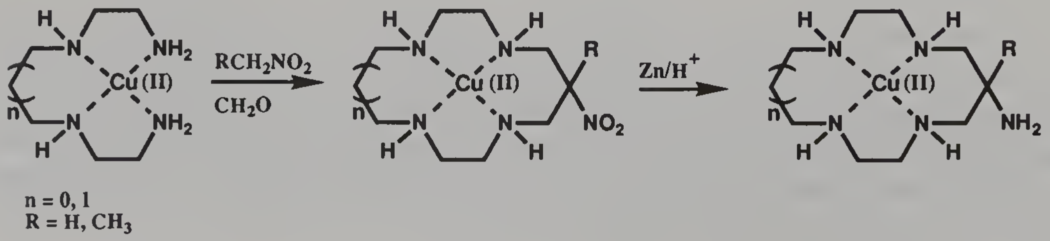


This reaction is thought to be a stepwise, template-assisted cyclization and worked well when Ni(II) perchlorate or chloride was used. Others found only linear compounds under similar conditions but were able to prepare the macrocycle from primary amines using Ni(II) or Cu(II) as metal template ions (Suh and Kang, 1988).

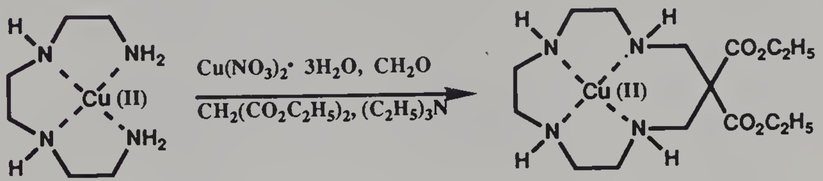
Smith and Raymond (1985) produced a hexaazacyclohexadecane by reacting tris(aminoethyl)amine with bis(methylamino)methane in the presence of La(III). The bis(methylamino)methane was the source of the methylene group in the macrocycle. The La(III) complex prepared in this reaction is 10-coordinate using eight nitrogen atoms from the lariat macrocycle and two oxygen atoms from two trifluoromethanesulfonate anions. These peraza-crowns containing methylene groups between ring nitrogen atoms are probably not useful for metal extractive purposes because the diaminomethane function is not very stable without the complexed metal ion.



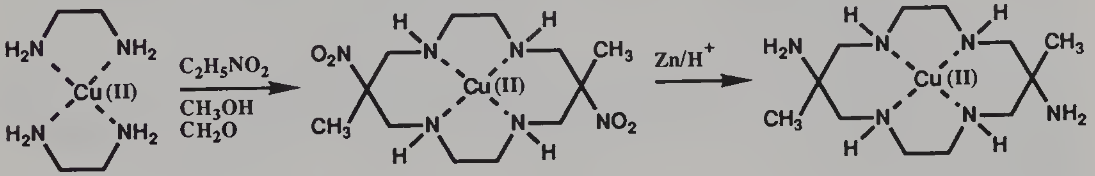
Condensation of the Cu(II) complex of a linear aliphatic tetraamine with formaldehyde and a nitroalkane or diethyl malonate in basic methanol gave the peraza macrocycle with 13 to 16 ring members (Lawrance et al., 1987).

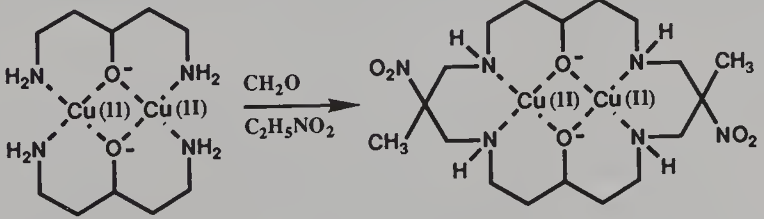


When the 3,7-diaza-1,9-nonanediamine-Cu(II) complex ($n = 1$) was treated with formaldehyde and nitroethane, the nitro-substituted macrocycle was the only product. Reduction of the nitro group by zinc in aqueous acid gave the amine-substituted macrocycle as shown above. Other peraza-crowns were obtained starting with other tetraamines (Comba et al., 1988a, 1988b; Lawrance and O'Leary, 1987). A similar reaction with diethyl malonate gave only a 2% yield of the corresponding macrocycle (Lawrance and O'Leary, 1987).



Formaldehyde and nitroethane when treated with the Cu(II) complex of ethylenediamine in base gave a Cu(II)–dinitrocyclam complex and some linear product (not shown) (Comba et al., 1986; Lawrance et al., 1988). The substituent nitro groups were reduced to the primary amines by using zinc or tin in acid or by catalytic hydrogenation. The new ligands coordinated metal ions by the amine substituents in addition to the amine groups of the macrocyclic ring. Lawrance and coworkers noted that considerable fragmentation occurred during the reduction step, resulting in low yields for the diaminomacrocycle (Lawrance et al., 1988). An interesting dinuclear complex was formed by a similar condensation reaction of the [Cu(II)]$_2$ complex of 3-hydroxy-1,5-pentanediamine with formaldehyde and nitroethane in basic methanol (Comba et al., 1990).

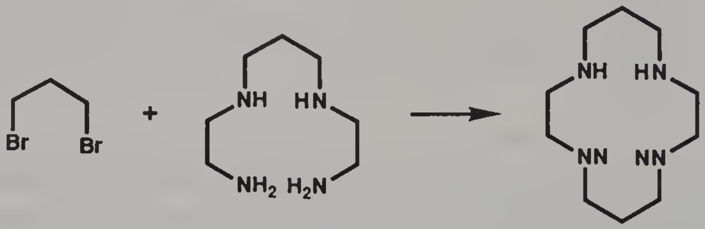




These peraza-crown syntheses will have increasing applications as methods to remove the metal template are discovered. More practical applications to form the benzoperaza-crowns (peraza-cyclophanes) via Schiff base formation will be discussed in Chapter XI.

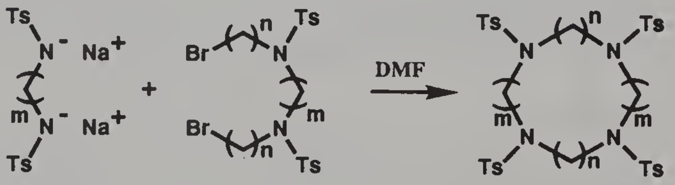
D. RING CLOSURE TO FORM CARBON–NITROGEN SINGLE BONDS

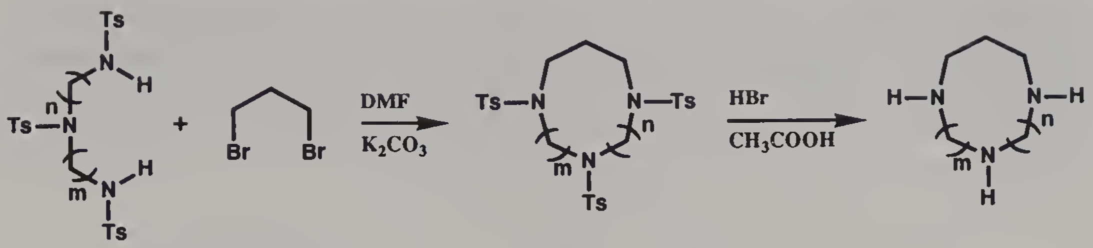
Historically, the first peraza-crown (cyclam) was prepared by a simple reaction of 1,3-dibromopropane and 3,7-diaza-1,9-nonanediamine in the presence of alkali (Alphen, 1937; Bosnich et al., 1965). Because the secondary amines were not protected, this reaction gave a yield of only 5% due to the formation of many side products. Bosnich and coworkers found it more convenient to use a modification of the one-step Alphen method to prepare the peraza-crowns than to use the time-consuming multistep process of Stetter and Mayer (1961) via the diacid dichlorides with the amine nitrogen atoms protected by tosyl groups (Bosnich et al., 1965). The one-step Alphen method can give yields of up to 19% in the preparation of sterically hindered cyclams (Kobiro et al., 1990).



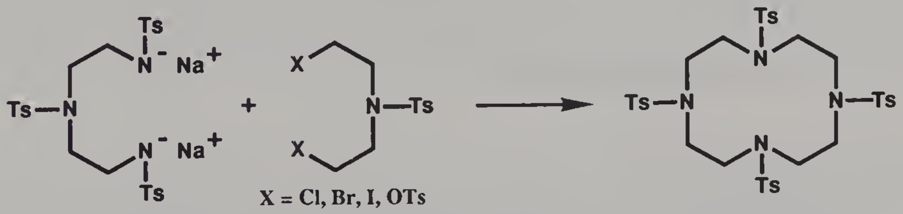
1. The Reaction of a Sulfonamide with a Dihalide or Ditosylate Ester

Higher yields of the peraza-crowns were achieved when the nitrogen atoms were protected by tosyl groups. However, additional steps are necessary since the starting polyamine needs to be tosylated and the product macrocycle needs to be detosylated. This method does allow the preparation of peraza-crowns of different sizes and numbers of nitrogen atoms (Stetter and Mayer, 1961; Stetter and Roos, 1954; Tomohiro et al., 1988, 1990a). This process has been used to prepare 10- to 12-membered triaza-crowns in yields of 8–25% using high dilution conditions (Koyama and Yoshino, 1972). The low yields in this reaction could be caused by decomposition of the 1,3-dibromopropane at the





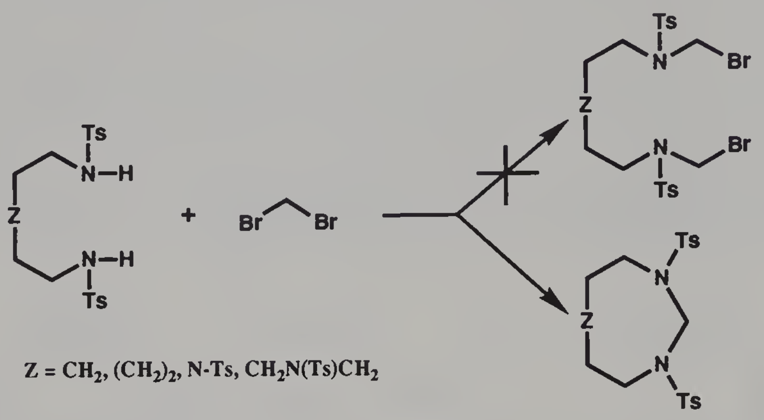
high temperatures required for this cyclization reaction. Often, 2:2 cyclizations are the most important products (Uoto et al., 1990). Halogen ions are not always the best leaving groups in these reactions. For example, in the formation of tetraaza-12-crown-4, the yield was about 40% using the dichloride or dibromide and only 25% when the diiodide was used. On the other hand, an 80% yield was realized using the corresponding ditosylate ester (Atkins et al., 1978; Richman and Atkins, 1974).



The bistosylamide cyclization reaction, the "Richman–Atkins" process, has been used to prepare a variety of peraza-crowns. Large macrocyclic diamines were prepared by using Cs_2CO_3 in DMF to deprotonate the bistosylamide followed by a slow addition of the dibromoalkane. Excellent yields were reported for the formation of 17- to 28-membered rings, but low yields and incomplete reactions were reported for the 11- and 12-membered rings and for the larger rings when Li_2CO_3, Na_2CO_3, or K_2CO_3 was used as the base (Vriesema et al., 1984).

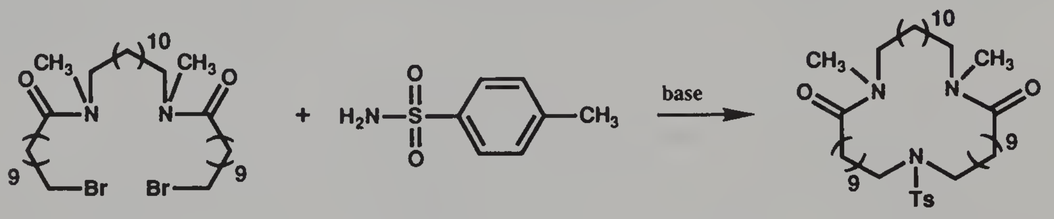
The dibromide starting materials are more useful than ditosylates or dimesylates because the dibromides are much cheaper and are usually available. Recently, yields of up to 75% were reported in the cyclization step when the reaction was carried out at 30°C using K_2CO_3 in DMF (Chavez and Sherry, 1989). An excess of 1,2-dibromoethane and longer reaction times were required than when using 1,3-dibromopropane. The metal carbonate base (Ag_2CO_3, Li_2CO_3, Na_2CO_3, K_2CO_3, or Cs_2CO_3) also has a profound effect on the yields of these cyclization reactions. Yields can vary from 0% to 75% depending on the base. It is more important to have a strong base to deprotonate the tosylamide than to have the right metal ion to act as a template. Indeed, metal ion templates probably play a minor role in these cyclization reactions. In general, K_2CO_3 is the preferred reagent because it is inexpensive (Chavez and Sherry, 1989).

Linear oligomers are generally formed from the α,ω-dihalides. Dibromoethane can be used in excess in a first step to obtain new α,ω-dibromoperazaalkanes. These intermediates can then be used to prepare the peraza-crowns. They are particularly useful for the preparation of 12- to 16-membered peraza-crowns (Stetter, 1953; Stetter and Roos, 1954, 1955). The peraza macrocycle was the major product when dibromomethane was reacted with a bistosylamide in base (Krakowiak et al., 1983).

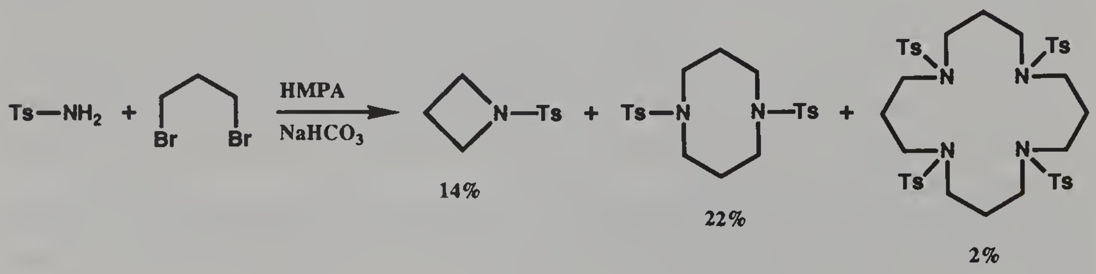


Z = CH_2, $(CH_2)_2$, N-Ts, $CH_2N(Ts)CH_2$

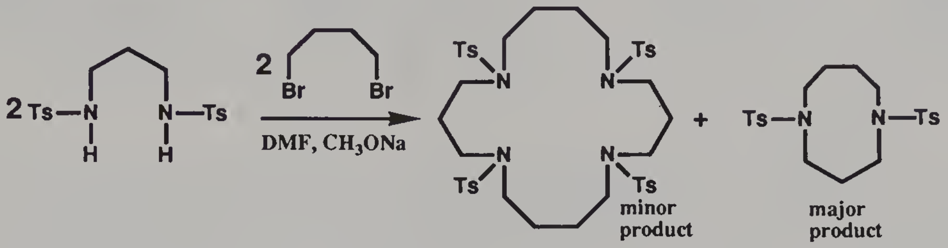
The preceding reactions use a bistosylamide as a reactant in the ring-closure step. Tosylamide itself can react with both alkyl halide functions of an α,ω-dihalide. Tosylamide is very reactive without using drastic conditions particularly when in the presence of phase transfer agents (Isele and Martinez, 1981).



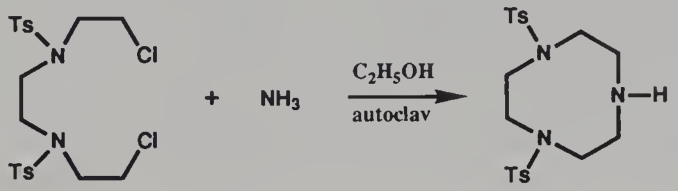
The reaction rate for the formation of small cyclic amines from open-chain precursors varies according to ring size as follows: 5 members > 3 > 6 > 7 > 4 (Di Martino et al., 1985). This rule does not apply if four or more bonds are formed as in 2:2 and higher-order cyclizations (Juaristi and Madrigal, 1989). Thus, only a minimal yield of a 16-membered macrocycle was obtained when 1,3-dibromopropane was reacted with tosylamide. In a similar manner,



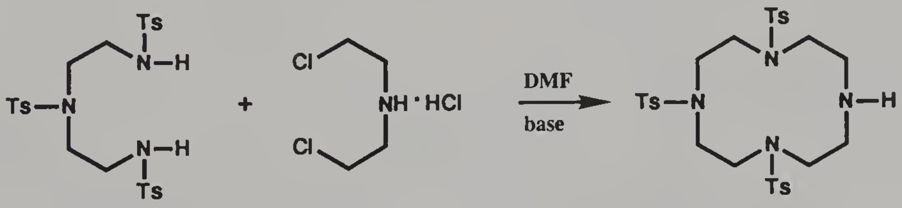
only a minimal yield of the 18-membered macrocycle was formed from the cyclocondensation of *N*,*N*′-ditosyl-1,3-propanediamine and 1,4-dibromobutane (Kimura et al., 1982a).



Monofunctionalized peraza macrocycles have been made from the reaction of a dihalide with ammonia (Peacock and Gwan, 1937). The ditosyl-substituted triaza-9-crown-3 was prepared in a 15% yield. The reaction with a

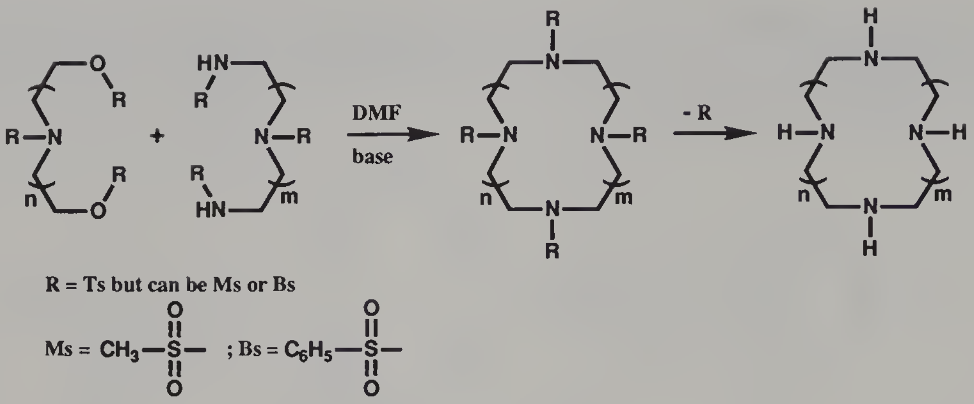


tristosylamide and the hydrogen chloride salt of bis(2-chloroethyl)amine gave the tri-*N*-tosyl-substituted tetraaza-12-crown-4 (Ciampolini et al., 1984a). This mono-functionalized macrocycle was used for the preparation of bis(peraza-



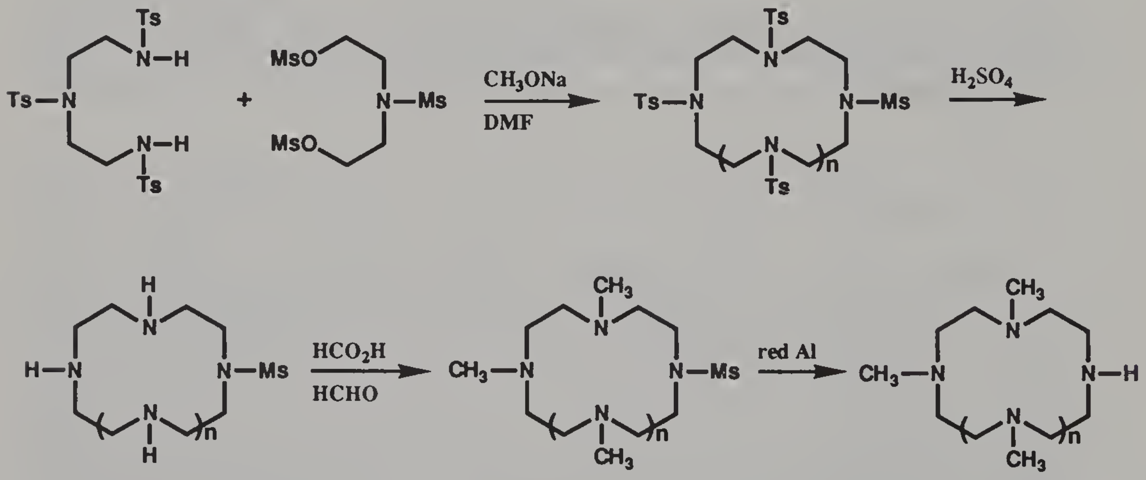
12-crown-4) ligands.

The *p*-toluenesulfonate, benzenesulfonate, or methanesulfonate esters are usually better leaving groups than the halides; hence the α,ω-bissulfonates are often used to prepare the peraza macrocycles. The tosylate esters are used most often because the starting bis-tosylates are generally solids and are easy to purify. This ring-closure procedure using bis-tosylates and bis-tosylamides, often called the “Richman–Atkins” method, has found use in the preparation of peraza-crowns of 9 to 50 ring members and with varying numbers of ring nitrogen atoms. Yields can be as high as 60%. Iwata and Kuzuhara (1989a, 1989b) have reported a quantitative yield for a 20-membered peraza-



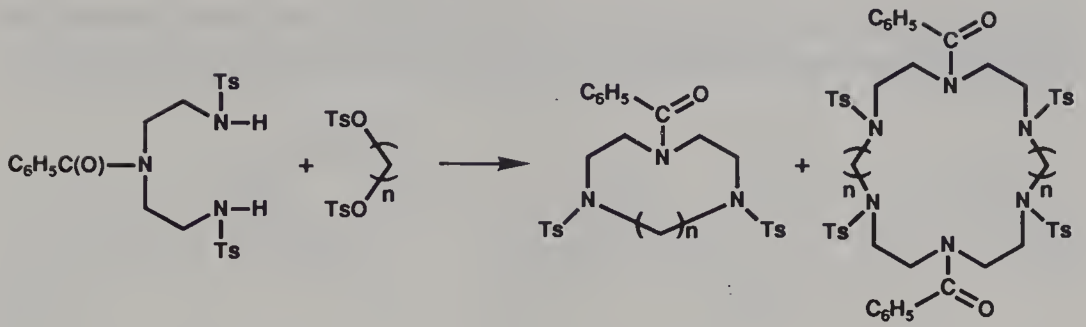
crown using Cs_2CO_3 in DMF. This method for ring closure was discussed extensively in Chapter IV along with methods to detosylate the cyclic product.

Recently, mono-functionalized peraza-crowns have been prepared using benzoyl, benzyl, trityl, and diethoxyphosphoryl groups to protect the interior nitrogen atoms (Kaden, 1984; Qian et al., 1991). These protecting groups can be removed without removing the *N*-tosyl or *N*-mesyl groups. Also, *N*-tosyl and *N*-mesyl protecting groups can be removed sequentially by different reactions. This latter process was used to prepare a mono-functionalized tetraaza-12-crown-4 (Pilichowski et al., 1985; Qian et al., 1991). Rapid progress in the synthesis of peraza-crowns is noted by the preparation of the same

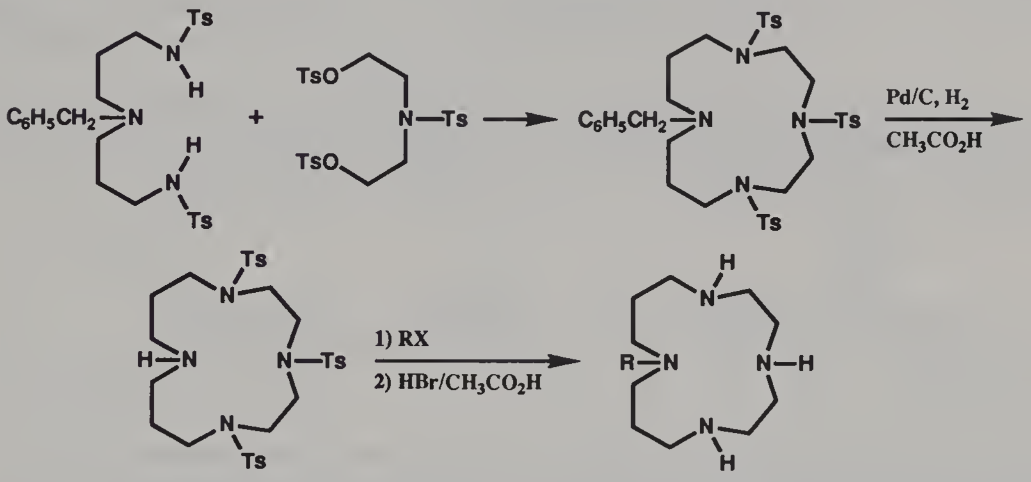


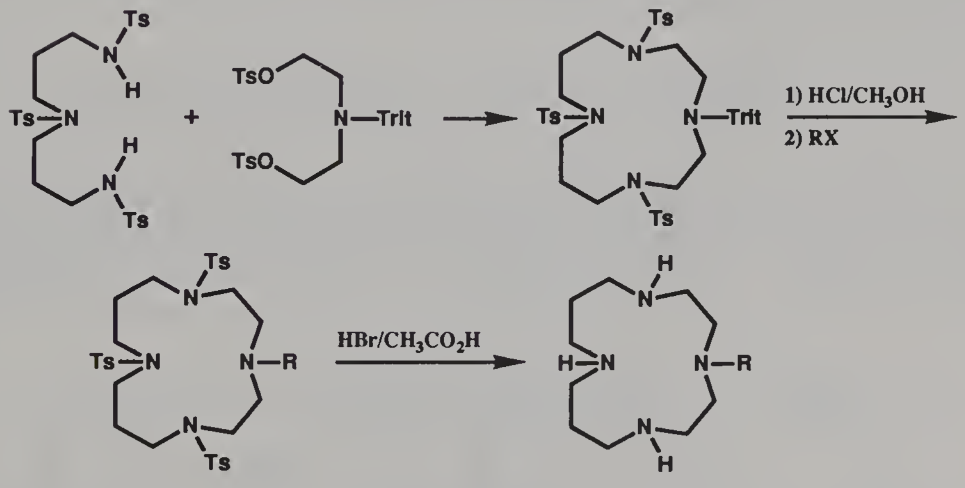
mono-functionalized peraza-12-crown-4 in only three steps by the "crab-like" cyclization process (Krakowiak et al., 1990b). This crab-like process was discussed extensively in Chapter IV and will be discussed later in this chapter (Section D.5).

As mentioned above, protecting certain internal nitrogen atoms using the benzoyl moiety is useful for the preparation of mono- or di-functionalized peraza-crowns. The selective removal of the benzoyl group was accomplished

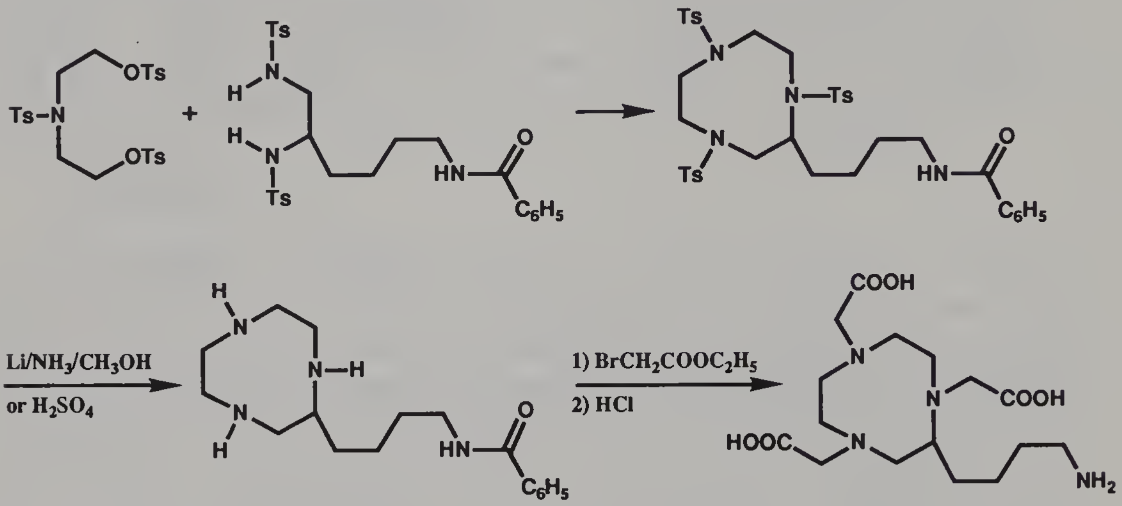


in a 90% yield using potassium *t*-butoxide (Martin et al., 1982). Benzyl or trityl groups also are used to protect one or more nitrogen atoms. These groups are easily removed by hydrogenation using Pd/C as catalyst (benzyl group) or by acid in methanol (trityl group) (Hediger and Kaden, 1983).

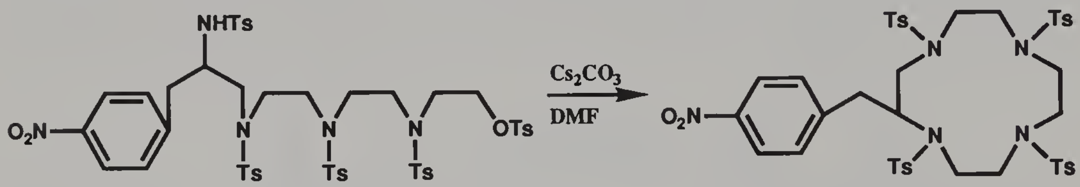




Some interesting peraza-crowns containing a functional group on an arm connected to a ring carbon atom also have been prepared using the bis-sulfonamide method (Benabdallah and Guglielmetti, 1988). For example, the following is an elegant synthesis of a macrocycle that is capable of complexing with indium(III) and being attached to an antibody for delivery to a tumor. The tumor then can be radioimaged (Cox et al., 1990; Craig et al., 1989).

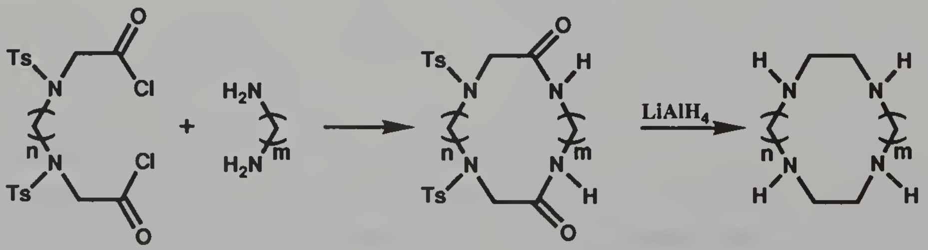


Intramolecular ring closure using a sulfonamide reacting with a tosylate ester also has been observed (Moi et al; 1988). A long-chain per-*N*-tosylpolyamine, which contained a tosylate ester on one end, cyclized to form a peraza-crown in a 79% yield. This internal cyclization process previously was used to form 9- and 12-membered peraza-crowns, but the starting material was prepared in a different way (Iwata and Kuzuhara, 1985).



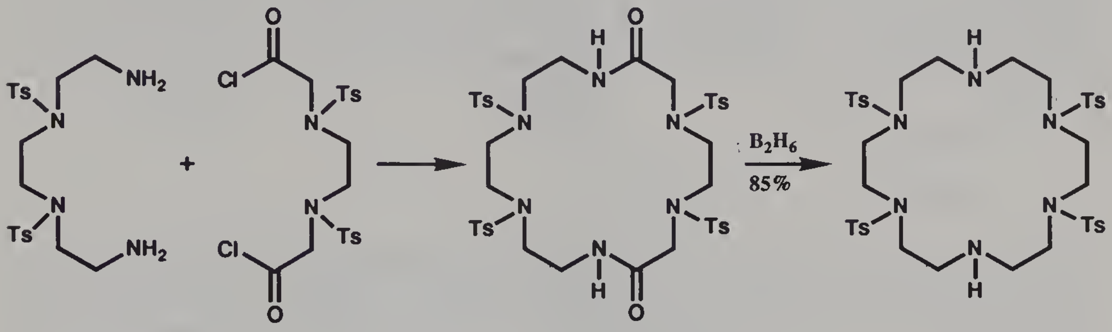
2. The Reaction of a Diacid Dichloride and a Diamine

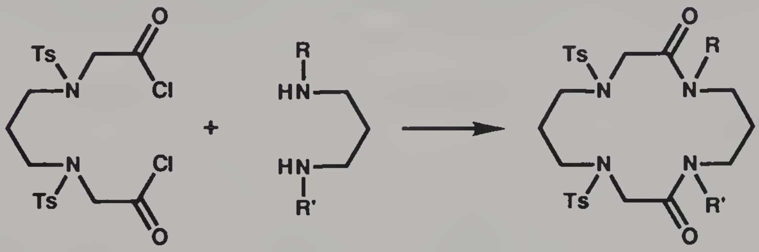
The high-dilution cyclocondensation of diacid dichlorides with diamines has been used to form the peraza-crown macrocycles (Stetter and Marx, 1957; Stetter and Mayer, 1961). In these cases, the internal secondary amines were protected by tosyl groups. This cyclization reaction was very clean and gave



n = 2, 3
m = 2, 3, 6, 12

little or no by-products. The method is a good route to peraza-crowns with large numbers of ring nitrogen atoms as shown (Dietrich et al., 1989). Alkyl-substituted peraza-crowns were prepared by treating the diacid dichloride with a bis-secondary amine (Buxtorf and Kaden, 1974).



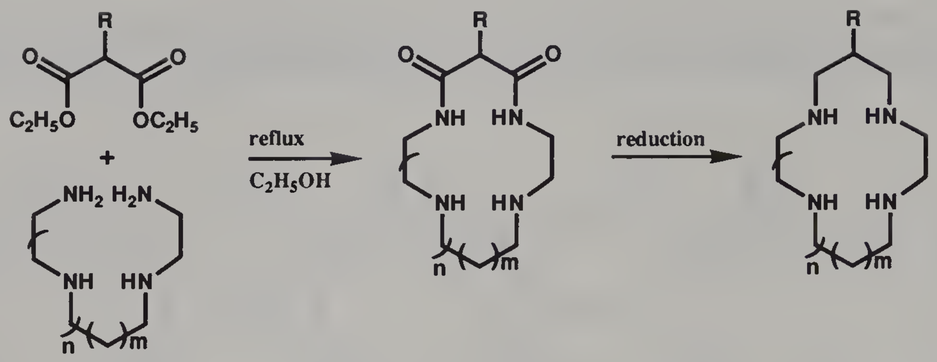


R, R' = alkyl; H

The preparation of macrocycles via the formation of cyclic diamides, as shown above, is convenient. The diacid dichlorides and diamines are generally available or are easy to prepare. Also, the amide nitrogen is not reactive toward further reactions, thereby providing a protection for that particular nitrogen atom. This latter advantage is clearly evident in the cyclization reaction of diacid dichlorides and diamines and the crab-like cyclization of bis-α-chloroamides to form cyclic diamides. These cyclic diamides are reduced to form peraza-crowns wherein the amide nitrogen atoms become secondary amines.

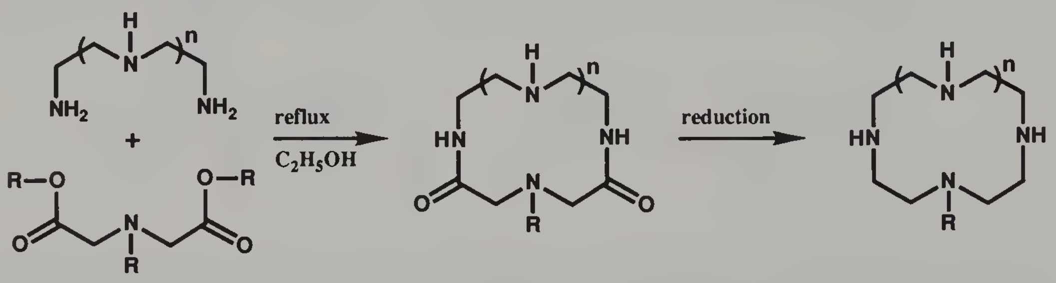
3. The Reaction of a Diester or Other Activated Dicarboxylic Acid Derivative and a Diamine

Esters readily react with primary but not with secondary amines in alcohol solvents. This reactivity is used to advantage in the formation of peraza-crown diamides by treating a polyamine with a diester (Tabushi et al., 1976, 1977). This cyclization process, often called the "Tabushi" method, has broad ap-

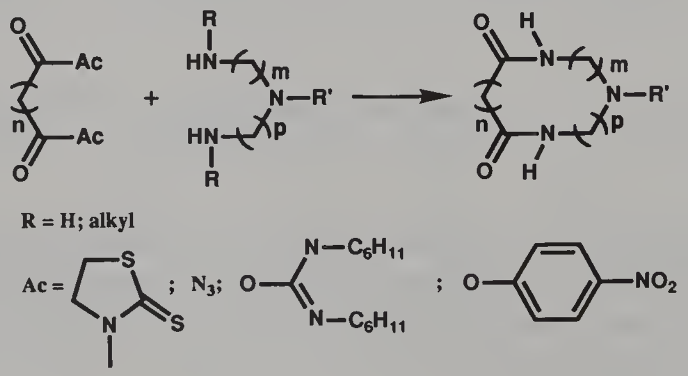


plication for the preparation of peraza-crowns because the internal secondary amine groups do not need to be protected. Thus, the final peraza-crown, after reduction of the amides, contains only secondary amine groups. The main disadvantages of this method is the low yields (2–30%). This “Tabushi” process was discussed extensively in Chapter IV.

Diethyl malonate derivatives are the most used diesters for these reactions. The R group on diethyl malonate in the reaction shown above can contain other functional groups such as a secondary amine or an alcohol. Diesters containing internal amine functions have also been used in these reactions.

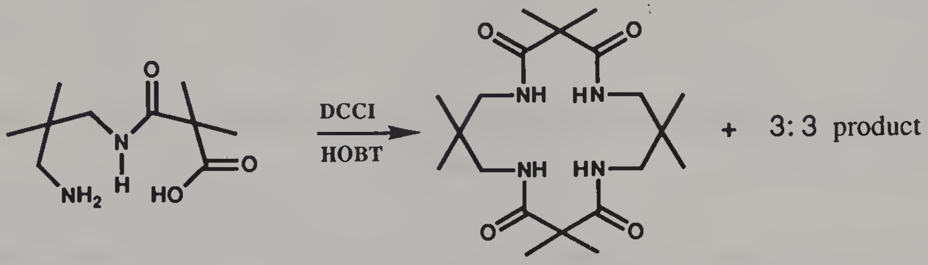


The ester–amine reaction is slow and requires long reaction times (see Chapter IV). Many active carboxylic acid derivatives such as the azides, *p*-nitrophenyl esters, and thiazolidine-2-thiones as well as carboxylic acid activators, such as dicyclohexylcarbodimide (DCCI), have been used to improve this reaction (see Chapter IV) (Kimura et al., 1989a, 1989b; Krakowiak et al., 1989, 1990a; Nagao et al., 1980, 1981; Uoto et al., 1990). These cyclization reactions seldom need high-dilution conditions. Even though ex-



cellent product yields are possible, these reagents are not used as often as they are in peptide chemistry.

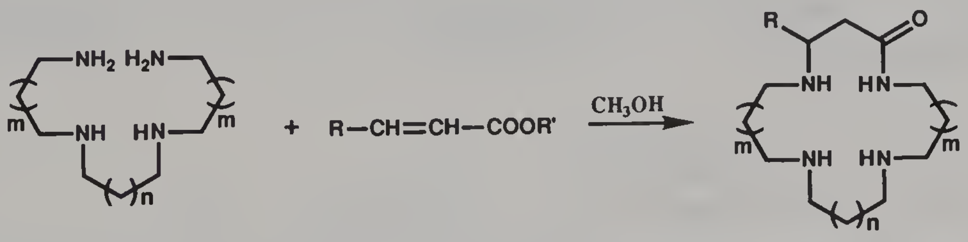
An ω-aminocarboxylic acid can react internally to form a macroring with one amide function. More often this type of starting material reacts to give 2:2 and 3:3 cyclization products (Vellaccio et al., 1977). The larger products are particularly evident where the 1:1 product would be a medium sized ring.



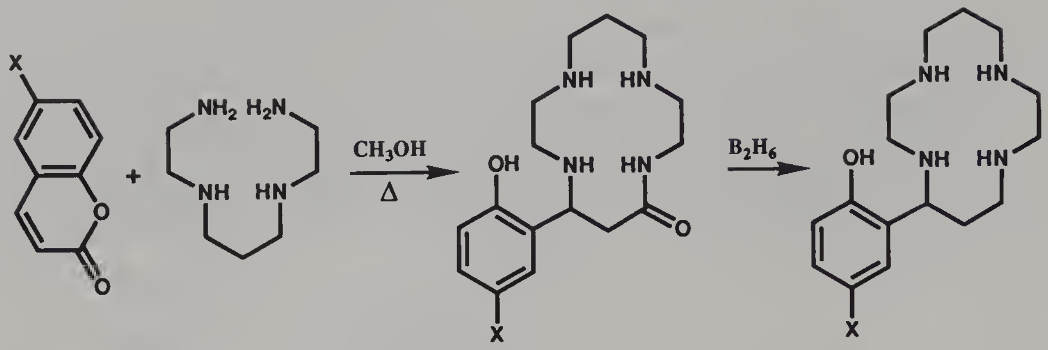
In the above case and in similar peptide-like reactions, hydroxybenzotriazole (HOBT) was used because it prevents side reactions.

4. The Reaction of an α,β-Unsaturated Ester and a Diamine

The peraza-crown monoamide ligands also have been prepared via the reaction of a polyamine and an α,β-unsaturated ester such as an acrylate or cinnamate (Kimura et al., 1986b, 1987a, 1987b). This cyclization process involves a Michael addition of one amine to the unsaturated ester followed by amide formation by the action of the other amine on the ester function. The yields for this process are usually low, although some syntheses have been moderately successful. This method has produced many peraza-crowns containing phenol, catechol and pyridine side groups. These side groups can also coordinate with the complexed metal ion. Coumarin has a hidden acrylate function and can react with a diamine to produce a hydroxyphenyl-substituted macrocyclic amide (Kimura, 1986, 1989; Kimura et al., 1985, 1986a, 1987a).

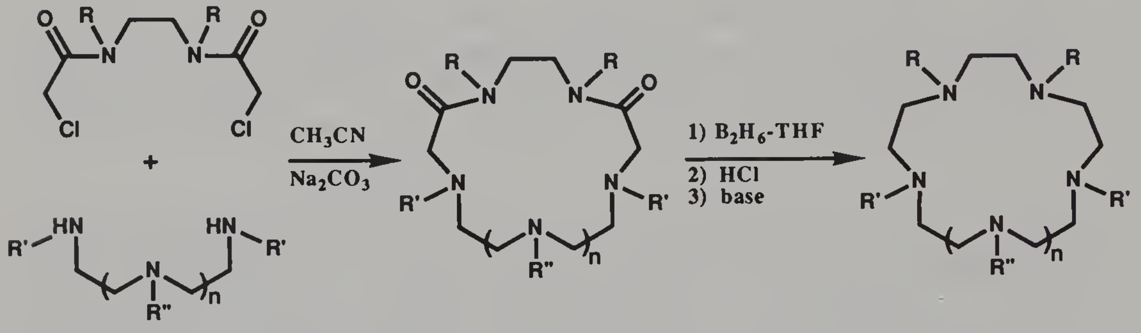


R = H; 2-pyridyl; C_6H_5; 2-HOC_6H_4; 2-HO-5-$NO_2C_6H_3$; 2,3-$(CH_3O)_2C_6H_3$



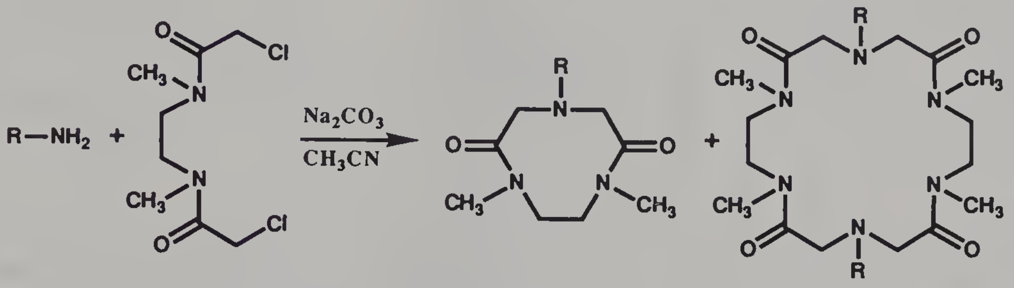
5. The Reaction of a "Crab-like" Bis-α-chloroamide and an Amine or Diamine

The new Krakowiak–Bradshaw crab-like cyclization reaction also produces macrocyclic diamide compounds, but the amide functions are not produced in the ring-closure step. In this process, a bis-α-chloroamide is treated with an α,ω-diamine to form the macrocyclic diamide (Bradshaw et al., 1989a, 1989b, 1990a, 1990b; Krakowiak et al., 1989, 1990a, 1990b). This method is very useful for the preparation of 9–20-membered rings containing both secondary and tertiary amines and with additional functional groups on side chains. It is particularly easy to prepare peraza-crowns with one or two secondary amine functions since the amide nitrogen atoms in the starting bis-α-chloroamides are not reactive nucleophiles. Macrocycles with 12–15 ring members were formed with yields of 70–80% in the ring closure step. The reduction step was carried out using borane–THF. The borane formed a complex with the peraza-crown, which was decomposed with hydrochloric acid. After neutralization with ammonia or sodium hydroxide, the macrocycle was purified on silica gel using methanol–aqueous ammonia as the eluant. Because of the ease of preparing the starting bis-α-chloroamide and the availability of the polyamine starting materials, this process should become the method of choice for preparation of medium-sized peraza-crown macrocycles.



R = H; alkyl; other functionalized chain
R' = alkyl
R'' = alkyl or other functionalized chain

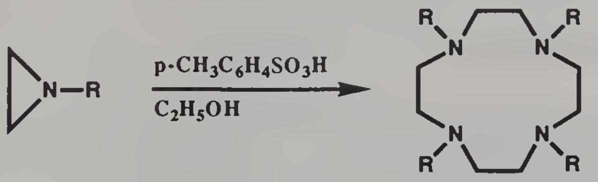
The bis-α-chloroamide can react with a primary amine to form a small peraza-crown such as triaza-9-crown-3 (Bradshaw et al., 1989a; Krakowiak et al., 1990b). In the case shown, a hydroxyether function on the side chain [R = $HO(CH_2)_2O(CH_2)_2$] facilitated peraza-9-crown-3 formation. Where there was no group on the side arm to coordinate a sodium ion or provide a hydrogen bond, 2:2 cyclization to form the peraza-18-crown-6 predominated. More details concerning the Krakowiak–Bradshaw bis-α-chloroamide cyclization process are given in Chapter IV.



R = $C_6H_5CH_2$; $CH_3C(O)N(CH_2)_2$
where R = $HO(CH_2)_2O(CH_2)_2$, no 2:2 product formed

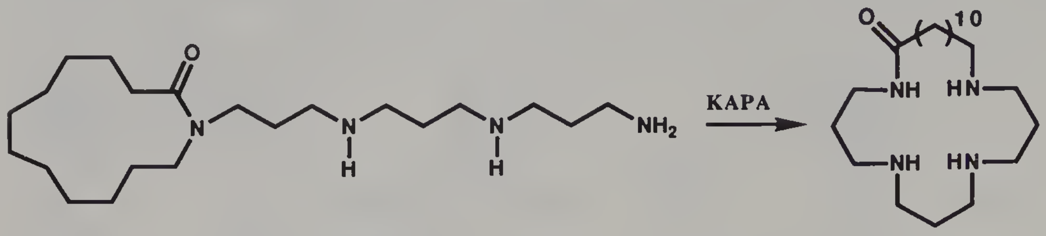
E. MISCELLANEOUS RING-CLOSURE REACTIONS TO FORM ALIPHATIC PERAZA-CROWN MACROCYCLES

Some unusual reactions for preparation of peraza-crowns need to be mentioned. Aziridine molecules readily polymerize and, in some cases, macrocycles can be isolated. For example, 1-benzylaziridine reacted to give good yields of the tetra-*N*-benzyl-substituted peraza-12-crown-4 (Ham, 1980; Hansen and Burg, 1968; Kossai et al., 1980). 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.

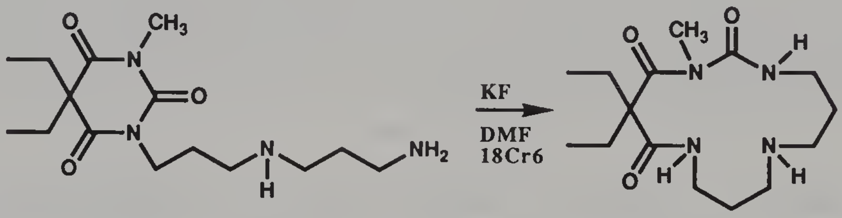


R = C_2H_5; $HO(CH_2)_2$; $C_6H_5CH_2$; o- or p-$CH_3C_6H_4CH_2$; etc.

The "zip" reaction is another route to the peraza-crowns. This process is a ring expansion from a small cyclic amide to a much larger cyclic amide by the rearrangement of the amide carbonyl carbon to the end amine unit on a substituent oligo(trimethylenepolyamine) as shown (Kramer et al., 1977, 1978a, 1978b, 1979; Stephanou et al., 1979). The yields for this "zip" reaction are usually very good. In the example shown, the 13-membered lactam re-



cyclized to a 25-membered triaza lactam in KAPA (a mixture of 1,3-propanediamine and potassium 3-aminopropanamide). A similar ring enlargement to form a tetraaza macrocycle was observed for an *N*-(aminoazaalkyl)-substituted barbiturate in the presence of KF and 18-crown-6 in DMF (Jenny and Hesse, 1981).



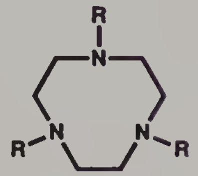
Tables containing a listing of peraza-crown macrocycles are given in the next section. The tables are arranged by numbers of ring nitrogen atoms.

Tables 10.1–10.6—three nitrogen atoms
Tables 10.7–10.21—4 nitrogen atoms
Tables 10.22–10.24—5 nitrogen atoms
Tables 10.25–10.27—6 nitrogen atoms
Table 10.28—8 or more nitrogen atoms
Table 10.29—bis(peraza-crown) macrocycles.

Tables are also arranged by the complexity of substituents on ring nitrogen atoms and then on ring carbon atoms.

F. TABLES OF COMPOUNDS

TABLE 10.1. PERAZA-9-CROWN 3 MACROCYCLES



R		Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula Index	Structure			
H	H			Akkaya et al., 1990
			87	Briellmann et al., 1987
				Buttafava et al., 1986
			80	Diril et al., 1989
				Erhardt et al., 1980
				Graham and Weatherburn, 1981
			88	Koyama and Yoshino, 1972
			73	Lukyanenko et al., 1990a
				McAuley et al., 1984
				Nonoyama and Nonoyama, 1980

TABLE 10.1. *(Continued)*

R		Other Substitutents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula Index	Structure			
			55	Reinen et al., 1987
			70	White et al., 1979
				Yang and Zompa, 1976
				Zompa, 1978
		as HBr salt		Angley et al., 1980
		as salt	90	Searle and Geue, 1984
H	H	2-CH_3		Graham and Weatherburn, 1983
			59	McAuley and Xu, 1988
H	H	3-CH_3, as salt		Mason and Peacock, 1976
H	H	2-$(CH_2)_4NHC(O)C_6H_5$	71	Cox et al., 1990
			64	Craig et al., 1989
H	H	3-$(CH_2)_4NHC(O)C_6H_5$		Parker and Millican, 1989a
CH_3	CH_3			Geraldes et al., 1985
CH_4O_3P	$H_2O_3PCH_2$-		55	Geraldes et al., 1989
				Iveson and Lockhart, 1990

			58	Kabachnik et al., 1984a
			58	Polikarpov et al., 1982
$C_2H_3O_2$	HO_2CCH_2-			Bevilacqua et al., 1987
			83	Cortes et al., 1990
				Geraldes et al., 1985
				Takahashi and Takamoto, 1977
				Wieghardt et al., 1982
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4NH_2$		Cox et al., 1990
			100	Craig et al., 1989
				Parker and Millican, 1989a
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4NH_3^+$, as salt		Cox et al., 1990
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4NHC(O)C_6H_5$		Cox et al., 1990
				Parker and Millican, 1989a
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4NHC(O)(CH_2)_2$-maleimidyl	35	Cox et al., 1990
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4NHC(O)CH_2OCH_2$-pyridine-2-yl-6-$CH=CH_2$		Craig et al., 1989
				Parker and Millican, 1989a
C_2H_5O	$HO(CH_2)_2$-	as HBr salt		Sayer et al., 1983
C_2H_5S	$HS(CH_2)_2$-			Moore et al., 1990
$C_2H_5O_3S$	$HO_3S(CH_2)_2$-			Wieghardt et al., 1983

TABLE 10.1. *(Continued)*

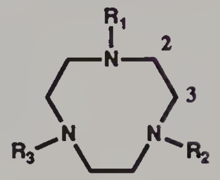
R		Other Substitutents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula Index	Structure			
C_2H_6N	$NH_2(CH_2)_2$-			Hammershoi and Sargeson, 1983
$C_2H_6O_2P$	$HO_2P(CH_3)CH_2$-			Broan et al., 1990a
$C_2H_6O_2P$	$HO_2P(CH_3)CH_2$-	2-$(CH_2)_4NH_2$		Broan et al., 1990a
$C_2H_6O_2P$	$HO_2P(CH_3)CH_2$-	2-$(CH_2)_4NHCO(CH_2)_2CO_2C_6H_4NO_2$		Broan et al., 1990a
C_3H_4N	$NC(CH_2)_2$-		70	Bushnell et al., 1988
$C_3H_5O_2$	$CH_3O_2CCH_2$-		80	Cortes et al., 1990
C_3H_8N	$NH_2(CH_2)_3$-		65	Bushnell et al., 1988
$C_4H_7O_2$	$C_2H_5O_2CCH_2$-	2-$(CH_2)_4NHC(O)C_6H_5$		Cox et al., 1990
			77	Craig et al., 1989
C_4H_8NO	$(CH_3)_3NC(O)CH_2$-		54	Kataky et al., 1990
$C_4H_{10}O_2P$	$C_2H_5O_2P(CH_3)CH_2$-		60	Broan et al., 1990a
$C_4H_{10}O_2P$	$C_2H_5O_2P(CH_3)CH_2$-	2-$(CH_2)_4NHC(O)C_6H_5$		Broan et al., 1990a
$C_5H_7N_2$	1-CH_3-imidazolyl-2-CH_2-		74	Di Vaira et al., 1989
$C_5H_9O_2$	$C_2H_5O_2C(CH_2)_2$-			Wieghardt et al., 1983
$C_5H_{10}NO$	$(CH_3)_2NC(O)(CH_2)_2$-		53	Kataky et al., 1990

C_6H_5S	2-thiophenyl		Tsukube et al., 1989
C_6H_6N	2-pyridyl-CH_2-		Christiansen et al., 1986
C_6H_7N	2-picolyl		Tsukube et al., 1989
C_7H_7	$C_6H_5CH_2$-		Tsukube et al., 1989
C_7H_7O	2-$HOC_6H_4CH_2$-	20-30	Auerbach et al., 1990a
$C_7H_7O_2S$	Ts		Angley et al., 1980
		71	Atkins et al., 1978
		50	Briellmann et al., 1987
			Buttafava et al., 1986
		81	Chavez and Sherry, 1989
		90	Iwata and Kuzuhara, 1985
		80	Lukyanenko et al., 1990a
		74	McAuley et al., 1984
			Nonoyama and Nonoyama, 1980
		57	Rasshofer and Vögtle, 1978
		71	Richman and Atkins, 1974
		83	Searle and Geue, 1984
		65	White et al., 1979
			Yang and Zompa, 1976

TABLE 10.1. *(Continued)*

R		Other Substitutents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula Index	Structure			
$C_7H_7O_2S$	Ts	2-CH_3	20	Graham and Weatherburn, 1983
$C_7H_7O_2S$	Ts	3-CH_3	60	Mason and Peacock, 1976
			50	McAuley and Xu, 1988
$C_7H_7O_2S$	Ts	2-$(CH_2)_4NHC(O)C_6H_5$	71	Cox et al., 1990
			71	Craig et al., 1989
$C_7H_7O_2S$	Ts	3-$(CH_2)_4NHC(O)C_6H_5$		Parker and Millican, 1989a
$C_7H_7O_3S$	4-$CH_3OC_6H_4SO_2$-	2-$(CH_2)_4NHC(O)C_6H_5$		Cox et al., 1990
C_8H_{13}	$CH_2{=}CH(CH_2)_3CH{=}CHCH_2$-			Fakhretdinov et al., 1987
$C_{10}H_8NO_2$	phthalimidyl-$(CH_2)_2$-			Hammershoi and Sargeson, 1983
$C_{11}H_{14}KO$	2-KO-5-t-$C_4H_9C_6H_3CH_2$-			Auerbach et al., 1990b
$C_{11}H_{15}O$	2-HO-3-i-$C_4H_9C_6H_3CH_2$-		60	Auerbach et al., 1990a
$C_{13}H_{12}OP$	$(C_6H_5)_2P(O)CH_2$-			Yatsimirskii et al., 1984
$C_{27}H_{45}O_3$	3,4-$(C_{10}H_{21}O)_2C_6H_3C(O)$-			Lattermann, 1990

TABLE 10.2. PERAZA-9-CROWN-3 MACROCYCLES (DIFFERENT R_1, R_2, AND R_3)



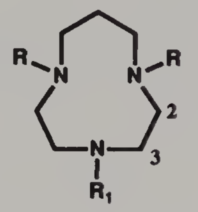
$R_1 = R_2$	R_2 (where different)	R_3	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H		HC(O)-			Weisman et al., 1987
H		HO_2CCH_2-		35	Studer and Kaden, 1986
H		$HO_2P(CH_3)CH_2$-			Broan et al., 1990a
H		Ts			Qian et al., 1990
				91	Sessler et al., 1990
H		Ts	2-CH_3, as complex		Graham and Weatherburn, 1983
H		2,2'-bipyridyl-6-CH_2-		86	Alcock et al., 1989
H		anthracenyl-9-CH_2-			Akkaya et al., 1990
H		$C_6H_5C(O)NH(CH_2)_4CH(CO_2C_2H_5)$-			Cox et al., 1990
					Jankowski et al., 1990
					Parker et al., 1990

TABLE 10.2. (*Continued*)

$R_1 = R_2$	R_2 (where different)	R_3	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
HO_2CCH_2-		H	as salt		Neves et al., 1988
$NC(CH_2)_2$-		H			Fortier and McAuley, 1990
$H_2N(CH_2)_2$-		H			Gahan et al., 1982
$H_2N(CH_2)_3$-		H			Fortier and McAuley, 1990
$C_2H_5O_2CCH_2$-		H			Neves et al., 1988
Ts		H			Peacock and Gwan, 1937
				82	Sessler et al., 1990
					Weisman et al., 1987
				70	Wieghardt et al., 1985
$C_6H_5C(O)NH(CH_2)_4CH$- $(CO_2C_2H_5)$-		H			Cox et al., 1990
					Jankowski et al., 1990
					Parker et al., 1990
CH_3		$CH_3C(O)NH(CH_2)_2$-	5,9-$(O)_2$		Krakowiak et al., 1990b
CH_3		$C_2H_5NH(CH_2)_2$-			Krakowiak et al., 1990b
CH_3		$HO(CH_2)_2O(CH_2)_2$-		40 overall	Bradshaw et al., 1989a

CH_3		$HO(CH_2)_2O(CH_2)_2$-	5,9-$(O)_2$		Bradshaw et al., 1989a
					Krakowiak et al., 1990b
CH_3		$C_6H_5CH_2$-	5,9-$(O)_2$		Krakowiak et al., 1990b
CH_3		2,2'-dipyridyl-6-CH_2-			Alcock et al., 1989
HO_2CCH_2-		$H_2N(CH_2)_4CH(CO_2H)$-			Jankowski et al., 1990
					Parker et al., 1990
HO_2CCH_2-		maleimidyl$(CH_2)_2C(O)NH$-$(CH_2)_4CH(CO_2H)$-			Cox et al., 1990
					Jankowski et al., 1990
					Parker et al., 1990
$C_2H_5O_2CCH_2$-		$C_6H_5C(O)NH(CH_2)_4$-$CH(CO_2C_2H_5)$-			Cox et al., 1990
$H_2N(CH_2)_4CH(CO_2H)$-		HO_2CCH_2-			Jankowski et al., 1990
					Parker et al., 1990
Ts		$HC(O)$-			Weisman et al., 1987
Ts		$C_6H_5C(O)$-		85	Martin et al., 1982
$C_6H_5C(O)NH(CH_2)_4CH$-$(CO_2C_2H_5)$-		$C_2H_5O_2CCH_2$-			Cox et al., 1990
					Parker et al., 1990
maleimidyl$(CH_2)_2C(O)$-$NH(CH_2)_4CH(CO_2H)$-		HO_2CCH_2-			Cox et al., 1990
					Jankowski et al., 1990
H	$HC(O)$-	$C_6H_5CH_2$-			Weisman et al., 1987

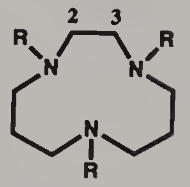
TABLE 10.3. PERAZA-10-CROWN-3 MACROCYCLES



R	R_1	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H	H		56	Briellmann et al., 1987
				Buttafava et al., 1986
				Graham and Weatherburn, 1981
			82	Koyama and Yoshino, 1972
				Nonoyama and Nonoyama, 1980
				Riedo and Kaden, 1977
			62	Searle and Geue, 1984
				Zompa, 1978

H	H	6-CH_3		Graham and Weatherburn, 1983
HO_2CCH_2-	HO_2CCH_2-			Takahashi and Takamoto, 1977
HO_2CCH_2-	HO_2CCH_2-	9-$CH_2C_6H_4CH_2NHC(O)$-cyclohexyl-CH_2-maleimidyl		Parker and Millican, 1989a
Ts	Ts		84	Atkins et al., 1978
			57	Briellmann et al., 1987
				Buttafava et al., 1986
			75	Chavez and Sherry, 1989
			24	Koyama and Yoshino, 1972
				Nonoyama and Nonoyama, 1980
			84	Richman and Atkins, 1974
			79	Searle and Geue, 1984
Ts	Ts	5 or 6-CH_3	46	Graham and Weatherburn, 1983
H	Ts	5-CH_3		Graham and Weatherburn, 1983

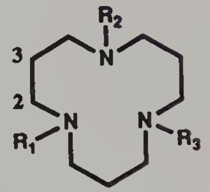
TABLE 10.4. PERAZA-11-CROWN-3 MACROCYCLES



R	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H		83	Briellmann et al., 1987
			Buttafava et al., 1986
			Graham and Weatherburn, 1981
		79	Koyama and Yoshino, 1972
		86,75	Lukyanenko et al., 1988b, 1990a
			Nonoyama and Nonoyama, 1980
			Zompa, 1978

$(CH_3)_3Si$-			Richman et al., 1980
Ts		58	Atkins et al., 1978
		53	Briellmann et al., 1987
			Buttafava et al., 1986
		50	Chavez and Sherry, 1989
		25	Koyama and Yoshino, 1972
		79,80	Lukyanenko et al., 1988b, 1990a
			Nonoyama and Nonoyama, 1980
Ts	2 or 3-CH_3	26	Graham and Weatherburn, 1983
Ts	3,3-$(CH_3)_2$		Graham and Weatherburn, 1983

TABLE 10.5. PERAZA-12-CROWN-3 MACROCYCLES



$R_1 = R_2 = R_3$	R_2 (where different)	R_3 (where (different)	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H				58	Briellmann et al., 1987
					Erhardt et al., 1980
					Graham and Weatherburn, 1981
				62	Koyama and Yoshino, 1972
				63	Lukyanenko et al., 1988a, 1988b, 1990a
					Nonoyama and Nonoyama, 1980
					Riedo and Kaden, 1977
				30	Van Winkle et al., 1966
H			$2,4\text{-}(O)_2$	14	Helps et al., 1989a
H			$2,6,10\text{-}(O)_3$	11	Van Winkle et al., 1966
H			$2,2\text{-}(CH_3)_2;4\text{-}CH_3$	60	Renfrew et al., 1979

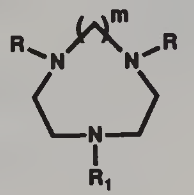
H	3,7,11-$(CH_3)_3$;4,8,12-$(O)_3$		Guaita and Thomas, 1968
H	4-imidazolyl-4		Kimura et al., 1987c
H	2-C_6H_5;4-O	18	Kimura et al., 1986d
H	2-(2-HOC_6H_4)	40	Kimura et al., 1986d
H	2-(2-HOC_6H_4);4-(O)	10	Kimura et al., 1986d
H	2,4-$(O)_2$;3-CH_2(4-NCC_6H_4)	18	Helps et al., 1989a
			Parker and Millican, 1989a
H	3-CH_2(4-NCC_6H_4);6,8-$(O)_2$	16	Craig et al., 1989
H	3-CH_2(4-$H_2NCH_2C_6H_4$)		Craig et al., 1989
			Helps et al., 1989a
			Parker and Millican, 1989a
H	3-CH_2[(4-$CH_3C(O)NHCH_2C_6H_4$)]		Craig et al., 1989
			Helps et al., 1989a
			Parker and Millican, 1989a
$H_2O_3PCH_2$-			Geraldes et al., 1989
HO_2CCH_2-			Craig et al., 1989
			Helps et al., 1989a
HO_2CCH_3-	3-CH_2(4-$H_2NCH_2C_6H_4$)		Craig et al., 1989
			Parker and Millican, 1989a

TABLE 10.5. *(Continued)*

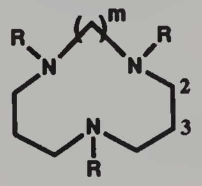
$R_1 = R_2 = R_3$	R_2 (where different)	R_3 (where different)	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
HO_2CCH_2-			3-CH_2(4-maleimidyl-CH_2-1,4-hexyl-C(O)$NHCH_2C_6H_4$)		Craig et al., 1989
					Helps et al., 1989a
					Parker and Millican, 1989a
$C_2H_5O_2CCH_2$-				28	Helps et al., 1989a
$C_2H_5O_2CCH_2$-			3-CH_2[(4-CH_3C(O)$NHCH_2C_6H_4$)]		Craig et al., 1989
					Helps et al., 1989a
					Parker and Millican, 1989a
$(CH_3)_2$NC(O)CH_2-				75	Helps et al., 1989a
				60	Kataky et al., 1990
2-pyridyl-CH_2-					Christiansen et al., 1986
Ts				67	Atkins et al., 1978
				35	Briellmann et al., 1987
				70	Chavez and Sherry, 1989
					Erhardt et al., 1980
				8	Koyama and Yoshino, 1972
				90,66	Lukyanenko et al., 1988a, 1988b, 1990a

					Nonoyama and Nonoyama, 1980
3,4-$(C_{10}H_{21}O)_2C_6H_3C(O)$-					Lattermann, 1990
2,2'-bipyridyl-CH_2-	H	H			Alcock et al., 1989
Ts	H	H		89	Helps et al., 1989a
Ts	H	H	6,8-$(O)_2$	53	Helps et al., 1989a
Ts	H	H	3-$CH_2(4\text{-}NCC_6H_4)$; 6,8-$(O)_2$		Craig et al., 1989
					Helps et al., 1989a
					Parker and Millican, 1989a
Ts	H	H	2,4-$(O)_2$;3-$CH_2(4\text{-}NCC_6H_4)$		Parker and Millican, 1989a
Ts	H	H	3-$CH_2(4\text{-}H_2NCH_2C_6H_4)$		Craig et al., 1989
					Helps et al., 1989a
$HO_2C(CH_2)_2$-	$HO_2C(CH_2)_2$-	H		76	Helps et al., 1989a
$(CH_3)_2NC(O)CH_2$-	$(CH_3)_2NC(O)CH_2$-	H		34	Helps et al., 1989a
					Kataky et al., 1990
$(CH_3)_2NC(O)CH_2$-	$(CH_3)_2NC(O)CH_2$-	Ts		61	Helps et al., 1989a
$C_2H_5O_2C(CH_2)_2$-	$C_2H_5O_2C(CH_2)_2$-	Ts		75	Helps et al., 1989a
H	HC(O)-	$C_6H_5CH_2$-			Weisman et al., 1987
Ts	H	$C_6H_5CH_2$-			Weisman et al., 1987
Ts	HC(O)-	$C_6H_5CH_2$-			Weisman et al., 1987

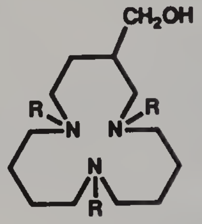
TABLE 10.6. MISCELLANEOUS PERAZA-CROWN-3 MACROCYCLES



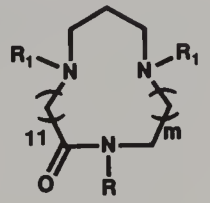
10.6 A



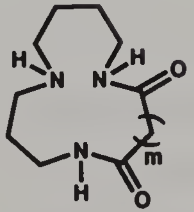
10.6 B



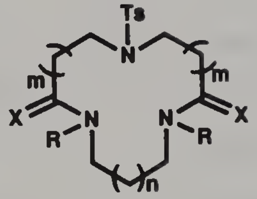
10.6 C



10.6 D



10.6 E



10.6 F

Structure	R	R_1	m	n	X or Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
10.6 A	H	H	4			78	Briellmann et al., 1987
	H	Ts	4				Qian et al., 1990
							Richman and Atkins, 1974
	Ts	$C_6H_5C(O)$-	4			30	Martin et al., 1982

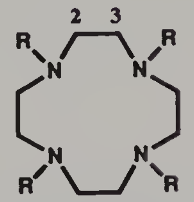
	Ts	Ts	4		81	Atkins et al., 1978
					38	Briellmann et al., 1987
	H	H	5		34	Briellmann et al., 1987
	Ts	Ts	5		55	Atkins et al., 1978
					31	Briellmann et al., 1987
						Richman and Atkins, 1974
	H	H	6		50	Briellmann et al., 1987
	Ts	H	6		91	Martin et al., 1982
	Ts	$C_6H_5C(O)$-	6		56	Martin et al., 1982
	Ts	Ts	6		40-50	Atkins et al., 1978
					23	Briellmann et al., 1987
						Richman and Atkins, 1974
10.6 B	Ts		1		23	Krakowiak et al., 1983
	H		4			Graham and Weatherburn, 1981
					46	Briellmann et al., 1987
					100 (as salt)	Weitl and Raymond, 1979
	H		4	3-(O)		Yamamoto and Maruoka, 1981b

TABLE 10.6. *(Continued)*

Structure	R	R_1	m	n	X or Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
	H		4		2-C_6H_5;3-(O)		Yamamoto and Maruoka, 1981b
	2,3-$(HO)_2C_6H_3C(O)$-		4			60	Weitl and Raymond, 1979
	2,3-OCH_2O-(ring)$C_6H_3C(O)$-		4			50	Weitl and Raymond, 1979
	Ts		4			45	Briellmann et al., 1987
						76	Weitl and Raymond, 1979
10.6 C	H						Marecek et al., 1988
	Ts						Marecek et al., 1988
10.6 D	H	H	1				Stephanou et al., 1979
	CH_3	H	1				Guggisberg et al., 1978

	H	$CH_3C(O)$-	1				Stephanou et al., 1979
	H	H	2			90	Kramer et al., 1977, 1978a
	CH_3OC-	$CH_3C(O)$-	2				Kramer et al., 1978a
	H	H	3				Stephanou et al., 1979
	H	$CH_3C(O)$-	3				Stephanou et al., 1979
10.6 E			8			89	Nagao et al., 1980
			12			85	Nagao et al., 1980
10.6 F	H		4	4	H_2	93	Schmidtchen, 1977, 1980
	H		6	6	H_2	95	Schmidtchen, 1980
	H		4	4	O	55	Schmidtchen, 1977, 1980
	H		6	6	O	40	Schmidtchen, 1980
	CH_3		9	10	O		Isele and Martinez, 1981

TABLE 10.7. PERAZA-12-CROWN-4 MACROCYCLES



R		Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula	Structure			
H	H			Akkaya et al., 1990
				Buoen et al., 1984
		(deuterated)		Desreux and Loncin, 1986
			53	Kabachnik et al., 1984b
			96	Kossai et al., 1979
			70,85	Lukyanenko et al., 1988b, 1990a
			90	Richman and Atkins, 1974
				Stetter and Mayer, 1961
H	H	2,6-$(O)_2$	10	Fabbrizzi et al., 1986a
H	H	2-CH_3		Schaefer et al., 1990
H	H	2-CH_2OH		Deutsch et al., 1988

H	H	2-$CH_2(4-NO_2C_6H_4)$		Gansow, 1988
			91	Moi et al., 1988
H	H	2,5,9-$(O)_3$ 3-$CH_2(4-NO_2C_6H_4)$		Gansow, 1988
H	H	2-$CH_2(4-HOC_6H_4)$		Deutsch et al., 1988
H	H	2-$(CH_2)_4NHCH_2C_6H_5$	10	Cox et al., 1989
H	H	2-$(CH_2)_4NHC(O)C_6H_5$	61	Cox et al., 1989, 1990
				Parker and Eaton, 1990
				Parker and Millican, 1989b
H	H	2-n-$C_{14}H_{29}$; Cu complex		Tundo, 1978
CH_3	CH_3	3,8-$(O)_2$		Krakowiak et al., 1990b
CH_4O_3P	$H_2O_3PCH_2$-		65	Kabachnik et al., 1984b
				Delgado et al., 1990
$C_2H_3O_2$	HO_2CCH_2-			Delgado and da Silva, 1982
			82	Desreux, 1980
		deuterated		Desreux and Loncin, 1986
			42	Stetter et al., 1981
				Stetter and Frank, 1976
$C_2H_3O_2$	HO_2CCH_2-	2-CH_3		Schaefer et al., 1990
$C_2H_3O_2$	HO_2CCH_2-	2-CH_2OH		Deutsch et al., 1988

TABLE 10.7. (*Continued*)

R		Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula	Structure			
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2OCH_2C{\equiv}CH$		Deutsch et al., 1988
$C_2H_3O_2$	HO_2CCH_2-	2-CH_2OCH_2-oxiranyl		Deutsch et al., 1988
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4NH_2$		Parker and Millican, 1989b
			100	Cox et al., 1989, 1990
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4NH_3^+$		Cox et al., 1990
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2O(CH_2)_3NH_2$		Deutsch et al., 1988
$C_2H_3O_2$	HO_2CCH_2-	2-CH_2(4-$NO_2C_6H_4$)		Gansow, 1988
			58	Moi et al., 1988
$C_2H_3O_2$	HO_2CCH_2-	2-CH_2(4-HOC_6H_4)		Deutsch et al., 1988
$C_2H_3O_2$	HO_2CCH_2-	2-CH_2(4-$H_2NC_6H_4$)		Gansow, 1988
				McCall et al., 1990
$C_2H_3O_2$	HO_2CCH_2-	2-CH_2(4-$NCSC_6H_4$)		Gansow, 1988
$C_2H_3O_2$	HO_2CCH_2-	2-CH_2(4-$HO_2CC_6H_4$)		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_2$(4-$NO_2C_6H_4$)		Gansow et al., 1989

$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_2(4\text{-}H_2NC_6H_4)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2O(CH_2)_3$-maleimidyl	Deutsch et al., 1988
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_2(4\text{-}NCSC_6H_4)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2(4\text{-}BrCH_2CONHC_6H_4)$	Gansow et al., 1989
			McCall et al., 1990
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2[4\text{-}ICH_2C(O)NHC_6H_4]$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2[4\text{-}H_2N(CH_2)_3OC_6H_4]$	Deutsch et al., 1988
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_2(4\text{-}HO_2CC_6H_4)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2(4\text{-}HO_2CCH_2OC_6H_4)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_3(4\text{-}NO_2C_6H_4)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_3(4\text{-}H_2NC_6H_4)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2(4\text{-}CH{\equiv}CCH_2OC_6H_4)$	Deutsch et al., 1988
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_3(4\text{-}NCSC_4H_6)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-CH_2(4-oxiranyl-$CH_2OC_6H_4$)	Deutsch et al., 1988
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_2(4\text{-}BrCH_2CONHC_6H_4)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_2(4\text{-}ICH_2CONHC_6H_4)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_3(4\text{-}HO_2CC_6H_4)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_2(4\text{-}HO_2CCH_2OC_6H_4)$	Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4(4\text{-}NO_2C_6H_4)$	Gansow et al., 1989

TABLE 10.7. (*Continued*)

R		Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula	Structure			
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4(4\text{-}H_2NC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2[4\text{-}H_2N(CH_2)_3C_6H_4]$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4(4\text{-}NCSC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_3(4\text{-}BrCH_2CONHC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_3(4\text{-}ICH_2CONHC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_3(4\text{-}HO_2CCH_2OC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4NHC(O)C_6H_5$	52	Cox et al., 1989
$C_2H_3O_2$	HO_2CCH_2-			Parker and Millican, 1989b
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_5(4\text{-}NO_2C_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_5(4\text{-}H_2NC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_5(4\text{-}NCSC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4(4\text{-}BrCH_2CONHC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4(4\text{-}ICH_2CONHC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4NHC(O)(CH_2)_2$-maleimidyl		Cox et al., 1990
$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_5(4\text{-}HO_2CC_6H_4)$		Gansow et al., 1989

$C_2H_3O_2$	HO_2CCH_2-	2-$(CH_2)_4(4\text{-}HO_2CCH_2OC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$-	HO_2CCH_2-	2-$(CH_2)_5(4\text{-}BrCH_2CONHC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$-	HO_2CCH_2-	2-$(CH_2)_5(4\text{-}ICH_2CONHC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$-	HO_2CCH_2-	2-$(CH_2)_5(4\text{-}HO_2CCH_2OC_6H_4)$		Gansow et al., 1989
$C_2H_3O_2$-	HO_2CCH_2-	2-CH_2[4-maleimidyl-$(CH_2)_3OC_6H_4$]		Deutsch et al., 1988
$C_2H_3O_2$-	HO_2CCH_2-	2-$CH_2OCH_2CH(OH)CH_2NH(CH_2)_{10}NHNH_2$		Deutsch et al., 1988
$C_2H_3O_2$-	HO_2CCH_2-	2-$(CH_2)_4NHC(O)CH_2OCH_2$- 2-pyridyl-6-$CH=CH_2$		Parker and Millican, 1989b
				Cox et al., 1989
$C_2H_3O_2$-	HO_2CCH_2-	2-CH_2[4-$H_2NHNC(O)(CH_2)_{10}HN$- $CH_2CH(OH)CH_2OC_6H_4$		Deutsch et al., 1988
C_2H_5	C_2H_5			Ham, 1980
C_2H_5O	$HO(CH_2)_2$-			Ham, 1980
			52	Buoen et al., 1982, 1984
				Grace and Krane, 1983
C_2H_6	$(CH_3)_2$			Bianchi et al., 1988
$C_2H_6O_2P$	$HO_2P(CH_3)CH_2$-			Broan et al., 1990b
$C_2H_6O_2P$	$HO_2P(CH_3)CH_2$-	2-$(CH_2)_4NH_2$		Broan et al., 1990b
				Parker and Eaton, 1990
$C_2H_6O_2P$	$HO_2P(CH_3)CH_2$-	2-$(CH_2)_4NHC(O)$- $(CH_2)_2$-maleimidyl		Broan et al., 1990b
				Parker and Eaton, 1990

TABLE 10.7. *(Continued)*

R		Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula	Structure			
$C_2H_6O_3P$	$H_2O_3P(CH_2)_2$-			Polikarpov et al., 1989
C_3H_7O	$CH_3O(CH_2)_2$-		86	Buoen and Dale, 1986
C_3H_7O	$CH_3CH(OH)CH_2$-		50	Hancock et al., 1988
C_3H_9Si	$(CH_3)_3Si$-		42	Richman, 1977
$C_4H_5N_2$	1-pyrozolyl-CH_2-			Norante et al., 1990
$C_4H_7O_2$	$C_2H_5O_2CCH_2$-	2-$(CH_2)_4NHC(O)C_6H_5$		Parker et al., 1989
C_4H_8NO	$(CH_3)_2NC(O)CH_2$-		55	Kataky et al., 1990
C_4H_9O	$C_2H_5O(CH_2)_2$-			Buoen and Dale, 1986
$C_4H_{10}O_2P$	$C_2H_5O_2P(CH_3)CH_2$-			Broan et al., 1990b
$C_4H_{10}O_2P$	$C_2H_5O_2P(CH_3)CH_2$-	2-$(CH_2)_4NH_2$		Parker and Eaton, 1990
$C_4H_{10}O_2P$	$C_2H_5O_2P(CH_3)CH_2$-	2-$(CH_2)_4NHC(O)C_6H_5$		Broan et al., 1990b
$C_5H_7N_2$	1-CH_3-imidazolyl-2-CH_2-		72	Di Vaira et al., 1989
$C_5H_{10}NO_2$	$C_2H_5O_2CNH(CH_2)_2$-			Ham, 1980
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-CH_2OH		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-CH_2O-$CH_2C{\equiv}CH$		Deutsch et al., 1988

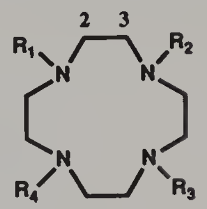
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-CH_2OCH_2-oxiranyl		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-$CH_2O(CH_2)_3NH_2$		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-CH_2(4-HOC_6H_4)		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-$CH_2O(CH_2)_3$-maleimidyl		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-CH_2(4-$CH{\equiv}CCH_2OC_6H_4$)		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-CH_2(4-oxiranyl-$CH_2OC_6H_4$)		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-CH_2[4-$H_2N(CH_2)_3OC_6H_4$]		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-$CH_2O(CH_2)_3NHCO_2CH_2C_6H_5$		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-CH_2[4-maleimidyl-$(CH_2)_3OC_6H_4$]		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-$CH_2OCH_2CH(OH)CH_2NH(CH_2)_{10}NHNH_2$		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-CH_2[4-$C_6H_5CH_2O_2CNH(CH_2)_3OC_6H_4$]		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-$CH_2OCH_2CH(OH)CH_2NH(CH_2)_{10}$-$NHNHCO_2C_4H_9$		Deutsch et al., 1988
$C_6H_{11}O_2$	$C_4H_9O_2CCH_2$-	2-CH_2[4-$C_4H_9O_2CNHNHC(O)$-$(CH_2)_{10}NHCH_2CH(OH)CH_2OC_6H_4$		Deutsch et al., 1988
$C_6H_{13}O$	i-$C_4H_9O(CH_2)_2$-			Buoen and Dale, 1986
$C_6H_{14}OP$	$(C_2H_5)_2P(O)(CH_2)_2$-			Polikarpov et al., 1989
C_7H_6Cl	4-$ClC_6H_4CH_2$-			Ham, 1980
$C_7H_6NO_2$	4-$NO_2C_6H_4CH_2$-			Kruper, 1989
C_7H_7	$C_6H_5CH_2$-		95	Hansen and Burg, 1968

TABLE 10.7. (*Continued*)

R		Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula	Structure			
			50	Kalligeros and Blinn, 1972
			6-80	Kossai et al., 1980
				Ham, 1980
$C_7H_7O_2S$	Ts		80	Atkins et al., 1978
			61	Chavez and Sherry, 1989
		deuterated		Desreux and Loncin, 1986
			95	Iwata and Kuzuhara, 1985
			72	Kabachnik et al., 1984b
			90,86	Lukyanenko et al., 1988a, 1988b, 1990a
			80	Richman and Atkins, 1974
			50	Tomohiro et al., 1988
$C_7H_7O_2S$	Ts	$2\text{-}CH_3$		Schaefer et al., 1990

$C_7H_7O_2S$	Ts	$2\text{-}CH_2OH$		Deutsch et al., 1988
$C_7H_7O_2S$	Ts	$2\text{-}NHC(O)C_6H_5$		Parker and Eaton, 1990
$C_7H_7O_2S$	Ts	$2\text{-}CH_2(4\text{-}NO_2C_6H_4)$	79	Moi et al., 1988
$C_7H_7O_2S$	Ts	$2\text{-}CH_2(4\text{-}HOC_6H_4)$		Deutsch et al., 1988
$C_7H_7O_2S$	Ts	$2\text{-}(CH_2)_4NHC(O)C_6H_5$	72	Cox et al., 1989, 1990 Parker and Millican, 1989b
$C_7H_7O_3S$	$4\text{-}CH_3OC_6H_4SO_2\text{-}$	$2\text{-}CH_2(4\text{-}NO_2C_6H_4)$		Gansow, 1988
$C_8H_8NO_2$	$4\text{-}NO_2C_6H_4CH_2\text{-}$			Kruper, 1989
C_8H_{13}	$CH_2{=}CH(CH_2)_3CH{=}CHCH_2\text{-}$			Fakhretdinov et al., 1987
C_8H_9	$C_6H_5(CH_2)_2\text{-}$			Ham, 1980
C_8H_9	$2\text{-}CH_3C_6H_4CH_2\text{-}$			Ham, 1980
C_8H_9	$4\text{-}CH_3C_6H_4CH_2\text{-}$			Ham, 1980
$C_{10}H_{21}$	$n\text{-}C_{10}H_{21}$			Ham, 1980
$C_{11}H_{12}NO_4$	$4\text{-}NO_2C_6H_4(CH_2)_2CH(CO_2CH_3)\text{-}$			Kruper, 1989
$C_{13}H_{11}$	$(C_6H_5)_2CH\text{-}$			Ham, 1980
$C_{13}H_{16}NO_4$	$4\text{-}NO_2C_6H_4(CH_2)_2CH(CO_2\text{-}i\text{-}C_3H_7)\text{-}$			Kruper, 1989
$C_{20}H_{39}O_2$	$C_{17}H_{35}O_2CCH_2\text{-}$			Ham, 1980

TABLE 10.8. PERAZA-12-CROWN-4 MACROCYCLES (DIFFERENT SUBSTITUENTS ON NITROGEN ATOMS)



R_1	R_2	R_3	R_4	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H	H	H	CH_3SO_2-		70	Lukyanenko et al., 1990b
					93	Pilichowski et al., 1985
H	H	H	$(CH_3)_3COC(O)$-	2,5,11-$(O)_3$ 3-$CH_2(4\text{-}NO_2C_6H_4)$		Gansow, 1988
H	H	H	$C_6H_5CH_2$-			Gries et al., 1988
					58	Kruper, 1989
					37	Tweedle et al., 1987
H	H	H	$C_6H_5CH_2$-	8,12-$(O)_2$		Tweedle et al., 1987
H	H	H	4-$NO_2C_6H_4CH_2$-		87,34-73	Kruper, 1989
H	H	H	3-$CH_2{=}CHC_6H_4CH_2$-			Handel and Chaumeli, 1988

H	H	H	Ts			Ciampolini et al., 1984a
					70	Lukyanenko et al., 1988a
H	H	H	3-$NC_6H_4CH_2$-			DelDonno et al., 1990
H	H	H	3-$HO_2CC_6H_4CH_2$-	as complex		DelDonno et al., 1990
H	H	H	4-$NO_2C_6H_4(CH_2)_2$-		43	Kruper, 1989
H	H	H	4-$NO_2C_6H_4CH{=}CHCH_2$-		69	Kruper, 1989
H	H	H	$C_6H_5CH_2OCH_2CH(CO_2H)$-			Felder et al., 1989
H	H	H	4-$NO_2C_6H_4(CH_2)_2CH(CO_2CH_3)$-		70,81,94	Kruper, 1989
H	H	H	$(HOCH_2)_2CHNHC(O)CH$- $(CH_2OCH_2C_6H_5)$-		salt	Felder et al., 1989
H	H	H	9-anthracenyl-CH_2-			Akkaya et al., 1990
H	H	H	$(C_6H_5)_2CHO(CH_2)_2$-			Handel and Chaumeli, 1988
H	H	H	phthalamidyl-$(CH_2)_2$- $CH[CO_2CH(CH_3)_2]$-		83	Kruper, 1989
H	H	H	$C_6H_5CONH(CH_2)_4CH$- $(CO_2C_2H_5)$-			Cox et al., 1990
						Jankowski et al., 1990
						Parker et al., 1990
H	H	H	$C_{16}H_{33}$			Handel and Chaumeli, 1988
CH_3	CH_3	CH_3	H			Pilichowski et al., 1985
					69	Lukyanenko et al., 1990b

TABLE 10.8. *(Continued)*

R_1	R_2	R_3	R_4	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
CH_3	CH_3	CH_3	CH_3SO_2-		78	Lukyanenko et al., 1990b
					47	Pilichowski et al., 1985
CH_3	CH_3	CH_3	$C_{11}H_{23}C(O)$-		67	Pilichowski et al., 1985
CH_3	CH_3	CH_3	$(C_{11}H_{23})_2CHO(CH_2)_2$-			Pilichowski et al., 1985
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	H			Riesen et al., 1989
						Tweedle et al., 1987
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	CH_3			Tweedle et al., 1987
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$CH_3C(O)$-	complex		Gries et al., 1988
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	C_2H_5	complex		Gries et al., 1988
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$HO(CH_2)_2$-			Gries et al., 1988
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$H_2N(CH_2)_2$-			Gries et al., 1988
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$CH_3OCH_2C(O)$-			Gries et al., 1988
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$HO(CH_2)_2NHC(O)CH_2$-			Gries et al., 1988
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$C_3H_7NHC(O)CH_2$-			Schaefer et al., 1990
					30	Sherry et al., 1989

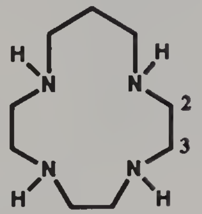
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$H_2N(CH_2)_4CH(CO_2H)$-			Jankowski et al., 1990
						Parker et al., 1990
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$CH_3CH(OH)CH(OH)N$- $(CH_3)C(O)CH_2$-		as complex	Gries et al., 1988
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$C_6H_5CH_2$-			Tweedle et al., 1987
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$C_6H_5CH_2OCH_2CH(CO_2H)$-			Felder et al., 1989
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	maleimidyl$(CH_2)_2C(O)NH$- $(CH_2)_4CH(CO_2H)$-			Cox et al., 1990
						Jankowski et al., 1990
						Parker et al., 1990
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	$(HOCH)_2CHNHC(O)CH$- $(CH_2OCH_2C_2H_5)$-			Felder et al., 1989
C_2H_5	C_2H_5	C_2H_5	$C_2H_5NH(CH_2)_2$-		25,19	Krakowiak et al., 1989
C_2H_5	C_2H_5	C_2H_5	$CH_3C(O)NH(CH_2)_2$-	3,11-$(O)_2$		Krakowiak et al., 1989
$(CH_3)_2$	$(CH_3)_2$	$(CH_3)_2$	CH_3			Bianchi et al., 1988
$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	H			Gries et al., 1988
$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	HO_2CCH_2-			Gries et al., 1988
$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$H_2NC(O)CH_2$-			Gries et al., 1988
$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_2H_5NHC(O)CH_2$-			Gries et al., 1988
$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$HO(CH_2)_2NHC(O)CH_2$-			Gries et al., 1988

TABLE 10.8. (*Continued*)

R_1	R_2	R_3	R_4	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$CH_3CH(OH)CH(OH)N$- $(CH_3)C(O)CH_2$-			Gries et al., 1988
$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_6H_5CH_2$-			Gries et al., 1988
$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_2H_5O_2CCH_2$-	$C_6H_5C(O)NH(CH_2)_4$- $CH(CO_2C_2H_5)$-			Cox et al., 1990
						Parker et al., 1990
4-$NO_2C_6H_4CH_2$-	4-$NO_2C_6H_4CH_2$-	4-$NO_2C_6H_4CH_2$-	H		27	Kruper, 1989
Ts	Ts	Ts	H		90	Lukyanenko et al., 1990b
Ts	Ts	Ts	CH_3SO_2-		80	Pilichowski et al., 1985
					35,75	Lukyanenko et al., 1990b
Ts	Ts	Ts	$C_6H_5CH_2$-			Gries et al., 1988
					72,47	Lukyanenko et al., 1990b
						Tweedle et al., 1987
H	H	HO_2CCH_2-	HO_2CCH_2-	5,12-$(O)_2$	22	Qin, 1984

H	H	4-$NO_2C_6H_4CH_2$-	4-$NO_2C_6H_4CH_2$-		9-19	Kruper, 1989
H	H	Ts	Ts		40	Alfheim et al., 1986
H	H	Ts	Ts	5,12-$(O)_2$	68	Stetter and Mayer, 1961
H	H	Ts	Ts	5,12-$(O)_2$;3-n-$C_{14}H_{29}$	42	Tundo, 1978
H	H	4-$CH_3OC_6H_4SO_2$-	4-$CH_3OC_6H_4SO_2$-	2-CH_2(4-$NO_2C_6H_4$)		Gansow, 1988
H	H	4-$CH_3OC_6H_4SO_2$-	4-$CH_3OC_6H_4SO_2$-	2-CH_2(4-$NO_2C_6H_4$); 5,12-$(O)_2$		Gansow, 1988
CH_3	CH_3	$HO(CH_2)_2$-	$HO(CH_2)_2$-	5,12-$(O)_2$		Krakowiak et al., 1990b
H	CH_3	H	CH_3		40,90	Ciampolini et al., 1984b
H	CH_3SO_2-	H	CH_3SO_2-		61	Lukyanenko et al., 1990b
H	$C_6H_5(CH_2)_2CH$-(CO_2H)-	H	$C_6H_5(CH_2)_2CH$-(CO_2H)-			Felder et al., 1989
H	$C_6H_5CONH(CH_2)_4$-$CH(CO_2C_6H_5)$-	H	$C_6H_5CONH(CH_2)_4$-$CH(CO_2C_6H_5)$-			Jankowski et al., 1990
CH_3	Ts	CH_3	Ts			Ciampolini et al., 1984b
Ts	CH_3SO_2-	Ts	CH_3SO_2-		30,60	Lukyanenko et al., 1990b
HO_2CCH_2	$H_2N(CH_2)_4CH$-(CO_2H)-	HO_2CCH_2-	$H_2N(CH_2)_4CH$-(CO_2H)-			Jankowski et al., 1990
CH_3	CH_3	C_2H_5	H			Bradshaw et al., 1990b
CH_3	CH_3	C_2H_5	H	6,11-$(O)_2$		Bradshaw et al., 1990b

TABLE 10.9. PERAZA-13-CROWN-4 MACROCYCLES



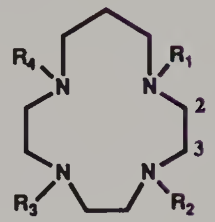
Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
	32	Fabbrizzi, 1979
	72	Hung, 1980
		Kimura et al., 1987a
	50	Stetter and Mayer, 1961
		Wohrle and Nicolaus, 1986
13-(O)		Kimura et al., 1987a
11,13-$(O)_2$		Buttafava et al., 1984
		Wohrle and Nicolaus, 1986
12-CH_3	70	Stetter et al., 1981

$12\text{-}CH_3;12\text{-}NO_2$	as complex	16	Comba et al., 1988a
$12\text{-}C_2H_5$		70	Stetter et al., 1981
$12\text{-}C_2H_5;12\text{-}NO_2$	as complex		Comba et al., 1988a
$12,12\text{-}(CH_3)_2$		61,86	Steinmann and Kaden, 1975
		78	Stetter et al., 1981
	as complex	90	Curtis and Reader, 1971
$11,13\text{-}(CH_3)_2$		63,93	Steinmann and Kaden, 1975
$11,11\text{-}(CH_3)_2;13\text{-}CH_3$		81,87	Steinmann and Kaden, 1975
$12\text{-}(CH_2)_3CN;11,13\text{-}(O)_2$		25	Tabushi et al., 1978
$12\text{-}(CH_2)_4NH_2$			Tabushi et al., 1978
$11\text{-}(2\text{-}HOC_6H_4)$			Kimura et al., 1987a
$13\text{-}(2\text{-}HOC_6H_4)$			Kimura et al,. 1986e
$11\text{-}(2\text{-}HOC_6H_4);13\text{-}(O)$			Kimura et al,. 1987a
$11\text{-}(2\text{-}HO\text{-}5\text{-}H_2NCH_2C_6H_3)$			Morphy et al., 1989
			Parker et al., 1989
$12\text{-}CH_2(4\text{-}NO_2C_6H_4)$			Ruser et al., 1990
$12\text{-}CH_2(4\text{-}NO_2C_6H_4);11,13\text{-}(O)_2$			Ruser et al., 1990
$12\text{-}CH_2(4\text{-}HOC_6H_4)$	as salt		Deutsch et al., 1988
$12\text{-}CH_2(4\text{-}HOC_6H_4);11,13\text{-}(O)_2$			Deutsch et al., 1988

TABLE 10.9. (*Continued*)

Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
12-$CH_2C_6H_5$;11,13-$(O)_2$		Lampeka and Gavrish, 1990
12-$CH_2(4\text{-}H_2NCH_2C_6H_4)$		Morphy et al., 1989
		Parker et al., 1989
12-$(CH_2)_2$-(2-pyridyl)-N-oxide		Kimura et al., 1984b
12-$(CH_2)_2$-(2-pyridyl);11,13-$(O)_2$		Kimura et al., 1984b
	47	Lederle, 1984
12-$(CH_2)_2$-(2-pyridyl-N-oxide);11,13-$(O)_2$	47	Lederle, 1984
12-$(CH_2)_2C_6H_5$;11,13-$(O)_2$		Kimura et al., 1984b
	28	Lederle, 1984
12-$(CH_2)_4$-pyrrolyl		Singh, 1990
6-n-$C_{14}H_{29}$		Tundo, 1978
11-[2-HO-5-(2-CH_2=CH-pyridyl-6)$CH_2OCH_2C(O)NHCH_2C_6H_2$]		Morphy et al., 1989
12-CH_2[4-(2-CH_2=CH-pyridyl-6)$CH_2OCH_2C(O)NHCH_2C_6H_3$]		Morphy et al., 1989

TABLE 10.10. PERAZA-13-CROWN-4 MACROCYCLES (SUBSTITUTED ON NITROGEN)



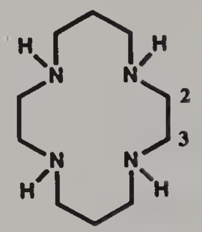
R_1=R_2=R_3=R_4 or R_1	R_2 (where different)	R_3 (where different)	R_4 (where different)	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
CH_3				12,12-$(CH_3)_2$		Buxtorf et al., 1974
					35	Steinmann and Kaden, 1975
$H_2O_3PCH_2$-						Delgado et al., 1990
HO_2CCH_2-						Delgado and da Silva, 1982
						Stetter and Frank, 1976
					18	Stetter et al., 1981
HO_2CCH_2-				12-CH_3	44	Stetter et al., 1981
HO_2CCH_2-				12-C_2H_5	39	Stetter et al., 1981

TABLE 10.10. (*Continued*)

$R_1=R_2=R_3=R_4$ or R_1	R_2 (where different)	R_3 (where different)	R_4 (where different)	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
HO_2CCH_2-				12,12-$(CH_3)_2$	47	Stetter et al., 1981
HO_2CCH_2-				12-$CH_2(4\text{-}HOC_6H_4)$		Deutsch et al., 1988
HO_2CCH_2-				12-$CH_2(4\text{-}NO_2C_6H_4)$		Ruser et al., 1990
HO_2CCH_2-				12-$CH_2[4\text{-}H_2N(CH_2)_3OC_6H_4]$		Deutsch et al., 1988
HO_2CCH_2-				12-CH_2[4-maleimidyl-$(CH_2)_3OC_6H_4$]		Deutsch et al., 1988
$C_4H_9O_2CCH_2$-				12-$CH_2(4\text{-}HOC_6H_4)$		Deutsch et al., 1988
$C_4H_9O_2CCH_2$-				12-$CH_2[4\text{-}H_2N(CH_2)_3OC_6H_4]$		Deutsch et al., 1988
$C_4H_9O_2CCH_2$-				12-CH_2[4-maleimidyl-$(CH_2)_3OC_6H_4$]		Deutsch et al., 1988
$C_4H_9O_2CCH_2$-				12-$CH_2[4\text{-}C_4H_9O_2CNH(CH_2)_3OC_6H_4]$		Deutsch et al., 1988

Ts					77	Atkins et al., 1978
					62	Chavez and Sherry, 1989
					32	Fabbrizzi, 1979
					40	Hung, 1980
					82	Stetter et al., 1981
					30	Wöhrle and Nicolaus, 1986
Ts				12-CH_3	85	Stetter et al., 1981
Ts				12-C_2H_5	75	Stetter et al., 1981
Ts				12,12-$(CH_3)_2$	79	Stetter et al., 1981
H	CH_3	CH_3	CH_3			Bradshaw et al., 1990b
H	CH_3	CH_3	CH_3	2,9-$(O)_2$		Bradshaw et al., 1990b
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	H	12-$CH_2(4\text{-}NO_2C_6H_4)$		Ruser et al., 1990
H	HO_2CCH_2-	HO_2CCH_2-	H	3,9-$(O)_2$	29	Qin, 1984
H	Ts	Ts	H	2,9-$(O)_2$	70	Stetter and Mayer, 1961
Ts	H	H	Ts	3,8-$(O)_2$	73	Stetter and Mayer, 1961
Ts	H	H	Ts	3,8-$(O)_2$;6-n-$C_{14}H_{29}$	43	Tundo, 1978

TABLE 10.11. PERAZA-14-CROWN-4 MACROCYCLES (CYCLAM) (UNSUBSTITUTED NITROGEN ATOMS)



Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
		Alphen, 1937
	50	Barefield and Wagner, 1973
		Barefield, 1972; Barefield et al., 1976a, 1976b, 1981
as Ni complex		Barefield et al., 1976b
		Bosnich et al., 1965
	95	Kossai et al., 1979
	68	Lukyanenko et al., 1990a
		Martin et al., 1977
	85	Pisareva et al., 1986
	50	Stetter and Mayer, 1961

	80	Tabushi et al., 1977
		Wehner and Vögtle, 1975
6-F	45	Kimura et al., 1988a
		Shionoya et al., 1990
6-F;5,7-$(O)_2$	39	Kimura et al., 1988a
		Shionoya et al., 1990
6,6-F_2	54	Kimura et al., 1988a
		Shionoya et al., 1990
6,6-F_2;5,7-$(O)_2$	33	Kimura et al., 1988a
		Shionoya et al., 1990
6,6,13,13-$(F)_4$		Shionoya et al., 1990
6,6,13,13-$(F)_4$;5,7-$(O)_2$		Shionoya et al., 1990
5-(O)		Helps et al., 1989b
	50	Machida et al., 1983
7-(O)		Marchi et al., 1990
5,7-$(O)_2$	28	Tabushi, 1978
	30	Tabushi et al., 1977
5,7,14-$(O)_3$		Kimura et al., 1984b
6,13-$(OH)_2$	25	Barefield et al., 1976b

TABLE 10.11. *(Continued)*

Other Substituents (Numbers indicate position on macrocycle)		Yield (%)	References
6-CH_3			Machida et al., 1983
10-CH_3		70	Barefield et al., 1976b
6-CH_3;6-F		34	Kimura et al., 1988a
6-F;6-CH_3;5,7-$(O)_2$		54	Kimura et al., 1988a
2-CH_2OH	as salt		Bremer et al., 1989
5-CH_2OH			Wagler and Burrows, 1987
6-CH_3;5,7-$(O)_2$			Machida et al., 1983
6-CH_3;6-NO_2	as complex		Lawrance et al., 1987
6-CH_3;13-NH_2			Bernhardt et al., 1989
6-CH_3;6-NH_2	as complex		Lawrance et al., 1987
6-C_2H_5			Machida et al., 1983
6-$(CH_2)_2OH$		55	Tabushi et al., 1977
6-C_2H_5;5,7-$(O)_2$			Machida et al., 1983
6-$(CH_2)_2OH$;5,7-$(O)_2$		40	Tabushi et al., 1977
2,3-$(CH_3)_2$			Jackels et al., 1972

5,12-$(CH_3)_2$			Fairbank et al., 1985
			Hay and Piplani, 1977
			Kolinski and Korybut-Daszkiewicz, 1969
5,14-$(CH_3)_2$	as Ni complex	50	Barefield et al., 1976b
6,6-$(CH_3)_2$		75	Stetter et al., 1981
2,2-$(CH_3)_2$	as Ni complex	55	Barefield et al., 1976b
6,13-$(CH_3)_2$; 6,13-$(NO_2)_2$	as Cu complex		Comba et al., 1986
6,6-$(CH_3)_2$;5,7-$(O)_2$		23	Kimura et al., 1989a
7-(5-imidazolyl)	as salt	75	Kimura et al., 1987b
6-allyl;5,7-$(O)_2$		25	Tabushi et al., 1977
6-$(CH_2)_2CONH_2$		66	Benabdallah and Guglielmetti, 1988
6-C_3H_7			Machida et al., 1983
6-C_3H_7;5,7-$(O)_2$			Machida et al., 1983
5*-CH_3;5*-CH_2NH_2;12-CH_3 (chiral)			Korybut-Daszkiewicz, 1988
6-$(CH_2)_3CN$;5,7-$(O)_2$		30	Tabushi et al., 1978
		30	Tabushi et al., 1977
6-C_4H_9			Machida et al., 1983
		60	Tabushi et al., 1977

TABLE 10.11. *(Continued)*

Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
6-$(CH_2)_4OH$	66	Benabdallah and Guglielmetti, 1988
6-C_4H_9;5,7-$(O)_2$	25	Tabushi et al., 1977
		Machida et al., 1983
5,12-$(C_2H_5)_2$		Fairbank et al., 1985
6-$(CH_2)_4NH_2$		Bremer et al., 1989
		Kimura et al., 1984a
	70	Tabushi et al., 1977, 1978
6-$(CH_2)_4NH_2$;5,7-$(O)_2$		Kimura et al., 1984a
6,6,13,13-$(CH_3)_4$	5	Barefield et al., 1976b
	55	Stetter et al., 1981
2,2,3,3-$(CH_3)_4$		Kobiro et al., 1990
5,7,12,14-$(CH_3)_4$	52	Kasprzyk and Kolinski, 1984
5,12-$(CH_3)_2$;2 or 3,9 or 10-$(CH_3)_2$	45	Kasprzyk and Kolinski, 1984
5,14-$(CH_3)_2$;7,12-$(CH_3O)_2$	7	Hideg and Lloyd, 1971
7-(2-pyridyl)	24	Kimura et al., 1986c

5-(2-pyridyl);7-(O)			Kimura et al., 1986c, 1988b
5-(O);7-(2-pyridyl)		40	Kimura et al., 1986c
7-(3-HO-2-pyridyl)			Kimura et al., 1990a
6-$(CH_2)_4CONH_2$		63	Benabdallah and Guglielmetti, 1988
6-$(CH_2)_4SCH_3$		69	Benabdallah and Guglielmetti, 1988
2,5*,10,12-$(CH_3)_4$;5*-CH_2NH_2(chiral)			Hay et al., 1989a
			Korybut-Daszkiewicz, 1985
2,5,10,12-$(CH_3)_4$;5-CH_2NH_2	as Ni complex		Korybut-Daszkiewicz, 1985
3,5,9,12*-$(CH_3)_4$;12*-CH_2NH_2 (chiral)			Korybut-Daszkiewicz, 1988
5-(2-HO-5-$NO_2C_6H_3$)		50	Kimura et al., 1987a
5-[2-HO-3,5-$(NO_2)_2C_6H_2$]		67	Kimura et al., 1987a
5-(2-HO-5-$NO_2C_6H_3$);7-(O)	as salt	13	Kimura et al., 1987a
			Parker and Millican, 1987
5-(O);7-(2-HO-5-$NO_2C_6H_3$)		19	Kimura et al., 1985
5-C_6H_5			Kimura et al., 1985
5-C_6H_5	as salt	50	Kimura et al., 1987a
5-(2-HOC_6H_4)		50	Kimura et al., 1987a
		50	Kimura et al., 1985
5-C_6H_5;7-(O)		30	Kimura et al., 1985, 1987a, 1988b

TABLE 10.11. (*Continued*)

Other Substituents (Numbers indicate position on macrocycle)		Yield (%)	References
5-(O);7-(2-HOC_6H_4)		20	Kimura et al., 1985
5-(2-HOC_6H_4);7-(O)	as salt		Kimura, 1986
		20	Kimura et al., 1987a
5-(2-HO-5-$H_2NCH_2C_6H_3$)			Morphy et al., 1989
5-(O);7-(2-HO-5-$NH_2C_6H_3$)			Kimura, 1986
6-C_6H_{13}		35	Tabushi and Fujiyoshi, 1977
6-C_6H_{13};5,7-$(O)_2$		28	Tabushi and Fujiyoshi, 1977
6-$(CH_2)_6OH$;5,7-$(O)_2$		14	Kobayashi et al., 1987
			Shirai and Kato, 1988
3,9-$[CH(CH_3)_2]_2$;5,7-$(O)_2$		75	Wagler et al., 1989
5*,7,7,12*,14,14$(CH_3)_6$;(chiral)		22-45	Curtis, 1964
			Hay et al., 1975, 1989b
			Tait and Busch, 1972
5,7,7,12,14,14-$(CH_3)_6$			Alcock et al., 1980
			Bakac and Espenson, 1990
	as complex	22-45	Curtis, 1964

	as complex		Curtis, 1965
		65	Kasprzyk and Kolinski, 1984
			Olson and Vasilevskis, 1969
			Tait and Busch, 1978b
	as complex	40	Warner and Busch, 1969
5,5,7,12,12,14-$(CH_3)_6$	as complex		Barefield and Mocella, 1975
			Curtis et al., 1973
5,7,7,12,12,14-$(CH_3)_6$			Curtis, 1967
5,12-$(CH_3)_2$;7,7,14,14-$(CH_3)_4$;2 or 3,9 or 10-$(CH_3)_2$		55	Kasprzyk and Kolinski, 1984
2,2,3,3,9,9,10,10-$(CH_3)_8$			Kobiro et al., 1990
3,5,7,7,10,12,14,14-$(CH_3)_8$		19,22,38	Bembi et al., 1989b
			Ito and Busch, 1973
			Tait and Busch, 1972
5,7,12,12,14-$(CH_3)_5$;5-CH_2OH			House et al., 1984
6-$CH_2(4\text{-}NO_2C_6H_4)$	as salt		Moi et al., 1985
5-$(2\text{-}CH_3O\text{-}5\text{-}NO_2C_6H_3)$			Parker and Millican, 1987
6-$CH_2(4\text{-}NO_2C_6H_4)$;5,7-$(O)_2$			Moi et al., 1985
6-$CH_2C_6H_5$			Machida et al., 1983
		65	Tabushi et al., 1977

TABLE 10.11. *(Continued)*

Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
5-(2-$CH_3OC_6H_4$)		Kimura et al., 1987a
6-$CH_2C_6H_5$;5,7-$(O)_2$		Fabbrizzi et al., 1983
		Machida et al., 1983
	25	Tabushi et al., 1977
5-(2-$CH_3OC_6H_4$);7-(O)		Kimura et al., 1987a
6-CH_2(4-$H_2NCH_2C_6H_4$)		Morphy et al., 1988, 1989
6-$(CH_2)_2$-pyridyl-2;5,7-$(O)_2$	45	Lederle, 1984
		Kimura et al., 1984b
6-$(CH_2)_2$-2-pyridyl-N-oxide;5,7-$(O)_2$	55	Lederle, 1984
		Kimura et al., 1984b
6-$(CH_2)_2$-2-pyridyl;5,7,14-$(O)_3$		Kimura et al., 1984b
6-$(CH_2)_2$-2-pyridyl-N-oxide;5,7,14-$(O)_3$		Kimura et al., 1984b
5-(2-HO-5-NCC_6H_3);7-(O)		Parker and Millican, 1987
6-CH_2(4-NCC_6H_4);5,7-$(O)_2$	19	Morphy et al., 1988
		Parker and Millican, 1987

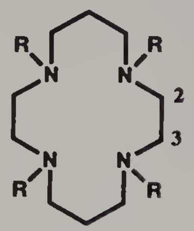
5-(2-HO-5-$H_2NCH_2C_6H_3$)		Morphy et al., 1988
		Parker and Millican, 1987
5-(2-HO-5-$CH_3C(O)NHCH_2C_6H_3$)		Morphy et al., 1988
6-$(CH_2)_4$-pyrrolyl	24	Collin and Sauvage, 1987
2,3,9,10-$(CN)_4$;2,3,9,10-$(CH_3)_4$		Settimj et al., 1966
3,9-$[CH_2CH(CH_3)_2]_2$	12	Wagler et al., 1989
5,12-$(CH_3)_2$;7,14-($\underline{i}$-C_3H_7)$_2$	58	Kasprzyk and Kolinski, 1984
6-$CH_2[4\text{-}CH_3C(O)NHCH_2C_6H_4]$	83	Morphy et al., 1988
6-$(CH_2)_2C_6H_5$;5,7-$(O)_2$		Kimura et al., 1984b
	47	Lederle, 1984
6-$(CH_2)_2C_6H_5$;5,7,14-$(O)_3$		Kimura et al., 1984b
6-$CH_2(4\text{-}H_2NCH_2C_6H_4)$	83	Parker and Millican, 1987
6-$CH_2C_{10}H_7$		Machida et al., 1983
6-$CH_2C_{10}H_7$;5,7-$(O)_2$		Machida et al,. 1983
6-$(CH_2)_{11}OH$		Bremer et al., 1989
6-$(CH_2)_4NHCO_2CH_2C_6H_5$;3,9-$(O)_2$		Kimura et al., 1984a
		Muller and Handel, 1982
6-n-$C_{12}H_{25}$	87	Tabushi, 1978

TABLE 10.11. (*Continued*)

Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
as salt	28	Yamada et al., 1989
6-$C_{12}H_{25}$;5,7-$(O)_2$	30	Yamada et al., 1989
5,14-$(CH_3)_2$;7,12-$(4\text{-}ClC_6H_4)_2$	66	Hideg and Lloyd, 1971
3,9-$(CH_2C_6H_5)_2$;5,7-$(O)_2$	8	Wagler et al., 1989
	8	Wagler and Burrows, 1988
5,14-$(CH_3)_2$;7,12-$(C_6H_5)_2$	92	Hideg and Lloyd, 1971
	68	Ketring et al., 1982, 1984
7,14-$(CH_3)_2$;5,12-$(C_6H_5)_2$		Caulkett et al., 1978
		Hankovszky et al., 1984
7,14-$(CH_3)_2$;5,12-$(2\text{-}HOC_6H_4)_2$		Hankovszky et al., 1984
5,14-$(CH_3)_2$;7,12-$(2\text{-}CH_3OC_6H_4)_2$	74	Hideg and Lloyd, 1971
7,14-$(CH_3)_2$;5,12-$(2\text{-}CH_3OC_6H_4)_2$		Hankovszky et al., 1984

7,14-$(CH_3)_2$;5,12-(2-HO-3-$CH_3OC_6H_3)_2$		Hankovszky et al., 1984
5,14-$(CH_3)_2$;7,12-(4-$CH_3C_6H_4)_2$	75	Hideg and Lloyd, 1971
5,7-$(O)_2$;6-$C_{16}H_{33}$	10.5	Tabushi, 1978
6-CH_2[4-(2-CH_2=CH-pyridyl-6)$CH_2OCH_2C(O)NHCH_2C_6H_4$]		Morphy et al., 1988, 1989
	90	Parker and Millican, 1987
5-[2-HO-5-(2-CH_2=CH-pyridyl-6)$CH_2OCH_2C(O)NHCH_2C_6H_4$]		Morphy et al., 1988, 1989
7,14-$(CH_3)_2$;5,12-(2-$C_2H_5OC_6H_4)_2$		Hankovszky et al., 1984
6-CH_2(4-maleimidyl-CH_2-1,4-cyclohexane-$C(O)NHCH_2C_6H_4$)		Morphy et al., 1989
		Parker and Millican, 1987
7,14-$(CH_3)_2$;5,12-(2-CH_2=$CHCH_2OC_6H_4)_2$		Hankovszky et al., 1984
7,14-$(CH_3)_2$;5,12-(4-CH_2=$CHCH_2OC_6H_4)_2$		Hankovszky et al., 1984
7,14-$(CH_3)_2$;5,12-(2-$\underline{i}C_3H_7OC_6H_4)_2$		Hankovszky et al., 1984
7,14-$(CH_3)_2$;5,12-(2-$C_3H_7OC_6H_4)_2$		Hankovszky et al., 1984
7,14-$(CH_3)_2$;5,12-(2-CH_2=$CHCH_2CH_2OC_6H_4)_2$		Hankovszky et al., 1984
7,14-$(CH_3)_2$;5,12-(2-$C_6H_5CH_2OC_6H_4)_2$		Hankovszky et al., 1984
7-imidazolyl-$C(C_6H_5)_3$	8	Kimura et al., 1987b

TABLE 10.12. PERAZA-14-CROWN-4 MACROCYCLES (CYCLAM) (SAME SUBSTITUENT ON NITROGEN ATOMS)



R					
Formula Index	Structure	Other Substituents (Numbers indicate position on macrocycle)		Yield (%)	References
CH_3	CH_3			52	Barefield and Wagner, 1973
				40	Buxtorf and Kaden, 1974
					Buxtorf et al., 1974
		as complex			D'Aniello et al., 1975
				98,60	Jurczak and Ostaszewski, 1988
		as Ni complex		88	Wagner and Barefield, 1976
		as Ni complex	chiral		Wagner and Barefield, 1976
		as complex			Wagner et al., 1974
				87	Weitl et al., 1978
CH_3	CH_3	5,12-$(CH_3)_2$			Hay and Piplani, 1977

CH_3	CH_3	7,14-$(CH_3)_2$			Buxtorf et al., 1974
			chiral		Miyamura et al., 1987
CH_3	CH_3	5,12-$(CH_3)_2$;7,7,14,14-$(CH_3)_4$			Clark and Harrowfield, 1984
					Jurban et al., 1984
CH_3	CH_3	5,14-$(CH_3)_2$;7,7,12,12-$(CH_3)_4$	chiral		Wagner and Barefield, 1976
CH_3	CH_3	7,14-$(CH_3)_2$;5,5,12,12-$(CH_3)_4$	chiral		Wagner and Barefield, 1976
			complex		Wagner et al., 1974
CH_3	CH_3	7,12-$(CH_3)_2$;5,5,14,14-$(CH_3)_4$	complex		Wagner et al., 1974
CH_4O_3P	$H_2O_3PCH_2$-				Delgado et al., 1990
				85	Pisareva et al., 1986
C_2F_3O	$CF_3C(O)$-	5-(2-HOC_6H_5		94	Kimura et al., 1987a
C_2F_3O	$CF_3C(O)$-	5-[2-HO-3,5-$(NO_2)_2C_6H_2$]		36	Kimura et al., 1987a
$C_2H_3O_2$	HO_2CCH_2-				Delgado and da Silva, 1982
					Stetter and Frank, 1976
				29	Stetter et al., 1981
$C_2H_3O_2$	HO_2CCH_2-	6,6-$(CH_3)_2$		53	Stetter et al., 1981
$C_2H_3O_2$	HO_2CCH_2-	5,12-$(CH_3)_2$		51	Hafliger and Kaden, 1979
$C_2H_3O_2$	HO_2CCH_2-	6,6,13,13-$(CH_3)_4$		26	Stetter et al., 1981

TABLE 10.12. *(Continued)*

R		Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula Index	Structure			
$C_2H_3O_2$	HO_2CCH_2-	6-$CH_2(4\text{-}NO_2C_6H_4)$		Moi et al., 1985, 1987
				Deshpande et al., 1988
$C_2H_3O_2$	HO_2CCH_2-	5-$(3\text{-}NO_2\text{-}5\text{-}CH_3OC_6H_3)$		Parker and Millican, 1987
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2(4\text{-}NH_2C_6H_4)$		McCall et al., 1990
$C_2H_3O_2$	HO_2CCH_2-	5-$(2\text{-}CH_3O\text{-}5\text{-}NH_2C_6H_3)$		Parker and Millican, 1987
$C_2H_3O_2$	HO_2CCH_2-	6-$CH_2[4\text{-}BrCH_2C(O)NHC_6H_4]$		Deshpande et al., 1988
				Moi et al., 1987
$C_2H_3O_2$	HO_2CCH_2-	2-$CH_2[4\text{-}BrCH_2C(O)NHC_6H_4]$		McCall et al., 1990
C_2H_5	C_2H_5			Bradshaw et al., 1990a
C_2H_5	C_2H_5	2,10-$(O)_2$		Bradshaw et al., 1990a
C_2H_5O	$HO(CH_2)_2$-			Hay and Clark, 1984
				Hay et al., 1987
			100	Madeyski et al., 1984
C_2H_6N	$H_2N(CH_2)_2$-		95	Murase et al., 1986
		as salt		Murase et al., 1984

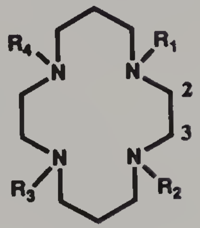
C_3H_4N	$NC(CH_2)_2$-	78	Freeman et al., 1984
			Wainwright, 1980
C_3H_6NO	$H_2NC(O)(CH_2)_2$-	91	Freeman et al., 1984
			Wainwright, 1980
C_3H_8N	$H_2N(CH_2)_3$-	92	Wainwright, 1983
$C_5H_3O_2$	2-furanylC(O)-		Tsukube, 1984
C_5H_5O	2-furanylCH_2-		Tsukube, 1984
			Tsukube et al., 1984
C_6H_6N	2-pyridyl-CH_2-	70	Alcock et al., 1986
			Asato et al., 1989
			Tsukube et al., 1988
			Tsukube et al., 1989
$C_7H_4NO_5$	2,3-$(HO)_2$-4 or 5-$NO_2C_6H_2C(O)$-		Weitl and Raymond, 1980
C_7H_5O	$C_6H_5C(O)$-	80	Tsukube, 1985
			Tsukube et al., 1984
$C_7H_5O_2$	2,3-$(HO)_2C_6H_3C(O)$-	95	Weitl et al., 1978
			Weitl and Raymond, 1980
C_7H_7	$C_6H_5CH_2$-	80	Tsukube, 1983, 1985
			Tsukube et al., 1984

TABLE 10.12. (*Continued*)

R		Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
Formula Index	Structure			
$C_7H_7O_2S$	Ts		70	Atkins et al., 1978
			70	Chavez and Sherry, 1989
			54	Helps et al., 1988
			83	Lukyanenko et al., 1990a
				Martin et al., 1977
			65	Pisareva et al., 1986
				Wehner and Vögtle, 1975
$C_7H_7O_2S$	Ts	5-CH_2CO_2H		Wagler and Burrows, 1987
		6-$(CH_2)_2OH$		Benabdallah and Guglielmetti, 1988
		6,6-$(CH_3)_2$	69	Stetter et al., 1981
		6-$(CH_2)_2CN$	70	Benabdallah and Guglielmetti, 1988
		6,6,13,13-$(CH_3)_4$	75	Stetter et al., 1981
		6-$(CH_2)_4OH$		Benabdallah and Guglielmetti, 1988
		6-$(CH_2)_4CN$	70	Benabdallah and Guglielmetti, 1988

		6-$(CH_2)_4SCH_3$	65	Benabdallah and Guglielmetti, 1988
		6-$(CH_2)_2$O-pyranyl-2	72	Benabdallah and Guglielmetti, 1988
		2-$CH_2OC_6H_5$	50	Bremer et al., 1989
		5-$CH_2OSiC_4H_9(CH_3)_2$	80	Wagler and Burrows, 1987
		6-$(CH_2)_4$O-pyranyl-2	86	Benabdallah and Guglielmetti, 1988
		6-$(CH_2)_2$OTs	80	Benabdallah and Guglielmetti, 1988
		6-$(CH_2)_4$OTs	80	Benabdallah and Guglielmetti, 1988
		6-$(CH_2)_4$NHTs		Bremer et al., 1989
		6-$(CH_2)_{11}$OH		Bremer et al., 1989
		6-$C_{12}H_{25}$		Muller and Handel, 1982
				Tabushi, 1978
$C_9H_7O_5$	1,3-benzodioxolyl-C(O)-		92	Weitl et al., 1978
$C_9H_{12}NO_2S$	TsNH$(CH_2)_2$-		85	Murase et al., 1984, 1986
$C_{10}H_8NO$	N-oxide-guinolinyl-2-CH_2-			Pietraszkiewicz et al., 1990
$C_{10}H_{14}NO_2S$	TsNH$(CH_2)_3$-			Bembi et al., 1989a
$C_{11}H_9N_2$	2,2'-dipyridyl-6-CH_2-		75	Lehn and Ziessel, 1987
$C_{13}H_{12}P$	$(C_6H_5)_2PCH_2$-		74	Hope et al., 1984
$C_{19}H_{29}O_2$	4-$C_{12}H_{25}OC_6H_4C(O)$-			Tatarsky et al., 1990

TABLE 10.13. PERAZA-14-CROWN-4 MACROCYCLES (CYCLAM) (DIFFERENT SUBSTITUENTS ON NITROGEN ATOMS)



R_1	R_2	R_3	R_4	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H	H	H	CH_3	as Ni complex		Wagner and Barefield, 1976
	H	H			70	Barefield et al., 1976b
	H	H			85	Ciampolini et al., 1986
	H	H			35	Buxtorf and Kaden, 1974
H	H	H	HO_2CCH_2-		69	Studer and Kaden, 1986
H	H	H	HO_2CCH_2-	5,5,12,12-$(CH_3)_4$ as salt 7,14-$(CH_3)_2$	75	Jide et al., 1988
H	H	H	$H_2N(CH_2)_2$-	as salt	45	Pallavicini et al., 1987
H	H	H	$O_2N(CH_2)_2C(O)$-			Bremer et al., 1989
H	H	H	$HO_2C(CH_2)_2$-		59	Studer and Kaden, 1986
H	H	H	$H_2N(CH_2)_3$-			Bremer et al., 1989

H	H	H	$HO_2C(CH_2)_3$-		40	Studer and Kaden, 1986
H	H	H	$NC(CH_2)_4$-			Handel and Chaumeli, 1988
H	H	H	$H_2N(CH_2)_5$-			Handel and Chaumeli, 1988
H	H	H	C_6H_{13}		60	Tabushi and Fujiyoshi, 1977
H	H	H	C_6H_{13}	2,14-$(O)_2$	17	Tabushi and Fujiyoshi, 1977
H	H	H	$HO(CH_2)_6$-			Handel and Chaumeli, 1988
H	H	H	4-$NO_2C_6H_4CH_2$-		72	Helps et al., 1989b
					100	Kruper, 1989
H	H	H	2-HO-5-$NO_2C_6H_3CH_2$-		94	Helps et al., 1989b
H	H	H	$C_6H_5CH_2$-	as Ni complex	60	Barefield et al., 1976b
H	H	H	Ts			Calligaris et al., 1990
H	H	H	3-thiophenylCH_2-		70	Helps et al., 1989b
H	H	H	3-$NCC_6H_4CH_2$-		73	Helps et al., 1989b
H	H	H	4-$NCC_6H_4CH_2$-		82	Helps et al., 1989b
H	H	H	4-$CO_2C_6H_4CH_2$-	as complex		Kaden et al., 1989
H	H	H	3- or 4-CH_2=$CHC_6H_4CH_2$-			Handel and Chaumeli, 1988
H	H	H	2-$HO_2CC_6H_4CH_2$-		16,70	Studer and Kaden, 1986
H	H	H	4-$HO_2CC_6H_4CH_2$-			Studer et al., 1990
	H	H			70	Studer and Kaden, 1986

TABLE 10.13. (*Continued*)

R_1	R_2	R_3	R_4	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H	H	H	C_8H_{17}		83	Ketring et al., 1982, 1984
H	H	H	$4\text{-}NH_2CH_2C_6H_4CH_2\text{-}$		85	Helps et al., 1989b
H	H	H	$4\text{-}CH_2{=}CHC_6H_4CH_2\text{-}$			Handel and Chaumeli, 1988
H	H	H	C_9H_{19}			Ketring et al., 1984
H	H	H	C_9H_{21}			Ketring et al., 1984
H	H	H	2,2'-dipyridyl-6-CH_2-			Alcock et al., 1989
H	H	H	pyrrolyl-$OCH_2C_6H_4CH_2$-			Bartlett et al., 1990
H	H	H	$4\text{-}\underline{i}\text{-}C_4H_9NHC(O)C_6H_4CH_2\text{-}$			Kaden et al., 1989
	H	H				Studer et al., 1990
H	H	H	$C_{12}H_{25}$			Handel and Chaumeli, 1988
						Ketring et al., 1984
H	H	H	4-[2-pyridyl$CH_2NHC(O)$]$C_6H_4CH_2$-			Kaden et al., 1989
	H	H				Studer et al., 1990
H	H	H	pyrrolyl-$(CH_2)_3OCH_2C_6H_4CH_2$-			Bartlett et al., 1990

H	H	H	$C_{16}H_{33}$		91	De Santis et al., 1989
						Fabbrizzi, 1989
H	H	H	$C_{16}H_{33}$	12,14-$(O)_2$	17	Tabushi, 1978
H	H	H	pyrrolyl-$(CH_2)_6OCH_2C_6H_4CH_2$-			Bartlett et al., 1990
H	H	H	3-quinuclidinyl- $OC(O)C(C_6H_5)(OH)CH_2C{=}CCH_2$-			Eckelman et al., 1984
H	H	H	$C_{18}H_{37}$			Ketring et al., 1984
CH_3	CH_3	CH_3	H		80	Barefield et al., 1986a
						Bradshaw et al., 1990a
				chiral	75	Wagner and Barefield, 1976
				as Ni complex	75	Wagner and Barefield, 1976
CH_3	CH_3	CH_3	H	2,10-$(O)_2$		Bradshaw et al., 1990a
CH_3	CH_3	CH_3	H	5,14-$(CH_3)_2$;7,7,12,12-$(CH_3)_4$	70	Wagner and Barefield, 1976
CH_3	CH_3	CH_3	$NCCH_2$-		88	Barefield et al., 1986a
						Schibler and Kaden, 1981
						Tschudin et al., 1989a
CH_3	CH_3	CH_3	HO_2CCH_2-			Tschudin et al., 1988
CH_3	CH_3	CH_3	$HS(CH_2)_2$-	as salt	45	Tschudin et al., 1988
CH_3	CH_3	CH_3	$H_2N(CH_2)_2$-		65	Basak and Kaden, 1983
	CH_3	CH_3				Barefield et al., 1986a

TABLE 10.13. (*Continued*)

R_1	R_2	R_3	R_4	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
CH_3	CH_3	CH_3	$NC(CH_2)_2$-		100	Barefield et al., 1986a
				as salt	59	Tschudin et al., 1988
CH_3	CH_3	CH_3	$HO_2C(CH_2)_2$-	as complex	51	Barefield et al., 1986a
						Tschudin et al., 1988
CH_3	CH_3	CH_3	$CH_3O_2CCH_2$-		29	Tschudin et al., 1988, 1989a
CH_3	CH_3	CH_3	$H_2NC(O)(CH_2)_2$-		100	Barefield et al., 1986a
				as salt	57	Tschudin et al., 1988
CH_3	CH_3	CH_3	$H_2N(CH_2)_3$-			Barefield et al., 1986a
					42	Tschudin et al., 1988
CH_3	CH_3	CH_3	$(CH_3)_2NC(O)CH_2$-		35	Tschudin et al., 1988, 1989a
CH_3	CH_3	CH_3	$C_2H_5O_2CCH_2$-		20	Tschudin et al., 1988, 1989a
CH_3	CH_3	CH_3	$CH_3O_2C(CH_2)_2$-		100	Barefield et al., 1986a
			$(CH_3)_2N(CH_2)_2$-		52	Basak and Kaden, 1983
CH_3	CH_3	CH_3	$(HO)(C_2H_5O)P(O)(CH_2)_2$-			Tschudin et al., 1988

CH_3	CH_3	CH_3	$C_2H_5O_2C(CH_2)_2$-			46	Tschudin et al., 1988,1989a
			$(C_2H_5O)_2PO(CH_2)_2$-		as salt	32	Tschudin et al., 1988,1989a
CH_3	CH_3	CH_3	$C_6H_5CH_2$-	as complex		95	Barefield et al., 1986b
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	H				Riesen et al., 1989
						95	Helps et al., 1989b
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	4-$NO_2C_6H_4CH_2$-				Riesen et al., 1989
						51	Helps et al., 1989b
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	4-$H_2NC_6H_4CH_2$-				Helps et al., 1989b
$NC(CH_2)_2$-	$NC(CH_2)_2$-	$NC(CH_2)_2$-	H			20	Freeman et al., 1984
Ts	Ts	Ts	H			51	Helps et al., 1989b
Ts	Ts	Ts	CH_3			90	Ciampolini et al., 1986
Ts	Ts	Ts	2-HO-5-$NO_2C_6H_3CH_2$-			73	Helps et al., 1989b
Ts	Ts	Ts	$TsNH(CH_2)_2$-			54	Pallavicini et al., 1987
H	H	$C_6H_{13}OC_6H_4N$=N- $C_6H_4O(CH_2)_{10}$-	H				Kunitake and Ishikawa, 1986
H	H	CH_3	CH_3	as Ni complex		75	Barefield et al., 1976b
							Wagner and Barefield, 1976
				as Ni complex			Wagner and Barefield, 1976
				as Ni complex	chiral		Wagner and Barefield, 1976
H	H	CH_3	CH_3	5,14-$(CH_3)_2$;7,7,12,12-$(CH_3)_4$		85	Wagner and Barefield, 1976

TABLE 10.13. (*Continued*)

R_1	R_2	R_3	R_4	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H	H	C_2H_5	C_2H_5	as Ni complex	70	Barefield et al., 1976b
H	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	as Ni complex	50	Barefield et al., 1976b
				as Ni complex		Wagner and Barefield, 1976
				as Ni complex chiral		Wagner and Barefield, 1976
H	H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	5,12-$(CH_3)_2$;5,5,14,14-$(CH_3)_4$	50	Wagner and Barefield, 1976
CH_3	CH_3	$NCCH_2$-	$NCCH_2$-			Schibler and Kaden, 1981
CH_3	CH_3	H_2NCH_2-	H_2NCH_2-	as complex		Kaden et al., 1989
CH_3	CH_3	$H_2NC(O)(CH_2)_2$-	$H_2NC(O)NH(CH_2)_2$-	as complex	46	Freeman et al., 1984
CH_3	CH_3	$C_6H_5CH_2$-	$C_6H_5CH_2$-			Wagner and Barefield, 1976
CH_3	CH_3	$C_6H_5C(O)NH(CH_2)_2$-	$C_6H_5C(O)NH(CH_2)_2$-			Kaden et al., 1989
H	CH_3	CH_3	H			Bradshaw et al., 1990a
					20	Buxtorf and Kaden, 1974
H	CH_3	CH_3	H	2,10-$(O)_2$		Bradshaw et al., 1990a
H	CH_3	CH_3	H	12,14-$(O)_2$	30	Bachmann et al., 1981

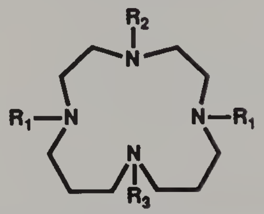
H	CH_3	CH_3	H	12,14-$(O)_2$;13-CH_3		29	Bachmann et al., 1981
H	CH_3	CH_3	H	12,14-$(O)_2$;13,13-$(CH_3)_2$		15	Bachmann et al., 1981
H	C_2H_5	C_2H_5	H				Bradshaw et al., 1990a
H	C_2H_5	C_2H_5	H				Bradshaw et al., 1990a
H	Ts	Ts	H			79	Helps et al., 1988, 1989b
H	Ts	Ts	H	2,10-$(O)_2$		75	Stetter and Mayer, 1961
H	Ts	Ts	H	12,14-$(O)_2$		79	Helps et al., 1989b
H	$C_{16}H_{33}$	$C_{16}H_{33}$	H			70	Tabushi, 1978
						70	Tabushi and Fujiyoshi, 1977
H	$C_{16}H_{33}$	$C_{16}H_{33}$	H	12,14-$(O)_2$		23	Tabushi, 1978
						23	Tabushi and Fujiyoshi, 1977
CH_3	C_2H_5	C_2H_5	CH_3				Bradshaw et al., 1990a
CH_3	C_2H_5	C_2H_5	CH_3	3,9-$(O)_2$			Bradshaw et al., 1990a
CH_3	Ts	Ts	CH_3			20	Buxtorf and Kaden, 1974
CH_3	Ts	Ts	CH_3	2,10-$(O)_2$			Buxtorf and Kaden, 1974
H	CH_3	H	CH_3	as Ni complex	chiral		Wagner and Barefield, 1976
H	CH_3	H	CH_3	7,14-$(CH_3)_2$; 5,5,12,12-$(CH_3)_4$	as complex		Wagner et al., 1974
CH_3	H	CH_3	H	7,14-$(CH_3)_2$; 5,5,12,12-$(CH_3)_4$	as complex		Wagner et al., 1974

TABLE 10.13. (*Continued*)

R_1	R_2	R_3	R_4	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
HO_2CCH_2-	H	HO_2CCH_2-	H		70,60	Helps et al., 1988, 1989b
H	$H_2NC(O)(CH_2)_2$-	H	$H_2NC(O)(CH_2)_2$-	as complex	15	Freeman et al., 1984
H	Ts	H	Ts		30	Helps et al., 1988, 1989b
$C_2H_5O_2CCH_2$-	Ts	$C_2H_5O_2CCH_2$-	Ts		75,91	Helps et al., 1988, 1989b
$NH_2(CH_2)_3$-	CH_3	H	H		41	Franz et al., 1987
CH_3	$C_6H_5CH_2$-	H	H	as complex	83	Barefield et al., 1986b
$HS(CH_2)_3C(NH)$-	CH_3	H	H			Franz et al., 1987
CH_3	CH_3	C_2H_5	H			Bradshaw et al., 1990a
$H_2NC(O)(CH_2)_2$-	H	$NC(CH_2)_2$-	$NC(CH_2)_2$-	as Ni complex	25	Freeman et al., 1984
H	2-pyridyl-$(CH_2)_2$-	CH_3	CH_3	as salt	70	Tschudin et al., 1989b

$H_2N(CH_2)_2$-	$C_6H_5C(O)NH$- $(CH_2)_2$-	CH_3	CH_3			Kaden et al., 1989
				as complex		Kaden et al., 1989
H	CH_3	CH_3	n-C_3H_7			Bradshaw et al., 1990a
H	CH_3	CH_3	n-C_3H_7	2,10-$(O)_2$		Bradshaw et al., 1990a
H	C_2H_5	C_2H_5	CH_3			Bradshaw et al., 1990a
H	C_2H_5	C_2H_5	CH_3	2,10-$(O)_2$		Bradshaw et al., 1990a
H	C_2H_5	C_2H_5	n-C_3H_7			Bradshaw et al., 1990a
H	$HO(CH_2)_2$-	$HO(CH_2)_2$-	CH_3			Krakowiak et al., 1990b
H	$HO(CH_2)_2$-	$HO(CH_2)_2$-	CH_3	2,10-$(O)_2$		Krakowiak et al., 1990b
H	Ts	Ts	CH_3	2,10-$(O)_2$	60	Buxtorf and Kaden, 1974
H	$(C_2H_5)_2N(CH_2)_3$-	$(C_2H_5)_2N(CH_2)_3$-	CH_3			Bradshaw et al.,1990a,1990b
H	$(C_2H_5)_2N(CH_2)_3$-	$(C_2H_5)_2N(CH_2)_3$-	CH_3	2,10-$(O)_2$		Bradshaw et al.,1990a,1990b
$NC(CH_2)_2$-	$H_2NC(O)(CH_2)_2$-	H	$H_2NC(O)(CH_2)_2$-	as Ni complex	51	Freeman et al., 1984

TABLE 10.14. PERAZA-14-CROWN-4 MACROCYCLES (ISOCYCLAM)



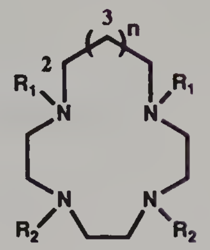
R_1	R_2	R_3	Yield (%)	References
H	H	H		Hediger and Kaden, 1983
			72	Leugger et al., 1978
			60	Sabatini and Fabbrizzi, 1979
$H_2N(CH_2)_2$-	$H_2N(CH_2)_2$-	$H_2N(CH_2)_2$-		Murase et al., 1990
Ts	Ts	Ts	58,80	Atkins et al., 1978
			68	Chavez and Sherry, 1989
			32	Leugger et al., 1978
			58	Richman and Atkins, 1974
			20	Sabatini and Fabbrizzi, 1979
$TsNH(CH_2)_2$-	$TsNH(CH_2)_2$-	$TsNH(CH_2)_2$-		Murase et al., 1990
H	H	CH_3	55	Ciampolini et al., 1986
			23	Alcock et al., 1984c

H	H	$H_2NC(O)CH_2$-	57,68	Hediger and Kaden, 1978, 1983
				Kaden, 1980
H	H	$H_2N(CH_2)_2$-		Schiegg and Kaden, 1990
H	H	$H_2NC(O)(CH_2)_2$-	79,66	Hediger and Kaden, 1978, 1983
H	H	$H_2N(CH_2)_3$-		Schiegg and Kaden, 1990
H	H	$(CH_3)_2N(CH_2)_2$-	26	Alcock et al., 1984b, 1984c
				Schiegg and Kaden, 1990
H	H	$C_2H_5OC(O)(CH_2)_2$-		Hediger and Kaden, 1978
Ts	Ts	H	85,95	Hediger and Kaden, 1978, 1983
				Kaden, 1980
Ts	Ts	CH_3		Alcock et al., 1984c
			45	Ciampolini et al., 1986
Ts	Ts	$NCCH_2$-		Schiegg and Kaden, 1990
Ts	Ts	$H_2NC(O)CH_2$-	88	Hediger and Kaden, 1978, 1983
				Kaden, 1980
Ts	Ts	$NC(CH_2)_2$-	86	Hediger and Kaden, 1978, 1983
				Schiegg and Kaden, 1990
Ts	Ts	$C_6H_5CH_2$-	45,50	Hediger and Kaden, 1978, 1983
				Kaden, 1980

TABLE 10.14. *(Continued)*

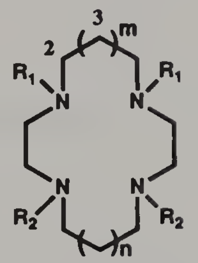
R_1	R_2	R_3	Yield (%)	References
H	CH_3	H	50	Ciampolini et al., 1986
H	$H_2NC(O)CH_2$-	H	27,37	Hediger and Kaden, 1978, 1983
Ts	H	Ts	91,96	Hediger and Kaden, 1978, 1983
Ts	CH_3	Ts	37	Ciampolini et al., 1986
Ts	$H_2NC(O)CH_2$-	Ts	62	Hediger and Kaden, 1978, 1983
Ts	$NC(CH_2)_2$-	Ts	80,28	Hediger and Kaden, 1978, 1983
Ts	$TsNH(CH_2)_2$-	Ts	50,29	Hediger and Kaden, 1978, 1983
Ts	$(C_6H_5)_3C$-	Ts	45,40	Hediger and Kaden, 1978, 1983
Ts	CH_3SO_2-	$(CH_3)_2N(CH_2)_2$-		Alcock et al., 1984b

TABLE 10.15. SYMMETRIC PERAZA-14, 15 AND 16-CROWN-4 MACROCYCLES



R_1	R_2	n	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H	H	2			Machida et al., 1983
					Micheloni et al., 1982
H	H	2	2,5,8,13-$(O)_4$	10,15	Lukyanenko et al., 1979, 1981
H	H	3			Bianchi et al., 1984
					Machida et al., 1983
H	H	4			Machida et al., 1983
H	H	4	2,7,10,15-$(O)_4$	10	Lukyanenko et al., 1981
Ts	Ts	2			Micheloni et al., 1982
Ts	Ts	3			Bianchi et al., 1984
H	HO_2CCH_2-	2	7,14-$(O)_2$	22	Qin, 1984
H	H	2	2,3-(O-allyl)$_2$	3	Lukyanenko et al., 1979

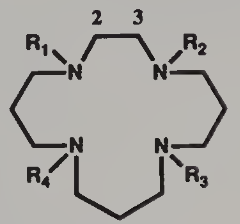
TABLE 10.16. SYMMETRIC AND UNSYMMETRIC PERAZA-15- TO 28-CROWN-4 MACROCYCLES



R_1	R_2	m	n	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H	H	1	2			Bartolini et al., 1982
						Machida et al., 1983
H	H	1	3			Machida et al., 1983
					40	Bembi et al., 1984
H	H	1	3	$2,4\text{-}(O)_2$		Kimura et al., 1984a
H	H	1	4		40	Bembi et al., 1984
H	H	2	2	$2,5,8,15\text{-}(O)_4$	16,20	Lukyanenko et al., 1979, 1981
					84	Nagao et al., 1980

H	H	2	4	2,5,8,17-$(O)_4$	15	Lukyanenko et al., 1979, 1981
H	H	1	4			Yamamoto and Maruoka, 1981a
H	H	1	10			Yamamoto and Maruoka, 1981a
H	H	4	1		75	Stetter and Mayer, 1961
H	H	4	2	2,7,10,17-$(O)_4$	15	Lukyanenko et al., 1981
H	H	4	4	2,7,10,19-$(O)_4$	12	Lukyanenko et al., 1981
H	H	10	1		65	Stetter and Mayer, 1961
H	H	6	6	11,12,23,24-$(O)_4$	60	Vögtle and Dix, 1977
C_2H_5	C_2H_5	3	3	2,6,11,15-$(O)_4$	24	Schwartz et al., 1985
$C_6H_5CH_2$-	$C_6H_5CH_2$-	3	3	2,6,11,15-$(O)_4$	31	Schwartz et al., 1985
$C_6H_5CH_2$-	$C_6H_5CH_2$-	5	5	2,8,13,19-$(O)_4$	12	Schwartz et al., 1985
$C_6H_5CH_2$-	$C_6H_5CH_2$-	6	6	2,9,14,21-$(O)_4$	22	Leyque et al., 1988
$C_6H_5CH_2$-	$C_6H_5CH_2$-	7	7	2,10,15,23-$(O)_4$	40	Schwartz et al., 1985
H	Ts	4	1	9,17-$(O)_2$	70	Stetter and Mayer, 1961
H	Ts	10	1	15,23-$(O)_2$	60	Stetter and Mayer, 1961

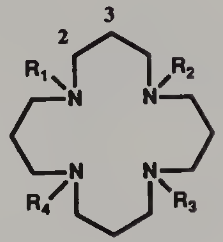
TABLE 10.17. PERAZA-15-CROWN-4 MACROCYCLES



All R = same or R_1	R_2	R_3	R_4	Other Substituents		Yield (%)	References
H						48	Barefield and Freeman, 1980
						45	Barefield et al., 1976b
							Kimura et al., 1987a
						58	Leugger et al., 1978
						63,60,70	Lukyanenko et al., 1988a, 1990b
							Martin et al., 1977
H				9-(O)			Kimura et al., 1987a
H				$10-CH_3;10-NO_2$	as complex	74	Lawrance and O'Leary, 1987
H				$10-CH_3;10-NH_2$			Lawrance et al., 1988
H				$10,10-(C_2H_5O_2C)_2$	as complex	2	Lawrance and O'Leary, 1987

H			11-(2-OH)C_6H_4		Kimura et al., 1987a
H			9-(O):11-(2-HOC_6H_4)		Kimura et al., 1987a
H			9,11-$(O)_2$;10-$(CH_2)_2$- 2-pyridyl		Kimura et al., 1984b
H			9,11-$(O)_2$;10-$(CH_2)_2C_6H_5$		Kimura et al., 1984b
CH_3					Che et al., 1986
HO_2CCH_2-					Delgado and da Silva, 1988
$H_2N(CH_2)_2$-					Murase et al., 1990
2-picolyl					Tsukube et al., 1989
2,3-$(HO)_2C_6H_3C(O)$-					Weitl and Raymond, 1980
2,3-$(HO)_2$-4 or 5-$KO_3SC_6H_2C(O)$-					Weitl and Raymond, 1980
Ts				63	Leugger et al., 1978
				85	Lukyanenko et al., 1988a,1988b,1990a
					Martin et al., 1977
$TsNH(CH_2)_2$-					Murase et al., 1990
H	H	H	3- or 4- CH_2=$CHC_6H_4CH_2$-		Handel and Chaumeli, 1988
H	H	3- or 4- CH_2=$CHC_6H_4CH_2$-	H		Handel and Chaumeli, 1988

TABLE 10.18. PERAZA-16-CROWN-4 MACROCYCLES



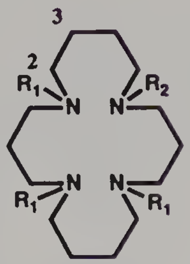
All R = same or R_1	R_2	R_3	R_4	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H					75	Leugger et al., 1978
					60	Lukyanenko et al., 1988b
						Martin et al., 1977
					55	Smith and Raymond, 1980
					98	Smith et al., 1978
H				2,10-$(CH_3)_2$		Bembi et al., 1988
H				12-CH_3;2,2,4,4,10,10-$(CH_3)_6$		Barefield and Busch, 1971
H				3,3,7,7,11,11,15,15-$(CH_3)_8$	75	Vellaccio et al., 1977
H				3,3,7,7,11,11,15,15-$(CH_3)_8$; 2,4,10,12-$(O)_4$	50-55	Vellaccio et al., 1977

H	2,4,10,12-$(O)_4$;7,7,15,15-$(OH)_4$		Vellaccio et al., 1977
H	7,7,15,15-$(OH)_4$	25	Vellaccio et al., 1977
H	3-$(CH_2)_4CONH_2$	67	Benabdallah and Guglielmetti,1988
H	3-n-$C_{12}H_{25}$		Muller and Handel, 1982
CH_3		92	Alcock et al., 1984a
$H_2N(CH_2)_2$-			Murase et al., 1990
2,3-$(HO)_2$-4 or 5-$NaO_3SC_6H_2C(O)$-			Weitl and Raymond, 1980
2,3-$(HO)_2C_6H_3C(O)$-		100	Weitl et al., 1978
$C_6H_5C(O)$-		100	Weitl et al., 1978
			Weitl and Raymond, 1980
4-$CH_3C_6H_4$-			Juaristi and Madrigal, 1989
Ts			Smith and Raymond, 1980
		90	Atkins et al., 1978
		69	Leugger et al., 1978
		85	Lukyanenko et al., 1988b
			Martin et al., 1977
		60	Smith et al., 1978
Ts	3-$(CH_2)_4OH$		Benabdallah and Guglielmetti,1988
	3-$(CH_2)_4CN$	70	Benabdallah and Guglielmetti,1988

TABLE 10.18. *(Continued)*

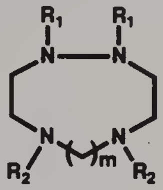
All R = same or R_1	R_2	R_3	R_4	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
				3-$(CH_2)_4CONH_2$	67	Benabdallah and Guglielmetti,1988
				3-$(CH_2)_4$O-pyranyl-2	92	Benabdallah and Guglielmetti,1988
				3-$(CH_2)_4$OTs	80	Benabdallah and Guglielmetti,1988
				3-n-$C_{12}H_{25}$		Muller and Handel, 1982
2-3-OCH_2O(ring)$C_6H_3C(O)$-					63	Weitl et al., 1978
TsNH$(CH_2)_2$-						Murase et al., 1990
H	H	H	$(CH_3)_2N(CH_2)_2$-		18	Alcock et al., 1985
H	H	H	3- or 4- $CH_2=CHC_6H_4CH_2$-			Handel and Chaumeli, 1988
H	H	H	$C_{12}H_{25}$			Handel and Chaumeli, 1988
CH_3	CH_3	CH_3	$(CH_3)_2N(CH_2)_2$-		89	Alcock et al., 1985
Ts	CH_3O_2S-	Ts	$(CH_3)_2N(CH_2)_2$-			Alcock et al., 1985

TABLE 10.19. PERAZA-18-CROWN-4 MACROCYCLES

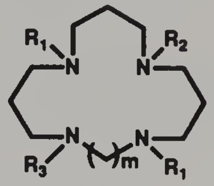


R_1	R_2	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H	H	salt		Kimura et al., 1982a
H	H	2,5,10,13-$(O)_4$	82	Nagao et al., 1980
H	H	5-CH_2OH		Marecek and Burrows, 1986
H	H	8-n-$C_{12}H_{25}$		Muller and Handel, 1982
C_2H_5	C_2H_5	2,5,11,14-$(O)_4$	21	Schwartz et al., 1985
Ts	Ts		99	Iwata and Kuzuhara, 1989a
				Kimura et al., 1982a
Ts	Ts	5-CH_2OH	55	Marecek and Burrows, 1986
Ts	Ts	8-n-$C_{12}H_{25}$		Muller and Handel, 1982
H	$HO(CH_2)_6$-			Handel and Chaumeli, 1988
H	$C_{16}H_{33}$			Handel and Chaumeli, 1988

TABLE 10.20. MISCELLANEOUS PERAZA-CROWN-4 MACROCYCLES



10.20 A



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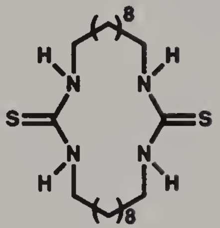

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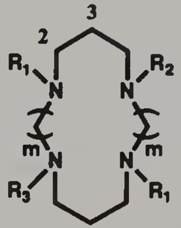

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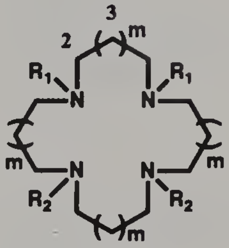
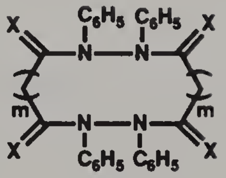
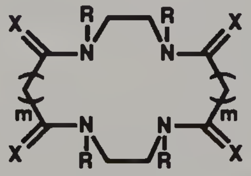


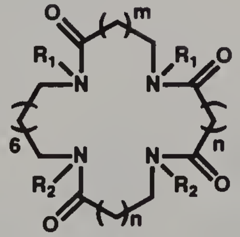
10.20 E



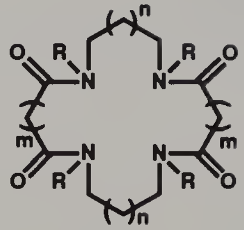
10.20 F



10.20 G



10.20 H



10.20 I

Structure	X	All R same or R_1	R_2	R_3	m	n	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
10.20 A		$C_6H_5C(O)$-	$C_6H_5SO_2$-						Goss and Grudzinski, 1988
		$C_6H_5C(O)$-	Ts						Goss and Grudzinski, 1988
		$CH_3C(O)$-	Ts						Goss and Grudzinski, 1988
10.20 B		H	H	CH_3	1		10,12,14-$(O)_3$; 13,13-$(C_2H_5)_2$	34	Jenny and Hesse, 1981
		H	$CH_3C(O)$-	CH_3	1		10,12,14-$(O)_3$; 13,13-$(C_2H_5)_2$	82	Jenny and Hesse, 1981
		H			12		10-(O)	84	Kramer et al., 1978a
		$CH_3C(O)$-	$CH_3C(O)$-	H	12		21-(O)		Kramer et al., 1978a
10.20 C								45	Bogatskii et al., 1980
10.20 D		H			5		8,18-$(O)_2$ as complex		Comba et al., 1990
		H			5		3,13-$(CH_3)_2$;3,13-$(NO_2)_2$; 8,18-$(SH)_2$		Lawrance et al., 1990
		H			6		2,2,13,13-$(CH_3)_4$;4,15-$(CH_3)_2$ (two isomers)		Hay and Pujari, 1985

TABLE 10.20. (*Continued*)

Structure	X	All R same or R_1	R_2	R_3	m	n	Other Substituents (Numbers indicate position on macrocycles)	Yield (%)	References
		H			6		2,13-$(CH_3)_2$;4,4,15,15-$(CH_3)_4$		Yamashita et al., 1983
		Ts	H	Ts	6		6,17-$(O)_2$		Guggisberg et al., 1978
10.20 E		H			2				Suet and Handel, 1984
		H			2		3,4,8,9,13,14,18,-19-$(OC_2H_5)_8$	80	Naemura et al., 1989
		H			2		3,4,8,9,13,14,18,19-$(OC_2H_5)_8$;7,10,17,20-$(O)_4$	12	Naemura et al., 1989
		Ts			2			90	Suet and Handel, 1984
		Ts			2		3,4,8,9,13,14,18,-19-$(OC_2H_5)_8$	12	Naemura et al., 1989
		H			4			68	Tomohiro et al., 1990a
		$HSC(CH_3)_2CH_2C(O)$-			4				Tomohiro et al., 1990b
		Ts			4			70	Tomohiro et al., 1988, 1990a
		$CH_3C(O)SC(CH_3)_2CH_2C(O)$-			4				Tomohiro et al., 1990b
		H			5			74	Tomohiro et al., 1990a

$HSC(CH_3)_2CH_2C(O)$-			5			Tomohiro et al., 1990b
Ts			5		66	Tomohiro et al., 1988, 1990a
$CH_3C(O)SC(CH_3)_2CH_2C(O)$-			5			Tomohiro et al., 1990b
H			6			Okuno et al., 1987, 1990
					91	Tomohiro et al., 1990a
H			6	9,18,27,35-$(O)_4$		Okuno et al., 1983
						Uoto et al., 1990
$HSC(CH_3)_2CH_2C(O)$-			6			Okuno et al., 1990
						Tomohiro et al., 1990b
4-$HSC_6H_4C(O)$-			6			Okuno et al., 1987, 1990
Ts			6			Okuno et al., 1987, 1990
					62,77	Tomohiro et al., 1988, 1990a
					9	Uoto et al., 1990
$CH_3C(O)SC(CH_3)_2CH_2C(O)$-			6			Okuno et al., 1990
						Tomohiro et al., 1990b
4-$HSCH_2C_6H_4C(O)$-			6			Okuno et al., 1990
4-$CH_3C(O)SC_6H_4C(O)$-						Okuno et al., 1990
4-$CH_3C(O)SCH_2C_6H_4C(O)$-			6			Okuno et al., 1990
$C_6H_5CH_2$-	H	H	6			Uoto et al., 1990

TABLE 10.20. *(Continued)*

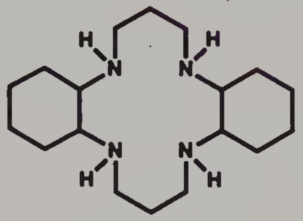
Structure	X	All R same or R_1	R_2	R_3	m	n	Other Substituents (Numbers indicate position on macrocycles)	Yield (%)	References
		H			7			75	Tomohiro et al., 1990a
		$HSC(CH_3)_2CH_2C(O)$-			7				Tomohiro et al., 1990b
		Ts			7			63	Tomohiro et al., 1988, 1990b
		$CH_3C(O)SC(CH_3)_2CH_2C(O)$-			7				Tomohiro et al., 1990b
		H			9			80	Tomohiro et al., 1990a
		$HSC(CH_3)_2CH_2C(O)$-			9				Tomohiro et al., 1990b
		Ts			9			59	Tomohiro et al., 1988, 1990a
		$CH_3C(O)SC(CH_3)_2CH_2C(O)$-			9				Tomohiro et al., 1990b
10.20 F	H_2				5			47	Witting et al., 1966
	H_2				6			32	Witting et al., 1966
	H_2				7			39	Witting et al., 1966
	H_2				10			51	Witting et al., 1966
	H_2				14			5	Witting et al., 1966
	O				4			3,4	Witting et al., 1966

	O		5		11-15	Witting et al., 1966
	O		6		12	Witting et al., 1966
	O		7		11	Witting et al., 1966
	O		8		27	Witting et al., 1966
	O		10		16	Witting et al., 1966
	O		14		16	Witting et al., 1966
10.20 G	H_2	H	4		80	Stetter and Roos, 1954
	H_2	Ts	4		39	Stetter and Roos, 1954
	O	C_2H_5-	3			Schwartz and Shanzer, 1981
	O	$C_6H_5CH_2$-	3		31	Schwartz and Shanzer, 1981
	O	$C_6H_5CH_2$-	5		25	Schwartz and Shanzer, 1981
	O	$C_6H_5CH_2$-	7			Schwartz and Shanzer, 1981
10.20 H		H	5	5	59	Okuno et al., 1984
		H	5	6	60	Okuno et al., 1984
		H	6	5	60	Okuno et al., 1984
		H	6	6	30,68	Okuno et al., 1984

TABLE 10.20. (*Continued*)

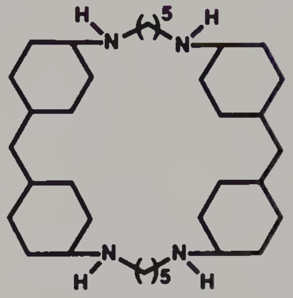
Structure	X	All R same or R_1	R_2	R_3	m	n	Other Substituents (Numbers indicate position on macrocycles)	Yield (%)	References
		H	$C_6H_5CH_2$-		6	6			Uoto et al., 1990
		H			7	5		62	Okuno et al., 1984
		H			7	6		64	Okuno et al., 1984
10.20	I	H			1	4		89	Nagao et al., 1980
		H			2	4		80	Nagao et al., 1980
		H			4	4		37	Nagao et al., 1980
		H			4	8		12	Nagao et al., 1980
		H			4	12		8	Nagao et al., 1980
		C_2H_5			1	4		15	Schwartz et al., 1985

TABLE 10.21. PERAZADI- AND TETRACYCLOHEXANOCROWN-4 MACROCYCLES



10.21 A

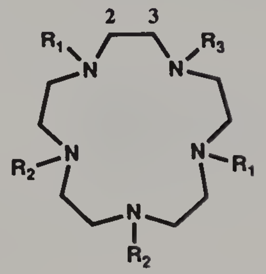
10.21 B



10.21 C

Structure	n	Method	Yield (%)	References
10.21 A				Settimj et al., 1966
				Sakata et al., 1986
10.21 B	2			Settimj et al., 1966
	3			Settimj et al., 1966
10.21 C				Soga et al., 1980
				Odashima, 1988

TABLE 10.22. PERAZA-15-CROWN-5 MACROCYCLES



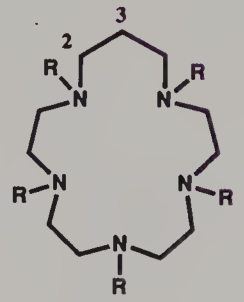
All R same or R_1	R_2	R_3	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H					Akkaya et al., 1990 Bencini et al., 1981 Buoen et al., 1984 Hay et al., 1982 Kodama and Kimura, 1978

			70	Lukyanenko et al., 1990a
			49	Osvath et al., 1987
$HO(CH_2)_2$-			33	Buoen et al., 1984
Ts			83	Atkins et al., 1978
			58	Chavez and Sherry, 1989
				Hay et al., 1982
			85	Lukyanenko et al., 1990a
			87	Osvath et al., 1987
			83	Richman and Atkins, 1974
H	H	CH_3SO_2-	79	Pilichowski et al., 1985
H	H	4-$NO_2C_6H_4(CH_2)_2CH(CO_2CH_3)$-	61	Kruper, 1989
H	H	9-anthracenyl-CH_2-		Akkaya et al., 1990
H	H	benzo-15-crown-5-CH_2-		Kimura, 1988
CH_3	CH_3	H		Pilichowski et al., 1985
CH_3	CH_3	CH_3SO_2-		Pilichowski et al., 1985

TABLE 10.22. *(Continued)*

All R same or R_1	R_2	R_3	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
CH_3	CH_3	$C_{11}H_{23}C(O)$-		67	Pilichowski et al., 1985
CH_3	CH_3	$C_{12}H_{25}$-		94	Pilichowski et al., 1985
C_2H_5	C_2H_5	$C_2H_5NH(CH_2)_2$-		23	Krakowiak et al., 1989
C_2H_5	C_2H_5	$C_2H_5NH(CH_2)_2$-	9,14-$(O)_2$		Krakowiak et al., 1989
Ts	Ts	CH_3SO_2-		88	Pilichowski et al., 1985
C_2H_5	CH_3	C_2H_5			Krakowiak et al., 1990b
C_2H_5	CH_3	C_2H_5	9,14-$(O)_2$		Krakowiak et al., 1990b
C_2H_5	CH_3	$C_2H_5NH(CH_2)_2$-			Krakowiak et al., 1990a
C_2H_5	CH_3	$HO(CH_2)_2O(CH_2)_2$-		60	Bradshaw et al., 1989a
C_2H_5	CH_3	$HO(CH_2)_2O(CH_2)_2$-	9,14-$(O)_2$		Bradshaw et al., 1989a

TABLE 10.23. PERAZA-16-CROWN-5 MACROCYCLES



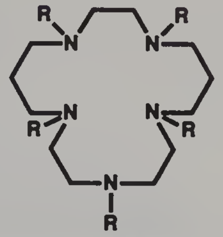
R	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H			Bencini et al., 1981
			Kodama and Kimura, 1978
		59	Osvath et al., 1987
H	4-(O)	42	Kimura et al., 1984a
H	2,4-$(O)_2$		Chen and Martell, 1990
		10	Drain et al., 1990
			Kimura et al., 1982b, 1984a
			Showa Denko, 1982

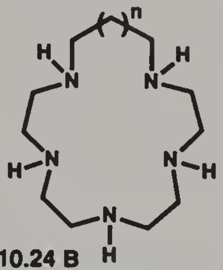
TABLE 10.23. (*Continued*)

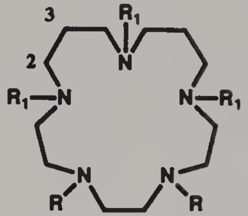
R	Other Substituents (Numbers indicate position on macrocycles)		Yield (%)	References
H	2,4-$(O)_2$;3-OH			Chen and Martell, 1990
H	2,4-$(O)_2$;3-CH_3			Kimura et al., 1984a
H	3-CH_3;3-NH_2			Elliot and Lawrance, 1990
H	2,4-$(O)_2$;3-C_2H_5			Chen and Martell, 1990 Kimura et al., 1984a
H	2,4-$(O)_2$;3-C_2H_5;3-OH			Chen and Martell, 1990
H	2,4-$(O)_2$;3,3-$(CH_3)_2$	as salt	7,16	Kimura et al., 1989c
H	2,4-$(O)_2$;3-$(CH_2)_2OH$			Shirai et al., 1987a
H	2-(4-imidazolyl)			Kimura et al., 1987c

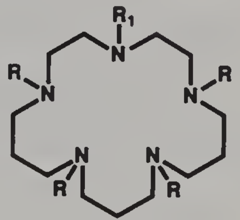
H	$2,4\text{-}(O)_2;3\text{-}CH_2C_6H_5$			Chen and Martell, 1990
				Kimura et al., 1982b, 1984a
H	$2,4\text{-}(O)_2;3\text{-}CH_2C_6H_5;3\text{-}OH$			Chen and Martell, 1990
H	$2,4\text{-}(O)_2;3\text{-}(CH_2)_6OH$			Shirai et al., 1987a
H	$2,4\text{-}(O)_2;3\text{-}(CH_2)_2$-pyridyl-2			Kimura et al., 1984a
H	$3\text{-}CH_2(CH_2OCH_2)_2CH_2OCH_3$			Kuramoto and Kimura, 1987
H	$3\text{-}CH_2(CH_2OCH_2)_2CH_2OCH_3;2,4\text{-}(O)_2$			Kuramoto and Kimura, 1987
H	$2,4\text{-}(O)_2;3\text{-}(CH_2)_2C_8F_{17}$			Shirai and Kato, 1987
H	$2,4\text{-}(O)_2;3\text{-}CH_2$-naphthyl			Kimura et al., 1984a
H	$2,4\text{-}(O)_2;3\text{-}C_{12}H_{25}$	as salt	25	Yamada et al., 1989
H	$2,4\text{-}(O)_2;3\text{-}C_{16}H_{33}$		30	Shirai et al., 1987b
H	$2,4\text{-}(O)_2;3\text{-}C_{18}H_{37}$	as salt	35	Yamada et al., 1989
Ts			51	Atkins et al., 1978
			93	Osvath et al., 1987

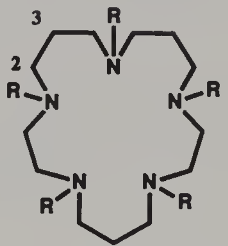
TABLE 10.24. PERAZA-17, 18, 19, 20, AND 21-CROWN-5 MACROCYCLES

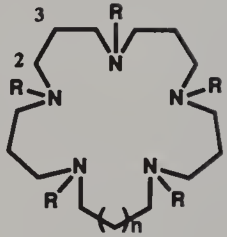

10.24 A


10.24 B


10.24 C


10.24 D


10.24 E


10.24 F

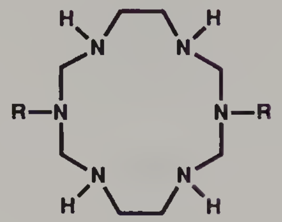
Structure	R	R_1	n	Yield (%)	References
10.24 A	H				Bencini et al., 1981
					Kodama and Kimura, 1978
				70	Lukyanenko et al., 1990a

					74	Osvath et al., 1987
	Ts				87	Lukyanenko et al., 1990a
					60	Osvath et al., 1987
10.24 B			2			Machida et al., 1983
			3			Machida et al., 1983
			4			Machida et al., 1983
10.24 C	H	H			83	Lukyanenko et al., 1990a
					47	Osvath et al., 1987
	Ts	Ts			90	Lukyanenko et al., 1990a
					82	Osvath et al., 1987
	CH_3	C_2H_5		11,16-$(O)_2$		Krakowiak et al., 1990b
10.24 D	H	H			49	Osvath et al., 1987
	Ts	Ts			75	Osvath et al., 1987
	CH_3	$C_2H_5NH(CH_2)_2$-				Krakowiak et al., 1990a

TABLE 10.24. (*Continued*)

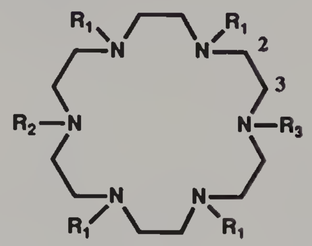
Structure	R	R_1	n	Yield (%)	References
10.24 E	H			68	Osvath et al., 1987
	Ts			87	Osvath et al., 1987
10.24 F	H		0	56	Osvath et al., 1987
	Ts		0	84	Osvath et al., 1987
	H		1	32	Osvath et al., 1987
	Ts		1	88	Osvath et al., 1987
	Ts		2	98	Iwata and Kuzuhara, 1989a

TABLE 10.25. PERAZA-14-CROWN-6 MACROCYCLES



R		Yield (%)	References
H	as complex		Rout. and Sahoo, 1984
		50	Suh and Kang, 1988
C_2H_5	as complex	40	Suh and Kang, 1988
C_3H_7	as salt	30	Jung et al., 1989
C_4H_9	as salt	25	Jung et al., 1989
i-C_4H_9	as salt	20	Jung et al., 1989
$HO(CH_2)_n$-			Suh et al., 1990
$H_2N(CH_2)_n$-			Suh et al., 1990
$NC(CH_2)_n$-			Suh et al., 1990
$CH_3(CH_2)_n$-			Suh et al., 1990
$C_6H_5CH_2$-	as salt	35	Jung et al., 1989
$C_4H_9CH(C_2H_5)CH_2$-	as salt	20	Jung et al., 1989

TABLE 10.26. PERAZA-18-CROWN-6 MACROCYCLES



All R same or R_1	R_2	R_3	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
H					Akkaya et al., 1990
					Atkins et al., 1978
					Buoen et al., 1984
					Kuchermeister and Dye, 1989
					Lehn et al., 1985
				75	Lukyanenko et al., 1990a
			as salt	87	Micheloni et al., 1985
				73	Stetter et al., 1981
			as salt		Tabushi et al., 1979b
H			2,6-$(O)_2$		Tabushi et al., 1979a

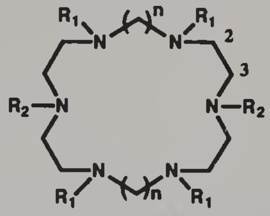
$H_2O_3PCH_2$-			Morris et al., 1990
HO_2CCH_2-			Kimura, 1985
		37	Stetter et al., 1981
$HO(CH_2)_2$-		16	Buoen et al., 1984
$C_6H_5CH_2$-		70	Tsukube, 1983, 1985
Ts			Atkins et al., 1978
		85	Lukyanenko et al., 1990a
		42	Micheloni et al., 1985
		60,75	Richman and Atkins, 1974
2,2'-bipyridyl-6-CH_2-		40	Lehn and Ziessel, 1987
$C_{12}H_{25}$	2,6-$(O)_2$		Tabushi et al., 1979a
$C_{11}H_{23}C(O)$-			Malthete et al., 1989
4-$C_6H_{13}OC_6H_4C(O)$-			Tatarsky et al., 1990
4-$C_8H_{17}OC_6H_4C(O)$-			Malthete et al., 1989
$C_{17}H_{35}$	2,6-$(O)_2$		Tabushi et al., 1979a
4-$C_{12}H_{25}OC_6H_4C(O)$-			Malthete et al., 1989
			Lehn et al., 1985
			Tatarsky et al., 1990
3,4-$(C_{10}H_{21}O)_2C_6H_3C(O)$-			Lattermann, 1990

TABLE 10.26. (*Continued*)

All R same or R_1	R_2	R_3	Other Substituents (Numbers indicate position on macrocycles)	Yield (%)	References
tetralauryl			2,6-$(O)_2$		Tabushi et al., 1979b
H	H	HC(O)-			Jiang et al., 1989
H	H	$HO(CH)_{12}$-			Tatarsky et al., 1989
H	H	benzo-15-crown-5-3-CH_2-			Kimura, 1988
					Kimura et al., 1986b
H	H	anthracenyl-9-CH_2-			Akkaya et al., 1990
$C_{12}H_{25}OC_6H_4C(O)$-	$C_{12}H_{25}OC_6H_4C(O)$-	$HO(CH_2)_{12}$-			Tatarsky et al., 1989
H	$C_6H_5CH_2$-	$C_6H_5CH_2$-		69	Takada et al., 1988
H	$C_6H_5CH_2$-	$C_6H_5CH_2$-	2,6,11,15-$(O)_4$		Krakowiak et al., 1990b

H	C_8H_{17}	C_8H_{17}		60	Takada et al., 1988
H	$C_{18}H_{37}$	$C_{18}H_{37}$	2,6-$(O)_2$		Tabushi et al., 1979b
CH_3	$CH_3C(O)NH(CH_2)_2$-	$CH_3C(O)NH(CH_2)_2$-	2,6,11,15-$(O)_4$		Krakowiak et al., 1990b
CH_3	$C_2H_5NH(CH_2)_2$-	$C_2H_5NH(CH_2)_2$-			Krakowiak et al., 1990b
Ts	H	H		85	Dietrich et al., 1989
				81	Takada et al., 1988
Ts	H	H	5,12-$(O)_2$	38	Dietrich et al., 1989
					Qian et al., 1990
				50	Takada et al., 1988
Ts	$C_6H_5C(O)$-	$C_6H_5C(O)$-		83	Takada et al., 1988
Ts	$C_6H_5CH_2$-	$C_6H_5CH_2$-		72	Takada et al., 1988
Ts	$C_7H_{15}C(O)$-	$C_7H_{15}C(O)$-		94	Takada et al., 1988
Ts	C_8H_{17}	C_8H_{17}		81	Takada et al., 1988
					Tabushi et al., 1979b

TABLE 10.27. MISCELLANEOUS PERAZA-CROWN-6 MACROCYCLES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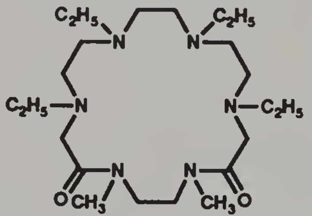
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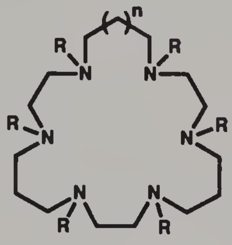
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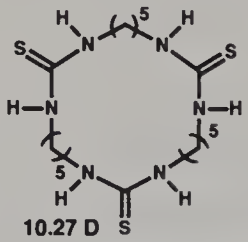
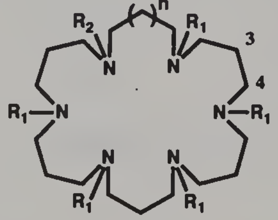

10.27 D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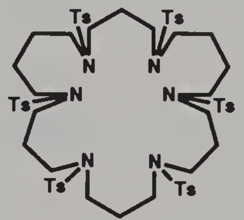
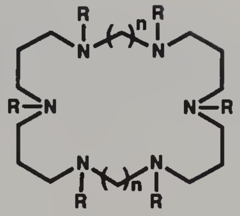
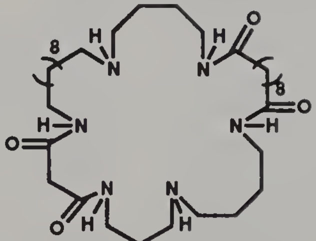

10.27 F


10.27 G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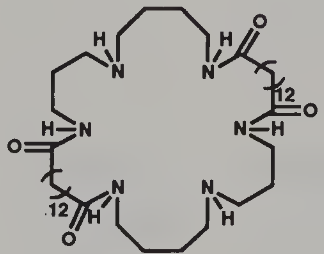
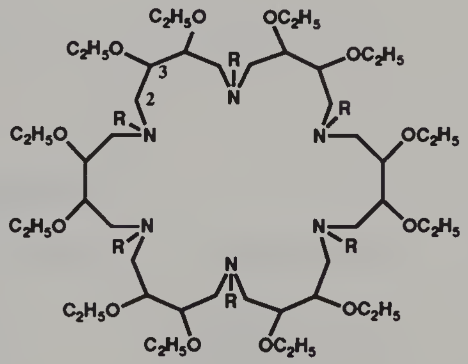

10.27 I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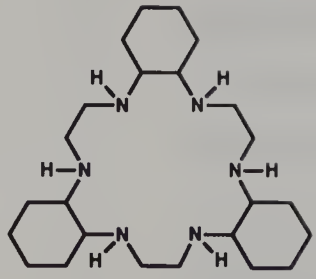

10.27 K

Structure	R_1	R_2	n	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
10.27 A	H	H	1	complex		Martin and Bulkowski, 1982
						Naik and Sahoo, 1982
	H	$H_2N(CH_2)_2$-	1	complex		Smith and Raymond, 1985
	H	H	3			Marqulis and Zompa, 1979
				complex		Searle and Geue, 1984
	Ts	Ts	3		40	Martin and Bulkowski, 1982
	H	H	4		70	Briellmann et al., 1987
						Hosseini and Lehn, 1987
						Hosseini et al., 1987
					61	Martin and Bulkowski, 1982
	Ts	Ts	4		11	Briellmann et al., 1987
						Hosseini and Lehn, 1987
					25	Martin and Bulkowski, 1982
	Ts	$C_6H_5C(O)$-	4		20	Martin et al., 1982
	H	H	5		54	Coughlin et al., 1980

TABLE 10.27. (*Continued*)

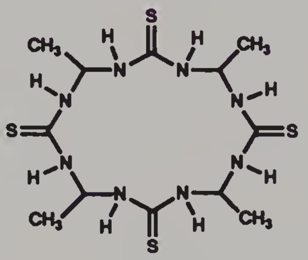
Structure	R_1	R_2	n	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
						Hosseini and Lehn, 1987
						Hosseini et al., 1987
					56	Martin and Bulkowski, 1982
	Ts	Ts	5		20	Coughlin et al., 1980
						Hosseini and Lehn, 1987
					20	Martin and Bulkowski, 1982
						Richman and Atkins, 1974
	H	H	6		83	Briellmann et al., 1987
	Ts	H	6		85	Martin et al., 1982
	Ts	$C_6H_5C(O)$-	6		17	Martin et al., 1982
	Ts	Ts	6		3	Briellmann et al., 1987
						Richman and Atkins, 1974
	H	H	9		90	Hosseini and Lehn, 1986,1987
	Ts	Ts	9		47	Hosseini and Lehn, 1986

10.27 B			2,15-$(O)_2$			Krakowiak et al., 1990b
10.27 C	H		0		78	Lukyanenko et al., 1990a
	Ts		0		73	Lukyanenko et al., 1990a
	H		1			Royer et al., 1982
10.27 D					40	Dietrich et al., 1978
10.27 E	H	H	1	as complex		Schaber et al., 1988
				as salt	92	Dietrich et al., 1983
	H	H	1	3,3,7,7,11,11,15,15,19,19,23,23-$(CH_3)_{12}$	75	Vellaccio et al., 1977
	H	H	1	3,3,7,7,11,11,15,15,19-19,23,23-$(CH_3)_{12}$;2,4-10,12,18,20-$(O)_6$	7	Vellaccio et al., 1977
	Ts	Ts	1	as complex		Schaber et al., 1988
	Ts	Ts	1		50	Dietrich et al., 1983
	Ts	Ts	2		61	Iwata and Kuzuhara, 1989a
	H	H	10	22-(O)	85	Kramer et al., 1979
	$CH_3C(O)$-	H	10	22-(O)		Kramer et al., 1979

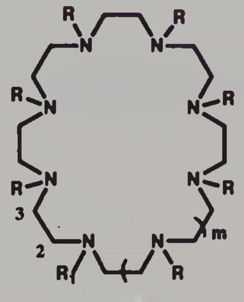
TABLE 10.27. *(Continued)*

Structure	R_1	R_2	n	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
10.27 F					56	Iwata and Kuzuhara, 1989a
10.27 G	H		7		92	Hosseini and Lehn, 1982, 1986
	Ts		7		25	Hosseini and Lehn, 1982, 1986
	H		10		93	Hosseini and Lehn, 1982, 1986
	Ts		10		25	Hosseini and Lehn, 1982, 1986
10.27 H						Nagao et al., 1980
10.27 I					5	Nagao et al., 1980
10.27 J	H				75	Naemura et al., 1989
	H			2,5,12,15,22,25-$(O)_6$	19	Naemura et al., 1989
	Ts					Naemura et al., 1989
10.27 K					30	Royer et al., 1982

TABLE 10.28. PERAZA-CROWN MACROCYCLES WITH 8, 9, 10, 11, AND 12 NITROGEN ATOMS



10.28 A



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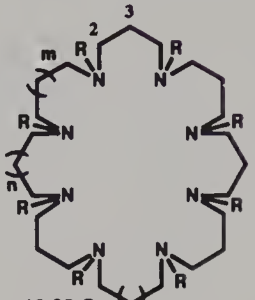

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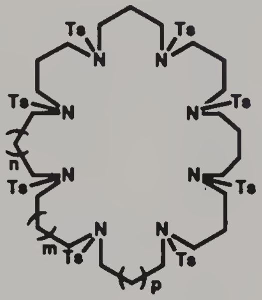

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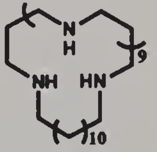
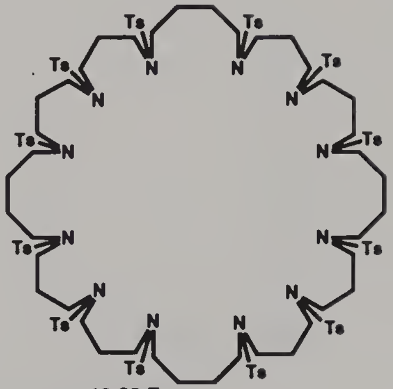


10.28 E

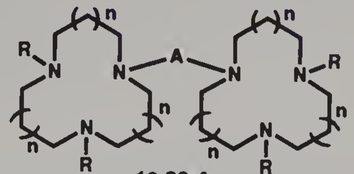


10.28 F

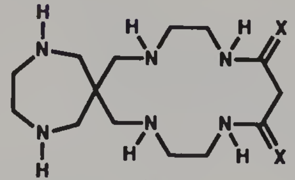
TABLE 10.28. (*Continued*)

Structure	R = R_1 or R	R_1	m	n	p	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
10.28 A								Yadava et al., 1981
10.28 B	Ts		0				45	Atkins et al., 1978
							45	Richman and Atkins, 1974
	H		1				63	Bianchi et al., 1985
								Hosseini et al., 1987
	H	HC(O)-	1					Jiang et al., 1989
	Ts		1				73	Atkins et al., 1978
							36	Bianchi et al., 1985
	H		2				86	Bencini et al., 1987a
	H		2			3,11,15,23-$(O)_4$	65	Kimura et al., 1990b
	Ts		2				16	Bencini et al., 1987a
	H		3				85	Bencini et al., 1987b
								Hosseini and Lehn, 1987
	Ts		3				12	Bencini et al., 1987b
								Hosseini and Lehn, 1987
	$4\text{-}C_{12}H_{25}OC_6H_4C(O)\text{-}$		3					Malthete et al., 1989

	H	4				82	Bencini et al., 1988
	Ts	4				19	Bencini et al., 1988
	H	5				76	Bencini et al., 1988
	Ts	5				19	Bencini et al., 1988
10.28 C	H	1	1	1	2,4,10,12,18,20,26,28-$(O)_8$; 3,3,7,7,11,11,15,15,19,19, 23,23,27,27,31,31-$(CH_3)_{16}$	3	Vellaccio et al., 1977
	Ts	1	1	2		55	Iwata and Kuzuhara, 1989a
						35	Dietrich et al., 1983
	Ts	1	2	2		64	Iwata and Kuzuhara, 1989a
	Ts	2	1	2		47	Iwata and Kuzuhara, 1989a
	H	1	1	2	as salt	80	Dietrich et al., 1983
10.28 D		1	1	1		75	Iwata and Kuzuhara, 1989a
		1	1	2		86,37	Iwata and Kuzuhara, 1989a
		1	2	1		53	Iwata and Kuzuhara, 1989a
		2	1	1		38-64	Iwata and Kuzuhara, 1989a
		2	2	1		48	Iwata and Kuzuhara, 1989a
10.28 E					42-(O)	38	Kramer et al., 1978b
10.28 F							Iwata and Kuzuhara, 1989b



10.29 A



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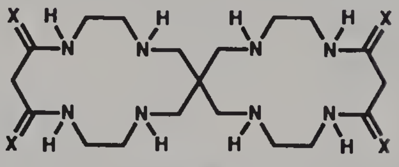
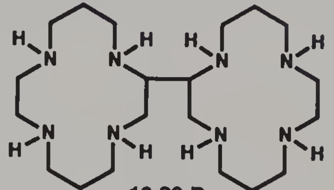


10.29 C



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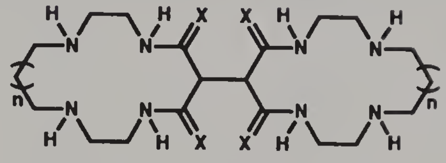

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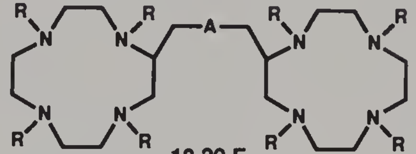
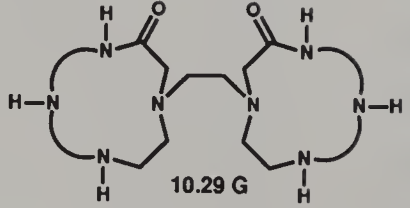
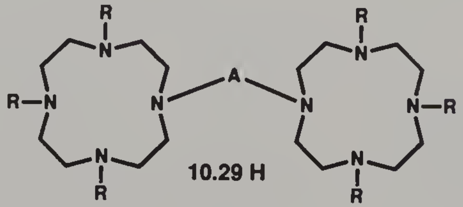


10.29 F



10.29 G



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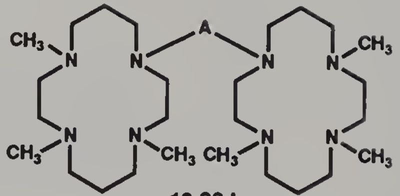

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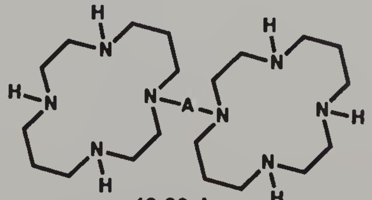

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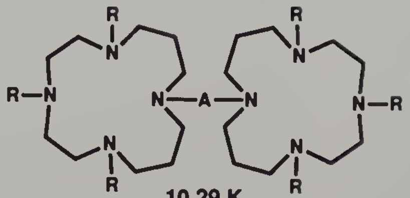

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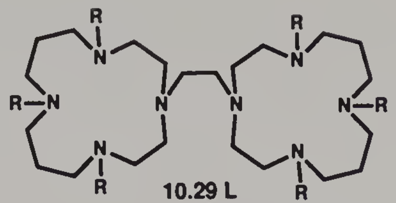

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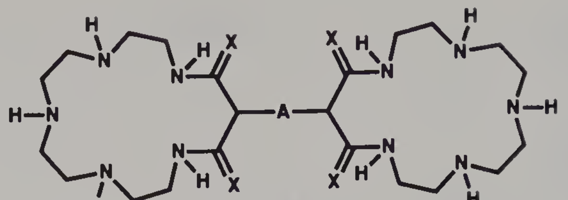

10.29 M

Structures	X	A	R	n	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
10.29 A		-$(CH_2)_2$-	H	0		80	Wieghardt et al., 1985
						83	Tanaka et al., 1977
		-$(CH_2)_2$-	$C_6H_5SO_2$-	0		1	Tanaka et al., 1977
		-$(CH_2)_2$-	Ts	0		81	Wieghardt et al., 1985
		-$(CH_2)_3$-	H	0		88	Weisman et al., 1987
							Wieghardt et al., 1985
		-$(CH_2)_3$-	Ts	0			Wieghardt et al., 1987
		-$(CH_2)_4$-	H	0			Sessler et al., 1990
						87	Weisman et al., 1987
		-$(CH_2)_4$-	Ts	0			Sessler et al., 1990
		-$(CH_2)_2O(CH_2)_2$-	H	0		58	Weisman et al., 1987

TABLE 10.29. *(Continued)*

Structures	X	A	R	n	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
		$-C(O)(CH_2)_2C(O)-$	Ts	0			Sessler et al., 1990
		$-CH_2$-1,5-(3-CH_3-6-HOC_6H_2)CH_2-	H	0		49	Diril et al., 1989
		$-(CH_2)_3-$	H	1		80	Weisman et al., 1987
		$-(CH_2)_4-$	H	1		71	Weisman et al., 1987
10.29 B	H_2						McAuley et al., 1989
	O						McAuley et al., 1989
10.29 C	H_2					8-10 overall	McAuley et al., 1987, 1989
	O						McAuley et al., 1987, 1989
10.29 D					as complex	3	Barefield et al., 1981

10.29 E	H_2			1	38	Fabbrizzi et al.,1986b,1987
	O			0	29	Buttafava et al., 1984
	O			1	30	Buttafava et al., 1982
					24	Fabbrizzi et al., 1984
10.29 F		$-OCH_2C\equiv C-C\equiv CCH_2O-$	HO_2CCH_2-			Deutsch et al., 1988
		$-OCH_2C\equiv C-C\equiv CCH_2O-$	$C_4H_9O_2CCH_2-$			Deutsch et al., 1988
		$-O(CH_2)_3C_3H_6O-$	HO_2CCH_2-			Deutsch et al., 1988
		$-O(CH_2)_3C_3H_6O-$	$C_4H_9O_2CCH_2-$			Deutsch et al., 1988
		$-O(CH_2)_3NHC(O)(CH_2)_2-$ $-C(O)NH(CH_2)_3O-$	HO_2CCH_2-			Deutsch et al., 1988
		$-O(CH_2)_3NHC(O)(CH_2)_2-$ $-C(O)NH(CH_2)_3O-$	$C_4H_9O_2CCH_2-$			Deutsch et al., 1988
		$-C_6H_4O(CH_2)_2OC_6H_4-$	HO_2CCH_2-			Deutsch et al., 1988
		$-C_6H_4O(CH_2)_2OC_6H_4-$	$C_4H_9O_2CCH_2-$			Deutsch et al., 1988
		$-C_6H_4OCH_2C\equiv C-C\equiv CCH_2OC_6H_4-$	HO_2CCH_2-			Deutsch et al., 1988
		$-C_6H_4OCH_2C\equiv C-C\equiv CCH_2OC_6H_4-$	$C_4H_9O_2CCH_2-$			Deutsch et al., 1988
		$-C_6H_4O(CH_2)_3(CH_2)_3OC_6H_4-$	HO_2CCH_2-			Deutsch et al., 1988
		$-C_6H_4O(CH_2)_3(CH_2)_3OC_6H_4-$	$C_4H_9O_2CCH_2-$			Deutsch et al., 1988

TABLE 10.29. *(Continued)*

Structures	X	A	R	n	Other Substituents (Numbers indicate position on macrocycle)	Yield (%)	References
10.29 G							Fabbrizzi et al., 1984
10.29 H		$-(CH_2)_2-$	H			43,7 overall	Ciampolini et al., 1984a
		$-(CH_2)_4C_6H_4(CH_2)_4-$	H				Chung et al., 1990
		$-(CH_2)_2-$	Ts				Ciampolini et al., 1984a
		$-C(O)C(O)-$	Ts				Ciampolini et al., 1984a
		$-(CH_2)_3-$	HO_2CCH_2-				Gries et al., 1988
10.29 I		$-(CH_2)_5-$					Barefield et al., 1986a
		$-C(O)(CH_2)_3C(O)-$					Barefield et al., 1986a
10.29 J		$-(CH_2)_2-$					Ciampolini et al., 1987
		$-(CH_2)_3-$					Ciampolini et al., 1987
		$-(CH_2)_4-$					Ciampolini et al., 1987
		$-CH_2-1,3-C_6H_4CH_2-$					Ciampolini et al., 1987

		$-CH_2-1,4-C_6H_4CH_2-$				Ciampolini et al., 1987
10.29 K		$-(CH_2)_2-$	H		74 as salt	Schneider et al., 1985
					36	Murase et al., 1986
		$-(CH_2)_2-$	Ts		30	Schneider et al., 1985
		$-C(O)(CH_2)_2C(O)-$	Ts		88	Schneider et al., 1985
		$-CH_2-1,4-C_6H_4CH_2-$	H	as salt	89	Schneider et al., 1985
		$-CH_2-1,4-C_6H_4CH_2-$	Ts		83	Schneider et al., 1985
10.29 L			H	as salt	55	Garcia-Espana et al., 1985
			Ts		24	Garcia-Espana et al., 1985
10.29 M	O	$-(CH_2)_2-$				Kodama et al., 1987
	H_2	$-(CH_2)_3-$			80	Kimura et al., 1990b
	O	$-(CH_2)_3-$			8	Kimura et al., 1990b
	H_2	$-CH_2(CH_2OCH_2)_2CH_2-$				Kuramoto and Kimura, 1987
				as salt	78	Kimura et al., 1990b
						Kodama et al., 1987
	O	$-CH_2(CH_2OCH_2)_2CH_2-$			4	Kimura et al., 1990b
						Kuramoto and Kimura, 1987

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CHAPTER XI

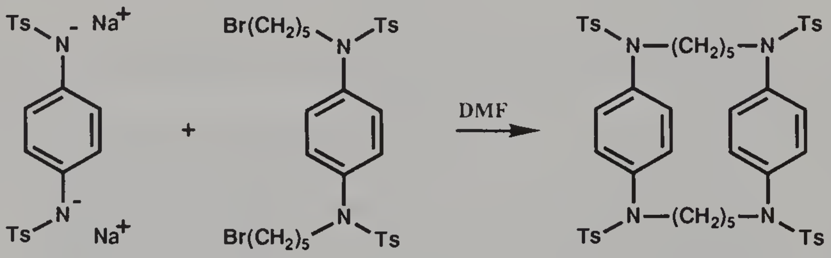
Peraza-cyclophanes

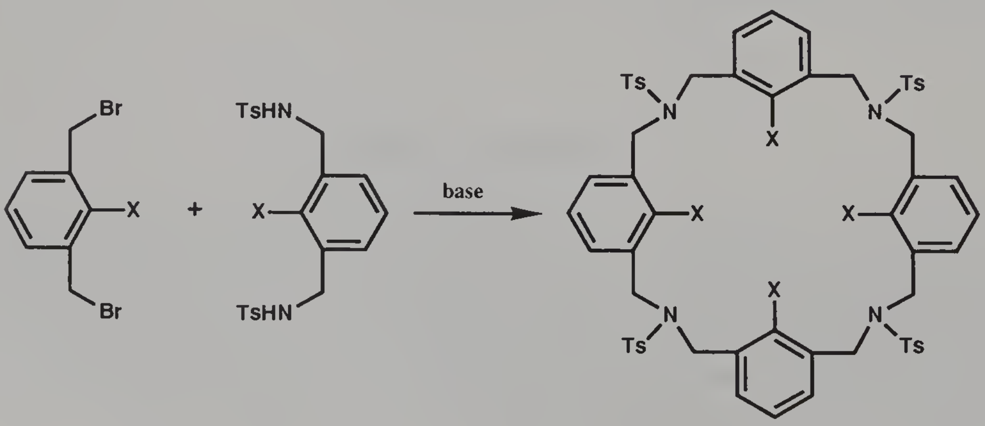
A. INTRODUCTION

This group of nitrogen-containing macrocycles is treated separately from the peraza-crowns because the methods used to prepare them and their host–guest interactions are different due to the rigidness of their structures (Franke and Vögtle, 1986; Odashima and Koga, 1983). Water-soluble cyclophanes are promising synthetic hosts because they have hydrophobic cavities to capture organic guests. These new hosts need to have large and deep cavities in order to have selectivity for organic molecules (Franke and Vögtle, 1986). Preliminary experiments show that heteroatoms in cyclophane hosts might play a role in the formation of inclusion complexes. For example, a number of large cyclophanes containing four or more benzene rings, but with no heteroatoms, do not form inclusion complexes with organic molecules (Takemura et al., 1984). On the other hand, some large cyclophanes containing amide groups in the macroring do form inclusion complexes with certain organic compounds (Odashima and Koga, 1983). One of the first peraza-cyclophane inclusion complexes was observed by Stetter and Roos (1955), but in this case, the guest benzene molecules were not in the cyclophane cavity, but in the crystal lattice surrounded by several host molecules (Hilgenfeld and Saenger, 1982).

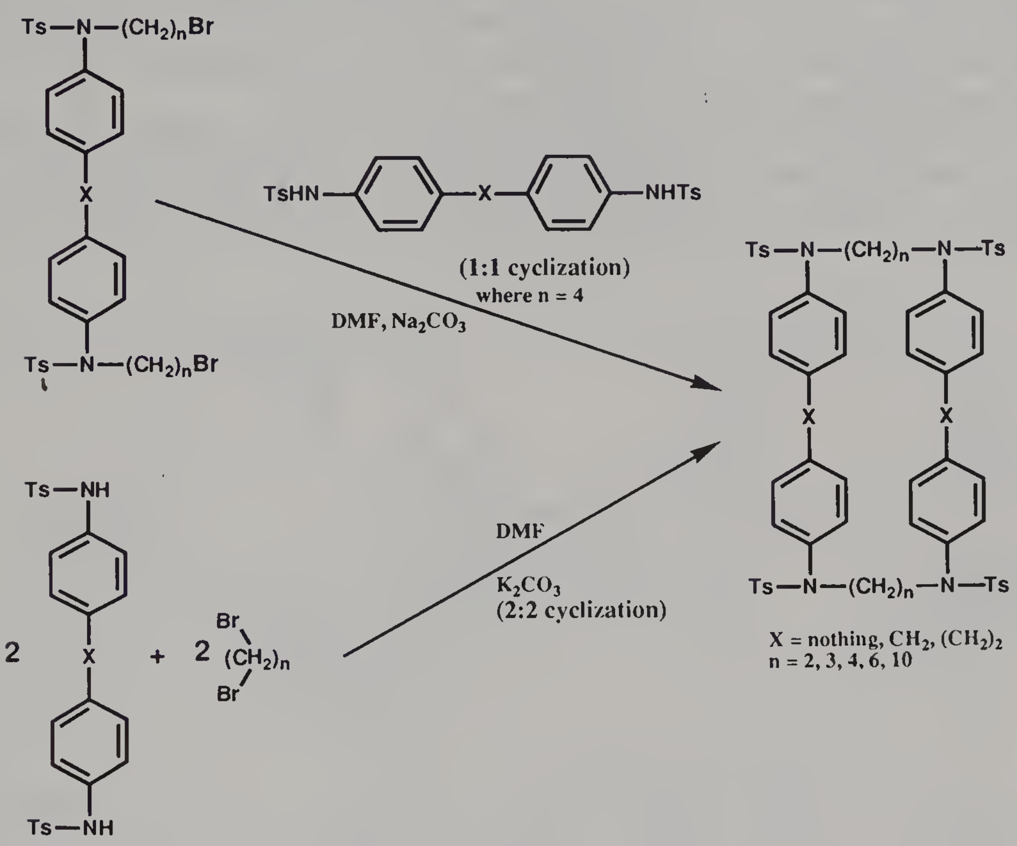
B. RING CLOSURE TO FORM TWO C—N BONDS BY REACTION OF A BISTOSYLAMIDE AND A DIHALIDE

The first peraza-cyclophane containing more than two nitrogen atoms was prepared in a 40% yield by Stetter and Roos (1954, 1955) by treating the disodium salt of *N*,*N*′-ditosyl-*p*-phenylenediamine with a dibromide under high-dilution conditions. A similar reaction of the bistosylamide of *m*-phenylenediamine gave the 2:2 cycloadduct containing four *m*-phenylene units (Vögtle and Neumann, 1970).





This simple approach has been used to prepare many peraza-cyclophanes containing more than two benzene rings, some of which formed inclusion complexes with organic molecules. The synthesis of the peraza-cyclophanes could involve both 1:1 and 2:2 cyclization reactions. In the second reaction

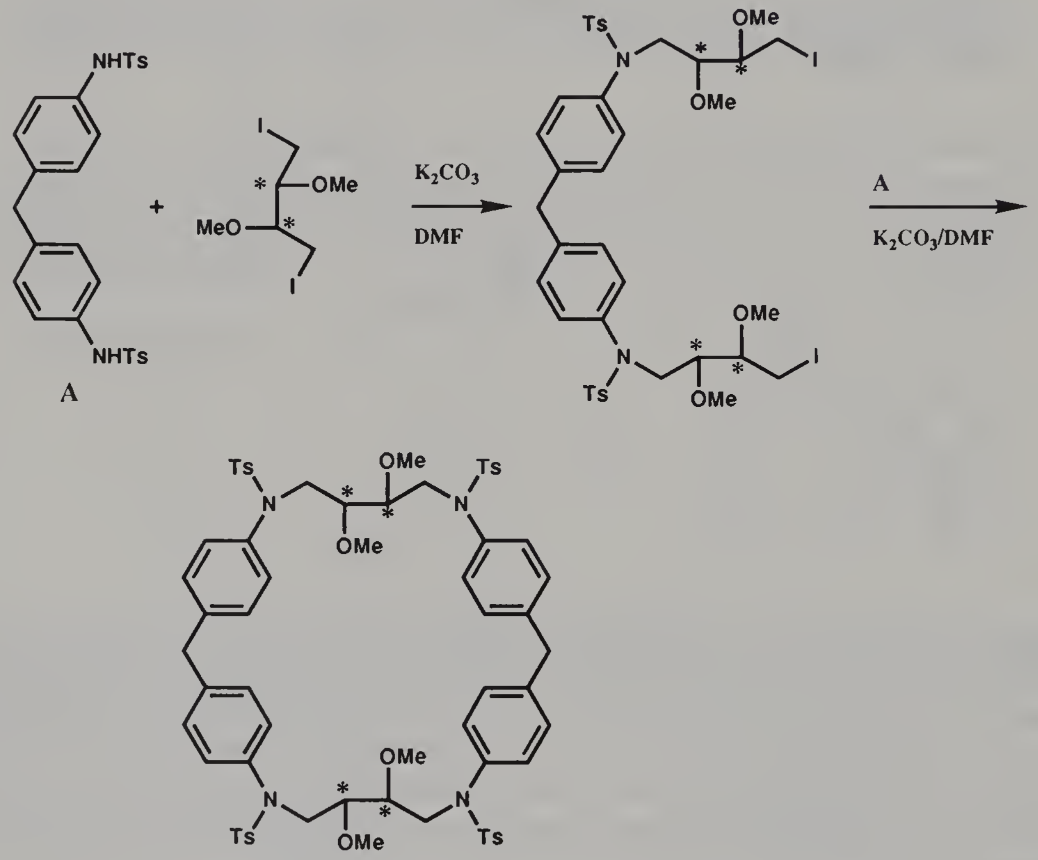


shown above, some 1:1 cyclization product containing only two nitrogens was isolated where $n = 6$ or 10 or when X = CH_2 or $(CH_2)_2$. Thus, 2:2 cyclizations were only favorable where there were six or fewer methylene units between the two nitrogen atoms. The more rigid biphenyl-containing macrocycle (X = nothing) required a greater number of methylene units in the starting dihalide to form the cyclophane containing only one biphenyl unit (Faust and Pallas, 1960; Odashima et al; 1980; Schneider and Busch, 1986; Schneider and Philipi, 1984).

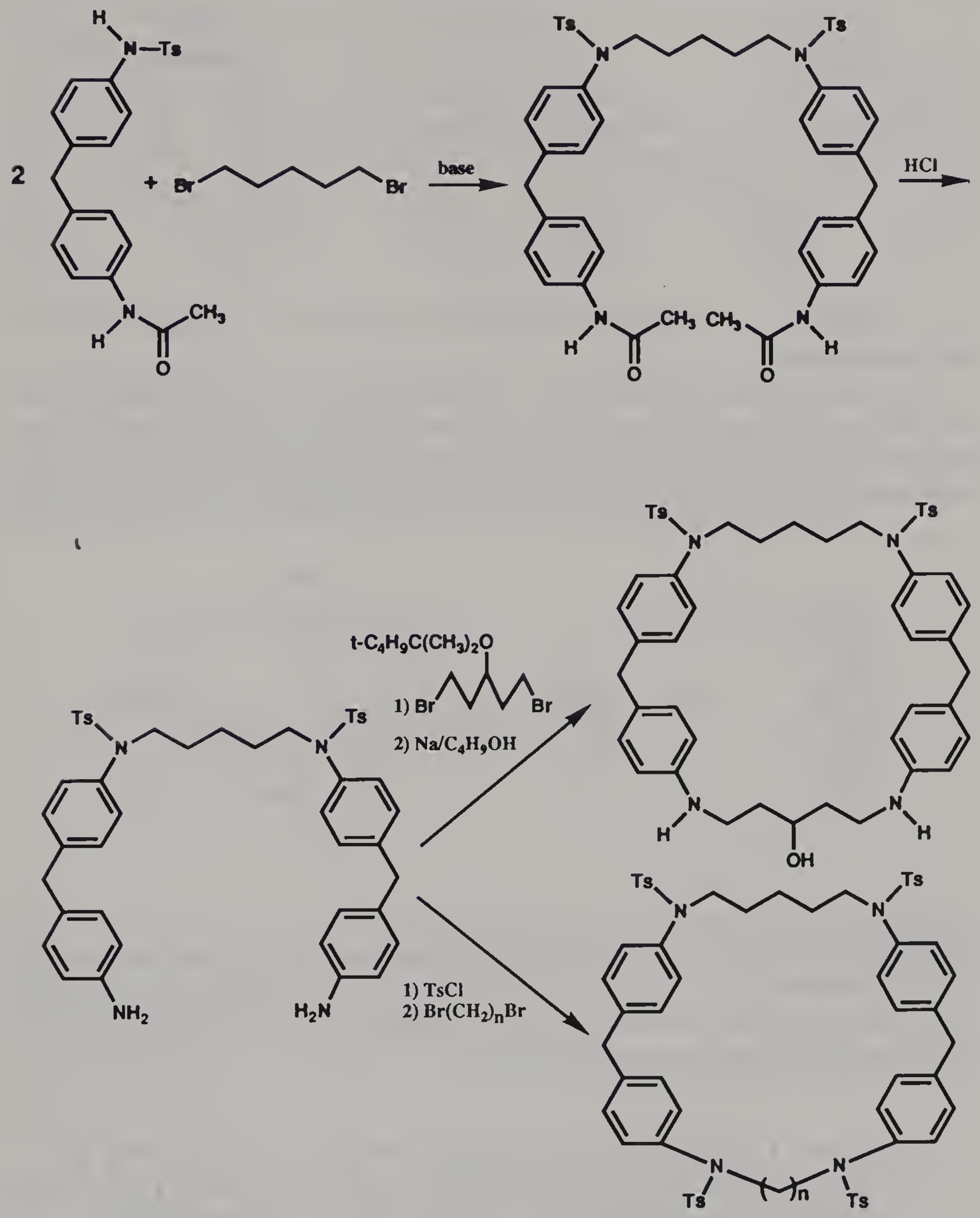
Some interesting observations have been made for the preceding 1:1 and 2:2 cyclization reactions. Where $n = 4$ and X = CH_2, the 1:1 cyclization method gave a 73% yield of the tetraphenylene-containing cyclophane while the 2:2 cyclization route gave only a 24% yield (Odashima et al., 1985). Not only are the yields better in the 1:1 cyclization method, but often the 2:2 cyclization process gave 3:3, 4:4, and higher-order condensation products. In these cases, purification of the 2:2 cyclization product required column chromatography (Odashima et al., 1985). It is significant that where $n = 8$ and $X = CH_2$, the 1:1 cyclization method to form the 38-membered ring gave a remarkably high yield (79%) while the yield for the 2:2 process was only 4% (Uoto et al., 1990a).

Schneider and Busch (1986) studied the effect of temperature and potassium carbonate concentrations on the above reactions where $n = 10$, $X = CH_2$ and $n = 6$, $X = (CH_2)_2$. The average yields were 45–62% for both methods. They found that the 2:2 process could be maximized at low temperatures and high potassium carbonate concentrations.

Two diphenylmethane molecules have been bridged by a pair of chiral chains prepared from L-tartaric acid. The process required two steps since a direct 2:2 cyclization did not work (Takahashi et al., 1984). A similar two-step process was used to prepare cyclophanes with two or four cyclohexane rings (Soga et al., 1980).

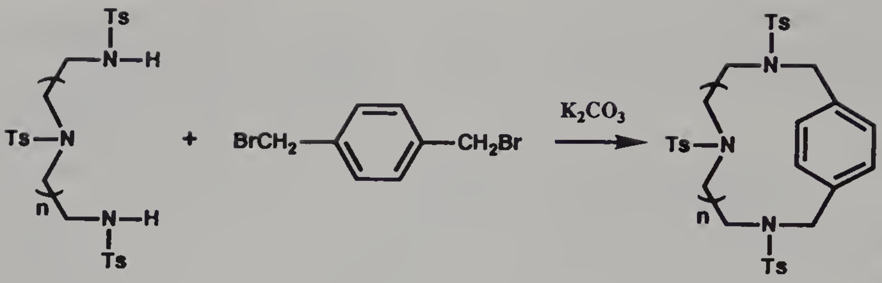


A slightly different synthetic route was used to prepare unsymmetric cyclophanes. In this case, each amine of the diamine had a different blocking group, which allowed them to react sequentially as shown (Kawakami et al., 1985; Soga et al., 1980; Winkler et al., 1983). After reaction of the tosylamides



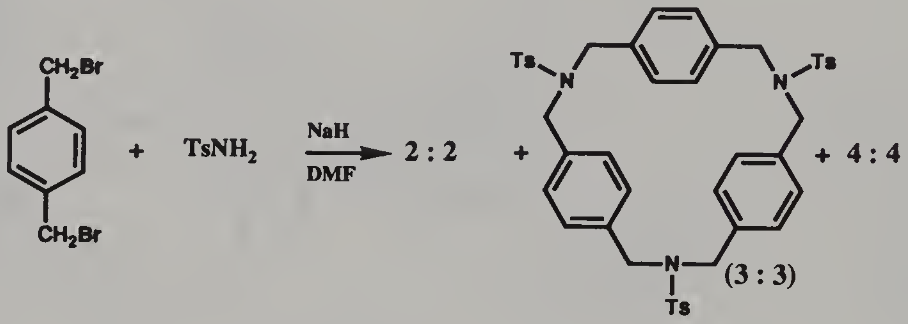
in the first step, the acetamide groups were hydrolyzed and the second arm was installed.

Nearly quantitative yields were obtained when peraza-paracyclophanes were prepared from α,α'-dibromo-*p*-xylene and pertosylated polyamines in DMF in the presence of potassium carbonate (Iwata and Kuzuhara, 1986).



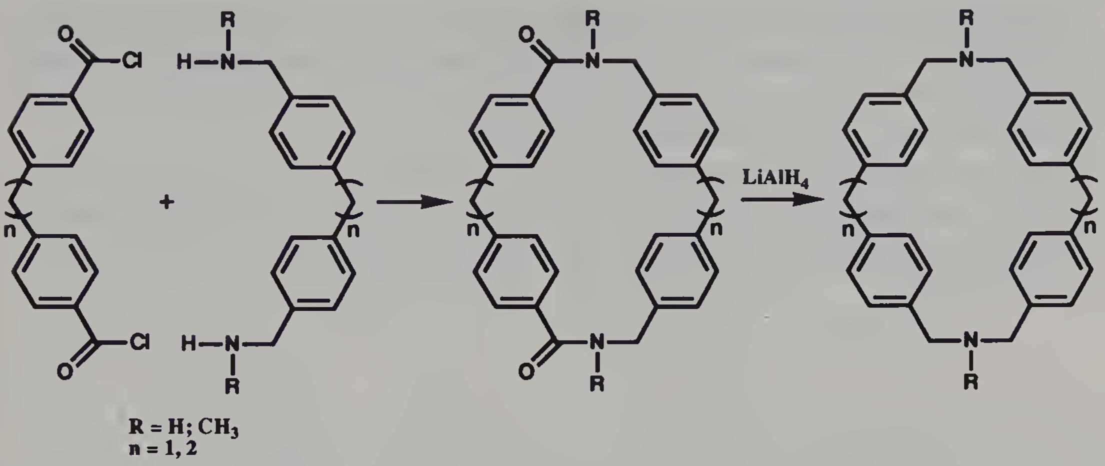
The reaction was carried out at room temperature and gave good yields and few by-products.

The coupling reaction between *p*-toluenesulfonamide and the appropriate bis(halomethyl)aromatic compound, followed by removal of the tosyl groups, was developed as a simple and general route to the peraza-cyclophanes (Bottino et al., 1988; Takemura et al., 1984). In this reaction, carried out under a variety of conditions, the 2:2 condensation product was produced in a yield of about 6%, the 3:3 product in about 23%, and the 4:4 product in about 12% (Takemura et al., 1984). A similar procedure was proposed at about the same time for the preparation of bipyridinophane from 3,3′-bischloromethyl-2,2′-bipyridine (Newkome et al., 1983).

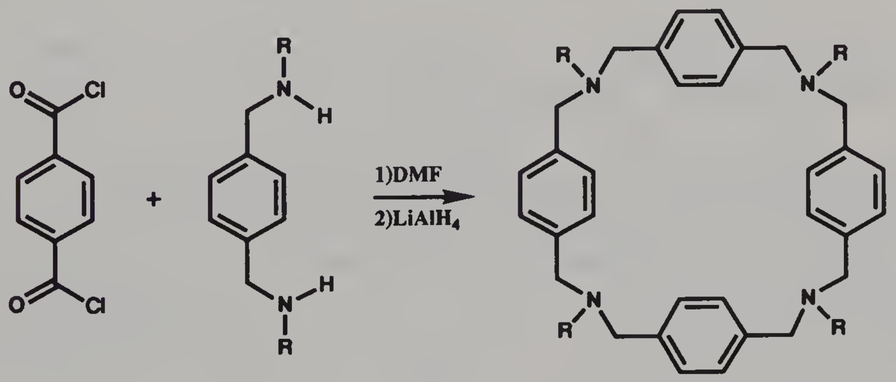


C. RING CLOSURE TO FORM TWO C—N BONDS BY REACTION OF AN ACTIVATED DERIVATIVE OF AN ARENEDICARBOXYLIC ACID AND A DIAMINE

The reaction of an aromatic diacid dichloride with a diamine, followed by reduction, is also a common method for producing 1:1, 2:2, 3:3, and higher-order cyclocondensation products (Urushigawa et al., 1971; Vögtle et al., 1982). Where the diacid dichloride is part of an aromatic system, the cyclocondensation product is a peraza-cyclophane. A 1:1 cyclocondensation was favored for the reaction of two extended aromatic systems as shown. The yields of these reactions were 20–65%. A 2:2 cyclization was observed when

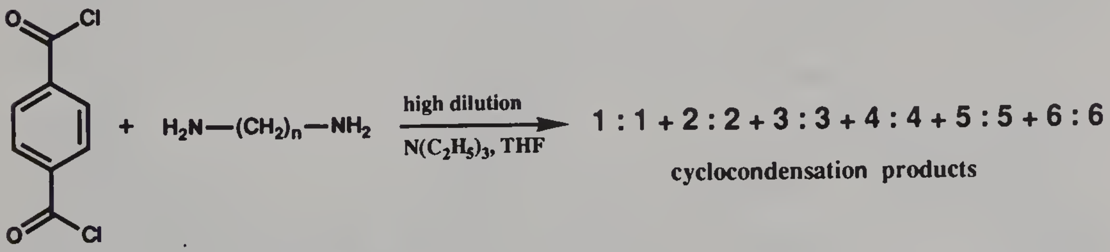


using more compact diacid dichlorides and diamines (Urushigawa et al., 1971). This procedure was repeated by others to give only 11% of the 2:2 cycloadduct



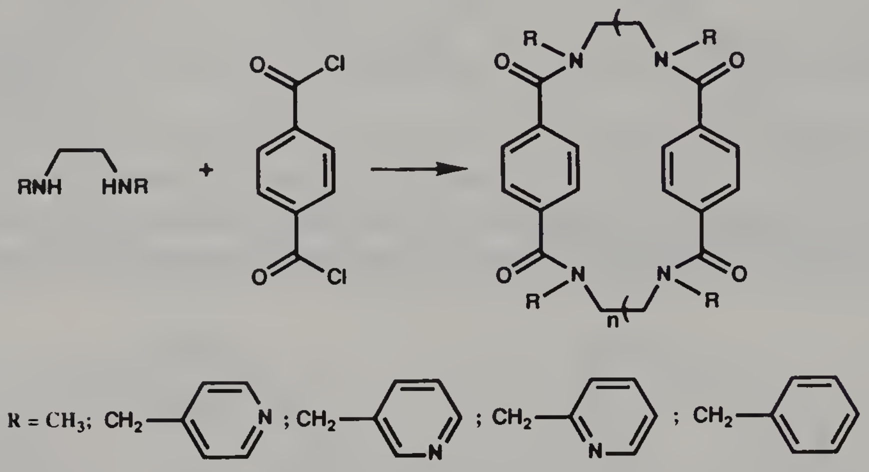
along with some 3:3 cyclocondensation product (Murakami et al., 1979, 1981; Tabushi et al., 1981).

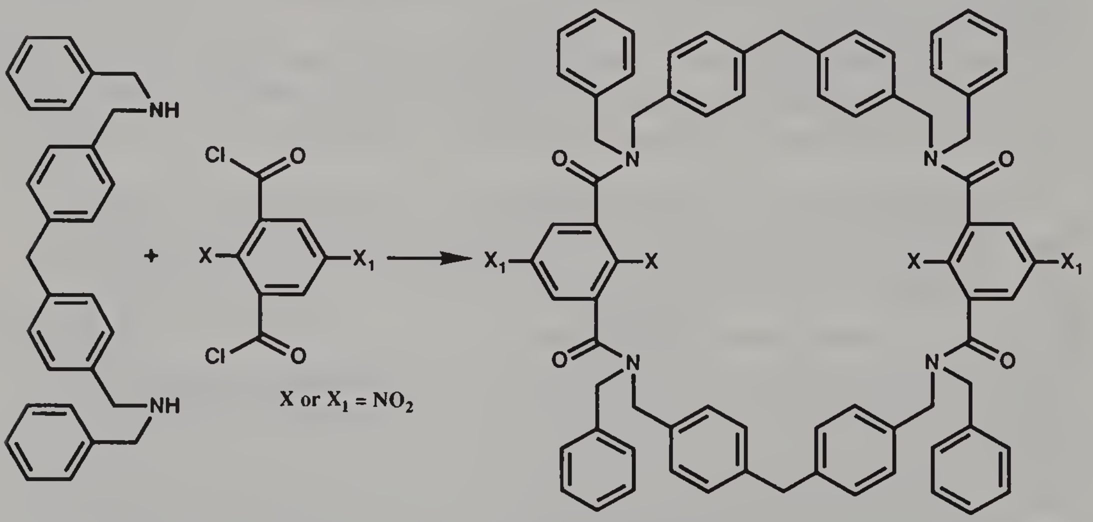
The most detailed study of this type of cyclocondensation reaction was done by Rodgers and coworkers for the reactions of terephthalyl dichloride with various diamines (Rodgers et al., 1985). Where *n* = 2, the cyclocondensation products included the trimer (the product of three diacid dichlorides with three diamines) to the hexamer. Where *n* = 4, dimer to pentamer products were isolated; and where *n* = 6, monomer to pentamer 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 with 1,6-diaminohexane ($n = 6$) and for the trimer (17%), a 30-membered ring, in the reaction with ethylenediamine ($n = 2$).

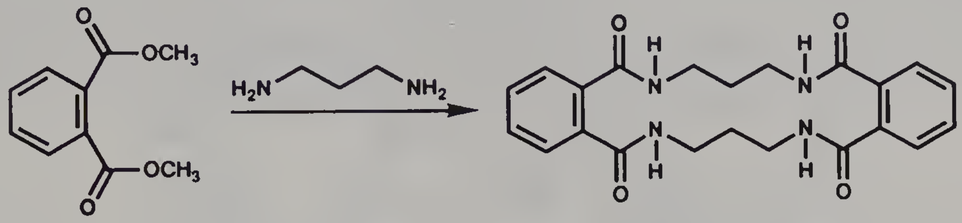
Vögtle and coworkers prepared the cyclocondensation products when terephthalyl dichloride was treated with various derivatives of ethylenediamine (Vögtle and Müller, 1982a, 1982b, 1984). Where R = benzyl, the 3:3 cyclocondensation product ($n = 2$) was isolated in a 25% yield and the 4:4 product in a 3% yield. Diacid dichlorides derived from di- and tribenzene-containing materials gave 2:2 cyclocondensation products when treated with certain diamines (Vögtle and Müller, 1982a, 1982b). The reaction of isophthalyl dichloride containing a nitro substituent gave 2:2 cyclocondensation products in yields of 10–17% (Werner et al., 1986). The substituent nitro groups were reduced to the amines in a second step.



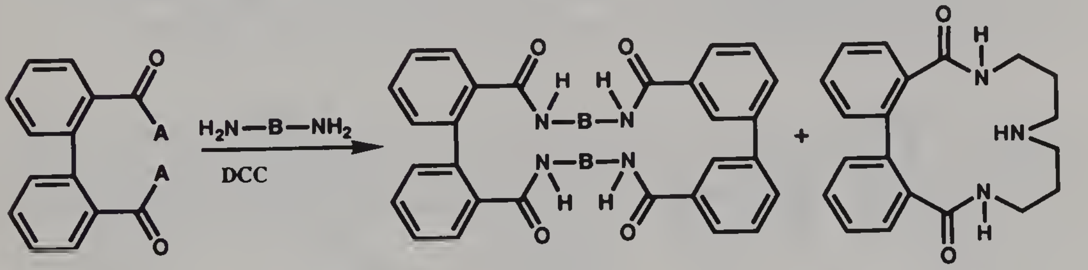


Esters and active esters have been used in cyclocondensation reactions in place of the more reactive diacid dichlorides. Dimethyl phthalate reacted with

1,3-propanediamine to give the 18-membered 2:2 cyclocondensation product in an 8% yield (Gaozza et al., 1972). No 1:1 cyclization product was observed in this case.



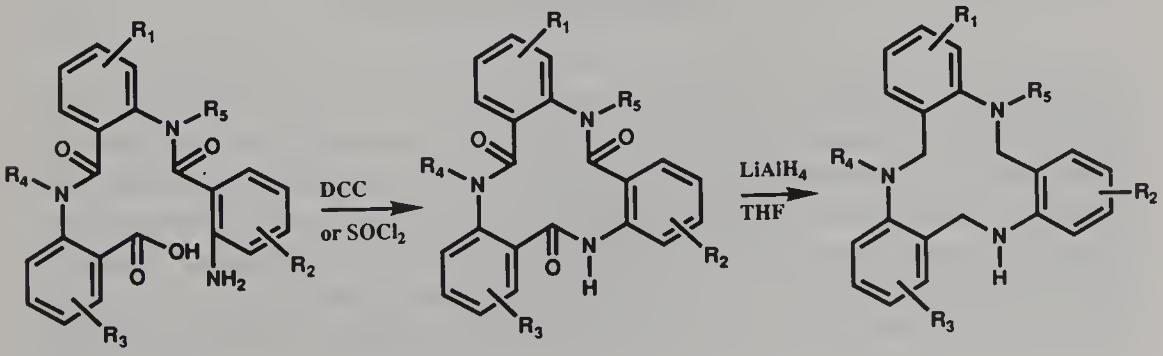
2,2′-Biphenyldicarboxylic acid, when activated by 4-*N*,*N*-dimethylaminopyridine or thiazolidine-2-thione and in the presence of dicyclohexylcarbodimide (DCC) gave the cyclic peraza polyamide (Nagao et al., 1981). With ethylenediamine, the reaction gave only the 2:2 cyclization product in a 79% yield. A small yield (11%) of the 1:1 cyclization product also was isolated when 1,7-diamino-4-azaheptane was used. These reactions were carried out by simultaneously adding the diamine (or triamine) and the active ester each in methylene chloride to stirred methylene chloride.



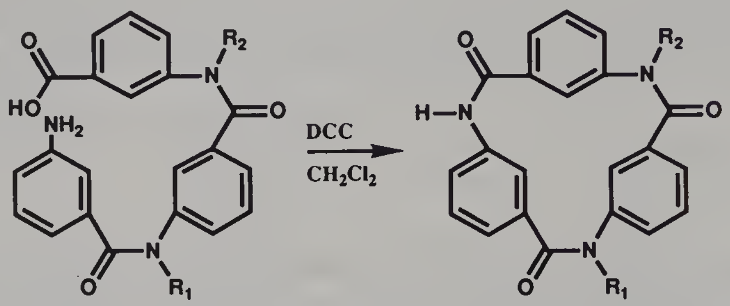
B = $(CH_2)_2$; $(CH_2)_3NH(CH_2)_3$
A = active group

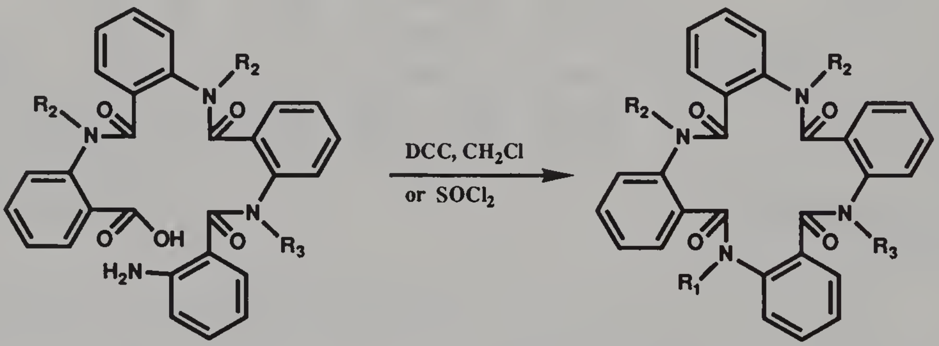
where B = $(CH_2)_3NH(CH_2)_3$

A "head to tail" arrangement was observed for the intermolecular reaction of activated *o*-aminobenzoic acid. The final cyclization step used DCC activation on the ω-amino trimeric acid, which first had to be prepared (Edge et al., 1981, 1982; Hoorfar et al., 1982a; Ollis et al., 1975). Thionyl chloride



also was used to activate the acid. By-products were often obtained in these reactions. This same stepwise approach to making the cyclic trimer of anthranilic acid was extended to the *m*-aminobenzoic acid derivatives (Elhadi et al., 1980, 1982). The reaction of *m*-aminobenzoic acid with *m*-nitrobenzoyl chloride, followed by reduction and a further reaction with *m*-nitrobenzoyl chloride and reduction, led to the *ω*-amino trimeric acid intermediate. A similar process to form the cyclic tetramer of anthranilic acid gave only a 1–2% yield in the final cyclization step (Hoorfar et al., 1980, 1982b).



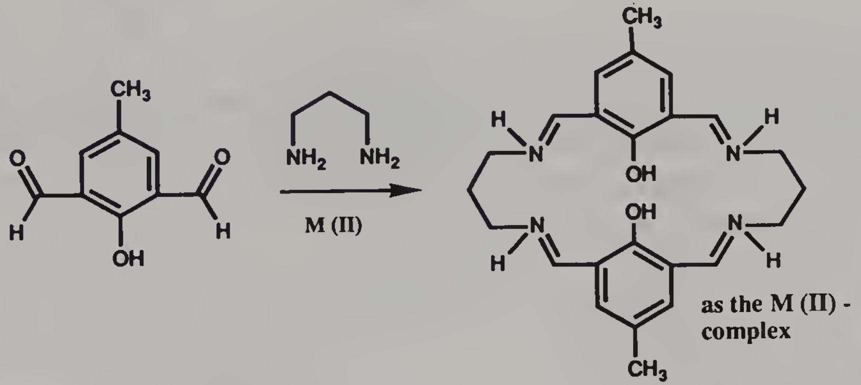


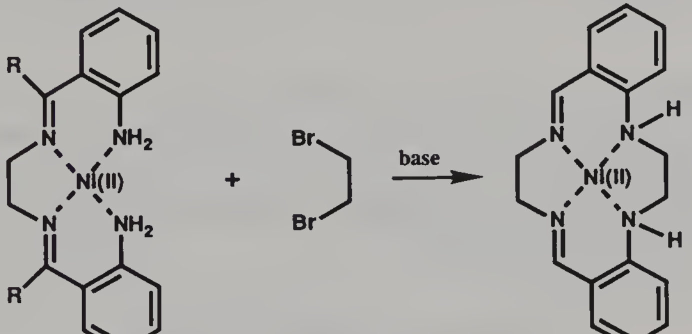
R_1, R_2, R_3 = alkyl

D. RING CLOSURE TO FORM A BIS SCHIFF BASE BY REACTION OF AN AROMATIC DIALDEHYDE AND A DIAMINE

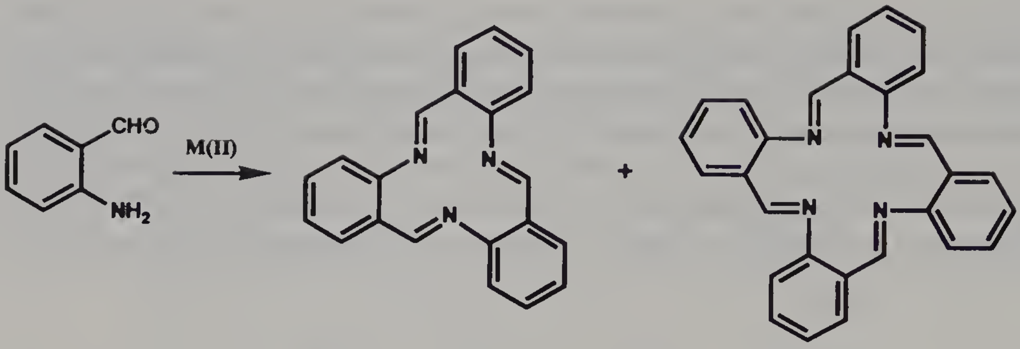
1. With Metal Ion Templates

Template-catalyzed syntheses of peraza-cyclophanes via the cyclic oligo Schiff bases are common (Mandal et al., 1987). The reaction of a dialdehyde and a diamine to form a cyclic oligo Schiff base is usually successful, but only a few of the di or tetra Schiff bases have been reduced to the cyclic amines. Some examples of these cyclic Schiff base-forming reactions have been reported, but this subject will not be reviewed extensively because this book covers the saturated polyaza-crowns and cyclophanes. Reducing the Schiff bases and removing the metal ions are often difficult as discussed in Chapter III (see also Lindoy, 1989). As an example of the difficulty in isolating products in these reactions, only gummy materials were isolated when 5-methylisophthaldialdehyde was treated with 1,3-propanediamine. However, the desired 2:2 cyclization product was isolated when the reaction was carried out in the presence of an appropriate metal template ion such as Cu(II), Ni(II), or Co(II) (Pilkington and Robson, 1970). These template-catalyzed cyclization reactions also can be carried out by condensing a complexed linear Schiff base with an appropriate diamine (Uhlemann and Phath, 1969). It is often difficult to choose the correct metal template ion or to predict the site of cyclization when the metal ion does not complex with all the amine nitrogen atoms (Bailey et al., 1984; Cabral et al., 1984; Kahwa et al., 1988).

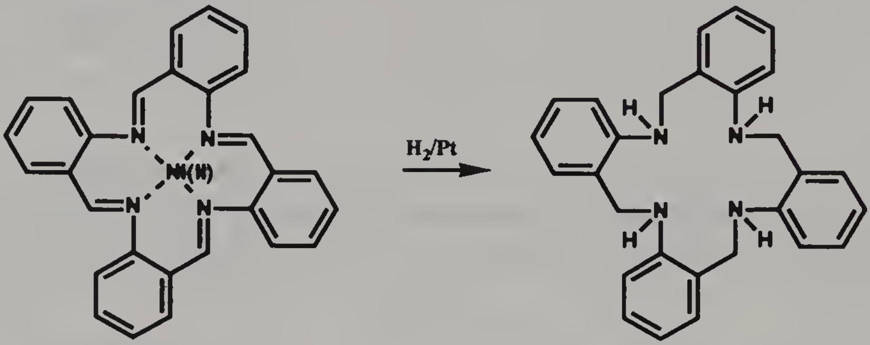




The self-condensation of *o*-aminobenzaldehyde has been studied extensively. This material undergoes a variety of cyclic self-condensation reactions depending on reaction conditions. In the presence of metal ions or BF_3, self-condensation gave trimer with VO_2^+ as the template, tetramer with Cu(II) or Zn(II) or a mixture of trimer and tetramer with Co(II) and Ni(II) as templates (Hawley and Blinn, 1975; Melson and Busch, 1965; Sahajpal and Thornton, 1984; Tait and Busch, 1978; Taylor and Busch, 1969; Taylor et al., 1966). Other derivatives containing methyl substituents on the benzene rings were



also prepared (Jircitano et al., 1983; Sheldon et al., 1983). We give no further details of these reactions since this book is devoted to the saturated nitrogen heterocycles. The Ni(II) complex of the tetramer was hydrogenated to form the tetraaza-cyclophane (Busch, 1967).



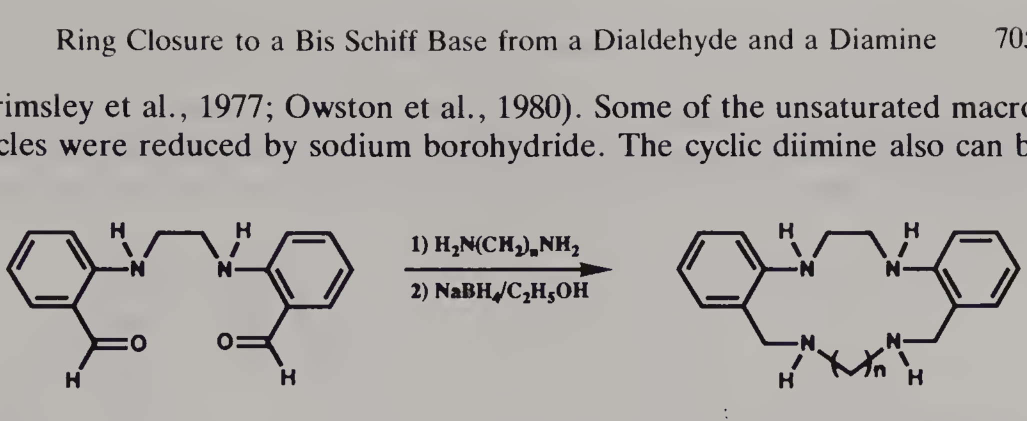
The propensity for *o*-aminobenzaldehyde to self-condense is very sensitive to the chemical environment. The nature of the products formed was clarified as early as 1926 (Seidel, 1926; Seidel and Dick, 1927). In the absence of the metal ions, various polycyclic products were formed, most of which were very different from those shown above.

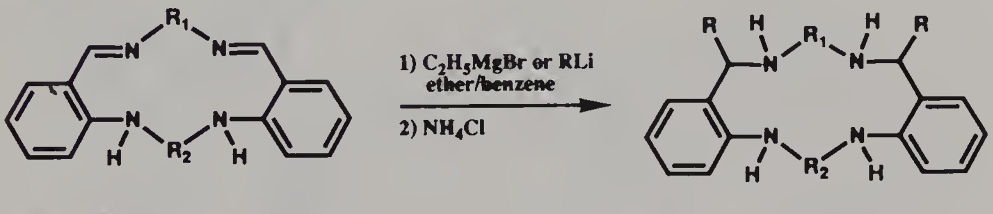
2. Without Metal Ion Templates

Nontemplate macrocyclic Schiff-base formation also has been used to prepare the peraza-cyclophanes. These nontemplate cyclizations require rigid starting materials such as those containing benzene, pyridine, and thiophene rings. We will report here only those cyclizations involving benzene-containing materials (Jazwinski et al., 1987; Menif and Martell, 1989; Owston et al., 1980; Pietraszkiewicz and Gasiorowski, 1990).

The first examples of the non-template-catalyzed cyclo-Schiff base-forming reaction was reported by Lindoy and coworkers in 1977 and Owston and coworkers in 1980. The reaction of a bisbenzaldehyde with various diamines gave the cyclic bis Schiff base in yields of 74–94% (Adam et al., 1987, 1990a;

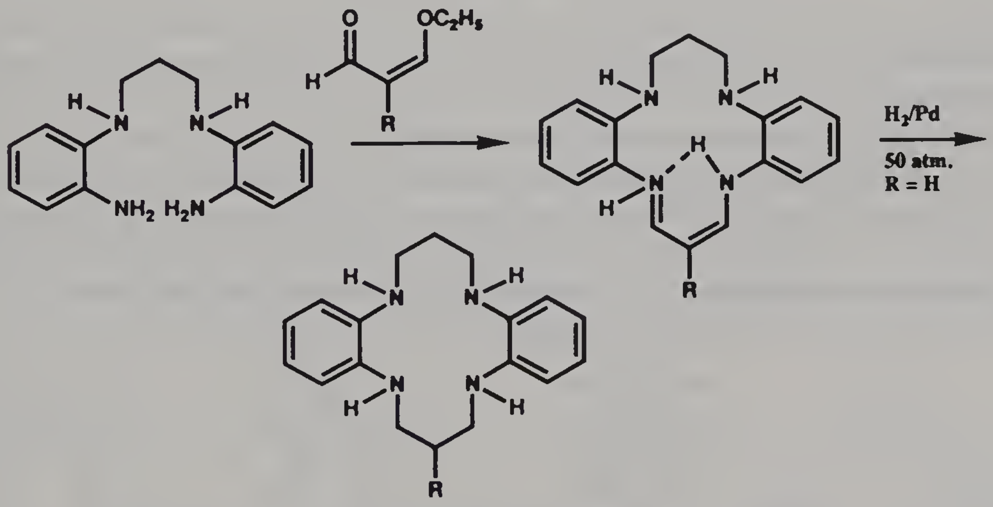
Grimsley et al., 1977; Owston et al., 1980). Some of the unsaturated macrocycles were reduced by sodium borohydride. The cyclic diimine also can be converted to the saturated macrocycle by using 2 mol of ethylmagnesium bromide or methyl or *n*-butyllithium (Adam et al., 1990b; Henrick et al., 1983). Other dialkyl-substituted macrocycles were prepared with additional amine functions in the ring (R_2 contained NH groups) (Adam et al., 1987).



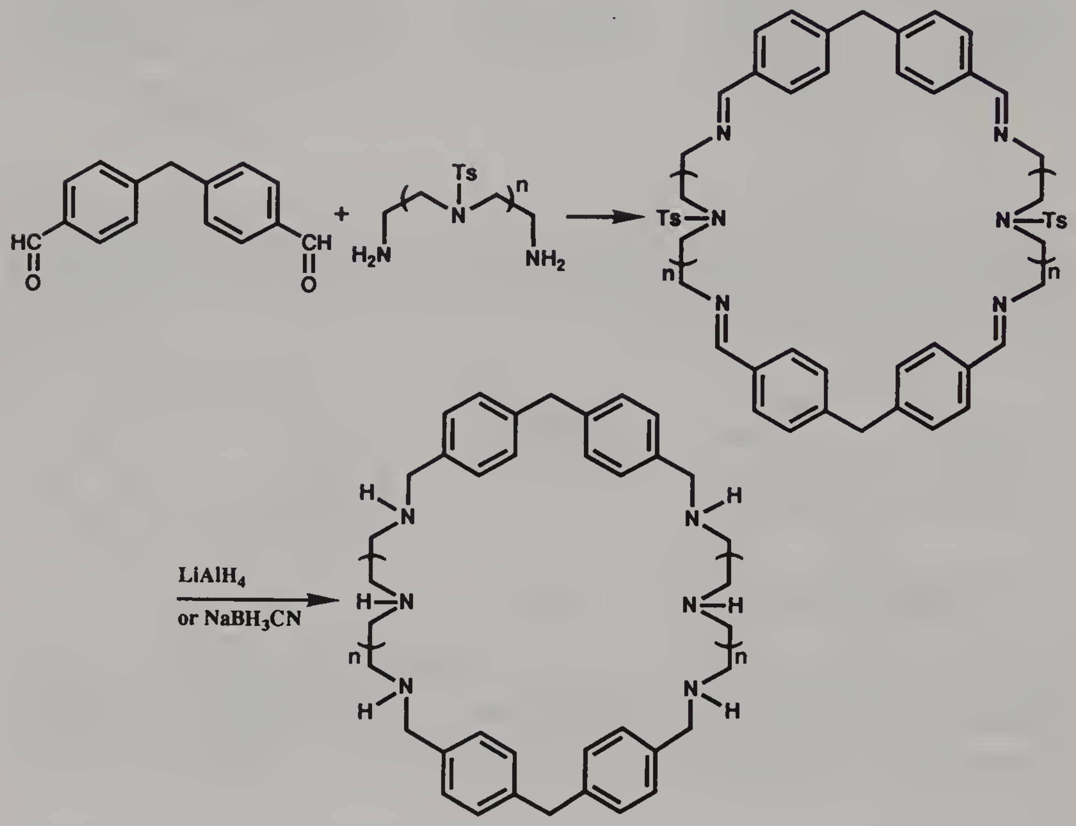


R = C_2H_5, CH_3, C_4H_9
R_1, R_2 = alkyl chain or o-C_6H_4

Ethoxyacrylaldehyde was condensed with a bisaniline compound to form an unsaturated peraza-cyclophane (Ansell et al., 1982; Behr and Breitmaier, 1978). The cyclic imine was hydrogenated to form the dibenzotetraaza-14-crown-4 ligand. This cyclization reaction was carried out in the absence of a metal ion template. It is possible that internal hydrogen bonding in the starting tetraamine acts as a template to help in the cyclization process.

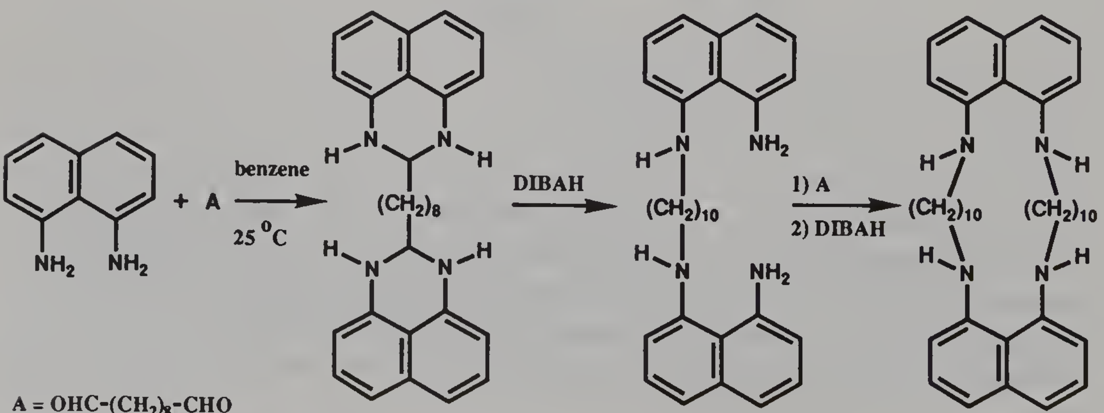


Large peraza-cyclophanes have been prepared by the non-template-catalyzed cyclo-Schiff base-forming reaction. For example, a bis-benzaldehyde was condensed with a diamine to form the 2:2 cyclic tetra Schiff base (Jazwinski et al., 1987). The 1:1 cyclocondensation product did not form because



the diamines used in this process were not long enough to react with the rigid dialdehyde.

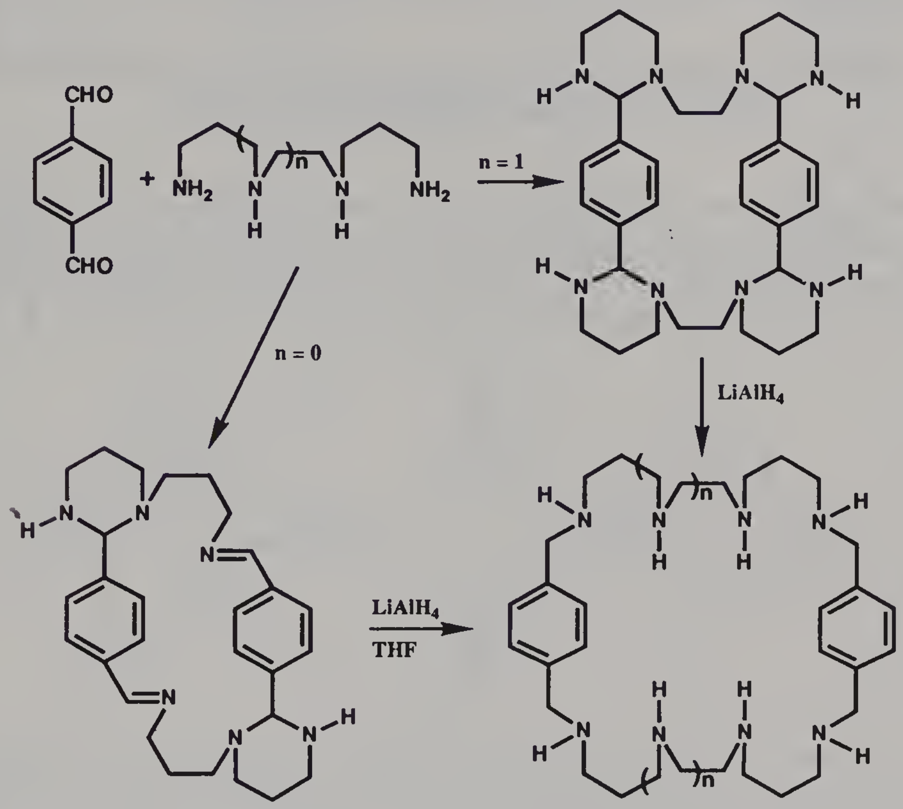
Peraza-cyclophanes have been prepared by first condensing the dialdehyde with a 1,8-naphthalenediamine to form two 1,3-diazacyclohexane units as shown below. The small diaza rings open on reduction to form a long-chain molecule with primary amines on each end. This material can be cyclized with another molecule of the dialdehyde (Yamamoto and Maruoka, 1981).



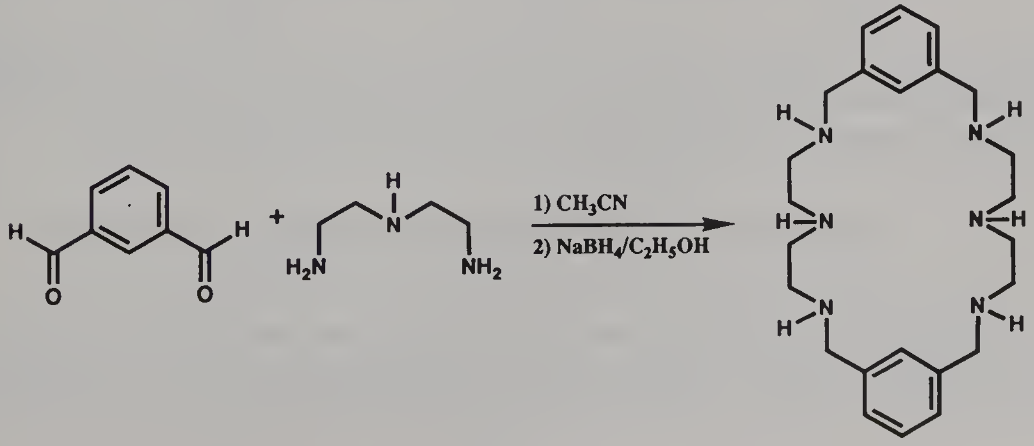
A = $OHC\text{-}(CH_2)_8\text{-}CHO$

DIBAH = diisobutylaluminium hydride

Pietraszkiewicz and Gasiorowski (1990) used this type of reaction with a rigid aromatic dialdehyde and an open-chain polyamine to make two peraza-cyclophanes. Terephthaldialdehyde was treated with 1,7-diamino-4-azaheptane or 1,10-diamino-4,7-diazadecane in THF followed by reduction to give the macrocyclic products in a 95% yield. The driving force for these reactions could be the formation of macrocycles with 1,3-diazacyclohexane units. These macrocycles precipitated during the course of the reaction. A similar reaction with 1,5-diamino-3-azapentane gave only polymeric material. Other practical information concerning the formation of the small 1,3-diaza rings in a polyamine chain has been published (Bergeron, 1986; Dutasta et al., 1988; McManis and Ganem, 1980).



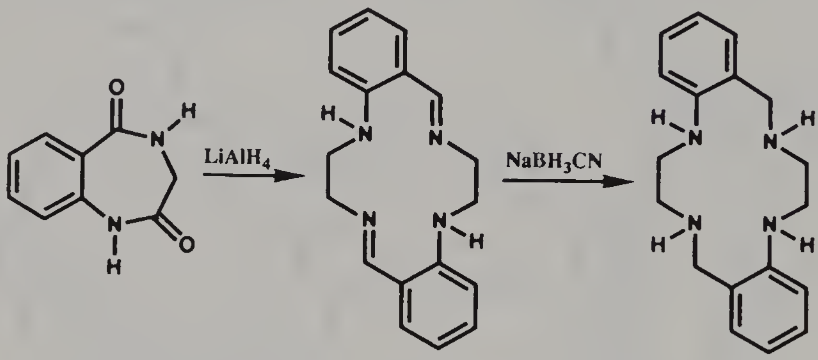
Isophthaldialdehyde cyclocondensed with 1,5-diamino-3-azapentane followed by reduction to give the 2:2 hexaaza-cyclophane product (Menif and



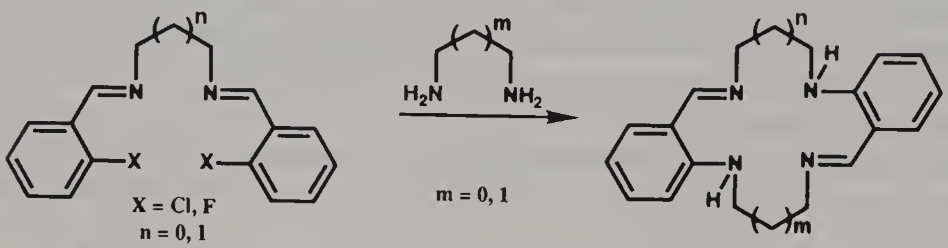
Martell, 1989). The authors suggested that the macrocycle was formed through the cyclic tetra Schiff base or through aminal formation.

E. MISCELLANEOUS RING-CLOSURE REACTIONS TO FORM PERAZA-CYCLOPHANES

A few miscellaneous reactions have been used to prepare one or more peraza-cyclophanes. Benzodiazepinedione, when partially reduced, gave a 14-membered macrocyclic diimine (Bergman and Brynolf, 1989). The diimine was reduced to the dibenzocyclam. In earlier work, this product was thought to be a derivative of the starting benzodiazepine (Uskokovic et al., 1962). A similar process of converting a small macrocycle to a larger one was described by Goldman and coworkers (Goldman et al., 1969).

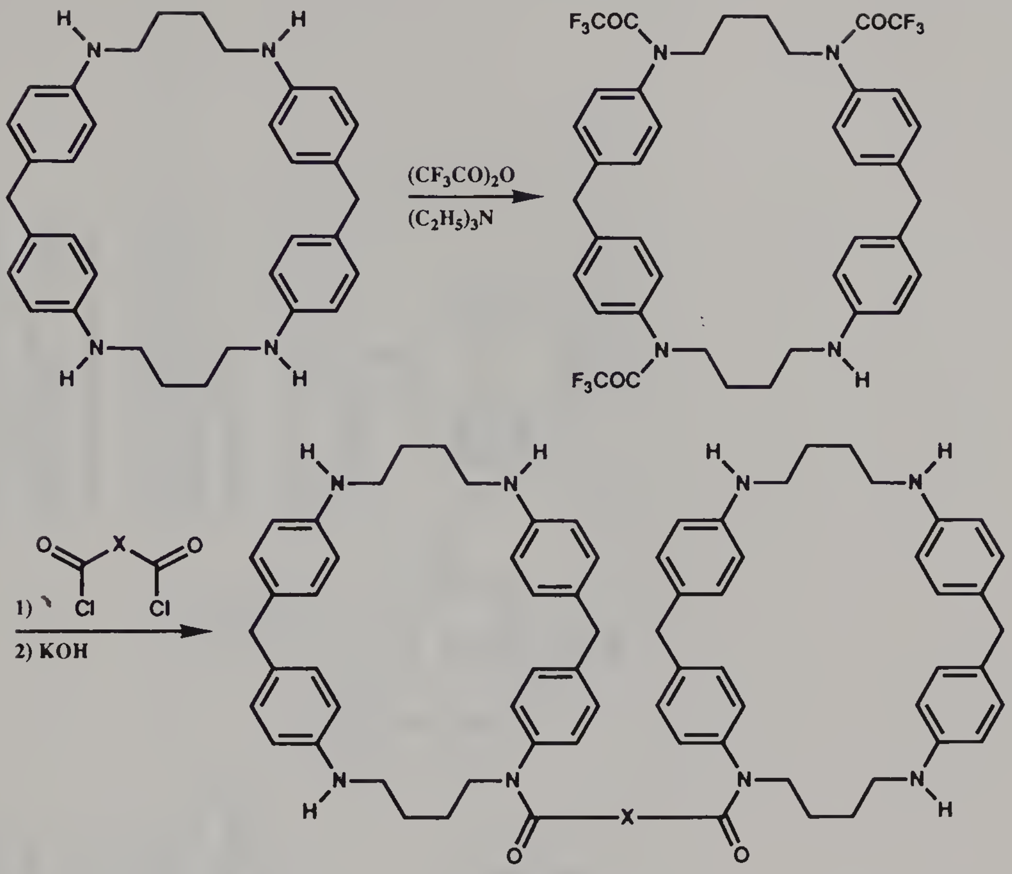


Bergman and Brynolf (1989) reported an interesting synthesis of a cyclic bis Schiff base. They treated a linear bis Schiff base containing two chloro- or fluorophenyl units with a diamine to form the symmetrical cyclic bis Schiff base similar to that shown above. It is evident that one of the imine carbon atoms in the starting material rearranged to one of the nitrogen atoms of the diamine substrate. The concurrent or subsequent reaction of the resulting amines with the aromatic halide function led to the products shown.



F. FORMATION OF BIS(PERAZA-CYCLOPHANE)S

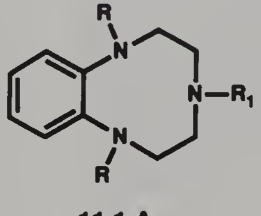
A bis(peraza-cyclophane) was prepared from two molecules of a mono-functionalized peraza-cyclophane and a diacid dichloride (Lai et al., 1985).



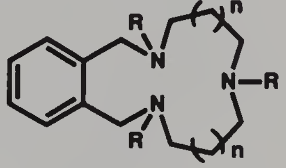
Extensive tables of peraza-cyclophane compounds are given at the end of this chapter. The tables are organized by number of ring nitrogen atoms (Tables 11.1–11.4 list cyclophanes with three nitrogen atoms; Tables 11.5–11.11-four nitrogen atoms; Tables 11.12-five nitrogen atoms; Table 11.13-six nitrogen atoms; and Table 11.14-eight nitrogen atoms), by number of benzo units (Tables 11.1, 11.5 and 11.12 list cyclophanes containing one benzo unit; Tables 11.2 and 11.6-two benzo units; Tables 11.3 and 11.4-three benzo units; Tables 11.7–11.9-four benzo units; and Tables 11.10, 11.11, 11.13 and 11.14 list cyclophanes having various numbers of benzo units), by ring size (all tables) and by the complexity of ring substituent atoms (all tables). Table 11.15 lists bis(benzoperaza-crown) cyclophanes.

G. TABLES OF COMPOUNDS

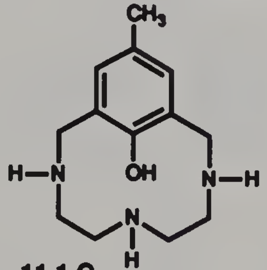
TABLE 11.1. BENZOPERAZA-CROWN-3 CYCLOPHANES



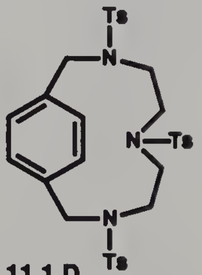
11.1 A



11.1 B



11.1 C

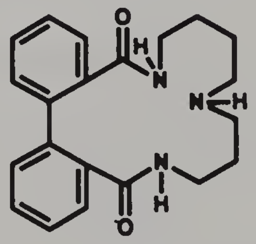


11.1 D

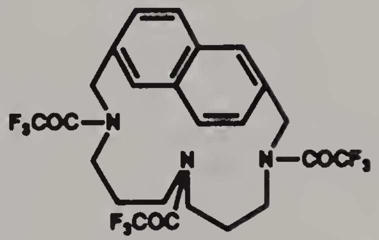
Structure	R	R_1	n	Other Substituents	Yield (%)	References
11.1 A	H	$C_6H_5CH_2$-		2,6-$(O)_2$		Mikiciuk-Olasik, 1990
	H	4-$CH_3C_6H_4$-		2,6-$(O)_2$		Mikiciuk-Olasik, 1990
	H	2,4-$(CH_3)_2C_6H_3$-		2,6-$(O)_2$		Mikiciuk-Olasik, 1990
	H	4-$C_2H_5OC_6H_4$-		2,6-$(O)_2$		Mikiciuk-Olasik, 1990

	H	2,4,6-$(CH_3)_3$-3-Br-C_6HNHC(O)CH_2-				Mikiciuk-Olasik, 1990
	Ts	Ts			26	Atkins et al., 1978
11.1 B	H		0	as salt	84	Chavez and Sherry, 1989
	H		1	as salt	65	Chavez and Sherry, 1989
	Ts		0		85	Chavez and Sherry, 1989
	Ts		1		87	Chavez and Sherry, 1989
11.1 C						Wu, 1988
11.1 D					96	Iwata and Kuzuhara, 1986, 1988

TABLE 11.2. DIBENZOPERAZA-CROWN-3 CYCLOPHANES



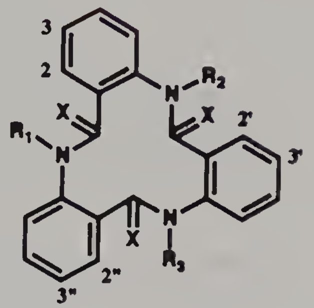
11.2 A



11.2 B

Structure	Yield (%)	References
11.2 A	79	Nagao et al., 1981
11.2 B	26	Pratt et al., 1988

TABLE 11.3. TRIBENZOPERAZA-CROWN-3 CYCLOPHANES



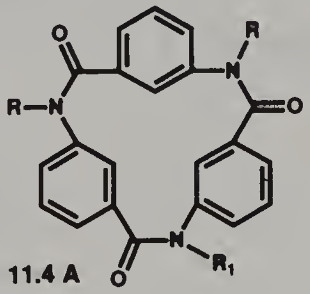
R_1	R_2	R_3	X	Other Substituents	Yield (%)	References
CH_3	CH_3	CH_3	H_2		38	Hoorfar et al., 1982a
$C_6H_5CH_2$-	$C_6H_5CH_2$-	$C_6H_5CH_2$-	D_2		94	Hoorfar et al., 1982a
H	H	H	O			Hoorfar et al., 1982a Imagawa et al., 1987
CH_3	H	H	O			Hoorfar et al., 1982a
CH_3	CH_3	H	O			Hoorfar et al., 1982a Ollis et al., 1974
CH_3	CD_3	H	O		72	Hoorfar et al., 1982a

TABLE 11.3. (*Continued*)

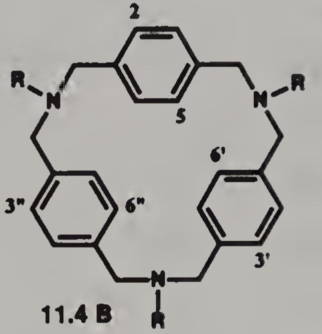
R_1	R_2	R_3	X	Other Substituents	Yield (%)	References
CH_3	CH_3	H	O	5,5',5''-$(CH_3)_3$	19	Edge et al., 1981, 1982
CH_3	C_2H_5	H	O		67	Hoorfar et al., 1982a
CH_3	$C_6H_5CH_2$-	H	O			Hoorfar et al., 1982a
CH_3	$C_6H_5CH_2$-	H	O	5,5',5''-$(CH_3)_3$		Edge et al., 1982
$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	O		50	Hoorfar et al., 1982a
$C_6H_5CH_2$-	$C_6H_5CH_2$-	H	O	5,5',5''-$(CH_3)_3$		Edge et al., 1982
CH_3	CH_3	CH_3	O		76	Hoorfar et al., 1982a
					76	Ollis et al., 1974, 1975
CH_3	CH_3	CD_3	O		73	Hoorfar et al., 1982a
CH_3	CD_3	CD_3	O		68	Hoorfar et al., 1982a

CH_3	CH_3	CH_3	0	5,5',5''-$(CH_3)_3$		Edge et al., 1981, 1982
CH_3	CH_3	$C_6H_5CH_2$-	0		81	Hoorfar et al., 1982a
CH_3	CD_3	$C_6H_5CH_2$-	0		76	Hoorfar et al., 1982a
CH_3	CH_3	$C_6H_5CH_2$-	0	5,5',5''-$(CH_3)_3$		Edge et al., 1981, 1982
CH_3	CH_3	$CH_3C(O)$-	0		49	Hoorfar et al., 1982a
CH_3	CH_3	$C_6H_5C(O)$-	0		38	Hoorfar et al., 1982a
CH_3	C_2H_5	$C_6H_5CH_2$-	0		63	Hoorfar et al., 1982a
CH_3	$C_6H_5CH_2$-	C_2H_5	0		65	Hoorfar et al., 1982a
$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3	0			Hoorfar et al., 1982a
$C_6H_5CH_2$-	$C_6H_5CH_2$-	CH_3	0	5,5',5''-$(CH_3)_3$		Edge et al., 1982
$C_6H_5CH_2$-	$C_6H_5CH_2$-	$C_6H_5CH_2$-	0			Hoorfar et al., 1982a
					50	Ollis et al., 1976
$C_6H_5CH_2$-	$C_6H_5CH_2$-	$C_6H_5CH_2$-	0	5,5',5''-$(CH_3)_3$		Edge et al., 1982

TABLE 11.4. MISCELLANEOUS TRIBENZOPERAZA-CROWN-3 CYCLOPHANES



11.4 A

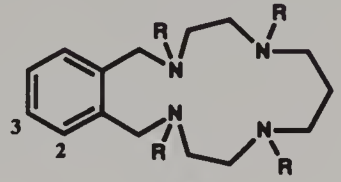


11.4 B

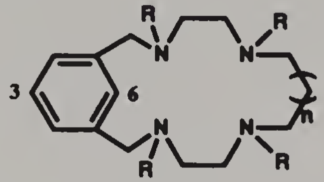
Structure	R	R_1	Other Substituents	Yield (%)	References
11.4 A	CH_3	H		26	Elhadi et al., 1980, 1982
	CH_3	CH_3		72	Elhadi et al., 1980, 1982

	CH_3	$C_6H_5CH_2$-		65	Elhadi et al., 1980, 1982
11.4 B	H			99	Takemura et al., 1984
	NO				Takemura et al., 1984
	CH_3			60	Takemura et al., 1984
	Ts			20	Bottino et al., 1988
				23	Takemura et al., 1984
	Ts		2,5,3',6',3'',6''-$(CH_3)_6$	12	Bottino et al., 1988
	$(C_{14}H_{29})_2NC(O)$-2,3-$(CH_3O)_2C_6H_2C(O)$-				Hisaeda et al., 1990
	$(C_{14}H_{29})_2NCH_2$-2,3-$(HO)_2C_6H_2CH_2$-				Hisaeda et al., 1990

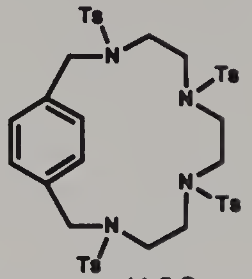
TABLE 11.5. BENZOPERAZA-CROWN-4 CYCLOPHANES



11.5 A



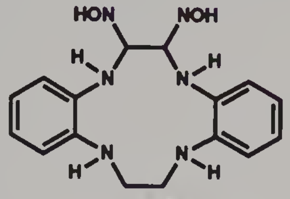
11.5 B



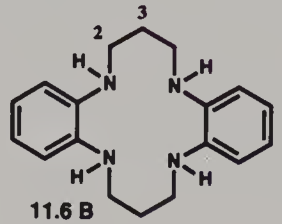
11.5 C

Structure	R	n	Other Substituents	Yield (%)	References
11.5 A	H		3-NO_2		Parker and Millican, 1987
	H		3-NH_2		Parker and Millican, 1987
	Ts		3-NO_2		Parker and Millican, 1987
11.5 B	CH_3	0	3-CH_3;6-OH		Wu, 1988
	H	1	3-Br;6-OH		Kimura et al., 1987 Kimura, 1989a
	Ts	1	6-OCH_3		Kimura et al., 1987
	Ts	1	3-Br;6-OCH_3		Kimura, 1989a
11.5 C				96	Iwata and Kuzuhara, 1986, 1988

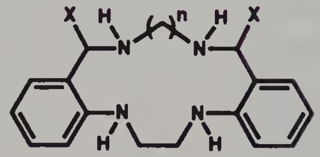
TABLE 11.6. DIBENZOPERAZA-CROWN-4 CYCLOPHANES



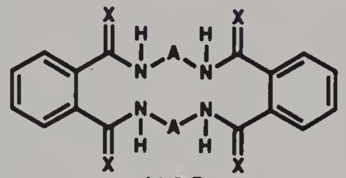
11.6 A



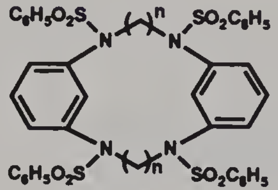
11.6 B



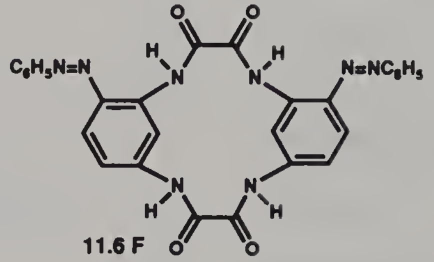
11.6 C



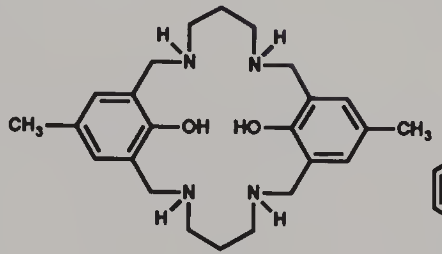
11.6 D



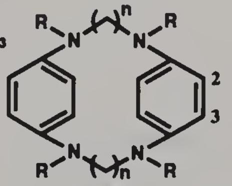
11.6 E



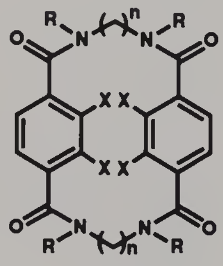
11.6 F



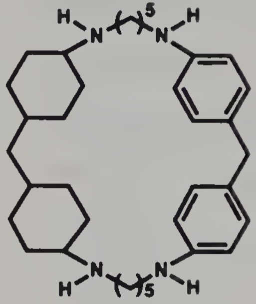
11.6 G



11.6 H



11.6 I



11.6 J

TABLE 11.6. (*Continued*)

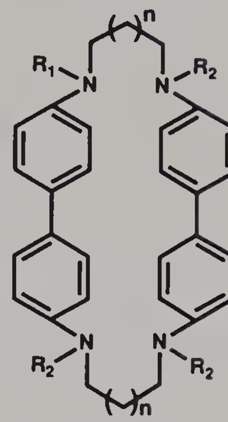
Structure	X	A	R	n	Other Substituents	Yield (%)	References
11.6 A							Bank et al., 1984
						52	Bank and Bekaroglu, 1983
11.6 B							Hiller et al., 1968
					3-CH_3		Adam et al., 1990b
					2,2,3,4,4,9,9,10,11,11-$(CH_3)_{10}$; 3,10-$(C_2H_5)_2$		Hashimoto et al., 1990
11.6 C	H			2			Bergman and Brynolf, 1989
	C_2H_5			2		89	Henrick et al., 1983
	C_2H_5			3		94	Henrick et al., 1983
							Adam et al., 1990b
	C_3H_7			3			Adam et al., 1990b
	C_4H_9			3			Adam et al., 1990b
	C_2H_5			4		87	Henrick et al., 1983
	C_2H_5			5		92	Henrick et al., 1983

11.6 D	H_2	CS				75	Dietrich et al., 1978
	O	$(CH_2)_3$					Gaozza et al., 1972
11.6 E				1			Hinsberg and Kessler, 1905
				2			
				3			
11.6 F							Crippa and Galimberti, 1932
11.6 G						61	Mandal et al., 1987
11.6 H			$C_6H_5OC(O)$-	3			Hinsberg and Kessler, 1905
			H	5			Schneider and Philippi, 1984
						90	Stetter and Roos, 1954
			H	5	2-I		Schneider and Philippi, 1984
			Ts	5		40	Stetter and Roos, 1954
			Ts	5	2-I		Stetter and Roos, 1954

TABLE 11.6. (*Continued*)

Structure	X	A	R	n	Other Substituents	Yield (%)	References
11.6 I	OH		H	4		80	Rodgers et al., 1985
	OH		H	6		80	Rodgers et al., 1985
	OCH_3		H	4		3	Rodgers et al., 1985
	OCH_3		H	6		24	Rodgers et al., 1985
	H		$C_6H_5CH_2$-	2			Vögtle and Muller, 1982b
11.6 J							Odashima, 1988
							Soga et al., 1980

TABLE 11.7. TETRABENZOPERAZA-CROWN-4 CYCLOPHANES (BIS-BIPHENYL)



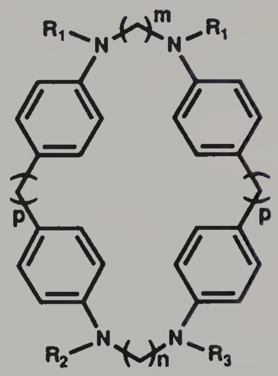
R_1	R_2	n	Yield (%)	References
H	H	0	92	Stetter and Roos, 1955
H	H	1	93	Stetter and Roos, 1955
H	H	2	90	Stetter and Roos, 1955
H	H	6		Schneider and Philippi, 1984

TABLE 11.7. *(Continued)*

R_1	R_2	n		Yield (%)	References
H	H	5		14,34	Witting et al., 1966
H	H	6		2,11	Witting et al., 1966
H	H	7		8	Witting et al., 1966
H	H	8		4	Witting et al., 1966
H	H	14		26	Witting et al., 1966
NO	NO	5		40	Witting et al., 1966
CH_3	CH_3	6			Schneider and Philippi, 1984
$(CH_3)_2$	$(CH_3)_2$	6	as salt		Schneider and Philippi, 1984
$4\text{-}IC_6H_4C(O)\text{-}$	$4\text{-}IC_6H_4C(O)\text{-}$	6			Schneider and Philippi, 1984

Ts	Ts	0		15	Stetter and Roos, 1955
Ts	Ts	1		20	Stetter and Roos, 1955
Ts	Ts	3		24	Stetter and Roos, 1955
Ts	Ts	6			Schneider and Philippi, 1984
Ts	Ts	5		8	Witting et al., 1966
Ts	Ts	6		1	Witting et al., 1966
Ts	Ts	7		11	Witting et al., 1966
Ts	Ts	8		6	Witting et al., 1966
4-$IC_6H_4CH_2$-,CH_3	4-$IC_6H_4CH_2$-,CH_3	6	as salt		Schneider and Philippi, 1984
3-$IC_6H_4C(O)$-	H	6			Schneider and Philippi, 1984
4-$IC_6H_4CH_2$-	H	6			Schneider and Philippi, 1984
4-$IC_6H_4CH_2$-,CH_3	$(CH_3)_2$	6	as salt		Schneider and Philippi, 1984

TABLE 11.8. TETRABENZOPERAZA-CROWN-4 CYCLOPHANES (TETRAKIS-*p*-PHENYLENYL)



R_1	R_2	R_3	m	n	p	Yield (%)	References
H	H	H	3	3	1		Soga et al., 1980
H	H	H	4	4	1		Koga and Odashima, 1989
							Odashima, 1988
						67	Odashima et al., 1980, 1985
						69	Takahashi et al., 1984
H	H	H	5	3	1		Odashima, 1988
							Soga et al., 1980
H	H	H	5	4	1		Odashima, 1988
							Soga et al., 1980

H	H	H	5	5	1		Odashima, 1988
							Soga et al., 1980
H	H	H	5	8	1		Odashima, 1988
							Soga et al., 1980
H	H	H	6	5	1		Odashima, 1988
							Soga et al., 1980
H	H	H	6	6	1		Odashima, 1988
							Schneider and Junker, 1986
H	H	H	6	6	2		Schneider and Junker, 1986
							Schneider and Junker, 1986
H	H	H	7	7	1		Odashima, 1988
H	H	H	8	8	1		Kumar and Schneider, 1989
							Odashima, 1988
							Okuno et al., 1987
							Uoto et al., 1990a
H	H	H	10	10	1		Schneider and Busch, 1986
CH_3	CH_3	CH_3	5	5	1		Winkler et al., 1983
$(CH_3)_2$	$(CH_3)_2$	$(CH_3)_2$	4	4	1	as salt	Lai et al., 1985
						as salt	Odashima, 1988
							Winkler et al., 1983

TABLE 11.8. *(Continued)*

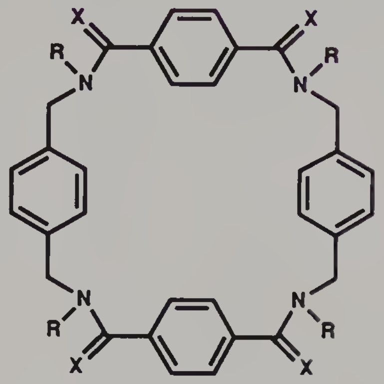
R_1	R_2	R_3	m	n	p		Yield (%)	References
$(CH_3)_2$	$(CH_3)_2$	$(CH_3)_2$	5	5	1	as salt		Odashima, 1988
								Winkler et al., 1983
$(CH_3)_2$	$(CH_3)_2$	$(CH_3)_2$	6	6	1	as salt		Odashima, 1988
$(CH_3)_2$	$(CH_3)_2$	$(CH_3)_2$	8	8	1	as salt		Kumar and Schneider, 1989
$F_3CC(O)$-	$F_3CC(O)$-	$F_3CC(O)$-	4	4	1			Lai et al., 1989
$NCCH_2$-	$NCCH_2$-	$NCCH_2$-	6	6	1			Schneider and Junker, 1986
$NCCH_2$-	$NCCH_2$-	$NCCH_2$-	6	6	2			Schneider and Junker, 1986
$CH_3C(O)$-	$CH_3C(O)$-	$CH_3C(O)$-	4	4	1		100,92	Odashima et al., 1980
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	4	4	1			Odashima, 1988
HO_2CCH_2-	HO_2CCH_2-	HO_2CCH_2-	6	6	1			Schneider and Junker, 1986
$H_2N(CH_2)_2$-	$H_2N(CH_2)_2$-	$H_2N(CH_2)_2$-	6	6	1			Schneider and Junker, 1986
$H_2N(CH_2)_2$-	$H_2N(CH_2)_2$	$H_2N(CH_2)_2$-	6	6	2			Schneider and Junker, 1986
$H_2NCH_2C(O)$-	$H_2NCH_2C(O)$-	$H_2NCH_2C(O)$-	4	4	1	as salt		Odashima, 1988
$HO_2C(CH_2)_2C(O)$-	$HO_2C(CH_2)_2C(O)$-	$HO_2C(CH_2)_2C(O)$-	4	4	1	as salt		Odashima, 1988
$CH_3O_2C(CH_2)_2(O)$-	$CH_3O_2C(CH_2)_2(O)$-	$CH_3O_2C(CH_2)_2(O)$-	4	4	1			Odashima and Koga, 1981

$HSC(CH_3)_2CH_2C(O)$-	$HSC(CH_3)_2CH_2C(O)$-	$HSC(CH_3)_2CH_2C(O)$-	8	8	1		Uoto et al., 1990b
3-$HO_3SC_6H_4SO_2$-	3-$HO_3SC_6H_4SO_2$-	3-$HO_3SC_6H_4SO_2$-	6	6	1		Schneider and Blatter, 1988
$(NCCH_2)_2N(CH_2)_2$-	$(NCCH_2)_2N(CH_2)_2$-	$(NCCH_2)_2N(CH_2)_2$-	6	6	1		Schneider and Junker, 1986
$H_2N(CH_2)_5C(O)$-	$H_2N(CH_2)_5C(O)$-	$H_2N(CH_2)_5C(O)$-	4	4	1		Odashima, 1988
4-$HSC_6H_4C(O)$-	4-$HSC_6H_4C(O)$-	4-$HSC_6H_4C(O)$-	8	8	1		Okuno et al., 1987
							Uoto et al,. 1990b
Ts	Ts	Ts	4	4	1		Odashima, 1988
						25,77	Odashima et al., 1980
Ts	Ts	Ts	5	5	1	74	Odashima, 1988
Ts	Ts	Ts	6	6	1	88	Odashima, 1988
Ts	Ts	Ts	6	6	2		Schneider and Busch, 1986
Ts	Ts	Ts	7	7	1	63	Odashima, 1988
Ts	Ts	Ts	8	8	1		Kumar and Schneider, 1989
						60	Odashima, 1988
							Uoto et al., 1990a
Ts	Ts	Ts	10	10	1		Schneider and Busch, 1986
$CH_3OC(S)C(CH_3)_2$ $CH_2C(O)$-	$CH_3OC(S)C(CH_3)_2$- $CH_2C(O)$-	$CH_3OC(S)C(CH_3)_2$- $CH_2C(O)$-	8	8	1		Uoto et al., 1990b
$HO_2C(CH_2)_5C(O)$-	$HO_2C(CH_2)_5C(O)$-	$HO_2C(CH_2)_5C(O)$-	4	4	1		Odashima, 1988

TABLE 11.8. *(Continued)*

R_1	R_2	R_3	m	n	p	Yield (%)	References
$4-HSCH_2C_6H_4C(O)-$	$4-HSCH_2C_6H_4C(O)-$	$4-HSCH_2C_6H_4C(O)-$	8	8	1		Uoto et al., 1990b
$2-HO_2CC_6H_4C(O)-$	$2-HO_2CC_6H_4C(O)-$	$2-HO_2CC_6H_4C(O)-$	6	6	1		Schneider and Blatter, 1988
$CH_3O_2C(CH_2)_5C(O)-$	$CH_3O_2C(CH_2)_5C(O)-$	$CH_3O_2C(CH_2)_5C(O)-$	4	4	1		Odashima and Koga, 1981
$(CH_3O_2CCH_2)_2N(CH_2)_2-$	$(CH_3O_2CCH_2)_2-N(CH_2)_2-$	$(CH_3O_2CCH_2)_2-N(CH_2)_2-$	6	6	1		Schneider and Junker, 1986
$4-CH_3OC(S)C_6H_4-C(O)-$	$4-CH_3OC(S)C_6H_4-C(O)-$	$4-CH_3OC(S)C_6H_4-C(O)-$	8	8	1		Uoto et al., 1990b
$4-CH_3OC(S)CH_2-C_6H_4C(O)-$	$4-CH_3OC(S)CH_2-C_6H_4C(O)-$	$4-CH_3OC(S)CH_2-C_6H_4C(O)-$	8	8	1		Uoto et al., 1990b
$C_6H_5CH_2O_2C-NH(CH_2)_2C(O)-$	$C_6H_5CH_2O_2C-NH(CH_2)_2C(O)-$	$C_6H_5CH_2O_2C-NH(CH_2)_2C(O)-$	4	4	1		Odashima and Koga, 1983
$C_6H_5CH_2O_2C-NH(CH_2)_2C(O)-$	$C_6H_5CH_2O_2C-NH(CH_2)_2C(O)-$	$C_6H_5CH_2O_2C-NH(CH_2)_2C(O)-$	4	4	1		Odashima and Koga, 1983
H	H	$CH_3C(O)-$	4	4	1		Lai et al., 1989
H	H	C_2H_5	4	4	1		Lai et al., 1989
$F_3CC(O)-$	$F_3CC(O)-$	H	4	4	1		Lai et al., 1989
$F_3CC(O)-$	$F_3CC(O)-$	$CH_3C(O)-$	4	4	1	as salt	Lai et al., 1989
$(CH_3)_2$	$(CH_3)_2$	$CH_3C(O)-$	4	4	1	as salt	Lai et al., 1985
HO_2CCH_2-	$HON{=}C(NH_2)CH_2-$	$HON{=}C(NH_2)CH_2-$	6	6	1	as salt	Schneider and Junker, 1986

TABLE 11.9. TETRABENZOPERAZA-CROWN-4 CYCLOPHANES (TETRAKIS-*p*-XYLYLENYL)



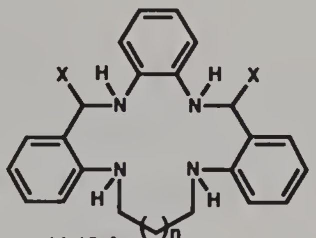
R	X	Yield (%)	References
H	H_2	100	Takemura et al., 1984
CH_3	H_2		Murakami et al., 1979
		17	Tabushi et al., 1981
		47	Takemura et al., 1984
		37	Urushigawa et al., 1971
$(CH_3)_2$	H_2 as salt		Murakami et al., 1979
			Tabushi et al., 1978

TABLE 11.9. (*Continued*)

R	X	Yield (%)	References
	as salt	40	Tabushi et al., 1981
HO_2CCH_2-	H_2	80	Lepropre and Fastrez, 1987
$HO(CH_2)_2$-	H_2	65	Lepropre and Fastrez, 1987
$HONHC(O)CH_2$-	H_2	70	Lepropre and Fastrez, 1987
$CH_3O_2CCH_2$-	H_2	18	Lepropre and Fastrez, 1987
Ts	H_2	12	Takemura et al., 1984
4-$HO_2CC_6H_4C(O)$-	H_2		Murakami et al., 1987
C_8H_{17}	H_2	33	Murakami et al., 1979
$(CH_3)_3COC(O)NHCH(CH_2CO_2H)C(O)$-	H_2		Murakami et al., 1990
$(CH_3)_3COC(O)NHCH(CH_2CO_2CH_2C_6H_5)C(O)$-	H_2		Murakami et al., 1990
$(C_{14}H_{29})_2NC(O)CH(NH_2)CH_2C(O)$-	H_2		Murakami et al., 1990
$(C_{14}H_{29})_2NC(O)CH_2CH(NH_2)C(O)$-	H_2		Murakami et al., 1990
$(CH_3)_3COC(O)NHCH[C(O)N(C_{14}H_{29})_2]CH_2C(O)$-	H_2		Murakami et al., 1990
$(CH_3)_3COC(O)NHCH[CH_2C(O)N(C_{14}H_{29})_2]C(O)$-	H_2		Murakami et al., 1990

$(CH_3)_3NCH_2C(O)NHCH[CH_2C(O)N(C_{14}H_{29})_2]C(O)$-	H_2		Murakami et al., 1990
$(CH_3)_3NCH_2C(O)NHCH[C(O)N(C_{14}H_{29})_2]CH_2C(O)$-	H_2		Murakami et al., 1989, 1990
CH_3	O		Tabushi et al., 1981
			Urushigawa et al., 1971
$ClC(O)(CH_2)_2$-	O		Murakami et al., 1984
$HO_2C(CH_2)_2$-	O		Murakami et al., 1984
$CH_3(CH_2)_7$-	O	29	Murakami et al., 1979
$HO_2C(CH_2)_{10}$-	O	80	Murakami et al., 1979
$CH_3O_2C(CH_2)_{10}$-	O	11	Murakami et al., 1979
$(CH_3)_2N(CH_2)_{10}$-		5-25	Murakami et al., 1981
$Cl^- \cdot (CH_3)_2HN^+(CH_2)_{10}$-	O	79	Murakami et al., 1981
$Br^- \cdot (CH_3)_3N^+(CH_2)_{10}$-	O	60	Murakami et al., 1981
$I^- \cdot (CH_3)_3N^+(CH_2)_{10}$-	O	82	Murakami et al., 1981
$Br^- \cdot (CH_2CH_2OH)(CH_3)_2N^+(CH_2)_{10}$-	O	54	Murakami et al., 1981
$Cl^- \cdot$4-$ClCH_2$-imidazolyl-5-$CH_2(CH_3)_2N^+(CH_2)_{10}$-	O	66	Murakami et al., 1981
$(C_{14}H_{29})_2NC(O)CH[(CH_2)_4NH_2]NHC(O)(CH_2)_2$-	O		Murakami et al., 1984

TABLE 11.10. MISCELLANEOUS TRI- AND TETRABENZOPERAZA-CROWN-4 CYCLOPHANES



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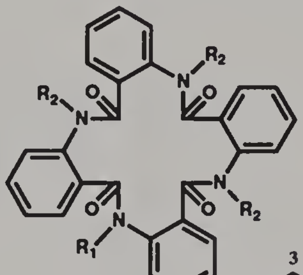

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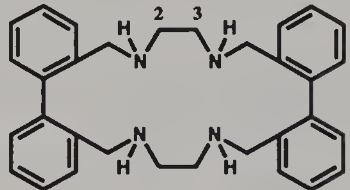

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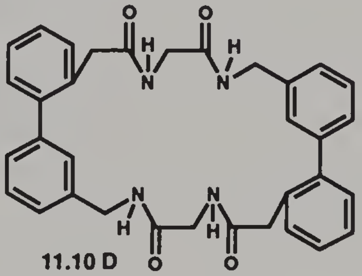

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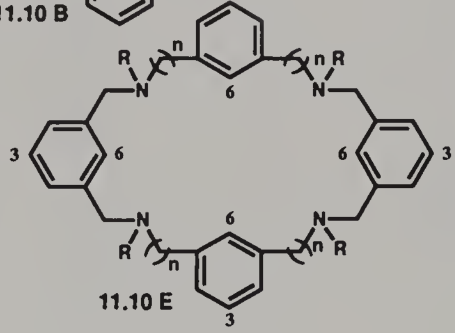

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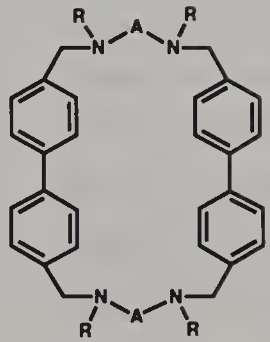
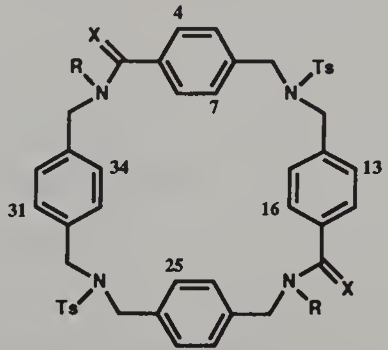
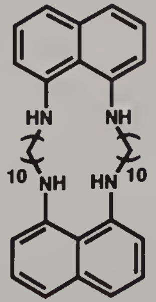


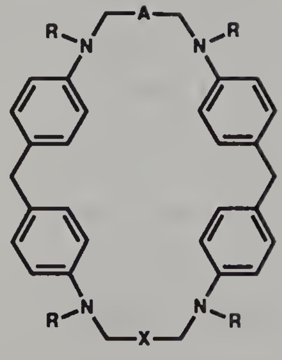
11.10 F



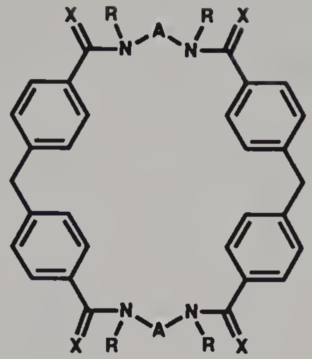
11.10 G



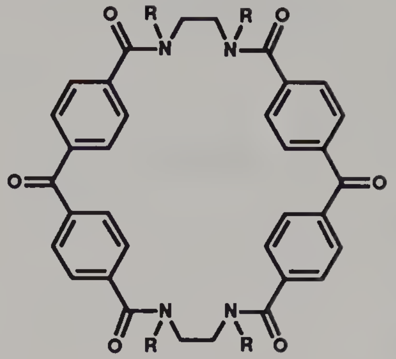
11.10 H



11.10 I



11.10 J



11.10 K

Structure	X	A	R or R_1	R_2	n	Other Substituents	Yield (%)	References
11.10 A	CH_3				0		74	Henrick et al., 1983
	C_2H_5				0		92	Henrick et al., 1983
	CH_3				1		78	Henrick et al., 1983
	C_2H_5				1		87	Henrick et al., 1983
	C_4H_9				1		74	Henrick et al., 1983
11.10 B			H	CH_3				Hoorfar et al., 1980
			CH_3	CH_3				Hoorfar et al., 1980

TABLE 11.10. (*Continued*)

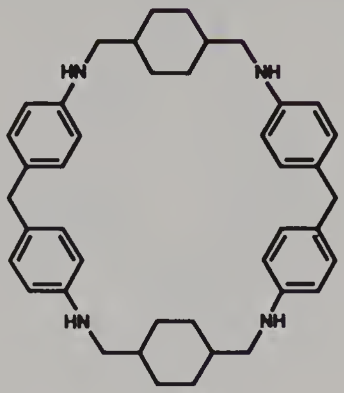
Structure	X	A	R or R_1	R_2	n	Other Substituents	Yield (%)	References
			H	$C_6H_5CH_2$-				Hoorfar et al., 1980
			$C_6H_5CH_2$-	CH_3				Hoorfar et al., 1980
			$C_6H_5CH_2$-	$C_6H_5CH_2$-				Hoorfar et al., 1980
11.10 C						5,10,15,20-$(O)_4$	93	Nagao et al., 1981
						2,12-$(O)_2$; 3,13-i-C_3H_7		Brandmeier et al., 1989
11.10 D								Brandmeier & Feigel, 1989
11.10 E			Ts		0		5	Vögtle and Neumann, 1970
			H		1	3-CH_3;6-OH		Grannas et al., 1990
11.10 F		CH_2	$C_6H_5CH_2$-					Vögtle & Muller, 1982a,1982b
		C=S	H					Strakosch, 1872

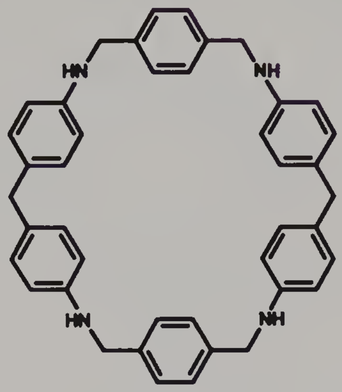
11.10 G	H_2		Ts	4,7,13,16,22-25,31,34-$(CH_3)_8$	12	Bottino et al., 1988
	H_2		H		100	Hamilton and Kazanjian, 1985
	O		H		60	Hamilton and Kazanjian, 1985
11.10 H						Yamamoto and Maruoka, 1981
11.10 I	$-[CH(OCH_3)]_2-$	$-[CH(OCH_3)]_2-$	H			Takahashi et al., 1984
	$-[CH(OCH_3)]_2-$	$-[CH(OCH_3)]_2-$	$(CH_3)_2$			Odashima, 1988
	$-[CH(OCH_3)]_2-$	$-[CH(OCH_3)]_2-$	Ts		24	Takahashi et al., 1984
	$-[CH(OCH_2CH_2OCH_3)]_2-$	$-[CH(OCH_2CH_2-OCH_3)]_2-$	H			Odashima, 1988
	$-CH_2[CH(OCH_3)]_2CH_2-$	$-CH_2[CH(OCH_3)]_2-CH_2-$	$(CH_3)_2$			Odashima, 1988
	$-CH_2CH(OH)CH_2-$	$-(CH_2)_5-$	H			Breslow et al., 1986
	$-CH_2CH(OH)CH_2-$	$-(CH_2)_5-$	CH_3			Breslow et al., 1986
	$-CH_2CH(OH)CH_2-$	$-(CH_2)_5-$	Ts		26	Breslow et al., 1986
	$-CH_2CH[SC(O)CH_3]CH_2-$	$-(CH_2)_3-$	$(CH_3)_2$			Winkler et al., 1983
	$-C_6H_5-$	$-C_6H_5-$	H			Odashima, 1988
	-(hexanediyl)-	-(hexandiyl)-	H			Odashima, 1988
	$-CH_2CH[SCH_2-2-CH_3-3-HO-4-CH_2NH_2-$pyridyl-5)]$CH_2-$	$-(CH_2)_5-$	$(CH_3)_2$			Breslow et al., 1986
						Winkler et al., 1983

TABLE 11.10. *(Continued)*

Structure	X	A	R or R_1	R_2	n	Other Substituents	Yield (%)	References
11.10 J	H_2	$-(CH_2)_2-$	H				60	Jazwinski et al., 1987
	H_2	$-[CH(CO_2CH_3)]_2-$	H				60	Jazwinski et al., 1987
	H_2	$-(CH_2)_3-$	C_2H_5					Vögtle et al., 1985
	H_2	$-(CH_2)_4-$	C_2H_5					Vögtle et al., 1985
	O	$-(CH_2)_3-$	C_2H_5					Vögtle et al., 1985
	O	$-(CH_2)_4-$	C_2H_5					Vögtle et al., 1985
	O	$-(CH_2)_3-$	3-pyridyl-CH_2-					Vögtle et al., 1985
11.10 K			CH_3					Vögtle et al., 1985
			$C_6H_5CH_2$-					Vögtle et al., 1985
			3-pyridyl-CH_2-					Vögtle et al., 1985

TABLE 11.11. MISCELLANEOUS TETRAAZA-CROWN-4 CYCLOPHANES CONTAINING BENZO, CYCLOHEXANO, OR NAPHTHALENO GROUPS


11.11 A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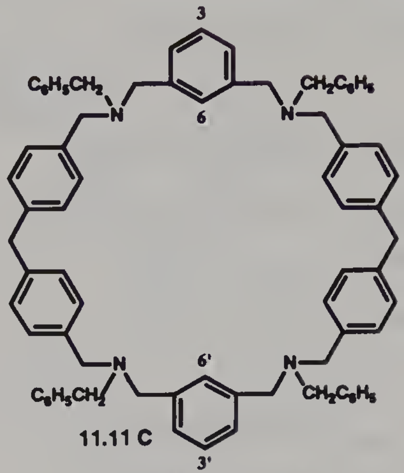

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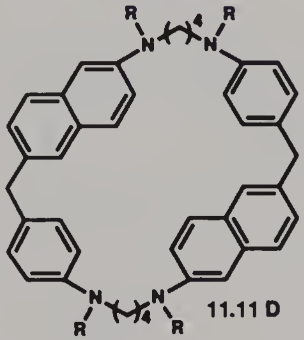
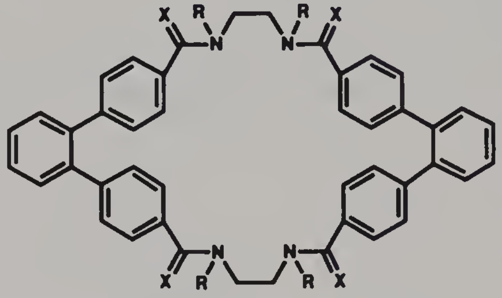
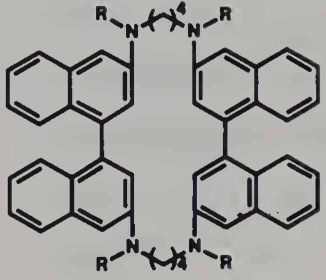


11.11 D



11.11 E



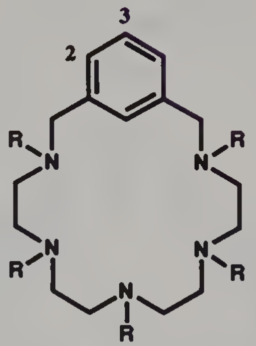
11.11 F

Structure	R	Other Substituents	Yield (%)	References
11.11 A				Soga et al., 1980
11.11 B				Soga et al., 1980

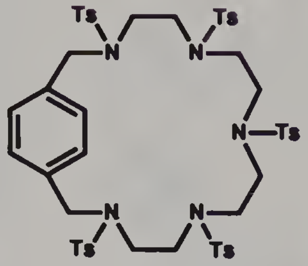
TABLE 11.11. (*Continued*)

Structure	X	R	n	Other Substituents	Yield (%)	References
11.11 C				6,6'-$(NO_2)_2$	10	Werner et al., 1986
				3,3'-$(NO_2)_2$	17	Werner et al., 1986
				3,3'-$(NH_2)_2$	91	Werner et al., 1986
				6,6'-$(NH_2)_2$	70	Werner et al., 1986
11.11 D		H				Kawakami et al., 1985
						Koga and Odashima, 1989
		$(CH_3)_2$		as salt		Kawakami et al., 1985
						Koga and Odashima, 1989
		Ts				Kawakami et al., 1985
11.11 E	H_2	CH_3				Vögtle and Müller, 1982a, 1982b
	H_2	$C_6H_5CH_2$-				Vögtle and Müller, 1982a, 1982b
	O	CH_3				Vögtle and Müller, 1982a, 1982b
	O	$C_6H_5CH_2$-				Vögtle and Müller, 1982a, 1982b
11.11 F		H			65	Faust and Pallas, 1960
		Ts			36	Faust and Pallas, 1960

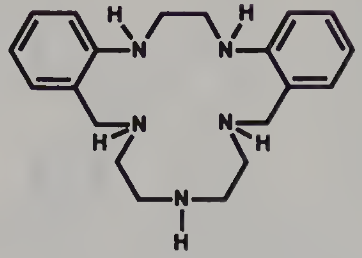
TABLE 11.12. BENZOPERAZA-CROWN-5 CYCLOPHANES



11.12 A

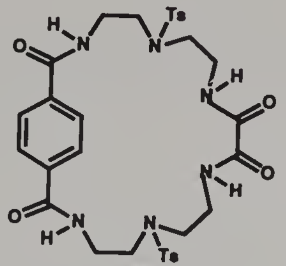


11.12 B

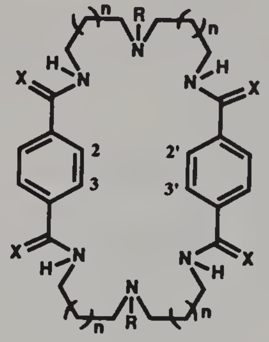


11.12 C

Structure	R	Other	Yield (%)	References
11.12 A	H	3-Br;6-OH		Kimura, 1989b
				Kimura et al., 1987
	H	3-Br;6-OH		Wu, 1988
	Ts	6-OCH_3		Kimura et al., 1987
	Ts	3-Br;6-OH_3		Kimura, 1989b
	Ts	6-CO_2CH_3	70	Kimura et al., 1990
11.12 B			72	Iwata and Kuzuhara, 1986, 1988
11.12 C				Adam et al., 1987



11.13 A



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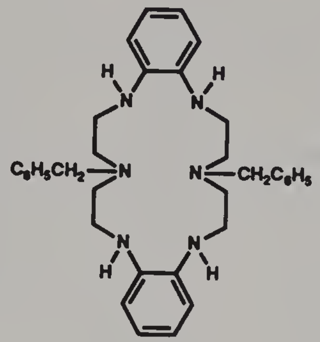

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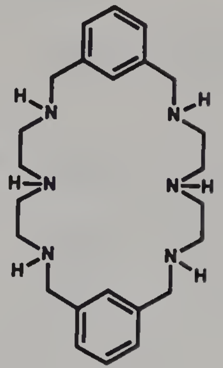

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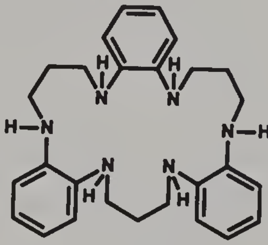

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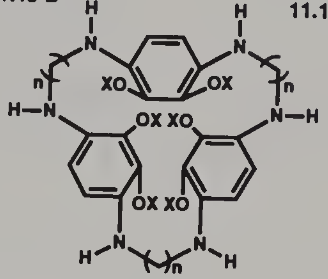
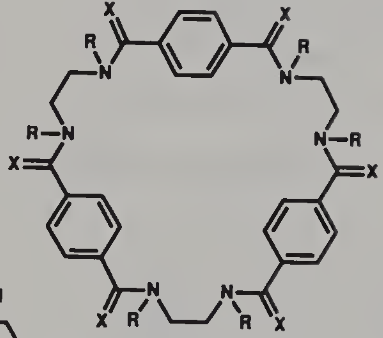
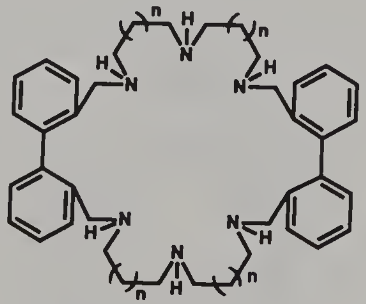


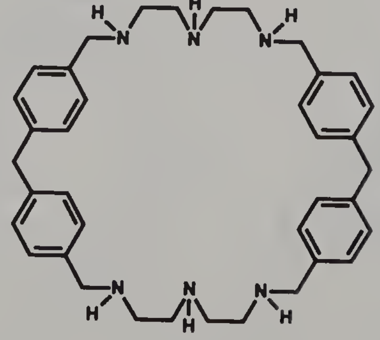
11.13 F



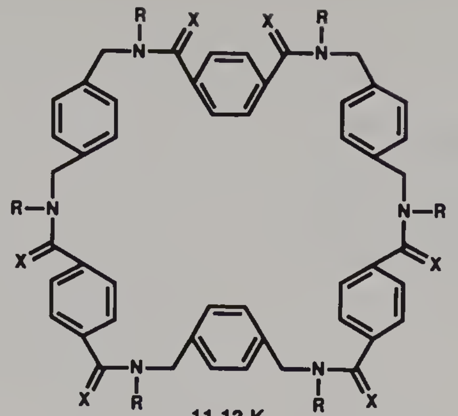
11.13 G



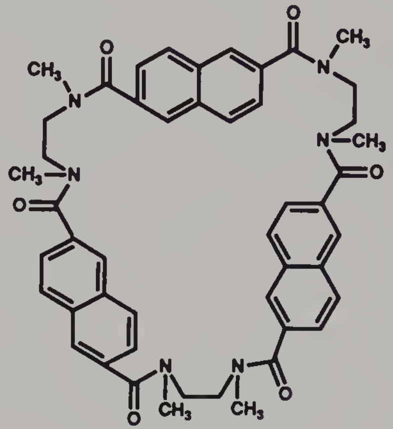
11.13 H



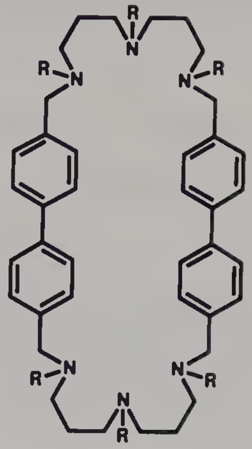
11.13 I



11.13 K



11.13 L



11.13 J

Structure	R	X	n	Other Substituents	Yield (%)	References
11.13 A					4	Sun et al., 1986
11.13 B	H	H_2	0			Krassig and Greber, 1955
	H	O	0	2,2',3,3'-$(OH)_4$	45	Sun et al., 1986
	HO_2CCH_2-	O	0	2,2',3,3'-$(OH)_4$	42	Sun et al., 1986
	Ts	O	0	2,2',3,3'-$(OCH_3)_4$	14	Sun et al., 1986

TABLE 11.13. (*Continued*)

Structure	R	X	n	Other Substituents		Yield (%)	References
	2,3-HO-4- $C_4H_9NHC(O)$- $C_6H_2C(O)NH(CH_2)_2$-	O	0	2,2',3,3'-$(OH)_4$	as complex		McMurry et al., 1987
	H	H_2	1				Pietraszkiewicz and Gasiorowski, 1990
	CH_3	H_2	1				Pietraszkiewicz and Gasiorowski, 1990
	H	O	1	2,2',3,3'-$(OH)_4$		77	Sun et al., 1986
	HO_2CCH_2-	O	1	2,2',3,3'-$(OH)_4$		78	Sun et al., 1986
	Ts	O	1	2,2',3,3'-$(OCH_3)_4$		30	Sun et al., 1986
11.13 C							Pedersen and Bromels, 1977

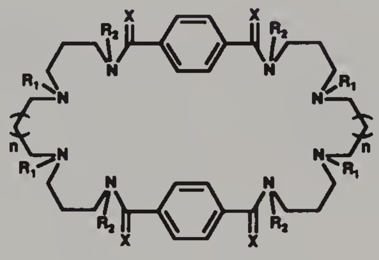
11.13 D				as salt		Menif and Martell, 1989
						Menif et al., 1990
11.13 E				as complex	67,25	Grant and Royer, 1981
11.13 F		H	2		80	Rodgers et al., 1985
		H	4		80	Rodgers et al., 1985
		H	6		80	Rodgers et al., 1985
		CH_3	2		17	Rodgers et al., 1985
		CH_3	4		10	Rodgers et al., 1985
		CH_3	6		9	Rodgers et al., 1985
11.13 G	$C_6H_5CH_2$-	H_2				Vögtle and Müller, 1982a, 1982b

TABLE 11.13. *(Continued)*

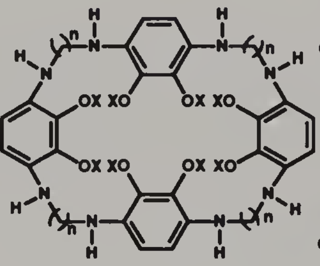
Structure	R	X	n	Other Substituents	Yield (%)	References
	CH_3	O				Vögtle and Müller, 1984
	2-pyridinyl-CH_2-	O				Vögtle and Müller, 1984
	3-pyridinyl-CH_2-	O				Vögtle and Müller, 1984
	4-pyridinyl-CH_2-	O				Vögtle and Müller, 1984
	$C_6H_5CH_2$-	O				Vögtle et al., 1982
						Vögtle and Müller, 1982a, 1982b
11.13 H			1 or 2		12	Nagao et al., 1981

11.13 I				20	Jazwinski et al., 1987
11.13 J	H			96	Pratt et al., 1988
	$F_3CC(O)$-			5	Pratt et al., 1988
11.13 K	CH_3	H_2			Murakami et al., 1979
	$(CH_3)_2$	H_2	as salt	91	Murakami et al., 1979
	$HO(CH_2)_2$-	H_2		65	Lepropre and Fastrez, 1987
	$CH_3O_2CCH_2$-	H_2		13	Lepropre and Fastrez, 1987
	CH_3	O			Murakami et al., 1979
11.13 L					Vögtle et al., 1985

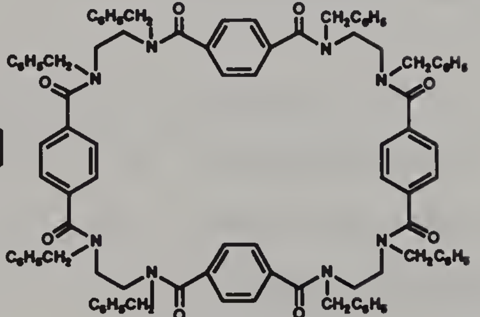
TABLE 11.14. BENZOPERAZA-CROWN-8 CYCLOPHANES



11.14 A



11.14 B

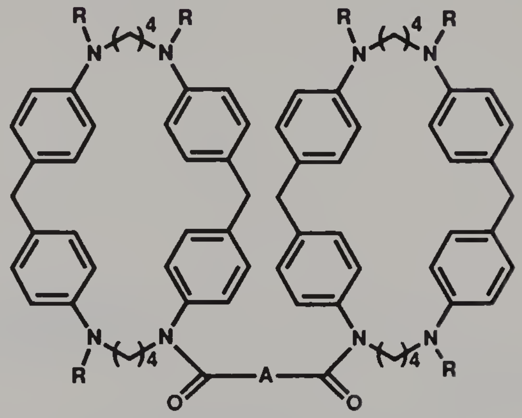


11.14 C

Structures	X	R_1	R_2	n	Yield (%)	References
11.14 A	H_2	H	H	0		Pietraszkiewicz and Gasiorowski, 1990
	H_2	CH_3	CH_3	0		Pietraszkiewicz and Gasiorowski, 1990

	H_2	H	H	1	21	Pratt et al., 1988
	O	Ts	H	1	26	Pratt et al., 1988
11.14 B	H			2	80	Rodgers et al., 1985
	H			4	80	Rodgers et al., 1985
	H			6	80	Rodgers et al., 1985
	CH_3			2	8	Rodgers et al., 1985
	CH_3			4	4	Rodgers et al., 1985
	CH_3			6	2	Rodgers et al., 1985
11.14 C						Vögtle et al., 1982

TABLE 11.15. BIS(BENZOPERAZA-CROWN) CYCLOPHANES



A	R		References
$(CH_2)_3$	H		Lai et al., 1989
$(CH_2)_3$	$(CH_3)_2$	as salt	Lai et al., 1985, 1989
$(CH_2)_3$	$F_3CC(O)$-		Lai et al., 1989
1,3-C_6H_4	H		Lai et al., 1989
1,3-C_6H_4	$(CH_3)_2$	as salt	Lai et al., 1985, 1989
1,3-C_6H_4	$F_3CC(O)$-		Lai et al., 1989
1,4-C_6H_4	H		Lai et al., 1989
1,4-C_6H_4	$(CH_3)_2$	as salt	Lai et al., 1985, 1989
		as salt	Odashima, 1988
1,4-C_6H_4	$F_3CC(O)$-		Lai et al., 1989

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Vögtle, F. and W. M. Müller (1982b) *Angew Chem. Suppl.*, 185.

Vögtle, F. and W. M. Müller (1984) *Angew Chem. Int. Ed. Eng.*, **23**, 712.

Vögtle, F., H. Puff, E. Friedrichs, and W. M. Müller (1982) *J. Chem. Soc., Chem. Commun.*, 1398.

Vögtle, F., W. M. Müller, U. Werner, and J. Franke (1985) *Naturwissenschaften*, **72**, 155.

Werner, U., W. M. Müller, H. W. Losensky, T. Merz, and F. Vögtle (1986) *J. Incl. Phenom.*, **4**, 379.

Winkler, J., E. C. Argyropoulou, R. Leppkes, and R. Breslow (1983) *J. Am. Chem. Soc.*, **105**, 7198.

Witting, G., P. Börzel, F. Neumann, and G. Klar (1966) *Liebigs Ann. Chem.*, 109.

Wu, C., G. Xue, C. Niu, Z. Ji, and W. Xiao (1988) *Abstr. 13th Int. Symp. Macrocyclic Chem.*, Hamburg, **1988**, p. 138.

Yamamoto, H. and K. Maruoka (1981) *J. Am. Chem. Soc.*, **103**, 4186.

CHAPTER XII

Aza- and Peraza-crown Macrocycles as Part of Macromolecular Compounds

A. INTRODUCTION

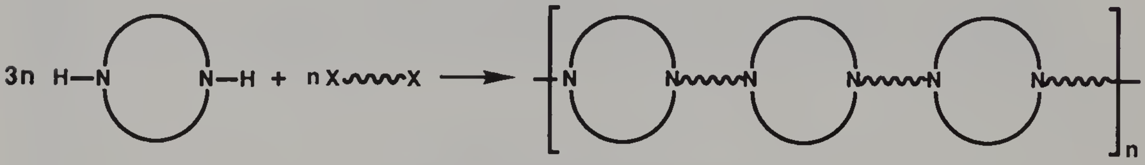
This chapter presents a brief review of aza- and peraza-crowns as part of macromolecular materials. This book concerns the preparation of macrocyclic ligands, so the synthesis of macromolecules is mentioned only briefly in this chapter. The chapter is divided into two sections. The first section reviews polymers containing aza-crown macrocycles and the second, a more recent development, antibodies containing aza- and peraza-crown macrocycles.

B. POLYMERS CONTAINING AZA- OR PERAZA-CROWN MACROCYCLES

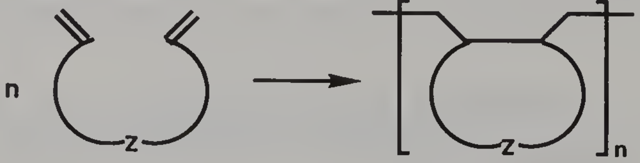
A number of polymer systems containing macrocyclic ligands, such as the crown ethers, have been prepared. This subject has been reviewed a number of times (Blasius and Janzen, 1982; Gramain, 1982; Sahni and Reedijk, 1984; Smid, 1976, 1981a, 1981b; Smid et al., 1979; Takagi and Nakamura, 1986; Yokota, 1989). These reviews report on crown ethers or cryptands attached to solid supports or as part of a polymer system. There have been no separate reviews of polymers containing only aza- or peraza-crown macrocycles.

The lack of selectivity of conventional ion-exchange resins has prompted research into the development of new classes of specific and selective exchange resins and molecular recognition polymers. Crown ethers attached to or part of a polymer have shown high selectivity and, in some cases, high capacity for certain metal ions. The size of the macroring as well as the number and nature of the heteroatoms are important variables of the crown ethers used in these polymer systems. The type of group used to attach the macrocycle to a polymer backbone is also an important consideration (Gramain and Frere, 1980). The crown ether–polymer systems allow the separation of metal ions, anions, neutral organic molecules, organic cations, or optically active materials from solutions containing mixtures of these species. The polymer systems also can be used as heterogeneous or homogeneous catalysts.

Macrocycles can be part of the polymer backbone or attached to the backbone on a side chain. The methods of preparation of these two types of systems are different. Polymers with macrocycles as part of the backbone were prepared by polymerization of macrocycles containing special functional groups or, more often, by copolymerization of di-functionalized macrocycles with other di-functionalized molecules. The preparation of a diaza-crown-containing polymer is an example of this latter process (Yokota et al., 1986).



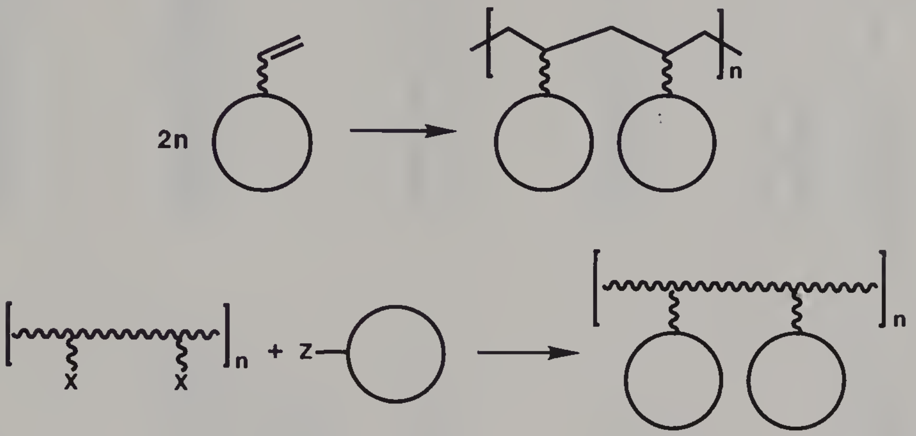
Some polymers containing macrocycles in the backbone have been prepared by a cyclopolymerization process. This is a new method for preparing polymers with macrocycles containing oxygen and sulfur atoms in the backbone. An open chain α,ω-diene containing the heteroatoms in the chain was polymerized as shown below (Yokota, 1989). This process has not been used



Z contains heteroatom(s)

to prepare polymers containing aza- or peraza-crowns, but this should be possible using a suitable di-functionalized amine-containing compound.

Polymers containing macrocyclic ligands on side arms can be prepared by polymerizing the macrocycle containing a functional group, such as an alkene, or by attaching the macrocycle to a specially prepared polymer backbone. Both of these processes are shown below. In the first case, the macrocycle is attached to a repeating unit of the polymer chain. In the second case, the macrocycle is randomly attached to the polymer. The number of macrocycles attached in the second case can be estimated from the amount of metal ions removed from solutions when the polymer is used.



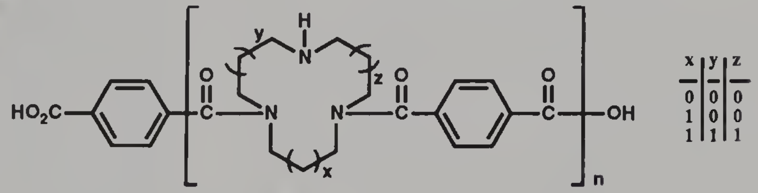
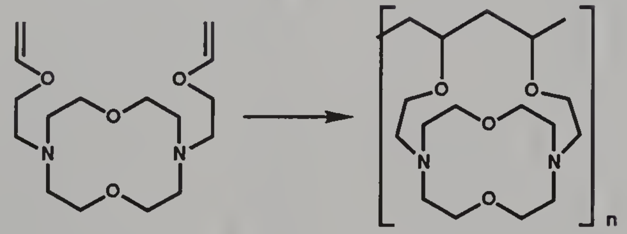
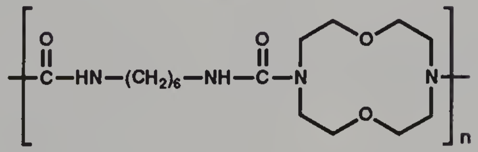
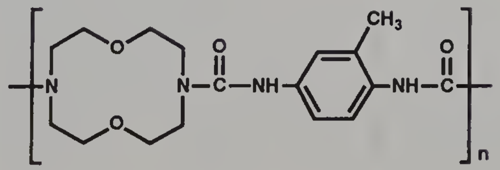
The solid support material can be synthetic organic polymers as mentioned above, natural polymers, such as cellulose, or inorganic materials, such as silica gel or alumina. Macrocycles have been bonded to these supports by chemical reactions involving attached functions such as alcohols, amines, halogens, epoxy groups, and allyloxy groups (Kahovec and Svec, 1981). For example, macrocycles have been attached to silica gel by amide linkages (Dudler et al., 1987) and by covalent carbon-silane bonds through a hydrosilylation process (Bradshaw et al., 1988a). Many types of compounds have been immobilized on agarose or cellulose for affinity chromatography (Carlsson et al., 1989; Dean et al., 1985). It should be possible to attach macrocyclic ligands to these supports.

The methods used to prepare solid supported macrocyclic ligands are not difficult. These materials have been used to remove cations from water and other solvents. This is an exciting new area of research that can lead to important new methods to remove, concentrate, and recover toxic heavy metals and the precious metals from industrial waste streams (Blain et al., 1990, 1991; Bradshaw et al., 1988a, 1989a, 1989b; Izatt et al., 1988; 1990; Porath, 1991).

Tables 12.1, 12.2, and 12.3 contain a listing of aza- and peraza-crown macrocycles as part of or attached to synthetic polymers or other solid supports. The tables are organized by ring size.

C. TABLES OF POLYMERS CONTAINING AZA- OR PERAZA-CROWN MACROCYCLES OR AZA-CROWN MACROCYCLES ATTACHED TO SOLID SUPPORTS

TABLE 12.1. POLYMERS CONTAINING AZA- OR PERAZA-CROWN ETHERS IN THE POLYMER BACKBONE

Structure of Polymer or Reaction to Produce Polymer	Remarks	Reference
		Fujiwara et al., 1990
		Yokota et al., 1986
		Cowie and Wu, 1988b
		Cowie and Wu, 1988b

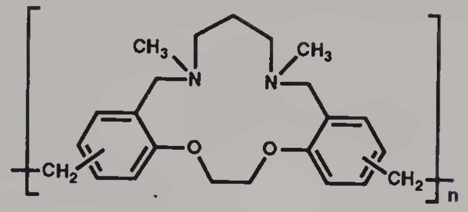
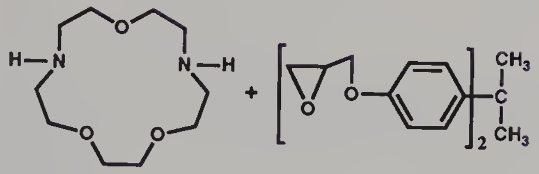
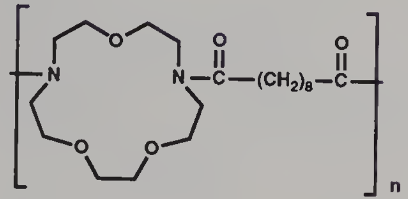
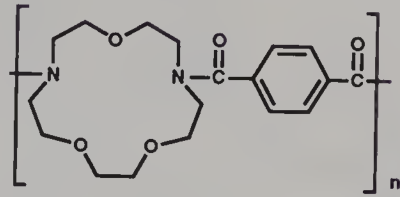
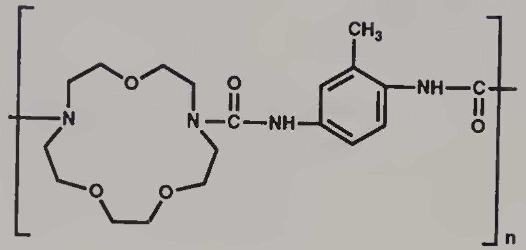
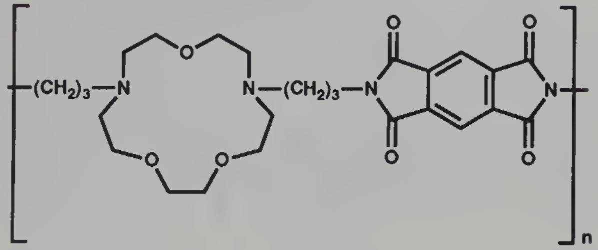
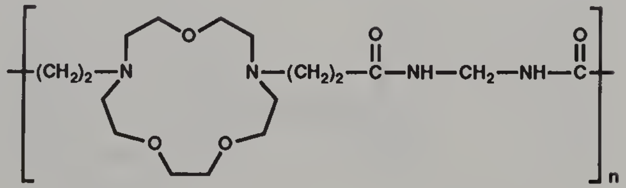
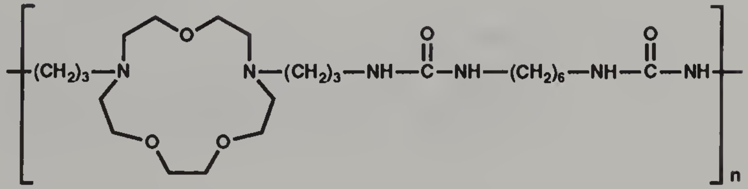
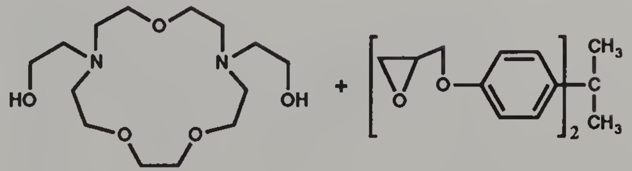
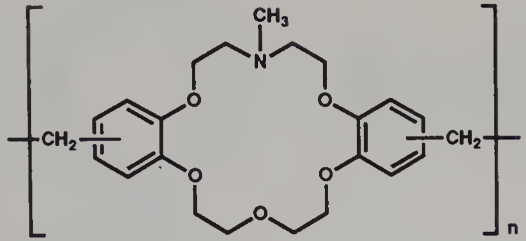
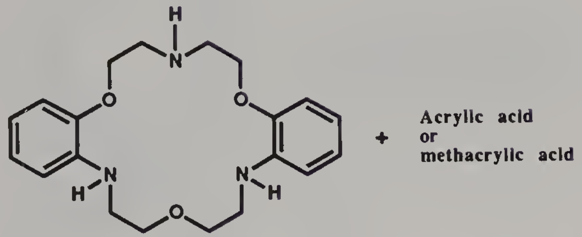
		Blasius et al., 1980
	Resins were cured by using 3,9-bis (3-aminopropyl) -2,4,8,10-tetraoxaspiro [5.5]undecane	Kakiuchi and Okamoto, 1982; Bormann et al., 1975
	Used to extract alkali metals	Bormann et al., 1975
	Used to extract alkali metals	Bormann et al., 1975
	Used to extract alkali metals	Bormann et al., 1975

TABLE 12.1. *(Continued)*

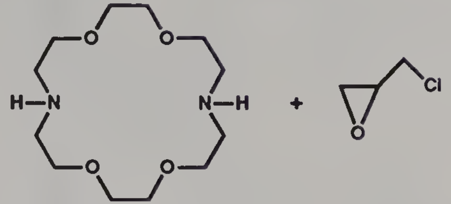
Structure of Polymer or Reaction to Produce Polymer	Remarks	References
		Cho and Chang, 1981
		Cho and Chang, 1981
		Cho and Chang, 1981
		Gramain and Frere, 1979



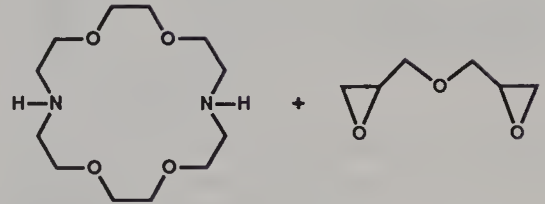
Blasius et al., 1980



Lishchinski et al., 1988

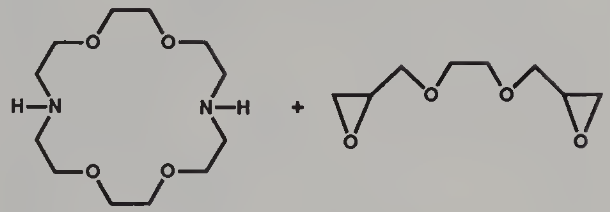
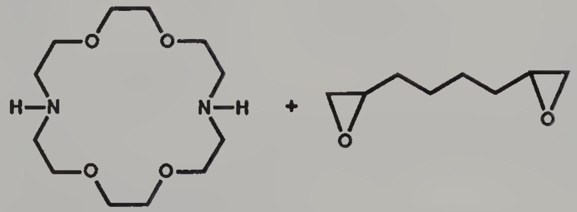
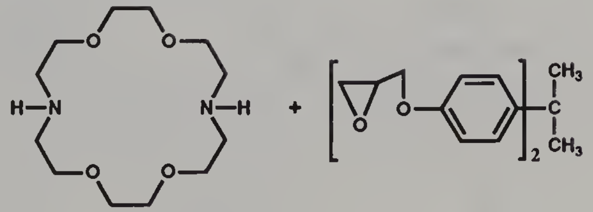
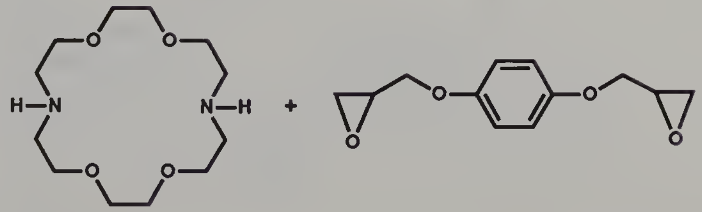


Gramain and Frere, 1980



Ergozhin et al., 1989

TABLE 12.1. *(Continued)*

Structure of Polymer or Reaction to Produce Polymer	Remarks	References
		Ergozhin et al., 1989
		Gramain and Frere, 1980
		Kakiuchi and Okamoto, 1982; Bormann et al., 1975
		Ergozhin et al., 1989

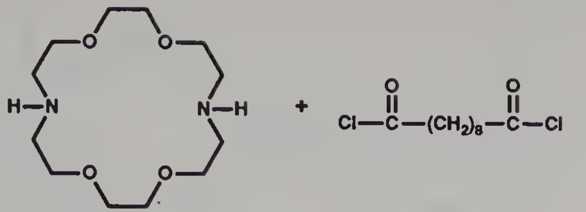
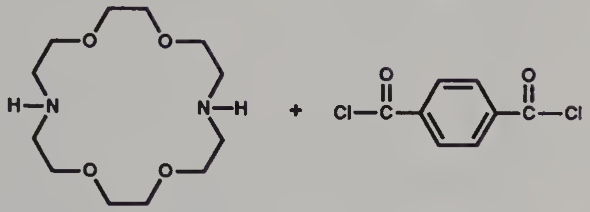
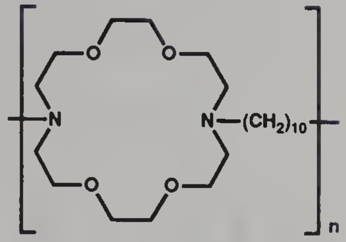
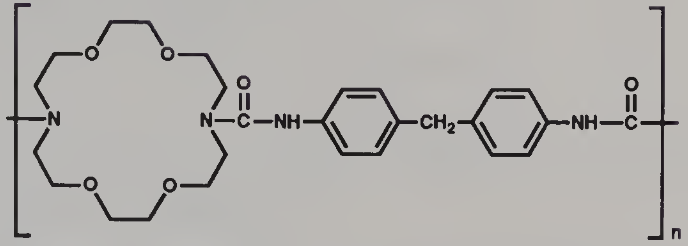
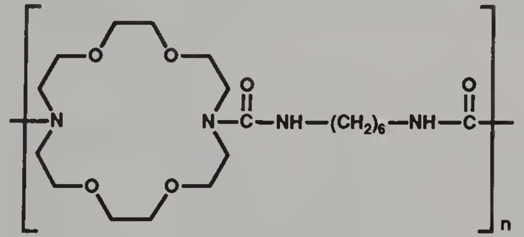
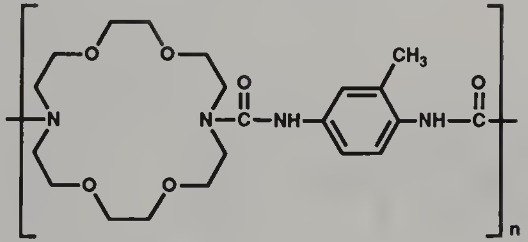
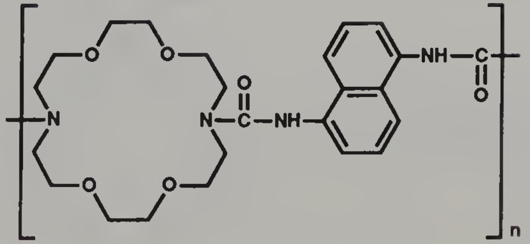
	Bormann et al., 1975; Gramain et al., 1980
	Bormann et al., 1975; Gramain et al., 1980
	Gramain et al., 1980
	Cho and Chang, 1981; Cowie and Wu, 1988b

TABLE 12.1. *(Continued)*

Structure of Polymer or Reaction to Produce Polymer	Remarks	References
		Cowie and Wu, 1988b
		Cowie and Wu, 1988b
		Cowie and Wu, 1988b

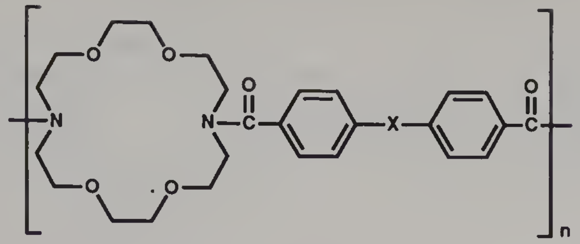
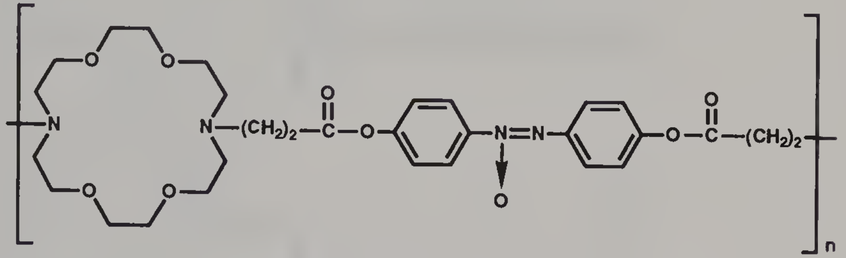
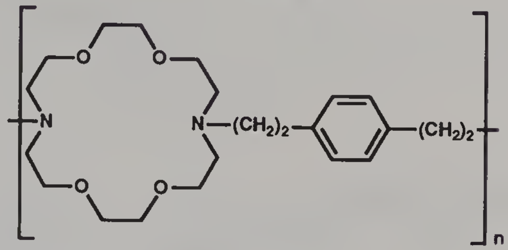
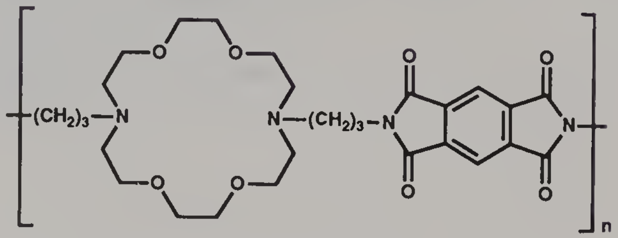
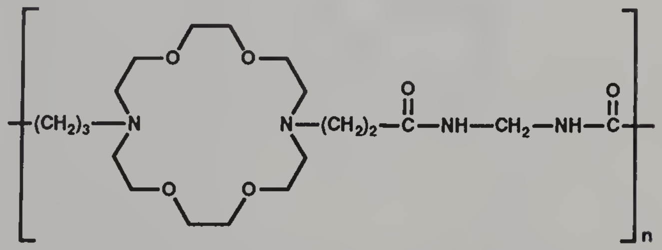
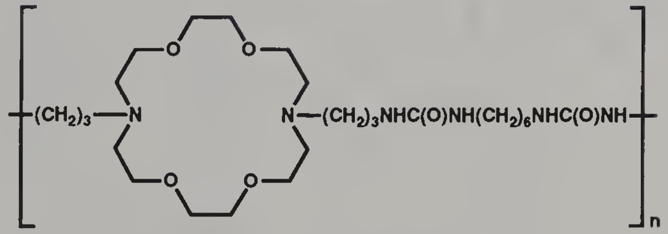
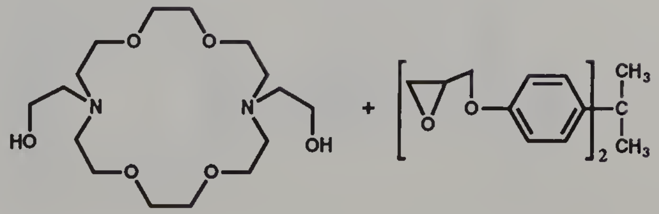
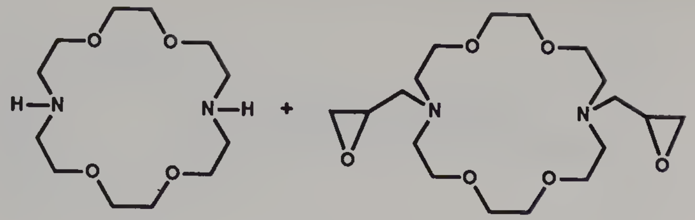
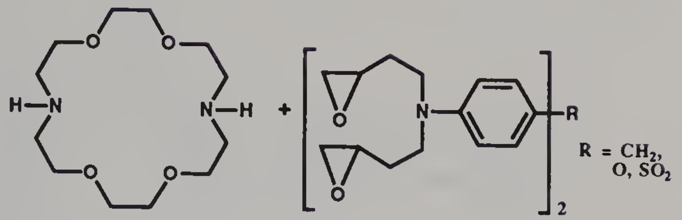
 X = N=N; N=NO; CH=CH; 1,4-C_6H_4; $OCOC_6H_4CO_2$	Material was a liquid crystal. When complexed with K^+, the flexible section of the polymer changed and the polymer no longer had liquid crystalline properties.	Cowie and Wu, 1988a
		Cowie and Wu, 1988b
		Nishimura et al., 1981
		Cho and Chang, 1981

TABLE 12.1. *(Continued)*

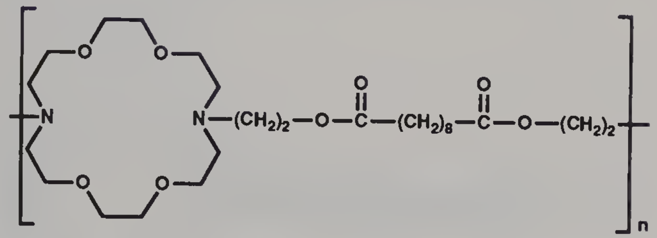
Structure of Polymer or Reaction to Produce Polymer	Remarks	References
		Cho and Chang, 1981
		Cho and Chang, 1981
		Gramain and Frere, 1979



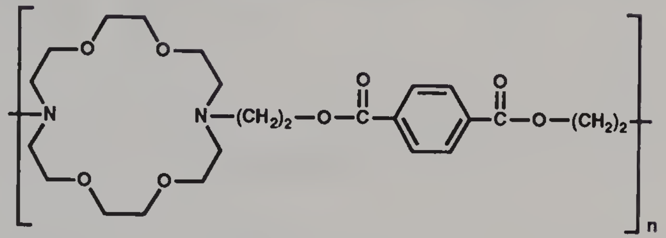
Ergozhin et al., 1989



Ergozhin et al., 1989

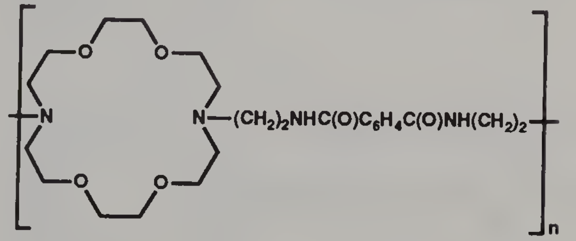
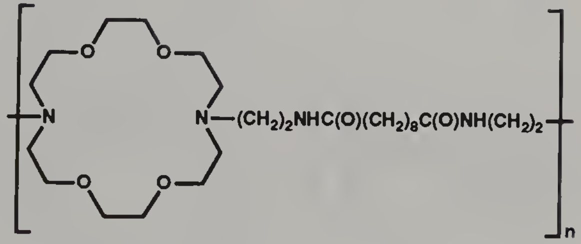
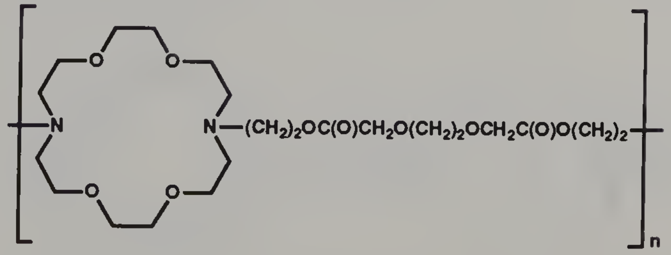


Gramain et al., 1980



Gramain et al., 1980

TABLE 12.1. *(Continued)*

Structure of Polymer or Reaction to Produce Polymer	Remarks	References
		Gramain et al., 1980
		Gramain et al., 1980
		Gramain et al., 1980

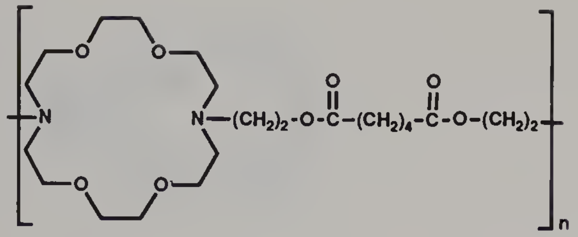
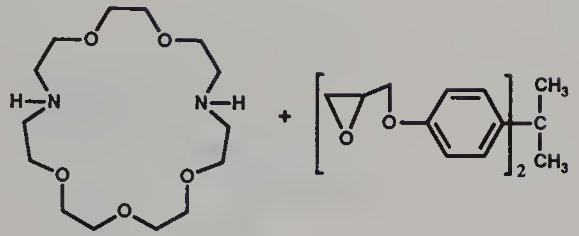
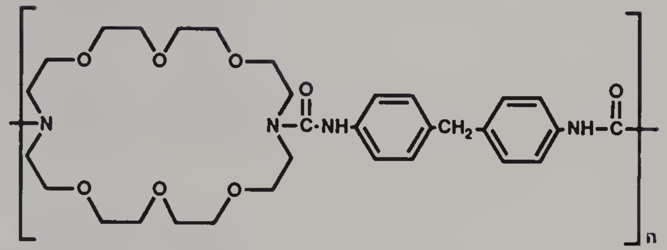
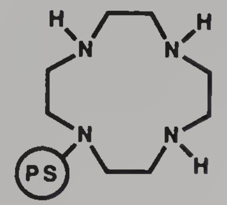
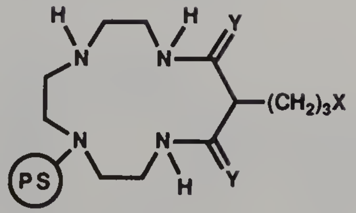
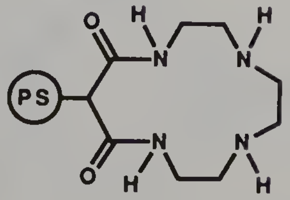
	Gramain et al., 1980
	Kakiuchi and Okamoto, 1982
	Cowie and Wu, 1988b

TABLE 12.2. POLYMERS CONTAINING AZA- OR PERAZA-CROWN MACROCYCLES ON A SIDE ARM

Structure of Polymer or Reaction to Produce Polymer[a]	Remarks	Reference
		Handel and Chaumell, 1988; Louvet et al., 1982
	The cyanopropyl-substituted diester ($Y = O$, $X = CN$) was attached to chloromethylated polystyrene and reduced to give the polymer-bound aminobutylcyclam ($Y = H_2$, $X = CH_2NH_2$).	Tabushi, 1978
		Wöhrle and Nicolaus, 1986

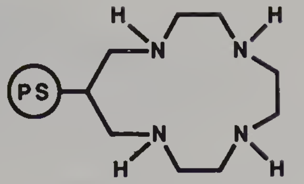
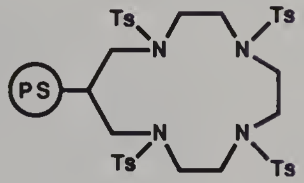
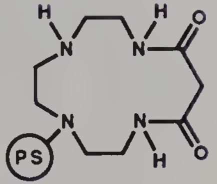
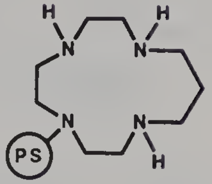
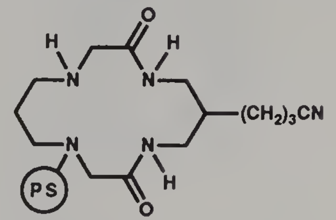
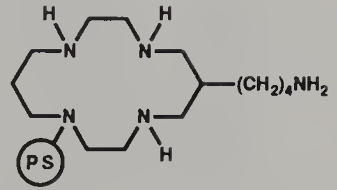
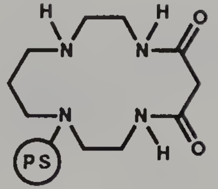
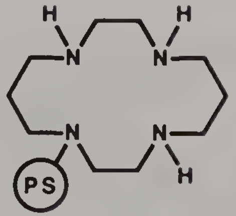
	This material was obtained by reduction of the above material or by detosylation of the following compound.	Wöhrle and Nicolaus, 1986
		Wöhrle and Nicolaus, 1986
		Tabushi, 1978
		Tabushi, 1978

TABLE 12.2. (*Continued*)

Structure of Polymer or Reaction to Produce Polymer[a]	Remarks	Reference
	See remarks above for cyanopropyl-substituted cyclam	Tabushi, 1978
		Tabushi, 1978
		Tabushi, 1978
	Used to separate metal ions from seawater. Used to absorb cations.	Tabushi, 1976, 1978 Handel and Chaumell, 1988 Percelay et al., 1985, 1988 Louvet et al., 1982, 1987 Sczepaniak and Kuczynski, 1985

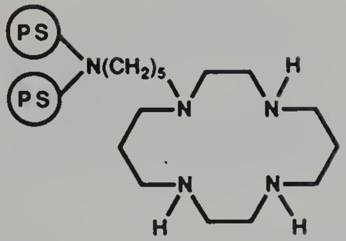
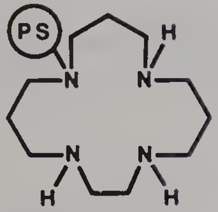
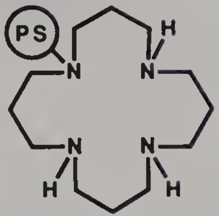
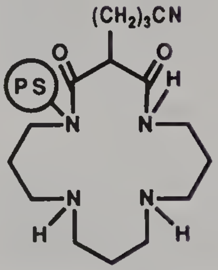
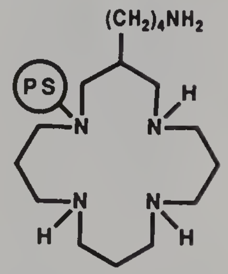
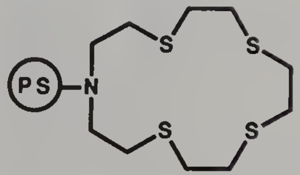
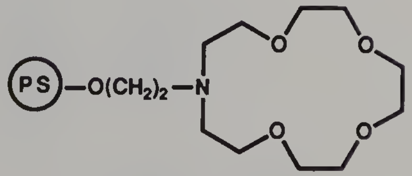
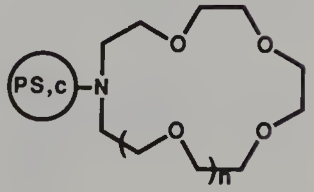
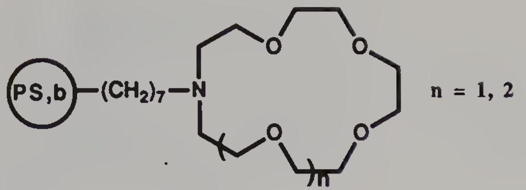
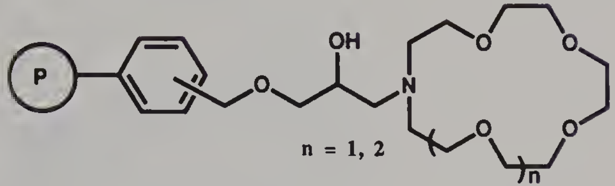
	Handel and Chaumell, 1988
	Handel and Chaumell, 1988
	Handel and Chaumell, 1988
	Tabushi, 1978

TABLE 12.2. *(Continued)*

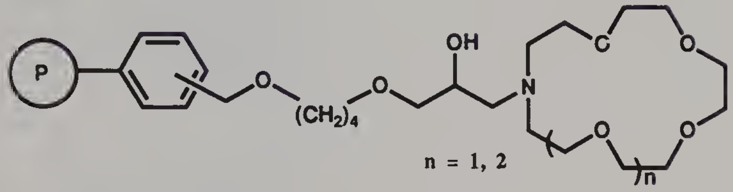
Structure of Polymer or Reaction to Produce Polymer[a]	Remarks	Reference
		Tabushi, 1978
		Yatsimirskii et al., 1989
	Material used as a catalyst.	Yatsimirskii et al., 1989 Valter et al., 1989
 n = 1, 2		Tomoi et al., 1984



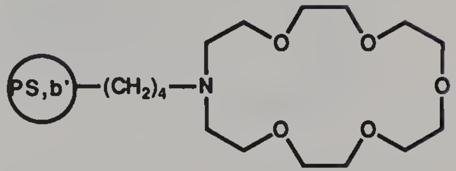
Tomoi et al., 1984



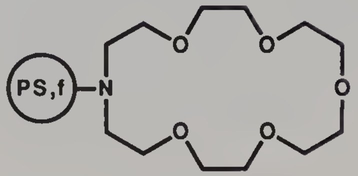
Ogawa and Tomoi, 1990



Ogawa and Tomoi, 1990

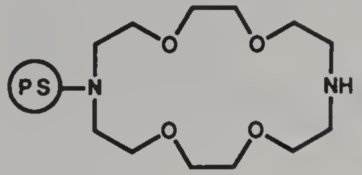
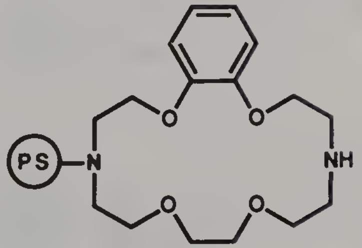
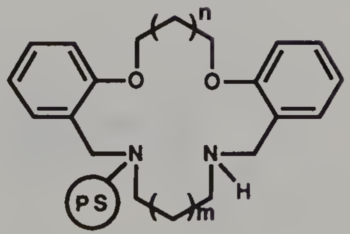


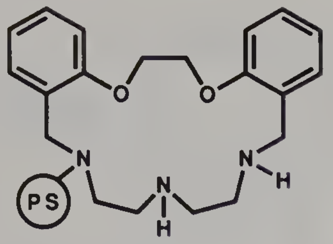
Tomoi et al., 1984



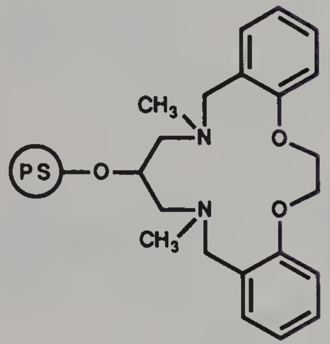
Tomoi and Kakiuchi, 1984

TABLE 12.2. (*Continued*)

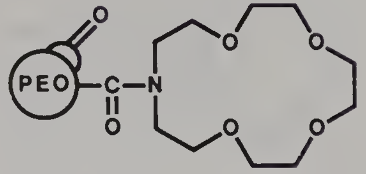
Structure of Polymer or Reaction to Produce Polymer[a]	Remarks	Reference
	One or two bonds to the solid support.	Blasius and Janzen, 1975; Blasius et al., 1977a, 1977b, 1980; Blasius and Maurer, 1977; Ricard et al., 1980, 1984
		Blasius and Janzen, 1975; Blasius et al., 1977a, 1977b, 1980; Blasius and Maurer, 1977
 n m 0 0 0 1 1 1		Paredes et al., 1986



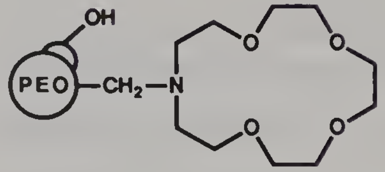
Paredes et al., 1986



Paredes et al., 1986

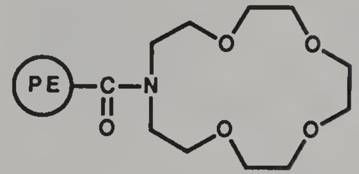
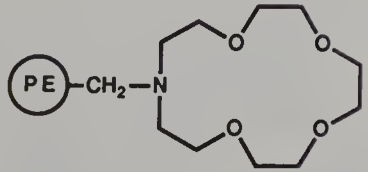
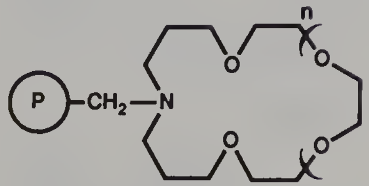
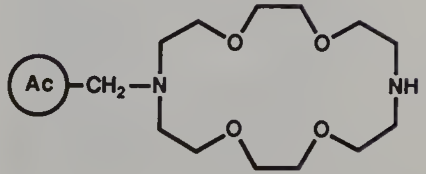


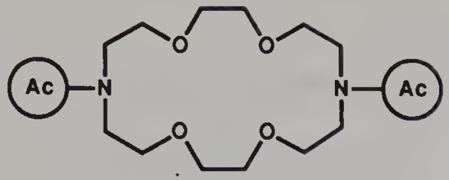
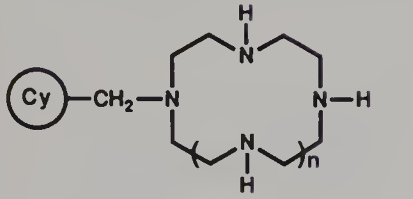
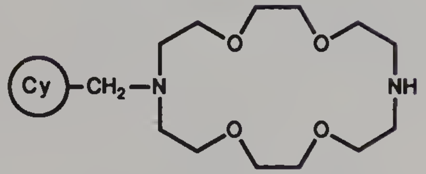
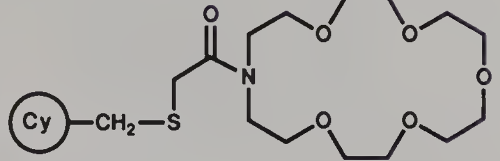
Bergbreiter and
Blanton, 1985



Bergbreiter and Blanton, 1985

TABLE 12.2. *(Continued)*

Structure of Polymer or Reaction to Produce Polymer[a]	Remarks	Reference
		Bergbreiter and Blanton, 1985
		Bergbreiter and Blanton, 1985
 n = 0, 1, 2		Kahana et al., 1990
		Ricard et al., 1982, 1984

	Kutchukov et al., 1980
 n = 1, 2	Akkaya and Czarnik, 1988
	Fujii et al., 1989; Willner and Goren, 1983
	Fujii et al., 1989 Bremer et al., 1989

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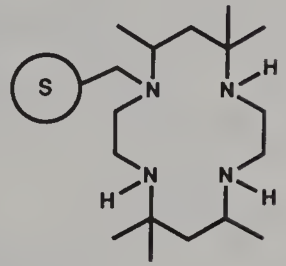
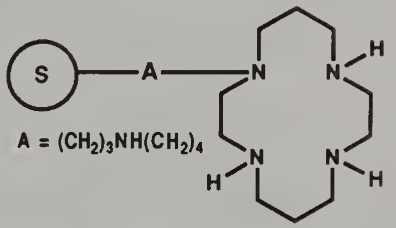
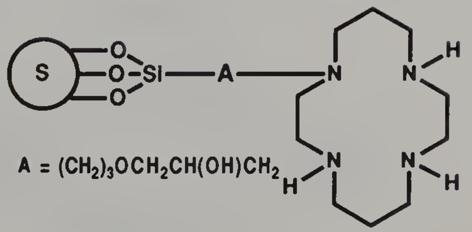
[a] Ac = Polyacrylamide; Cycl = Cyclodextrin; PE = Polyethylene; PEO = Oxidized polyethylene; PS = Polymer derived from p-chloromethylstyrene; PS,b = Polymer derived from styrene and (7-bromoheptyl)styrene; PS,b' = Polymer derived from styrene and (4-bromobutyl)styrene; PS,c = Polymer derived from styrene, p-chloromethylstyrene and divinylbenzene; PS,f = Polymer derived from crosslinked polystyrene and polypropylene fibers.

TABLE 12.3. SILICA-GEL-BOUND AZA- AND PERAZA-CROWN MACROCYCLES

Structure[a]	Remarks	Reference
		Basyuk and Chuiko, 1990
 A = $(CH_2)_3NH(CH_2)_4$		Basyuk and Chuiko, 1990
 A = $(CH_2)_3OCH_2CH(OH)CH_2$	Used to pre-concentrate amines and acids.	Bagnoud et al., 1990 Veuthey et al., 1986

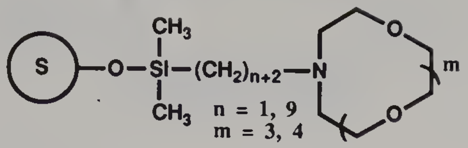
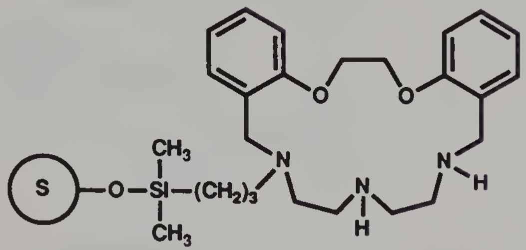
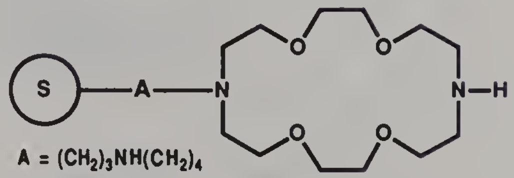
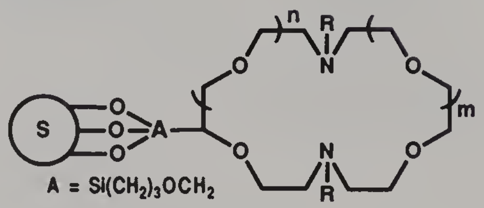
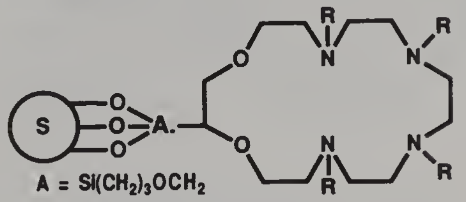
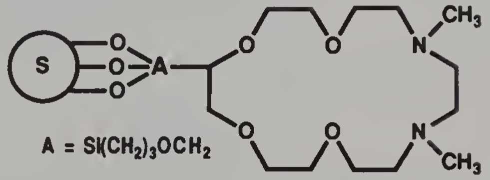
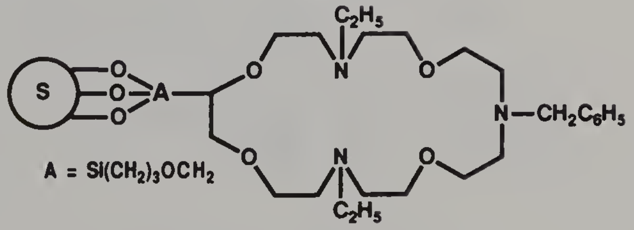
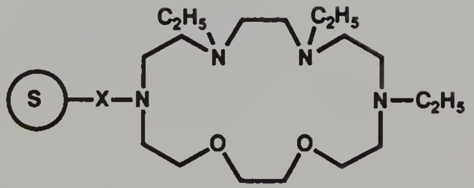
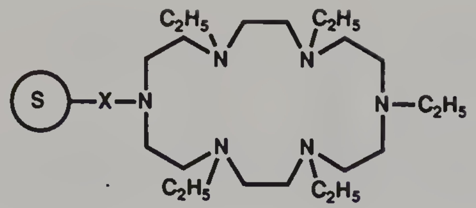
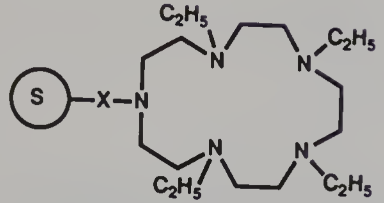
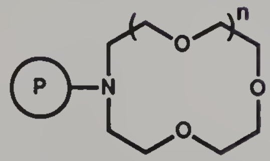
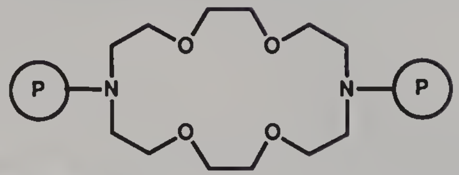
	Used as phase transfer catalysts.	Chen et al., 1989
		Dudler et al., 1987
		Basyuk and Chuiko, 1990
	m = n = 1, R = hexyl	Izatt et al., 1988 Bradshaw et al., 1988b, 1989c
	m = n = 1, R = ethyl	Bradshaw et al., 1988b, 1989c
	m = n = 1, R = benzyl	Bradshaw et al., 1988a, 1989a, 1989c; Izatt et al., 1988
	m = 0, n = 1, R = benzyl	Bradshaw et al., 1988a
	m = 1 n = 2 R = benzyl	Bradshaw et al., 1988a

TABLE 12.3. (*Continued*)

Structure[a]	Remarks	Reference
	R = ethyl	Bradshaw et al., 1989a
		Bradshaw et al., 1989c
		Bradshaw et al., 1989c
	X = unspecified connection between silica gel and ligand	Izatt et al., 1990

	X = unspecified connection between silica gel and ligand	Izatt et al., 1990
	X = unspecified connection between silica gel and ligand	Izatt et al., 1990
		Abed-Ali et al., 1989
		Abed-Ali et al., 1989

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[a] S = Silica gel, P = Polysiloxane

D. AZA- AND PERAZA-CROWN MACROCYCLES BONDED TO ANTIBODIES

A challenging new aspect of clinical oncology involves the development of effective methods for radioimmunoimaging to detect tumors and radioimmunotherapy to eradicate tumors without surgery. These techniques are currently being studied using complexes of certain radioactive metal ions with the aza- and peraza-crown macrocycles bound to antibodies. In general, open-chain ligands such as EDTA are not used because metal ion complexes with open-chain molecules are relatively unstable in vivo as a result of acid-catalyzed decomposition or competitive complexation with Ca^{2+} or Zn^{2+}. Recently, complexes of DTPA with $^{212}Bi^{2+}$ were found to have good stability in vivo (Brechbiel et al., 1991). If the radiometal complex is decomposed in the body, healthy tissue will be affected and the imaging process will be impossible.

Macrocyclic ligands, such as the cyclams, were suggested for radioimmunoimaging in the mid-1980s (Gansow et al., 1984; Moi et al., 1985). The use of radiolabeled peraza-crown complexes attached to various antibodies has been studied extensively in the past few years (Broan et al., 1991; Craig et al., 1990; Roberts et al., 1990; Ruser et al., 1990). These materials were stable in vivo and can be used for cancer treatment.

Care must be taken not to change the antibody when connecting it to the macrocycle. The linking group is generally attached to the moab part of the antibody. The lyophilized antibody–ligand conjugates can be prepared and stored. A specific radiopharmaceutical agent can then be prepared by simply adding a buffered solution of the radiometal ion prior to application.

Reviews covering recent advances in monoclonal antibody drug targeting for cancer treatment have been published (Liu and Wu, 1991; Koppel, 1990; Parker, 1990). Some preliminary data of clinical trials of these antibody-bound complexes have shown good results for the treatment of a number of cancer patients (Gansow et al., 1991). Recently, it has been reported that steriods and other similar natural products can replace the antibody for delivery of the radionucleotide to cancer cells (DiZio et al., 1991).

Table 12.4 lists peraza-crowns bonded to protein molecules, including antibodies. The table is organized by the size of the macrocycle.

TABLE 12.4. PERAZA-CROWN MACROCYCLES BONDED TO PROTEIN MOLECULES

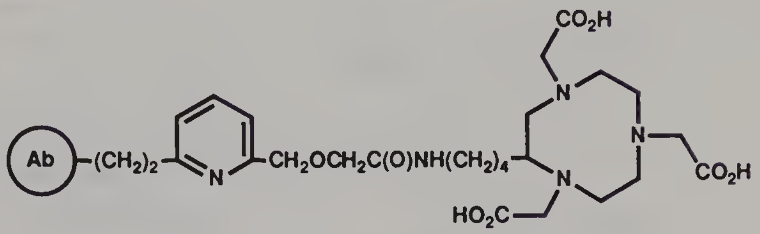
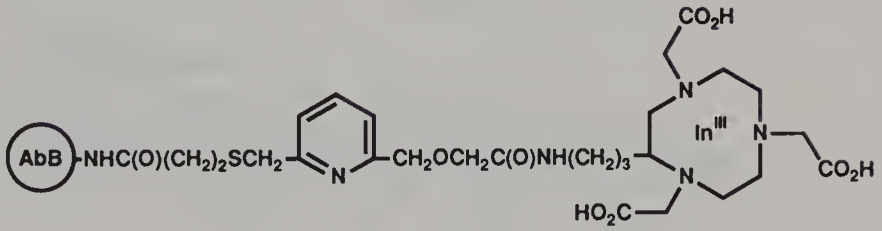
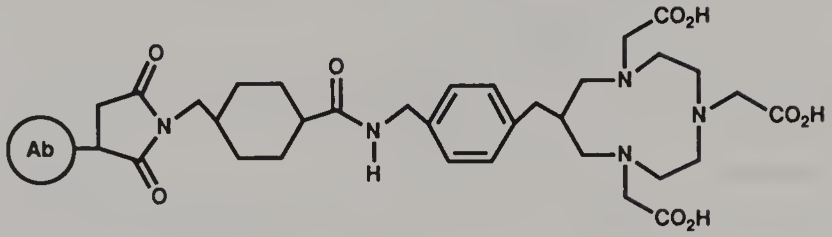
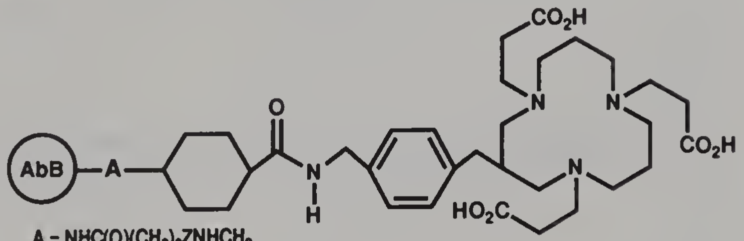
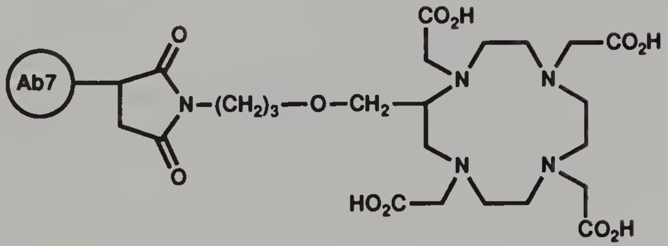
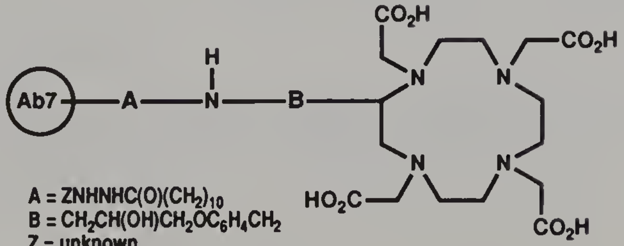
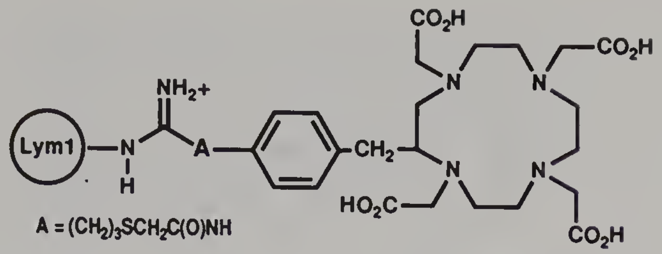
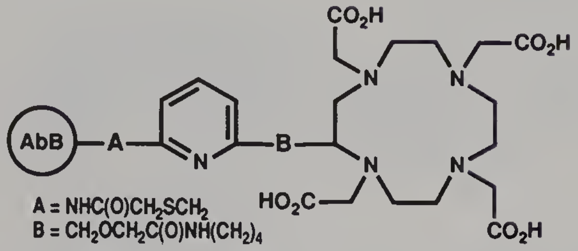
Structure[a]	Remarks	Reference
		Craig et al., 1989
		Craig et al., 1989
		Parker and Millican, 1989a

TABLE 12.4. (*Continued*)

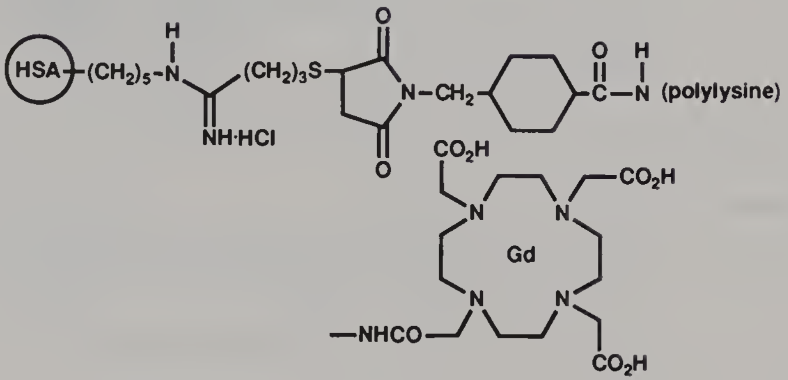
Structure[a]	Remarks	Reference
 A = $NHC(O)(CH_2)_2ZNHCH_2$ Z = unknown		Parker and Millican, 1989a; Craig et al., 1989
		Deutsch et al., 1988
 A = $ZNHNHC(O)(CH_2)_{10}$ B = $CH_2CH(OH)CH_2OC_6H_4CH_2$ Z = unknown		Deutsch et al., 1988


A = $(CH_2)_3SCH_2C(O)NH$

McCall et al., 1990

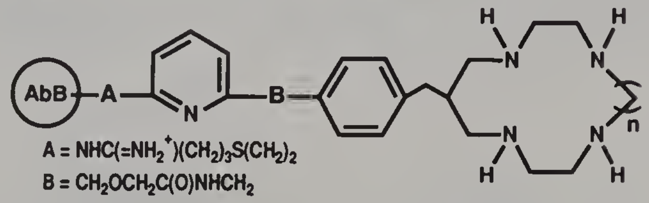
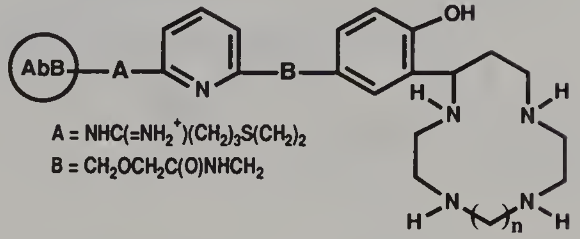
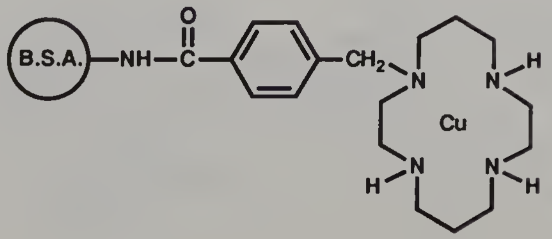

A = $NHC(O)CH_2SCH_2$
B = $CH_2OCH_2C(O)NH(CH_2)_4$

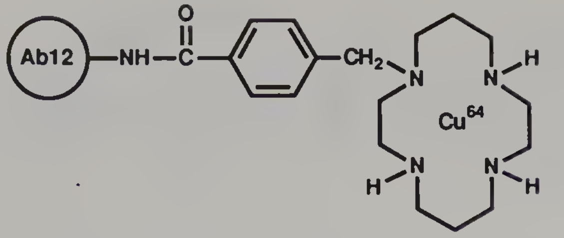
Cox et al., 1989;
Parker and Millican, 1989b



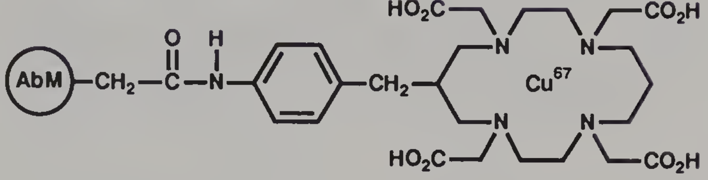
Sieving et al., 1990

TABLE 12.4. (*Continued*)

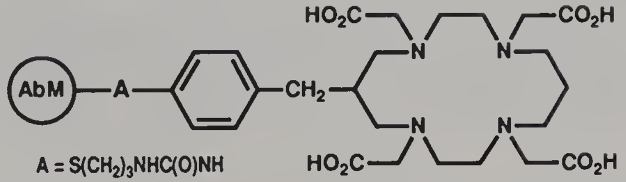
Structure[a]	Remarks	Reference
 A = NHC(=NH$_2^+$)(CH$_2$)$_3$S(CH$_2$)$_2$ B = CH$_2$OCH$_2$C(O)NHCH$_2$		Morphy et al., 1989, 1990
 A = NHC(=NH$_2^+$)(CH$_2$)$_3$S(CH$_2$)$_2$ B = CH$_2$OCH$_2$C(O)NHCH$_2$		Morphy et al., 1989, 1990
		Kaden et al., 1989



Kaden et al., 1989

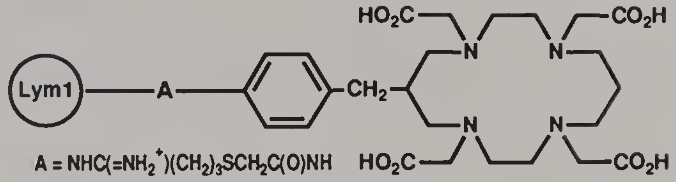


Moi et al., 1985



A = S(CH$_2$)$_3$NHC(O)NH

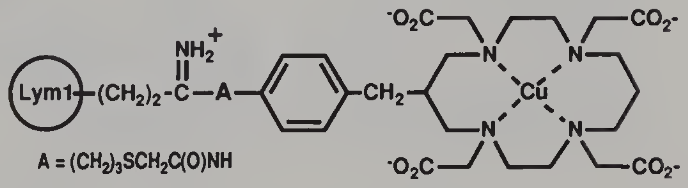
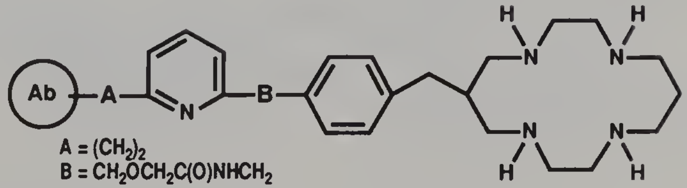
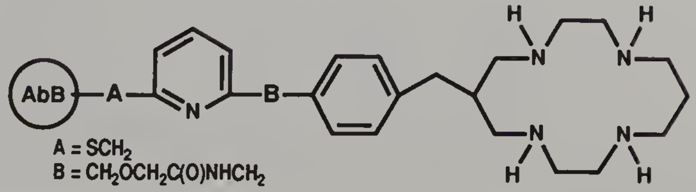
Moi et al., 1985

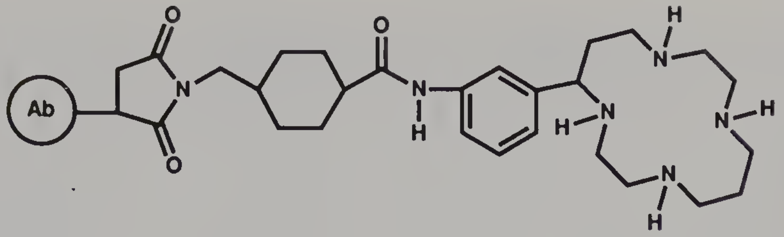
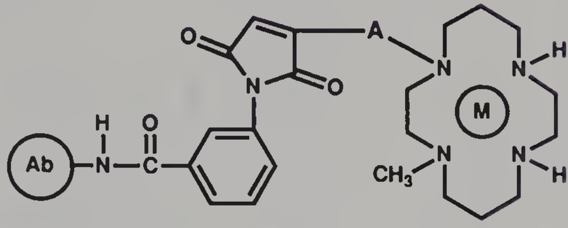


A = NHC(=NH$_2^+$)(CH$_2$)$_3$SCH$_2$C(O)NH

McCall et al., 1990

TABLE 12.4. (*Continued*)

Structure[a]	Remarks	Reference
 A = $(CH_2)_3SCH_2C(O)NH$		Deshpande et al., 1988
 A = $(CH_2)_2$ B = $CH_2OCH_2C(O)NHCH_2$		Parker and Millican, 1987
 A = SCH_2 B = $CH_2OCH_2C(O)NHCH_2$		Morphy et al., 1988, 1989

	Parker and Millican, 1987
 M = ^{64}Cu, ^{99}Tc A = $S(CH_2)_3C(=NH_2^+)NH(CH_2)_3$	Franz et al., 1987a, 1987b

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[a] Ab = Rabbit anti-HSA-JgG; AB7 = Antibody 713 10D11; Ab12 = Antibody 612; AbB = Antibody B 72.3; AbM = Mouse monoclonal antibody lym-1; BSA = Bovine serum albumin; HSA = Human serum albumin; Lym1 = Lym-1 antibody.

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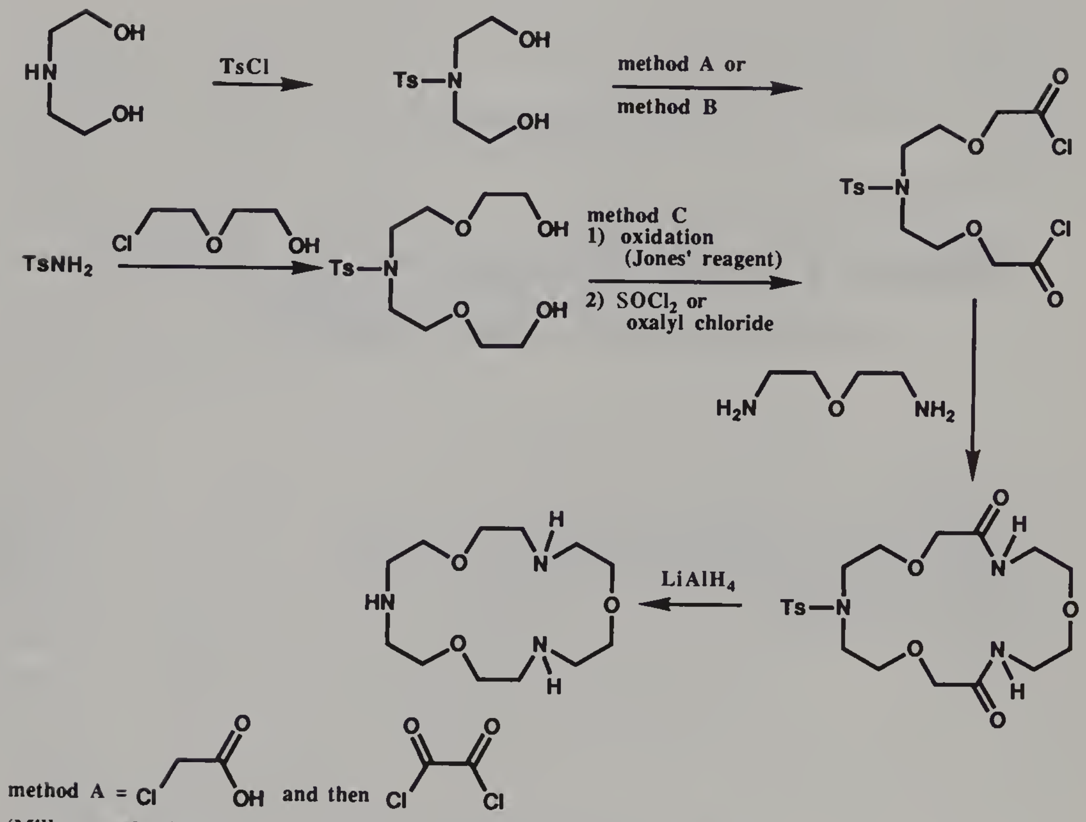
CHAPTER XIII

Some Practical Approaches to the Aza-crown Macrocycles

A. INTRODUCTION

The aza-crown macrocycles often can be prepared by more than one route. Choosing the best pathway can be a problem. Often, the preparation of starting materials for the ring-closure reaction is the most difficult part of the synthesis. Obviously, a multistep synthesis is not preferred unless the overall yield is higher than a shorter route or purification of the product is easier in the multistep process. Sometimes a particular ring-closure reaction will give a multitude of cyclic products that are difficult to separate (Krakowiak et al., 1990a).

Unfortunately, only a few aza- and peraza-crowns can be purchased. On the other hand, many polyamines and diaminoethers are available and can be used for the synthesis of the desired aza-crown macrocycles. A most useful starting material, 4-oxa-1,7-heptanediamine, is very expensive ($50 per gram in 1992). Even so, this material was used in the ring closure step to prepare triaza-18-crown-6 as shown in the following sequence (Graf and Lehn, 1981; Miller et al., 1989).



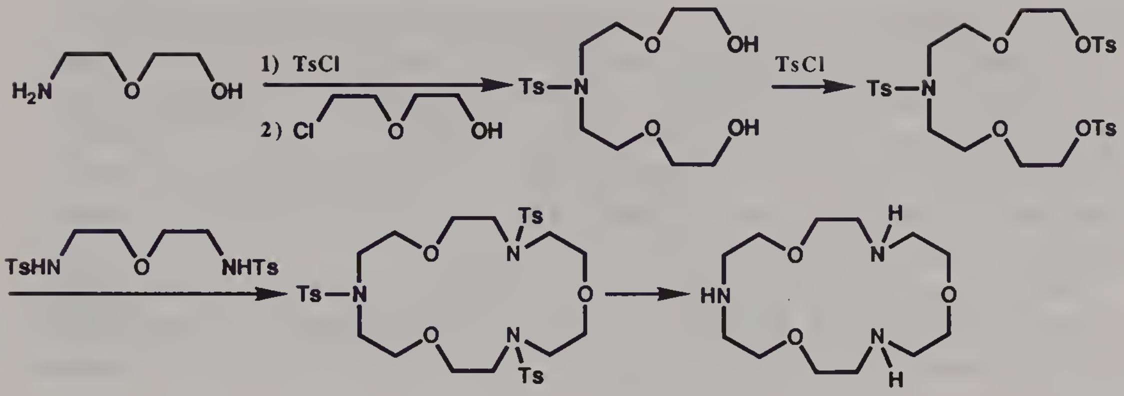
(Miller et al., 1989)

method B = CH_2O/HCl, NaCN, DMF, $Ba(OH)_2$, and $SOCl_2$
(Graf and Lehn, 1981)

B. POSSIBLE SYNTHESES OF TRIAZA-18-CROWN-6

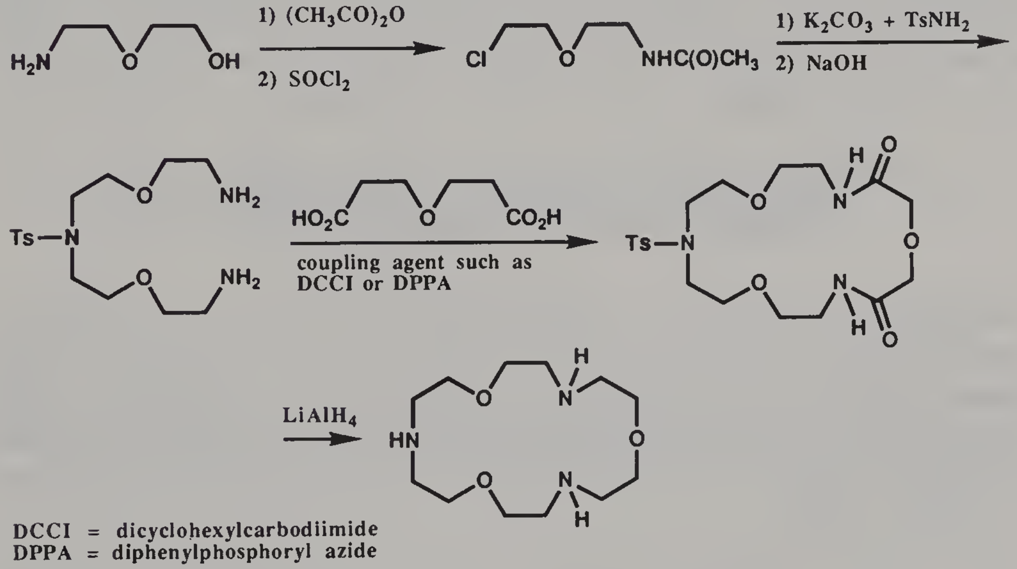
The 4,10,16-triaza-18-crown-6 macrocycle shown above was first prepared by Lehn and coworkers (Graf and Lehn, 1975; Lehn, 1985) and was an important intermediate for the synthesis of the first macrotetracyclic polyethers (Canceill et al., 1982; Kotzyba-Hibert et al., 1981; Pratt et al., 1988). The key step in this synthesis was conversion of *N*-tosyldiethanolamine [$TsN(CH_2CH_2OH)_2$] into the diacid dichloride, $TsN(CH_2CH_2OCH_2COCl)_2$. As shown above, this conversion was accomplished by reaction with chloroacetic acid followed by oxalyl chloride (method A) (Miller et al., 1989) or by chloromethylation, sodium cyanide, hydrolysis and conversion of the diacid to the diacid dichloride (method B) (Graf and Lehn, 1981). The third hypothetical method to the diacid dichloride shown above starts with tosylamide and 5-chloro-3-oxa-1-pentanol followed by Jones' oxidation and thionyl chloride (method C) (Qian et al., 1990).

Martell and coworkers used another strategy to prepare triaza-18-crown-6 as shown below (Chen et al., 1990). In this case, the hard-to-prepare diacid



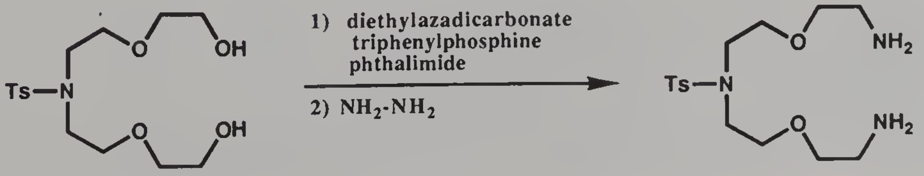
dichloride was avoided, but expensive 4-oxa-1,7-heptanediamine (in the form of its *N*,*N'*-bistosylamide) was used in the ring-closure step.

Alternative routes to triaza-18-crown-6, using published reactions, can be planned to avoid the use of expensive starting materials. One hypothetical method would use the building-block procedure as shown below (Krakowiak and Bradshaw, 1991; Krakowiak et al., 1988, 1989b; Qian et al., 1990).



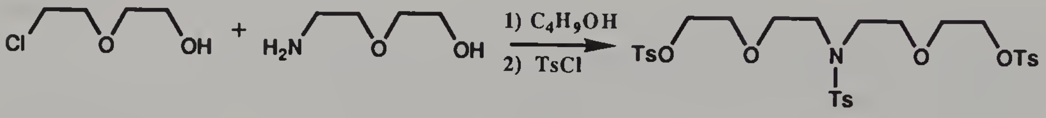
DCCI = dicyclohexylcarbodiimide
DPPA = diphenylphosphoryl azide

Another possible method for preparation of the hypothetical 6-tosyl-6-aza-3,9-dioxa-1,11-undecanediamine intermediate in the above reaction is shown below.



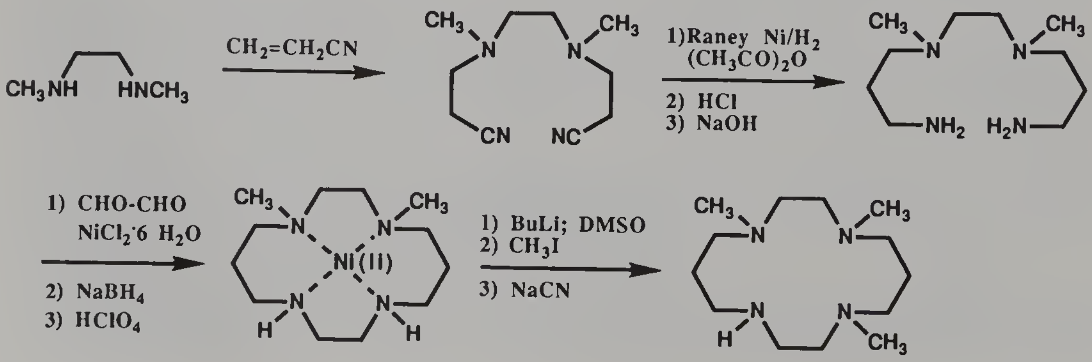
The first intermediate in the above reaction (6-tosyl-6-aza-3,9-dioxa-1,11-undecanediol) was prepared by Anelli and coworkers in a 77% yield (Anelli et al., 1988). The next step would use the Mitsunobu (1981) reaction to convert an alcohol to an amine in a one-pot synthesis. Although these two sequences have not been investigated, we believe that the desired unsubstituted triaza-18-crown-6 could be prepared in four or five steps from inexpensive starting materials in an overall yield of more than 30%.

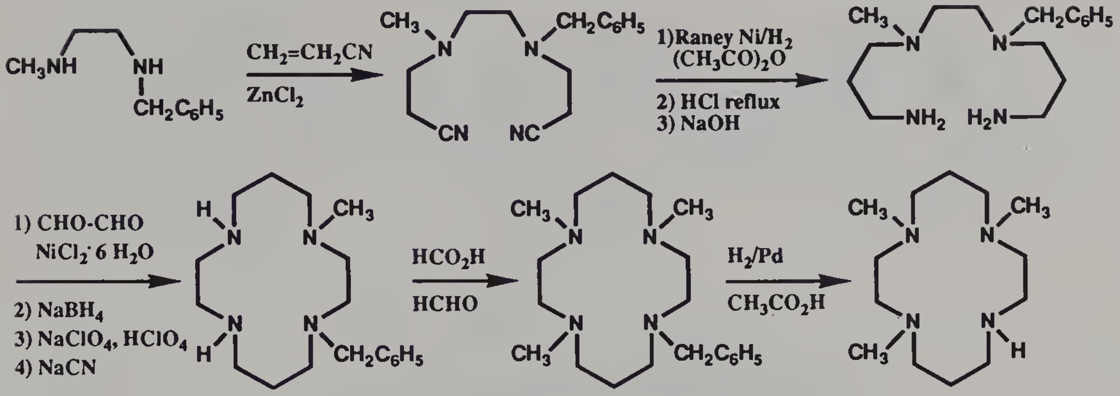
Another route to triaza-18-crown-6 could also be possible. The tritosyl derivative of 6-aza-3,9-dioxa-1,11-undecanediol was prepared in a moderate yield in a two-step reaction as shown below (Sun et al., 1991). The first step should be carried out using an excess (3:1) of 2-(2-aminoethoxy)ethanol to avoid double substitution on the amine. Krespan (1975) and Sun and coworkers got only a 35–40% yield of this product when they used a 1:1 ratio of starting materials. A higher yield could be expected when using starting materials in a ratio of 3:1. The tritosylate could be treated with expensive 4-oxa-1,7-heptanediamine to form the triaza-18-crown-6 in only a few steps.



C. SYNTHESES OF MONO-FUNCTIONALIZED PERAZA-CROWN MACROCYCLES

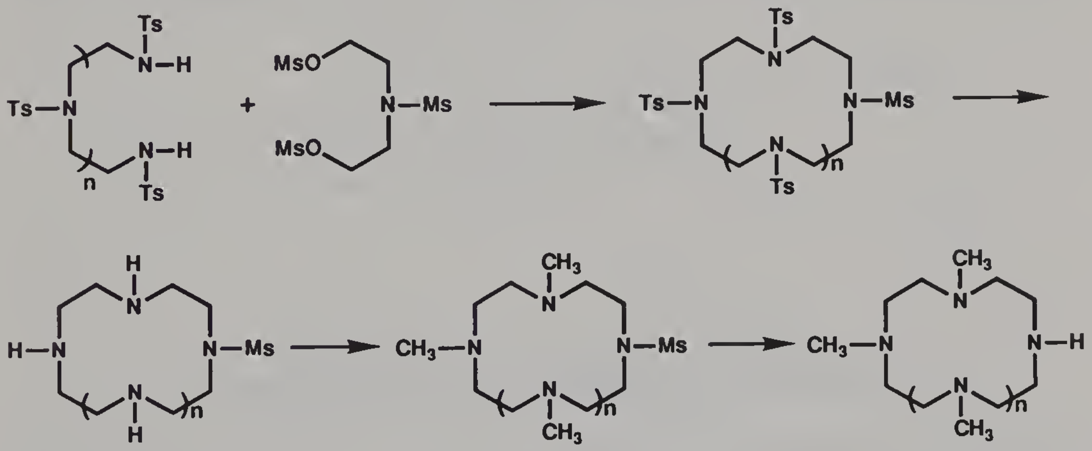
The mono-functionalized cyclams (tetraaza-14-crown-4) are important complexing agents. For example, they can be attached to antibodies for use in cancer immunotherapy (see Chapter I) (Broan et al., 1991; Parker, 1990; Liu and Wu, 1991). Mono-functionalized cyclam was first prepared by Barefield and coworkers by two different routes as shown below (Barefield et al., 1976, 1986a, 1986b).





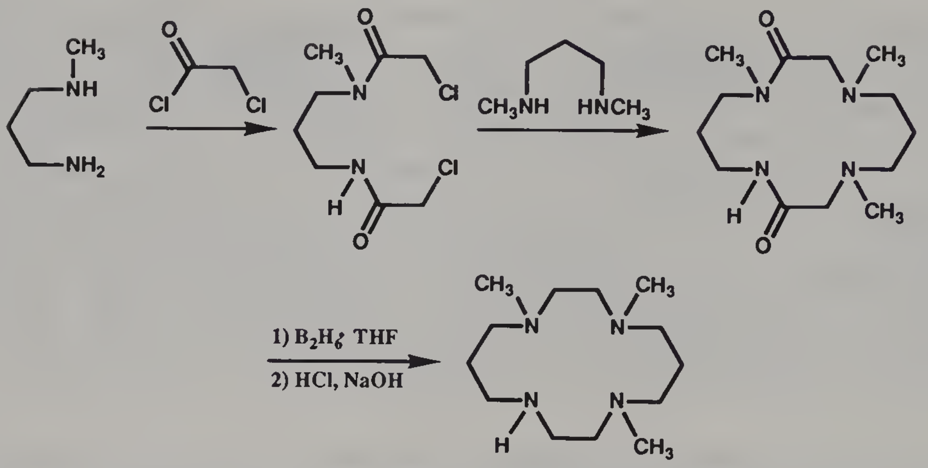
Barefield and coworkers employed a template process in multi-steps using autoclaves and perchlorate salt intermediates. Even with the many steps, a yield of 52% for the *N*,*N′*,*N″*-trimethylcyclam was realized. These procedures, however, are good only for certain ring systems and macrocycle sizes. Each ring size with differing numbers of nitrogen atoms requires a particular templating metal cation.

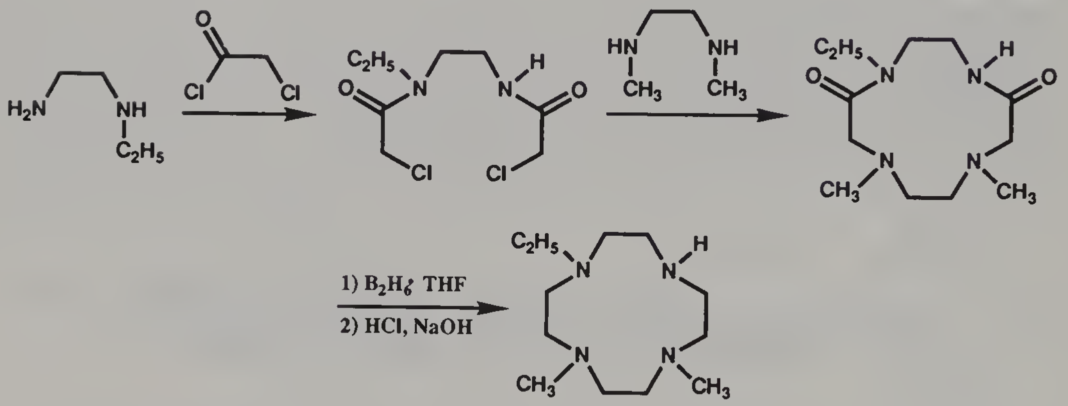
Mono-functionalized peraza-12-crown-4 and 15-crown-5 ligands also have been prepared by multistep sequences (Pilichowski et al., 1985). Their process



required *N*-tosyl and *N*-mesyl protecting groups, which were removed in sequence. The overall yields for these reactions were low.

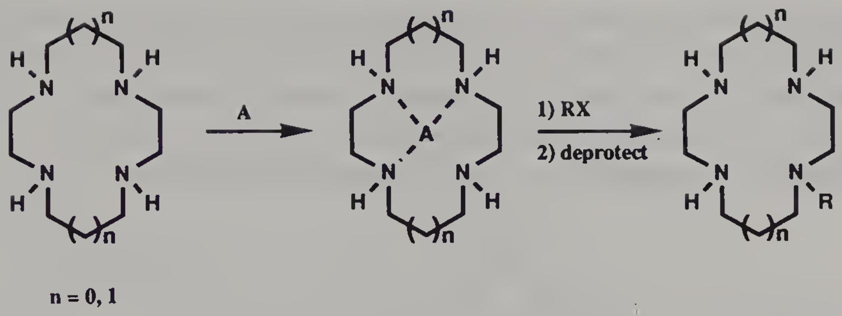
The recently introduced "crab-like" process for the preparation of polyaza- and peraza-crown macrocycles can be used to prepare a variety of mono-functionalized aza-crown macrocycles in good to excellent yields (Bradshaw et al., 1989a, 1989b; Krakowiak et al., 1989a, 1990b). This is an important method because the required starting materials are inexpensive, the number of steps are few, and the overall yields are excellent. Two examples of the preparation of monofunctionalized peraza-crown macrocycles using this process are given below. A more detailed discussion of the crab-like synthesis of the polyaza-crown macrocycles is given in Chapter IV.





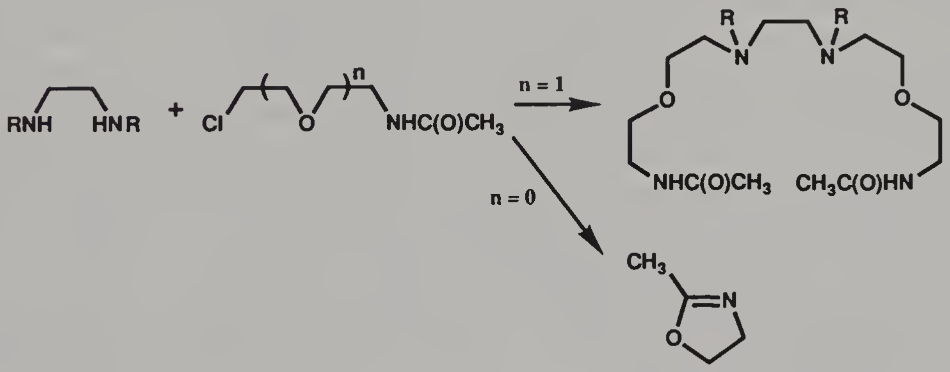
D. MONOALKYLATION OF TETRAAZA-CROWN MACROCYCLES

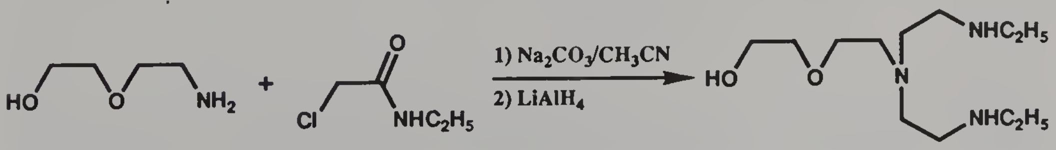
Recently, a new method has been devised to prepare a tetraaza-crown containing only one *N*-alkyl group. In general, mono-*N*-alkyl-substituted peraza-crowns are not easy to prepare. These ligands have been prepared by employing a multiple protection process or a large excess of the polyaza-crown has been used (Kaden, 1984; Pilichowski et al., 1985; Schiegg and Kaden, 1990; Studer and Kaden, 1986). The new method used a complex of the tetraaza-crown wherein three of the amine groups were complexed and only the uncomplexed amine was alkylated. The complexing agents were tris(dimethylamino)borane, hexamethylphosphoric triamide, dimethylformamide acetal, or certain metal carbonyls (Anelli et al., 1991; Bernard et al., 1991; Filali et al., 1991; Handel et al., 1990; Yaouanc et al., 1991).



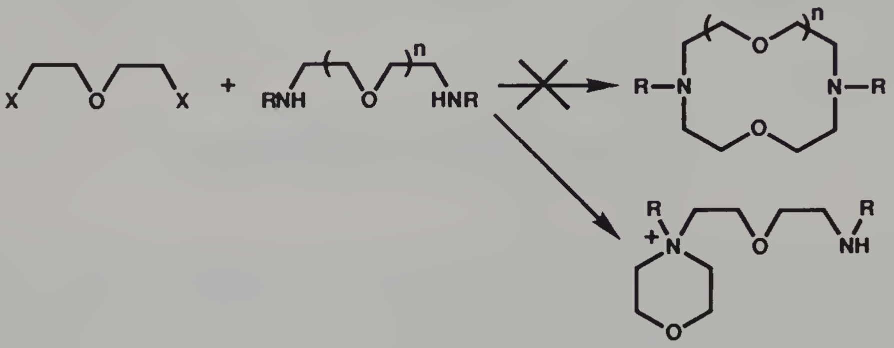
E. UNEXPECTED REACTIONS

Despite more than 20 years of research in macrocyclic chemistry, there are many cyclic systems that have not been prepared. In thinking about methods to prepare these new systems, one should be aware of the many unexpected reactions that can take place during the preparation of the polyaza-crown macrocycles. The most aggravating side reaction is the formation of unwanted five- or six-membered rings from linear starting materials. *N*-[2-(2-Chloroethoxy)ethyl]acetamide, for example, was developed to elongate polyamine chains (Bradshaw et al., 1990; Krakowiak and Bradshaw, 1991; Krakowiak et al., 1989b). The shorter *N*-(2-chloroethyl)acetamide, on the other hand, reacted in basic conditions to form the 2-oxazoline rather than a linear elongation product (Franco and Muchowski, 1980). *N*-(2-Chloroethyl)acetamide reacted to form linear products in acid conditions, but the yields were low. 2-Chloroacetamide or *N*-ethyl-2-chloroacetamide, which are commercially available, will not form cyclic materials in basic solution. These compounds can be used to form useful linear polyamines in moderate yields (Bradshaw et al., 1989a, 1989b).





1,5-Dihalo-3-oxapentane is a desirable starting material for the preparation of macrocycles. When treated with an amine, however, this material forms a morpholine product. Even secondary amines react with 1,5-dihalo-3-oxapentane to form a quaternary morpholine derivative (Gatto et al., 1986). These same dihalo compounds, or their ditosylate analogs, do react with the appropriate *N*-tosyl derivatives of aliphatic diamines or with aromatic diamines to form the corresponding macrocycles (Rasshofer et al., 1976; Richman and Atkins, 1974).



Unwanted elimination reactions can also be a problem in the preparation of the diamine-containing linear intermediates. For example, the tritosyl derivative of diethanolamine eliminates *p*-toluenesulfonic acid to give *N*,*N*-divinyltosylamide when treated with a strong base (An et al., 1992; Bradshaw and Krakowiak, 1990; Gokel, 1991). This same material, on the other hand, reacted well with polyamines in DMF, in the presence of sodium carbonate, to form various polyaza macrocycles. Strong base also caused the ditosylate derivative of ethylene glycol to eliminate (Bradshaw and Krakowiak, 1988), although ethylene glycol derivatives have been used in the presence of carbonate bases to form the polyaza macrocycles (Alfheim et al., 1986).

We have mentioned only a few of the problems encountered in the synthesis of the polyaza-crown macrocycles. Other problem reactions have been reported (Alfheim et al., 1986; Amble and Dale, 1979; Buoen and Dale, 1986; Rasshofer and Vögtle, 1978).

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Author Index

Citations followed by page numbers indicate that an author's work is discussed on that page. Page numbers in italics indicate the full literature reference at the end of a chapter. In a general way, the italicized numbers may be used to indicate chapter separations.

Subject Index

This index contains the names of compounds listed in the text. The individual macrocycles listed in the numerous tables are not in this index. The tables are organized, first, by ring size and number of ring nitrogen atoms and, second, by the complexity of the substituents attached to ring nitrogen and/or carbon atoms. The subject of each table is listed in this index.

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