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CROWN COMPOUNDS

their characteristics and applications

BY

MICHIO HIRAOKA

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Michio HIRAOKA
Counselor and Director of the Department of Science Investigation, Technology Division, Nippon Soda Co. Ltd., Toyko, Japan

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Foreword

Since 1967, when the discovery of the macrocyclic polyethers was first announced publicly, the term "crown ethers" picked to identify these compounds has found its place in the lexicon of chemistry.

As attested by the numerous references, many new crown ethers have been synthesized, and these compounds with unique complexing properties not previously available, have been studied variously in many different fields. Moreover, this interest seems to be continuing.

It is timely, then, that Dr. Michio Hiraoka has gathered the references on the synetheses, the properties and the uses of crown ethers to show systematically the progress made in this field to date since their discovery.

His book "KURAUN KAGOUBUTSU" (CROWN COMPOUNDS) in Japanese was published in 1978. It is fortunate for many that the present book has not only been brought up to date but is in English. This should make it find a wider audience and contribute more broadly to the field.

So again, it gives me great pleasure in welcoming the publication of this book with the hope that it will stimulate and facilitate new studies with crown ethers and their analogues.

Charles J Pedersen

Charles J. PEDERSEN
Salem, N. J., U.S.A.
February 11, 1982

Preface

On July 5, 1962, Mr.C.J. Pedersen at the Du Pont Company identified a macrocyclic polyether as an unexpected by-product and discovered that it had the unusual property of complexing with alkali anions. He subsequently synthesized a series of macrocyclic polyethers, which he named "crown compounds," and in 1967 reported on them and his pioneering research work on the characteristics of the compounds. This was the memorable dawning of the chemistry of crown compounds.

Since that time, the chemistry and applications of crown compounds have been elaborated rapidly, and with remarkable results. Several hundred kinds of novel crown compounds and their analogues, including aza- and thiacrown compounds, cryptands, optically active crown compounds, and polymeric crown compounds, have been synthesized so far and their specific properties have been investigated. In addition to the basic research, application research on crown compounds has been fruitful in a wide variety of utilization fields such as organic synthesis, polymer synthesis, analytical chemistry, capture and separation of metal ions, resolution of optical isomers, biochemistry, and biophysics, and several types of crown compounds have been put to practical use. Over one thousand scientific papers relating to crown compounds have been published so far.

Many scientists believe that the unique properties of crown compounds hold the potential to break fresh ground in such new areas of science as "host-guest chemistry" and "biomimetic chemistry," which provide an interface between chemistry and biology as well as innovative technology. This potential is surely the principal explanation for the great attention to crown compounds attracted and for the rapid progress in research on the chemistry and applications of the compounds.

While many reviews are available that address various aspects of crown compounds, only a few books covering the synthesis, characteristics, and applications of the compounds have been published. As a matter of course no book can provide totally comprehensive coverage of the voluminous information concerning crown compounds.

The intent of this book is to review and systematize the progress made in the chemistry of crown compounds since discovery. It also summarizes current knowledge of the synthetic methods and characteristics of a large number of crown compounds and their analogues and discusses a wide spectrum of application research as well as current topics such as optically active crown compounds, immobilized crown compounds, and toxicological data. The author hopes that this book will contribute to a more widespread recognition of the potential of crown compounds and that it will catalyze and stimulate further research and applications in the field.

The author would like to offer special acknowledgement to Mr. C. J. Pedersen, the pioneer of crown compounds, for his unfailing encouragement during the preparation of this book. Thanks and appreciation are also extended to Dr. K. Hattori, Dr. H. Mizobe, Dr. Y. Mizuta, Mr. T. Takahashi and Ms. P. S. Allinson for their contributions in preparing the manuscript, and to Ms. M. Kajino for her skillful typing.

Michio HIRAOKA
February, 1982

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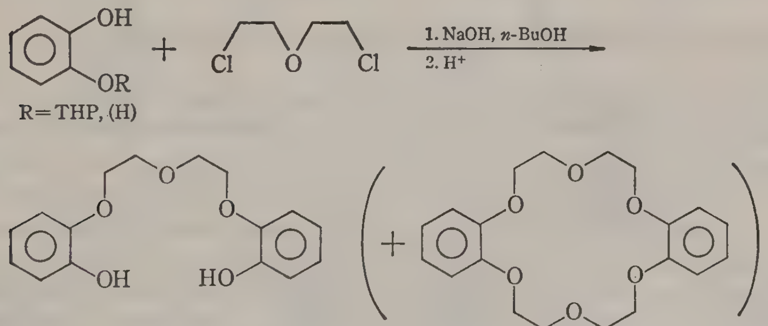
CHAPTER 1

Introduction

1.1 DISCOVERY OF CROWN COMPOUNDS

It was in 1967 that Pedersen published the first report on crown compounds.1) Like many important discoveries in the history of chemistry, crown compounds were not the object of synthesis in his experiments but were obtained unexpectedly. Careful observation followed by excellent research established the foundation for further development.

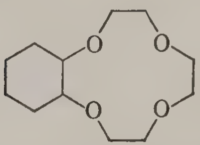
At the Du Pont company, Pedersen observed that a tiny amount of white fibrous crystals was produced as a by-product when catechol, in which one of hydroxyl groups was protected by tetrahydropyrane, was reacted with dichloroethyl ether during the preparation of bis [2–*o*–hydroxyphenoxy) ethyl] ether (**1**). An investigation of the structure of the isolated by-product identified the compound as a macrocyclic polyether (**2**) formed by the cyclic condensation of 2 moles of isolated catechol, a small amount of which was present in the raw material, with 2 moles of dichlorodiethyl ether.



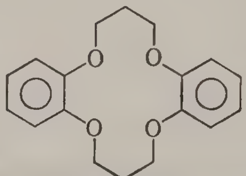
1 2

Finding a remarkable increase in the solubility of the macrocyclic polyether in methanol in the presence of NaOH, Pedersen decided to investigate its properties in detail. He observed that the macrocyclic polyether had the following specific characteristics: it formed stable complexes with salts of alkali metals and alkaline earth metals, and these complexes were soluble in organic solvents. Pedersen speculated that formation of the complexes might be a result of ion-dipole interaction between cations and the negatively charged oxygen atoms symmetrically placed in the polyether ring.

Starting with this hypothesis, Pedersen prepared 49 kinds of macrocyclic polyether with 9- ~ 60-membered rings containing 3 ~ 20 ether linkages. Included were 33 kinds with aromatic rings, 15 kinds with alicyclic rings prepared by hydrogenation of the aromatic rings, and cyclic hexamer of ethylene oxide, some of which are shown in Fig. 1.1.



3
cyclohexyl-12-crown-4



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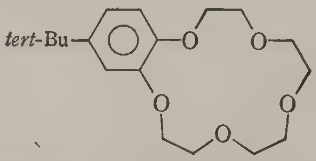

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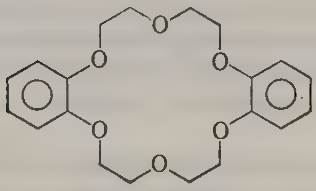
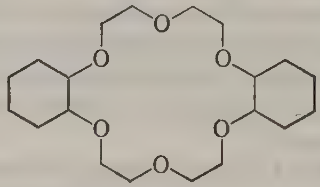
tert-butylbenzo-15-crown-5



2
dibenzo-18-crown-6



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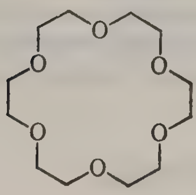
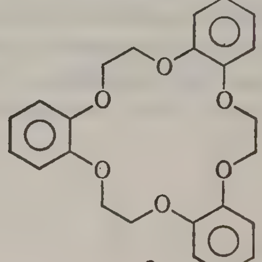


7
18-crown-6



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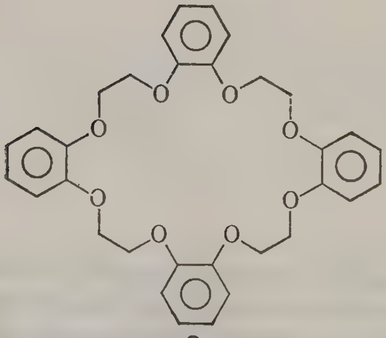
tribenzo-18-crown-6



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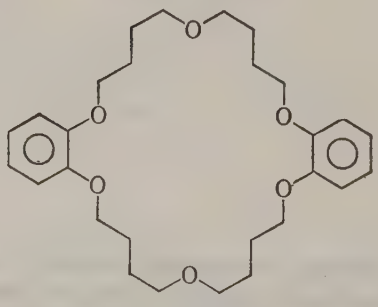
tetrabenzo-24-crown-8



10
dibenzo-26-crown-6

Fig. 1.1 Structural formulas and nomenclature of typical crown ethers

As a result of detailed investigation into complex formation between these macrocyclic polyethers and various metal salts, the following important characteristics were observed which formed the basis for subsequent studies: 1) many of the macrocyclic polyethers having 5 ~ 15 oxygen atoms formed stable complexes with each metal salt of elements in the periodic table—Group Ia (Li^+, Na^+, K^+, Rb^+, Cs^+), Ib (Ag^+, Au^+), IIa (Ca^{2+}, Sr^{2+}, Ba^{2+}), IIb (Cd^{2+}, Hg^+, Hg^{2+}), IIIa (La^{3+}, Ce^{3+}), IIIb (Tl^+), and IVb (Pb^{2+}); 2) the stability of these complexes depended upon the relative size between the ionic radius of the cation and the cavity in the macrocyclic polyether; 3) various inorganic salts of these metal cations were soluble in many organic solvents, including nonpolar or low-polar solvents such as carbon tetrachloride, benzene, and cyclohexane, in the presence of the macrocyclic polyether.2) Pedersen named the macrocyclic polyethers with these specific characteristics "crown compounds" because of their chemical structure and because of the complex, which resembled a crown placed on an ion.

Prior to 1971, Pedersen reported on a series of complex crystals,3) 9 kinds of novel crown compounds,4) 9 kinds of macrocyclic polyether sulfides having S atoms in addition to O atoms,5) and complexation between crown compounds and thiourea and its derivatives.6) His wide-ranging research broke new ground that stimulated the interest of many chemists. Since then, various new crown compounds and their analogues have been synthesized, the structure of the complexes analyzed, and their specific characteristics investigated. In addition, considerable research has explored a wide range of applications in such areas as organic synthesis, polymer synthesis, separation of metal ions, and ion-selective electrode and chemical analysis. Other examples of the rapid and extensive development of this new area are the use of optically active crown compounds for the D, L resolution of amino acids, applications to enzyme models, and employment of the biological activity of crown compounds in biochemistry, biophysics, medicine, and agrochemicals. Many reviews7) and several books8) have been published that discuss crown compounds.

1.2 CLASSIFICATION AND NOMENCLATURE OF CROWN COMPOUNDS

As noted above, "crown" compounds were so named because of their chemical structure and the shape of the complex formed when metal ions were enclosed into the cavity. All of the crown compounds synthesized by Pedersen were macrocyclic polyethers whose basic skeletons were cyclic oligomers of alkylene oxide, mainly ethylene oxide, combined with one or more benzene rings or cyclohexyl rings.

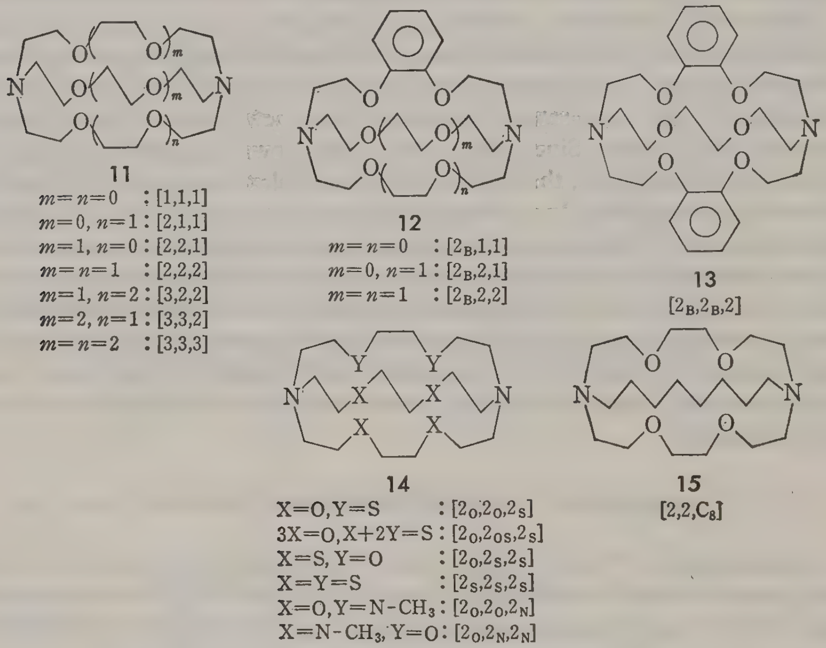
After Pedersen's report, a variety of other macrocyclic compounds were prepared, including some with N and/or S atoms as donors. The review by Christensen *et al.*, published only 7 years after Pedersen's first article, listed 221 kinds of macrocyclic compounds,7,24) and many new crown compounds have been prepared since then. Crown compounds now encompass a wide range of cyclic compounds, including the macrocyclic polyethers defined by Pedersen, now known as crown ethers.

Crown compounds have not yet been defined strictly, but they are generally described as "macrocyclic compounds having hetero atoms such as O, N, or S as the electron donor atoms in their ring structures and the property of incorporating cations into their cavities." Multicyclic compounds consisting of two or more rings may also be crown compounds. Crown compounds in a broad sense are sometimes termed "multidentate macrocyclic compounds" or "macroheterocycles."

The macrocyclic polyethers having only O atoms as the donor atoms are termed crown ethers. Cyclic amino ethers in which N (NH, NR) substitutes for some of the O donor atoms of a crown ether are known as azacrown ethers, and cyclic polyether sulfides in which S substitutes for some of the O donors are called thiacrown ethers. Cyclic compounds with 3 kinds of donor atoms, O, N, and S, are called azathiacrown ethers. Macrocyclic polyamines having only N atoms as donors are termed azacrowns, and macrocyclic polysulfides having only S atoms as donors are labeled thiacrowns, in a broad sense.

Among the multicyclic crown compounds are the cage-type bicyclic crown compounds, whose two bridgeheads consist of two N⋞ groups (shown in Fig. 1.2), synthesized by Lehn *et al.*[8.1,9~11)] Compared to crown ethers, these compounds bind metal ions tightly into the space in their lattices with higher ion selectivity and greater stability of the resulting complexes. For these reasons, considerable attention has been paid to these compounds, as well as to crown ethers. These cage-type bicyclic crown compounds were named "cryptands" and their complexes "cryptates" by Lehn *et al.* The origin of the terms is the Greek word *χρυπτεω* ("hide" in English), meaning cavity, from which is also derived the name for the rare gas krypton.

The various types of crown compounds are classified in Table 1.1 and typical examples are shown in Fig. 1.3.



11

$m=n=0$: [1,1,1]
$m=0, n=1$: [2,1,1]
$m=1, n=0$: [2,2,1]
$m=n=1$: [2,2,2]
$m=1, n=2$: [3,2,2]
$m=2, n=1$: [3,3,2]
$m=n=2$: [3,3,3]

12

$m=n=0$: $[2_B,1,1]$
$m=0, n=1$: $[2_B,2,1]$
$m=n=1$: $[2_B,2,2]$

13

$[2_B,2_B,2]$

14

X=O, Y=S : $[2_O,2_O,2_S]$
3X=O, X+2Y=S : $[2_O,2_{OS},2_S]$
X=S, Y=O : $[2_O,2_S,2_S]$
X=Y=S : $[2_S,2_S,2_S]$
X=O, Y=N-CH$_3$: $[2_O,2_O,2_N]$
X=N-CH$_3$, Y=O : $[2_O,2_N,2_N]$

15

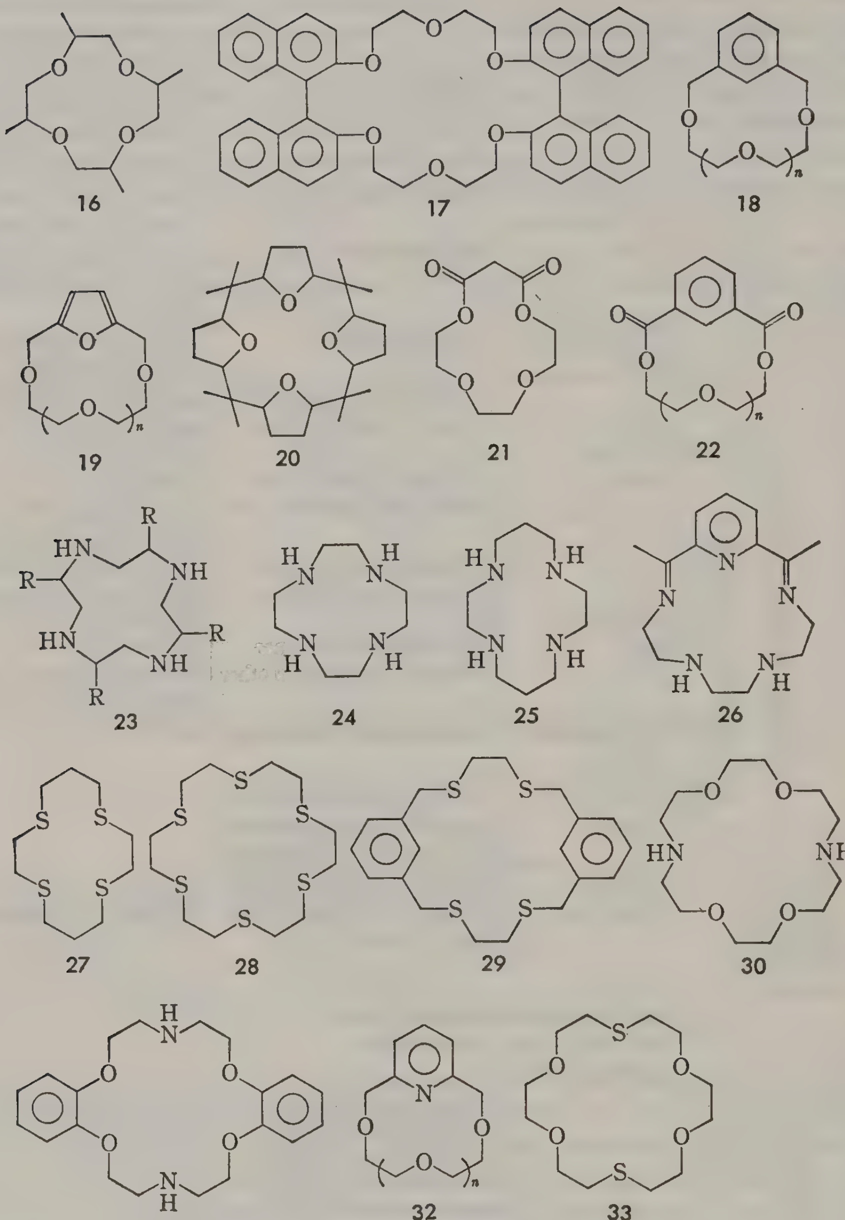
$[2,2,C_8]$

Fig. 1.2 Structural formulas and nomenclature of cryptands

Table 1.1 Classification of crown compounds.

Number of crown ring	Classification by donor atom(s)			Subclass	Examples
Monocyclic crown compound	Single donor crown compound	O	Cyclic polyether (crown ether in a narrow sense)	Aliphatic crown ether	cyclic oligomers of alkylene oxides (**7**, **16**†)
				Aromatic crown ether	benzo-(**2**, **4**, **5**, **8**, **9**, **10**), binaphthyl-(**17**†), cyclophane-type (**18**†), etc.
				Alicyclic crown ether	cyclohexyl-type (**3**, **6**)
				Heterocyclic crown ether	Containing furane ring (**19**†) and THF ring (**20**†)
				Cyclic polyether ester	lactone-type (**21**†, **22**†)
		N	Cyclic polyamine	Cyclic oligomer of azilidine	cyclic oligomers of ethylene imine derivaltives (**23**†)
				Cyclic polyamine	cyclen (**24**†), cyclam (**25**†); Containing pyridine ring (**26**†), etc.
		S	Cyclic polythiaether	Cyclic polysulfide	cyclic polyalkylene sulfide, etc. (**27**†, **28**†, **29**†)
	Multi-donor crown compound	O, N	Azacrown ether	Aliphatic azacrown ether	aminocrown ether (**30**†)
				Aromiatic azacrown ether	benzo-(**31**†), cyclophane-type, etc.
				Alicyclic azacrown ether	cyclohexyl-type
				Heterocyclic azacrown ether	Containing pyridine ring (**32**†), etc.
		O, S	Thiacrown ether	Aliphatic thiacrown ether	cyclic polyether sulfide (**33**†)
				Aromatic thiacrown ether	benzo-(**34**†), cyclophane-type, etc.
				Alicyclic thiacrown ether	cyclohexyl-type
				Heterocyclic thiacrown ether	Containing thiophene ring **35**†), furane ring, etc.
		N, S	Cyclic azathia ether	Aliphatic cyclic azathia ether	**36**†
		O,N,S	Azathiacrown ether	Aliphatic azathiacrown ether	**37**†
				Aromatic azathiacrown ether	
				Heterocyclic azathiacrown ether	
Multicyclic crown compound	Single donor multicyclic crown compound	O	Multicyclic crown ether	Separated bicyclic crown ether	**38**†, **41**
				Bicyclic crown ether (2 bridgeheads: C atoms)	**39**† (can be classified as one kind of cryptands)
	Multi-donor multicyclic crown compound	O, N, S	Separated multicyclic multi-donor crown compound	Separated bicyclic azacrown ether	**40**†
		O, N	Cryptand	Bicyclic crown ether (2 bridgeheads: N atoms)	**11**, **12**, **13**, **15**
		O, N		Tricyclic crown ether (4 bridgeheads: N atoms)	**42**†
		O, N		Spherical cryptand (4 bridgeheads: N atoms)	**43**†
		O, N		Bicyclic azacrown ether (2 bridgeheads: N atoms)	**14** (X = O, Y = N − CH_3; X = N − CH_3, Y = 0)
		N, S		Bicyclic polythiaether (2 bridgeheads: N atoms)	**14** (X = Y = S)
		O,N,S		Bicyclic thiacrown ether (2 bridgeheads: N atoms)	**14** (X = O, Y = S; 3X= O, X + 2Y = S; X =S, Y = 0)
		O,N, B, P		Cryptand whose bridgeheads consist of B or P atoms.	**44**†, **45**†

†, *See* Fig. 1.3



16 17 18

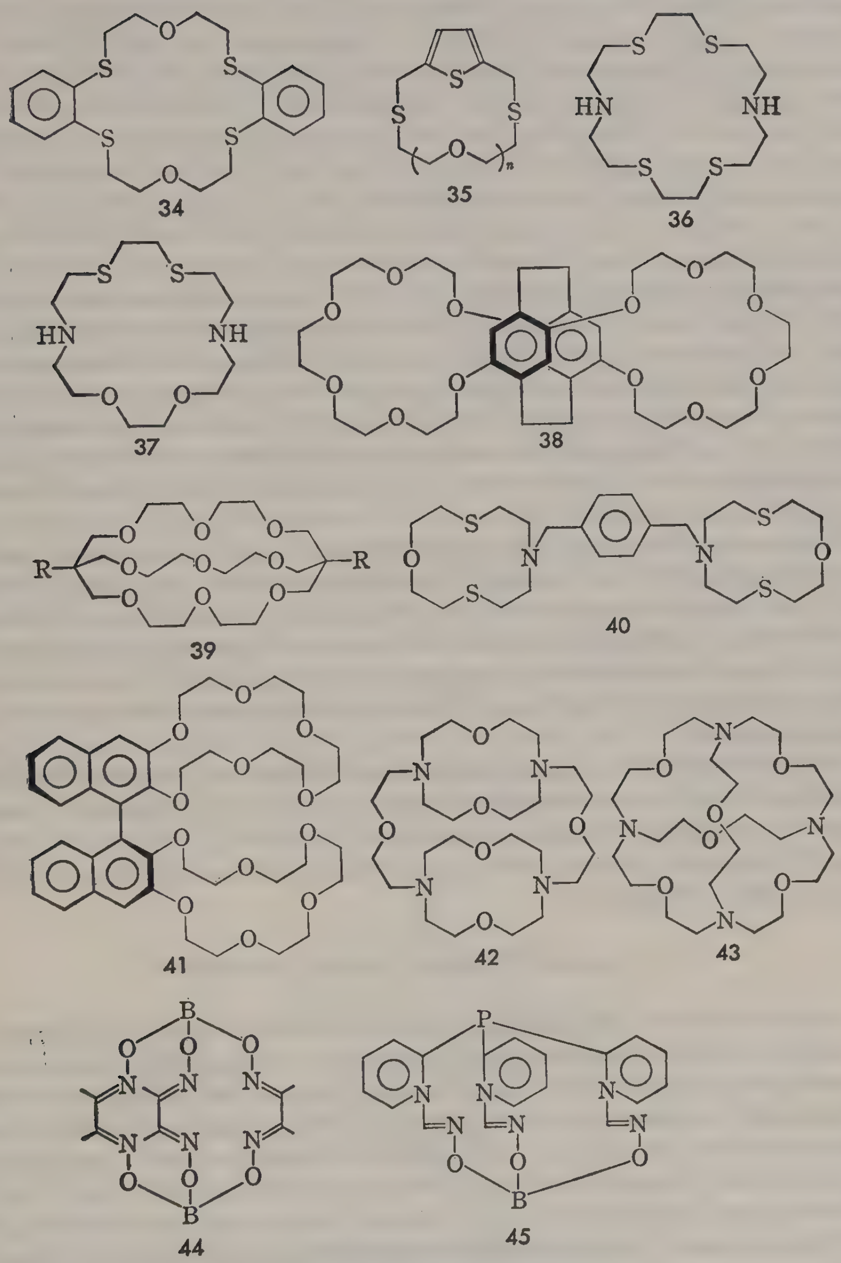
19 20 21 22

23 24 25 26

27 28 29 30

31 32 33

Fig. 1.3 Typical examples of crown compounds



34 35 36 37 38 39 40 41 42 43 44 45

Fig. 1.3—*Continued*

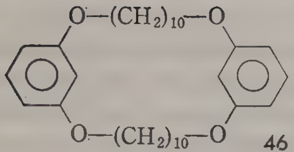
Pedersen proposed convenient, brief names for the nomenclature of the crown ethers, because their formal names, following IUPAC nomenclature rules, are quite long and complicated; for example, crown ether 2, the first one synthesized, is formally labeled "2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene." The names appended to the structural formulas for typical crown ethers in Fig. 1.1 follow Pedersen's usage. His general rules for nomenclature are as follows: for crown ethers having an aromatic or cyclohexyl ring, the crown names consist of 1) the kind and number of the group substituted in the polyether ring, 2) the total number of atoms which constitute the crown ring (corresponding to the cavity size), 3) the term "crown," and 4) the number of O donor atoms, that is, the ether linkage in the crown ring combined with hyphens, such as "benzo-15-crown-5" and "dicyclohexyl-18-crown-6." For crown ethers without any substituted group, the crown names consist of [the total number of atoms which constitute the crown ring]-["crown"]-[number of O donor atoms], such as "18-crown-6." These nomenclature rules cannot always completely describe the exact mode of bonding and position of the substituents, or the kind and position of the alkylene group in the crown ring, but they are very convenient for conventional crown ethers with symmetrical or comparatively simple structures. These crown names are now commonly used and have been adopted in science magazines, including *Chemical Abstracts.*

For azacrown ethers and thiacrown ethers, similar crown names are sometimes used idiomatically, as, for example, "18-diazacrown-6" (or "diamino-18-crown-6") (**30**), "1,10-dithia-18-crown-6" (or "18-dithiacrown-6") (**33**), but it is difficult or impossible to express the exact position of the hetero atoms. Thus, in order to represent azacrown ethers, thiacrown ethers, and crown compounds other than conventional crown ethers exactly, it is preferable to follow IUPAC nomenclature or to show the structural formula.

For cryptands, Lehn *et al.* proposed a nomenclature using three numbers or letters in brackets for the kind and number of hetero atoms which constitute the rings and the kind of substituents; examples are cryptand [1,1,1] and [2,2,2]-crypt.[8.1)] The complexes of bicyclic and tricyclic cryptands are sometimes known in general as [2]-cryptates and [3]-cryptates, respectively.

1.3 BACKGROUND OF CROWN COMPOUNDS

Since the discovery of crown compounds there has been remarkable expansion in the research on the characteristics and applications of this particular group of compounds within a period of only 10 years. It is likely that such an explosive development was historically inevitable. Of course, many cyclic compounds were known before the discovery of crown compounds. Of those related to crown compounds, cyclic polyether (**46**) derived from resorcinol was synthetized by Lüttringhaus and Ziegler[12)] in 1937. In the same year, Lüttringhaus *et al.* synthesized a series of cyclic polyethers derived from hydroquinone,[13)] 1,5- and 2,6-dihydronaphthalene,[13)] 4,4′-dihydroxydiphenyl and 4,4′-dihydroxydiphenylmethane,[14)] and 4,4′-dihydroxyphenyl ether.[15)] Cyclic polyethers derived from hydroquinone were also synthesized by Adams and Whitehill[16)] in 1941.



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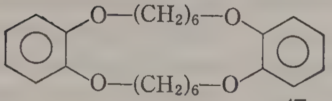

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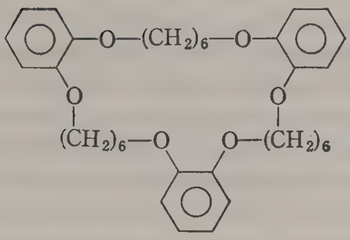
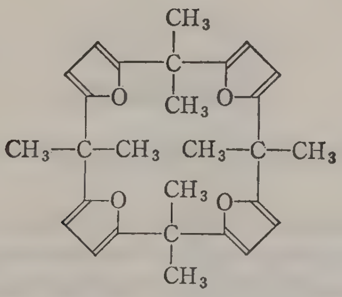


48

Among the compounds more closely related to crown compounds, Lüttringhaus and Sichert-Modrow synthesized compounds **47** and **48** derived from cathecol in 1956.17)

Subsequently, Stewart *et al.* found in 1957 that ethylene oxide led to a cyclic tetramer, 12-crown-4, in 10% yield as a by-product along with high molecular weight linear polyoxyethylene, when ethylene oxide was treated with $AlEt_3$ or $ZnEt_3$ catalyst in benzene.18) In the same year, Wilkinson *et al.* obtained a cyclic tetramer of propylene oxide in 38% yield by means of cationic polymerization of the monomer using $BF_3 \cdot Et_2O$ as a catalyst,19,20) and Colclough and Wilkinson reported in 1966 that small amounts of cyclic dimer, trimer, and tetramer of propylene oxide were formed by treatment of $AlMe_3$.21) Furthermore, Wilkinson *et al.* found that a cyclic tetramer of propylene oxide dissolved trace amounts of metallic potassium and sodium-potassium alloy to give an an unstable blue solution,19,20) but they did not identify the complex formation.

In other work, Brown *et al.* reported between 1955 and 1958 that a cyclic tetramer, pentamer, or hexamer, as shown in example **49**, was formed as the by-product of linear dimer, trimer, or tetramer when furan and ketone were condensed with an acid catalyst.22~24) These cyclic oligomers are now broadly classified as heterocyclic crown ethers.



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While some macrocyclic polyethers had been synthesized before the discovery of crown compounds in 1967, the formation of stable complexes by binding of cations such as alkaline metal ions had not been achieved so Pedersen is given the credit as the one who first recognized the complexation ability and described the specific characteristics of the complexation.

It has long been known that an ether such as diethyl ether is an excellent solvent for Grignard reactions and for syntheses of organo-sodium compounds. Cyclic ethers such as 1,4-dioxane and THF have also been found to be excellent solvents for various ionic reactions, and particular properties of such cyclic ethers were observed during the formation of sodium-naphthalene complex and living polymerization with this complex,25~27) in the solubilization of metallic potassium,28) and so on. In addition, linear polyethers named "glymes," such as monoglyme (1,2-dimethoxyethane) and diglyme (diethylene glycol dimethyl ether),29) which were synthesized in 1925, were found to act as even better solvents than THF in the 1950s. Since then, many chemists have been interested in the action mechanism of such aprotic polar solvents having ether linkages, both from the standpoint of solution theory and of reaction theory, and various phenomena related to solvation, ionization, and solvent effect on reaction rate have been clarified.30~35)

It is currently thought that the action of THF and glymes is due to stabilization by coordination of an ether linkage having two lone pairs, that is, negatively charged O atoms linked to a cation, as shown in Fig. 1.4. Thus, in terms of solvent properties, crown ethers could be viewed as lying on an extension line from THF and glymes. In fact, the characteristics of linear polyethers have attracted new interest under the stimulant of the research and development of crown ethers. Non-cyclic polyethers, such as longer chain glymes and polyethylene glycols, such as the analogues of crown ethers, have been reassessed in terms of their complexation abilities, solubilization abilities for inorganic salts, and applications for organic syntheses.8,12,36~39)

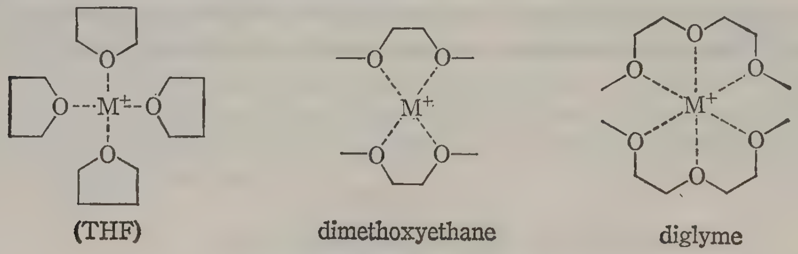


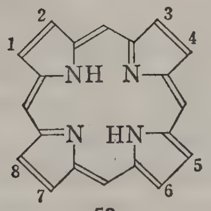
Fig. 1.4 Coordination of THF and glymes to a cation

In these noncylic polyethers, however, the relative position between O donor atoms and a coordinated cation is not fixed when the complexes are formed because ligating molecules are not restricted by each other and their degree of freedom is large. In contrast, ligating O atoms are located in a regular manner with an equal distance to the cation in complexes of cyclic crown ethers, so they are very stable to entropy, and crown ethers have excellent cation selectivities because the bound cation is fitted to the cavity size. Furthermore, the complexes are soluble in organic solvents because of hydrophobic residual groups on the crown ethers. These points illustrate the advantages to crown ethers which cannot be matched by linear polyethers.

Dipolar aprotic solvents such as DMF, DMSO, and HMPA also have an excellent capacity for ionization and can dissolve inorganic salts such as alkali metal salts and alkaline earth metal salts, so they have been used for nucleophilic substitution reactions since around 1950. The molecules of these solvents also have negatively charged O atoms which can coordinate to a metallic cation and stabilize it; they form so few anions that the activity of negatively charged nucleophilic reagents is not diminished. Furthermore, the negatively charged O atoms undergo electrostatic interactions with carbonium ions, which are the intermediates of nucleophilic substitution reactions, and ionization is accelerated by the stabilization resulting from solvation.

Although crown ethers resemble these dipolar aprotic solvents in the mechanism of solubilization in various organic reactions, as described in detail in Chapters 2 and 3, they differ in that only one molecule of a crown compound such as a crown ether or cryptand acts as the solvent. It is thus possible to dissolve inorganic salts in nonpolar or low-polar solvents such as benzene, hexane, and halogenated hydrocarbons and to carry out reactions in solution in the presence of a catalytic amount of crown compound or a quantity stoichiometric to the inorganic salt.

Together with the development of crown ether chemistry, there has been progress in coordination chemistry and complex chemistry concerned with transition metal complexes, as well as commercialization of complex catalysts, and the mechanism of binding of metallic ions by porphyrin derivatives such as hemoglobin and chlorophyll has been investigated. Porphyrin derivatives (**50**) have a skeleton composed of cyclic amines with N atoms as the donors, and they have an affinity for soft cations such as transition metal ions and heavy metal ions because the N donor is classified as a base. Various complexes of porphyrin derivatives with transition metals and heavy metals have been prepared, and their characteristics and catalytic activity have been examined.[40,41] Other kinds of macrocyclic polyamines, azacrown compounds such as cyclen (**24**) and cyclam (**25**), have been available since around 1960 and their complexation abilities and the characteristics of their complexes have been investigated.[42~45]



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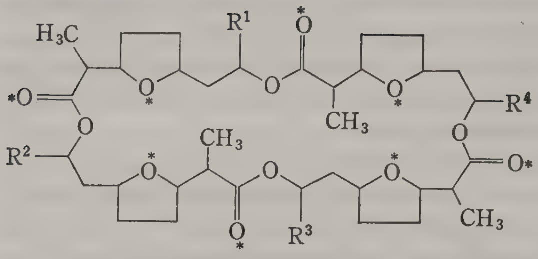
Similarly, a variety of macrocyclic polysulfides (cyclic polythiaethers, thiacrown compounds) with S donors, which are classified as soft bases, have been formulated and found to form stable complexes with transition metal ions and heavy metal ions which are considered to be soft cations.[44,46]

In contrast to the complexes of cyclic polyamines and cyclic polysulfides which are formed by coordinative bonds with transition metal ions or heavy metal ions, crown ethers form complexes by ion-dipole interactions with hard cations such as Group I macrotetrolides



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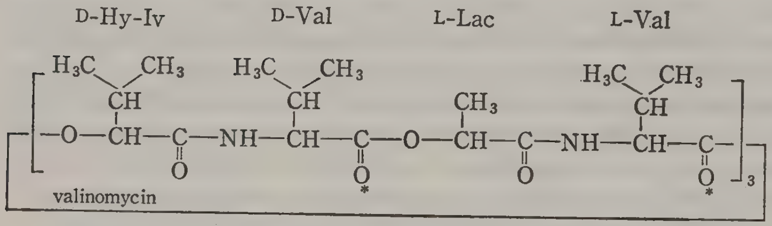
$R^1=R^2=R^3=R^4=CH_3$	nonactin
$R^1=R^2=R^3=CH_3$, $R^4=C_2H_5$	monactin
$R^1=R^3=CH_3$, $R^2=R^4=C_2H_5$	dinactin
$R^1=CH_3$, $R^2=R^3=R^4=C_2H_5$	trinactin
$R^1=R^2=R^3=R^4=C_2H_5$	tetranactin

depsipeptides



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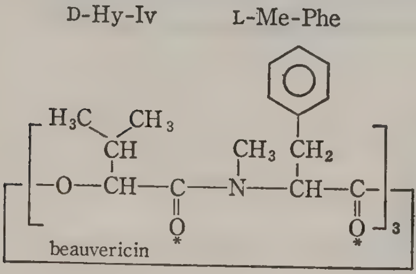

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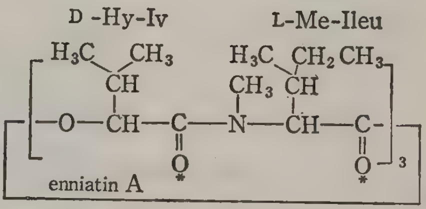

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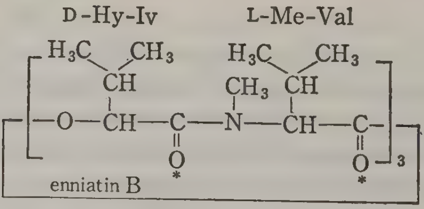

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Fig. 1.5 Examples of chemical structures of ionophore antibiotics and II metal cations which were previously unknown to form complexes. This is the main reason why many chemists have had such an interest in crown ethers.

Recent progress in biochemistry and biophysics is also closely related to the development of crown compounds. An example is the case of valinomycin, an antibiotic which was isolated from radiobacilli in 1955 and whose structure Shemyakin *et al.* determined to be a cyclic dodecadepsipeptide (**52**) in 1963.[47] Its mechanism of action was investigated after Pressman and Moore observed activity by alkali metal ions in the mitochondria of rat liver.[48] The investigation revealed that valinomycin selectively formed a complex with K^+, and that K^+ was transported actively in a direction opposite to the concentration gradient and energy was consumed when valinomycin was added to mitochondrial fraction. This was an important discovery for understanding the function in living membrane of Na^+-K^+-ATPase as an ion pump for active transport across a cell membrane, selective permeation of Na^+ and K^+ in the excitation of nerve membrane, and the transport of protons through membrane by oxidative phosphorylation. Subsequently, a series of antibiotics called "ionophores" were developed in which a specific ion was selectively bound and transported through living membrane.[8,6] It was hypothesized that a cyclic structure carrying donor atoms was necessary for the characteristic activity of an ionophore because almost all antibiotics that function as selective ion carriers are cyclic tetrolides or cyclic depsipeptides, like the examples shown in Fig. 1.5. It was thus considered possible that compounds that acted as selective ion carriers might be synthesized. At just this time, crown ethers were discovered and their importance was recognized not only in the field of chemistry but also in biochemistry and biophysics.

Life science has recently attracted considerable attention. Clearly, research on the phenomena of life fills the gap between biology and chemistry and also provides an impetus for the creation of an innovative chemical industry employing both biochemical and synthetic chemical techniques. When the results of research in life science can be applied, the chemical industry may be brought closer to the ideal state, saving resources, saving energy, and using pollution-free processes.

The most important issues which chemical technology must address in life science are a clarification of the mechanism of natural processes and then synthetic replication of the mechanism in a living system, as, for example, development of a catalyst that functions like an enzyme and an artificial membrane that behaves like a living membrane. In enzyme reactions, only the desired material is selectively produced at a surprisingly fast rate of reaction under very mild conditions such as ordinary temperature, atmospheric pressure, a water medium, and an almost neutral pH. As the structures and the reaction mechanisms of enzymes have been gradually elucidated, research on enzyme models has recently provided a basic framework with which to understand the function of enzymes. There are many observations which suggest similarities between crown compounds and naturally occurring substances; for example, the behavior of cycloamylose resembles that of hydrolase[49,50] and the catalytic activity of porphyrin derivatives is caused by binding of metal ions.

It is anticipated that crown compounds will play a role in the preparation of catalysts that function like enzymes. As described in Chapter 5, Cram *et al.* have already synthesized optically active crown compounds having chiral cavity with and without the substituents which act, tentacle-like, as the bonding arm, and they have achieved optical resolution of diastereomers with these optically active crown compounds. They have subsequently performed experiments in which the optically active crown compounds were employed as models of the incorporation site of enzymes on the substrates.[7.31, 7.32, 8.9)] This research area has been named "host-guest" chemistry by Cram.

The remarkable development of crown compounds in the short time since Pedersen's accidental discovery had its foundation in the history and background described here. Further growth in this new field, including practical application of crown compounds, can be anticipated because of their abundant possibilities.

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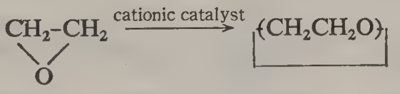
CHAPTER 2

Synthesis and Properties of Crown Compounds

2.1 General Aspects

As shown in the classification in Table 1.1 and illustrated in Fig. 1.3, "crown compounds" are defined generically as macrocyclic compounds having electron donor atoms such as O, N, and S on the cyclic structure; the term also includes bi- or polycyclic crown compounds consisting of two or more rings, which are represented by cryptands. As a matter of course, there is a great variety of synthetic methods for such crown compounds, but the most important aspect of any synthesis is a reduction of the side reaction that produces linear polymers in order to obtain the cyclic compound preferentially from the cyclization reaction.

In general, the Williamson reaction Eq. (2.2) or other basic reactions for the synthesis of ethers, secondary amines, and thioethers, shown in Eqs. (2.1) ~ (2.5), are often applied to bifunctional compounds for the synthesis of crown compounds. To depress the formation of linear polymer by-products, the following methods are frequently employed: 1) a high dilution method, 2) two-step condensation, and 3) a template reaction.



(2.1)

$$ROH + R'Cl \xrightarrow{NaOH} ROR' \tag{2.2}$$

$$ROH + R'OTs \xrightarrow{KOH} ROR' \tag{2.3}$$

$$ROH_2 + R'\underset{\overset{\|}{O}}{C}Cl \longrightarrow RNH\underset{\overset{\|}{O}}{C}R' \xrightarrow{H_2} RNHCH_2R' \tag{2.4}$$

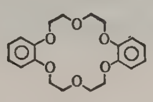
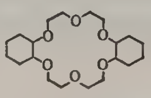
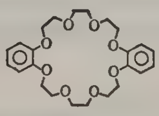
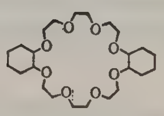
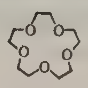
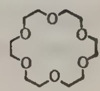
$$RSH + R'Cl \xrightarrow{NaOH} RSR' \tag{2.5}$$

Method 1 is a reaction procedure which is carried out in a highly diluted solution to lower the probability of intermolecular collisions after the condensation of one of the terminal groups on both bifunctional compounds; this depresses chain extension, caused by intermolecular reaction, and encourages ring closure, which is an intramolecular reaction. In practice, the reactants are held in separate dropping funnels and are added drop by drop to a large amount of a solvent containing the condensing agent. Method 2 has two steps, condensation of one of the terminal groups on both bifunctional compounds and separation of the reaction product followed by a ring closure reaction. Method 3 is a reaction using a metal ion whose ionic diameter corresponds to the cavity size of the desired crown ring and thus acts as a template. Recently, there has been significant progress in the development of such template condensation or template polymerization reactions for the synthesis of crown compounds.

Since 1978, typical aromatic and alicyclic crown ethers such as dibenzo-18-crown-6, dibenzo-24-crown-8, and dicyclohexyl-18-crown-6, and cyclic oligomers of ethylene oxide such as 15-crown-5 and 18-crown-6, have been produced commercially using the above techniques and have been offered for sale by Nippon Soda Company[1] in Japan, and by Aldrich Chemical Company, Parrish Chemical Company, and PCR in the United States. Borregaard Industries in Norway has also commercialized the cyclic tetramer, pentamer, and hexamer of ethylene oxide. Some of cryptands have been offered for sale as chemical reagents by E. Merck & Company in West Germany. Physical properties of the crown ether sold by Nippon Soda Company are shown in Table 2.1.

This chapter will discuss the methods for synthesizing the crown compounds

TABLE 2.1 "NISSO-CROWN ETHERS," commercialized in Japan

Crown Name	Dibenzo-18-crown-6	Dicyclohexyl-18-crown-6	Dibenzo-24-crown-8	Dicyclohexyl-24-crown-8	15-crown-5	18-crown-6
Abridged commercial name	B–18	C–18	B–24	C–24	O–15	O–18
						
Molecular formula	$C_{20}H_{24}O_6$	$C_{20}H_{36}O_6$	$C_{24}H_{32}O_8$	$C_{24}H_{44}O_8$	$C_{10}H_{20}O_5$	$C_{12}H_{24}O_6$
Molecular weight	360.41	372.47	448.52	460.61	220.27	264.32
Appearance	white fine needle crystal	colorless crystal	fine white crystal	colorless viscous liquid	colorless viscous liquid	colorless crystal
Melting point (°C)	163 ~ 164[2] 164[4] 162.5 ~ 163.5[5]	mixture of isomers†1 38 ~ 53[2] 38 ~ 54[5]	103 ~ 104[2] (113 ~ 114)[4] †2 103 ~ 104[6]	<26[4]	−32.4[2] freezing point	34 ~ 42[2] 39 ~ 40[4,7] 36.5 ~ 38.0[8]
Boiling point (°C)	380[9]				102.0 (0.12mmHg)[3] 108.0 (0.2mmHg)[3] 78 (0.05mmHg)[10]	117 (0.1mmHg)[3] 130 (0.2mmHg)[3] 149 (0.5 mmHg)[3] 164 (1 mmHg)[3]

(*Continued*)

TABLE 2.1—*Continued*

Crown Name	Dibenzo-18-crown-6	Dicyclohexyl-18-crown-6	Dibenzo-24-crown-8	Dicyclohexyl-24-crown-8	15-crown-5	18-crown-6
	380				100 ~ 135 (0.2 mmHg)10)	
Specific gravity2)				$d_4^{19.3}$1.102	$d_4^{20.3}$1.113	
Viscosity(cp)2)				290 (24.3°C)	28.8 (20°C)	
n_D^{20} 2)				1.489	1.464	
Flash point (closed)(°C)2)					132	
Hygroscopicity (Moisture wt%)2) [25 ± 0.5°C, RH 50 ~ 55%, 10 days]	0.4	0.72	0.6	1.3	7.38	2.29
ir	*cf.* Fig. 2.3	*cf.* Fig. 2.5			(melt smear, cm^{-1})10) 2875, 1445 1350, 1280 1250, 1185 975, 925	(melt smear, cm^{-1})8) 2875 (alkane CH) 1450 (alkane CH) 1350 (alkane CH) 1120 ether
uv	*cf.* Fig. 2.1, Fig. 2.2 (methanol solution)5) 223 nm (ε 17500) 275 nm (ε 5500)					
¹H nmr	*cf.* Fig. 2.6 ⟨$CDCl_3$ solution⟩5) 6.8 ~ 7.0 ppm (8H, aryl CH) 3.8 ~ 4.3 ppm (16H, CH_2–O)	cf. Fig. 2.7 ⟨C_6D_6 solution⟩5) 3.3 ~ 4.0 ppm (2 OH, O–CH) 0.9 ~ 2.2 ppm (10H, aliph CH)	⟨$CDCl_3$ solution⟩4) 232 cps, 237 } (8H, CH_2–O) 247 cps (8H, CH_2–O) 414 cps (8H, aryl CH)		⟨CCl_4 solution⟩10) 3.58 ppm ¹³C nmr10) ⟨$CDCl_3$ Solution⟩ 70.21 ppm	⟨CCl_4 solution⟩5) 3.56 ppm

†1*cis-syn-cis*: mp 61–62.5°C11)
cis-anti-cis: double melting point at 69–70°C and 83–84°C.12)
†2This value was corrected to be 103–104°C.6)

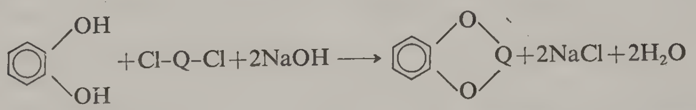
classified in Table 1.1 and the physical properties of typical crown compounds. The reader is asked to refer to the original papers or the review by the author13) for the details of each synthetic method. The syntheses and properties of various crown compounds including heterocycles have been summarized in a recent review.14)

2.2 CYCLIC POLYETHERS (CROWN ETHERS)

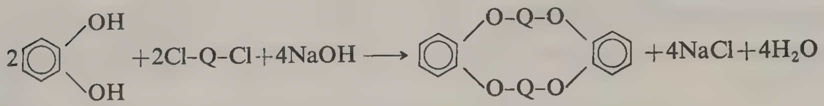
2.2.1 Aromatic Crown Ethers

An aromatic crown ether has a basic skeleton consisting of a cyclic oligomer of alkylene oxide and one or more aromatic rings attached to the skeleton. Benzo- or dibenzo-crown ethers, including dibenzo-18-crown-6, the crown compound first synthetized, are typical aromatic crown ethers.

The basic method for the synthesis of aromatic crown ethers, and the one used by Pedersen,[4)] is the Williamson condensation reaction using catechol and dichloroether as the raw materials. The reactions are shown in Eqs. (2.6) ~ (2.8).



(2.6)



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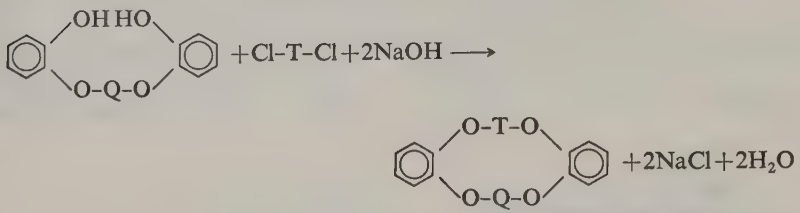


(2.8)

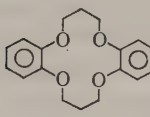
In general, Q and T represent divalent organic group, $\{CH_2CH_2O\}_nCH_2CH_2$- ($n \geq 1$)

Equation (2.8) illustrates the two-step condensation method. First, one of the hydroxyl groups of catechol is blocked by a protective group, such as a benzyl or tetrahydropyranyl group which is stable against alkalis, then 2 moles of the product is condensed with Cl–Q–Cl, followed by removal of the protective group and condensation with Cl–T–Cl. The aromatic crown ethers with odd numbers of oxygen donor atoms are generally synthesized with this method, but it is also applicable for the synthesis of those with even numbers.

In both aromatic crown ethers and the other crown compounds, the most common alkylene group $(-CH_2-)_n$ in Q and T, which compose the polyether ring, is the ethylene group, $n = 2$, and the next most frequent is the propylene group, $n = 3$. The reasons for this are as follows: 1) ethylene oxide and its derivatives are readily available as the starting material, 2) the structure of the polyether ring exhibits less strain and greater stability, 3) the complexes formed with cation are very stable, 4) these groups provide suitable values for the hydrophilic/lipophilic ratio, which is the factor controlling the solubilization of formed complexes in organic solvents. Only a few crown compounds have been synthesized with a methylene group, $n = 1$, $-CH_2-$, as the alkylene group in the polyether ring because of difficulties in the syntheses and instability of the ring structure analogous to acetals or trioxane. In general, for the syntheses represented in Eqs. (2.6) ~ (2.8), 1-butanol or dioxane is used as a solvent and the reaction is carried out by the high-dilution method under reflux for 12 ~ 24 hours. Pedersen synthesized 33 kinds of aromatic crown ethers with this method.[4)] Table 2.2 lists the synthetic methods, yields, and melting points of the aromatic crown ethers synthesized by Pedersen.

TABLE 2.2 Synthetic methods of typical crown ethers[4)]

Constitutional	Crown name (abridged)	Reaction equation	Yield (%)	mp (°C)
4	Dibenzo-14-crown-4	(2.8)	27	150 ~ 152
56 $n = 1$	Benzo-15-crown-5	(2.6)	62	79 ~ 79.5
56 $n = 2$	Benzo-18-crown-6	(2.6)	60	43 ~ 44
57 $m = n = 1$	Dibenzo-18-crown-6	(2.7)	45	164
	Dibenzo-18-crown-6	(2.8)	80	164
57 $m = 1, n = 2$	Dibenzo-21-crown-7	(2.8)	36	106.5 ~ 107.5
57 $m = n = 2$	Dibenzo-24-crown-8	(2.7)	38	103 ~ 104†
57 $m = n = 3$	Dibenzo-30-crown-10	(2.7)	>6	106 ~ 107.5
57 $m = n = 8$	Dibenzo-60-crown-20	(2.8)	41	<25
8	Tribenzo-18-crown-6	(2.8)	28	190 ~ 192
9	Tetrabenzo-24-crown-8	(2.7)	18	150 ~ 152



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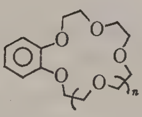

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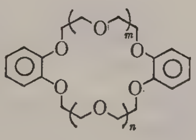

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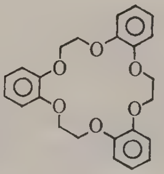

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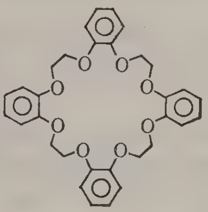

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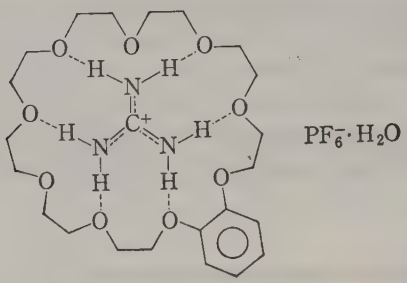
†Pedersen reported the temperature to be 113 ~ 114°C.[4)] However, it was recently corrected to 103–104°C.[6)]

Some of compounds were obtained in good yields without utilization of the high-dilution technique. For example, dibenzo-18-crown-6 (**2**) was prepared by means of the two-step condensation method in a 39 ~ 48% yield.[5)] In this procedure a, 1-butanol (2 *l*) solution of catechol (3 moles) was refluxed after adding NaOH (3.05 moles), and then a 1-butanol (150 m*l*) solution of dichloroethylether (1.55 moles) was added dropwise with stirring. Then, NaOH (3.05 moles) and a 1-butanol (150 m*l*) solution of dichloroethylether (1.55 moles) were again added and refluxed. In this case, it is thought that Na^+ acts as the template, so that the cyclization reaction predominates.

Madan and Cram reported that guanidium ion was used as the template in the synthesis of benzo-27-crown-9 (**58**).[15)]

After Pedersen's reports appeared, a variety of aromatic crown ethers were synthesized with aromatic ring other than benzene, such as biphenyl,[16)] 2, 3-naphthayl,[4)] binaphthyl,[16,17)] and hydroquinone[18)] groups. Among these compounds, the crown



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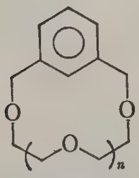
ethers with a 1, 1′-binaphthyl group have an optical activity (atrop isomerism) caused by rotational hindrance of the binaphthyl group. Cram and his coworkers have developed techniques to study the optical resolution of diastereomers, and they have used such chiral crown ethers as enzyme models, as described in Chapter 5.

In addition to the aromatic crown ethers prepared from divalent phenols as the starting material, methacyclophane-type crown ethers **18, 59** have been synthesized by several investigators[18~20] from 1, 3-bis[hydroxymethyl]benzene or 1, 3-bis[bromomethyl] benzene. The template effects of K^+ were observed in these syntheses. Paracyclophane-type crown ethers were also produced.[19,20]



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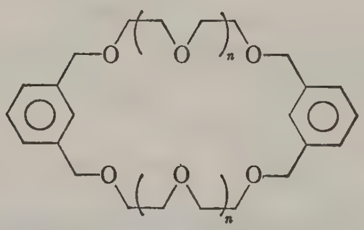

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Generally speaking, aromatic crown ethers are barely soluble in water, alcohols, and conventional solvents at room temperature, but they are readily soluble in methylene chloride, chloroform, pyridine, and formic acid. The solubility of dibenzo-18-crown-6 and its complex with KSCN in different solvents at 26 ± 0.5°C is shown in Table 2.3. However, the temperature coefficients of the solubilities generally have such large values that recrystallization may be possible. For example, white fibrous or fine needle-like crystals (mp 162.5 ~ 163.5°C[5]) of dibenzo-18-crown-6 can be obtained by means of recrystallization using benzene or 1, 4-dioxane as a solvent. The temperature dependence of the solubility and the solubility curves of aromatic crown ethers are given in Section 2.2.2, Tables 2.6 ~ 2.11 and Figs. 2.9 ~ 2.12, in comparison with those of alicyclic crown ethers and cyclic oligomers of ethylene oxide.

Although aromatic crown ethers themselves have low solubilities, a remarkable

TABLE 2.3 Solubilities of dibenzo-18-crown-6 and its KSCN complex in different solvents at 26 ± 0.5°C[4)]

Solvent	Dielectric constant	solubility (mol/*l*) Dibenzo-18-crown-6	solubility (mol/*l*) KSCN complex
Cyclohexane	2.05	0.00067	0.000007
Carbon tetrachloride	2.24	0.005	—
Benzene	2.28	0.018	—
Chloroform	5.05	0.21	0.02
Ethyl acetate	6.4	0.01	—
THF	7	0.022	—
1–Butanol	7.8	0.001	—
Pyridine	12.5	0.12	0.13
Acetone	21.4	0.0092	0.014
Ethanol	25	0.0089	—
Methanol	33.1	0.001	0.107
Formic acid	58.5 (16°C)	1.06	—
DMF	36.7	0.056	—
Acetonitrile	38.8	0.079	0.063
Nitromethane	39	0.047	0.063
DMSO	45	0.048	>0.27
Water	80	0.00009	†

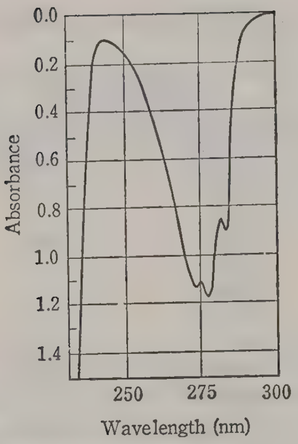
†Decomposed by a high excess of water

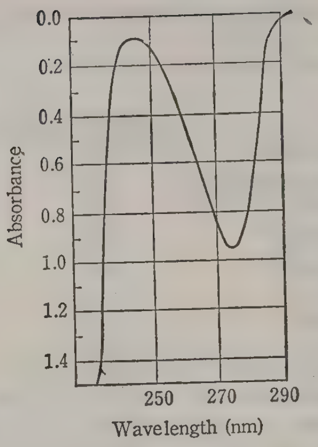
increase in solubility has been observed in many cases when the crown ethers formed complexes with inorganic salts. This is one of the noteworthy characteristics of crown compounds.

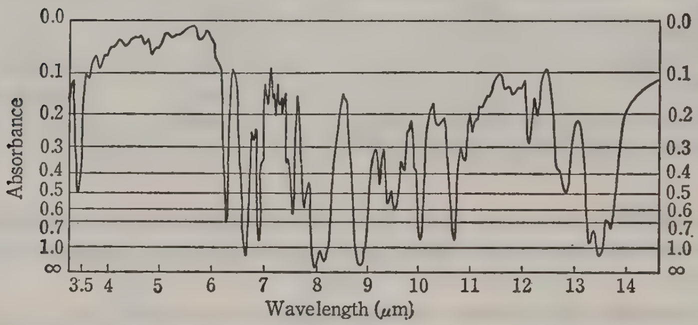
Both aromatic crown ethers and the usual crown compounds are generally stable to heat; for example, it was reported that dibenzo-18-crown-6 was distilled at a boiling temperature of 380°C under atmospheric pressure.[9)] However, there is some chance of oxidation, particularly at higher temperatures and in the molten state because crown ethers have ether linkages, so it is best to store them under nitrogen, and the distillation should be carried out under a nitrogen atmosphere. As the reactivity of crown ethers is the same as that of linear polyethers like polyethylene glycols, crown ethers can be handled in the same manner that these compounds are. The toxicity of crown ethers is described in Chapter 7.

The chemical reactivity of aromatic crown compounds depends, of course, on the aromatic nuclei, and various derivatives can be prepared utilizing this reactivity. As described in Section 2.7, many derivatives have been synthesized so far. Some of these derivatives are especially important in the method of "immobilization" of crown compounds described in detail in Chapter 6.

The uv, ir, nmr, mass, and Raman spectra have been measured for a variety of crown compounds. The uv and ir spectra of dibenzo-18-crown-6, a typical aromatic crown ether, are shown in Figs. 2.1 ~ 2.5 in comparison with those of its KSCN-complex and dicyclohexyl-18-crown-6; the nmr spectrum and data on the mass spectrum are shown in Figs. 2.6 and 2.7 and in Table 2.4 together with those of dicyclohexyl-18-crown-6, 15-crown-5, and 18-crown-6.







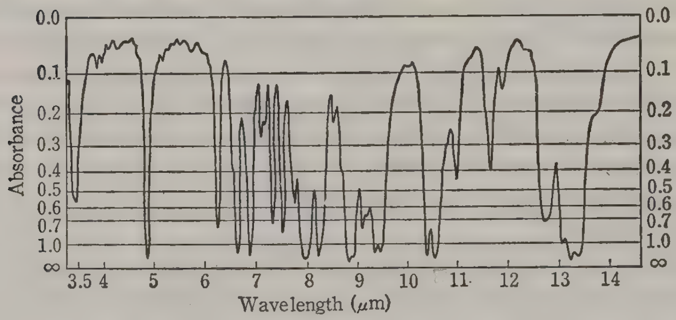


Fig. 2.1 (*above left*) Ultraviolet spectrum of dibenzo-18-crown-6 in cyclohexane. Concentration 0.000255 mol/1; cell path 1 cm; λ_{max} 274nm (ε 4400), 278nm (ε 4700), and 283nm (ε 3600). (Source: Ref. 4. Reproduced by kind permission of the American Chemical Society.)

Fig. 2.2 (*above right*) Ultraviolet spectrum of dibenzo-18-crown-6 in methanol. Concentration 0.000183 mol/1; cell path 1cm; λ_{max} 274nm (ε 5200). (Source: Ref. 4. Reproduced by kind permission of the American Chemical Society).

Fig. 2.3 (*middle*) Infrared spectrum of dibenzo-18-crown-6, KBr pellet. (Source: Ref. 4. Reproduced by kind permission of the American Society.)

Fig. 2.4 (*bottom*) Infrared spectrum of KSCN complex of dibenzo-18-crown-6, KBr pellet. (Source: Ref. 4. Reproduced by kind permission of the American Chemical Society.)

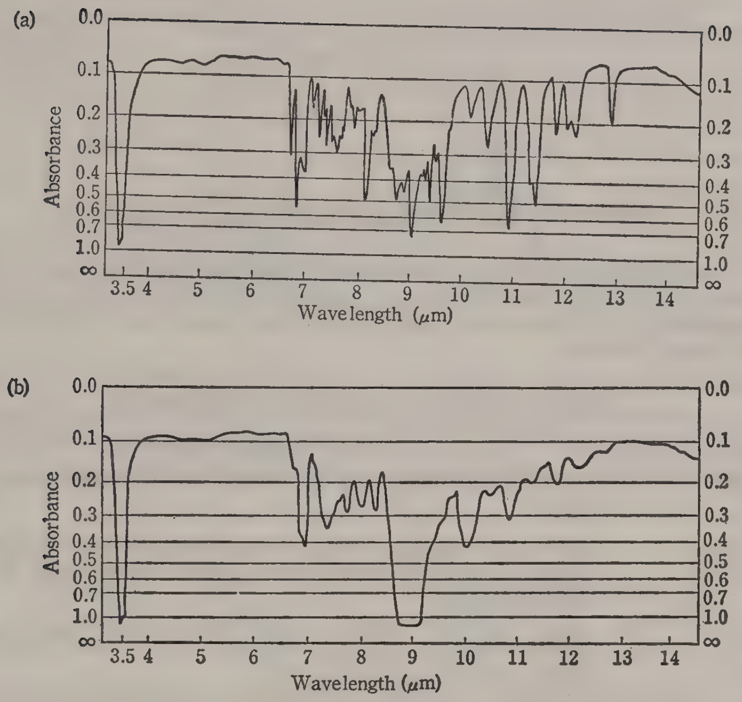


Fig. 2.5 Infrared spectrum of dicyclohexyl-18-crown-6. (a) Isomer B (*cis-anti-cis*), KBr pellet; (b) mixture of isomer A and B, melt smear. (Source: Ref. 4. Reproduced by kind permission of the American Chemical Society.)

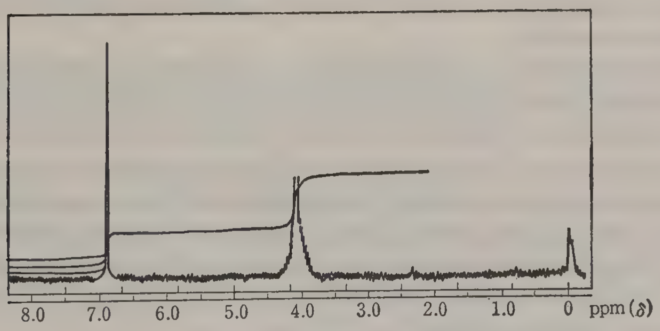


Fig. 2.6 NMR spectrum of dibenzo-18-crown-6. (Upper) multiplet, 4.11 ppm downfield from TMS, are ratio 2.2; (lower) singlet, 6.92 ppm downfield from TMS, are ratio 1.0. (Source: Ref. 4. Reproduced by kind permission of the American Chemical Society.)

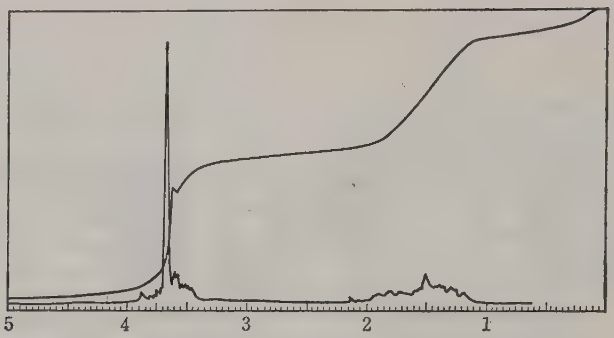


Fig. 2.7 NMR spectrum of dicyclhexyl-18-crown-6. (Upper) multiplet, 1.50 ppm downfield from TMS, are ratio 1.17; (lower) singlet, 3.67 ppm downfield from TMS, are ratio 1.17; (lower) singlet, 3.67 ppm downfield from TMS, area ratio 1.00. (Source: Ref. 4. Reproduced by kind permission of the American Chemical Society.)

TABLE 2.4 Mass spectrum data for crown ethers†

Crown ether	*m/e* (Relative intensity %)
Dibenzo-18-crown-6[5]	360(M$^+$, 29), 137(29), 136(74), 121(100), 109(23), 80(31), 52(21), 45(27), 43(34)
Dicyclohexyl-18-crown-6[5]	372(M$^+$, 2), 187(35), 143(100), 141(47), 99(92), 98(46), 97(41), 89(66), 87(41), 83(45), 82(55), 81(99), 73(77), 72(46), 69(58), 67(42), 57(50), 55(58), 45(77), 43(61), 41(58)
15-crown-5[10]	220(magnified, P$^+$), 133(74), 89(100), 87(66), 73(75), 59(60), 45(78), 265(M),
18-crown-6[8]	264(M + 1), 89, 87, 59, 45, 44, 43, 31

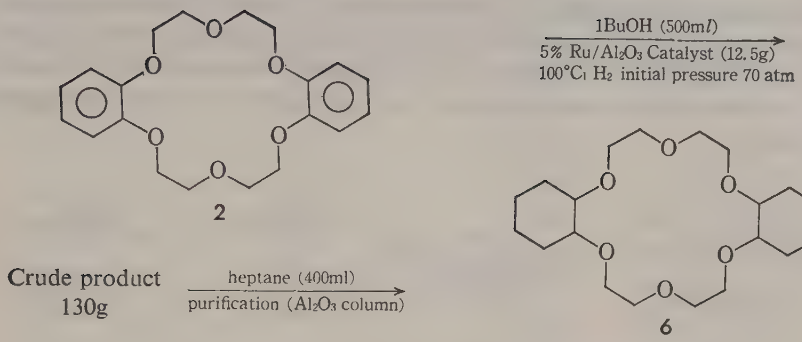
†The data for 12-crown-4 are shown in Table 2.14. Other mass spectrum data have been reported for benzo-3*n*-crown-*n*(*n*3,4,5,6)[21] and 18-crown-6.[22–24]

2.2.2 Alicyclic Crown Ethers

Alicyclic crown ethers, with one or more saturated aliphatic rings, as represented by dicyclohexyl-18-crown-6, are commonly prepared by hydrogenation of the corresponding aromatic crown ethers. Pedersen synthesized 13 kinds of alicyclic crown ethers with this method.[4]

Hydrogenation of the aromatic rings of crown ethers is usually carried out with a ruthenium catalyst under hydrogen pressure. As an example, the reaction conditions[5] for the hydrogenation of dibenzo-18-crown-6 leading to dicyclohexyl-18-crown-6 are shown in Eq. (2.9). The crude reaction products are purified by passing a heptane solution through a column packed with alumina (80 ~ 100 mesh) which has been previously washed with acid, eluting with heptane, and collecting the fractions in which the ir absorption of hydroxyl groups is not detected. After removal of the solvent from the elute by distillation, a diastereomeric mixture of dicyclohexyl-18-crown-6 is obtained as white, prism-like crystals (mp 38 ~ 54°C).

Theoretically there could be five stereoisomers of dicyclohexyl-18-crown-6 because of *cis* and *trans* isomerism of the four bridgeheads on the cyclohexyl rings, but the product of this hydrogenation is a diastereomeric mixture of isomer A (mp 61 ~ 62.5°C)



(2.9)

and isomer B (double melting point at 69 ~ 70°C and 83 ~ 84°C).[25~27] Each isomer, A and B, was separated by elution chromatography using an alumina column and ether/hexane eluate,[25] and it was determined by nmr and X-ray analyses that the conformation was *cis-syn-cis*[11] for isomer A and *cis-anti-cis*[12,28] for isomer B, as shown in Fig. 2.8.

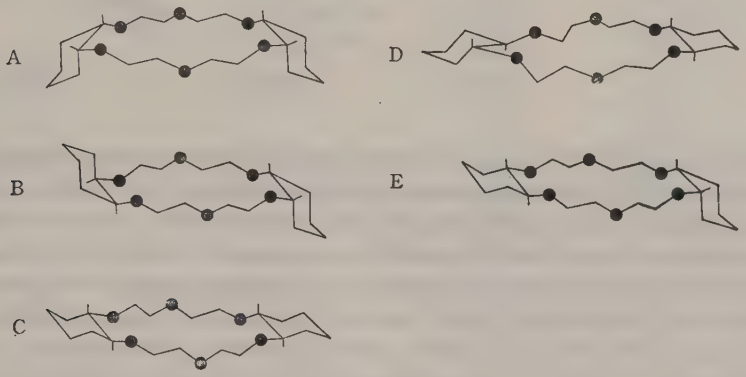
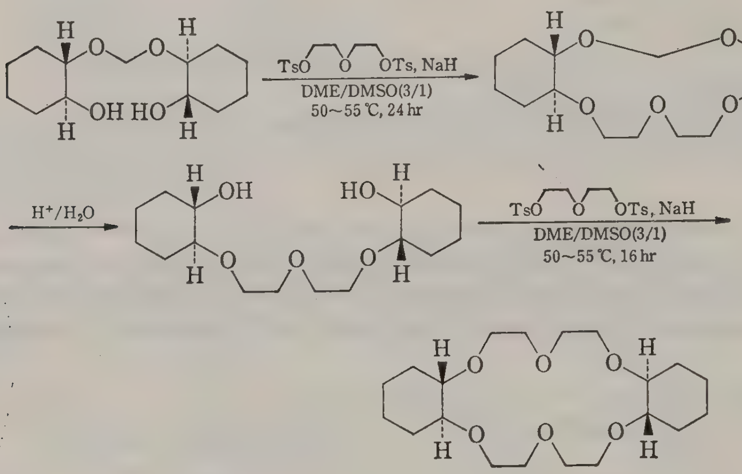


Fig. 2.8 Theoretically possible stereoisomers of dicyclohexyl-18-crown-6. A, *cis-syn-cis* (*meso*); B, *cis-anti-cis*; C, *cis-anti-cis* A and B were isolated from the hydrogenation product of dibenzo-18-crown-6,[12,12,28–30] D and E were prepared from cyclohexane-*trans*-diol.[31]

Recently, Izatt *et al.* isolated isomers A and B in yields of 44% and 39%, respectively, utilizing the difference in the solubilities of the Pb(II) and H_3O^+ complexes (the anion was ClO_4^- in both cases) of each isomer in water.[29] The isolation procedure consisted of precipitation and recrystallization only. Crystal data from X-ray analyses were also reported for each isomer.[30]

As an alternate method for the synthesis of alicyclic crown ethers, it was proposed that an alicyclic compound such as cyclohexane diol or cyclohexene oxide could be used as the starting material. Stoddart and Wheatley synthesized the *trans-anti-trans* form (mp 77 ~ 80°C) and the *trans-syn-trans* form (mp 120 ~ 121°C) of dicyclohexyl-18-

crown-6 by means of the following method.[31] First, a diastereomeric mixture of methylene acetal was prepared by condensation of (±)-cyclohexane-*trans*-diols with HCHO in the presence of an acid catalyst, followed by separation of the (±) form and the *meso* form by means of fractional crystallization, then each desired isomer was prepared via the synthetic route shown in Eq. (2.10). (Only the *trans-anti-trans* form (**60**) is shown.)



60

(2.10)

Alicyclic crown ethers are more soluble than the corresponding aromatic crown ethers. They are easily dissolved in organic polar solvents and also in low- or nonpolar solvents such as aromatic hydrocarbons and aliphatic hydrocarbons. In water, the higher the temperature, the lower the solubility, as shown in Table 2.5. The same phenomenon is also observed with nonionic surfactants, including polyethylene glycols or polyoxyalkylenes, and is thought to result from the decrease in hydrogen bonding.[4] It has also been reported that the distribution ratio of dicyclohexyl-18-crown-6 in benzene/water is higher than 170 at 26°C.[9] As shown in Table 2.5, the solubility of dicyclohexyl-18-crown-6 in water increases markedly in the presence of KOH and KCl, which accounts for the very high solubility of the complexes formed with inorganic salts.

Tables 2.6 ~ 2.11 and Figs. 2.9 ~ 2.12 summarize the solubilities of aromatic crown ethers (dibenzo-18-crown-6, dibenzo-24-crown-8), alicyclic crown ethers (di-

TABLE 2.5 Solubility of dicyclohexyl-18-crown-6 in water and aqueous solutions of salts[4]

Solvent	Temperature (°C)	Solubility (mol/*l*)
water	26	0.036
	53	0.026
	82	0.010
1N KOH aq. solu.	26	0.89
1N KCl	26	>0.93

TABLE 2.6 Solubility of dibenzo-18-crown-6 in different solvents[32]

Solvent	Dielectric constant	Temperature (°C)	Solubility (g/100g solution)
Water	78.39†1	26.0	0.1
DMSO	46.68†1	51.3	2.0
		61.3	3.6
		65.3	4.5
		73.9	6.7
Acetonitrile	37.50†2	63.3	5.0
		72.4	7.5
		81.4	11.1
Methanol	32.7†1	60.8	0.1
		63.7	0.4
Acetone	20.70†1	43.3	0.7
		48.0	0.8
		56.3	1.3
1-Butanol	17.51†1	77.0	0.5
		93.0	2.8
		98.0	4.1
		105.0	6.9
		115.0	14.5
1,2-Dichloroethane	10.36†1	31.8	3.2
		51.3	4.8
		74.6	12.5
Chloroform	4.80†2	30.8	5.5
		45.0	7.1
		55.8	10.0
Benzene	2.27†1	28.0	0.5
		47.0	1.3
		60.0	3.0
		69.0	4.6
		78.5	7.1
1,4-Dioxane	2.21†1	30.0	0.7
		45.0	1.7
		65.5	4.5
		70.0	6.2
		78.5	9.5
		80.0	10.4
		89.0	15.5
Heptane	1.92†2	91.0	0.1
		95.0	0.3

†1, 25°C †2, 20°C

cyclohexyl-18-crown-6, dicyclohexyl-24-crown-8; diastereomeric mixture in each case), and cyclic oligomers of ethylene oxide (15-crown-5, 18-crown-6) as measured by the author and his coworkers.[32] The precautions necessary in the handling of alicyclic crown ethers are the same as those of aromatic crown ethers mentioned in Section 2.2.1. Toxicities are described in Chapter 7.

TABLE 2.7 Solubility of dicyclohexyl-18-crown-6 in different solvents[32)]

Solvent	Dielectric constant	Temperature(°C)	Solubility (g/100 solution)
Water	78.39†^{1}	11.0	1.0
		19.5	0.6
		37.0	0.28
		58.0	0.12
Methanol	32.70†^{1}	28.0	33.0
		35.0	45.5
		40.3	57.7
Acetone	20.70†^{1}	21.0	30.0
		23.0	36.0
		27.0	66.7
1-Butanol	17.51†^{1}	28.0	20.0
		39.5	38.5
		45.3	49.5
1,2-Dichloroethane	10.36†^{1}	21.0	12.5
		25.2	19.7
		30.8	50.0
THF	7.58†^{1}	20.2	20.0
		23.5	31.0
		26.0	50.0
Chloroform	4.80†^{2}	22.0	16.7
		23.7	24.7
		29.0	50.0
Benzene	2.27†^{1}	30.8	50.0
		36.5	58.0
		38.3	61.0
1,4-Dioxane	2.21†^{1}	24.0	25.0
		26.0	33.3
		30.0	50.0
Heptane	1.92†^{2}	23.0	26.7
		30.5	48.4
		33.5	59.6
Hexane	1.88†^{1}	23.0	31.6
		31.0	59.0
		33.0	66.9

†^{1}, 25°C †^{2}, 20°C

2.2.3 Cyclic Oligomers of Alkylene Oxides

As mentioned in Section 1.3, some of the cyclic oligomers of ethylene oxide and propylene oxide figured in the prehistory of crown compounds. After that period, the following experiments with cyclic oligomers of alkylene oxides were reported: formation of a mixture of cyclic oligomers of propylene oxide, consisting mainly of tetramer, in a total yield of about 60%, with BF_3 or $Et_3O^+BF_4^-$ as the catalyst;[33)] formation of a mixture of cyclic oligomers of 1, 2-butylene oxide, consisting of dimer, tetramer, and

TABLE 2.8 Solubility of dibenzo-24-crown-8 in different solvents[32)]

Solvent	Dielectric constant	Temperature (°C)	Solubility (g/100g Solution)
Water	78.39$\dagger^{1}$	86.2	0.1
		94.0	0.2
Methanol	32.70$\dagger^{1}$	36.0	0.9
		50.0	4.2
		58.0	10.7
Acetone	20.70$\dagger^{1}$	8.0	1.1
		28.9	3.9
		42.0	11.1
		56.3	29.6
MEK	18.51$\dagger^{2}$	27.0	3.2
		45.0	16.9
		79.6	71.6
1-Butanol	17.51$\dagger^{1}$	40.0	0.6
		56.0	3.5
		60.0	4.9
		70.0	13.4
1, 2-Dichloroethane	10.36$\dagger^{1}$	26.5	13.8
		36.0	20.0
		48.0	33.3
Chloroform	4.80$\dagger^{2}$	32.3	19.3
		46.3	32.4
		51.3	41.8
Benzene	2.27$\dagger^{1}$	27.0	3.6
		41.0	15.4
		57.0	33.3
1,4-Dioxane	2.21$\dagger^{1}$	29.0	7.4
		38.0	10.7
		60.0	38.5
		65.0	50.0
Heptane	1.92$\dagger^{2}$	63.3	0.2
		78.9	0.4

$\dagger^{1}$, 25°C $\dagger^{2}$, 20°C

TABLE 2.9 Solubility of dicyclohexyl-24-crown-8 in different solvents[32)]

Soluent	Dielectric constant	Temperature (°C)	Solubility (g/100g solution)
Water	78.39$\dagger^{1}$	25.0	$<$ 0.5
Methanol	32.70$\dagger^{1}$	22.0	$>$50.0
Acetone	20.70$\dagger^{1}$	22.0	$>$50.0
1-Butanol	17.51$\dagger^{1}$	22.0	$>$50.0
1,2-Dichloroethane	10.36$\dagger^{1}$	22.0	$>$50.0
THF	7.58$\dagger^{1}$	22.0	$>$50.0
Chloroform	4.80$\dagger^{2}$	22.0	$>$50.0
Benzene	2.27$\dagger^{1}$	22.0	$>$50.0
1,4-Dioxane	2.21$\dagger^{1}$	22.0	$>$50.0
Heptane	1.92$\dagger^{2}$	22.0	$<$ 0.6
Hexane	1.88$\dagger^{1}$	22.0	$<$ 0.6

$\dagger^{1}$, 25°C $\dagger^{2}$, 20°C

TABLE 2.10 Solubility of 15-crown-5 in different solvents[32]

Solvent	Dielectric constant	Temperature (°C)	Solubility (g/100g Solution)
Walter	78.39†[1]	19.0	>50.0
Methanol	32.70†[1]	19.0	>50.0
Acetone	20.70†[1]	19.0	>50.0
1-Butanol	17.51†[1]	19.0	>50.0
1,2-Dichloroethane	10.36†[1]	19.0	>50.0
THF	7.58†[1]	19.0	>50.0
Chloroform	4.80†[2]	19.0	>50.0
Benzene	2.27†[1]	19.0	>50.0
1,4-Dioxane	2.21†[1]	19.0	>50.0
Heptane	1.92†[2]	22.0	< 0.5
Hexane	1.88†[1]	22.0	< 0.5

†[1], 25°C †[2], 20°C

TABLE 2.11 Solubility of 18-crown-6 in different solvents[32]

Solvent	Dielectric constant	Temperature (°C)	Solubility (g/100g solution)
Walter	78.39†[1]	24.0	>50.0
Methanol	32.70†[1]	20.2	33.3
		22.5	45.0
		25.0	65.8
Acetone	20.70†[1]	21.0	50.0
		23.0	58.0
		24.3	66.7
1-Butanol	17.51†[1]	22.5	25.0
		25.2	32.0
		30.8	50.0
1,2-Dichloroethane	10.36†[1]	23.0	12.5
		35.0	22.5
		41.0	30.5
THF	7.58†[1]	22.0	>50.0
Chloroform	4.80†[2]	25.0	50.0
		33.0	66.7
		36.5	75.0
Benzene	2.26†[1]	22.0	50.0
		29.0	59.0
		33.5	66.7
1,4-Dioxane	2.21†[1]	22.0	50.0
		27.0	59.5
		30.2	66.7
Heptane	1.92†[2]	22.0	< 0.5
Hexane	1.88†[1]	22.0	< 0.5

†[1], 25°C †[2], 20°C

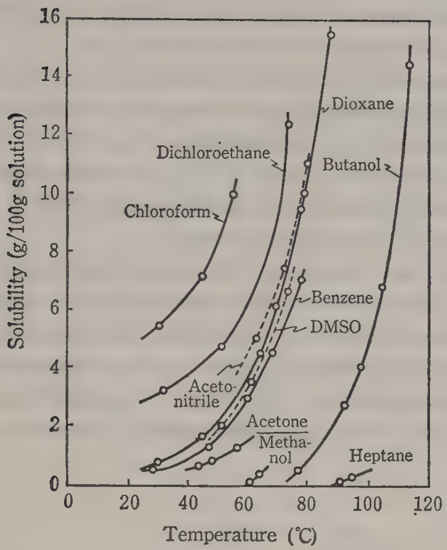


Fig. 2.9 Solubility curves of dibenzo-18-crown-6

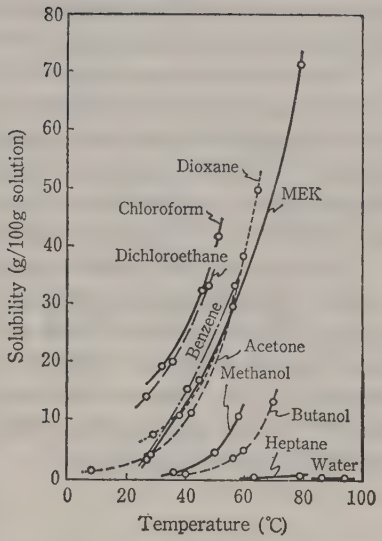


Fig. 2.10 Solubility curves of dibenzo-24-crown-8

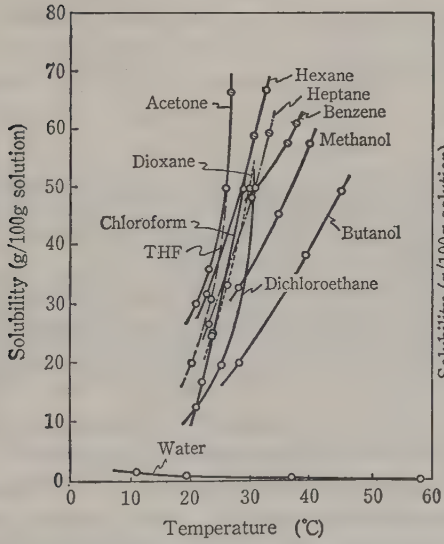


Fig. 2.11 Solubility curves of dicyclohexyl-18-crown-6

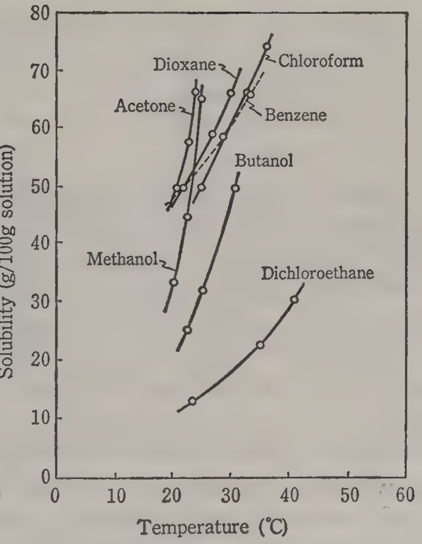


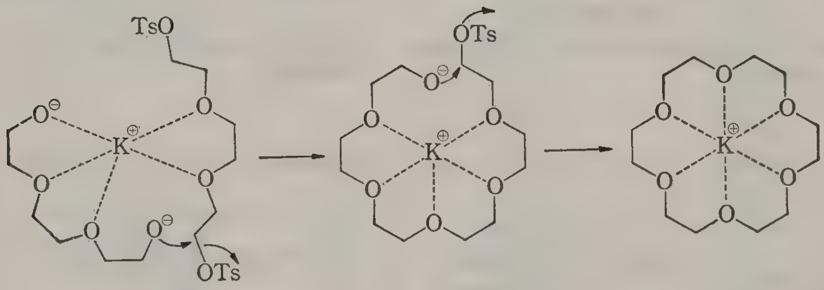
Fig. 2.12 Solubility curves of 18-crown-6

higher polymer as the by-products of linear polymer, by the catalytic action of $Et_3O^+BF_4^-$;[34,35] formation of cyclic dimer and tetramer as the by-products of cationic polymerization of epichlorohydrin.[34,36~38]

In contrast to this cyclic oligomerization of alkylene oxides, Pedersen prepared 18-crown-6, which is the cyclic hexamer of ethylene oxide, by means of an intramolecular cyclic condensation of hexaetheylene glycol monochloride in the presence of *tert*-BuOK using a high-dilution technique in DME; however, the yield was only 1.8%.[4]

Dale and Kristiansen prepared 15-crown-5 (20% yield), 18-crown-6 (33% yield), and 21-crown-7 (26% yield) without using a high-dilution technique by adding a solution of diol and ditosylate in benzene dropwise to a suspension of *tert*-BuOK in hot benzene.[39,40] Greene achieved a high yield of 18-crown-6 by the condensation of triethylene glycol with its ditosylate in the presence of *tert*-BuOK, using DMSO (84% yield), THF (30 ~ 60% yield), or DME (93% yield) as a solvent.[7]

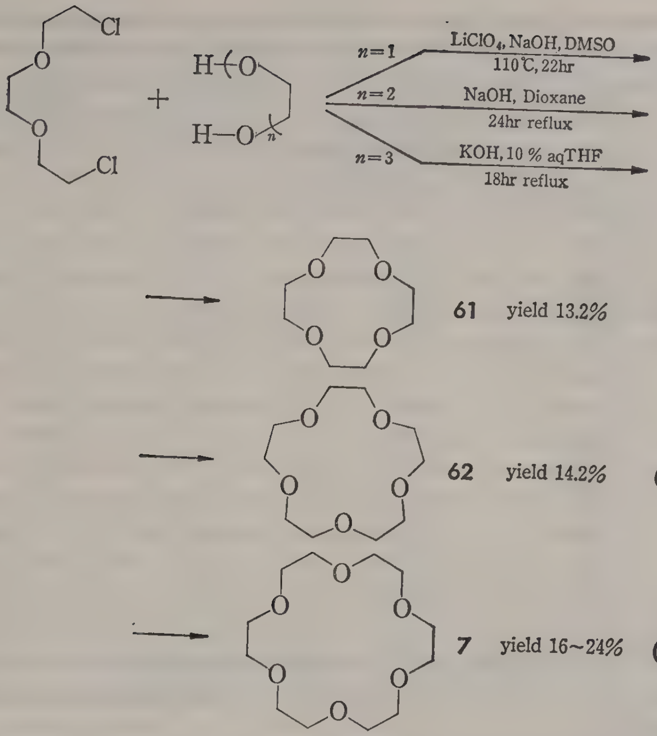
The results of this reaction suggested that such high yields were due to the template effect of K^+ as shown in Eq. (2.11) because the product was isolated as the 1 : 1 complex of 18-crown-6 with TsOK and the yield did not depend on the concentration; furthermore, the yield was markedly lower, and linear polymer was the main product, when n-Bu N^+OH^- was used instead of *tert*-BuOK.[7] Similarly, 21-crown-7 and 24-crown-8 were also prepared in yields of 18% and 15%, respectively, from the corresponding diols and ditrosylates.



(2.11)

Liotta *et al.* prepared 12-crown-4 (13.2% yield) and 15-crown-5 (14.2% yield) from dichlorides and diols using Li^+ and Na^+ as the respective templates[10] (Eqs. 2.12 ~ 2.14). They also made 18-crown-6 using K^+ as a template.[8]

The following purification methods have been reported for crown ethers. Greene obtained pure 18-crown-6 with a chromatographic technique using an alumina column and THF elute.[7] Liotta *et al.* reported using fractional distillations under reduced pressure for the purification of 12-crown-4 (bp 67 ~ 70°C/0.5 mm Hg,[10] 118 ~ 119°C/15 mm Hg[41]) and 15-crown-5 (bp 100 ~ 135°C/0.2 mm Hg,[10] 78°C/0.05 mm Hg[10]). For 18-crown-6, they employed the complexation of 18-crown-6 with acetonitrile.[8] The procedure they used was the following. The crude fraction (bp 125 ~ 160°C/0.2 mm Hg) of 18-crown-6 was dissolved in acetonitrile by warming. After cooling, the deposited crystals of the complex of 18-crown-6 and acetonitrile were filtered, then pure



61 yield 13.2% (2.12)

62 yield 14.2% (2.13)

7 yield 16~24% (2.14)

18-crown-6 was obtained (40 ~ 60% yield after purification) decomposition of the complex and removal of acetonitrile by heating below 40°C under reduced pressure (0.1 ~ 0.5 mm Hg).

Recently Dale *et al.* prepared cyclic tetramer, pentamer, and hexamer from ethylene oxide directly by using several kinds of metal ions as the template. A mixture of cyclic oligomers was formed with about 20% conversion when ethylene oxide was polymerized in dioxane, diethyl ether, benzene, or hexane at a temperature below 30°C, using BF_3, PF_5, or SbF_5 as a catalyst and HF as a cocatalyst.[42)] The distribution of oligomers obtained is shown in Table 2.12. In contrast, a mixture of cyclic tetramer, pentamer, and hexamer was obtained in the distribution shown in Table 2.13 together with 1, 4-dioxane, a cyclic dimer, when ethylene oxide was polymerized in ice-cooled dioxane, benzene, or methylene chloride using a BF_3, PF_5, or SbF_5 catalyst along with BF_4^-, PF_6^-, or SbF_6^- salts of alkali, alkali earth, or transition metals.[43)] The reaction products were deposited as a mixture of the complexes, and each free crown ether was obtained by means of pyrolysis of the complexes under reduced pressure followed by

TABLE 2.12 Distribution of cyclic oligomers $(CH_2CH_2O)_n$ formed in the oligomerization of ethylene oxide catalyzed by BF_3–HF[42)]

n	2	3	4	5	6	7	8	9	10	11	≥12
Ratio (%)	40	1	15	5	4	3	2	2	1	1	25

TABLE 2.13 Distribution of cyclic oligomers obtained in the complex mixture separated from the oligomerization product of ethylene oxide in dioxane in the presence of metal salts[43]

Metal salt	Ionic diameter of cation (Å)	Tetramer (12-crown-4)	Pentamer (15-crown-5)	Hexamer (18-crown-6)
		Cavity diameter ~ 1.2 Å	1.7 ~ 2.2 Å	2.6 ~ 32Å
$LiBF_4$	1.20	30%	70%	–%
$NaBF_4$	1.90	25	50	25
KBF_4	2.66	—	50	50
KPF_6	2.66	20	40	40
$KSbF_6$	2.66	40	20	40
$RbBF_4$	2.96	—	—	100
$CsBF_4$	3.34	—	—	100
$Ca(BF_4)_2$	1.98	50	50	—
$Sr(BF_4)_2$	2.26	10	45	45
$Ba(BF_4)_2$	2.70	10	30	60
$AgBF_4$	2.52	35	30	35
$Hg(BF_4)_2$	2.20	20	70	10
$Ni(BF_4)_2$	1.44	20	80	—
$Cu(BF_4)_2$	1.44	5	90	5
$Zn(BF_4)_2$	1.48	5	90	5

fractional distillation, or alternatively, by fractional crystallization of the complexes followed by pyrolysis. The mother liquor of the reaction mixture and the salts generated pyrolysis could be reused.

The advantages of using BF_4^-, PF_6^-, or SbF_6^- salts are as follows. 1) These salts do not inhibit the catalytic activity of the Lewis acids for polymerization, but the Lewis acid catalysts are neutralized immediately by the basic anion when the usual salts such as halides or sulfate are employed. 2) There is no formation of terminal groups that would hinder the cyclization. 3) It is possible to liberate the crown ethers by pyrolysis of the formed complexes because the complexes are not soluble in the reaction systems, and the generated salts can be used repeatedly.

As shown in Table 2.13, the cavity size of the crown ether formed in the largest quantity corresponds closely to the ionic diameter of the metal cation added, so the template effects of the metal cations can be observed. Dale *et al.* proposed a reaction mechanism in which the propagating chains wind around the metal cations, that is, the templates and the rings are formed by reacting with the nearest terminal. They also considered the cyclization reaction to be an equilibrium reaction in which the dioxane solvent takes part since the fragments of deuterized dioxane were incorporated into the crown ring when deuterized dioxane was used as a solvent. They also suggested that the template effects of the metal cations inhibit decomposition of the formed cyclic oligomers to dioxane besides accelerating the winding of the chain.

Borregaard Industries in Norway has been planning to commercialize this ingenious technique utilizing the template effect. The conversions and the yields were not reported, but it was noted that the conversions and the yields depended on stirring and on the ratio between the rate of polymerization and the rate of dissolution of the salt; in addition, at least twice the theoretical amount of ethylene oxide was needed.

As described earlier, the cyclic tetramer, pentamer, and hexamer of ethylene oxide can be distilled *in vacuo* because of their lower molecular weights. However, Stott reported that an explosion occurred when a large amount (on a kilogram scale) of 18-crown-6, the hexamer of ethylene oxide, was distilled under conditions of 100 ~ 160°C and 0.2 mm Hg.[44] He gave the following details about the accident. The contents of the flask were overheated for a long period during the distillation, the inner pressure was increased by the thermal decomposition products with low boiling points, the temperature at the top of the distillation column rose to 196°C, and the cold trap was clogged. The explosion occurred within a few seconds after the trap was disconnected allowing contact with air. A refutation from Gouw asserted that the distillation technique was not skillful and stated that such handling would naturally cause accidents even in the preparation of compounds other than crown ethers.[45] Stott answered this assertion by arguing that the explosion was caused by ignition of 1, 4-dioxane (ignition point in air: 180°C), formed by thermal decomposition, at the distillation temperature because 1, 4-dioxane was detected after the explosion. He recommended that two cold traps be set in parallel to prevent clogging, and that the distillation be performed under nitrogen.[46] In any case, the following precautions should be taken in the distillation of cyclic oligomers of ethylene oxide: one should avoid distilling a large amount over a long period to prevent thermal decomposition due to overheating; the distillation should be carried out under highly reduced pressure together with a flow of nitrogen; the contents of the flask should be prevented from contact with air during the distillation. It is also desirable to store the products under nitrogen atmosphere and to take into consideration the high hygroscopic property (see Table 2.1) of each cyclic oligomer. The other precautions necessary in handling these compounds are similar to those for polyethylene glycols.

The solubilities of 15-crown-5 and 18-crown-6 are listed in Tables 2.10 and 2.11, and the solubility curves of 18-crown-6 are shown in Fig. 2.11.

The toxicity of the cyclic oligomers of alkylene oxide is discussed in Chapter 7. Careful handling is particularly required for 12-crown-4 as it has a vapor pressure of 0.03 mm Hg at room temperature, and Leong *et al.* stated that its vapor is toxic when inhaled.[47] Table 2.14 presents data on the ir, nmr, and mass spectra of 12-crown-4.

TABLE 2.14 Data on ir, nmr, and mass spectra of 12-crown-4[10]

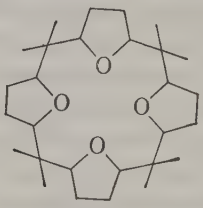
ir melt smear (cm^{-1})	2925, 1465, 1365, 1280, 1250, 1130, 1100, 920
^1H nmr ($CDCl_3$)	3.65 ppm
^{13}C nmr ($CDCl_3$)	70.621 ppm
mass *m/e* (relative intensity %)	176 (magnified, P^+), 133(30), 89(94), 87(56), 73(70), 59(57), 45(100)

2.2.4 Heterocyclic Crown Ethers

Section 1.3 noted that a heterocyclic polyether with furan rings was obtained as a by-product in the period before the discovery of crown compounds. Chastrette and Chastrette reported the template effect in the condensation reaction of furan with acetone in ethanol, catalyzed by HCl.[48] The yield of the tetramer (**49**) increased to

39 ~ 49% when ClO_4 salts of Li, Zn, or Mg were added, compared to a yield of 18 ~ 20% without the salts. The heterocyclic polyether having a THF ring (**20**), which is prepared by hydrogenation of **49** with a Ni catalyst, forms a 1 : 1 complex with Li salts.

Recently, Kobuke *et al.* prepared cyclic polyethers with a THF ring by means of ring closure of linear oligomers;49) these linear oligomers were obtained by successive condensation of furan and several kinds of carbonyl compounds such as acetaldehyde and acetone, followed by hydrogenation of the resulting cyclic tetramer, pentamer, and hexamer. These hetero-alicyclic crown ethers have the ability to extract and solubilize alkali metal ions, NH^+, and Ag^+ from an aqueous solution into an organic phase as the complexes. They also reported the active transport of alkali ions by a liquid membrane using the same crown ethers. A hetero-alicyclic crown ether with a carboxyl group was also prepared using ethyl levulinate, $CH_3COCH_2CH_2COOC_2H_5$, as the carbonyl compound.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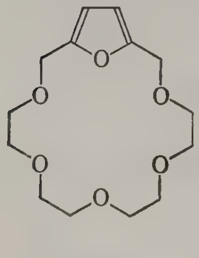
Various kinds of hetero-alicyclic crown ethers of the 18-crown-6 type with furan or THF rings, such as **61** ~ **63**, were synthetized by Timko and Cram50) by condensation of 2, 5-bis(hydroxymethyl)furan with polyether ditosylate in THF. Reinhoudt and Gray also reported on the synthesis of 15- ~ 30-membered crown ethers having one or two furan rings by the same technique19) and on the complexation with Zeise salt, $KPtCl_3.C_2H_4$.51) A 16-membered cyclic compound (**64**) having double bonds conjugated with furan rings was prepared by Cresp and Sargent.52) The array of heterocyclic crown ethers with furan or THF rings has been described in a recent reivew.14)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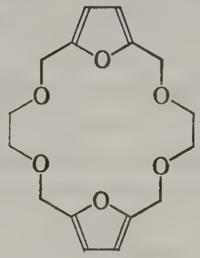
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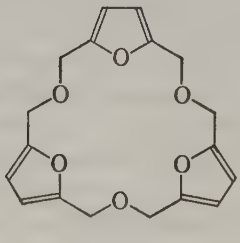
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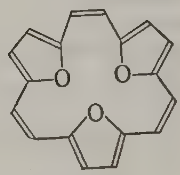
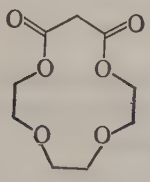

64

2.2.5 Cyclic Polyether Esters and Others

Crown ethers containing carbonyl groups such as cyclic polyether esters are the analogues of natural ionophore antibiotics like valinomycin, mentioned in Section 1.3, so it can be anticipated that these compounds will have complexation characteristics slightly different from those of conventional crown ethers consisting only of polyether rings; for example, they may have the higher selectivity for K^+ that valinomycin does.

With these considerations in mind, Christensen *et al.* prepared cyclic polyether esters with 1, 3-diketone groups (**21**, **65**, **66**) in yields of about 40% each by the reaction of malonyl chloride with polyether glycol in benzene at 60 ~ 70°C using a high-dilution technique.[53] Both carbonyl groups on these crown rings tend toward the outside of the ring, and the carity size of **66**, for example, is large enough that K^+ can be bound. Compounds **65** and **66** form complexes with alkaline earth metal ions such as Ca^{2+}, Sr^{2+}, and Ba^{2+} in aqueous solution. It was observed that compound **65** formed a complex with Mg^{2+}, the first Mg^+ complex found for crown ethers. Christensen *et al.* also prepared **67** in 35% yield by the reaction of diglycolic acid chloride with tetraethylene glycol in benzene at 50°C for 48 hours.[54] They measured the stability constants (K), enthalpies (ΔH), and entropies ($T\Delta S$) of Na^+, K^+, and Ba^{2+} complexes of **66** and **67** in methanol at 25°C and compared the values with those of 18-crown-6 and valinomycin. The results indicated that $Ba^{2+} > K^+$ for the stability constants (K) of the complexes of 18-crown-6 and **67**, while $Ba^{2+} < K^+$ for the K of **66**. The latter relation is also true for valinomycin.



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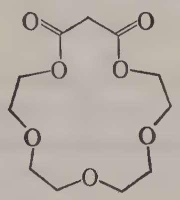
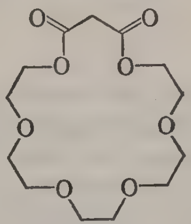


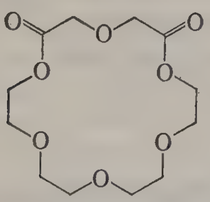
2,4-diketo-16-crown-5
mp 66.5~68℃

65



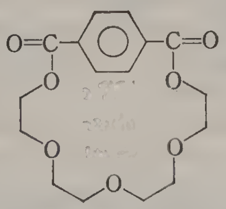
2,4-diketo-19-crown-6
mp 68~69℃

66

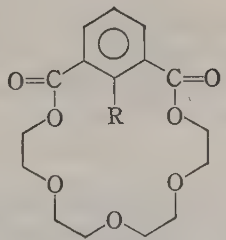


2,6-dioxo-18-crown-6
mp 78.5~79.5℃

67



68

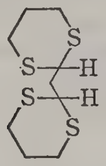


R=H, NO_2

69

Recently, Frensch and Vögtle prepared the cyclic polyether esters **68** and **69** from terephthaloyl chloride, isophthaloyl chloride, and tetraetheylene glycol using the high-dilution technique.[55]

Albert and Cram prepared crown ethers (**71**) with 1 ~ 3 β-diketone units from compound **70** as the starting material;[56] their procedure involved lithiation, conversion to diol by the addition of HCHO, cyclization with polyether ditosylate and methanolysis. These cyclic polyether esters with the additional chelating action of a β-diketone group form complexes with transition metal ions such as Cu(II), Ni(II), Co(II), Mn(II), and Cr(II), and with UO_2(II) ion, in addition to alkaline earth metal ions and lanthanide ions. These cyclic compounds have complexation constants which are significantly larger ($10^{1.8} \sim 10^{6.3}$ times) than those of linear β-diketones.



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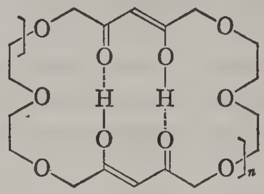

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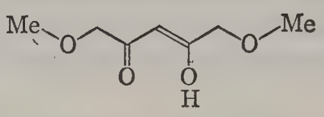
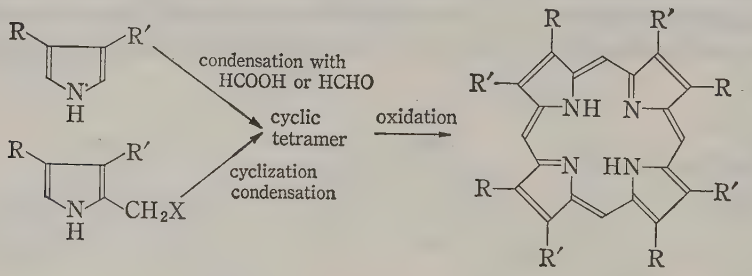


72

2.3 CYCLIC POLYAMINES (AZACROWN COMPOUNDS)

Cyclic polyamines with a nitrogen donor atom, which is a softer base than oxygen atom, have an affinity for soft cations such as transition metal or heavy metal ions, while crown ethers have an affinity for hard cations such as alkali and alkaline earth metal ions.

One of the representative cyclic compounds carrying a donor nitrogen atom is the porphyrin described in Section 1.3. Porphyrin (**73**) is basically prepared from pyrrole derivatives, as shown in Eq. (2.15),[57] but it is necessary to carry out repeated condensations in order to construct a porphyrin skeleton resembling the natural one.[58]



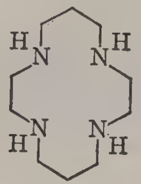
73

(2.15)

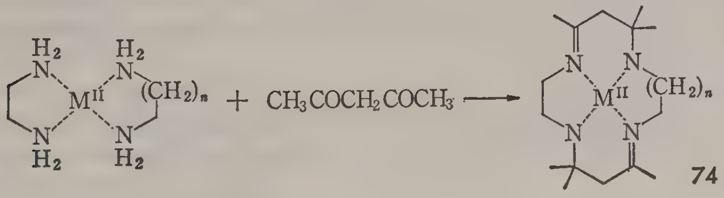
In the synthesis of cyclic polyamines, the template effect of metal ions and the high-dilution technique can both be effectively utilized to preferentially elicit cyclization. In the cyclization of pyrrole, Co(II) or Zn(II) is used as a template. The template reaction was employed in the famous syntheses of vitamin B_{12} and corrin by Woodward.

As there are many reviews[59~62] that cover the syntheses of cyclic polyamines, the discussion here will focus on the syntheses of azacrown compounds which are the cyclic polyamines corresponding to crown ethers.

Stetter *et al.* prepared various cyclic diamides in 24 ~ 78% yields by the condensation of diamines with dibasic acid chloride using the high-dilution technique;[63,64] they then produced cyclic diamines by reduction using $LiAlH_4$, with reduction yields of 70 ~ 80%. Cyclam (**25**), which is a typical 14-membered cyclic tetramine, was obtained by Tobe *et al.* by the reaction of 1, 3-bis(2′-aminoethylpropane) with 1, 3-dibromopropane in the presence of EtOK in ethanol using the high-dilution technique; however, the yield was less than 3%.[65,66]


25

Another method for the preparation of various cyclic polyamines involves the reaction of diamine with ketone or diketone using a transition metal ion as a template. Curtis first synthesized cyclic tetramine complexes (**74**) by a famous coordinative template condensation reaction using Cu(II), Ni(II), or Co(II) as a template (Eq. (2.16)).[60]

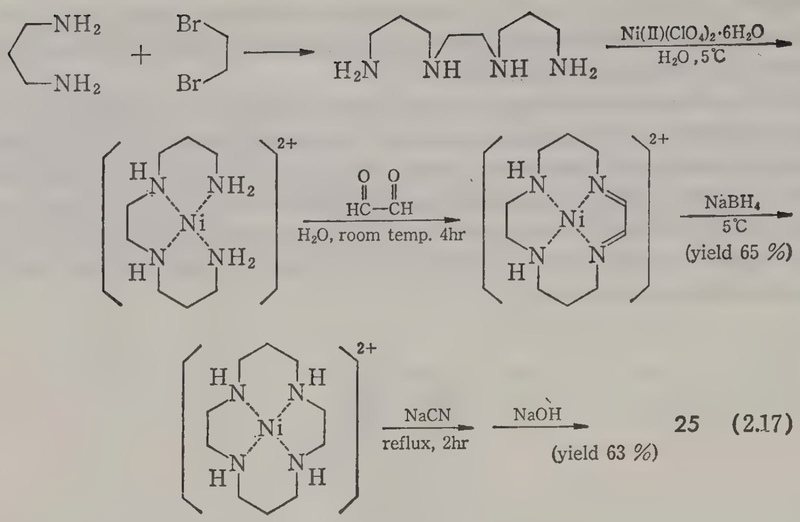


(2.16)

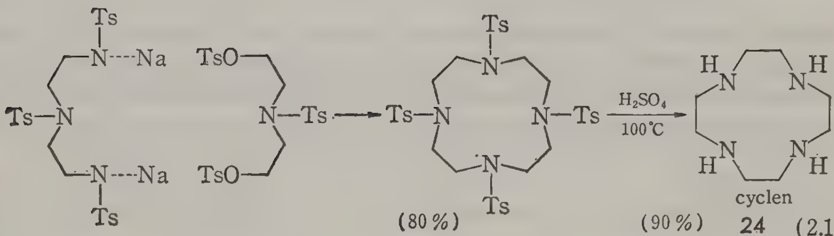
74

Saturated cyclic tetramines were liberated from these complexes by $NaBH_4$ reduction followed by treatment with CN^-. Equation (2.17) shows an example of the synthesis of cyclam which was carried out by Barefield *et al.*[67] using Ni(II) as a template.

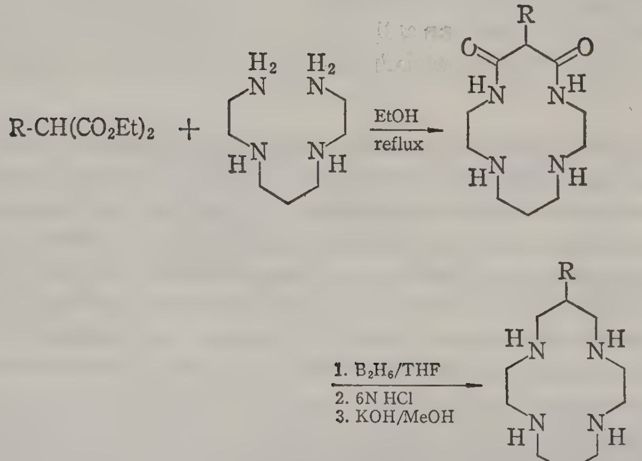
Other synthetic methods for preparing cyclic polyamines in high yields without utilizing the high-dilution technique or the template effect have also been reported. Curtis and Hay obtained **74** ($n = 1$) in 75% yield by the condensation of ethylenediamine monoperchlorate with mestiyl oxide.[68] Koyama and Yoshino,[69] Richman *et al.*,[70,71] and Busch *et al.*[72] described the cyclization of linear polyamines after *N*-tosylation with *p*-toluensulfonyl chloride as shown in Eq. (2.18); various cyclic tri-, tetra-, penta-, and hexamines were also prepared with this method. The effects of internal enthalpy and entropy are thought to explain the high yields obtained without utilization of the high-dilution technique or the template effect.[73]



25 (2.17)



cyclen
24 (2.18)

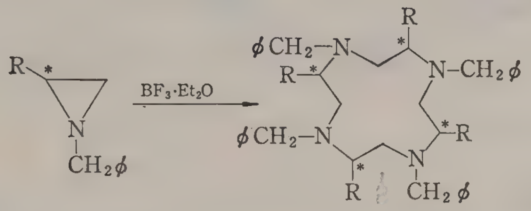


(2.19)

R = H, $CH_2C_6H_5$, CH_2CH_2OH, $CH_2CH_2CH_2CN$, $CH_2CH{=}CH_2$ etc.

Recently, Tabushi *et al.* prepared cyclam and its *C*-substituted derivatives (**75**) from 1, 3-bis(2′-aminoethylpropane) and diethyl malonate or its derivatives via cyclic polyamide,[74] as shown in Eq. (2.19). This is important as a synthetic method for cyclams with functional groups. Kemp *et al.* also prepared cyclic tetramine and hexamine via cyclic polyamide in a similar way.[75]

There have been a few reports of direct syntheses of cyclic oligomers from aziridines, 3–membered ring compounds having an NH group. Hansen and Burg prepared cyclic tetramer almost quantitatively by treatment of 1-benzylaziridine with *p*-toluenesulfonic acid in boiling ethanol.[76] Tsuboyama *et al.* obtained a mixture of isomers of optically active cyclic tetramer **76**, together with linear oligomers, by treatment of 1-benzylarizidines having an ethyl or ethoxycarbomethyl group at the 2-position with $BF_3 \cdot Et_2O$.[77,78]

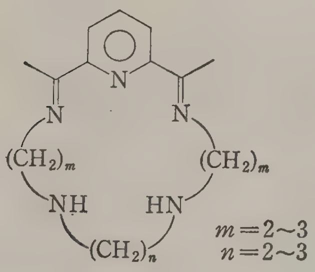


(2.20)

76

Drew *et al.* prepared cyclic polyamines having a nitrogen atom on a pyridine ring as one of the donors (**77**) in 40 ~ 60% yields by the reaction of 2, 6-diacetylpyridine with tetramine in the presence of MgCl , and they reported on the complexes formed with various transition metal compounds.[79~81] Their work was particularly interesting in relation to chlorophyll because it provided the first example in which Mg^{2+} was used as a template. Other cyclic polyamines with pyridine groups have been described in a recent review.[14]

Heterocyclophane (**78**) carrying an N donor has been synthesized.[82,83] Compound **78** is soluble in water (pH 6) and has a square hydrophobic cavity (about 5 Å distance between the two parallel side walls) surrounded by walls of benzene rings, in accordance with a CPK model.



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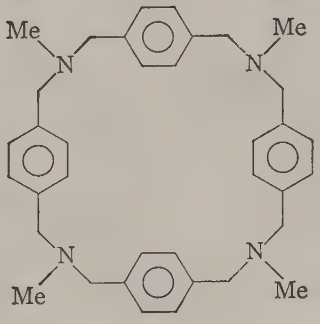
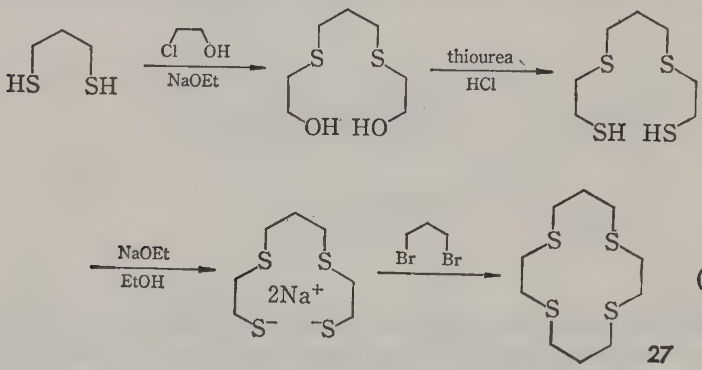


78

2.4 CYCLIC POLYTHIAETHERS (THIACROWN COMPOUNDS)

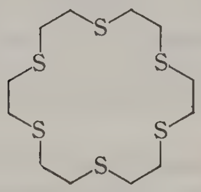
Cyclic polythiaethers (thiacrown compounds) have a greater affinity for heavy metal and transition metal ions than for alkali metal and alkaline earth metal ions, so they form stable complexes with the former because the S atom is a softer base than the O atom as a donor. Synthetic methods for cyclic polythiaethers have been reviewed.[61,84)]

Busch *et al.* prepared various cyclic polythiaethers including cyclam analogue **27** by means of a cyclic condensation of dithiol with dibromide in ethanol using Na,[85~89)] as shown in Eq. (2.21). The yield of cyclic condensation was 55% when the high-dilution technique was employed, but only 7.5% when it was not.

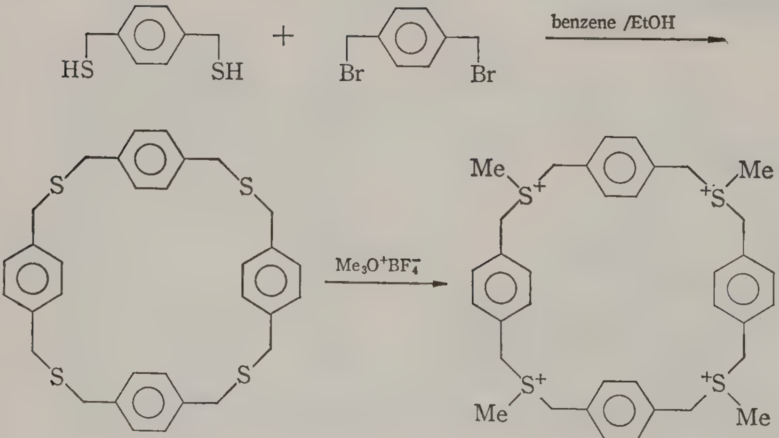


27

(2.21)



28



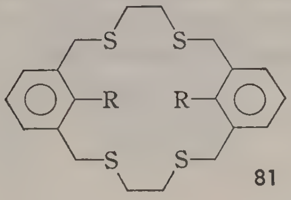
79

80

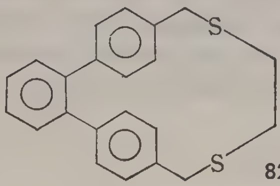
(2.22)

The thiacrown compound named 18-thiacrown-6 (**28**), corresponding to 18-crown-6, was obtained in a 31% yield by Black and McLean[90] by a cyclic condensation of 1, 2-dibromoethane with 3-thiapentane-1, 5-dithiol in ethanol utilizing the high-dilution technique. Ochrymowycz *et al.* used Black's method to prepare 19 kinds of thiacrown compounds having 3 ~ 6 S donors.[91~94]

Heterocyclophanes (**79**, **80**) having S donors were prepared by Tabushi *et al.* by the procedure shown in Eq. (2.22).[95] Heterocyclophane **80** is soluble in water and has the characteristic of binding tightly to hydrophobic guests in aqueous solution. Thiacrown **81**,[96,97] classified as a type of methacyclophane, and thiacrown **82**,[98] with an *o*-terphenyl ring, were also prepared by Vögtle *et al.*



81

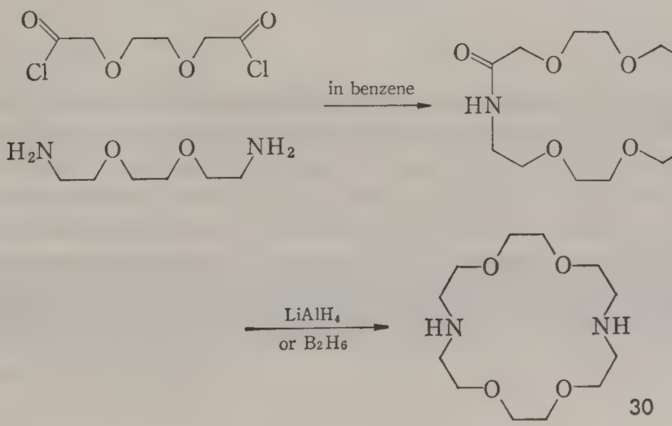


82

2.5 COMPOSITE DONOR CROWN COMPOUNDS

2.5.1 Azacrown Ethers

The basic method for the synthesis of azacrown ethers, in which NH or NR groups substitute for some of the O donor atoms of crown ethers, consists of the condensation of α, ω-diaminoether with dibasic acid chloride by the high-dilution technique, followed by reduction of the resulting cyclic diamide.[25,99~101] The synthetic route for diamino-18-crown-6 (**30**) reported by Lehn *et al.*[99] is shown in Eq. (2.23) as an example. This is the first step in the synthesis of cryptand, described in Section 2.6.1.



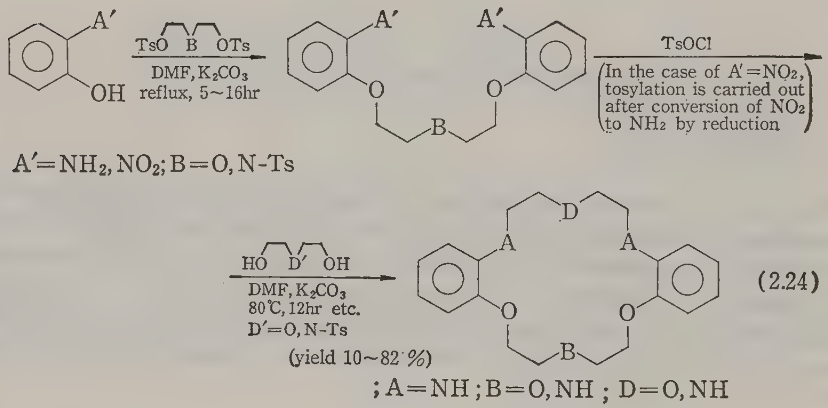
30

(2.23)

Another method for the synthesis of **30** was reported to be the following.[102] Triethylene glycol dichloride was converted to diamine by treatment with NH_3, reacted with CF_3COOEt to convert to trifluoroacetamide, cyclized by condensation with triethylene glycol ditosylate, and then hydrolyzed.

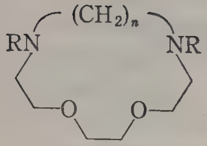
Ashby *et al.* obtained a series of azacrown ethers by a combination of acylation and the Williamson reaction.[103] Tabushi *et al.* prepared aza- (or thia-) crown ethers from polyethylene polyamine and *α,ω*-dicarboxylic acid esters having an ether (or thioether) linkage by aminolysis followed by reduction.[104]

In the area of aromatic azacrown ethers, Lockhart *et al.* produced benzo-12-azacrown-4 and benzo-15-azacrown-5 from dichloropolyether and *o*-hydroxyaniline or *o*-phenylene diamine.[105] Högberg and Cram formulated 16 kinds of benzo- or dibenzo-azacrown ethers mainly by the method shown in Eq. (2.24).[106] First, 2 moles of *o*-nitrophenol were crosslinked with diethylene glycol ditosylate or diethanolamine ditosylate, then the nitro groups were reduced to diamine, finally, tosylation and cyclization with diols were carried out.

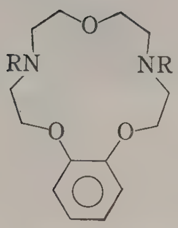


(2.24)

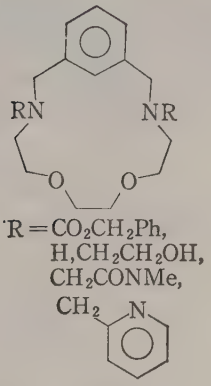
Using *N*-tosylated reagents, Richman and Atkins prepared diaza-12-crown-4 and diaza-18-crown-6 in 80% yields by the same procedure used for the synthesis of cyclic polyamines, without the high-dilution technique.[70] Gokel and Garcia produced monoaza-18-crown-6 in 25% yield by cyclization of *N*-benzylethanolamine with tetraethylene glycol in DMF at 25°C for 48 hours in the presence of NaH, followed by hydrogenative debenzylation using a Pd/C catalyst.[107] Azacrown ethers (**83, 84**) and diazaoxamethacyclophanes (**85, 86**) were prepared by Leigh *et al.* from polyether ditosylates and *N*-substituted derivatives of diamine such as *N*-methyl and *N*-carboxylic acid ester derivatives.[108~110]


R=Me, CO_2Et

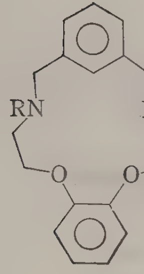
83


R=Me, CO_2Et

84

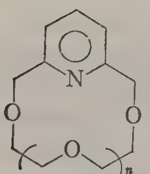

R=CO_2CH_2Ph,
H, CH_2CH_2OH,
CH_2CONMe,
CH_2

85


R=CO_2CH_2Ph,
H, CH_2CH_2OH,
CH_2CONMe

86

A number of azacrown ethers have been obtained with an N atom in a pyridine nucleus as one of the donors. Cram *et al.*[18,111)] and Vögtle and Weber[97)] prepared **87**, and Newkome and Robinson[112)] prepared **88**. Newkome *et al.* made **89** and **90** from 2, 6-dibromopyridine.[113)] Recently, Frensch and Vögtle reported on the syntheses of **91** and **92**, which are classified as cyclic polyether esters having pyridine nuclei.[55)] Fenton and Cook prepared **93** using Pb^{2+} as a template.[114)]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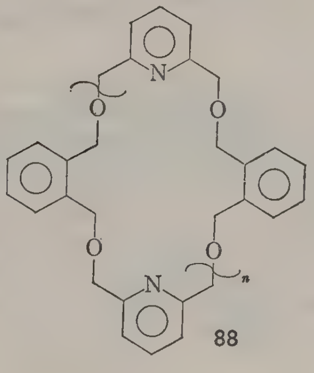
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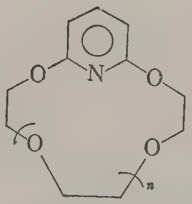
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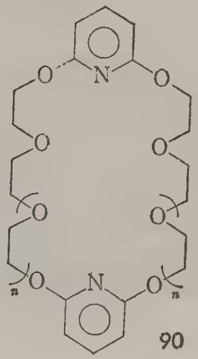
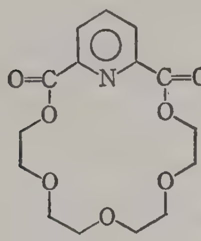
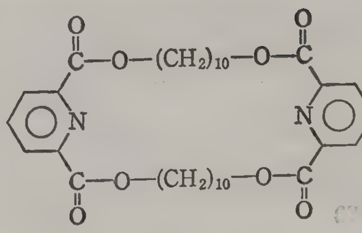

90

Azacrown ethers with a pyroridone ring have also been produced,[115)] and azacrown ethers with 3, 5-di(alkoxycarbonyl)pyridine moiety were prepared by the treatment of ethyl acetoacetate and polyether diols with $(NH_4)_2CO_3$ and HCHO followed by the Hantsch condensation.[116)]



91



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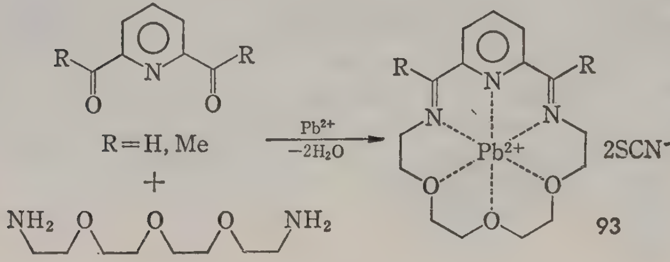
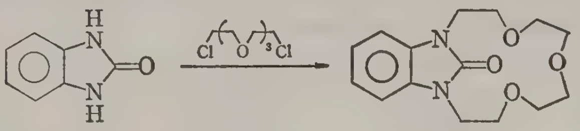
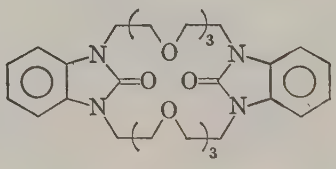


93

Hayward *et al.* prepared a series of compounds (**94, 95, 96**) by the reaction of benzimidazolone or quinoquisaline-2, 3-dion with dichloropolyether in DMF at 20°C in the presence of NaH.[117~119]



94



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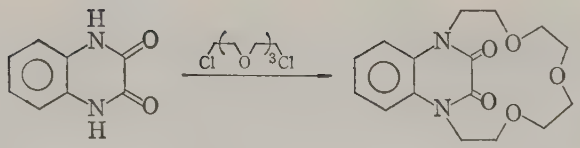
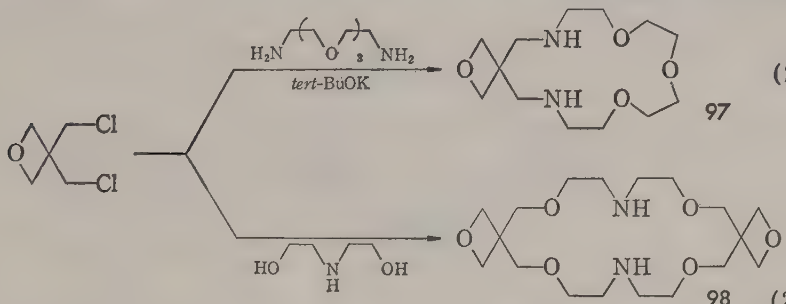


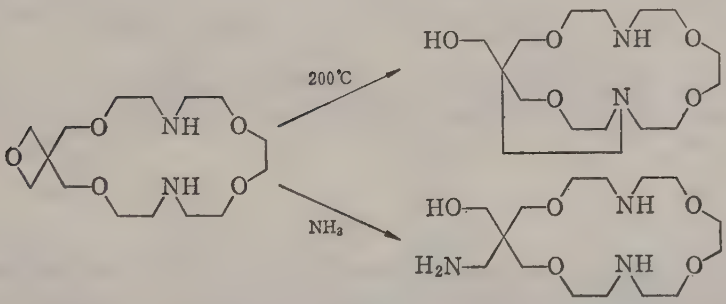
96

Krespan[120] formulated azacrown ethers having 1 ~ 2 spirooxetane rings (**97, 98**) in 17 ~ 71% yield by the condensation of 3, 3-bischloromethyloxetane with diamines or diethanolamine (Eqs. 2.25, 2.26).[120] Crown ethers and thiacrown ethers with spirooxetane rings were also prepared by the same procedure.[121] An interesting aspect of the synthesis that pertains to the introduction of functional groups into crown compounds was the observation that an OH group is formed when the oxetane ring is opened by heating as shown in Eq. (2.27), while an OH group and a NH_2 group are formed as shown in Eq. (2.28) in the reaction with NH_3; a crosslinked compound is formed by the reaction of the NH group on the ring with $ClOCCH_2OCH_2COCl$.



97 (2.25)

98 (2.26)



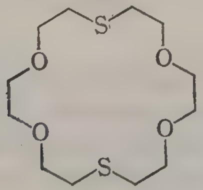
(2.27)

(2.28)

2.5.2 Thiacrown Ethers

There have been many reports of syntheses of cyclic polyether sulfides (thiacrown ethers) in which S atoms are substituted for some of the oxygen donors of crown ethers. Before the discovery of crown ethers, Dann *et al.* isolated a tiny amount of a crystalline compound (**33**) as a by-product of linear polymer formation in the reaction of triethylene glycol dichloride with Na_3S,[122] and Mortillans *et al.* obtained **99** and **100** as the by-products of linear polymer produced by the reaction of bischloromethyl ether with Na_2S,[123] but they did not recognize the complexation abilities of the cyclic compounds.

After the discovery of crown ethers, Black and McLean synthesized **101** in a 7%



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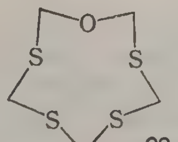

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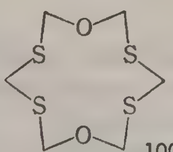
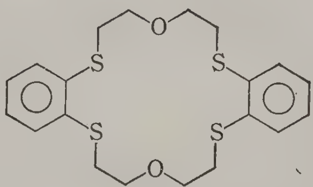


100

yield by the reaction of 1, 2-dibromoethanol using the high-dilution technique.[90] Pedersen synthesized 10 kinds of aromatic or alicyclic thiacrown ethers, including **102, 103**, and **34**;[124] he applied synthetic methods for the corresponding crown ethers, condensation of *o*-mercaptophenol, toluene dithiol, or cyclohexane dithiol with dichloropolyether in *n*-BuOH in the presence of NaOH. He also investigated their complexation abilities with Na^+, K^+, and Ag^+.



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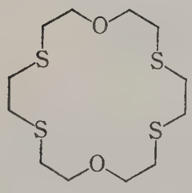

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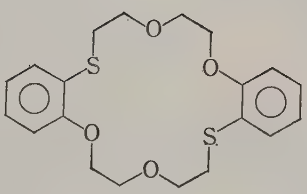

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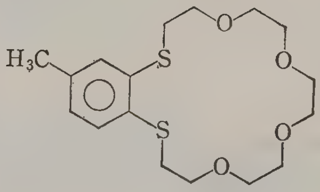
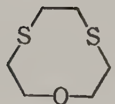


103

Izatt *et al.* prepared a variety of thiacrown-3 ~ 8, including **104, 105**, and **106**, by the cyclic condensation of thioglycol or polyether dithiol with dichloropolyether in ethanol in the presence of NaOH, utilizing the high-dilution technique followed by column purification;[125~127] they also performed X-ray analysis on the structures.[128]



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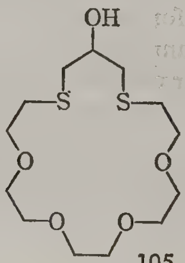
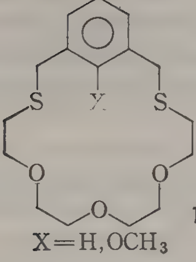


105

106

Vögtle and Weber produced thiacrown ethers classified as the cyclophane type (**107, 108**) and the thiophenophane type (**109**) and examined their complexation abilities with alkali metal ions.[96,97] Unsaturated cyclic compounds having furan rings and thiophene rings (**110, 111**) were prepared by Cresp and Sargent.[52] Crown compounds with hetero rings have been discussed in a recent review.[14]



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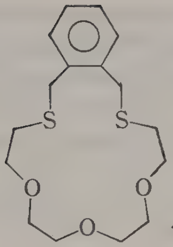

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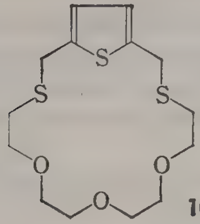

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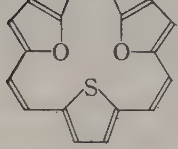

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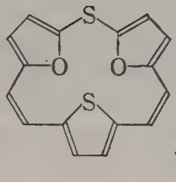
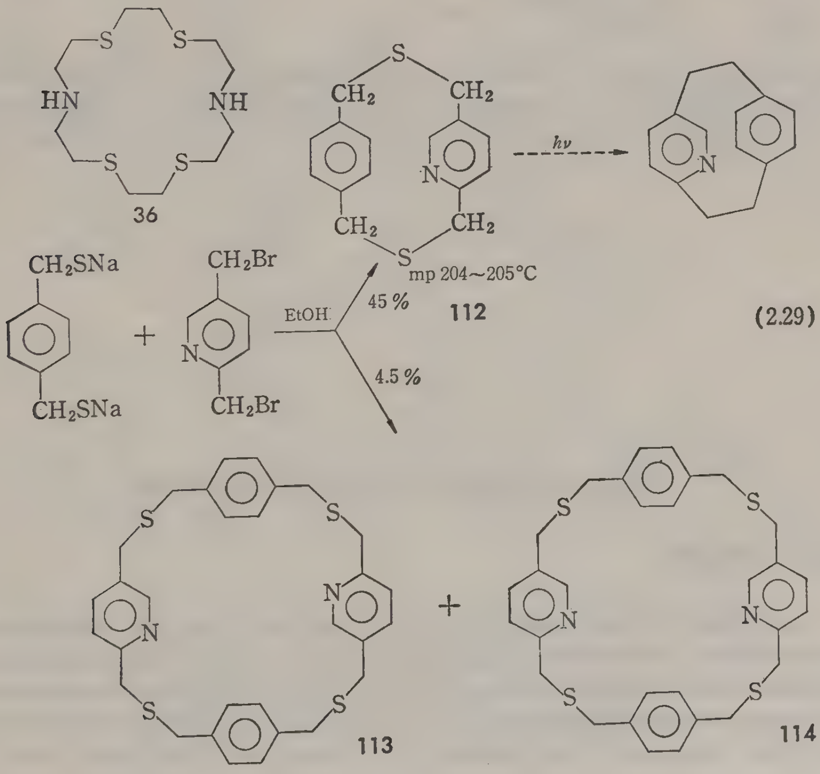


111

2.5.3 Crown Compounds with N and S Donor Atoms

Black and McLean prepared **36** in 8% yield by the cyclic condensation of di(2-bromoethyl)amine and the Na salt of ethane-1, 2-dithiol in ethanol using the high-



36

112

113

114

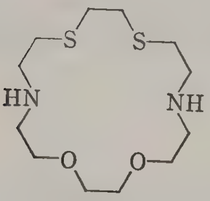
(2.29)

dilution technique.[90,129] Lehn *et al.* also prepared **36** using a method analogous to the first step in the synthesis of cryptand,[130] described previously in Section 2.5.1.

Busch *et al.* prepared a series of cyclic compounds with N and S donor atoms using Ni(II) and Co(II) as templates.[61,131~134] Thiaparacyclophanes having pyridine nuclei (**112**, **113**, **114**) were obtained by Bruhin and Jenny.[135]

2.5.4 Crown Compounds with O, N, and S Donor Atoms (Azathiacrown Ethers)

Several investigators have reported on the synthesis of azathiacrown ethers, which have 3 kinds of donor atoms, O, N, and S. Compound **115** was prepared by Black and McLean by the condensation of di(2-bromoethyl)amine with the Na salt of 3-oxapentane-1, 5-dithiol in ethanol using the high-dilution technique.[90] Lehn *et al.* made **37** using a method similar to the condensation and reduction procedure applied in the synthesis of cryptand.[130] Azathiacrown ethers **116** and **117** were prepared by Pelissand and Louis with an equivalent technique.[136] Vögtle *et al.* produced azathiacrown ethers **118** and **119**.[55,97]



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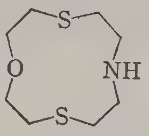

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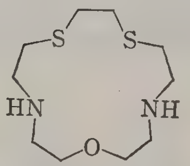

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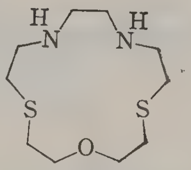

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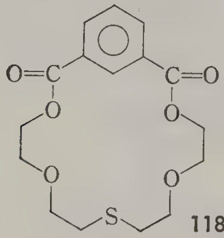

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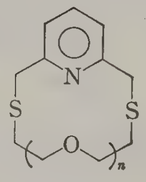


119

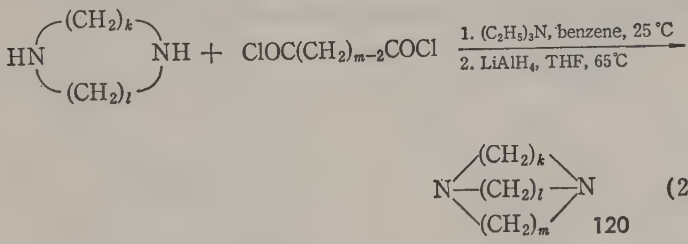
2.6 Bi- and Tricyclic Crown Compounds

2.6.1 Cryptands

In addition to the monocyclic crown compounds, there are many cyclic compounds with two or three crown rings that have been prepared. These multicyclic crown compounds are classified into two types: 1) bicyclic or tricyclic crown compounds with a cage structure whose bridgeheads are C or N atoms, 2) compounds consisting of two or more crown rings which are separated from each other. The former were termed "cryptands" by Lehn.[137] Compared to monocyclic crown ethers, the ability of cryptands to selectively form complexes and the stability of the complexes are much greater. In addition, they have the particular properties of inducing alkali metals to solubilize in organic solvents[138] and of forming complexes containing alkali metal anions.[138] Because of these characteristics, companies doing research on crown ethers are pursuing many studies on the chemistry and applications of cryptands.

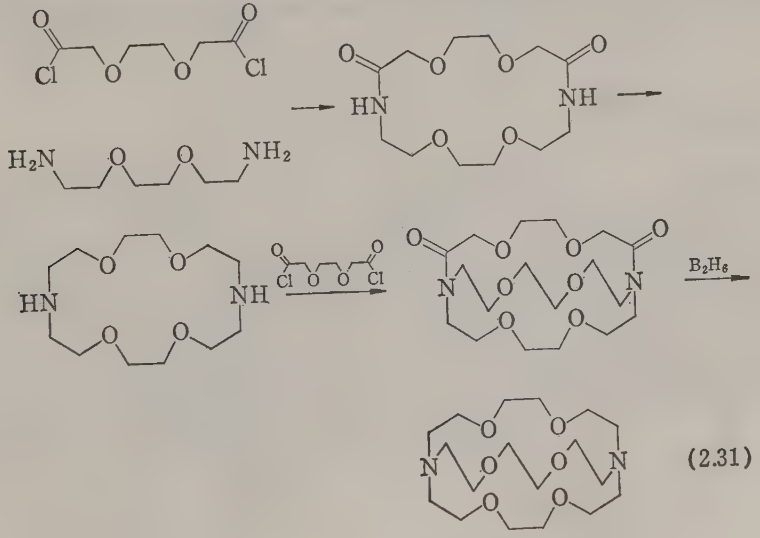
As for the cage molecules whose bridgeheads are trivalent atoms, small bicyclic compounds were prepared several decades ago. Brown and Fletcher made $N(CH_2CH_2O)_3B$ from triethanolamine and $B(OH)_3$ in 1951,[139] and Greenwood *et al.* produced $N(CH_2CH_2CH_2)_3B$ from triallylamine and BH_3 in 1964.[140]

In 1968, Simmons and Park prepared diazabicycloalkanes[141] whose bridgeheads are both nitrogen atoms (**120**) by repeated application of the synthetic method for cyclic diamine developed by Stetter *et al.*[63,64] (Eq. 2. 30). Subsequently, in 1969, Lehn *et al.* prepared bicyclic crown compounds with a cage structure, both of whose bridgeheads were nitrogen atoms, as shown in Fig 1.2, by intramolecular crosslinking between two nitrogen atoms of a diazacrown compound such as diamino-18-crown-6 as shown in



120

(2.30)

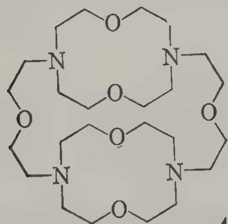


(2.31)

overall yield 25 %

Eq. (2.31)[99,137,142~144] They found that these bicyclic crown compounds form complexes by tight binding of metal ions into their space lattice, resulting in a more selective complexation with ions and more stable complexes than are observed with monocyclic crown compounds. Lehn *et al.* named these bicyclic crown compounds "cryptands" and their complexes "cryptates."

The synthetic procedure for cryptands reported by Lehn *et al.* also required two repetitions of Stetter's method for cyclic diamine; that is, cyclic diamide was prepared by the condensation of linear diamine with dicarboxylic acid chloride using the high-dilution technique, and the product was converted to azacrown ether (see Section 2.5.1) by reduction, then additional crosslinking of azacrown ether was achieved by condensation with dicarboxylic acid chloride followed by reduction with B_2H_6.[99] Utilizing this procedure, Lehn *et al.* prepared a series of cryptands,[137,145] as well as the composite donor cryptands with (N,S) or (N,S,O) donor atoms[130,146] shown in Fig. 1.2. They also formulated tricyclic cryptand **42**,[147~149] in which two azacrown ether rings were crosslinked intramolecularly, and tetracyclic cryptand **121**.[148,149]



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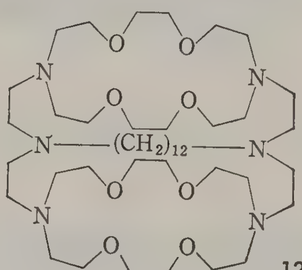
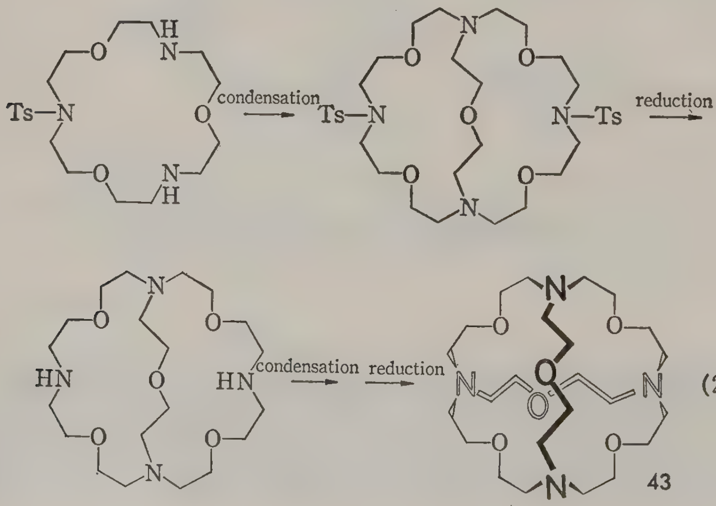


121

In addition to these compounds Lehn *et al.* prepared an optically active cryptand having binaphthyl groups (see Chapter 5), and they recently obtained a spherical

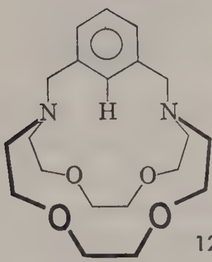


43

(2.32)

tricyclic cryptand (**43**)[150] by crosslinking two pairs of N–N atoms of tetraazacrown ether as shown in Eq. (2.32). It was found that this spherical tricyclic cryptand formed anion cryptates (see Section 3.3.2) in which a halogen anion was enclosed tightly by the addition of HCl, HBr, or HF because four quaternary ammonium cations formed by protonation.[151,152] In the synthesis of cryptand, it was reported that almost the same yields were obtained with the flow method in a short period of time[153] as with the high-dilution technique.

The cryptands classified as the methacyclophane and 2,6-pyridinophane types (**122, 123, 124**) were prepared by Wehner and Vögtle,[154] and "crowned" porphyrin (**125**) was prepared by Chang.[155]



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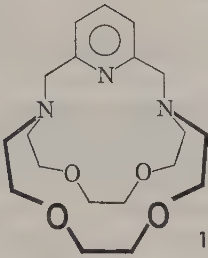

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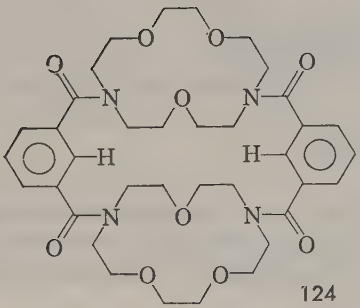

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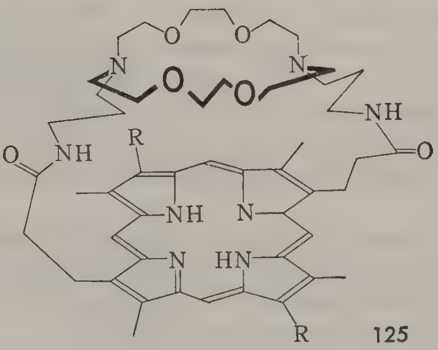

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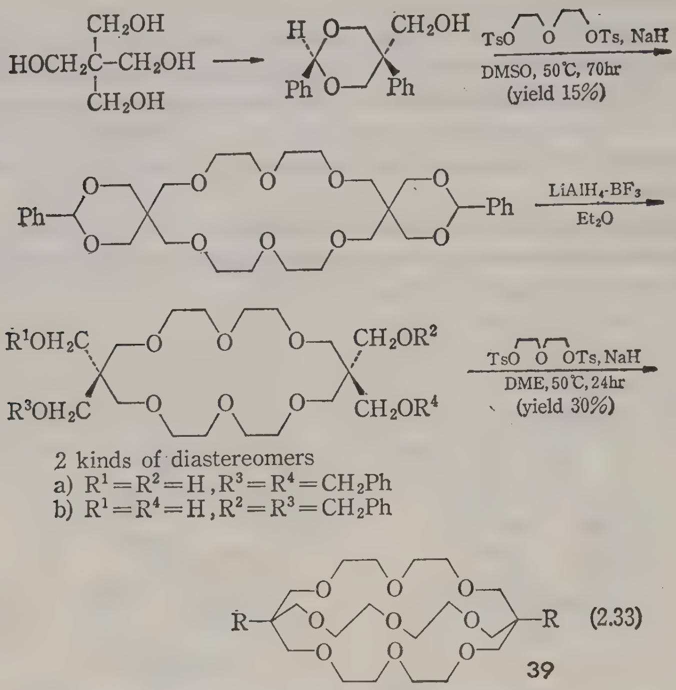
Bicyclic polyethers in which the bridgehead atoms were C (**39**) were obtained by Coxon and Stoddart[156,157] from pentaerythritol through four steps as shown in Eq. (2.33) They also reported complexation of the compounds with Na^+ and K^+.

Bicyclic compounds (**44**) in which the bridgehead atoms were two B atoms and donor atoms were O and N have been synthesized and complexes formed with Co^{2+} and Co^{3+}.[158,159] There was also a report on bicyclic compound **45** in which the bridgehead atoms were P and B and donor atoms O and N; complexation with Fe^{2+}, Co^{2+}, Ni^{2+}, and Zn^{2+} was carried out.[160]



2 kinds of diastereomers
a) $R^1=R^2=H, R^3=R^4=CH_2Ph$
b) $R^1=R^4=H, R^2=R^3=CH_2Ph$

(2.33)

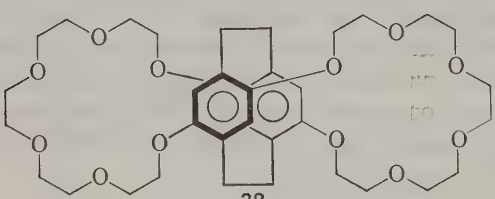
39

$R=CH_2OH$ is obtained by further reduction.

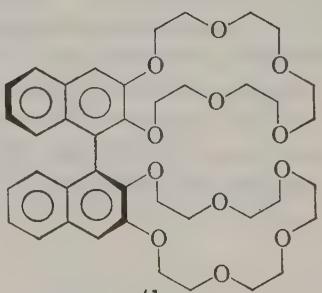
2.6.2 Other Bi- and Tricyclic Crown Compounds

Cram *et al.* prepared compounds which consist of two separated monocyclic crown compounds, **38**[161] with paracyclophane units and optically active bis-1, 1-(2, 3-naphto-18-crown-6) **41**.[162] Both compounds were synthesized by a method similar to that for monocyclic crown ethers.

Vögtle and Frensch prepared a bicyclic crown ether, whose structure was thought to be **126**, from papaverine, an alkaloid with an isoquinoline ring.[163] Compound **40**



38



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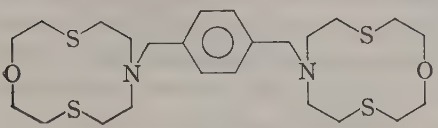
containing two azathiacrown ethers was recently produced by Bulkowski *et al.*,$^{164)}$ who also described the complex with Cu(I).



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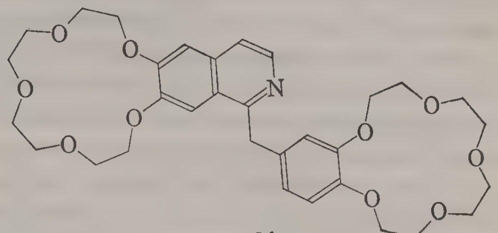


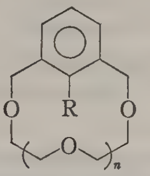
126

2.7 CROWN COMPOUNDS WITH FUNCTIONAL GROUPS

The syntheses of crown compounds bearing functional groups are important because 1) the functional group on the inside or outside of a crown ring may affect complexation and the stability of the complex formed, and 2) the reaction of the functional group may be used to prepare polymeric or "immobilized" crown compounds.

In order to assess the effects of functional groups, Cram *et al.* made a number of crown ethers in which various functional groups were introduced at the 2-position of crown ether **127**, carrying a 1,3-xylenyl group,$^{165,166)}$ and then systematically investigated the influence on the complex stability of the functional group, which faced the inside of the cavity and acted as the adding new bonding site.

Mckervay and Mulholland examined the effects of functional groups located outside the crown ring by introducing OH and NO_2 groups at the 5-position of **127**.$^{167)}$



$R = H, OCH_3$
$CH_2OCH_3,$
$COOCH_3,$
$CH_2OH,$
$COOH, CN,$
Br, Cl

127

As discussed more fully in Chapter 5, Cram *et al.* prepared optically active crown ethers in which various functional groups were introduced at the 3-position of the 1, 1′-binaphthyl group;$^{168\sim170)}$ in so doing, they achieved stereospecific binding of the guest by inducing cooperation between the new bonding site and the chiral cavity. These optically active crown ethers are thought to provide a model for the utilization of a substrate by an enzyme, and the development of this new field is expected.

The reactions of the functional groups may have very important practical applications in the industrialization of crown compounds. Much of the current research on crown compounds is directed toward employing their characteristics for a wide range of applications, but some problems remain, such as the solubility and the toxicity (see

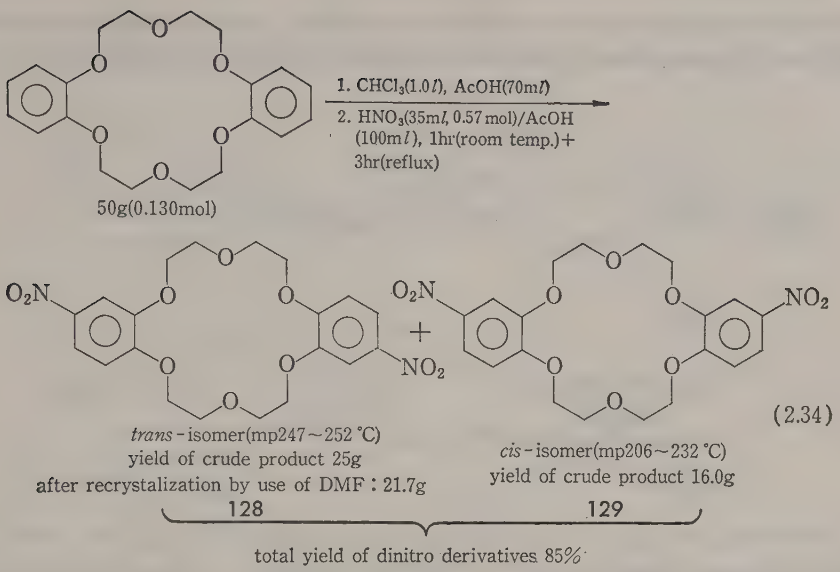
Chapter 7). It is thought that polymeric crown compounds or immobilized crown compounds supported on solid carriers might be useful as a means to overcome these problems, because it may become possible to use them both as a film or column for ion-selective separation and as particles of catalyst which are convenient for handling, recovery, and regeneration in organic syntheses. Moreover, their toxicity might be much lower than the original crown compounds so they could be used for practical applications. For these reasons, there is now considerable research on polymeric or immobilized crown compounds, and significant advances are anticipated in the near future.

There are basically two methods for the preparation of polymeric crown compounds: 1) vinyl polymerization or copolymerization of crown compounds having vinyl groups; 2) polycondensation, polyaddition, or additive condensation of crown compounds having two or more functional groups. The method for immobilizing a crown compound involves bonding the functional group of a crown compound with the functional group in the carrier, such as silica gel or chloromethylated polystyrene. Details are given in Chapter 6.

The synthetic methods for aromatic crown compounds having functional groups are grouped as follows: 1) methods using divalent phenols with another functional group as the starting material, 2) methods employing the reactions of aromatic rings for the secondary introduction of functional groups to aromatic crown compounds. In method 1, it is not necessary that the functional groups in the phenols be inactive to diols or ditosylates, which are the reactants for cyclization, or to alkali salts, used as the condensation agents. Using method 1, Pedersen prepared a series of benzo- and dibenzo-crown ethers with alkyl groups and Cl as the substituents.4) Crown ether **127**165,166) with a 1,3-xylenyl group and the optically active crown ethers with functional groups 168~170) which were reported by Cram *et al.* were also synthesized mainly by method 1.

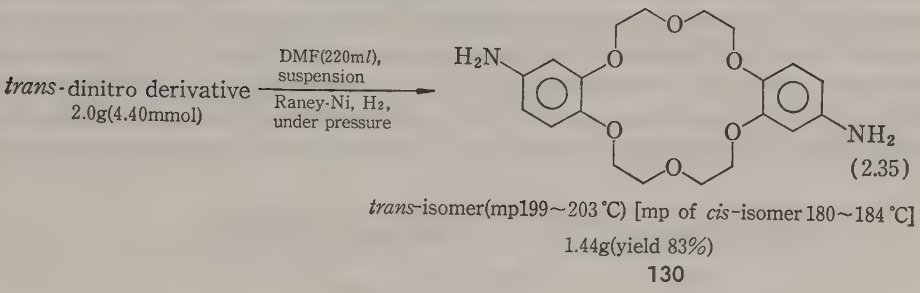
A patent for the preparation of polyester from 3,4-dihydroxybenzoic acid and triethylene glycol through the derivative of dibenzo-18-crown-6 with two carboxyl groups has been applied for.147) Smid *et al.* formulated each derivative of benzo-15-crown-5, dibenzo-15-crown-5, and dibenzo-18-crown-6 bearing vinyl groups using acetyl catechol as a starting material;175,176) these monomers were then polymerized (see Eq. 6.4).

Conventional reactions for introducing substituents on aromatic rings can be applied in method 2, and the position of substitution follows general rules of orientation. Feigenbaum and Michel prepared 4,4′-diamino-dibenzo-18-crown-6 (**130**) by the nitration of dibenzo-18-crown-6 using the reaction conditions shown in Eq. (2.34); this was followed by the reduction of the resulting 4,4′-dinitro derivatives (the isomeric mixture of *trans* form **128** and *cis* form **129**) under the conditions shown in Eq. (2.35).177) Shchori *et al.* obtained the *cis*-dinitro derivative (**129**) (mp 200 ~ 201°C) by a similar nitration of dibenzo-18-crown-6, followed by a refluxing of the crude products with ethylene glycol monomethyl ether, separation of the *trans*-isomer by hot filtration, and then recrystallization.178) The *cis*-dinitro derivative was converted to *cis*-diamino-dibenzo-18-crown-6 (mp 177 ~ 178°C,178) 178 ~ 179°C178)) by reduction in ethylene glycol monomethyl ether using 10% Pd/C catalyst and hydrazine. The polyamide prepared by polycondensation of this diamino derivative with terephthaloyl chloride



128 **129**

(2.34)



130

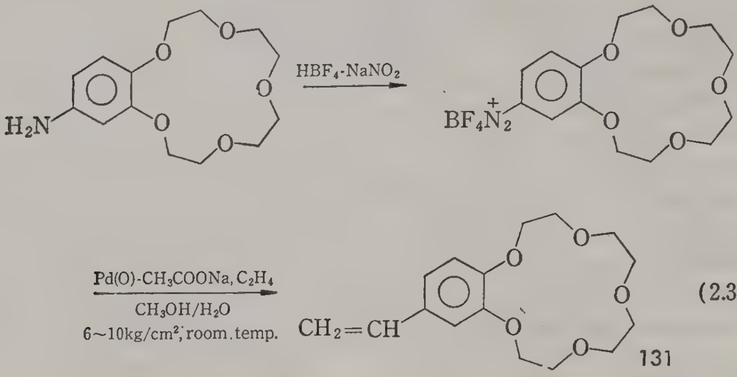
(2.35)

or isophthaloyl chloride can be formed as a film and can capture Na$^+$ and K$^+$[177,179,180] (see Chapter 6).

Nitro- and amino derivatives of benzo-15-crown-5 were prepared by Smid *et al.* with the same procedure.[181] Pannell *et al.* also produced dinitro derivatives (mp 245 ~ 248°C for the *trans*-form, 210 ~ 212°C for the *cis*-form) and diamino derivatives (mp 196 ~ 200°C for the *trans*-form, 178 ~ 184°C for the *cis*-form) of dibenzo-18-crown-6 with the same method, as well as octachloro-dibenzo-18-crown-6 (mp 80.6°C, 25% yield), tetrabromo-derivative (mp 212 ~ 215°C), and mono- and bis (tricarbonychromium derivative) by chlorination in chloroform, bromination, and treatment with Cr $(CO)_6$, respectively.[182] They also investigated the selective complexation of these compounds with Na$^+$ and K$^+$. Shchori and Jagur-Grodzinski also obtained the 4,4′-dibromo derivative (~ 83%) of dibenzo-18-crown-6, together with smaller amounts of monobromo derivative (~ 10%) and tribromo derivative (~ 7%), by refluxing with bromine in chloroform.[183]

Applying the method for secondary introduction of a vinyl group to an aromatic ring, Matsuda *et al.* recently prepared 4′-vinyl-benzo-15-crown-5 (**131**) in 20 ~ 25%

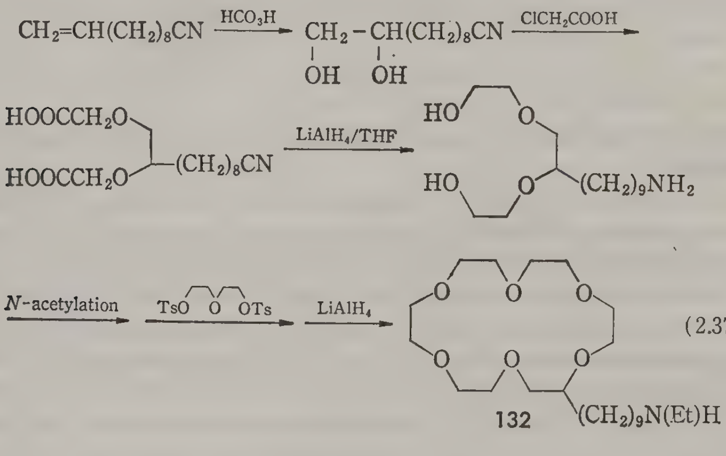
yield from benzo-15-crown-5 by nitration, amination, and conversion to diazonium salt, followed by a reaction with ethylene using Pd(O) catalyst, as shown in Eq. (2.36).[184]



(2.36)

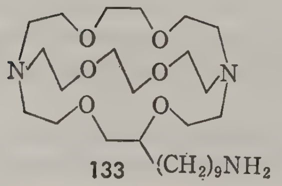
131

Concerning methods for the introduction of functional groups to crown compounds without an aromatic ring, the following examples of cyclization of a starting material with a substituent group have been mentioned earlier: cyclic oligomerization of propylene oxide, 1,2-butylene oxide, and epichlorohydrin (Section 2.2.3); heterocyclic crown ethers with carboxyl groups (Section 2.2.4); crown ethers with carbonyl groups (Section 2.2.5); *C*-substituted cyclam with such functional groups as $-CH_2C_6H_5$, $-CH_2CH_2OH$, $-CH_2CH_2CN$, and $-CH_2CH = CH_2$ (Section 2.3); cyclic oligomerization

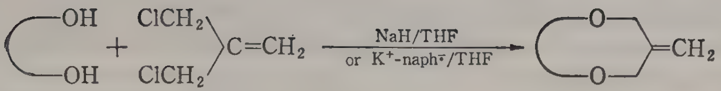


(2.37)

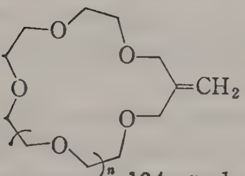
132



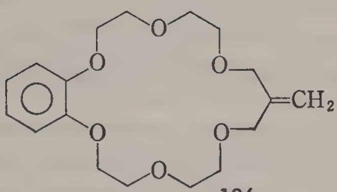
133



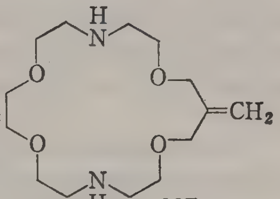
(2.38)



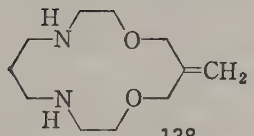
134 $n=1$
135 $n=2$



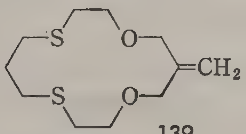
136



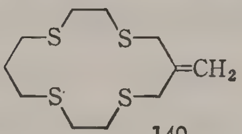
137



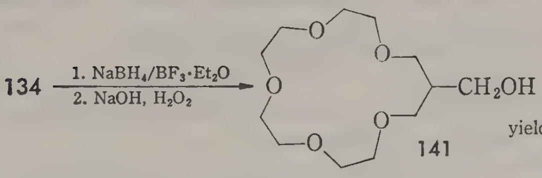
138



139

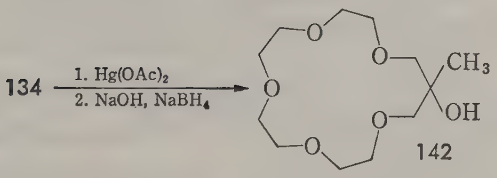


140



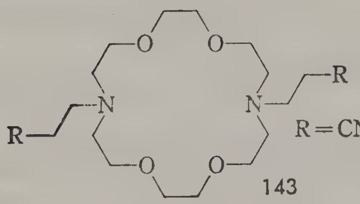
(2.39)

yield 88%



(2.40)

yield 78%



$R = CN, CH_2NH_2$

143

of aziridine derivatives (Section 2.3); *N*-substituted azacrown ethers (Section 2.5.1); crown ethers and aza- and thiacrown ethers with spirooxetane rings and their OH and NH_2 derivatives (Section 2.5.1).

Cinouini *et al.* prepared 18-crown-6 with an ω-ethylaminononyl group as a side chain and cryptand **133** with an ω-aminononyl group as a side chain, by following the synthetic route shown in Eq. (2.37).[185] Cryptand **133** was immobilized by reaction with chloromethylated polystyrene crosslinked by divinyl benzene and was used as a phase transfer catalyst (see Chapter 6).

Kakiuchi *et al.* prepared crown ethers **134**, **135**, and **136**, azacrown ethers **137**, and **138**, and thiacrown ethers **139**, and **140** with vinylidene groups by the reaction of diols with 3-chloro-2-chloromethyl-1-propene.[186,187] They also obtained crown ethers carrying -CH_2OH or -OH groups from **134** by hydroboration or reaction with mercuric acetate.

Functional groups can be introduced to crown compounds having an NH group in their ring structures, such as azacrown compounds and cryptands, by utilizing the reactions of the NH group. Several examples, such as *N*-substituted derivatives, were described previously (see Section 2.5.1). Recently, Chang prepared **143** by the reaction of diamino-18-crown-6 with acrylonitrile.[155]

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CHAPTER 3

Characteristics of Crown Compounds

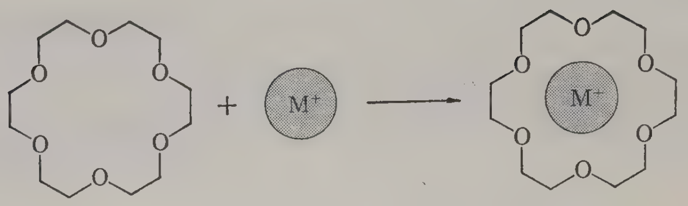
3.1 GENERAL ASPECTS

The most striking characteristic of crown compounds is the ability to form stable complexes. During complexation, the cation portion of a metal salt, ammonium salt, or organic ionic compound (guest) is bound by a crown compound (host) bearing donor atoms such as O, N, and S.

The complexation ability of a crown compound and the stability of the resulting complex depend on the relative sizes of the diameter of the cavity in the crown compound and the diameter of the cation; they are also influenced by the charge and "hardness" of the cation, as well as by the kinds of donor atoms present in the crown compound, which determine "hardness" and basicity. The ion-selective complexation ability of crown compounds is a product of these characteristics. Furthermore, such complexes become soluble in various organic solvents, including nonpolar solvents, because crown compounds have hydrophobic groups.

As described in Chapter 1, it was Pedersen who discovered crown ethers and who identified these characteristics, which have provided the basis for the development of the chemistry and applications of crown compounds. Pedersen synthesized a series of crown ethers[1)] and recognized that, in the presence of crown ethers, various inorganic salts could dissolve in organic solvents. He subsequently confirmed that complexes formed between crown ethers and inorganic salts by a variety of techniques, including change in the uv spectra. Pedersen also isolated a number of crystalline complexes and estimated the structures of the complexes by composition analyses and by comparing the relative sizes of the diameter of the crown ether cavity and the ionic diameter of the metal cations. His ground-breaking investigations were the origin and the impetus for the remarkable development we have seen in research on the characteristics of crown compounds.

The complex between crown ether and an inorganic salt is formed by ion-dipole interaction between the cation and the negatively charged O atoms on the polyether ring (Eq. 3.1). The structure of such comqlexes has been studied by X-ray analysis of the crystalline complexes or by other techniques, and the results substantiated the earlier finding that the structure is composed of a cation trapped in a crown ether cavity that is nearly the same size as the cationic diameter; furthermore, lone pairs of electrons belonging to the O atoms on the crown ether ring are directed toward the inside of the



ring. In the crown ether complex, each O donor atom is located at an equal distance from the cation. The regular arrangement of the ligands in crown ether complexes confers an advantage in entropy compared to the usual synthetic host molecules.

A large number of complexes between crown ethers and cations have been synthesized so far, embracing a wide range of cations—not only Group I and II metals, but also Group III metals and some typical and transition metals. There have also been reports of many complexes of crown ethers with such organic ionic compounds as primary ammonium salts and aromatic diazonium salts and molecular complexes of crown ethers with such organic polar compounds as nitro compounds and nitriles. Complexes of crown ethers with bromine, hydrogen bromide, and oxonium ion have been obtained recently.

Investigators have examined various aspects of complexation reactions. Complexation constants (stability constants) have been measured for a number of crown ether-inorganic salt-solvent combinations by uv spectrography, calorimetry, ion-selective electrodes and other means. A clear correspondence has been observed between the complexation constant and the diameter of the cation; that is, the maximum complexation constant corresponds to the cation whose ionic diameter is nearest in size to the cavity of the crown ether. Data on thermodynamics have been obtained, and it has recently became possible to measure kinetic aspects such as complexation constants or dissociation constants by means of ^{1}H, ^{7}Li, ^{23}Na, ^{39}K, and ^{133}Cs-nmr.

Researchers continue in their efforts to understand why inorganic salts dissolve in organic solvents in the presence of crown ethers. As described previously, complexes between crown ethers and cations become soluble even in nonpolar organic solvents because of the hydrophobic property of the organic residue located on the outside of the polyether ring. In these cases, the counter anions are highly active because they exist in the solvent as "naked" anions which are not dissolved by the solvent. These two characteristics are very important for the utilization of crown ethers. For example, it is possible with these complexes to use an inorganic salt as a reagent for various homogeneous organic reactions. They also offer us the opportunity to develop new reactions, as detailed in Section 4.2.

Many different kinds of substances can be solubilized by the action of crown ethers, including inorganic salts, transition metal complexes, organometal complexes, and organo-alkali metal compounds. It was recently discovered that alkali metals such as Na and K are also solubilized in organic solvents such as ethers and amines in the presence of crown ethers, and the mechanism of solubilization, the structure of the solution, and applications of the phenomenon are under investigation. Other research is directed toward an understanding of the structure and behavior of the ion-pair in solutions of organo-alkali metal-crown ether complex.

Many similar studies have examined the characteristics of crown compounds other than crown ethers, including azacrown ethers, thiacrown ethers, cryptands, cyclic polyamines, cyclic polythiaethers, and others which were described in Chapters 1 and 2, and considerable information has been accumulated regarding the mechanisms of complexation, the structures of complexes, complexation constants, thermodynamic and kinetic data, and the solubilization of inorganic salts and alkali metals. This chapter will first discuss the characteristics of crown ethers which have been studied in detail and will then turn to the characteristics of other crown compounds.

The following articles address various aspects of crown compounds:

1) The characteristics of crown ethers in general: reports[1,2] by Pedersen; reviews by Pedersen and Frensdorff,[3,4] Tabushi,[5,6] Hiraoka,[7] and Matsuda and Takagi.[8]
2) The characteristics of crown ethers and cryptands in general: reviews by Lehn[9] and Kappenstein.[10]
3) The characteristics of cyclic polyamines: reviews by Ogoshi[11,12] and Kimura.[13]
4) The characteristics of crown compounds, including crown ethers, cryptands, cyclic polyamines, and cyclic polythiaethers: review by Christensen *et al.*[14]
5) The characteristics of crown compounds, including useful tables of cation guests-crown compund hosts, complexation constants, and thermodynamic data: reviews by Christensen *et al.*[15,16]
6) Structure of complexes: reviews by Truter and Pedersen,[17] Truter,[18] and Lehn.[9]
7) Alkali metal salt complexes in aqueous solution: review by Midgley.[19]
8) Structure and behavior of ion-pairs: reviews by Smid[20] and Sumitomo.[21]
9) Solubilization of alkali metals in organic solvents: review by Dye *et al.*[22]

3.2 CHARACTERISTICS OF CROWN ETHERS

3.2.1 Complex Formation by Binding of Cations

The formation of complexes by binding of cations, which is the most important characteristic of crown ethers, is caused by electrostatic ion-dipole interaction between cations and negatively charged O donor atoms arranged regularly in the polyether ring.

Pedersen synthesized a number of aromatic and alicyclic crown ethers[1,2] and discovered that they were capable of complexation with salts of various metal cations comprising all of group Ia metal ions, almost all of group Ib, IIa metal ions and some of group IIb, IIIa, IIIb, IVb metal ions (Li^+, Na^+, K^+, Rb^+, Cs^+; Ag^+, Au^+; Ca^+, Sr^{2+}, Ba^{2+}; Cd^{2+}, Hg^{2+}; La^{2+}, Ce^{3+}; Tl^+; Pb^{2+}) and with NH_4^+ and RNH_3^+ salts, as detailed in Chapter 1. The formation of these complexes was detected qualitatively by measuring 1) solubility changes of the crown ethers and salts in various solvents and 2) characteristic changes in the uv spectra of the aromatic crown ethers. The composition was determined after isolation of the crystalline complexes.

An earlier section discussed solubility changes of crown ethers in the presence salts, compared the solubility of dibenzo-18-crown-6 with that of its KSCN complex (Table 2.3), and noted the solubility increase of dicyclohexyl-18-crown-6 in water in the presence of KOH and KCl (Table 2.5). Table 3.1 summarizes the effects of various salts on the solubility of dibenzo-18-crown-6 in methanol. The solubilization of salts in organic solvents in the presence of crown ethers is described in detail in Section 3.2.4.

TABLE 3.1 Effects of salts on the solubility of dibenzo-18-crown-6 in methanol at 30° C[1]

Salt	Concentration (mol/l) (mol/*l*)	Solubility increase of dibenzo-18-crown-6† (mol/*l*)	[Dissolved dibenzo-18-crown-6]/[salt] (molor ratio)
No salt	—	(0.0011)	—
LiSCN	0.025	0.003	0.032
NaSCN	0.025	0.024	0.96
NH_4SCN	0.025	0.0033	0.13
KSCN	0.025	0.025	1.00
KF	0.025	0.025	1.00
K-adipate	0.025	0.053	2.12
	0.0125	0.024	1.92
K_2SO_4	saturated	0.0012	—
RbSCN	0.025	0.026	1.04
CsSCN	0.025	0.030	1.20
$AgNO_3$	0.025	0.022	0.88
CuCl	saturated	0.0011	—
$MgCl_2 \cdot H_2O$	0.025	0.0017	0.068
$CaCl_2 \cdot 2H_2O$	0.025	0.002	0.080
$SrCl_2 \cdot 6\ H_2O$	0.025	0.018	0.072
$Ba(SCN)_2 \cdot 2H_2O$	0.025	0.027	1.08
$BaCl_2 \cdot 2\ H_2O$	0.025	0.023	1.92
$ZnCl_2$	0.025	0.001	0.04
$CdCl_2 \cdot 2.5\ H_2O$	0.025	0	0
$Hg(NO_3)_2 \cdot H_2O$	0.025	0.0046	0.18
Hg_2Cl_2	0.025	0	0

†Corrected for the amount of dibenzo-18-crown-6 normally soluble in the absence of salt (except the first value).

As shown in Figs. 2.1 and 2.2, aromatic crown ethers absorb light at approximately 275 nm due to catechol and its ether derivative, though alicyclic crown ethers do not absorb light at more than 220 nm. In contrast, when an aromatic crown ether forms a complex with an inorganic salt, a second peak appears at a wave length about 6 nm longer in general, as shown in Fig. 3.1, and these changes in uv spectra can be used for qualitative detection of complex formation.

Complexation can also be detected by adding picric acid to an aqueous solution of salt, followed by shaking with a solution of crown ether in an organic solvent.[23] When the complex is formed, the organic layer takes on a yellow color because of the complex between the crown ether and cation-picrate. Complex formation can also be identified by ir, nmr, and Raman spectrography[17,19,23] or by electrochemical methods[19,24] such as measurement of electroconductivity of the solution, potentiometry, and polarography. Figure 3.2 illustrates Frensdorff's results of electroconductivity titration of (a) a methanol solution of KCl and (b) a chloroform/methanol (90:10) solution of KCl with a solution of dicyclohexyl-18-crown-6.[23] In case (a), complex forma-

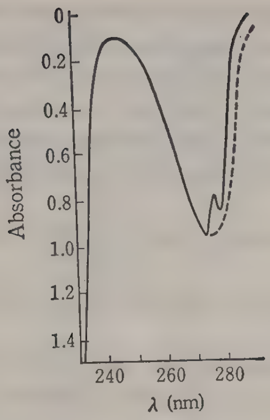


Fig. 3.1 Ultraviolet spectrum of KSCN complex of dibenzo-18-crown-6 in methanol, concentration 1.8×10^{-4} mol/l, cell path 1 cm. ------, dibenzo-18-crown-6;——, KSCN complex, λ_{max} 273 mm (ε 5300) and 279 mm (ε 4700). (Source: Ref. 1. Reproduced by kind permission of the American Chemical Society.)

tion by dissociated KCl in methanol led to an increase in cation diameter. This decreased the cation mobility and electroconductivity declined concomitantly. In contrast electroconductivity increased in case (b). This was explained as follows: The dissociation of ion-pairs increased because the K^+ charge was shielded by the polyether ring that resulted from complex formation by KCl, while KCl alone dissociated only slightly in the chloroform/methanol solution.

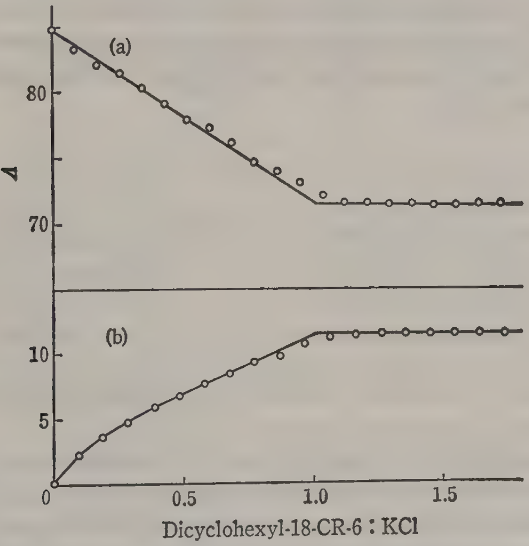


Fig. 3.2 Electroconductivity titration of KCl with dicyclohexyl-18-crown-6 (a) in methanol and (b) in chloroform/methanol (90:10); KCl concentration 10^{-3} mol/l. (Source: Ref. 4. Reproduced by kind permission of Verlag Chemie.)

Solvent extraction of the picrate complex, spectrography, and the electrochemical methods mentioned above can be used not only for identification of complex formation but also for quantitative measurement of the complexation constant, as described in Section 3.2.3. In complexation reactions involving crown ethers and salts without solvent, it has been shown by DTA that the complex is formed after the melting of the crown ether,[25] and this method may also be applied for identification of complex formation.

The methods for preparation and isolation of crystalline complex include the following:[1,2]

1) An equimolar mixture of crown ether and salt is heated under vigorous agitation in the absence of solvent.
2) An equimolar mixture of crown ether and salt is dissolved in a cosolvent, then the solution is concentrated under reduced pressure, and the deposited complex is filtered out.
3) A mixture of crown ether and at least an equimolar amount of salt is dissolved in a minimum amount of hot solvent, then the solution is cooled and the deposited complex is filtered out.
4) Crown ether is added to a solution or suspension of salt, then the mixture is heated with stirring. After filtration followed by cooling, the deposited complex is filtered out.

It is not always possible to obtain pure complex crystals with methods 1 and 2. Method 4 is the most productive. Typical examples of crystalline complexes prepared by method 4 are given in Table 3.2.

As shown in Table 3.2, the composition of the complex is not always 1 : 1 for the molar ratio of crown ether/salt. There are some complexes formed with a composition of 2 : 1 or 3 : 2. It was thought that the complex might have the sandwich structure illustrated in Fig. 3.3 in cases when the cation diameter was larger than the cavity size of the crown ether. This hypothesis was later proven by X-ray analysis and other means, as described in Section 3.2.2.

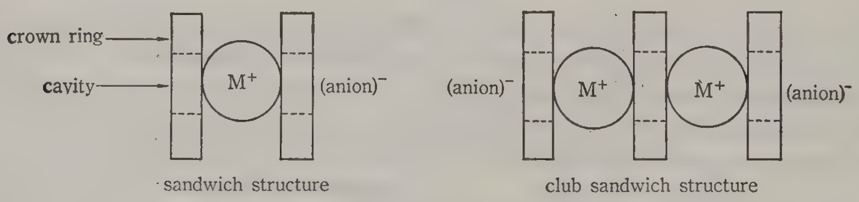


Fig. 3.3 Hypothesized structure of 2:1 and 3:2 complexes

Generally speaking, it is difficult to isolate the complex as a crystal in the cases of salts with a high crystal lattice energy, such as carbonates, acetates, nitrates, phosphates, and fluorides. Many difficulties also arise in the recrystallization of the complexes. The complexes of aromatic crown ethers with low solubility decompose with recovery of ether, while the complexes of aliphatic crown ethers and cyclic oligomers of ethylene oxide with low melting points and high solubility barely precipitate from the solutions.

TABLE 3.2 Typical examples of crystalline salt complexes of crown ethers.1~4)

Crown ether	mp (°C)	Salt	mp (°C)	[Crown ether]: [salt] (mol/mol)	mp of complex (°C)
Dibenzo-14-crown-4	150 ~ 152	LiSCN	—	1 : 1	300
Benzo-15-crown-5	79 ~ 79.5	$AgNO_3$	210	1 : 1	134 ~ 135
		NaSCN	323	1 : 1	162 ~ 165
		KSCN	175	2 : 1	176
		NH_4SCN	149	2 : 1	131 ~ 132
Benzo-18-crown-6	<25	$Ba(SCN)_2$	—	1 : 1	282
Dibenzo-18-crown-6	164	HI_3	—	1 : 1	—
		LiI_3	—	1 : 1	134 ~ 139
		NaSCN	323	1 : 1	230 ~ 232
		$NaNO_2$	271	1 : 1	154 ~ 157
		KI	685	1 : 1	232 ~ 234
		KI_3	—	1 : 1	258 ~ 267 (decomposes)
		KSCN	175	1 : 1	248 ~ 249
		NH_4SCN	149	1 : 1	187 ~ 189
		RbSCN	195	1 : 1	184 ~ 185
		RbSCN	195	2 : 1	175 ~ 176
		CsSCN	—	2 : 1	146 ~ 147
				3 : 2	145 ~ 146
		$CaCl_2$	772	1 : 1	>300
		$Ba(SCN)_2$	—	1 : 1	>360
		$CdCl_2$	568	1 : 1	>300
		HgCl	—	1 : 1	238 ~ 249
		$Pb(OAc)_2$	280	1 : 1	167 ~ 198
Dicyclohexyl-18-crown-6	38 ~ 54	KI	685	1 : 1	123 ~ 170
		KI_3	—	1 : 1	113 ~ 157
		KSCN	175	1 : 1	72 ~ 122
		NH_4SCN	149	1 : 1	107 ~ 110
Dibenzo-24-crown-8	103 ~ 104	KSCN	175	1 : 1	113 ~ 114
Dibenzo-30-crown-10	106 ~ 107.5	KSCN	175	1 : 1	176 ~ 178

The decomposition of the complex depends on the stability constant of the given system because the complexation reactions are in equilibrium. Almost all complexes are stable solutions containing an excess amount of salts, but the isolated complexes decompose on the addition of water, and the degree and rate of decomposition depend on the amount of water and the temperature.1) Some exceptions have been reported; for example, the complexes of KI_3 with dibenzo-18-crown-6 and with dicyclohexyl-18-crown-6 are insoluble and stable in water.1)

Pedersen listed the following factors that affect the stability of the complex:

1) The relative sizes of the cation and the cavity of the crown ether: the more closely they match, the more stable is the complex formed.
2) The number of O donor atoms: stability of the complex increases as the number of O donors increases.
3) The arrangement of O donor atoms: the more O donors are arranged on a plane, the more stable is the complex formed.

4) The symmetry of the arrangement of O donor atoms: the more O donors are arranged symmetrically, the more stable is the complex formed.
5) The basicity of O donor atoms: stability of the complex increases with increasing basicity. The basicity of an O atom bonded to an aliphatic C atom is greater than that of an O atom bonded to an aromatic ring.
6) Steric hindrance of the polyether ring: the less steric hindrance, the more stable is the complex formed.
7) Solvation of the cation: the less solvation, the more stable is the complex formed. Solvation energy decreases with increasing ionic diameter for cations belonging to Groups I ~ IV.
8) Electric charge on the cation.

Table 3.3 gives the values that have been calculated for the cavity diameters of 14- ~ 24-crown ethers; these relate to factor 1, which is the most specific factor for crown ethers. For reference, the metal cations which have been reported to form complexes with 15- ~ 24-crown ethers are listed in Table 3.4 together with the sizes of their ionic diameters.

TABLE 3.3 Cavity sizes of crown ethers[4)]

Polyether ring	Cavity diameter (Å)†
14-Crown-4	1.2 ~ 1.5
15-Crown-5	1.7 ~ 2.2
18-Crown-6	2.6 ~ 3.2
21-Crown-7	3.4 ~ 4.3
24-Crown-8	>4

†Lower values estimated from Corey-Pauling-Koltun atomic models, higher values from Fischer-Hirschfelder-Taylor models.

The close connection between the stability of a complex and the relative sizes of the crown ether cavity and the cation has been substantiated by X-ray analysis of the structures of crystalline complexes (Section 3.2.2) and by measurement of complexation constants (Section 3.2.3). As mentioned, a more stable 1 : 1 complex is formed when the cation has an ionic diameter fitted to the cavity size of the crown ether. When the cationic diameter is larger than the cavity size, the complex becomes less stable; then the cation may be located slightly apart from the plane in which the O donors on the crown ring are arranged, or a 2 : 1 or 3 : 2 complex with a sandwich structure may be formed. In contrast, when the cationic diameter is much smaller the conformation of the crown ring assumes a steric configuration such that each O donor atom is located the shortest distance from the cation, or occasionally a 1 : 2 complex is formed. Figure 3.4 illustrates schematically the structures of the complexes reported by Ponnia[26)] after determination of the complex composition of 15- ~ 30-crown ethers with Na^+ (ionic diameter: 1.90 Å, Na-O distance 2.34 ~ 3.43 Å) and K^+ (ionic diameter: 2.66 Å, K-O distance 2.78 Å) by ir and X-ray analysis. This figure clearly pictures the association between the structure of a complex and the relative sizes of the crown ether and the cation. Using the effects of the factors listed earlier, it is possible to form other special structures, but conformational change of the crown ring in the complex forma-

Table 3.4 Metal ions reported to form complexes with 15- ~ 24-crown ethers, and their ionic diameters (Å).

I				II				III				IV				V				VII		VIII	
Ia		Ib		IIa		IIb		IIIa		IIIb		IVa		IVb		Va		Vb		VIIa		VIIIa	
Li^+	1.20	Cu^{2+}	1.44	Mg^{2+}	1.30	Zn^{2+}	1.48	La^{3+}	2.30	Al^{3+}	1.00	Ti^{3+}	1.26	Pb^{2+}	2.40	V^{3+}	1.48	Bi^{3+}	1.92	Mn^{2+}	1.60	Fe^{3+}	1.28
Na^+	1.90	Ag^+	2.52	Ca^{2+}	1.98	Cd^{2+}	1.94	Ce^{3+}	2.20	Tl^+	2.88											Co^{2+}	1.48
K^+	2.66	Au^+	2.74	Sr^{2+}	2.26	Hg^+	1.52	Pr^{3+}	2.18													Ni^{2+}	1.38
Rb^+	2.96			Ba^{2+}	2.70	Hg^{2+}	2.20	Nd^{3+}	2.16														
Cs^+	3.34							Pm^{3+}	2.12														
(NH_4^+)	2.84							Sm^{3+}	2.08														
								Eu^{3+}	2.06														
								Gd^{3+}	2.04														
								Tb^{3+}	2.00														
								Dy^{3+}	1.98														
								Ho^{3+}	1.94														
								Er^{3+}	1.92														
								Tm^{3+}	1.90														
								Yb^{3+}	1.88														
								Lu^{3+}	1.86														
								U^{4+}	2.02														
								Th^{4+}	2.12														

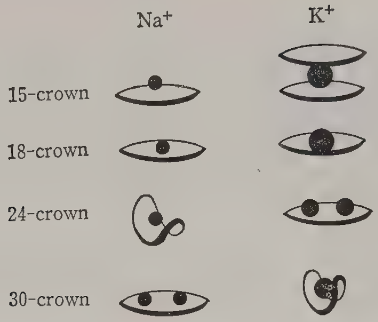
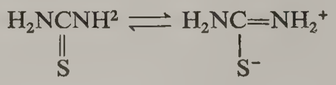


Fig. 3.4 Schematic structures of complexes of various crown ethers with Na^+ and K^+.[26] (Source: Ref. 26. Reproduced by kind permission of the American Chemical Society.)

tion generally depends on the relative sizes of the cation and the cavity of the crown ether. The energetic stability of the complex decreases with increasing deviation from the stable conformation and the value of the complexation constant becomes smaller.

Other than the metal cations listed in Table 3.4, a variety of ionic and polar organic compounds have been reported to form complexes with crown ethers. Pedersen discovered that RNH_3^+ salts such as $HONH_3Cl$, NH_2NH_3Cl, $(CH_3)_2CHCH_2NH_3Cl$, $(CH_3)_2CHCH_2CH_3NH_3Cl$, $(CH_3)_3CNH_3Cl$, $PhNH_3Cl$, $NH_2CH_2CH_2NH_3Cl$, HOOC CH_2NH_3Cl, $[NH_2C(=NH_2)NH_2]Cl$, and $[NH_2C(=NH_2)NH_2]_2CO_3$ form complexes in methanol with dibenzo-18-crown-6.[1] Cram *et al.* reported complexation between guadinium salts and dibenzo-27-crown-9,[27] as described previously in Section 2.2.1, and between *tert*-butyl ammonium salts and various crown ethers or their substituted derivatives.[28,29] Cram *et al.* extended their investigation to the optical resolution of amino acid esters (as ammonium salts) using optically active crown ethers,[30~34] as discussed in detail in Chapter 5.

It has also been reported that thiourea and related compounds such as *N*-phenylthiourea, 1-phenylasemicarbazide, 1- and 4-phenylthiosemicarbazide, 2-thiazolidinethione, and thiobenzamide form complexes with aromatic and alicyclic 14- ~ 18-crown ethers.[35] With these compounds, it is thought that a zwitter ion, produced by tautomerism as shown in Eq. (3.2), is held by the crown ethers.



$$H_2N\underset{\underset{\displaystyle S}{\|}}{C}NH^2 \rightleftharpoons H_2N\underset{\underset{\displaystyle S^-}{|}}{C}{=}NH_2^+ \tag{3.2}$$

Aromatic diazo compounds such as *p*-toluene diazonium BF_4, benzene dazonium BF_4, and *p*-methoxy-, *p*-chloro-, *p*-nitro-, and 3,4-dimethyl-benzene dazonium BF_4 also form complexes with 18-crown-6 (cavity size calculated from CPK model: 2.6 Å) and binaphtho-20-crown-6 (cavity size: 2.8 Å), but they do not form complexes with binaphto-17-crown-5 (cavity size: 2.2 Å).[36] As the diazonium group ($-\overset{+}{N}\equiv N$) is a cylinder with a diameter of 2.4 Å, the molecular complex is formed by insertion of the group into a crown ring with a cavity size fitted to the diameter of the cylinder, and $\overset{+}{N}$ bonded to an aryl group is located near the center of the plane in which the O donor atoms in the crown ring are arranged, as shown in Fig. 3.5. No complex is formed with

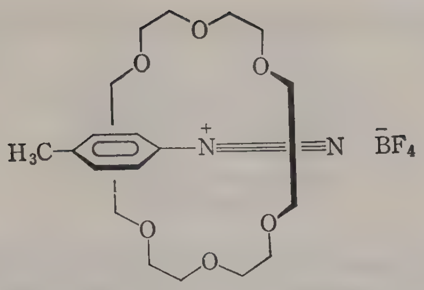


Fig. 3.5 Structure of 18-crown-6 complex with *p*-toluenediazonium BF_4.

2, 6-dimethylbenzene diazonium salt because of steric hindrance. Recently, it was confirmed by means of ^{13}C-nmr and ir that aromatic diazonium chlorides form complexes with 18-crown-6 in CH_2Cl_2 and $CHCl_3$.²⁷⁾ Aromatic acylonium salts such as benzoyl cation-PF_6^- also form molecular complexes with 18-crown-6 and binaphtho-20-crown-6. In this case it is thought that the $-\overset{+}{C}=O$ moiety is inserted into the crown ring.³⁶⁾

Diazonium salts and acylonium salts can be dissolved in nonpolar solvents by complexation with crown ethers. Current research is directed toward finding applications of this phenomenon to organic reactions.³⁷~⁴¹⁾

Cram *et al.* have examined in detail the complex formation of *tert*-butyl ammonium salts, guadinium salts, and aromatic diazonium salts with various crown ethers.⁴²⁾ They explained the effect of the structures of the crown ether and the substituent on complexation by the concept of "host-guest chemistry."

It was mentioned in Section 2.2.3 that acetonitrile, as a polar organic compound, forms a crystalline complex with 18-crown-6, and this can be utilized for the purification of 18-crown-6.⁴³⁾ Other than acetonitrile, nitromethane,⁴⁴⁾ acetic anhydride,⁴⁴⁾ and dimethyl acetylene-2-carboxylate (DAC)⁴⁵⁾ also form molecular complexes with 18-crown-6. By means of polarized Raman spectrography and X-ray analysis it was estimated that, in a single crystal of each complex of acetonitrile, nitromethane, and acetic anhydride, that the structure of the 18-crown-6 molecule in the complex had approximately D_{34} symmetry.⁴⁴⁾ The crystal of the DAC complex is triclinic, and the structure of the complex is column-like, formed by alternating molecules of 18-crown-6 and DAC in the direction of [011].⁴⁴⁾

Izatt *et al.* reported that dicyclohexyl-18-crown-6 forms a complex with $HClO_4$ in aqueous solution, and the complex was confirmed as an oxonium ion (OH_3^+) complex by ir spectrography.⁴⁶⁾ There is a difference in the solubility of the oxonium ion complexes formed with the two isomers of dicyclohexyl-18-crown-6 (A: *cis-syn-cis*, B: *cis-anti-cis*). The oxonium ion complex of isomer A is deposited more easily, and such complexes as $[OH_3, C_{20}H_{36}O_6]^+ ClO_4^-$(mp 143 ~ 144°C), $[OD_3, C_{20}H_{36}O_6]^+ClO_4^-$(mp 146 ~ 147°C) and $[OH_3, C_{20}H_{36}O_6]^+PF_6^-$ have been isolated and identified. The method for separating isomers A and B is based on this difference, reported by Izatt *et al.*,⁴⁷⁾ as noted in Section 2.2.2.

Shchori and Jagur-Grodzinski observed a molecular complex formation of crown ether with Br_2 when they tried the bromination of stilbene in the presence of dicyclohexyl-18-crown-6.⁴⁸,⁴⁹⁾ They also discovered complex formation with HBr and HBr_3

in chloroform(50) and suggested that the proton was bound to the crown ring as shown in Eqs. (3.3) and (3.4).

$$\mathrm{CR} + \mathrm{HBr} \rightleftharpoons [\mathrm{CR, H}]^+\mathrm{Br}^- \tag{3.3}$$

$$[\mathrm{CR, H}]^+\mathrm{Br}^- + \mathrm{Br}_2 \rightleftharpoons [\mathrm{CR, H}]^+\mathrm{Br}_3^- \tag{3.4}$$

(CR: crown ether)

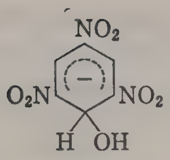
The complexation constant K (in chloroform, 25° C) in Eq. (3.3) was measured for dicyclohexyl-18-crown-6 ($K = 10^6\ \mathrm{mol}^{-1}$), dibenzo-18-crown-6 ($K = 210\ \mathrm{mol}^{-1}$), and 4,4′-dibromodibenzo-18-crown-6 ($K = 20\ \mathrm{mol}^{-1}$). These values are much larger than those for diglyme ($K = 0.17\ \mathrm{mol}^{-1}$) and triglyme ($K = 0.20\ \mathrm{mol}^{-1}$). From experiments with Eq. (3.4), the values of $K(3.7 \times 10\ \mathrm{mol}^{-1})$, enthalpy change ΔH (− 8.2 kcal), and entropy change ΔS (−6.6 eu) were reported for dicyclohexyl-18-crown-6.

Nae and Jagur-Grodzinski reported recently that several organic acids such as *p*-toluence sulfonic acid, picric acid, and benzoic acid also form complexes in which the proton is bound by 15–crown-5, benzo-15-crown-5, 18-crown-6, dibenzo-18-crown-6, and dicyclohexyl-18-crown-6 in 1,2-dichloroethane.(51) Measurements of the increase in electroconductivity during complex formation and data on the absorption spectra of complexes with picric acid (18-crown-6 complex: $\lambda_{\max} \sim 350$ nm; dicyclo-hexyl-18-crown-6-complex: $\lambda_{\max}$ 378 nm) indicated that the order of proton complexation ability for the organic acids coincides with the order of p*K*a; the largest complexation constant was observed for *cis-syn-cis*-dicyclohexyl-18-crown-6 (isomer A).(51) These organic acids did not form complexes with crown ethers with smaller size of cavities, such as benzo-12-crown-4, benzo-13-crown-4, and dibenzo-14-crown-4.

Grodzinski *et al.* speculated that the solvation of an ether to a proton may be same as the hydration of an acid(51) in which a proton is generally solvated by only 2 moles of water and the O–O distance is 2.4 ∼ 2.5Å.(52) They further hypothesized that the complexes may have a structure in which a proton, not a hydronium ion, is bound directly into the crown ring because of thermodynamic requirements for the conformation of the crown ring and because of the absence of water in the systems.(51)

Goldberg reported the complexation of 2,6-dimethylbenzoic acid with 18-crown-6 and suggested from the results of X-ray analysis of the crystalline complex that the conformation of the complex is due both to an $\mathrm{O} \cdots \mathrm{H{-}O}$ hydrogen bond and to $\mathrm{O} \cdots \mathrm{C = O}$ nonbonding interaction between the crown ring and a caboxyl group.(53)

While the reaction does not involve complex formation by binding of an organic polar compound into a crown ether, we can note that 1, 3, 5-trinitrobenzene and 1, 3-dininitrobenzene react with KOH in benzene in the presence of dicyclohexyl-18-crown-6 and produce a deep red color in the solutions.(54) This phenomenon is due to the formation of a Meisenheimer-Jackson complex (one kind of σ-complex) (**144, 145**) in which the negative charge is delocalized by the I effect and M effect of nitro groups. Htay and Meth-Cohn proposed a simple method for the qualitative detection of the complexation of a crown compound with alkali metal and alkaline earth metal ions using the coloration phenomeon.(55) The procedure is as follows. A crown compound is dissolved in a chloroform solution of trinitrobenzene, and a halide, carbonate,



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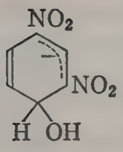

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or hydroxide of the alkali or alkaline earth metal is added. After shaking the solution, the characteristic coloration caused by the formation of a Meisenheimer Jackson complex is detected. With this method, they evaluated the complexation ability of 18-crown-6 and a series of novel azacrown ethers (**94**, **95**, and **96**, shown in Section 2.5.1) with Li^+, Na^+, K^+, Cs^+, NH_4^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+}.

3.2.2 Structures of Crown Ether Complexes

A. Crystal Structures of Crown Ether Complexes

The structures of 1 : 1, 2 : 1, 3 : 2, and 1 : 2 complexes, formed according to the relative sizes of the cavity of the crown ether and the ionic diameter of the cation, have been substantiated by X-ray diffraction, by ir, nmr, Raman, and nuclear quadrupole resonance spectrography, by measurement of dipole moments, and so on. Thus, the conformation both in crystal form and in solution has been determined for various complexes.

Using X-ray diffraction, Bright and Truter first identified the crystal structure of a RbSCN complex of dibenzo-18-crown-6 provided by Pedersen.[56,57] They demonstrated that the complex had a 1 : 1 composition, and that Rb^+ was coordinated by six coplanar oxygen atoms equidistant from the cation. The Rb-O distance (2.91Å) was nearly equal to the value expected from the sum of the radius of Rb^+ (1.48Å) and the van der Waals radius of O (1.4 Å). Thiocyanate anion formed an ion-pair by the coordination of N to Rb^+ (Rb-N distance: 2.94 Å).

Truter *et al.* also determined the crystal structures of the complexes between alkali

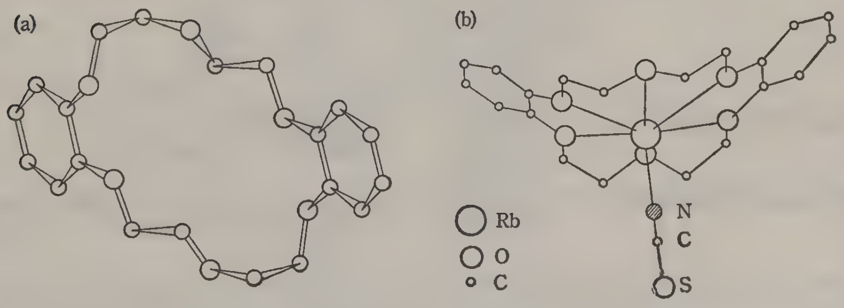


Fig. 3.6 Crystal structure and conformation of (a) dibenzo-18-crown-6[17] and (b) its RbSCN complex,[56,57] (Source: Ref. 17. Reproduced by kind permission of Imperial Chemical Industries Ltd.)

TABLE 3.5 Metal–oxygen distances (Å) in crown ether complexes[18)]

Complex	M–O (aliphatic)	M–O (aromatic)	M–O (H_2O)	M–N (NCS)
NaI (benzo-15-crown-5) H_2O	2.427 (12)	2.372 (11)	2.285 (14)	
	2.354 (11)	2.369 (12)		
	2.416 (12)			
NaSCN (dibenzo-18-crown-6)	2.735 (2)	2.783 (17)		3.322 (30)
	2.886 (21)	2.784 (21)		
		2.861 (17)		
		2.779 (21)		
NaBr (dibenzo-18-crown-6) $2H_2O$	2.66 (1)	2.64 (1)	2.31 (2)	
	2.71 (1)	2.77 (1)	2.27 (1)	
	2.89 (1)	2.82 (1)	2.35 (1)	
	2.54 (1)	2.63 (1)		
		2.69 (1)		
		2.86 (1)		
		2.71 (1)		
		2.67 (1)		
NaBr (dicyclohexyl-18-crown-6B) 2 H_2O	2.673 (4)		2.349 (5)	
	2.684 (4)			
	2.975 (4)			
NaSCN (18-crown-6) H_2O	2.45			
	2.48			
	2.55			
	2.61			
	2.62			
	2.58			
KI (benzo-15-crown-5)$_2$	2.955 (8)	2.821 (7)		
	2.908 (7)	2.777 (8)		
	2.855 (8)			
KSCN (18-crown-6)	2.77			
	2.81			
	2.83			
(KSCN) (dibenzo-24-crown-8)	3.01 (1)	2.79 (1)		2.84
	2.89 (1)	2.79 (1)		2.84
	2.85 (1)	2.74 (1)		8.89
K(p-$CH_3C_6H_4SO_3$) (18-crown-6)	2.78			
	2.94			
	2.84			
	2.89			
	2.82			
	2.92			
KI (dibenzo-30-crown-10)	2.850 (6)	2.895 (6)		
	2.879 (6)	2.931 (6)		
	2.850 (6)			
RbSCN (dibenzo-18-crown-6)	2.900 (12)	2.913 (9)		2.936 (18)
	2.909 (11)	2.939 (12)		
		2.927 (10)		
		2.861 (11)		

metal salts and 15- ~ 30-crown ethers having 5 ~ 10 O donor atoms, such as benzo-15-crown-5 (NaI,$^{57\sim59)}$ NaSCN,$^{57)}$ and KI$^{60)}$ complexes), dibenzo-18-crown-6 (NaBr$^{58,61)}$ and RbSCN$^{57)}$), dicyclohexyl-18-crown-6 (NaBr$^{62,63)}$), tetramethyldibenzo-18-crown-6 (CsSCN$^{64\sim66)}$), dibenzo-24-crown-8 (KSCN$^{67\sim69)}$), and dibenzo-30-crown-10 (KI$^{70)}$). The crystal structure of the complex of dicyclohexyl-18-crown-6 with K-*p*-toluene sulfonate was determined by Groth,$^{71)}$ and the structures of the complexes of 18-crown-6 with alkali metal (Na, K, Rb, Cs) thiocyanates were ascertained by Dunitz *et al.*$^{72\sim77)}$ Table 3.5 Summarizes the alkali metal-O distances for these complexes, and Figs. 3.7 ~ 3.10 present the crystal structures and conformations for typical complexes.

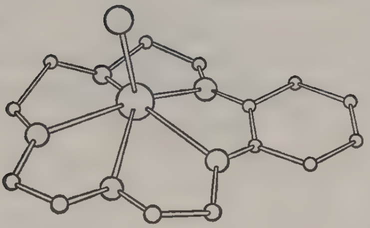


Fig. 3.7 Crystal structure of benzo-15-crown-5-complex with NaI. (Source: Ref. 58. Reproduced by kind permission of the Chemical Society.)

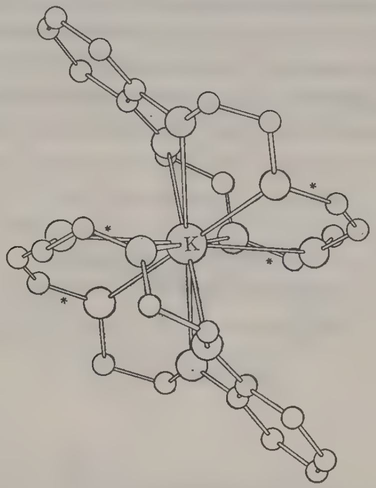


Fig. 3.8 Crystal structure of 2:1 complex of benzo-15-crown-5 with KI. (Source: Ref. 60. Reproduced by kind permission of the Chemical Society.)

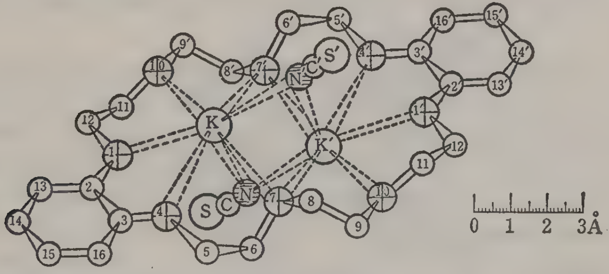


Fig. 3.9 Crystal structure of the 1:2 complex of dibenzo-24-crown-8 with KSCN. (Source: Ref. 67. Reproduced by kind permission of the Chemical Society.)

Benzo-15-crown-5 forms a 1 : 1 monohydrated complex with NaI. Sodium coordination, shown in Fig. 3.7, is a pentagonal pyramid with the Na^+ 0.75 Å out of the plane of the five O atoms towards the water molecule at the apex. Hydrogen bonding from water molecules holds the complex cations to the anions in chains (O ··· I 3.51

and 3.47 Å). In contrast, benzo-15-crown-5 forms a 2 : 1 complex having a sandwich structure with K$^+$, whose ionic diameter is larger than Na$^+$, as shown in Fig. 3.8. In the crystal, K$^+$ is on a center of symmetry so its ten O neighbors, lying in two planes 3.34 apart, form a pentagonal antiprism. The conformation of the ligand differs from that in the Na complex. The change is mainly in the torsion angles about two C–O bonds (asterisks in Fig. 3.8) In the crystal of KI complex, I$^-$ is surrounded by the neighboring eight K$^+$ complexes and is in contact with K$^+$.

Figure 3.9 shows the conformation of the 1 : 2 complex of dibenzo-24-crown-8 with KSCN as an example of a structure in which two cations are bound into a crown ring with a larger cavity size. Furthermore, dibenzo-30-crown-10 forms a 1 : 1 complex with KI in which K$^+$ is completely enclosed by the ligand, as shown in Fig. 3.10 The counter anion I$^-$ is surrounded by six complexes and has no contact with K$^+$. This conformation closely resembles that of the complex between K$^+$ and nonactin, one of the natural ionophore antibiotics (see Fig. 1.5), shown in Fig. 3.11.[78)] The relationship

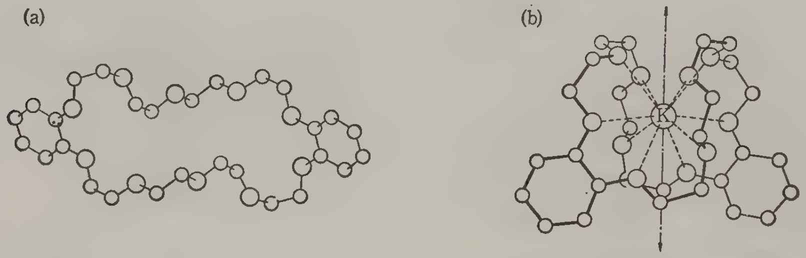


Fig. 3.10 Crystal structure and conformation of (a) dibenzo-30-crown-10 and (b) its KI complex. (Source: Ref. 70. Reproduced by kind permission of the Chemical Society.)

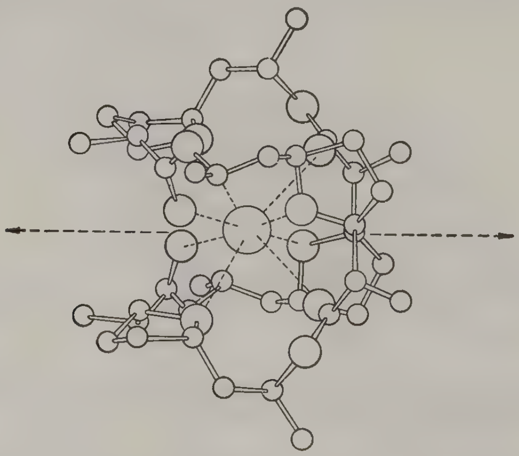


Fig. 3.11 Crystal structure and conformation of nonactin-K$^+$ complex viewed normal to the two-fold axis, indicated by an arrow. (Source: Ref. 78. Reproduced by kind permission of Verlag Helvetica Chimica Acta.)

between the conformation of the complex and the relative sizes of the crown ring and the cation was discussed by Poonia and Truter[79] and Poonia.[26] The schematic models are shown in Fig. 3.4

The structures were also determined for the complexes with Na^+ of the A and B isomers of dicyclohexyl-18-crown-6,[80] the complexes of 18-crown-6 with $NH^4Br\cdot 2H_2O$[81] and with K-ethylacetoacetate enolate,[82] and the complex of dibenzo-24-crown-8 with two molecules of Na (*o*-nitrophenolate).[69,83] In addition, the structures of crown ether complexes with alkali metal perchlorate were ascertained by ir spectrography and other techniques, and it was reported that dibenzo-15-crown-5 formed 1 : 1 complexes with $KClO_4$ and $CsClO_4$, while a 1 : 1 or 1 : 2 complex was formed with $NaClO_4$ depending on the conditions.[84] Calculations of the molecular orbital function of the complex of 12-crown-4 with Li^+ by the Hartree-Fock-Roothaan method (LCAOSCF method)[85] and determination of the structure of Li complexes by Raman and ir spectrography[86] were reported recently.

Among the complexes of crown ethers with alkaline earth metal ions, there have been determinations of the crystal conformation of the complexes of 18-crown-6 with $Ca(SCN)_2$[72,77] and of dicyclohexyl-18-crown-6 (isomer A[80,87] and B[80]) with $Ba(SCN)_2$. Isomer A of dicyclohexyl-18-crown-6 forms a 1 : 1 complex with Ba^{2+} in *cis-syn-cis* conformation, as shown in Fig. 3.12. The six O atoms lie in the same plane, and the Ba–O distance and Ba–N distance are 2.77 ~ 2.98 Å and 2.89 Å, respectively.

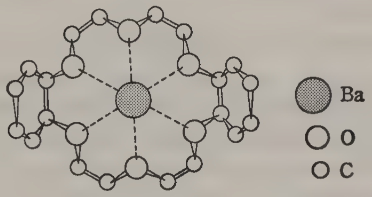


Fig. 3.12 Crystal structure and conformation of Ba^{2+} complex of dicyclohexyl-18-crown-6 (isomer A). (Source: Ref. 87. Reproduced by kind permission of the Chemical Society.)

X-ray analysis has recently been carried out for the complexes of dibenzo-15-crown-5 with Ca 3, 5-dinitrobenzoate,[88] Mg 2,4-dinitrophenolate, and Mg 2,4,6-trinitrophenolate.[89] The composition of the Ca complex is $Ca(crown)_2$ $(dinitrobenzoate)_2\cdot 3\ H_2O$; however, one of the crown rings and two molecules of dinitrobenzoate ion unexpectedly coordinate to Ca^{2+}, and the other crown ring forms hydrogen bonds to H_2O molecules. In the case of the Mg complexes, the composition is $Mg\ (crown)_2$ $(phenolate)_2\cdot 2\ H_2O$, and 2 : 1 complexes with a sandwich structure are formed in which Mg^{2+} is coordinated by two crown rings.

For Group IIb cations, structures of the complexes of 18-crown-6 with $ZnBr_2$ and $CdBr_2$ were assessed by ir, Raman, and nmr.[90] The number of O atoms coordinating to Hg^{2+} and the intermolecular interaction coefficient of Hg-Cl for a 1 : 1 complex of 18-crown-6 with $HgCl_2$ were calculated by ^{35}Cl-NOR (nuclear quadrupole resonance) and by measurement of Hg-Cl stretching with ir.[91]

After Pedersen reported the formation of complexes with La (III) and Ce(III),[1] which are lanthanide (Ln) ions belonging to Group III in the periodic table, Cassol *et al.* prepared lanthanide complexes by the reaction of benzo-15-crown-5 and dibenzo-18-crown-6 with Ln(III) $(No_3)_3 \cdot n$ H_2O for all kinds of lanthanide and with Ln (III) $(SCN)_2 \cdot n$ H_2O for all lanthanides except Pm in acetonitrile;[92)] they also determined the composition of the complexes by uv, ir, and electroconductivity measurements. These Ln complexes have been studied in detail by King and Heckley.[93)] With the so-called "light" lanthanides, La, Ce, Pr, and Sm, Ln (III) $(NO_3)_3 \cdot n$ H_2O forms a complex with the composition $[Ln, crown]^{3+}$ $(No_3^-)_3$ with benzo-15-crown-5 in acetone; "heavy" lanthanides, Sm (which forms both kinds of complex) Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu, form a complex with the composition $[Ln, crown]^{3+}$ $(NO_3^-)_3 \cdot 3$ H_2O (Me_2CO). With dibenzo-18-crown-6, the light lanthanide nitrates form $[Ln, crown]^{3+}$ $(NO_3^-)_3$ complexes in acetonitrile, but the heavy lanthanide nitrates do not form stoichiometric complexes. The stability of $[Ln, crown]^{3+}(No_3^-)_3$ complexes decreases with an increasing atomic number.

Cassol *et al.* determined the ΔH and the activation energy in the thermal dissociation of these complexes of Ln (III) $(NO_3)_3$ and Ln (III) $(SCN)_3$ (except Pm) with benzo-15-crown-5 and dibenzo-18-crown-6 by TG, DTG, and DTA measurements on thermal decomposition of the complexes under nitrogen and under reduced pressure (5×10^{-2} mm Hg).[94,95)] The results indicated that these values depended on the atomic number of the lanthanide and that $[Ln, crown]^{3+}$ $(NO_3^-)_3$ complexes were dissociated by decomposition of the ligands, while $[Ln, crown]^{3+}(SCN^-)_3$ complexes dissociated without decomposition of the ligands.

To determine the structure of a lanthanide complex, X-ray analysis was carried out on the complex between *cis-syn-cis* dicyclohexyl-18-crown-6 (isomer A) and La(III) $(NO_3)_3$ crystallized from an ether-ethanol solution for the first time by Harman *et al.*[96)] As shown in Fig. 3. 13, La is coordinated by six O atoms in the crown ring and three bidentate NO_3. This is the first example of an uncharged 12-coordinated molecular complex. All of the 12-coordinated complexes which were known previously were those in which the center metal was coordinated by anions such as $[Ce\ (NO_3)_6]^{n-}$ ($n = 2, 3$) and $CaTiO_3$.

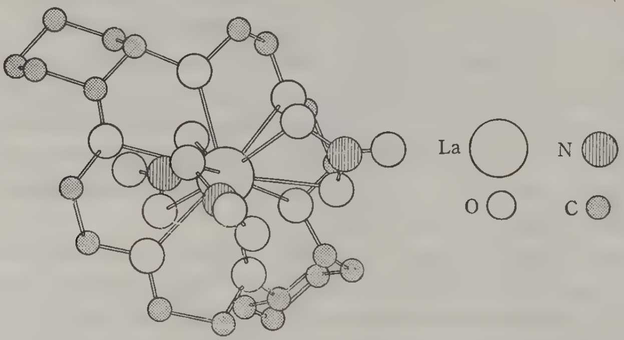


Fig. 3.13 Crystal structure and conformation of dicyclohexyl-18-crown-6 (isomer A)-La $(NO_3)_3$ complex. (Source: Ref. 96. Reproduced by kind permission of the Chemical Society.)

There are also crown complexes of actinides. Various crystals considered to be the complexes of crown ethers or cryptands with U^{4+}, UO_2^{2+}, and Th^{4+}, with the compositions shown in Table 3.6, have been isolated, and their structures determined.

Costes *et al.* observed that a yellow crystal was deposited gradually when absolute ethanol solutions of $UO_2(NO_3)_2 \cdot 6\ H_2O$ and 18-crown-6 were mixed and allowed to stand for 60 hours at 0°C, and they found that the complex had composition No. I in Table 3.6.97) They also isolated crystals or precipitates with compositions II ~ VIII in Table 3.6; these had been obtained by mixing, cooling, and allowing to stand THF solutions of UCl_4, $Th(NO_3)_4 \cdot 4H_2O$, $UO_2(NO_3)_2 \cdot 6\ H_2O$, and $UO_2(CH_3CO_2)_2$ together with a THF solution of 18-crown-6.98) The complexes of these actinide salts with cryptand [2,2,2] were also isolated.101) When a THF solution of UCl_4 was added to a THF solution of 18-crown-6, U^{4+} complex II was precipitated immediately as a pale green powder. The preparation and isolation of complex II were carried out under an argon atmosphere to prevent the oxidation of U^{4+} to UO_2^{2+}.

Costes *et al.* measured the uv, ir, and Raman spectra of these complexes and found that the shift of the NO_3^- absorption band from D_{3h} symmetry, which was observed in their spectrum of free NO_3^-, was slight for the complexes and that the charge transfer band of UO_2^{2+} or U^{4+} was not present in the electronic spectra. From these findings they proposed a complex structure in which actinide ion was enclosed into the cavity of 18-crown-6.

Knöchel *et al.* isolated pale yellow, needle-like crystals with composition IX in Table 3.6 by mixing a toluene or ether solution of $UO_2\ (NO_3)_2 \cdot 6\ H_2O$ and an ether solution of 18-crown-6, and confirmed that the crystal was a crown complex by ir, Raman, and nmr.90)

Recently it was shown that some of the UO_2^{2+} and Th^{4+} complexes do not have structures in which the ion is enclosed into the cavity of the crown ether, but rather the structures of one kind of adduct. From X-ray diffraction data on the crystalline complex of composition V prepared from 18-crown-6 and $UO_2(NO_3)_2 \cdot 6\ H_2O$, Bombieri *et al.*102) and Eller and Penneman103) reported that the UO_2 ion was not present in the crown ring, but that a neutral molecule of $UO_2\ (NO_3)_2 \cdot 2\ H_2O$ was linked to

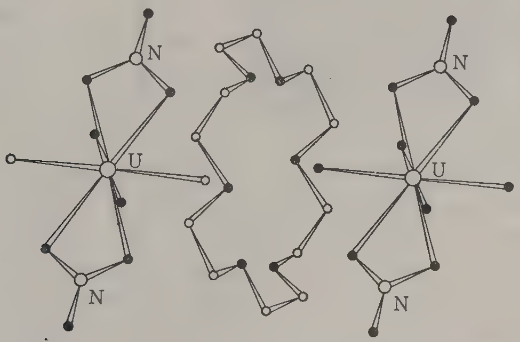


Fig. 3.14 Crystal structure and conformation of 18-crown-6 with $UO_2(NO_3)_2 \cdot 2H_2O$. (Source: Ref. 102. Reproduced by kind permission of the American Chemical Society.)

Table 3.6 Complexes of Actinide Salts with Crown Ethers or Crypstand

Crown compounds	Actinide salts	solution	Complex compositions (mp)	No.	Refs.
18–Crown–6 (L_I)	$UO_2(NO_3)_2 \cdot 6H_2O$	ethand	UO_2^{2+}, L_I, $2NO_3^-$, $4H_2O$	I	97)
	UCl_4	THF	U^{4+}, L_I, 4 Cl^- (> 280°C)	II	98)
	$Th(NO_3)_4 \cdot 4H_2O$	〃	Th^{4+}, L_I, $4NO_3^-$, H_2O (> 280°C)	III	〃
	〃	〃	Th^{4+}, L_I, 4 NO_3^-, THF, 3 H_2O	IV	〃
	$UO_2(NO_3)_2 \cdot 6H_2O$	〃	UO_2^{2+}, L_I, 2 NO_3^-, 2 H_2O (155°C)	V	〃
	〃	〃	UO_2^{2+}, L_I, 2 NO_3^-, $4H_2O$	VI	〃
	$UO_2(CH_3CO_2)_2$	〃	UO_2^{2+}, L_I, 2 $CH_3CO_2^-$, $3H_2O$	VII	〃
	〃	〃	UO_2^{2+}, L_I, 2 $Ch_3CO_2^-$, 4 H_2O	VIII	〃
	$UO_2(NO_3)_2 \cdot 6H_2O$	ether or toluene	UO_2^{2+}, L_I, $2NO_3^-$, $3H_2O$ (155°C)	IX	90)
Dibezo–18–Crown–6 (L_{II})	〃	acetonitrile	UO_2^{2+}, L_{II}, $2NO_3^-$, $2H_2O$	X	99)
	$UO_2(ClO_4)_2 \cdot nH_2O$	〃	UO_2^{2+}, L_{II}, 2 ClO_4^-, $6H_2O$	XI	〃
	$UO_2Cl_2 \cdot 3H_2O$	〃	UO_2^{2+}, L_{II}, 2 Cl^-, $2H_2O$	XII	〃
Benzo–15–Crown–5 (L_{III})	$UO_2(NO_3)_2 \cdot 6H_2O$	〃	UO_2^{2+}, L_{III}, 2 NO_3^-, $5H_2O$	XIII	〃
	$UO_2(ClO_4)_2 \cdot nH_2O$	〃	UO_2^{2+}, L_{III}, 2 ClO_4^-, $7H_2O$	XIV	〃
	$UO_2Cl_2 \cdot 3H_2O$	〃	UO_2^{2+}, L_{III}, 2 Cl^-, 2 H_2O	XV	〃
15–Crown–5 (L_{IV})	$UO_2(NO_3)_2 \cdot 6H_2O$	ether or toluene	UO_2^{2+}, L_{IV}, $2NO_3^-$, $2H_2O$ (176°C)	XVI	100)
Benzo–15–Crown–5 (L_{III})	〃	〃	UO_2^{2+}, L_{III}, 2 NO_3^-, $2H_2O$ (161°C)	XVII	〃
18–Crown–6 (L_I)	〃	〃	UO_2^{2+}, L_I, 2 NO_3^-, $2H_2O$ (155°C)	XVIII	〃
Dicyclohexyl–18–Crown–6 (L_V)	〃	〃	UO_2^{2+}, L_V, 2 NO_3^-, $2H_2O$ (153°C)	XIX	〃
15–Crown–5 (L_{IV})	$Th(NO_3)_4 \cdot 5H_2O$	〃	$[Th(NO_3)_4 \cdot 3H_2O]_3$, 5 L_{IV} (153°C)	XX	〃
Benzo–15–Crown–5 (L_{III})	〃	〃	$[Th(NO_3)_4 \cdot 3H_2O]_3$, 5 L_{III} (116°C)	XXI	〃
18–Crown–6 (L_I)	〃	〃	Th^{4+}, L_I, 4 NO_3^-, $3H_2O$ (180°C)	XXII	〃
dicyclohexyl–18–Crown–6 (L_V)	〃	〃	Th^{4+}, L_V, $4NO_3^-$, $3H_2O$ (152°C)	XXIII	〃
Dibenzo–24–Crown–8 (L_{VI})	〃	〃	Th^{4+}, L_{VI}, 4 NO_3^-, $3H_2O$ (177°C)	XXIV	〃
Crypstand [2,2,2] (L_{VII})	$UO_2(NO_3)_2 \cdot 6H_2O$	THF, $CHCl_3$ or alcohol	UO_2^{2+}, L_{VII}, $2NO_3^-$, $4H_2O$	XXV	101)
	$UO_2(CH_3CO_2)_2$	〃	UO_2^{2+}, L_{VII}, $2CH_3CO_2^-$, $3H_2O$	XXVI	〃
	〃	〃	UO_2^{2+}, L_{VII}, 2 $CH_3CO_2^-$	XXVII	〃
	$UO_2Cl_2 \cdot 3H_2O$	〃	UO_2^{2+}, L_{VII}, $2Cl^-$, $2H_2O$	XXVIII	〃
	$UO_2(SCN)_2$	〃	UO_2, L_{VII}, 2 SCN^-, H_2O	XXIX	〃
	UCl_4	〃	U, L_{VII}, $4Cl^-$	XXX	〃
	$U(SCN)_4$	〃	U^{4+}, L_{VII}, $4SCN^-$		〃
	$Th(NO_3)_4 \cdot 4H_2O$	〃	Th^{4+}, L_{VII}, $4NO_3^-$		〃

18-crown-6 by hydrogen bonds between H_2O molecules and the crown ether. Furthermore, they found that the O atoms of the linear UO_2 were linked only to U by coordination and that the 6-coordination in the equatorial plane of UO_2 was occupied by two molecules of H_2O and two bidendate NO_3^-, as shown in Fig. 3.14.

Seminara and Siracusa prepared complexes X ~ XV by refluxing acetonitrile solutions of benzo-15-crown-5 or dibenzo-18-crown-6 and $UO_2\ (NO_3)_2 \cdot 6\ H_2O$, $UO_2Cl_2 \cdot 3\ H_2O$, or $UO_2(ClO_4)_2 \cdot n\ H_2O$; they found from the results of electroconductivity measurements, ir, electronic spectra, and thermal analyses that U did not exist in the center of the crown ring.[99] Knöchel *et al.* prepared complexes XVI ~ XXIV from the reaction of 15-crown-5, benzo-15-crown-6, dicyclohexyl-18-crown-6, and dibenzo-24-crown-8 with $UO_2(NO_3)_2 \cdot 6\ H_2O$ and $Th(NO_3)_4 \cdot 5\ H_2O$; their measurements of ir, Raman, and nmr spectra indicated that U and Th were not bonded directly to the crown ethers in these complexes.[100] It is thought that the strong affinity of actinide ions for highly polar O donor atoms in H_2O or NO^{3-} induces these complex structures.

Investigators have obtained crown ether complexes with other ions as well. Using the ions of Group IIIb metals, Christensen *et al.* reported complexes of Tl^+ with various crown ethers,[16] and Wada *et al.* prepared a complex of $AlCl_3$ with benzo-15-crown-5 in benzene and confirmed the 1 : 1 structure by elementary analysis, ir, and nmr.[104] As to Groups IVb and Vb, complexes of Pb^{2+} with various crown ethers[16] and a complex between $BiCl_3$ and 18-crown-6[90] have been obtained, but the crystal structures of these complexes have not yet been reported.

There have been a few examples of crown ether complexes with transition metal ions which are soft cations. Su and Weiher reported complex formation between Ti^{3+}, V^{3+}, Fe^{3+}, and Co^{2+} and dicyclohexyl-18-crown-6, as determined by changes of color in the solutions, solubilities, and spectra.[105] After allowing a mixed solution of $CoCl_2$ and dicyclohexyl-18-crown-6 in acetic acid to stand for 2 ~ 3 days out of contact with air and moisture, blue crystals (mp 238 ~ 239°C) with the composition (crown)·2 $CoCl_2$ were obtained in a yield of about 90%. This complex was insoluble in low-polar solvents and dissociated to the original components in polar solvents such as nitromethane. Su and Weiher proposed the two probable structures, shown in Fig. 3.15(a) and (b), which could explain the ir, electronic spectra, and magnetism of the complex. Structure (a) is a sandwich structure in which two Co^{2+} are held between two molecules of the crown ether, and (b) is a polymeric structure in which Co^{2+} and the crown ether ring are arranged alternatively. In both cases the counter anion is $[CoCl_4]^{2-}$.

DeVos *et al.* isolated complexes with a composition of (crown)·2 MX_2 by the addition of 1 ~ 2 equivalents of 18-crown-6 to the methanol-orthoformic acid solutions of $CoCl_2$, $CoBr_2$, $NiCl_2$, and $NiBr_2$ and the hydrated salts of $CuCl_2$ and $CuBr_2$, followed by treatment with ethyl ether.[106] The magnetism, nmr, and near ir spectra of these complexes were measured, and complex structures similar to those proposed by Su *et al.* were inferred from the ligand field data.

Knöchel *et al.* prepared the complexes shown in Table 3.7 from $Mn(NO_3)_2$, $Co(NO_3)_2$, $CoCl_2$, $Ni(NO_3)_2$ (toluene or ether solution), and 18-crown-6 (ether solution) and measure the ir, Raman, nmr, esr, and mass spectra of these complexes.[90]

With respect to Cu(II), Bereman and Choi observed that $CuBr_2$ was dissolved in CH_2Cl_2 by the formation of complexes with dibenzo-18-crown-6 and dicyclohexyl-18-

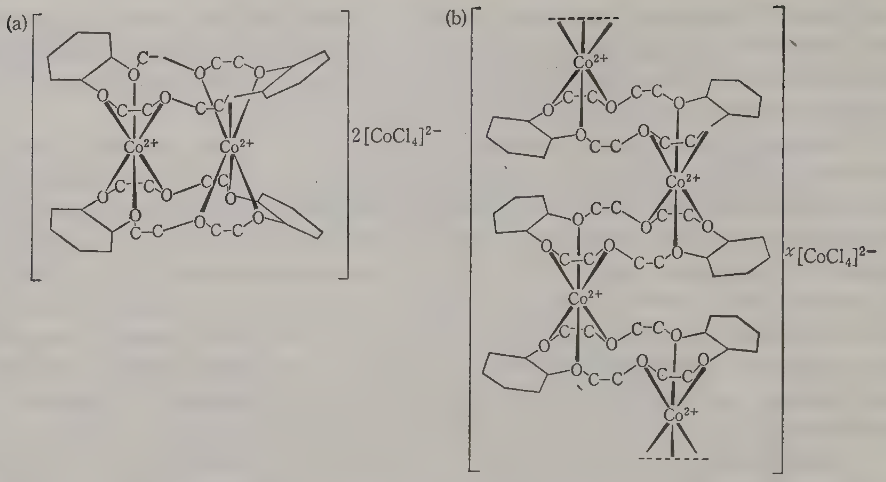


Fig. 3.15 Hypothesized structure of dicyclohexyl-18-crown-6 complex with $CoCl_2$. (Source: Ref. 105. Reproduced by kind permission.)

TABLE 3.7 Transition metal ion-crown ether complexes[90)]

Crown ether	Transition metal salt	Solvent	Composition	Complex mp (°C)	Appearance
18-Crown-6 (L_1)	$Ni(NO_3)_2 \cdot 6\ H_2O$	diethyl ether	$NiL_I(NO_3)_2 \cdot 2H_2O$	116	green needles
	$Co(NO_3)_2 \cdot 6\ H_2O$	diethyl ether	$CoL_I(NO_3)_2 \cdot 2\ H_2O$	121	pale red needles
	$CoCl_2$	diethyl ether	CoL_ICl_4	—	pale blue powder
	$Mn(NO_3)_2 \cdot 4\ H_2O$	diethyl ether	$MnL_I(NO_3)_2$	109	colorless needles
Dibenzo-18-crown-6	AgO_3SCF_3	toluene	$AgL_{II}O_3SCF_3$	195 ~ 197 (decomp.)	colorless needles

crown-6.[107)] By adding the latter solution dropwise to cyclohexane, a dark green complex with the composition (crown)$\cdot Cu_2Br_4$ was deposited. From ir, electronic spectra, and esr data, they proposed a sandwich structure similar to that shown in Fig. 3.15(a).

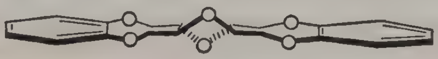
It is well known that transition metal ions form stable complexes with ligands having N or S donors, which are soft bases, but the affinities of crown ethers to soft transition metal ions are rather weak because crown ethers have hard O donors. In addition, because of the large solvation energy of transition metal ions, crown ethers rarely form complexes with transition metal ions.

The proposed structures of the complexes of crown ethers with NH_4^+, organic ion compounds such as primary ammonium salts, diazonium salts, and guadinium salts, and polar organic compounds such as acetonitrile and nitro compounds were described previously. Though as yet there have been no reports on the crystal structures of these complexes as determined by X-ray analysis or other methods, Cram *et al.* have been pursuing studies of host-guest chemistry in which the conformation of the complexes between crown ethers and organic ion compounds is estimated by the Corey-Pauling-Koltun (CPK) model. [30~32)]These investigations are described in Chapter 5.

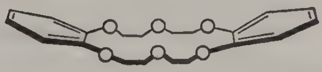
B. Structure of Complexes in Solution

The structures of crown ether complexes we discussed in the previous section are those of solid crystals, which are restricted by crystal lattice forces. In solution, the complexes are not restricted by lattice forces, but the structure and conformation of the complexes are affected by the polarization of cation-anion, by the behavior of solvent molecules, and, in particular, by the structure and behavior of the ion pair. As complexation reactions and their applications to the capture or separation of cations, organic syntheses, and other processes are usually carried out in solution, it is important to determine the structure or conformation of the crown ether complexes under these conditions.

I and Grunwald measured the dipole moments μ of the complexes of LiCl and potassium *p*-toluene sulfonate (KTs) with cyclohexyl-15-crown-5 and KTs with dibenzo-18-crown-6 in octanoic acid solutions;108) they deduced the conformation of the complexes in the solutions by calculating the positions of the cations and anions, as well as the distances between the electrostatic centers, by applying the obtained μ values to the Böttcher model.109) In the case of dibenzo-18-crown-6, $\mu = 1.37$ D for the solution before complexation, they concluded that the conformation was nonpolar, as shown in Fig. 3.16(a). This conformation agreed with the results of X-ray analysis of the crystal of the crown ether56) and also with ir experiments which showed that the 18-crown-6 ring did not have D_{3d} symmetry.110) The μ value of the solution increased to 8.27 D after complexation with KTs, and the polar conformation ($\mu = 4.3 + 0.3$ D) shown in Fig. 3.16(b) was proposed for the crown ring of the complex in solution.



(a) nonpolar conformation

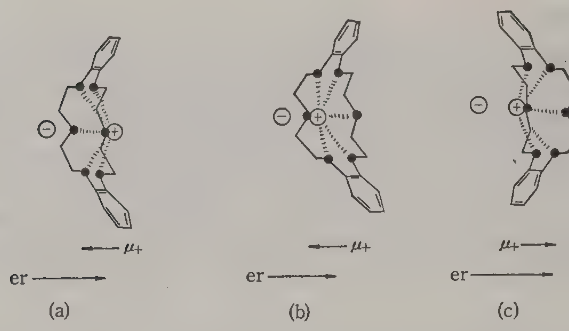


(b) polar conformation

Fig. 3.16 Conformation of dibenzo-18-crown -6

In this case there are three possible conformations of the complex between dibenzo-18-crown-6 and the KTs ion pair. Figures 3.17(a) and (b) present the case in which the dipole vector μ_+ of the complex (μ_+ is equal to the dipole vector of the complex because $\mu = 0$ for K^+) is directed toward the anion, and the ion pair forms a ligand-separated ion pair. In the other possible case, shown in Fig. 3.17(c), μ_+ is directed away from the anion, and the ion pair forms a contact ion pair. Calculations applying the observed μ values to the Böttcher model indicated that the structure of a contact ion pair, in which K^+, S, and the aryl group were situated on an axis, as shown in Fig. 3.18, was the most stable for the complexes of KTs with dibenzo-18-crown-6 and cyclohexyl-15 crown-5.

The electrostatic interaction energy W of these complexes was determined to be



(a) (b) (c)

Fig. 3.17 Types of ion pair complexes: (a) and (b) ligand-separated ion pairs, (c) a contact ion pair. (Source: Ref. 108. Reproduced by kind permission of the American Chemical Society.)

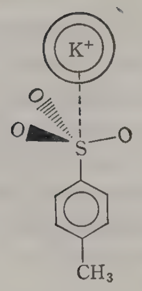


Fig. 3.18 Structure of the contact ion pair in KTs-crown complex. (Source: Ref. 108. Reproduced by kind permission of the American Chemical Society.)

–89.9 and –8.74 kcal/mol, respectively. In the case of 18-crown, the center of K^+ is attracted by the anion for 0.50 Å from the O plane of the crown ring. In the case of 15-crown, before formation of the ion pair, K^+ of the KTs complex is located 0.90 Å outside the O plane because of the smaller size of the 15-crown ring; after formation of the ion pair, the $K^+ \cdots Ts$ distance of the complex is 0.15 Å shorter. These results agreed with the X-ray analysis of the crystal structures of dibenzo-18-crown-6-NaBr complex (0.27 Å from the O plane)[61] and -NaSCN complex (0.54 Å from the O plane).[56] For the complex of cyclohexyl-15-crown-5 with LiCl, the ligand-separated ion pair structure was the most stable, and the electrostatic interaction energy W was determined to be -101.4 kcal/mol.

Live and Chan measured ^1H-nmr and ^{13}C-nmr for solutions of the complexes of benzo-18-crown-6, dibenzo-18-crown-6, and dibenzo-30-crown-10 with Na^+, K^+, Cs^+, and Ba^{2+} (counter anions: I^-, SCN^-, and ClO_4^-) dissolved in H_2O, H_2O-acetone, acetone, and chloroform, and inferred the conformations from the coupling constants, chemical shifts, and other data.[111] The results indicated that the conformation of the 18-crown complexes in these solutions was the same as that of the crystals, but the conformation of free dibenzo-18-crown-6 (before complexation) in the solutions was proposed to be the *syn* ↔ *anti-gauche* structure shown in Fig. 3.19(a); this is different from the conformation of dibenzo-18-crown-6 crystal consisting of of *trans* and *gauche* rotamers, shown in Fig. 3.19(b), as determined by X-ray analysis.[56] The conformations of the complexes of dibenzo-30-crown-10 with K^+, Cs^+, and Ba^{2+} in the solutions were considered to be the same as those of the K^+ complex crystals determined by X-ray analysis,[58] shown in Fig. 3.10(b), while the conformation of the complex between the 30-crown ether and Na^+, with a smaller ionic diameter, was thought to be one in which the 30-crown ring was not completely wrapped around the cation as shown in Fig. 3.20. This conclusion was drawn from the observation that the ^1H-nmr spectrum of the solution of Na^+ complex was not analogous to that of the solution of K^+, the coupling constant was smaller and the chemical shift was nearly equal to that of Na^+-18-crown complex. The Cs$^+$-dibenzo-18-crown-6 complex in solution was thought to have a sandwich structure in which one Cs$^+$ was bound between two crown rings.

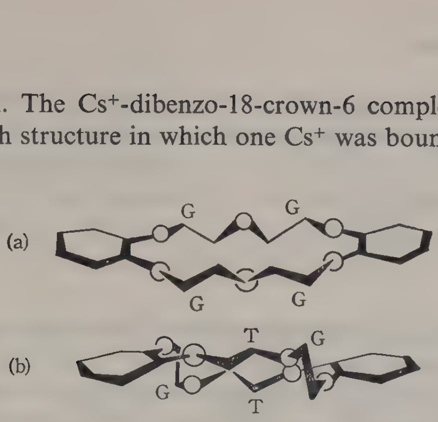


Fig. 3.19 Conformation of dibenzo-18-crown-6: (a) hypothesized structure in solutions,[111] (b) crystal structure determined by X-ray analysis.[56] (Source: Ref. 111. Reproduced by kind permission of the American Chemical Society.)

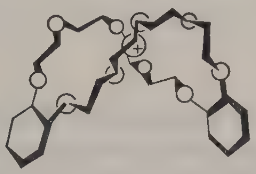


Fig. 3.20 Hypothesized conformation of dibenzo-30-crown-10-Na$^+$ complex in solutions.[111] (Source: Ref. 111. Reproduced by kind permission of the American Chemical Society.)

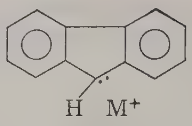
The structure and behavior of the ion pairs of crown ether complexes in solution relate closely to various applications such as solubilization of inorganic salts, organic syntheses, and ion transport. Generally speaking, a salt exists in a solution as free ions formed by dissociation or as an ion pair bonded by the interaction, mainly consisting of Coulomb forces, between the anion and the cation. Ion pairs may be further classified as contact ion pairs and solvent-separated ion pairs. A contact ion pair is a "tight" ion pair surrounded by solvent molecules, and a solvent-separated ion pair is a "loose" ion pair in which a solvent molecule intrudes into the space between cation and anion.

$$\mathrm{XY} \overset{\text{polarization}}{\rightleftharpoons} \mathrm{X}^{\delta+}\mathrm{Y}^{\delta-} \overset{\text{ionization}}{\rightleftharpoons} \underset{\substack{\text{contact}\\\text{ion pair}}}{\mathrm{X}^+, \mathrm{Y}^-} \overset{\substack{\text{solvent}\\\text{separation}}}{\rightleftharpoons} \underset{\substack{\text{solvent-separated}\\\text{ion pair}}}{\mathrm{X}^+//\mathrm{Y}^-} \overset{\text{dissociation}}{\rightleftharpoons} \underset{\text{free ion}}{\mathrm{X}^+ + \mathrm{Y}^-} \tag{3.5}$$

In an ionic reaction, the direction and rate of the reaction depend on the degree of polarization and on the ion species of the substrate. The reactivity of the ion species follows the order of free ion > solvent-separated ion pair > contact ion pair; in particular, the reactivity of the free ion which is not solvated, the so-called "naked" ion, is remarkably high.

The reactivity of an ion pair is also affected by the type of solvent and ion, temperature, and pressure. A contact ion pair is changed into a more reactive solvent-separated ion pair in a polar solvent having strong ionization ability and strong solvating power; a cation with a larger ionic diameter such as Cs$^+$ readily forms a contact ion pair, while a cation with a smaller ionic diameter such as Li$^+$ and Na$^+$ easily forms a solvent-separated ion pair.

Much current research has focused on the species and behavior of ion pairs, which are important factors related to the direction and rate of ionic reactions. Szwarc and his group have produced significant findings on the ion pairs of fluorenyl carbanion-alkali and alkaline earth metal ions (**146**).[112~115]



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With regard to crown ethers, Smid *et al.* have been pursuing investigations of the structure and interactions of the ion pairs in the complexes of 15- ~ 18-crown ethers with fluorenyl salts.[20,116)] When a 1 : 1 complex was formed by adding 4,4′-dimethyldibenzo-18-crown-6, 4-methylbenzo-18-crown-6, or dicyclohexyl-18-crown-6 to a solution of fluorenyl sodium (Fl^-Na^+) dissolved in THF or THP, a spectrum was observed with the same absorption maximum at $\lambda = 373$ nm (Fig. 3. 21(a)) as that of a solvent–separated ion pair of Fl^-Na^+. This finding confirmed that a crown-separated ion pair (ligand-separated ion pair) was formed in the solution of the complex.[117,118)] The stability constant K in Eq. (3.6) was more than 5×10^6 M^{-1} in each case; this is a large coordination ability compared to glyme-6, for which K was only 450 M^{-1}.

$$\mathrm{Fl^-, Na^+ + CR} \xrightleftharpoons{K} \mathrm{Fl^-, CR, Na^+} \tag{3.6}$$

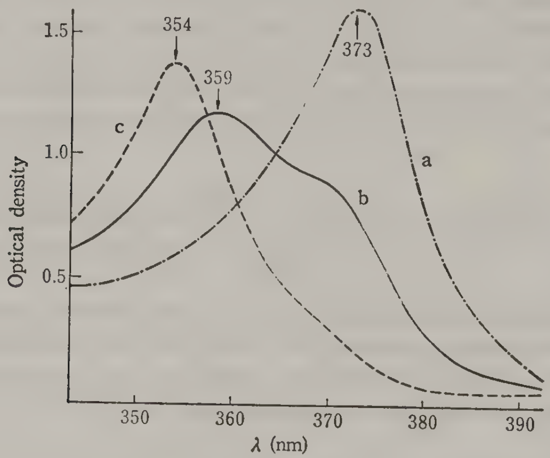


Fig. 3.21 Optical spectrum of fluorenylsodium in THP in the absence and presence of crown ethers. $[Fl^-, Na^+] = 5 \times 10^{-4}$ M, [crown ether] $= 6 \times 10^{-4}$ M. (a) Fl^-Na^+/18-crown/THP; (b) Fl^-Na^+/15-crown/THP; (c) Fl^-Na^+/THP. (Source: Ref. 118. Reproduced by kind permission of the American Chemical Society.)

Solutions of the Fl^-Na^+ complex with 4-methylbenzo-15-crown-5, with a smaller crown ring, contain two kinds of species, contact ion pairs and crown-separated ion pairs. The spectrum of a THP solution of the complex exhibits absorption peaks at 359 nm and 370 nm, as shown in Fig. 3.21(b). The former peak is due to the contact ion pair (Fl^-, Na^+), corresponding to the absorption peak at 354 nm for Fl^-Na^+ alone in THP solution (Fig. 3.21(c)), and the latter peak is due to the crown-separated ion pair (Fl^-, CR, Na^+).[118] Both ion pairs were also observed in solutions of the complexes of Fl^-K^+ with 15- and 18-crowns.

With these complexes, as well as with glyme-6 and -7,[119] there was competition between the complexation reactions forming crown-separated ion pairs and contact ion pairs, as shown in Eqs. (3.7) ~ (3.9).

$$Fl^-, M^+ + CR \overset{K_1}{\rightleftharpoons} Fl^-, M^+, CR \tag{3.7}$$

$$Fl^-, M^+ + CR \overset{K_1}{\rightleftharpoons} Fl^-, CR, M^+ \tag{3.8}$$

$$Fl^-, M^+, CR \overset{K_2}{\rightleftharpoons} Fl^+, CR, M^+ \tag{3.9}$$

As shown in Fig. 3.22, the concentration ratio of both types of ion pairs, $K_i^* = [Fl^-, CR, M^+]/[Fl^-, M^+, CR]$, increases markedly with an increasing amount of 15-crown in the Fl^-K^+ system, while K_i^* is not changed by an increase of 18-crown, and K_i^* increases only slightly with increasing 15-crown in the Fl^-Na^+ system. The explanation is based on the relative sizes of the 15-crown and the cation. Because the diameter of 15-crown is too small to enclose K^+, when the crown concentration is low, 15-crown forms a complex with the contact pair (Fl^-, K^+) at the outside of the ion pair, tending to separate the ion pair; when the crown concentration becomes higher, a 2 : 1 complex (Fl^-, CR, K^+, CR) having crown-separated ion pairs is formed by coordination of one more molecule of 15-crown.

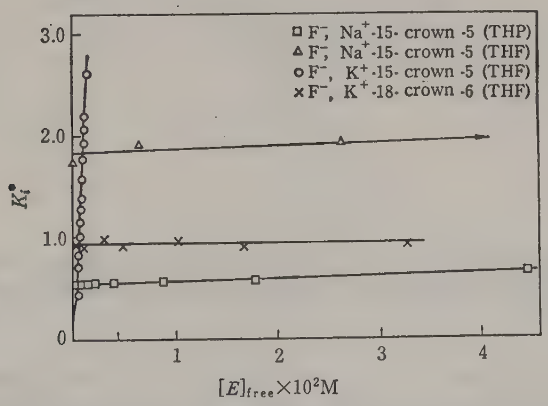


Fig. 3.22 Plots of K_i^*(= [crown-separated ion pair]/[contactaion pair]) vs. Crown concentration (E) for the systems crown–F^-Na^+ and crown–F^-K^+ in THP and THF solutions. [fluorenyl salt] ≈ 6×10^{-4} M. (Source: Ref. 118. Reproduced by kind permission of the American Chemical Society.)

$$Fl^+, K^+, CR + CR \overset{K_3}{\rightleftharpoons} Fl^+, CR, K^+, CR \tag{3.10}$$

The values of K_i, K_1, and K_2 obtained for various systems[118] suggested that the coordinating solvent molecules (THF, THP) are eliminated by the crown ether before the coordination, and that the solvent molecule does not interfere with the separation of the ion pair because of the plane structure of the crown ring. Thus, it is thought that the equilibrium shown in Eq. (3.11) exists during complexation and that the contact ion pair is formed more easily in a low-polar solvent in which a cation is barely solvated.

$$\text{Fl}^-, \text{M}^+, \text{CR} + n\,\text{S} \rightleftharpoons \text{Fl}^-, \text{CR}, \text{M}^+, \text{S}_n \qquad (3.11)$$

(S: solvent molecule)

For divalent cations, the structure and interaction of $\text{Fl}_2{}^-\text{Ba}^{2+}$-crown ether complexes in solution have been investigated by the same technique.[120~122] In THF or pyridine, 4-methylbenzo-18-crown-6 and 4,4′-dimethyldibenzo-18-crown-6 form the 1 : 1 complex with $\text{Fl}_2{}^-\text{Ba}^{2+}$ shown in Fig. 3.23, and both contact ion pairs and crown-separated ion pairs are present. In contrast, 4-methylbenzo-15-crown-5 with a smaller crown ring forms a 2 : 1 complex with a stability constant of $1.3 \times 10^8\ \text{M}^{-2}$, and all the ion pairs consist of crown-separated ion pairs having the structure Fl^-, CR, Ba^{2+}, CR, Fl^-.

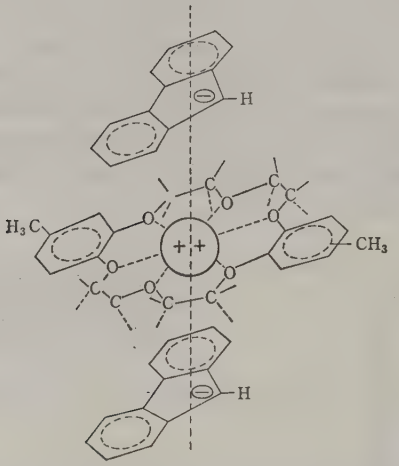


Fig. 3.23 Hypothesized structure of dimethyldibenzo-18-crown-6 complex with $(\text{fluorenyl})_2{}^-\text{Ba}^{2+}$ in THF or pyridine solution. (Source: Ref. 120. Reproduced by kind permission of the American Chemical Society.)

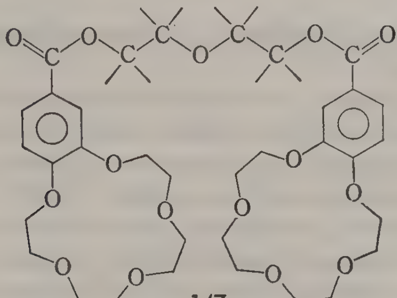
Hogen Esch and Smid also obtained kinetic data for the dissociation of Fl^-Na^+, $\text{Fl}_2{}^-\text{Sr}^{2+}$, and $\text{Fl}_2{}^-\text{Ba}^{2+}$ complexes with dimethyldibenzo-18-crown-6 in THF and THP by measurements of the electroconductivity of the ion pairs.[123]

Smid *et al.*[124] investigated complexation with picrates. They studied the ion pairs in THF solutions of dimethyldibenzo-18-crown-6, benzo-15-crown-5, and the isolated bicyclic crown ether having two 15-crown rings (**147**) with Na^+-, K^+-, and Cs^+-picrates. With Na^+ picrate, benzo-15-crown-5 forms a complex consisting of the contact ion pair Pi^-, Na^+, CR, which exhibits an absorption maximum at 357 nm in THF. With K^+ picrate, the 15-crown forms a 1 : 1 complex of contact ion pairs (λ_{max}

362 nm) at first, then forms a 2 : 1 complex of crown-separated ion pairs (λ_{max} 381 nm) with an increasing crown concentration. The stability constant K_1 of the 1 : 1 complex is 10^4 M^{-1}, and the equilibrium constant K_3 in the complexation reaction that produces the 2 : 1 complex (Eq. 3.12) is 2.0×10^2 M^{-1}, which is nearly 1/10 that of Fl^-K^+.

$$Pi^-, K^+, CR + CR \xrightleftharpoons{K_3} Pi^-, CR, K^+, CR \tag{3.12}$$

The bis-15-crown **147** forms only a 2 : 1 complex of crown-separated ion pairs (λ_{max} 381 nm) with K^+ picrate. The value of K_3 for the reaction is 1.7×10^5 M^{-1}.



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Smid *et al.* extended their investigations to the complexation ability and structure in solution of polymers with crown rings as pendant groups, such as polyvinylbenzo-15-crown-5 and polyvinylbenzo-18-crown-6.[125~132] The results are described in Chapter 6.

The results of other studies include the report by Ford that 9-phenylfluorenyl Li formed solvent-separated ion pairs and 9-phenylfluorenyl Na and K formed contact ion pairs in THF in the absence of crown ether.[133] However, crown-separated ion pairs were formed by the addition of 1 equivalent of dicyclohexyl-18-crown-6 to a K salt. In addition, 9-$PhFl^-$ was partially protonated when methanol was added to the solution of the ion pairs in the order of K^+-crown $< K^+ < Na^+ < Li^+$, though only slight changes were observed in the absorption maximum and ^1H chemical shift.

Watts *et al.* used esr to assess the effect of adding dibenzo-18-crown-6 on the Heisenberg spin exchange rate of the ion pair of K^+-tetracyanoethanalide in dimethoxyethane solution.[134] Boone and Kowalsky found that K^+ complexes of dibenzo-18-crown-6, dicyclohexyl-18-crown-6, and valinomycin formed ion pairs in solvents with a low dielectric constant by measuring the chemical shifts in ^1H-nmr of $(CD_3)_2CO$ or $CDCl_3$ solutions of the complexes; they used complexes with K salts whose counter anions were such paramagnetic anions as $CoBr_4^{2-}$, $Co(SCN)_4^{2-}$, $Co(CH_3COCHCOCH_3)_3^-$, and $Cr(NH_3)_4(SCN)_2^-$. They also calculated the distance between the cation and anion of the ion pairs.[135]

3.2.3 Thermodynamics and Kinetics of Complexation

A. Stability Constant *K*

The complexation reactions of crown ethers and inorganic salts are the equilbrium reactions shown in Eqs. (3.13) and (3.14) for the 1 : 1 complex and the 2 : 1 complex, respectively. The generalized equation is (3.15),

$$\mathrm{L} + \mathrm{M}^{+}\mathrm{X}^{-} \overset{K_1}{\rightleftharpoons} (\mathrm{LM}) + \mathrm{X}^{-} \tag{3.13}$$

$$\mathrm{L} + (\mathrm{LM})^{+} \overset{K_2}{\rightleftharpoons} (\mathrm{L}_2\mathrm{M})^{+} \tag{3.14}$$

(L: crown ether)

$$(\mathrm{L})_{\mathrm{solv}} + (\mathrm{M}^{n+}, m\mathrm{S}) \underset{k_\mathrm{d}}{\overset{k_\mathrm{f}}{\rightleftharpoons}} (\mathrm{L}, \mathrm{M}^{n+})_{\mathrm{solv}} + m\mathrm{S} \tag{3.15}$$

where S is a solvent molecule, and K_f and K_d are the rate constants of complexation and dissociation, respectively.

In the complexation reaction, the stability constant (also known as the complexation constant or complex formation constant), which is the equilibrium constant in the reaction and the reciprocal of the dissociation constant, indicates the degree of complex formation and the stability of the resulting complex in the solution. From the standpoint of thermodynamics, the stability constant can be thought of as a scale for the calorific value and the change of entropy in the complexation reaction because the stability of the complex formed increases with an increase in the calorific value and entropy in the reaction.

The stability constant, K_{th}, in the strictest thermodynamic sense is that given by Eq. (3.16), but the stability constants which have

$$K_{\mathrm{th}} = \frac{f_\mathrm{C}[\mathrm{L}, \mathrm{M}^{n+}]}{f_\mathrm{L}[\mathrm{L}]\, f_\mathrm{M}[\mathrm{M}^{n+}]} \tag{3.16}$$

generally been reported are the values obtained with Eq. (3.17), using the concentration of each component, because the activity coefficients of complex (f_C), crown ether (f_L), and cation (f_M) are usually unknown values.

$$K = K_{\mathrm{th}}\frac{f_\mathrm{L} f_\mathrm{M}}{f_\mathrm{C}} = \frac{[\mathrm{L}, \mathrm{M}^{n+}]}{[\mathrm{L}]\,[\mathrm{M}^{n+}]} \tag{3.17}$$

Methods for measuring the stability constants of crown ether complexes include calorimetric titration,[136~139] potentiometry using ion-selective electrodes,[24,140] electronic spectrometry,[23,117,141] electroconductivity[142~145], nmr,[28] and polarography.[146~149] The stability constants for a variety of crown compound complexes in a number of solvents, including water and methanol, have been measured so far. A review by Christensen *et al.* summarizes the values of the stability constants of the complexes of various crown ethers, cyclic polyamines, cyclic polythiaethers, azacrown ethers, and cryptands and includes the values of enthalpy changes (ΔH), entropy changes (ΔS), and heat capacity changes (ΔC_p).[16] These thermodynamic data have also been presented in other reviews.[14,15]

Table 3.8 summarizes the values of log K and K in aqueous solutions for the principal crown ethers which were reported up to 1976, together with the values for

TABLE 3.8 Stability constants of crown ether complexes (in water, concentration 0.1 mol/l)

Crown ether	Measuring	log K													
	method†[1]	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	Ag^+	Ti^+	Ca^{2+}	Sr^{2+}	Ba^{2+}	Hg_2^{2+}	Hg^{2+}	Rb^{2+}
15-Crown-5	C	—	0.70 ±0.10	0.74 ±0.08	0.62 ±0.10	0.8 ±0.2	1.71 ±0.16	0.94 ±0.08	1.23 ±0.04	—	1.95 ±0.08	1.71 ±0.06	—	1.68 ±0.07	1.85 ±0.03
Cyclohexyl-15-Crown-5	P	<1.0	<0.6	<—	—	—	—	—	—	—	—	—	—	—	—
18-Crown-6	C		0.80 ±0.10	2.03 ±0.10	1.56 ±0.02	0.99 ±0.07	1.23 ±0.06	1.50 ±0.03	2.27 ±0.04	<0.5	2.72 ±0.02	3.87 ±0.02	—	2.42 ±0.03	4.72 ±0.02
Cycloexhyl-18-Crown-6	P	—	<0.3	2.06	—	0.8	1.1	1.6	0.6	—	—	—	—	—	—
	P	<0.7	0.8	1.90	—	0.8	1.1	1.8	—	—	—	—	—	—	—
Dicyclohexyl-18-Crown-6 (isomer A)	C	—	1.21 ±0.09	2.02	1.52	0.96	— ±0.11	2.36 ±0.04	2.44	—	—	—	1.93 ±0.09	2.42 ±0.03	4.95 ±0.04
	P	0.6	1.5 1.85	2.18	—	1.25	1.4	2.3	—	—	3.24	—	—	—	—
Dicyclohexyl-18-Crown-6 (isomer B)	C	—	0.69 ±0.12	1.63	0.87	—	—	1.59	1.83 ±0.02				1.57 ±0.09	2.60 ±0.03	4.43 ±0.05
	P	—	1.2	1.78	—	0.9	0.8	1.8	—	—	2.64	3(27	—	—	—
Cyclohexyl-21-Crown-7	P	—	~1.6	—	—	1.9	—	—	—				—	—	—
EDTA†[2]	P	2.85	1.79	0.96	0.59	0.15	—	7.72	6.55	—	8.80	7.72	—	—	18.04
								K							
Dibenzo-18-Crown-6	S†[3]	13.5 ±1.1	44.2 ±0.4	9.8 ±0.4	6.3 ±0.3	1.6 ±0.5†[5]					8.8 ±0.6	94.5 ±0.6			
	S†[4]	14.7 ±0.4	49.0 ±0.4		6.5 ±0.2		±0.6	27.4 ±0.4	30.4	±1.5	11.4				79.0 ±1.5†[6]

†[1]C: calorimetric titration;[137,13] P:potentiometric titration;[24] S: spectrography[141]

†[2]Ref. 9 †[3]Cl salt †[4]NO_3 salt

†[5]Concentration 0.2 mol/l

†[6]Concentration 0.05 mol/l

the complexes with EDTA $(HOOCH_2C)_2N-CH_2CH_2-N(CH_2COOH)_2$, a well-known chelating agent.

Izatt *et al.* used calorimetric titration to determine thermodynamic values such as K, ΔH, ΔS, ΔC_p in various complexation reactions of crown ethers.[137~139)] Their findings for aqueous solutions of 15-crown-5, 18-crown-6, and dicyclohexyl-18-crown-6 (isomer A: *cis-syn-cis*, isomer B: *cis-anti-cis*) with Group I ~ IV and the data reported by Shchori *et al.*[141)] for dibenzo-18-crown-6 are shown in Figs. 3.24 (for monovalent cations) and 3.25 (for divalent cations) as plots of log K vs. cation diameter.

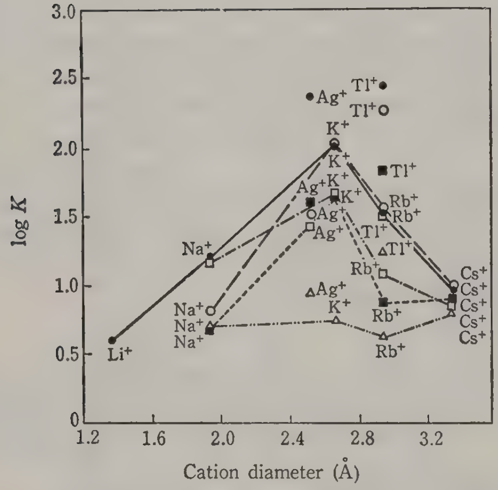


Fig. 3.24 Plot of log K for the reaction $M^+ + L = ML^+$ vs. cation diameter (in water, 25°C). △: 15-crown-5 (cavity diameter 1.7 ~ 2.2 Å); ○: 18-crown-6 (2.6 ~ 3.2 A); ●: dicyclohexyl-18-crown-6, isomer A [*cis-syn-cis*] (2.6 ~ 3.2 Å) ■: dicycloehxyl-18-crown-6, isomer B [*cis-anti-cis*] (2.6 ~ 3.2 Å) □: dibenzo-18-crown-6 (2.6 ~ 3.2 Å). (Source: Ref. 138. Reproduced by kind permission of the American Chemical Society.)

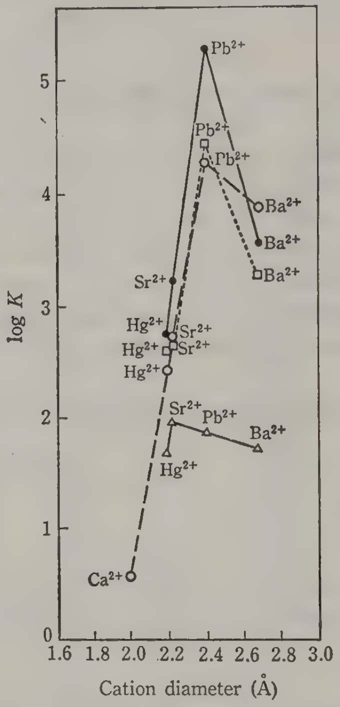


Fig. 3.25 Plot of log K for the reaction $M^{2+} + L$ —— ML^{2+} vs. cation diameter (in water, 25°C). △: 15-crown-5 (cavity diameter 1.7 ~ 2.2 Å); ○: 18-crown-6 (2.6 ~ 3.2 Å); ●: dicyclohexyl-18-crown-6, isomer A [*cis-syn-cis*] (2.6 ~ 3.2 Å); □: dicyclohexyl-18-crown-6, isomer B [*cis-anti-cis*] (2.6 ~ 3.2 Å). (Source: Ref. 138. Reproduced by kind permission of the American Chemical Society.)

Figure 3.24 indicates that, for monovalent cations (Ia: Li^+, Na^+, K^+, Rb^+, Cs^+; Ib: Ag^+; IIIb: Tl^+), the values of log K depend on the cation diameter in the complexes of four kinds of 18-crown ethers (cavity diameter calculated from the CPK model: 2.6 Å) with alkali metal ions. The maximum value is found with K^+, whose ionic diameter

(2.66 Å) is closest in size to the cavity diameter. In contrast, no selectivity is observed for 15-crown-5 (cavity diameter: 1.7 Å), even with Na^+, which has an ionic diameter (1.90 Å) close to the cavity diameter. It is thought that the formation of a complex by coordination with the crown ether ring is disrupted because Na^+ is solvated by water with a high solvation energy.

When K^+ was compared with Ag^+ (2.52 Å), and Rb^+ (2.96 Å) with Tl^+ (2.88 Å), it was found that the log *K* values of Ag^+ and Tl^+ complexes were larger than those of K^+ and Rb^+ complexes except Ag^+ complexes with 18-crown-6, isomer B of dicyclohexyl-18-crown-6, and dibenzo-18-crown-6, although the ionic diameters are nearly equal in each pair of cations. Ag^+ and Tl^+, which are classified as transition metal ions, belong to the b subgroup and are thus more highly polarized than K^+ and Rb^+, which belong to the a subgroup, and this difference apparently leads to a stronger covalent bond between the cation and the O atom in the crown ring.150) Eisenman and Krasne concluded from the values of free energy changes (ΔG) in the complexation of ionophore antibiotics (such as nonactin and valinomycin, Fig. 1.5) and dicyclohexyl-18-crown-6 with metal cations that, as a general rule, there would be excess bond energy in the complexation of the macrocyclic compounds having O donors with Ag^+ and Tl^+.151)

With regard to divalent cations, all 18-crown ethers show a marked selectivity for Pb^{2+} (ionic diameter: 2.40 Å), as shown in Fig. 3.25. The greater polarization of Pb^{2+} compared to Ba^{2+} and the increased nature of the covalent bonding of Pb^{2+} were thought to explain the larger values of log *K* for Pb^{2+} than for Ba^{2+} (2.70 Å), which has an ionic diameter much closer in size to the cavity diameter of 18-crowns.150)

The values of log *K* for 15-crown-5 complexes with divalent cations are smaller then those for 18-crown complexes. In general, large differences are not observed between the log *K* values of the cations, though relatively high values are observed for Sr^{2+} whose ionic diameter (2.26 Å) approximates the cavity diameter of 15-crowns. With both monovalent and divalent cations, log *K* values of 15-crown complexes are usually smaller than those of 18-crown complexes with the same cation. This finding is thought to result from the weak coordination of 15-crowns caused by the smaller number of O donor atoms. However, log *K* values are expected to increase even with 15-crown-5 in low-polar solvents having low solvation energy.

Frensdorff measured the stability constants in methanol for alkali metal complexes of various crown compounds by potentiometry, using cation-selective electrodes.24) The values of log *K* of 12- ~ 60-crown ether complexes in methanol at 25°C are shown in Table 3.9 together with those of pentaglyme, $CH_3(OCH_2CH_2)_5OCH_3$, nonactin,9) and valinomycin.9)

In comparing Table 3.9 with Table 3.8, it can be seen that *K* values in methanol are larger than those in aqueous solution by 1,000 ~ 10,000 times. Methanol competes only weakly against coordination of a crown ether to a cation because it has a smaller capacity to dissolve a cation than has water. The relationship between the cavity size of the crown ring and the cation diameter in the selectivity for a cation is similar to that observed in aqueous solutions for 14- ~ 18-crown ethers, and the highest value of log *K* is found with the cation whose ionic diameter fits the caivty size of the crown ether. The effect of substituent groups in an 18-crown ring on log *K* is rather small and no regularity was observed. For example, log *K* for dibenzo-18-crown-6 complex is larger

TABLE 3.9 Stability constants (log *K*) of crown ether complexes (in methanol, 25° C)[24)]

Crown ether	log *K*[†1]		
	Na^+	K^+	Cs^+
Tetramethyl-12-crown-4	1.41		
Dicyclohexyl-14-crown-4	2.18	1.30	
Cyclohexyl-15-crown-5	3.71	3.58[†2]	2.78[†2]
18-Crown-6	4.32	6.10	4.62
Cyclohexyl-18-crown-6	4.09	5.89	4.30[†2]
Dicyclohexyl-18-crown-6 (isomerA)	4.08	6.01	4.61
(isomer B)	3.68	5.38	3.49
Dibenzo-18-crown-6	4.36	5.00	3.55[†2]
21-Crown-7		4.41	5.02
Dibenzo-21-crown-7	2.40	4.30	4.20
24-Crown-8		3.48	4.15
Dibenzo-24-crown-8		3.49	3.78
Dibenzo-30-crown-10	2.0	4.60	
Dibenzo-30-crown-20		3.90	
Pentaglyme Analogue	1.52	2.20	
Nonactin[9)]	2.38 (30° C)	3.58 (30° C)	2.95 (30° C)
Valinomycin[9)]	0.67	4.90	4.41

[†1] *K* in *l*/mol.
[†2] Evidence of 2:1 complexing; *see* Table 3.10.

than for dicyclohexyl-18-crown-6 with Na^+, while the inverse is true for K^+ and Cs^+.

Values of *K* for pentaglyme, which is a linear polyether having six O donor atoms, are only 1/1,000 ~ 1/10,000 of those of 18-crown-6, which is the corresponding cyclic polyether; this illustrates the superiority of crown ethers in that entropy surrounds the cation in a regular manner. Valinomycin demonstrates a notably high selectivity for K^+ over Na^+ even though the values of log *K* are nearly equal to, or less than, those of crown ethers. This finding may be explained by the well-matched coordination of valinomycin to K^+; O donor atoms in the carbonyl and ether groups of valinomycin coordinate sterically to K^+, as observed in the molecular model.

That 2 : 1 complexes with sandwich structures were formed because the cation diameters were larger than the crown ring cavities was ascertained in four systems, shown in Table 3.9. The values of log K_1 and log K_2 for these systems are presented in Table 3.10.

Recently, Burdern *et al.* reported that the *K* values of the complexes of four diastereomers of dicyclohexyl-18-crown-6 with NaCl, KCl, and CsCl followed the order of *cis-syn-cis* (isomer A) > *cis-anti-cis* (isomer B) > *trans-syn-trans* > *trans-anti* > *trans*.[152)]

There are few reports of stability constants in solutions other than water and methanol. One may expect that *K* values will increase for small cations in low-polar solvents in particular, because of decreased competition between solvation of the solvent and coordination of the crown ring resulting from the weak solvation ability of the low-polar solvents to the cation. However, the situation is complicated by the effect of the counter anion because of the formation of an ion pair.

Evans determined *K* values of the complexes of dibenzo-18-crown-6 dicyclohexyl-

TABLE 3.10 Values of $\log K_1$ and $\log K_2$ of 2:1 complexes in methanol at 25° C[24]

Crown ether	Cation	$\log K_1$†1	$\log K_2$†1	K_2/K_1
Cyclohexyl-15-crown-5	K^+	3.58 ± 0.02	1.88 ± 0.07	0.02
Cyclohexyl-15-crown-5	Cs^+	2.78 ± 0.07	1.91 ± 0.23	0.13
Dibenzo-18-crown-6	Cs^+	3.55 ± 0.02	2.92 ± 0.07	0.23
18-Crown-6	Cs^+	4.62 ± 0.03	1.30 ± 0.20	0.0005
Cyclohexyl-18-crown-6	Cs^+	4.30 ± 0.02	1.52 ± 0.18	0.002
Dicyclohexyl-18-crown-6 (Isomer A)	Cs^+	4.61 ± 0.02	0.59 ± 0.05	0.0001
Dicyclohexyl-18-crown-6 (Isomer B)	Cs^+	3.49 ± 0.01	†2	0
21-Crown-7	Cs^+	5.02 ± 0.01	†2	0
Dibenzo-21-crown-7	Cs^+	4.20 ± 0.03	1.9 ± 0.3	0.005

†1 K_1 and K_2 in *l*/mol; 95% confidence limits shown.
†2 $K_2 = 0$ lies within the 95% confidence limits.

18-crown-6 (a mixture of isomers) with Na^+ and K^+ (counter anion: BPh_4^-) in acetonitrile at 25°C by measuring electroconductivity.[142] The resulting *K* values were as follows: with the former, 5.06 for the Na^+ complex and 4.85 for the K^+ complex; with the latter, 5.20 for the Na^+ complex and 5.33 for the K^+ complex. The *K* values of the K^+ complexes were nearly equal to those in methanol, while the *K* values of the Na^+ complexes in acetonitrile were larger than those in methanol. The explanation is based on the marked decrease in the solvation of Na^+ in acetonitrite compared to methanol.

As noted in Section 3.2.2.B, in their investigations of ion pairs, Smid *et al.* determined log *K* values of the complexes of dibenzo-14-crown-4, 4′-methylbenzo-15-crown-5, dibenzo-18-crown-6, and dicyclohexyl-18-crown-6 with the salts of fluorenyl-alkali metals and -alkaline earth metals in THF, THP, and pyridine by means of spectroscopy.[20,116~124] Matsuura *et al.* determined *K* values of the complexes of dibenzo-18-crown-6 with alkali metal salts in DMSO, DMF, and propylene carbonate (PC) by measuring electroconductivity.[145] They reported that the *K* values were in the order of DMSO < DMF < PC for every alkali metal ion and that no correlation was observed between the *K* value and the dielectric constant of the solvent. Furthermore, the *K* value decreased with an increasing number of donors in the solvent.

Smid *et al.* also determined *K* values for the Na^+ and K^+ complexes of derivatives of benzo-15-crown-5 and benzo-18-crown-6, in which various substituents were introduced at the 4′-position, in acetone at 25°C by electroconductivity measurements.[144] The results are shown in Tables 3.11 and 3.12. Table 3.11 indicates that the *K* value of the NH_2-substituted derivative, in which the NH_2 group is a typical electron donor group, is 25 times larger than that of the NO_2-substituted derivative, in which the NO_2 group is a typical electron acceptor group, for Na^+ complexes of 4′-substituted benzo-15-crown-5. As shown in Fig. 3.26, the relationship between log *K* and the $\sigma_p^- + \sigma_m$ value of the substitutent follows the Hammett rule, and the p value is calculated to be -0.45. In contrast, the substituent effect in 4′-substituted benzo-18-crown-6 is fairly small, as observed in Table 3.12, as it is only slightly affected by the electron acceptor groups and does not follow the Hammett rule. The *K* value of the Na^+ complex of the 4′-CH_3-substituted derivative is about twice that of the K^+ complexes of the 4′-CHO-, -$CONHC_4H_9$-, and -NO_2-substituted derivatives and is nearly equal to that of benzo-18-crown-6 with no substituent. These findings suggest that the substituent effect is more

TABLE 3.11 Stability constants (K) of Na^+-complexes with 4′-substituted benzo-15-crown-5 in acetone at 25°C.[144] $[NaBPh_4] = 5 \times 10^{-4}$ M

4′-Substituent	$K \times 10^{-3}$ (M^{-1})
NH_2	8.21
CH_3	3.96
H	3.44
Br	2.05
COOH	1.61
$COOCH_3$	1.23
CHO	1.11
NO_2	0.365
3′,4′-Dinitro	0.15

TABLE 3.12 Stability constants (K) of Na^+-and K^+-complexes with 4′-substituted benzo-18-crown-6 in acetone at 25°C[144] [Salt] $= 5 \times 10^{-5}$ M.

4′-Substituent	$K + 10^{-5}(M^{-1})$	
	Na^+	K^+
CH_3	1.23	3.83
H	0.52	1.27
CHO	0.39	0.77
$CONHC_4H_9$	0.32	0.56
NO_2	0.47	0.63

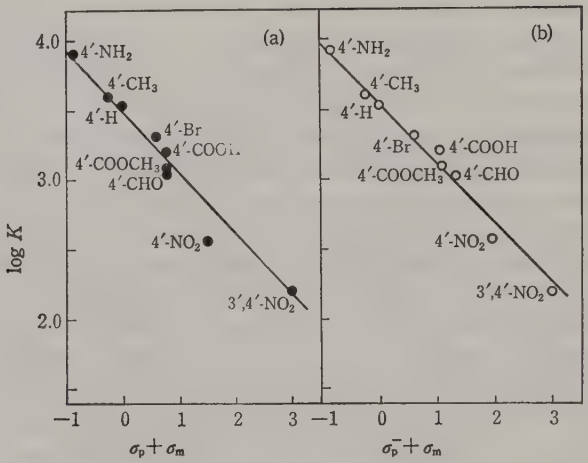


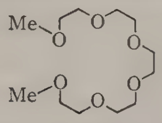
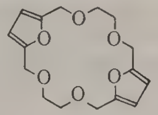
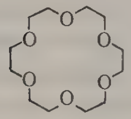
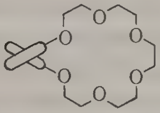
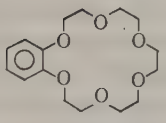
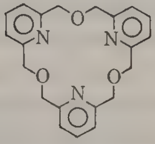
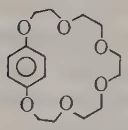
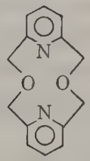
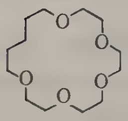
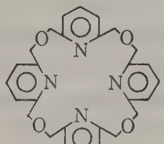
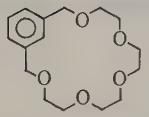
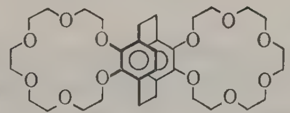
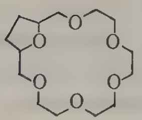
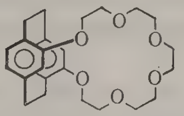
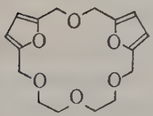
Fig. 3.26 Hammett plot for complexation of Na^+ with substituted benzo-15-crown-5 compounds in acetone at 25°C. (a) log K vs. $\sigma_p + \sigma_m$, $\rho = -0.47$, corr. coeff, $r = 0.978$, stand. dev. $s = 0.11$; (b) log K vs. $\sigma_p^- + \sigma_m$, $\rho = -0.45$, $r = 0.989$, $s = 0.082$. (Source: Ref. 144. Reproduced by kind permission of the American Chemical Society.)

important in some cases than the effect of the relationship between the cation diameter and the cavity size of the crown ring.

To assess the substituent effort on stability constants, Shchori and Jagur-Grodzinski prepared *cis*-4, 4′-dinitro- and diamino-derivatives of dibenzo-18-crown-6 and determined the K values of their Na^+ complexes in DMF and DME by electroconductivity measurements.[143] Pannell *et al.* also prepared *cis*-and *trans*-dinitro-, diamino-, tetrabromo-, actabromo-, mono-, and bis-(tricarbonyl Cr)-derivatives of dibenzo-18-crown-6 and determined the K values by measuring the ability of the complexes to extract K^+ and Na^+ from aqueous and CH_2Cl_2 solutions.[149] The K values of the Na^+ complexes of crown ether derivatives with electron acceptor substituents were larger than those of their K^+ complexes, while the inverse relation was observed for 18-crown rings.

Previously, in sections 2.2.5 and 2.7, we discussed the *K* values of other complexes of crown ethers. Included were the reports by Christensen *et al.*[153,154] on complexes of crown ethers bearing two carbonyl groups with alkali metal ions and alkaline earth metal ions, experiments by Cram *et al.*[155,156] to examine the effect on *K* values of sub-

TABLE 3.13 Formation constants (*K*) in the complexation reactions of *tert*-$BuNH_3$-SCN^- with crown ethers in chloroform at 24° C.[6,28,29]

	Crown ether	*K*		Crown ether	*K*
I		40	IX		80
II		7.5×10^5	X		420
III		1.4×10^5	XI		6.6×10^5
IV		<40	XII		240
V		500	XIII		210
VI		1.5×10^3	XIV		310
VII		1.1×10^6	XV		40
VIII		4.1×10^3			

stituents, facing toward the cavity, at the 2-position of the crown ether with a 1, 3-xylenyl group, and investigations by Mckervay and Mulholland on the effect of substituents at the outside of the crown ring on the introduction of additional OH and NO_2 groups at the 5-position of the crown ether.

Hydrogen bonds between the O atoms of crown ethers and the H atoms of ammonium ions take part in the complexation with NH_4^+ and primary ammonium ions, RNH_3^+, and the ammonium ions recognize the host molecules stereochemically because of the tetrahedron structure of the ammonium ions. Cram *et al.* determined the *K* value in chloroform at 24°C for Eq. (3.18).[28,29] The results are shown in Table 3.13. For

$$L + Bu^t\overset{+}{N}H_3{\cdot}SCN^- \overset{K}{\rightleftharpoons} Bu^t\overset{+}{N}H_3{\cdot}L{\cdot}SCN^- \qquad (3.18)$$

typical crown ethers II and III and their analogues VII and XI, the *K* values for $Bu^tNH_3^+$ are as much as 10,000 times that of pentaglyme I. The *K* value of paracyclophane type IV is about 1/1,000 that of isomer III, in which all six O atoms act as donors, because only three O atoms of IV interact with $Bu^tNH_3^+$, according to the CPK model. This finding reflects the control on cation binding exercised by the steric configuration of the hetero atoms. The important role of the hetero atoms is apparent from the decrease in the *K* values of V and VI in which a C atom substitutes for one of the hetero atoms. The contribution made to the complexation by the electron density on O atoms can be seen from the decrease in the *K* values of VIII, IX, and X containing aromatic O atoms. The largest *K* value is observed for an 18-membered ring; among azacrown ethers XI ~ XIII, the *K* values of XII, with a smaller ring, and XIII, with a larger ring, are much smaller than the *K* value of XI, with an 18-membered ring. Small *K* values of relatively rigid XIV and XV demonstrate that conformation change is necessary to some extent in complexation.

As to *sec-* and *tert-* ammonium ions, $RR'\overset{+}{N}H_2$, $RR'R''\overset{+}{N}H$, Schröder-Nielsen reported that the *K* values of their complexes were nearly equal to or less than those of quarternary ammonium ions as determened by extractions of (*N*-methyloctyl ammonium)$^+$-, (*N,N*-dimethyloctyl ammonium)$^+$-(2-naphthalene sulfonate)$^-$, and (salicylate)$^-$ by dibenzo-18-crown-6.[158]

B. ΔH, ΔS, ΔC_p

Other thermodynamic parameters of interest in complexations of crown ethers with cations are free energy change ΔG, enthalpy change ΔH, entropy change ΔS, and heat capacity change ΔC_p. The value of ΔG is calculated from the *K* value, and ΔH is measured by means of calorimetric titration.[136~139,159] An estimation of ΔH from the temperature dependence of *K* was also reported.[118] The value of ΔS can be calculated from ΔG and ΔH.

The calorific value and the entropy change during complexation are important factors relating to the stability of the complex. The larger the calorific value and the entropy change in a complexation reaction, the more stable a complex is formed. The value of ΔH for complexation in a solution reflects both the bond energy between the cation and the donor atom and the solvation energy of the reactant species and the

TABLE 3.14 Values of ΔH (kcal/mol), ΔS (cal/mol • deg), and ΔC_p (cal/mol • deg) for the complexation reactions of crown ethers with metal cations in water at 25°C (concentration = 0.1 mol/l)[14,15,137,138]

Crown ether		Na^+	K^+	Rb^+	Cs^+	NH_4^+	Ag^+	Tl^+	Sr^{2+}	Ba^{2+}	Hg_2^{2+}	Hg^{2+}	Pb^{2+}
15-Crown-5	ΔH	−1.50	−4.1	−1.90	−1.3	−0.24	−3.23	−4.01	−0.9	−1.14	—	−3.6	−3.26
		±0.04	±0.1	±0.01	±0.2	±0.04	±0.03	±0.05	±0.1	±0.10		±0.3	±0.03
	ΔS	−1.8	−10.4	−3.5	−0.5	+7.0	−6.5	−7.8	+6	+4.0	—	−4	−2.5
18-Crown-6	ΔH	−2.25	−6.21	−3.82	−3.79	−2.34	−2.17	−4.44	−3.61	−7.58		−4.69	−5.16
		±0.10	±0.01	±0.11	±0.10	±0.08	±0.09	±0.04	±0.02	±0.01		±0.03	±0.01
	ΔS	−3.7	−11.4	−5.7	−8.1	−2.2	−0.4	−4.5	+0.3	−7.9		−4.7	+2.2
Dicyclohexyl-18-crown-6 (isomer A)	ΔH	+0.16	−3.88	--3.33	−2.41	−2.16	0.07	−3.62	−3.68	−4.92	−2.16	−0.71	−5.58
		±0.04					±0.01	±0.02			±0.10	±0.01	±0.01
	ΔS	+6.1	−3.8	−4.2	−3.7	−1.2	+11.0	−1.0	+2.5	−0.2	+1.6	+10.2	+3.9
	ΔC_p		20						0	4			
Dicyclohexyl-18-Crown-6 (isomer B)	ΔH	−1.57	−5.07	−3.97		−3.41	−2.09	−4.29	−3.16	−6.20	−4.34	−2.55	−4.21
		±0.04						±0.03			±0.04	±0.04	±0.02
	ΔS	−2.1	−9.6	−9.3		−7.8	+0.3	−6.0	+1.5	−5.8	−7.4	+3.3	+6.2
	ΔC_p		53						17	35			

formed complex; the magnitude of ΔS is largely a result of electrostatic factors, as well as the relative hydration and number of product and reactant species.[160] Therefore, these values depend on the solvent just as the K values do. The contribution of ΔS to K is small unless there is a significant change in conformation during complexation because complex formation by crown ethers is due to electrostatic interaction between dipole and ion. The value of ΔC_p is also related to conformation change. When the size of a crown ring is large, the value of ΔC_p gives a strong clue about conformation change in the complexation. For example, large values of ΔC_p are observed in the K^+ complex of dibenzo-30-crown-10[70] and in K^+ complexes of valinomycin and nonactin.[161,162]

Table 3.14 summarizes values of ΔH, ΔS, ΔC_p, and log K for the complexation reactions of isomers A and B of dicyclohexyl-18-crown-6 with various metal ions in aqueous solutions at 25°C, as measured by Izatt *et al.*[14,15,137] by calorimetric titration. The ΔS values of alkali metal ion (K^+, Rb^+, Cs^+) complexes with isomer A are nearly equal to each other. However, the ΔH and ΔS values of the complex with Ba^{2+} are larger than those of the complex with K^+, which has an ionic diameter close to that of Ba^{2+}; these values indicate that Ba^{2+} forms a complex more easily. Na^+, with a smaller ionic diameter, gives small values of ΔH and ΔS because of large hydration energy. These facts suggest that, among the cations with smaller ionic diameters, the Na^+ complex is more stable than the Ca^{2+} complex because the hydration of divalent ions is larger than that of monovalent ions.

In the case of tri- and tetravalent ions, the solvation energy to the cation is markedly increased, although dipole-ion interactions are strong. Thus La^{3+} and Th^{4+} rarely form stable complexes in aqueous solution, while more stable complexes are formed and the values of ΔH and ΔS increase in low-polar solvents such as methanol.[15]

Among the ions of the transition metals and heavy metals, Ag^+ and Hg^{2+}, with the electron configuration of rare gases, form stable complexes because of the nature of covalent bonding, as mentioned in Section 3.2.3.A; though the absolute values of ΔH are rather small, there is an over all advantage for ΔS in complexation. Notably larger values of K, ΔH, and ΔS are observed in the complexes of Tl^+ and Pb^{2+} which have an electron configuration of a (rare gas $+ ns^2$) structure, compared to complexes of Rb^+ and Sr^{2+}, which have ionic diameters closely approximating those of Tl^+ and Pb^{2+}, respectively.

A comparison of isomer A (*cis-syn-cis*) with isomer B (*cis-anti-cis*) shows that $A > B$ for the values of K, ΔH, and ΔS, and $A < B$ for ΔC_p, except for ΔS and ΔH of Pb^{2+} and ΔH of Sr^{2+}.

Kodama and Kimura measured the values of K, ΔH, and ΔS of Pb^{2+} and Tl^+ complexes in aqueous solutions by means of polarography.[163] They obtained values of K in the order of 18-crown-6 and dicyclohexyl-18-crown-6 > pentaglyme and tetraglyme.

Izatt *et al.* showed that the values of K, ΔH, and ΔS for Na^+ and K^+ complexes of benzo-15-crown-5 in methanol-water systems increased with an increasing methanol content.[164] Izatt and his coworkers subsequently measured the K, ΔH, and ΔS of Na^+, K^+, Rb^+, Cs^+, Ca^{2+}, Sr^{2+}, snd Pb^{2+} complexes of benzo-15-crown-5, 18-crown-6, dibenzo-24-crown-8, and dibenzo-27-crown-9 in methanol-water systems and evaluated the contributions of ΔH and ΔS to K.[139] The results are summarized in Table 3.15.

Table 3.15 Log K_i, ΔH_i, and ΔS_i values for the complexation reactions of crown ethers with metal cations in methanol/water at 25° C (concentration = 0.1 mol/ l)[139]

Crown ether	M^{n+}	Solvent composition (wt% methanol)†[1]	log K_i	i	ΔH_i (kcal/mol)	ΔS_i (cal/ deg·mol)
Benzo-15-crown-5	Na^+	0	0.4†[2]	1		
		20	0.72 ± 0.03	1	−1.77 ± 0.02	−2.6
		40	1.17 ± 0.12	1	−2.63 ± 0.11	−3.5
		60	1.64 ± 0.04	1	−3.78 ± 0.08	−5.2
		70	1.99 ± 0.10	1	−3.82 ± 0.07	−3.7
		80	2.26 ± 0.02	1	−8.32 ± 0.03	−17.6
	K^+	0	0.38 ± 0.10	1	−2.33 ± 0.10	−6.1
		20	1.20 ± 0.10	1	−1.8 ± 0.2	−0.5
		40	1.92 ± 0.04	1	−2.51 ± 0.03	0.4
		70	1.5 ± 0.3	1	†[3]	
			4.15 ± 0.02	2	−13.9 ± 0.2	−27.6
		80	2.2 ± 0.2	1	†[3]	
			4.80 ± 0.05	2	−15.50 ± 0.13	−30.0
	Rb^+	70	1.8 ± 0.2	1	†[3]	
			3.77 ± 0.05	2	−12.0 ± 1.5	−23.5
	Cs†	70	1.70 ± 0.01	1	−2.43 ± 0.05	−0.4
	NH_4^+	70	†[4]			
	Ca^{2+}, Sr^{2+}, Ba^{2+}	70	†[4]			
	Pb^{2+}	70	2.04 ± 0.01	1	−5.11 ± 0.02	−7.8
	Co^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}	70	†[4]			
18-Crown-6	Na^+	70	2.76 ± 0.02	1	−4.89 ± 0.01	−3.8
	K^+	70	4.33 ± 0.05	1	−9.68 ± 0.01	−12.7
	Rb^+	70	3.46 ± 0.10	1	−9.27 ± 0.05	−15.3
	Cs^+	70	2.84 ± 0.01	1	−8.09 ± 0.01	−14.1
	Ca^{2+}	70	2.51 ± 0.02	1	−4.27 ± 0.02	−2.8
	Sr^{2+}	70	5.0 ± 0.1	1	−7.49 ± 0.01	−2.5
	Ba^{2+}	70	6.0†[5]	1	−10.66 ± 0.01	−8.5
	Pb^{2+}	70	6.5†[5]	1	−9.19 ± 0.01	−1.1
Dibenzo-24-crown-8	Na^+	70	1.54 ± 0.01	1	−7.75 ± 0.02	−18.9
	K^+	70	2.42 ± 0.01	1	−8.54 ± 0.01	−17.6
	Rb^+	70	2.55 ± 0.01	1	−8.72 ± 0.02	−17.6
	Cs^+	70	2.48 ± 0.01	1	−8.93 ± 0.02	−18.6
Dibenzo-27-crown-9	Na^+	70	1.50 ± 0.01	1	−11.74 ± 0.01	−32.5
	K^+	70	2.86 ± 0.01	1	−9.50 ± 0.01	−18.8
	Cs^+	70	1.42 ± 0.02	1	−6.14 ± 0.06	−14.1

†[1]Dielectric constant: 0% (78), 20% (70), 40% (61), 60% (52), 70% (47), 80% (43), 100% (33)
†[2]Estimated from the relationship between the dielectric constant and log *K*.
†[3]Did not calculated because of large measurement error of log *K*.
†[4]Slight exotherm. It is estimated that $\Delta H = 0$ or only slight complexation occurs.
†[5]Estimated from the relationship between cationic diameter and log *k*.

In a methanol (70 wt%)-water system, both ΔH and ΔS of Na^+ complexes take on larger and larger negative values with an increasing size of the crown rings. These differences in the values of ΔH and ΔS are small between 15-crowns and 18-crowns, which have rather inflexible rings, but there are large differences in the values between these crown ethers and flexible 24-crown, and between 24-crown and 27-crown. Greater conformational changes during the complexation large and flexible crown rings are thought to be responsible.

Reports on findings in other solvents include that by Smid *et al.*,[118] who determined ΔH and ΔS values in the complexation of isomers A and B of dicyclohexyl-18-crown-6 with fluorenyl K in THF at 25°C. The results were as follows: $\Delta H = -3.9$ kcal/mol, $\Delta S = -11.7$ cal/K.mol for isomer A; $\Delta H = -3.1$ kcal/mol, $\Delta S = -10.7$ cal/K.mol for isomer B. These values are the reverse of the tendency found in aqueous solutions. Arnett *et al.* measured ΔH in the complexation of dicyclohexyl-18-crown-6 with Li^+, Na^+, K^+, Cs^+, and NH_4^+ in DMSO, acetone, and THF by means of potentiometry.[165,166]

C. Complexation Reaction Rates and Dissociation Rates

Our understanding of the kinetics of crown ether complexation reactions lags well behind our extensive knowledge of the thermodynamics involved. In general, it is known that the reactions of alkali metal ions and alkaline earth metal ions proceed very quickly, and diffusion is considered to be the rate-determining stage. In the case of transition metal complexes, the rate of dissociation of the complexes with even so-called "labile" metal ions diminishes markedly when the ligands are multidentate; this is particularly true of macrocyclic ligands. There are even examples known of complexes that are stable because of the kinetics of the ligands, though the ions are very unstable in the free state.[167,168] It is very interesting to consider the rates of complexation and dissociation of crown ether complexes with alkali metal ions and alkaline earth metal ions from this standpoint.

Though the kinetics of complexation and dissociation have not been clarified in detail, for the overall complexation reaction (Eq. (3.15)), measurements have been made of the complexation rate constant k_f and the dissociation constant k_d. The ingress and egress of the cation can be observed directly by ^{23}Na-, ^{39}K-, ^{87}Rb-, and ^{133}Cs-nmr, and this serves as a useful method for measuring k_f and k_d. Shchori *et al.* first employed ^{23}Na-nmr to investigate the kinetics of the complexation of dibenzo-18-crown-6 with Na^+ in DME.[169] The chemical shift of ^{23}Na in a Na^+ complex is nearly equal to that of solvated Na^+, but the width of nuclear quadrupole relaxation of the complex is 25 times greater than that of solvated Na^+ because of steric asymmetry in the circumference of Na^+. The values of k_f and k_d are obtained from the mean lives of both species of Na^+, which are derived from this difference.

Shchori *et al.* also measured the values of k_f and k_d for the Na^+ complex of dibenzo-18-crown-6 in DMF, methanol, and DME, for the Na^+ complex of dicyclohexyl-18-crown-6 in methanol, and for the Na^+ complexes of *trans*-4, 4′-dinitrodibenzo-18-crown-6 and *trans*-diaminodibenzo-18-crown-6.[170] They also investigated the substituent effect on the complexation rate. Approximately the same value (12.6 ± 1.0 kcal/mol) was observed for the activation energy of the dissociation of dibenzo-18-crown-6 complex in each solvent. The agreement of this value with the value reported by Truter *et al.*[56,61] for the activation energy (12 kcal/mol) of the conformational change in the crown ring during the complexation of dibenzo-18-crown-6 with Na^+, as well as the small activation energy (8.3 kcal/mol) of the dissociation of dicyclohexyl-

18-crown-6 resulting from the flexibility of the crown ring; both suggest a close relationship between the activation energy and the conformation of the complex.

Kinetic data for the complexations of dibenzo-18-crown-6 with K^+ and Rb^+ in methanol were measured by Shporer and Luz by ^{39}K- and ^{87}Rb-nmr.171) Table 3.16 summarizes the kinetic data obtained by the nmr technique.

TABLE 3.16 Thermodynamic and kinetic parameters of crown ether complexes (^{23}Na–, ^{39}K–, ^{87}Rb-nmr method).170,171)

Cation	Crown ether†	Solvent	K (M^{-1}) (25°C)	ΔH (kcal/mol)	ΔS (eu)	E_a (kcal/mol)	k_d (sec^{-1}) (−13°C)	k_d (sec^{-1}) (25°C)	k_f ($M^{-1}sec^{-1}$) (25°C)
Na^+	DB–18	DMF	600	−6.0	−7	12.6	4,800	1×10^5	6×10^7
	NDB–18	DMF	115			12.5	9,200	2.0×10^5	2.3×10^7
	AmDB–18	DMF	615	−6.0	−7	13.1	7,600	1.9×10^5	1.2×10^8
	DB–18	Methanol	23,000			11.7	800	1.4×10^4	3.2×10^8
	DC-18(B)	Methanol	4,800	−5.6	−2	8.3		5.2×10^4	2.6×10^8
	DB–18	DME							
		Free ion	5,000	−3.9	+3.9				
		Ion pair	4,500	−3.4	+5.4	13.3	540	1.5×10^4	6.5×10^7
	MeDBC	THF	$>2 \times 10^7$			12.5			
K^+	DB–18	Methanol				12.6	610 (−34°C)		
Rb	DB–18	Methanol					10^4 (−50°C)		

†DB-18: dibenzo-18-crown-6; NDB-18: 4,4′-dinitrodibenzo-18-crown-6; AmDB-18: 4,4′-diaminodibenzo-18-crown-6; DC-18(B): dicycloehxyl-18-crown-6 (isomer B); MeDBc: 4,4′-dimethyldibenzo-18-crown-6

Mei *et al.* have investigated the complexation reactions of 18-crown-6 with Cs^+ in propylene carbonate, pyridine, acetone, DMF, DMSO, and acetonitrile by ^{133}Cs-nmr, and they showed from the graphed curve of ^{133}Cs shift vs. [crown]/[Cs] that the complexation in propylene carbonate, pyridine, and acetone involved a two-step reaction in which a 1 : 1 complex was followed by a 2 : 1 complex with a sandwich structure. 172,173)

Using a technique other than nmr, Liesengang *et al.* measured the values of k_f and k_d for the K^+ and Cs^+ complexes174) and for the Li^+, Na^+, NH_4^+, Ag^+, Ca^{2+}, and Tl^+ complexes175) of 18-crown-6 in aqueous solutions by means of ultrasonic (9 ~ 340 MHz) absorption. De Jong *et al.* examined the kinetics in the exchange reaction of *tert*-$BuNH_3 \cdot PF_6^-$ between two kinds of crown ethers.176) They found that complex formation was controlled by the diffusion rate of the solution, and they observed a large exchange rate and a small activation energy, which suggested a 1 : 2 complex as an intermediate.

3.2.4 Solubilization of Metal Salts and Alkali Metals in Organic Solvents

The complexes formed by binding of cations into the cavities of crown ethers are soluble in nonpolar solvents, as described in Section 3.1. In such cases, the counter anions show a very high activity because they exist in the solution as so-called "naked" anions (bare anions), anions which are not solvated or are solvated very weakly. Because of these two specific characteristics, homogeneous organic reactions with a high reaction rate can be carried out using inorganic salts which are insoluble or barely soluble in organic solvents, as can novel reactions that had previously been considered impossible.

The electrostatic ion-dipole interaction plays a significant role in the complexations of crown ethers with cations. In general, the potential energy (E) of the two kinds of ion pairs, $[A^{q1} \ldots B^{-q2}]$ and $[C^{q1} \ldots D^{-q2}]$, with the same charge but different ionic diameters, can be shown schematically as the function of the distance (r) between the cation and the anion, as shown in Fig. 3.27. The dashed line indicates the potential due to the electrostatic force of q_1 and $-q_2$. When q_1 and $-q_2$ are approached from infinity ($r = \infty$, $E = 0$), E is lowered along the dashed line, and when r becomes small, the ion pair $(A\cdots B]$ with the larger ionic diameter reaches the minimum value earlier than the ion pair $[C\cdots D]$ with the smaller ionic diameter because of the steep rise in the repulsion between the electron shells. The observation that more stable complexes of linear ligands are formed with smaller cations can be explained by this electrostatic model. The model is applicable not only to 1 : 1 ion pairs but also to ion-dipole interaction and crystal lattice energy.

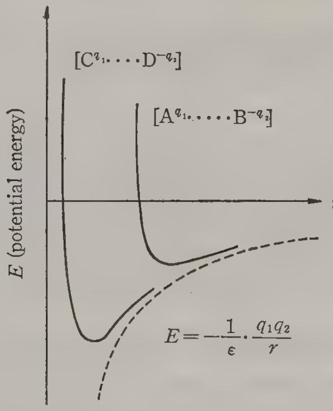


Fig. 3.27 Schematic presentation of potential energy of ion pair.[87] (Source: Ref. 8. Reproduced by kind permission of Nankodo Publishing. Co.)

From Fig. 3.27 it is clear that the ion pair with an increased distance between cation and anion is at a higher level of potential energy and is in an activated state. As an ion pair in the initial system is finally separated in an ionic process or reaction, naturally an ion pair which requires little energy to separate such as $[A1\cdots B^{-q2}]$ has greater activity. The same holds true when stripping a solvating molecule or a dipole of a neutral ligand from ions having different ionic diameters.

Based on these considerations, the solubilities of general ionic compounds can be

TABLE 3.17 Solubilization of metal salts in aprotic solvents by crown ethers (26°C).[1)]

Crown ether	Salt	Solvent	Method†[1]	Solubility (mol/*l*)
Butylbenzo-15-crown-5	NaSH	Benzene	2	Solution decomposes with evolution of H_2S
Butylbenzo-18-crown-6	$SrCl_2$	Nitromethane	2	>0.2
Bisbutylbenzo-18-crown-6	KOH	Benzene	2	>0.2
Bisbutylbenzo-18-crown-6	$KOC(CH_3)_3$	Benzene	2	>0.02
Bisbutylbenzo-18-crown-6	$KMnO_4$	Benzene	2†[2]	>0.15
Dicyclohexyl-18-crown-6	KC_6H_5	Benzene	1	0.2†[3]
Dicyclohexyl-18-crown-6	KOH	Toluene	2	0.32
Dicycloehxyl-18-crown-6	KOH	DMF	2	>0.3
Dicyclohexyl-18-crown-6	KOH	DMSO	2	>0.4
Dicyclohexyl-18-crown-6	CsOH	Benzene	2	0.065
Dicyclohexyl-18-crown-6	$KOC(CH_3)_3$	Benzene	1	0.12
	KCN	Nirtbmethane	2	>0.19
Dicyclohexyl-18-crown-6	$KOC(O)C(C_2H_5)H(n\text{-}C_4H_9)$	Benzene	2	>0.1
Dicyclohexyl-18-crown-6	K abietate	Benzene	2	very soluble
Dicyclohexyl-18-crown-6	$KSC(S)NC_6H_5$	Benzene	2	>0.4
Dicyclohexyl-18-crown-6	$KO_3SC(C_2H_5)H(n\text{-}C_4H_9)$	Benzene	2	>0.2
Dicyclohexyl-18-crown-6	$KOP(=O)(OC(C_2H_5)H\text{-}n\text{-}C_4H_9)_2$	Benzene	2	>0.6
Dicyclohexyl-18-crown-6	K_3PF_6	*O*-Dichlorobenzene	2	>0.08
Dicyclohexyl-18-crown-6	NaI	Benzene	2	>0.1
Dicyclohexyl-18-crown-6	$KAg(CN)_2$	*O*-Dichlorobenzene	1	0.27
Dicyclohexyl-18-crown-6	$KAgI_2$	*O*-Dichlorobenzene	1	0.17
Dicyclohexyl-18-crown-6	$KAu(CN)_2$	Benzonitrile	1	0.13
Dicyclohexyl-18-crown-6	$K_4Fe(CN)_6$	Nitrobenzene	2	0.022
Dicyclohexyl-18-crown-6	$KMnO_4$	Benzene	1	Intense purple solution which decomposes slowly with formation of MnO_2
Dicyclohexyl-18-crown-6	K_2CoCl_4	Xylene	2	0.021
Dicyclohexyl-18-crown-6	K_2CoCl_4	*O*-Dichlorobenzene	2	0.24
Dicyclohexyl-18-crown-6	K_2PdCl_4	*O*-Dichlorobenzene	1	0.18
Dicyclohexyl-18-crown-6	K_2PtCl_4	*O*-Dichlorobenzene	1	0.047

†[1] Method 1: the salt was added directly to the solvent containing an equimolar quantity or an excess of the crown ether; Method 2: the complex was formed in methanol, freed of solvent under vacuum, dissolved in the final solvent, and filtered.

†[2] Acetone was used instead of methanol. The purple solution in benzene gradually decomposed with deposition of MnO_2.

†[3] Decomposes within hours, probably by attack on the ether linkage. BuLi opens the polyether ring of dibenzo-18-crown-6 to produce a phenoxide group.

estimated qualitatively. In the case of organic ions, it is necessary to consider the effect of hydrophobic bonding; however, by adding only a small amount of energy for solvation and thereby overcoming the mutual attraction of the ion pairs and the hydration energy, the ions can be dissolved even in low-polar solvents. When the energy required to dissolve is supplied by the hydrophobic energy, the dissolution is more favorable.

In general, cations are smaller than anions, therefore a cation becomes more soluble in organic solvents when its size increases by incorporation into crown ether.

Crown ether complexes are generally soluble in the solvents with large dielectric constants, but the solubilities do not depend simply on the polarity of the solvent. Moderately polarized solvents are preferable because it is necessary to supply sufficient solvation energy. For this reason, aromatic hydrocarbons, halogenated hydrocarbons, nitrated hydrocarbons, ethers, nitriles, amides, and DMSO are good solvents for crown ether complexes. The complexes are insoluble or barely soluble in aliphatic saturated hydrocarbons.

To illustrate the solubilization of inorganic salts by crown ethers, Table 3.17 lists the solubilities of various salts in aprotic solvents in the presence crown ethers.[1] Table 3.18 summarizes the effects of adding 18-crown-6 on the solubilities of K salts in acetonitriles and benzenes,[177,178] and Table 3.19 shows the solubilization of alkali metal halides in organic solvents by dicyclohexyl-18-crown-6.[4]

Table 3.18 Effects of addition of 18-crown-6 on solubilities of potassium salts.

Solvent	18-Crown-6 (mol/*l*)	Solubility (mol/l)	
		KOAc[178]	KF[177]
Acetonitrile	—	0.0005	
	0.14	0.1	
Benzene	—	~0	
	0.55	0.4	
	1.0	0.8	
Benzene	—		~0
	0.34		0.014
	1.01		0.052

Table 3.19 Solubilization of alkali halides in organic solvents by addition of 50 mmol/*l* of dicyclohexyl-18-crown-6.[4]

Solvent	Methanol (mmol/*l*)	Solubility (mmol)				
		NaCl	NaBr	KCl	KBr	KI
C_6H_6	—	0.01	1.8	0.03	2.3	9.2
	250	0.48	24	8.7	30	46
CCl_4	—	0.03	2.7	0.6	4.1	0.8
	250	1.1	28	8.8	34	15
$CHCl_3$	—	1.8	37	21	41	43
	250	5.7	41	34	44	44
CH_2Cl_2	—	1.8	35	17	41	43
	250	5.8	42	33	42	44
THF	—	0.02	1.2	0.1	3.6	45
	250	0.04	5	0.4	13	50

As shown in Table 3.19, the solubilities of inorganic salts in organic solvents in the presence of crown ether are markedly increased by the addition of a small amount of methanol.4) It is therefore thought that methanol takes part in the complexation to form a more completely solvated ion sphere for the cation coordinated by the crown ether and ether and that the anion is also solvated by methanol.

The solubilities of inorganic salts also depend on type of anion involved; the solubility increases with an increasing diameter of anion, as shown in Table 3.19 and explained previously. Generally speaking, the inorganic salts having hard anions such as F^- and SO_4^{2-} are barely solubilized, while the salts having soft anions such as I^-, SCN^-, acylate and picrate are readily soluble in organic solvents.

The solubilization of inorganic salts in organic solvents can be extended to complex salts and organometallic complexes. It is well known that $KMnO_4$ is dissolved in benzene by the addition of crown ether,1) forming a purple solution called "purple benzene" which shows strong oxidizing power at room temperature.179) As shown in Table 3.7, $KAg(CN)_2$, $KAgI_2$, K_2CoCl_4, K_2PdCl_4, K_2PtCl_4, and KPF_6 are dissovled in *o*-dichlorobenzene, K_2CoCl_4 is dissolved in xylene, $KAu(CN)_2$ is dissolved in benzonitrile, and $K_4Fe(CN)_6$ is dissolved in nitrobenzene by dicyclohexyl-18-crown-6.1) Furthermore, it is known that $NaBH_4$ is dissolved in toluene and benzene by dibenzo- and dicyclohexyl-18-crown-6, and the solution has a capacity for reduction.180,181) Recently it was reported that $K_2Cr_2O_7$ is dissolved in HMPA by dibenzo- and dicyclohexyl-18-crown-6, and the resulting solution has strong oxidizing power.182)

There have been reports of organometallic complexes composed of an alkali metal as the cation and transition metal as the anion. For example, Zeise salt, $KPtCl_3 \cdot C_2H_4$, is dissolved in low-polar solvents such as chloroform by complexation with various crown ethers having a metacyclophane or furan ring moiety.183) $Cr(CO)_6$ and $W(CO)_6$ react with KOH and KF in CH_2Cl_2 in the presence of dibenzo-18-crown-6 or 18-crown-6 to form K^+-crown ether complexes having $M(CO)_5OH^-$ and $M(CO)_5F^-$ as the anion.184) The complex of $Na^+[\eta^5\text{-}C_5H_5)Fe(CO)_2]^-$ with dibenzo-18-crown-6 is dissolved in ether.185)

With regard to organoionic compounds which are usually insoluble or barely soluble in low-polar solvents, a series of aromatic acylonium salts36) and aromatic diazonium salts36,41) have been dissolved in $CHCl_3$ and CH_2Cl_2 by complexation with crown ethers, and these reactions have been applied to organic syntheses.38~41)

As to alkali metal compounds other than salts, Valentine *et al.* reported recently that potassium peroxide, KO_2, for which no adequate solvent had been found, can be dissolved in DMSO at room temperature by 18-crown-6 and dicyclohexyl-18-crown-6 forming superoxide anion, O_2^-, which is a specific oxidation reaction species.188,189) In addition, solubilization of KO_2 in DMF, DME, and ethyl ether by 18-crown-6190) and in benzene by dicyclohexyl-18-crown-6190) and 18-crown-6191~193) have also been described. Since these publications appeared, researchers have investigated the reactions of O_2^- such as S_N2, hydrogen abstraction, and nucleophilic addition with this technique (see Section 4.2.3.C).

Organoalkali metal compounds such as phenyl potassium are also dissolved by crown ethers in nonpolar solvents such as benzene, as shown in Table 3.17. Research on the structure and behavior of ion pairs of the carbanion in organic solvents using the complexes of fluorenyl-Na^+, K^+, and Ba^{2+} with crown ethers were described previously in Section 3.2.2.B.

It was discovered in 1864 that alkali metals are readily soluble in liquid ammonia, and it is also well known that a small amount of alkali metals is dissolved in amines such as methylamine, ethylamine, and ethylene diamine, in ethers such as THF and glymes, and in HMPA, showing a specific blue color which has been attributed to the solvated electron.194,195) After the discovery of crown compounds it was found that crown ethers and cryptands markedly increase the solubilities of Na, K, and Cs in ethers and amines and that these alkali metals are solubilzed by crown compounds even in nonpolar or low-polar solvents such as benzene and toluene. In addition, crystals of $NaC^+ \cdot Na^-$ (C: cryptand) containing Na anion have been isolated recently from a solution of Na in ethlamine in the presence of cryptand.22,195~197)

As Section 3.3.2.C discusses in detail recent progress in the research on alkali metal solutions using crown ethers and cryptands, we will present here only an outline of the solubilization of alkali metals by crown ethers.

Before the discovery of crown ethers, Wilkinson *et al.* reported that K and Na-K alloy are dissolved in the cyclic tetramer of propylene oxide ($\sim 10^{-4}$ M), as well as in glyme and amines, forming a blue solution.198) Dye *et al.* found that K and Cs are dissolved in THF (5×10^{-3} M) at room temperature in the presence of dicyclohexyl-18-crown-6; they also observed that a deep blue solution which is stable for several hours at $-78°C$ and for $5 \sim 10$ minutes at room temperature is formed by the solubilization of K in ethyl ether in the presence of dicyclohexyl-18-crown-6.199,200) By the use of esr and nir spectra it has been determined that the anionic species in these solutions are mainly alkali metal anions (M^-). When dicyclohexyl-18-crown-6 is added to an ethyl ether solution of Na^+[anthracene]$^-$ complex, the hyperfine structure (hfs) of the esr spectrum which is attributable to the contact ion pair of the cation-radical anion disappears. It is thus thought that the ion pair is separated by the crown ring.200)

$$M^- + h\nu \rightleftharpoons M\cdot + e^-_{solv} \tag{3.19}$$

Dye *et al.* also reported on the solubilization or increase in solubility of Na and K in ethylamine, 1,2-propanediamine, THF, glyme, diglyme, and ethyl ether by dicyclohexyl-18-crown-6.194) They measured the absorption maxima of nir, the temperature coefficients for M^-, and the level of solvated electron (e^-_{solv}) in the solutions, and discussed the equilibrium of each chemical species in the solutions.

Friedenberg and Levanon recently observed the esr spectra of the alkali metal radical $M\cdot$ and solvated electron, thought to form as in Eq. (3.19), by photoexcitation of THF solutions of K and Rb prepared by the addition of dicyclohexyl-18-crown-6.201)

The solubilization of alkali metals in nonpolar or low-polar aromatic hydrocarbons was discovered by Lehn *et al.*202,203) When an evaporating, thin film of K was exposed to a benzene or toluene solution of dicyclohexyl-18-crown-6, K dissolved gradually and the solution took on a dark blue color. The uv spectra of these solutions at $-70°C$ demonstrated the same absorptions at 300 and 400 nm as benzene radical anion in DME. An hfs corresponding to the radical anions of benzene (7 lines) and toluene (5 lines) was observed in the esr spectra, as shown in Fig. 3.28 These findings suggested that K^+, resulting from the release of an outer shell electron from K, is bound by the crown, then the electron is transferred to the lowest vacant orbital of the benzene or toluene molecule to form a radical anion, and the crown-separated ion pair, (crown, $K)^+$-(radical anion), is formed.

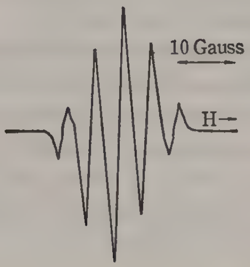


Fig. 3.28 The esr spectrum of K/18-crown-6/toluene solution (−70° C). (Source: Ref. 203. Reproduced by kind permission of Verlag Chemie.)

Komarynsky and Weissman also reported that K was solubilized in benzene and toluene by dicyclohexyl-18-crown-6, and esr spectra having hfs (coupling constant: 3.41 G for benzene solution, 4.5 G for toluene solution) were observed.[204)] Nelson and von Zelewsky reported that esr spectra with an hfs that showed the formation of the ion pair of (crown, $K)^+$-(radical anion) were observed for benzene, toluene, and mesitylene solutions of K solubilized by 18-crown-6.[205)] The formation of radical anions in mesitylene had not been reported previously because of its smaller electron affinity, and it is thought that the formation of such a radical anion was due to stabilization by the formation of an ion pair in the presence of the crown ether. According to Nelson and von Zelewsky, Cs is also solubilized. In toluene solution the esr spectrum has an hfs (8 lines) from the ^{133}Cs nucleus, but in benzene and mesitylene solution there is only one asymmetrical broad line, apparently because Cs^+ has a larger ionic diameter than the crown ring.

3.3 CHARACTERISTICS OF OTHER CROWN COMPOUNDS

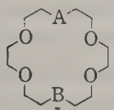
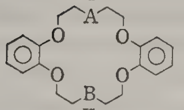
3.3.1 Composite Donor Crown Compounds

A variety of monocyclic composite donor crown compounds have been synthesized—azacrown ethers with O and N atoms as donors, thiacrown ethers with O and S atoms as donors, crown compounds with N and S atoms as donors, and azathiacrown ethers with O, N, and S atoms as donors, as discussed in Section 2.5, and their capacity to form complexes with cations has been investigated.[16)] However, little work has been reported so far on the structure of the complexes, the thermodynamics,[14,16)] or the kinetics of the complexation reactions.

When 1 or 2 of the O donors in 18-crown-6 and dibenzo-18-crown-6 are replaced with N or S atoms, the stability constants of the complexes of the resulting aza- or thiacrown ethers with alkali and alkaline earth metal ions are smaller than those of the corresponding crown ethers. As shown in Table 3.20, values of log *K* for the K^+ complexes are in the order of O > NR > NH > S,[24)] which is the same order as the electronegativities of the donors. That is to say, the ion-dipole interaction between the donor atom and the cation declines with the decreasing negative charge of the donor, and thus the complexation ability is reduced.

In contrast, the complexation abilities with transition metal ions and heavy metal ions which belong to a class of soft acid increase markedly to nearly the same level as the corresponding acyclic amines. Table 3.20 presents values of log *K* for Ag^+ complexes. Basides the electrostatic interaction, the coordinative bonding nature of N and S also contributes to the complexation. However, the`coordinative bonding force of these aza- or thiacrown ethers is smaller than that of azathicrown ethers, cyclic polyamines, and cyclic polythiaethers. For example, dithia-18-crown ether, shown in Table 3.20, does not form complexes with Ni(II) or Co(II).

TABLE 3.20 Complexation abilities (log *k*) of crown ethers in which some of the O donors are replaced by N or S atoms.[24)]

	Crown ether			log *K*	
	Type	A	B	K^+ (in methanol)	Ag^+ (in water)
 I	I	O	O	6.1	1.6
	II	O	O	5.0	—
	II	NR†	O	4.1	—
	I	NH	O	3.9	3.3
 II	II	NH	O	3.2	—
	I	NH	NH	2.0	7.8
	II	NH	NH	1.6	—
	I	S	S	1.2	4.3

† $R = C_8H_{17}$

The crystal structures of the free crown[206)] and the KSCN complex[207)] of diamino-18-crown-6 (**30**) have been determined by Weiss *et al.*, as shown in Fig. 3.29.

Azathiacrown ether **115**, with O, N, and S donors, forms a 1 : 1 complex with Ni(II) and Co(II), but the metal ions do not lie on the plane formed by the donor atoms in the crown ring because of the small cavity of the 12-membered ring.[208)] As measured by potentiometry in 0.1 N $NaClO_4$ aqueous solution, the values of log *K* of the complexes of azathiacrown ether **116**, with a 15-membered ring, follow the order of Cu(II) (11.55) > Ni(II) (7.98) > Pb(II) (5.67) > Co(II) (5.42) > Zn(II) (5.09).[209)] This agrees with the order given by the Irving-Williams rule concerning the stability of the first series of divalent transition metal complexes. X-ray analysis of the Ag(I) complex of **116** has been carried out.[210)] There has been a recent report that gives the values of

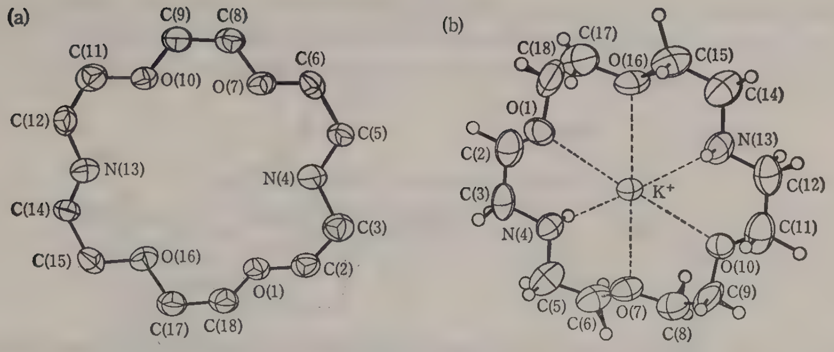
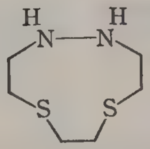


Fig. 3.29 Crystal structure and conformation of (a) diamino-18-crown-6[206] and (b) its KSCN complex. (Sources: Refs. 206, 207. Reproduced by kind permission.)

log *K* for the complexes of azathiacrown ether **117**, which has a 15-membered ring, with Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Pb(II), and Ag(I); the structure of the Ag(I) complex was also reported.[211]

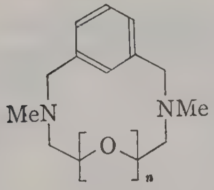
Among the crown compounds with N and S donors, compound **36** with an 18-membered ring was prepared by the use of Ni(II) or Co(II) as a template. In the complexes of this crown compound, the metal ion lies on the plane formed by the S donors and the N atoms lie above and below the plane.[212,213] The value of log *K* was not reported. The values of log *K* for the complexes of 1, 10-diaza-4, 7-dithiadecane (**148**) with Cu(II), Ni(II), Co(II), Pb(II), Zn(II), and Ag(I) have been measured recently.[214]



148

Other work has determined the conformation of the complex of diazaoxametacyclophane (**149**) with primary ammonium thiocyanates (Fig. 3.30), and the free energy change (ΔG) in the complexation reaction was measured by the temperature dependency of nmr.[215,216] The complex of crown compound **93** with a pyridine nucleus was prepared by using Pb^{2+} as a template (Fig.3.31), and X-ray analysis was carried out.[217]

Gokel and Garcia recently prepared monoaza-18-crown-6 and studied its complexation with K salts and protonic acids.[218] Their interesting results included the observations that KH is dissolved in THF by the complexation with monoaza-18-crown-6, forming a secondary amine salt, and that the azacrown ether forms a hydro-



149

a $n=2$
b $n=3$

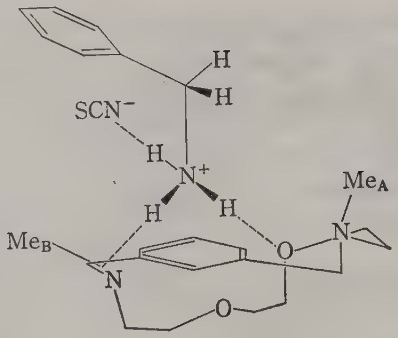


Fig. 3.30 Conformation of diazaoxamethacyclophane-primary ammonium salt complex. (Source: Ref. 216. Reproduced by kind permission of the Chemical Society.)

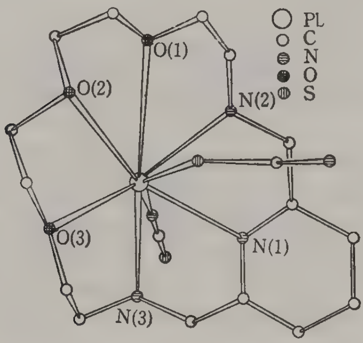


Fig. 3.31 Crystal structure and conformation of azacrown ether 93-$Pb(SCN)_2$ complex. (Source: Ref. 217. Reproduced by kind permission of the Chemical Society.)

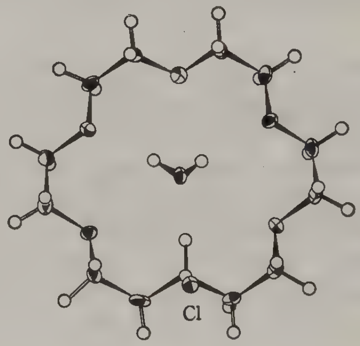


Fig. 3.32 Crystal structure and conformation of monoaza-18-crown-6 complex with hydronium chloride (H_3O^+ Cl^-). (Source: Ref. 218. Reproduced by kind permission of Pergamon Press.)

nium chloride ($H_3O^+Cl^-$) complex (Fig. 3.32) with concentrated hydrochloric acid in THF.

3.3.2 Cryptands

A. Formation and Structure of Complexes ("Cryptates")

Cryptands, the steric cage-type bicyclic crown compounds with two nitrogen atoms as both bridgeheads, form complexes called cryptates with metal ions by the strong binding of the ions into the space lattice. The ion-selectivity and stability of the complexes are larger than those of monocyclic crown ethers.[9,10,14,17,219~221]

As with crown ethers, the formation of cryptates can be ascertained by ir, uv, nmr, potentiometry, measurement of electroconductivity, extraction of picrate, and so on. The cavity sizes of typical cryptands previously illustrated in Fig. 1.2 are listed in Table 3.21. It is known that the ions of alkali metals, alkaline earth metals, Ag^+, and

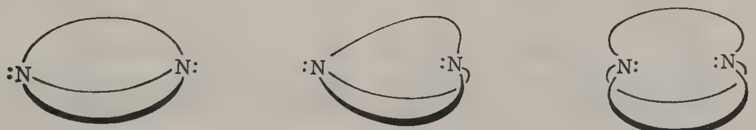
Tl^+ whose ionic diameters correspond to the cavity sizes are enclosed to form the complexes.[9] Other reports describe the complex formation of [2,2,2] with Co^{2+},[222] Cu^{2+}[223] ([2,1,1] and [2,2,1] complexes were also prepared with these ions), UO_2^{2+}, U^{4+}, and Th^{4+}.[101]

TABLE 3.21 Cavity diameters of cryptands

Cryptand†	Cavity diameter (Å)	Ref.
Cryptand [1, 1, 1]	1.0	229
Cryptand [2, 1, 1]	1.6	255
Cryptand [2, 1, 1]	2.2	255
Cryptand [2, 2, 2]	2.8	255
Cryptand [3, 2, 2]	3.6	255
Cryptand [3, 3, 2]	4.2	255
Cryptand [3, 3, 3]	4.8	255
Tricyclic cryptand **42**	6	240

†Structural formulas of cryptands are shown in Fig. 1.2

Figure 3.33 illustrates the three types of steric configuration of cryptands that are possible with the conformation of the bridgehead nitrogen atoms, *exo-exo* (out-out), *exo-endo* (out-in), and *endo-endo* (in-in). In solution, the three types probably coexist at equilibrium because of mutual conversion by inversion of the nitrogen atoms. In the of the complexes, however, it is thought that the *endo-endo* type, in which the lone pair of case electrons of the nitrogen atoms is directed inside, may be the most likely. In fact, the results of X-ray analyses of the crystalline complexes have shown that the cations are present in the space lattice and that the cryptands have an *endo-endo* conformation.



exo-exo *exo-endo* *endo-endo*

Fig. 3.33 Steric configurations of cryptands.

It has been ascertained by nmr that the tertiary nitrogen atoms located on the bridgehead are protonated to form the bicyclic quarternary ammonium salt having an *endo-endo* type configuration, in which both H^+ are directed inside, when diazabicycloalkane (**120**) is treated with HCl.[224~226] X-ray analysis recently demonstrated that the protonated diazabicycloalkane encloses Cl^- in the space lattice to form the complex, as shown in Fig. 3.34.[227] This was the first example of a clathrate compound in which an anion was included in a cyclic compound; it preceded a report[228] on the complex formation of cyclodextrin with a small anion.

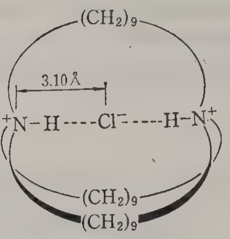


Fig. 3.34 Diazabicycloalkane incorporating Cl^- anion. (Source: Ref. 227. Reproduced by kind permission of The American Association for the Advancement of Science.)

The bridgehead nitrogen atoms in cryptands are also protonated by treatment with protonic acids. When carbonyl groups are reduced with B_2H_6 in the synthesis of cryptand shown in Eq. (2.31), the cryptands with larger cavities form a bisborane derivative with an *exo-exo* configuration in which both BH_3 are directed outside. However, [1,1,1], which has the smallest cavity, gives only a monoborane derivative of the *endo-exo* type shown in Fig. 3.35 (a). Treatment of monoborane derivative (a) with KOH/methanol gives free [1,1,1], but treatment of monoborane derivative (a) and [1,1,1] with protonic acid at room temperature produces a proton cryptate having an *endo-endo* configuration in which one proton is enclosed, as shown in Fig. 3.35 (b). Monoborane derivative (a) converts to a complex of the diammonium salt type (c), in which two protons are enclosed into the cavity, when (a) is hydrolyzed by boiling for 2 hours with 6 N HCl. Complex (b) is obtained by heating (c) with 5 N KOH for 80 hours at 60°C or by passing an aqueous solution of (c) through a column packed with an anion exchange resin of the RNH_4OH type.[229]

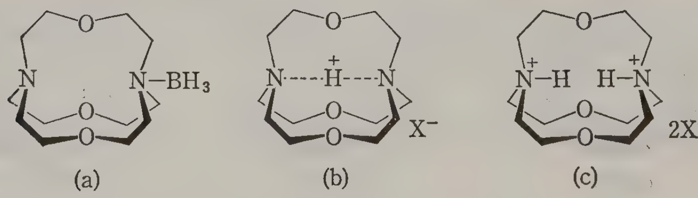


Fig. 3.35 Proton cryptates. (Source: Ref. 229. Reproduced by kind permission of the Chemical Society.)

The crystal structures of the following bicyclic cryptates have been determined so far: [2,1,1; Li^+]SCN^-,[230] [2,2,1; K^+]SCN^-,[222] [2,2,1; Co^{2+}] $[Co(SCN)_4]^{2-}$,[222] [2,2,2; M^+]X^-(MX=NaI,[231,232] KI,[231,233] RbSCN,[234] RbI,[235] CsSCN,[231] CsI,[235] $TlOOCH \cdot H_2O$,[236] AgSCN[236]), [2,2,2; Ca^{2+}] 2 SCN^-,[237] [2,2,2; Ba^{2+}] 2 $SCN^- \cdot H_2O$,[238] [2,2,2; K]$_2$$[Fe(CO)_4]^{2-}$,[239] [2,2,2; Na]$_2$$[Fe(CO)_4]^{2-}$,[239] [3,2,2; Ba^{2+}] 2 $SCN^- \cdot 2\ H_2O$.[238]

Figures 3.36, 3.37, and 3.38 illustrate the crystal structures of free cryptand [2,2,2] and its RbSCN complex, the conformation of the crystal of [2,2,1; Co^{2+}] $[Co(SCN)_4]^{2-}$

complex, and the crystal structure of [3,2,2; Ba^{2+}] 2 $SCN^- \cdot 2 H_2O$ complex, respectively.

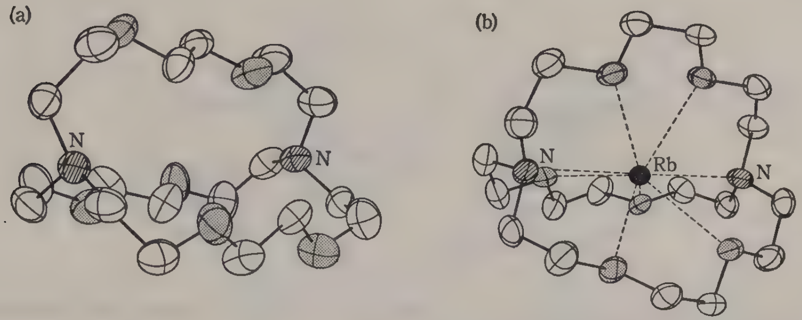


Fig. 3.36 Crystal structures of (a) cryptand [2, 2, 2] and (b) its RbSCN complex. (Source (a): Ref. 9. Reproduced by kind permission of Springer-Verlag. Source (b): Ref. 234. Reproduced by kind permission of the Chemical Society.)

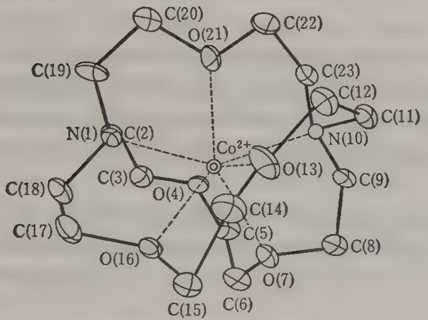


Fig. 3.37 Crystal structure of Co^{2+}-[2, 2, 1] cryptate. (Source: Ref. 219. Reproduced by kind permission of Pergamon.)

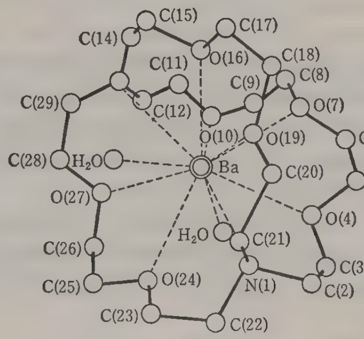


Fig. 3.38 Crystal structure of Ba^{2+}-[3, 2, 2]-2 H_2O cryptate. (Source: Ref. 238. Reproduced by kind permission of the American Chemical Society.)

All of these complexes of bicyclic cryptands are 1 : 1 complexes with an *endo-endo*-type configuration in which both of the bridgehead nitrogen atoms participate in the complexation as donors and the bound cation is located in the center of the cage nearly equidistant from each N and O donor. In a number of alkali metal complexes of cryptand [2,2,2] it was shown that the cavity size expands by the torsion of the polyether chains between N and N with increasing cationic diameter in the order of Na^+, K^+, Rb^+, and Cs^+.234)

The tricyclic cryptand **42** forms 1 : 1 complexes with alkali and alkaline earth metal ions.240) According to ^{13}C-nmr of the complexes of Ca^{2+}, Sr^{2+} Ba^{2+}, and La^{3+}, the cation is enclosed centripetally into one of the rings and the cation migrates to the other ring by heating, as shown in Fig. 3.39. The activation free energy $\Delta G^{\neq}$ of the migration is in the order of $Ca^{2+} > Sr^{2+} > Ba^{2+}$, which is the reverse of the order of the ionic diameter and hydration energy; the values of $\Delta G^{\neq}$ are larger than 19 kcal/mol for all of these cations.[241)]

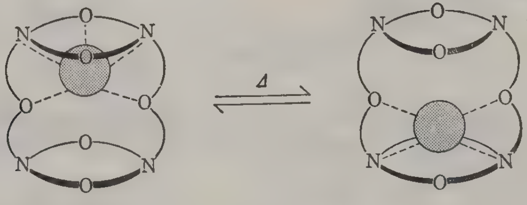


Fig. 3.39 Schematic presentation of the 1:1 complex of tricyclic cryptand **42** with alkaline earth metal ion. (Source: Ref. 241. Reproduced by kind permission of the American Chemical Society.)

A two-step complex formation process has been observed by ^{13}C-nmr and ^{1}H-nmr in the complexation of **42** with Ag^+,[240)] Tl^+,[240)] and Pb^{2+},[242)] and it was thought to involve the formation of an asymmetrical 1 : 1 complex followed by a 1 : 2 complex. However, the composition of the isolated crystalline complex was $C_{24}H_{48}N_4O_6 \cdot 3$ $AgNO_3$, and X-ray analysis demonstrated that the structure of the complex was a chain structure parallel with the [001] direction of the crystal, in which $C_{24}H_{48}N_2O_6$ Ag_2, formed by the binding of an Ag^+ into each of two rings of the tricyclic cryptand, was bonded through an O-bridge of the nitroso group to $AgNO_3$ lying outside the ring, as shown in Fig. 3.40.[243)]

The spherical tricyclic cryptand **43** which has been synthesized recently has a cavity radius of about 1.8Å, and it has been ascertained by ^{1}H-nmr that stable complexes are formed by binding of K^+, Rb^+, Cs^+, NH_4^+, and Ba^{2+} into the sphere.[244)]

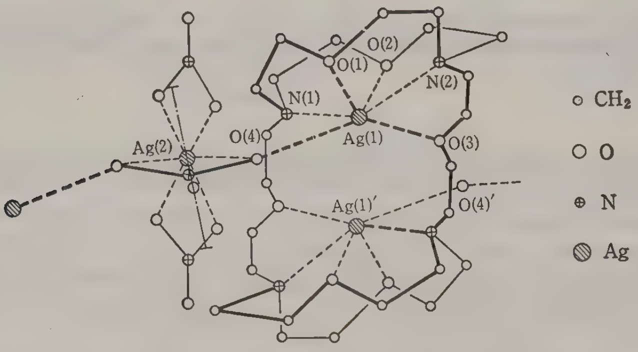


Fig. 3.40 Crystal structure of the complex of tricyclic cryptand **42**-3 $AgNO_3$ (Source: Ref. 243. Reproduced by kind permission of the Chemical Society.)

The conformation of the $[NH_4L]^+I^- \cdot H_2O$ complex, shown in Fig. 3.41, has been confirmed by X-ray analysis.[245)]

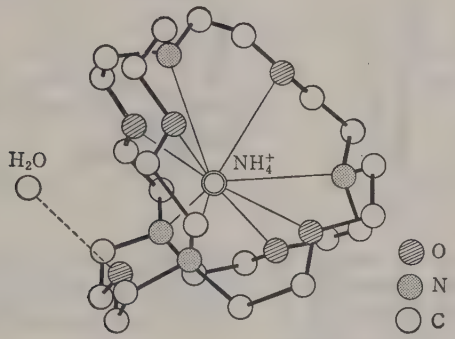


Fig. 3.41 Crystal structure of the complex of spherical tricyclic cryptand **43** with the composition $[NH_4L]^+I^- \cdot H_2O$. (Source: Ref. 245. Reproduced by kind permission of the Chemical Society.)

Special mention must be made of "anion cryptate," formed by the binding of an anion into the cage of the spherical cryptand in which four bridgehead nitrogen atoms are protonated. It has been found that Cl^-, Br^-, and F^- are strongly bound by four quaternary ammonium cations, which are produced by protonation as shown in Fig. 3.42, when HCl, HBr, and HF are added to an aqueous or methanol solution of the spherical cryptand **43**.[246)] The anions with larger onic diameters, such as I^-, and polyatomic anions (NO_3^-, CF_3^-, ClO_4^-, $RCOO^-$) are not bound. The stability constants of these anion cryptates are much larger than those of azabicycloalkane (see Table 3.28), and the selectivity for Cl^- is particularly large. These findings indicate that the structure shown in Fig. 3.42 is stable because of the topology for binding of the anion when it has an appropriate size. In fact, X-ray analysis has confirmed the structure shown in Fig. 3.43 for the Cl^- anion cryptate having the formula $[ClLH_4]^{3+}$ $3\ Cl^- \cdot 7\ H_2O$.

It is thought to be unlikely that the ion pair of a cryptate in solution exists as a contact ion pair because the cation is bound in a cage, but a cryptand-separated ion pair in which the counter anion is separated by the cryptand may be formed. In fact, only a single peak is observed at 373 nm in the absorption spectra of THF solutions of 1 : 1 complexes of [2,2,2] with $(\text{fluorenyl})_2^-$-Ba^{2+} and -Sr^{2+}, which indicates that the ion pair of a cryptate is a separated ion pair.[116)]

Other electrochemical research on cryptates has recently employed polarography and cyclic voltammetry,[247~250)] and it has been reported that the reduction potential of a cryptate is fairly negative against the free cation, that the dissociation of a cryptate occurs during the step of electrochemical reaction, and that the electrochemical reduction of alkaline earth metal cryptates proceeds by way of a bielectron reaction. In ad-

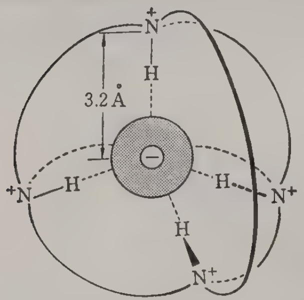


Fig. 3.42 Steric structure of the complex of protonated spherical tricyclic cryptand **43** incorporating an anion. $N^+ \cdots X^-$ distance: $X^- =$ F^-, 2.70 Å; Cl^-, 3.18 Å; Br^-, 3.33 Å; (I^-, 3.57 Å). (Source: Ref. 246. Reproduced by kind permission of the American Chemical Society.)

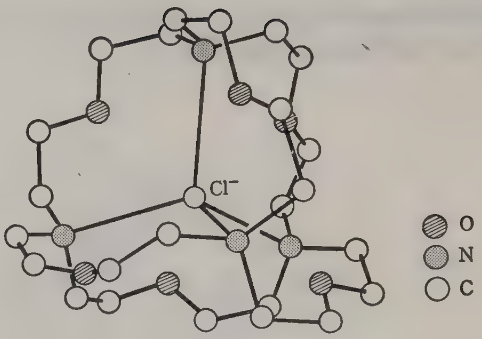


Fig. 3.43 Crystal structure of anion cryptate $[ClLH]^{3+}$ (L: spherical tricyclic cryptand **43**). (Source: Ref. 244. Reproduced by kind permission of the American Chemical Society.)

dition, far infrared spectra of nonaqueous solutions of Li^+ and Na^+ cryptate have been observed, and it was concluded that the ligand-cation interaction of a cryptate was substantially due to an electrostatic force because the broad absorption band was from vibration of the cation present in the cage and because the absorption band was inactive in the Raman spectrum.[251] Information regarding electrostatic interaction was also obtained by electroconductivity measurements of Na^+- and K^+-BPh_4^- cryptates in THF.[252]

B. Thermodynamics and Kinetics of Cryptate Formation

Stability constants (K) for the complexation of cryptands with various kinds of metal ions have been measured as the crown ethers have, and kinetic data such as ΔH, ΔS, ΔG, and K are also being collected.

Values of log K[9,15,148,253] for the complexes of various kinds of cryptands with mono- and divalent metal ions in water and methanol are summarized in Tables 3.22 and 3.23. When these values are compared with the values for log K of crown ethers (Tables 3.8, 3.9), the K values of cryptands are seen to be larger in general, and, in particular, much larger for Li^+, Na^+, alkaline earth metal ions, and Ag^+ in water. These findings suggest that 1) the topological interference by cryptands in the solvation process is particularly important for small alkali and alkaline earth metal ions such as Li^+ and Na^+, which are subject to solvation, because of steric binding of the cation in the cage of the cryptand; 2) for Ag^+, covalent bonds with N donors take part in the complexation.

The values of log K for cryptates correspond approximately to the relationship seen between the cavity diameter of the cryptands (Table 3.21) and the ion diameter of the cations for a series of metals belonging to the same group, but the correspondence is not as close as is observed with crown ethers. In general, K values for alkaline earth metal ions are larger than those for alkali metal ions. A comparison of K^+ and Ba^{2+}, whose ionic diameters are nearly the same, shows that the K for Ba^{2+} is much larger than

TABLE 3.22 Values of log *K* of cryptates (in water, 25° C).[9,15,253]

	log *K*													
Cryptand	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Ag^+	Tl^+	Pb^{2+}	Cd^{2+}	Hg^{2+}
[2, 1, 1]	5.5	3.2	<2.0	<2.0	<2.0	2.5 ± 0.3	2.50	<20	>20	—	—	—	—	—
[2, 2, 1]	2.50	5.40	3.95	2.55	<2.0	<2.0	6.95	7.35	6.30	10.6	—	—	—	—
[2, 2, 2]	<2.0	3.9	5.4	4.35	<2.0	<2.0	4.4	8.0	9.5	9.6	6.3	12.0	6.8	18.2
[3, 2, 2]	<2.0	1.65	2.2	2.05	2.0	<2.0	~2.0	3.4	6.0	—	—	—	—	—
[3, 3, 2]	<2.0	<2.0	<2.0	<0.7	<2.0	<2.0	~2.0	~2.0	3.65	—	—	—	—	—
[3, 3, 3]	<2.0	<2.0	<2.0	<0.5	<2.0	<2.0	2.0	<2.0	—	—	—	—	—	—
[2_B, 2, 2]	—	4.0	4.9	3.4	—	—	3.8	6.9	7.4	—	—	—	—	—
[2_O, 2_O, 2_N]	—	2.5	2.6	2.3	<0.5	—	—	—	—	—	4.8	—	—	—

TABLE 3.23 Values of log *K* of Cryptates (in methanol and in methanol/water, 25° C)[9,148]

Cryptand	Solvent[†1]	log *K*										
		Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Ag^+	Tl^+
[2, 1, 1]	M/W (95/5)	7.58	6.08	2.26	<2.0	<2.0	4.0 ± 0.8	4.34	2.90	<2.0	—	—
	M	>6.0	6.1	2.3	1.9	<2.0	—	—	—	—	—	—
[2, 2, 1]	M/W (95/5)	4.18	8.84	7.45	5.80	(3.90)[†2]	<2.0	9.61	10.65	9.70	—	—
	M	>5.0	>8.0	>7.0	>6.0	(~5.0)[†2]	—	—	—	—	—	—
[2, 2, 2]	M/W (70/30)	—	6.6	>8.0	—	—	—	—	—	—	—	—
	M/W (95/5)	1.8	7.21	9.75	8.40	3.54	<2.0	7.60	11.5	(12)[†3]	—	—
	M	2.6	>8.0	>7.0	>6.0	4.4	—	—	—	—	—	—
[3, 2, 2]	M/W (95/5)	<2.0	4.57	7.0	7.30	7.0	<2.0	4.74	7.06	10.40	—	—
	M	2.3	4.8	>7.0	>6.0	>6.0	—	—	—	—	—	—
[3, 3, 2]	M	—	3.2	6.0	6.15	>6.0	—	—	—	—	—	—
[3, 3, 3]	M	—	2.7	5.4	5.7	5.9	—	—	—	—	—	—
$[2_B, 1, 1]$	M	>7.0	>8.0	4.1	3.2	—	—	—	—	—	—	5.8
$[2_B, 2, 1]$	M	5.0	>8.0	>8.0	6.0	4.5	—	—	—	—	<8.0	<8.0
$[2_B, 2, 2]$	M/W (95/5)	—	7.4	9.05	—	—	—	—	—	11.05	—	—
	M	2.3	>8.0	>9.0	7.0	3.2	—	—	—	—	<8.0	<8.0
$[2_B, 2_B, 2]$	M/W (95/5)	—	7.3	8.60	—	—	—	—	—	8.5	—	—
	M	2.3	6.3	>8.0	4.8	2.8	—	—	—	—	>8.0	7.5
$[2, 2, C_8]$	M/W (70/30)	—	2.2	4.2	—	—	—	—	—	—	—	—
	M/W (95/5)	—	3.0	4.35	—	—	—	—	—	<2.0	—	—
	M	≤2.0	3.5	5.2	3.4	2.7	—	—	—	—	8.0	5.5
$[2_O, 2_O, 2_S]$	M	2.2	6.0	7.0	4.4	2.3	—	—	—	—	9.5	7.5
$[2_O, 2_O, 2_S]$	M	2.3	2.8	2.4	2.0	<2.0	—	—	—	—	8.0	5.2

[†1] M: methanol; W: water; M/W: wt/wt

[†2] There is the possibility here that a 2 = 1 complex (cryptand: cation) may form in which a cation is located outside of two cryptands.

[†3] Large measurement error of ± 0.7.

that for K^+. For ions with smaller diameters, however, the differences in the K values between, for example, Na^+ and Ca^{2+} and between Li^+ and Mg^{2+} are not as great. The low value of K for Mg^{2+}, with a small ionic diameter, is due to a large hydration energy for the divalent ion having a high electron density.

In methanol, which decreases the solvation of cations, K and the cation selectivity are increased markedly compared with those in water.

The cavity size of $[2,2,C_8]$ in which one of the N ··· N bridges is $-(C_8H_{16})-$ is nearly the same as that of [2,2,2], but the K value is much smaller because the number of O donors on $[2,2,C_8]$ is less than that on [2,2,2]. The electrostatic interaction of donor atoms with alkali metal ions which are hard acids are in the order of $O > N > S$; therefore K values for alkali metal ions decrease when N or S is substituted for an O donor in the cryptand.

Figure 3.44 gives plots of log K of [2]- and [3]-cryptates with alkali metal ions in methanol and methanol/water (95/5) vs. the cationic diameter,[254] and log K values of alkaline earth metal cryptates in water[253] are shown in Fig. 3.45 as a function of the cationic diameter. Table 3.24 shows the cation selectivities of cryptands compared to typical crown ethers and ionophore antibiotics.[9]

Enthalpy change ΔH and entropy change ΔS in the complexation reactions of [2,2,1] and [2,2,2] with alkali metal ions and alkaline earth metal ions have been measured,[219,220,254~257] and these data are shown in Table 3.25. Because of the cage-type con-

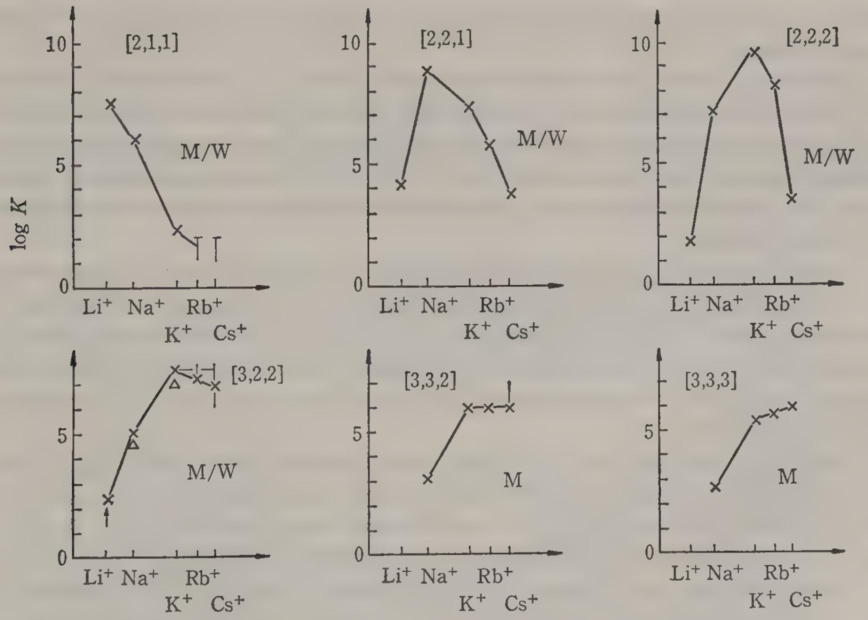


Fig. 3.44 Ionic diameter of alkali metal ions in relation to stability constants of cryptates. M/W: methanol/water (95/5), M: methanol (25°C). (Source: Ref. 253. Reproduced by kind permission of the American Chemical Society.)

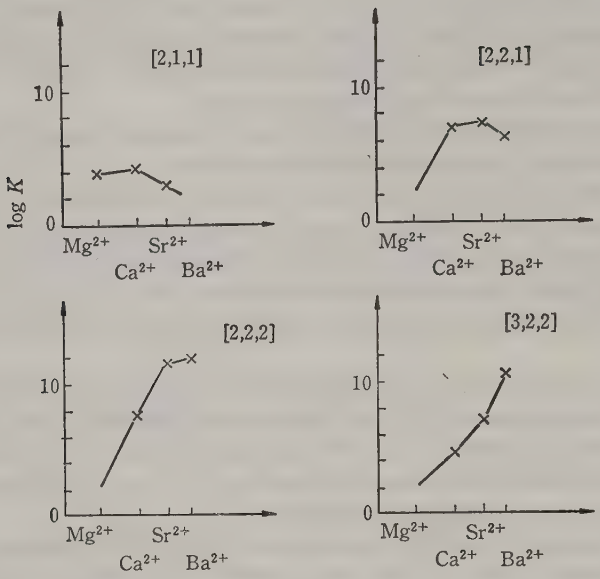


Fig. 3.45 Ionic diameter of alkaline earth metal ions in relation to stability constants of cryptates (in water, 25° C). (Source: Reproduced by kind permission of the American Chemical Society.)

formation, cryptates are stable in enthalpy, and values of ΔH increase with increasing cationic diameter.

Positive ΔS values are observed with alkali metal-[2,2,1] and alkaline earth metal-[2,2,1] and -[2,2,2] cryptates, but negative ΔS values are seen with alkali metal-[2,2,2]. This negative value may be a result of the fact that the inner entropy and perhaps the solvation energy of the ligand are very small; therefore the increased entropy produced by stripping water molecules from the solvated shell of the cations is compensated for by the inner entropy.

Table 3.26 summarizes data on the rates of complex formation reaction k_f, the rates of dissociation k_d, and the values of activation free energy $\Delta G^{\ddagger}$ that have been measured by nmr258) for [2,2,2] cryptates with alkali and alkaline earth metal ions. Recently, values for k_f and k_d of Na^+-[2,1,1] and -[2,2,1], and K^+-[2,2,1] and -[2,2,2], have been measured by the temperature jump relaxation technique.259) These results are shown in Table 3.27.

Rates of complexation k have also been measured for Cs^+-[2,2,2$_B$]172) and for Ca^{2+}-[2,1,1], -[2,2,1], and -2,2,2].256) Other recent experiments have measured k for Na^+-[2,2,2]260,261) and Na^+-[2,2,2$_S$]261) by ^{23}Na-nmr and k for Li^+-[2,1,1], -[2,2,1], and -[2,2,2] in water, pyridine, DMSO, DMF, and $HCONH_2$ by ^{7}Li-nmr.262,263)

Generally speaking, the rates of dissociation for cryptates are smaller than those for crown ether complexes, indicating that cryptates are thermodynamically more stable than crown ether complexes. For the same cryptand, the rate of dissociation for an alkaline earth metal cryptate is smaller than that for an alkali metal cryptate.

Cryptate is dissociated when a protonic acid is added to a solution of cryptate

TABLE 3.24 Selectivities in the complexation of crown ethers, cryptands, and ionophore antibiotics with alkali and alkaline earth metal ions.9) [†1]

	Solvent[†2]	Selectivity							
		Na^+/Li^+	K^+/Na^+	K^+/Rb^+	Rb^+/Cs^+	Sr^{2+}/Cr^{2+}	Ba^{2+}/Sa^{2+}	Ba^{2+}/K^+	Ti^+/K^+
Dicyclohexyl-18-crown-6 (isomer A)	W	12	3	5	2	—	2.5	25	—
Dibenzo-30-crown-10	M	—	80	25[†3]	—	—	—	—	—
	M	—	400	—	—	—	—	—	—
N, N-Methyldiamino-18-crown-6	M	—	40	10	—	—	—	—	—
	M/W (95/5)	—	13	—	—	—	—	200	—
Cryptand [2, 1, 1]	W	1/320	1/6	—	—	—	—	—	—
	M	1/>25	1/6,300	2.5	—	—	—	—	—
Cryptand [2, 2, 1]	W	800	1/32	22	>3	2.5	1/11	250	—
Cryptand [2, 2, 2]	W	>80	32	11	>220	4,000	32	12,500	8
	M/W (95/5)	20,000[†4]	320	1,000[†1]	—	—	—	110	—
Cryptand [2_B, 2, 2]	W	—	8	32	—	1,260	3	315	—
	M/W (95/5)	100,000[†4]	47	—	—	—	—	100	~1[†4]
Cryptand [2_B, 2_B, 2]	M	10,000	>50	>1,600	100	—	—	—	>1/3
	M/W (95/5)	—	20	—	—	—	—	1	—
Cryptand [2, 2, C_8]	M	20	50	63	5	—	—	—	2
	M/W (95/5)	—	22	—	—	—	—	1/>220	—
Cryptand [2_O, 2_O, 2_N]	W	—	1	2	<60	—	—	—	150
Nonactin	M	—	16	1	4	—	—	1/80	—
Enniatin B	E	—	3	1	2	—	—	1	1/2
Valinomycin	M	—	17,000	1/2	7	—	—	1/36	1/15
Antamanid	E	—	1/11	—	—	—	—	—	—

[†1] Calculated from each K value.
[†2] W: water; M: methanol; E: ethanol; M/W: wt/wt
[†3] K^+/Cs^+
[†4] Estimated from the values in methanol.

TABLE 3.25 Values of ΔH and ΔS in complexation reaction of cryptands (in water, 25° C).16,254,256)

Cryptand	Cation	ΔH (kcal/mol)	ΔS (cal/mol·deg)
[2, 1, 1]	Li^+	−4.6	+1
	Na^+	−4.7	−4
	Ca^{2+}	0	+13
		+5.1†	+32†
[2, 2, 1]	Li^+	+0.4	+13
	Na^+	−3.2	+14
		−4.7	+8
	K^+	−5.9	−2
	Rb^+	−3.2	+1
	Ca^{2+}	−1.7	+26
		−2.7	+23
		−7.1†	+7
	Ba^{2+}	−5.1	+12
	Sr^{2+}	−5.0	+17
[2, 2, 2]	Na^+	−5.8	−2
	K^+	−11.1	−13
	Rb^+	−10.5	−15
	Ca^{2+}	−0.15	+20
		−0.7†	+18†
	Ba^{2+}	−12.9	0
	Sr^{2+}	−8.1	9
[3, 2, 2]	K^+	−6.2	−11
	Rb^+	−5.4	−9
	Cs^+	−6.5	−14

†Calculated from kinetic data. Others were calculated from the results of potentiometric titration or calorimetric titration.16,254)

because one or two of the bridgehead N are protonated and converted quaternary ammonium cations.

The following values have been obtained for log *K* of the complexes of tricyclic cryptand **42**: 1 ~ 1.7 for the cryptates with alkali and alkaline earth metal ions in water; Na^+ 4.5, K^+ 4.8, Rb^+ 6.2, and $Cs^+ > 6.0$ in methanol; 6.0 in water and > 9.5 in methanol for a 1 : 1 complex with Ag^+.240) Values for *k* and ΔG have also been reported for the complexes with alkaline earth metal ions.241)

The approximate values of log *K* for the complexes of spherical cryptand **43** in water at 25°C are 3.4 for K^+, 4.2 for Rb^+, and 3.4 for Cs^+.244) This is the highest value reported for Cs^+ cryptates so far. The rates of dissociation of the complexes of the spherical cryptand have the smallest values among the known cryptands, and values of $\Delta G^{\neq}$ are 15.5 for K^+ (28° C), 16.7 for Rb^+ (51°C), and 16.1 for Cs^+ (41°C). These values reflect the effect of topology.

The ^{13}C-nmr technique has been used to measure the log *K* in water and water/methanol of Cl^- and Br^- "anion cryptates" (Fig. 3.42), formed by protonation of the spherical cryptand.246) Table 3.28 compares these values with those of anion cryptates obtained by protonation of analogue **150**,246) bicyclic cryptand **151**,244) and diazabicycloalkane $N[(CH_2)_{10}]_3N$ **152**.224)

As can be seen in Table 3.28, the Cl^- anion cryptates of the spherical cryptands

TABLE 3.26 Kinetic data from complexation reactions of cryptands (I).[9,258)]

Complex	Method	Solvent†	Temp. (°C)	k_f ($M^{-1}sec^{-1}$)	k_d(sec^{-1})	ΔG (kcal/mol)	
						Complexation	Dissociation
[2, 2, 2], NaCl	^{1}H-nmr	W	3	2×10^5	27	8.9	14.2
[2, 2, 2], NF	^{1}H-nmr	W	36	7.5×10^6	38	8.6	15.8
[2, 2, 2], KCl	^{1}H-nmr	W	36	7.5×10^6	38	8.6	15.8
[2, 2, 2], KBr	^{1}H-nmr	W	35	8×10^6	42	8.5	15.7
[2, 2, 2], RbCl	^{1}H-nmr	W	9	7.5×10^5	38	8.5	14.4
[2, 2, 2], TlCl	^{1}H-nmr	W	40	2.5×10^8	60		15.7
[2, ,2, 2], $TlNO_3$	^{1}H-nmr	W	−6	2×10^8	51	4.5	13.5
[2, 2, 2], $CaCl_2$	Potentiometric titration	W	25	$\geq 10^3$	~0.1	≤13	19
[2, ,2, 2], $SrCl_2$	Potentiometric titration	W	25	6×10^3	10^{-4}	12	23
[2, ,2, 2], $BaCl_2$	Potentiometric titration	W	25	3×10^4	10^{-5}	11	24
Nonactin, Na^+	T-jump relaxation	M	25	$\sim 2 \times 10^3$	4×10^4	6.1	11.2
Valinomycin, Na^+	T-jump relaxation	M	25	7×10^6	5×10^5	8.2	9.7
Valinomycin, K^+	T-jump relaxation	M	25	3.5×10^7	1.2×10^3	7.1	13.2

†W: water, M: methanol

TABLE 3.27 Kinetic data from complexation reactions of Cryptands (II).[259)]†

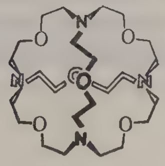
Complex	log K	k_f ($M^{-1}sec^{-1}$)	k_d(sec^{-1})
[2, 1, 1], Na^+	3.2	$(9 \pm 1) \times 10^4$	$(1.4 \pm 0.1) \times 10^2$
[2, 1, 1], Na^+	5.40	$(6 \pm 2) \times 10^6$	18 ± 2
[2, 2, 1], K^+	3.95	$(3 \pm 1) \times 10^7$	$(2 \pm 1) \times 10^3$
[2, 2, 2], K^+	5.4	$(2 \pm 1) \times 10^6$	9 ± 3

†Method: T-jump relaxation; solvent: water

TABLE 3.28 Stability constants of anion cryptates.[246)]

Anion	Solvent†¹	log K			
		43–H_4^{4+}	150–H_4^{4+}	151–H_4^{4+}	152–H_2^{2+}
Cl^-	W	>4.0	>4.5	1.7 ± 0.1	(~0.7)†²,³
Cl^-	M/W	—	—	3.1 ± 0.1	2.1 ± 0.1
Br^-	W	<1.0	1.55 ± 0.1	<1.0	<1.0†³
Br^-	M/W	1.75 ± 0.2	3.2 ± 0.1	1.7 ± 0.2	$\sim 1.2 \pm 0.3$

†¹W: water, ph 1.50 (HNO_3); M/W: methanol/water (9/1), pH 1.30 (NHO_3), 22°C.
†²Estimated from the value in M/W and the value for **151-H_4^{4+}**.
†³In 50% CF_3 COOH, log K > 1.0 at 23°C.



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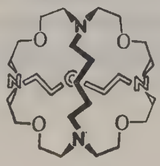

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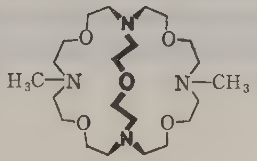

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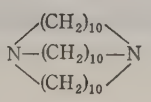


$N\overset{(CH_2)_{10}}{\underset{(CH_2)_{10}}{-(CH_2)_{10}-}}N$

152

43 and **150**, with four quaternary ammonium cations, are very stable, the values of log *K* are more than 10^3 times that of $H\overset{+}{N}[(CH_2)_{10}]_3\overset{+}{N}H$, which had been the highest log *K* for a complex with Cl^- among the cryptates known before the preparation of **43** and **150**. Furthermore, the Cl^- to Br^- ratio of selectivity exceeds 1000, which is much larger than the ratio for the other two protonated cryptands. These findings reflect the marked effect in the tricyclic spherical cryptands of topology, by which a cation is shielded with the aid of rigid molecular chains. It is not yet clear why the stability for Cl^- and Br^- cryptates of **150**, which has one N ··· N bridge consisting of $-(CH_2)_5-$, is higher than that of **43** cryptates, in which all of the bridges consist of ether chains. The explanation may lie in the mutual repulsion between the negatively charged O atoms in the chain and the anion. If so, the anion cryptate may have higher stability because quaternary ammonium cations are substituted for O.

We may say with confidence that the new field of anion cryptate chemistry will experience significant growth in the future.

C. Solubilization of Alkali Metals in Organic Solvents; Salts Containing Alkali Metal Anions

Like crown ethers, cryptands can be used for oganic syntheses with inorganic salts because the cryptates formed by the binding of the cation moiety of inorganic salts is soluble even in low-polar organic solvents.

That alkali metals are solubilized in amines, THF, glymes, benzene, and toluene with the aid of dicyclohexyl-18-crown-6 or 18-crown-6 was mentioned previously in Section 3.2.4. Cryptands also facilitate the solubilization of alkali metals in many kinds of organic solvents. Table 3.29 lists the combinations of solvent (amine or ether) and crown ether or cryptand by which alkali metals are solubilized.[22)]

Dye *et al.* found that K dissolves in diethyl ether in the presence of cryptand [2,2,2] to give a dark blue solution which is stable for a long time at –80° C and for 10 ~ 30 min at room temperature, and they observed the esr and nir spectra.[200)] A singlet with a high intensity of about 10^{-4} M based on the solvated electron, e^-_{solv}, was seen in the esr of the solution, while a weak singlet of about $10^{-6} \sim 10^{-7}$ M was found in the esr of the solution of K formed with dicyclohexyl-18-crown-6. In the nir spectrum, the absorption of both e^-_{solv} and K^- was observed with [2,2,2], while only the absorption band of K^- was observed at 0.8 ~ 1.0 μm with crown ether. The presence of [2,2,2] also induces the solubilization of K in diisopropyl ether, dipopryl ether, and diethylamine.

It was found that Ba was also dissolved in ethylenediamine by [2,2,2] to give a blue solution, but the spectra could not be observed because of the instability of the solution and the high melting point of the solvent. When [2,2,2] was added to the ethylenediamine solution of Na, the intensity of the esr signal increased and a strong absorption band of e^-_{solv} was observed in the vicinity of 1.3 μm in addition to the absorption of Na^- in the nir spectrum.

Dye *et al.* also found that the solubilities of Na and K in the primary mono- and diamines, the secondary amines, and the ethers shown in Table 3.29 and in HMPA increased markedly on addition of [2,2,2].[194)] For example, in the presence of [2,2,2] it was possible to obtain a solution of Na in ethylamine with a concentration as high as 10^{-1} M, which was about 400,000 times that possible without the cryptand. As shown in

Table 3.29 Combinations of solvent and crown ether or cryptand in which an alkali metal is solubilized or the solubility of and alkali metal is increased.[22]

Solvent	Crown ether, Cryptand$\dagger^1$	Alkali metal
Methylamine	DC–18–CR–6, 18–CR–6, [2, 2, 2]	Na, K, Rb, Cs
Ethylamine	DC–18–CR–6, 18–CR–6, [2, 2, 2]	Na, K, Rb, Cs
Diglyme	DC–18–CR–6	K
THF	18–CR–6	Na, K
THF	[2, 2, 2]	Na, K, Rb, Cs
THF	DC–18–CR–6	K, Cs
Diethyl ether	18–CR–6	K
Diethyl ether	[2, 2, 2]	Na$\dagger^2$, K
Diethyl ether	DC–18–CR–6	K, Cs
Dimethoxy ethane	[2, 2, 2]	K
1,2-Propane diamine	DC–18–CR–6	K
Diethylamine	[2, 2, 2]	K
Diisopropyl ether	[2, 2, 2]	K
Dipropyl ether	[2, 2, 2]	K

$\dagger^1$DC–18–CR–6: dicyclohexyl-18-crown-6; 18–CR–6; 18 crown 6; [2, 2, 2]: cryptand [2, 2, 2].
$\dagger^2$Formed a pale blue solution which demonstrated low solubility.

Fig. 3.46, the presence of e^-_{solv} as well as M^- anion can be observed with the nir spectrum in almost all of the solutions of alkali metals formed with the aid of cryptands.

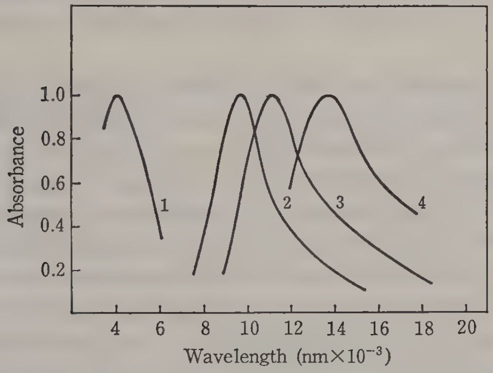


Fig. 3.46 Absorption spectra of THF solutions of alkali metals in the presence of cryptand at 25°C. (Source: Ref. 194. Reproduced by kind permission of the American Chemical Society.)

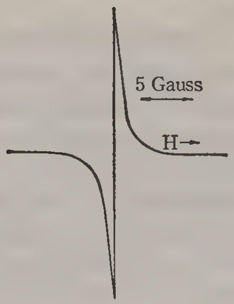


Fig. 3.47 The esr spectrum of K/cryptand [2, 2, 2]/toluene solution (−70°C). (Source: Ref. 203. Reproduced by kind permission of Verlag Chemie.)

The solubilities of Rb and Cs in THF and THP have also been found to increase in the presence of cryptands.[22,219,220]

Lehn *et al.* found that [2,2,2] facilitates the solubilization of Na and K in nonpolar hydrocarbon solvents.[202,203] When a solution of about 15 mg of [2,2,2] dissolved in 10 ml of benzene was put in contact with thin K film, K dissolved gradually to form a dark blue solution. Similarly, K is dissolved in toluene, and Na, which is not solubilized by dicyclohexyl-18-crown-6 (see Section 3.2.4), is dissolved in benzene and toluene by [2,2,2].

The esr spectrum of a K or Na/cryptand/benzene or toluene solution consists of a single signal with a high intensity, as shown in Fig. 3.47 and the coupling with M^+ is not observed, while the hfs is observed in the esr spectrum of K/crown/benzene or toluene solution, as shown in Fig. 3.28. In the uv spectrùm of a K/cryptand/benzene solution, the absorption maximum is observed at 435 nm; with a K/crown/benzene solution, absorption maxima are found at 300 and 435 nm, similar to the absorption of benzene radical anion[264)] in DME at –70° C.

These findings suggest that the radical anion of aromatic hydrocarbon $A^{\overline{\cdot}}$ is formed when the cryptand transfers the electron in the outer shell of the alkali metal to the lowest vacant orbital of the aromatic hydrocarbon. However, $A^{\overline{\cdot}}$ forms a free ion or a weak ion pair because of the weak interaction between M^+ and $A^{\overline{\cdot}}$ when M^+ is shielded by the bulky cage of the cryptand, so that the electron transfers quickly and the hfs disappears from the esr.

When a polynuclear aromatic hydrocarbon such as biphenyl, naphtalene, and anthracene is added to a K/cryptand/toluene solution, the uv spectrum becomes the same as that of the radical anion of the polynuclear aromatic hydrocarbon, reflecting the transfer of the excess electron of toluene radical anion to the polynuclear aromatic hydrocarbon. However, the esr still consists of a single signal, though the intensity increases, and there is no hfs, which indicates the interference of cryptand in the formation of the ion pair between M^+ and the polynuclear aromatic hydrocarbon radical anion.

During the 1970s, researchers identified the chemical species present in liquid ammonia, amine, and ether solutions of alkali metals. In ammonia, which is a good solvent, M^+ is readily stabilized by the interaction between M^- and the polar molecule of ammonia, and only e^-_{solv} remains as a chemical species with a negative charge. In dilute amine and ether solutions, however, the characteristic absorption of each alkali metal (except Li) is seen, in addition to the absorption maxima of e^-_{solv}, as shown in Fig. 3.48. Matalon *et al.* pointed out in 1969 that the characteristic absorptions were due to M^- anions.[265)] Since then, research on the stoichiometry and kinetics of the chemical species in the alkali metal solutions has made rapid progress by the application of paramagnetism, electroconductivity, Faraday effects, flush photolysis and so on.

The equilibria shown in Eqs. (3.20) ~ (3.22) are thought to occur in these solutions, and the process shown in Eq. (3.23) apparently also takes place in the presence of crown ether or cryptand. In some cases the equilibrium is preferentially represented by

$$M_{(S)} \overset{K_1}{\rightleftharpoons} M^+ + e_{\text{solv}} \tag{3.20}$$

$$\mathrm{M}^+ + \mathrm{e}_{\text{solv}} \overset{K_2}{\rightleftharpoons} \mathrm{M} \tag{3.21}$$

$$M^+ + 2\,\mathrm{e}_{\text{solv}} \overset{K_3}{\rightleftharpoons} \mathrm{M}^- \tag{3.22}$$

$$\mathrm{M}^+ + \mathrm{C} \overset{K_4}{\rightleftharpoons} \mathrm{MC}^+ \tag{3.23}$$

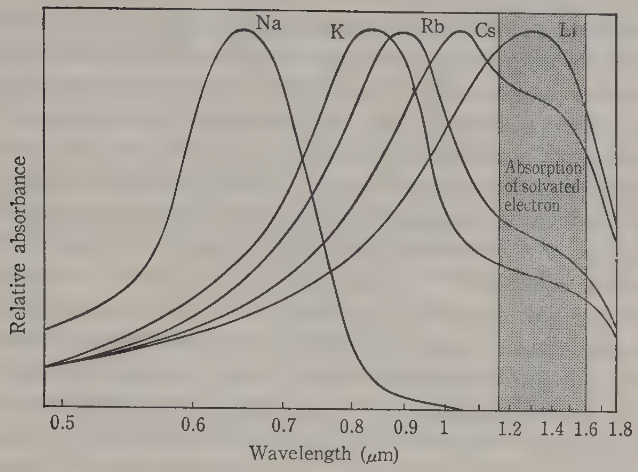


Fig. 3.48 Absorption spectra of ethylenediamine solutions of alkali metals. Absorption near 1.4 μm is observed in each case and has been assigned to the solvated electron e^-_{solv}. The second peak at a shorter wave length has been assigned recently to alkali metal anion M^-. In the case of Li, Li^- is considered not to be present because only the peak assigned to e^-_{solv} is observed. In the case of Na, only Na is formed.

Eq. (3.24), which summarizes Eqs. (3.20) ~ (3.22); then the equilibrium constant K_5 is equal to $K_1^2K_3$.

$$2\,M_{(S)} \xrightleftharpoons{K_5} M^+ + M^- \tag{3.24}$$

Dye *et al.* calculated the concentration of each ion species in a saturated methylamine solution of Na in the presence of 0.1 M dicyclohexyl-18-crown-6 and cryptand [2, 2, 2] by using the values of the equilibrium constants K_3, K_4 and K_5 estimated from solubilities, absorption spectra, and electroconductivities.[22] The results are shown in Table 3.30. The results demonstrate that, in the presence of crown ether or cryptands (C), highly concentrated M^- solutions are obtained which are nearly equal to the concentration of MC^+, and that the amount of e^-_{solv} remaining in the solution is small in the

TABLE 3.30 Concentration of ion species in saturated solutions of metallic sodium in methylamine and THF in the presence of crown ether or cryptand at 0° C.[22]

Solvent	Crown ether, cryptand (0.1 M)	Concentration of ion species (M) (calculated)				
		M^-	e^-	M^+	M^+C	C
Methylamine	—	10^{-4}	3×10^{-6}	10^{-4}	—	—
Methylamine	[2, 2, 2]	0.097	3.1×10^{-3}	10^{-7}	0.10	10^{-4}
Methylamine	18–CR–6	0.089	2.8×10^{-3}	1.1×10^{-7}	0.092	8.2×10^{-3}
THF	[2, 2, 2]	0.050	0.016	2×10^{-11}	0.066	0.34
THF	18- CR 6	0.008	0.008	1×10^{-10}	0.01	0.09

presence of a large excess of Na. When equimolar amounts of M atoms and crown ether or cryptand are present in the solution, MC^+ cation is formed by the binding of M into the crown ether or cryptand, and the anion species consists mainly of e^-_{solv} because no M remains to form M^-. Thus for the first time, the use of crown ethers and cryptands has made it possible to vary the amount of each species in the solution by regulating the relative amounts of M and C. In particular, the greater solubilizing ability of cryptands has provided new areas of study in the chemistry of alkali metal solution and in applications to organic syntheses and anionic polymerizations.

Recently, Dye *et al.* succeeded in isolating a crystal of $NaC^+ \cdot Na^-$ from a Na/[2, 2, 2]/ethylamine solution.[266,267] This was the first time a crystal containing M^- anion had been isolated. A golden, crystalline solid was precipitated when a 0.4 mol/*l* Na solution in ethylamine, prepared by adding the stoichiometric amount of [2, 2, 2] to form Na_2C, was chilled to the temperature of dry ice; the thin, hexagonal, single crystal was obtained by proceeding slowly with the chilling. The precipitate or crystal had a metallic gloss and a color varying reversibly from the initial gold to bronze in a temperature range between —190° C and 40° C; it decomposed at 83° C just after the color turned to dark brown. Washed with hexane or ethyl ether, the crystal is stable for several days *in vacuo* at room temperature, but it decomposes on contact with air, water, or proton donors.

Despite its metallic appearance, behavior analogous to semi-conductors is observed in the change of the relative resistance ρ of the crystal with temperature (0° C: $\sim 5 \times 10^{12}\ \Omega \cdot cm$; 60° C: $7 \times 10^{9}\ \Omega \cdot cm$) and in the electroconductivity characteristics. However, the plot of log ρ versus 1/T becomes a straight line with a low slope in the region of higher temperatures.

X-ray analysis demonstrated the crystal structure shown in Fig. 3.49. The conformation in which Na^+ is enclosed by the cage of the cryptand resembles that of the cryptate shown in Fig. 3.36(b), and the alternate layering of cryptate and Na^- can be observed. The effective size of Na^- and the position of Na^- in the crystal lattice closely approximate those of I^- in the NaI crystal, so that $NaC^+ \cdot Na^-$ is a salt which may be called "sodium sodiumate." One of the reasons why the crystal has a metallic gloss even though its structure is different from metals, which have free electrons, is that the crystal structure has the same size crystal face as a metal. Ceraso and Dye have measured the ^{23}Na-nmr of a solution of $NaC^+ \cdot Na^-$.[268]

Similar compounds containing metal anions have also been prepared from K, Rb, and Cs, but the structures have not yet been determined exactly because of the instability of the compounds. The half-life for the decomposition of the Na salt is several days *in vacuo* at room temperature, while that of the corresponding K salt is less than 1 second. It has been reported, however, that the K salt seems to be stable for a long period at —40° C.[197,267]

Because the formation of a solid salt has been achieved with NaC^+ and Na^-, it is thought that a solid referred to as an "extended metal" in which free electrons move in the layer of the complex may be obtained with NaC^+ and e^-_{solv}. Attempts to prepare this solid have been unsuccessful so far, but a deep blue film residue showing a strong esr signal has been produced by the rapid evaporation of a Na solution in methylamine prepared with dibenzo-18-crown-6, dicyclohexyl-18-crown-6, and cryptand.[267] In the

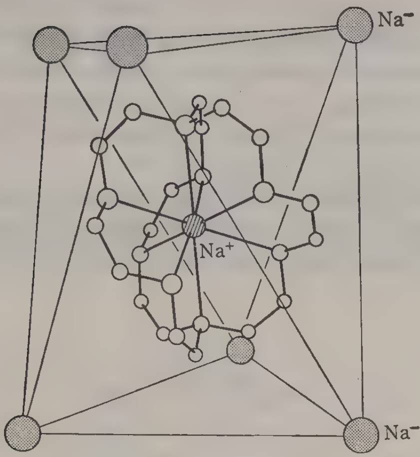


Fig. 3.49 Crystal structure of $NaC^+ \cdot Na^-$(C: cryptand [2, 2, 2]). (Source: Ref. 267. Reproduced by kind permission of the American Chemical Society.)

film, it is likely that the electrons are restricted to the vicinity of M^+. If so, the film is quite different from a metal, but it is the first example of what may be called an "electronated salt."

The field of chemistry concerned with alkali metal solutions and their applications certainly holds great promise of further interesting development. For example, the use of crown ethers and cryptands may permit the preparation of salts which combine a metal cation with the anion of a different kind of metal, such as $KC^+ \cdot Na^-$, and the preparation of salts consisting of 2 or 3 metal anions and one complex cation of a di- or trivalent metal such as alkaline earth metal and lanthanide.

An early report described solutions of alloys of post-transition metals, including Sn, Pb, As, Sb, Bi, Se, and Te, with Na in liquid ammonia that appeared in characteristic colors such as green for Pb-Na alloy and reddish brown for Sb-Na alloy.[269] The report noted that the so-called Zintl anions, which are homopolyatomic anions such as Pb_9^{4-}, Pb_7^{4-}, Sn_9^{4-}, Sb_7^{3-}, Bi_7^{3-}, and Bi_5^{3-}, were formed in the solutions as the counter-anions of Na^+. Corbett *et al.* observed that Zintl anions such as Sn_9^{4-}, Pb_5^{2-}, and Sn_5^{2-} formed on the addition of cryptand [2, 2, 2] to these solution systems.[270,271) Recently, they were able to isolate for the first time a crystal with the composition $(NaC)_3{}^+Sb_7{}^{3-}$ from the solution system of Sb–Na alloy, and they determined the crystal structure by X-ray analysis.[272)

3.3.3 Characteristics of Cyclic Polyamines

It is well known that cyclic amines, unlike crown ethers, form complexes with ions of transition metals and heavy metals, which are classified as "soft" acids, because the donors of cyclic amines are N atoms, which belong to the "soft" bases. Among the cyclic amines, significant advances have been made in the biochemistry and biophysics of porphyrins, including heme (porphyrin-Fe(II) complex) and chlorophyll (chlorin-Mg (II) complex), which are crown compounds in a broad sense. Researchers have synthesized the metal complexes and determined the complex structure, and the results of studies of reactions with nitrogen, oxygen, and so on related to metabolism have been applied to various model systems. Recent progress in porphyrin research has been reviewed by Yoshida and Ogoshi[273)] and Ogoshi.[11,12)]

Cyclic polyamines (azacrown compounds) form complexes with Ni(II), Ni(I), Cu (II), Cu(I), Co(III), Co(II), Fe(III), Fe(II), Pt(II), Pd(II), Mg(II), Mn(II), etc.,[16)] and many of these complexes have the structure shown in Fig. 3.50: the center metal is coordinated by the surrounding N atoms located on almost the same plane and the anions are located on the axis normal to the plane. Typical examples of the results obtained from X-ray analysis of structure are shown in Figs. 3.51 and 3.52. Triamine, with a 9-membered ring and a small cavity size, forms complexes with Cu(II), Sn(II), and Ni(II) in which each metal ion is located outside the ring.[13)]

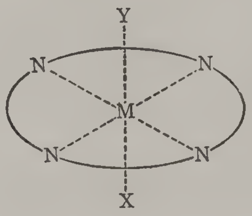
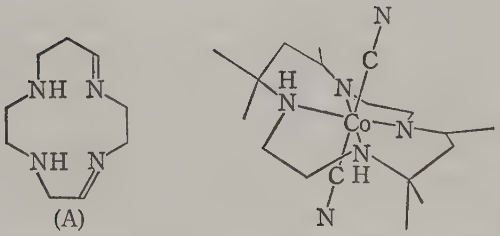


Fig. 3.50



(A)

Fig. 3.51 Crystal structure of Co^{2+} complex of cyclic polyamine (A).[14)]

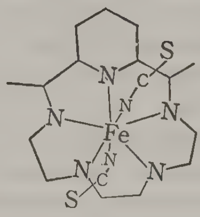
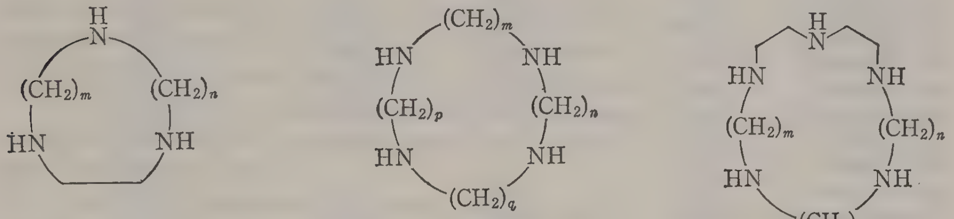


Fig. 3.52 Crystal structure of Fe^{3+} complex of cyclic polyamine **77a** ($m = n = 2$).[14)]

As we have seen, many of the cyclic polyamines are prepared by using metal ions as templates, and the complexes formed in these reactions are usually stable so that free cyclic polyamine is rarely produced by dissociation of the complexes, illustrating the large stability constants of cyclic amines in general. In some cases free cyclic polyamines are liberated by treatment with NaCN, as shown in Eq. (2.17), indicating that the stability constants of Ni(II)-cyclic polyamines are smaller than that of $Ni(CN)_4^{2-}$($\log K = 30.1$).

$$Ni(L)^{2+} + 4\,CN^- \longrightarrow Ni(CN)_4^{2-} + L \tag{3.25}$$

A recent review by Kimura *et al.* describes the mechanisms by which metal ions are bound into typical cyclic tri-, tetra-, and pentamines,[13)] shown in Fig. 3.53. Table 3.31 lists the log K, ΔH, and ΔS of these cyclic polyamines and the corresponding open-chain polyamines.



triamine
153

tetraamine
154

pentamine
155

cyclic
$m = n = 2$: [9]aneN_3
$m = 2, n = 3$:[10]aneN_3
$m = n = 3$: [11]aneN_3
linear
$m = 2, n = 0$: dien

cyclic
$m = n = q = p = 2$: [12]aneN_4
$m = n = q = 2, p = 3$:[13]aneN_4
$m = q = 2, n = p = 3$:[14]aneN_4
$m = n = q = 3, p = 2$: [15]aneN_4
$m = n = q = p = 3$: [16]aneN_4
linear
$m = n = q = 2, p = 0$: trien
$m = q = 2, n = 3, p = 0$: 2, 3, 2-tet
$m = q = 3, n = 2, p = 0$: 3, 2, 3-tet
$m = n = q = 3, p = 0$: 3, 3, 3-tet

cyclic
$m = n = p = 2$: [15] aneN_5
$m = n = 2, p = 3$:[16]aneN_5
$m = n = 3, p = 2$: [17]aneN_5
linear
$m = n = q = 2, p = 0$: tetren

Fig. 3.53 Basic skeletons and abbrevations of cyclic and linear *tri-*, *tetra-*, and pentamines.

The stability constants K for Zn(II) and Ni(II) complexes of the cyclic triamine [9] aneN_3 are 10^3 and 10^5 times, respectively, those of the complexes of corresponding open-chain diens, while K for the Cu(II) complex is nearly same as that of the dien. Both *mer-* and *fac-* type coordination are possible in the Cu(II)-dien complex, as shown in Fig. 3.54, and the former is more stable,[274)] but the planar coordination of the *mer*-type is impossible for the cyclic polyamine complex, so it is forced to assume the unstable *fac*-type coordination. Moreover, the cyclic structure produces a large intramolecular "non-bonding" repulsion. Consequently, the force of Cu–N bonding weakens so that ΔH becomes disadvantageous. In contrast, ΔS is more advantageous for cyclic polyamines in which the loss of freedom by coordination is less than that of the open-chain polyamines. Thus it is thought that cyclization does not change the K for Cu(II) because ΔS

TABLE 3.31 Values of log K, ΔH, and ΔS of polyamine complexes.13)

Complex	log K	$-\Delta H$ (kcal/mol)	ΔS (e. u.)	Ionic strength (M)
Cu^{II}-[9]aneN$_3$	16.2 (15.5)	13.0	30.5	0.2 (0.1)
Zn^{II}-[9]aneN$_3$	11.4 (11.6)	7.0	29	0.2 (0.1)
Ni^{II}-[9]aneN$_3$	16.2			0.1
Cu^{II}-dien	16.0	18	12	0.1
Zn^{II}-dien	8.9	6.5	18.5	0.1
Ni^{II}-dien	10.7	11.9	8.5	0.1
Cu^{II}-[12]aneN$_4$	24.8	18.3	51.4	0.2
Zn^{II}-[12]aneN$_4$	16.2	7.9	47	0.2
Cd^{II}-[12]aneN$_4$	14.3	8.2	38	0.2
Hg^{II}-[12]aneN$_4$	25.5	23.6	37.7	0.2
Pb^{II}-[12]aneN$_4$	15.9	6.6	51	0.2
Cu^{II}-[13]aneN$_4$	29.1	29.2	33.7	0.2
Zn^{II}-[13]aneN$_4$	15.6	7.8	45	0.2
Hg^{II}-[13]aneN$_4$	25.3	24.7	33.7	0.2
Cu^{II}-[14]aneN$_4$	27.2	30.4	22.4	0.2
Zn^{II}-[14]aneN$_4$	15.5	7.6	46	0.2
Ni^{II}-[14]aneN$_4$	22.7	31	2	0.1
Hg^{II}-[14]aneN	23.0	32.9	−4.9	0.2
Cu^{II}-[15]andN	24.4	26.5	22.7	0.2
Zn^{II}-[15]andN	15.0	8.2	41	0.2
Hg^{II}-[15]aneN	23.7	24.7	25.5	0.2
Cu^{II}-trien	20.2	21.6	19.5	0.1
Zn^{II}-trien	12.1	8.9	25.0	0.1
Ni^{II}-trien	13.8	14.0	16.0	0.1
Cd^{II}-trien	10.4	9.2	19.0	0.1
Hg^{II}-trien	24.5	30.2	10.8	0.2
Pb^{II}-trien	10.3	8.3	19.5	0.2
Cu^{II}-2, 3, 2-tet	23.9	27.7	16.5	0.5
Zn^{II}-2, 3, 2-tet	12.8	11.9	18.8	0.5
Ni^{II}-2, 3, 2-tet	15.8	19.4	7.2	0.1
Cd^{II}-2, 3, 2-tet	12.0	12.8	12.0	0.2
Hg^{II}-2, 3, 2-tet	22.1	27.4	9.1	0.2
Pb^{II}-2, 3, 2-tet	7.8	7.3	11	0.2
Cu^{II}-3, 2, 3-tet	21.8	25.9	13.1	0.5
Zn^{II}-3, 2, 3-tet	11.3	10.6	15.9	0.5
Cu^{II}-3, 3, 3-tet	17.3	19.5	12.8	0.1
Zn^{II}-3, 3, 3-tet	9.3	7.4	18.0	0.1
Cu^{II}-[15]aneN$_5$	28.3	32.9	21.5	0.2
Hg^{II}-[15]aneN$_5$	28.5	32.7	20.4	0.2
Cu^{II}-[16]aneN$_5$	27.1	32.7	14.3	0.2
Cu^{II}-[17]aneN$_5$	23.8	27.2	17.7	0.2
Cu^{II}-tetren	22.8	25.0	20.5	0.1
Hg^{II}-tetren	24.8	33.4	1.3	0.2

compensates for ΔH. Similarly, ΔS is advantageous for the cyclic polyamines of Zn(II) complexes, and ΔH is not so disadvantageous, but the large cyclic effect may be a product of the weak force of Zn-N bonding and the fact that strictly planar coordination is not required in the Zn(II) complex.

Among the tetramines having 12- ∼ 15-membered rings, the most stable com-

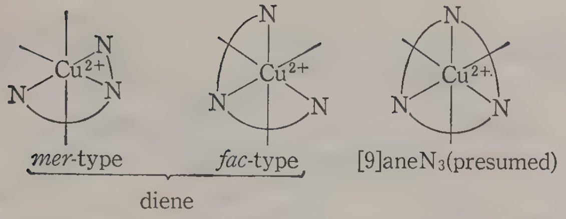


Fig. 3.54 Configurations of Cu^{2+} complexes of diene (linear triamine) and [9] $aneN_4$ (cyclic triamine).[13] (Source: Ref. 13. Reproduced by kind permission of the Society of Organic Synthetic Chemistry, Japan.)

plexes are formed between the 13-membered one and Cu(II) and between the 12-membered one and Zn(II), Hg(II), Cd(II), and Pb(II). In general, the *K* values of cyclic tetramines are much larger than those of corresponding open-chain tetramines. The principal reason for this is thought to be the contribution of entropy.

Cyclic polyamines are usually present in the protonated form, and the equilibrium constants of the successive protonation of 3 ~ 5 N have been measured for cyclic tri-, tetra-, and pentamines.[13]

The kinetic aspects of the complexation reactions of cyclic polyamines have also been measured.[13] The reaction rates of the complexation of cyclic polyamines are lower than those of open-chain polyamines, while the stabilities of the complexes decrease with cyclization of the ligands, as mentioned earlier. This results in the markedly slow rates of dissociation of the complexes. Busch *et al.* hypothesized that these phenomena could be explained by the "rigid" conformation produced by the inflexibility resulting from cyclization of the ligand, so that the usual stepwise dissociation of the complexes occurred only very slowly, and they named the effect the MJF Effect (Multiple Juxtapositional Fixedness Effect).[275]

3.3.4 Characteristics of Cyclic Polythiaethers

Like cyclic polyamines, cyclic polythiaethers form complexes with the ions of transition metals and heavy metals, which are classified as "soft" acids, because they carry S donors, which are "soft" bases. A number of investigators have reported on their work with thiacrown compounds having 4 ~ 8 S donors, which are the analogues of crown ethers. Complexes with Ni(II),[276~282] Co(III),[281] Rh(III),[283] Pd(II),[279] Hg (II),[284] Cu(II),[284~287] and Nb(V)[287~289] have been obtained and their structures determined.

X-ray analyses of the crystal structures of 12- ~ 18-thiacrown-4 ~ -6, which correspond to cyclic tetramer, pentamer, and hexamer of ethylene sulfide, indicate that all of the S donor atoms are located on the same plane situated outside of the ring, as shown in Fig. 3.55.[290]

In the case of 1, 4, 8, 11-tetrathiacyclotetradecane (ttp) which has a 14-membered ring with 4 S donors, an *endo*-type conformation (**27**) was observed for $[Ni(ttp)](BF_4)_2$[291] and $[Cu(ttp)](Cl_4)_2$,[292] while an *exo*-type conformation (**156**) was found for $[Cl_5Nb)_2(ttp)]$[287~289] and $[(Cl_2Hg)_2(ttp)]$.[284] Figure 3.56 illustrates the crystal structure of the $[(Cl_2Hg)_2 (ttp)]$ complex.

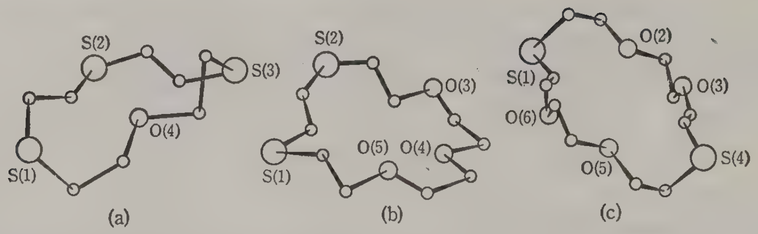
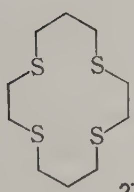


Fig. 3.55 Crystal structure of (a) 1, 4, 7-trithio-(12-crown-4), (b) 1,4-dithio-(15-crown-5), and (c) 1, 10-dithio-(18-crown-6). (Source: Ref. 290. Reproduced by kind permission of the Chemical Society.)



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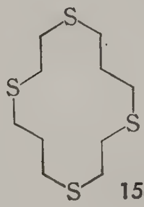

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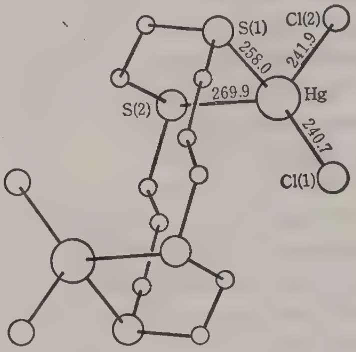
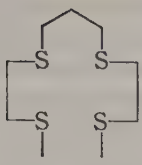


Fig. 3.56 Crystal structure of [$(Cl_2Hg)_2$(ttp)] complex. (Source: Ref. 284. Reproduced by kind permission of the Chemical Society.)

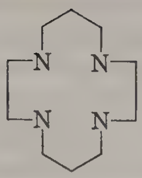
The stability constant K of the ttp-Ni(II) complex in nitromethane is only 180 times that of the complex of the corresponding open-chain thioether (ttt, **157**). In contrast, the ratio of the K value of the $Ni(FB_4)_2$ complex of cyclam (**25**), with N donors, to the corresponding open-chain tetramine 2, 3, 3-tet (**158**) is as large as $10^{6.4}$, illustrating the notably small macrocyclic effects of thioethers compared to polyamines.[293] Both the entropy of the steric configuration and the solvation of the ligand through the hydrogen bond are thought to contribute to the macrocyclic effect.

Cyclic polythiaethers are preferentially used for investigation of the macrocyclic effect because it is not necessary to account for the effect of protonation observed with cyclic polyamines. The influence of the ring size on the stability constants K, on the rates of the complexation reactions k_f, and on the rates of dissociation k_d has been investigated in the Cu(II) complexes of a series of cyclic tetrathiaethers having 12- ~ 18-membered rings (**159** ~ **163**) and in open-chain thioether (**164**) in methanol at 25° C.[294] The results are shown in Table 3.32. A tendency similar to that seen with cyclic tetramines was observed as follows: the maximum K value was found with the 14-membered ring, and the value decreased with increasing ring size. Approximately the same k_f values were observed in 13- ~ 16-membered rings, and in consequence, K was



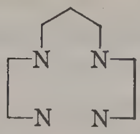
ttt

157



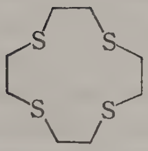
cyclam

25



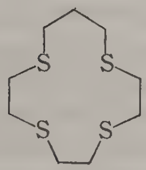
2,3,2-tet

158



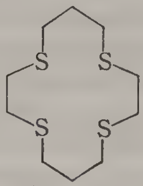
12-*ane*-S_4

159



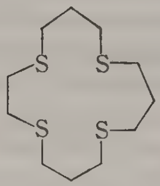
13-*ane*-S_4

160



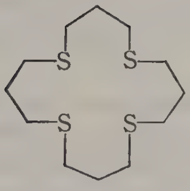
14-*ane*-S_4
(ttp)

27



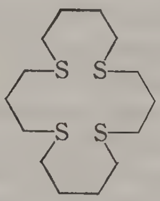
15-*ane*-S_4

161



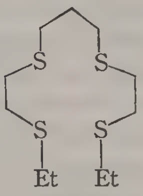
16-*ane*-S_4

162



18-*ane*-S_4

163



Et_2-ttu

164

TABLE 3.32 Values of stability constant (K), rate of complexation (k_f), and rate of dissociation (k_d) of Cu (II) complexes of cyclic tetrathiaethers (in 80% methanol, at 25° C, $\mu = 0.10$ M ($HClO_4$)).[294)]

Ligand		Method	$k_f(M^{-1}sec^{-1})$	$k_d(sec^{-1})$	K (kinetic)	K (equil)
12-ane-S_4	159	SF	1.2×10^3	4.4	2.7×10^2	3.3×10^2
13-ane-S_4	160	SF	1.4×10^4	51	2.7×10^2	—
14-ane-S_4	27	SF, TJ	2.8×10^4	9	3.1×10^3	3.0×10^3
15-ane-S_4	161	TJ	4.3×10^4	1.9×10^2	2.3×10^2	—
16-ane-S_4	162	TJ	2.9×10^4	3.2×10^3	9	11
18-ane-S_4	163		—†2	—†2	—	<10
Et_2-ttμ	164	TJ	4.1×10^5	3.0×10^4	14	13

†1SF: stopped flow method; TJ: T-jump method.
†2Could not measure because the complex is not stable.

governed by k_d, which increased about one order of magnitude with increasing ring size or with ring opening.

The complexes of cyclic polythiaether with Cu(II) have been called the models of so-called "blue" copper proteins.[295,296)] Copper protein, which is an important metal-containing enzyme for living organisms analogous to iron protein, participates in electron transfer, oxygen transport, and oxidation-reduction catalysis in cell respiration and metabolism. The three states of Cu contained in copper proteins are described as blue copper (II), non-blue copper(II), and esr non-detective copper. The blue copper proteins (plastocyanin, stellacyanin, laccase, ceruloplasmin, etc.) have such characteristics as a strong absorption near 600 nm, an abnormally high oxidation-reduction potential ($+0.2 \sim 0.8$ V) of Cu(II)/Cu(I), a very small hyperfine coupling constant ($0.003 \sim 0.09$ cm^{-1}) of Cu(II) in comparison with usual Cu(II) complexes; in addition, other elements rarely substituted for the Cu. An understanding of the active site of Cu and its structure in blue copper protein is essential for the elucidation of catalytic action, and investigators have examined these aspects[297)] and have used Cu(II) complexes of cyclic polythiaethers as models for biological reactions.[285,286,292)] Rorabacher *et al.* found that the strong absorption band near 600 nm observed in the spectra of Cu(II) complexes of 12- $\sim$ 21-membered cyclic polythiaethers having $3 \sim 6$ S donors was independent of the ring size, the number of S donors, and the steric structure of the coordination, but the absorption band was assigned to the CT (charge transfer) band from S to Cu(II). Furthermore, they reported that the oxidation-reduction potentials of these complexes were as high as $+0.67 \sim 0.86$ V. They concluded that their findings suggested the possibility of the coordination of the S of thioether in methionine residue to the Cu in blue copper protein.[286)] The Cu(II) complexes of open-chain Et_2-ttu (**164**) and of ttu both have SH end groups and also have high oxidation-reduction potentials, perhaps reflecting an effect by the SH group similar to that of thioether S.

The investigations on blue copper protein have employed the aid of the model complexes, and it has been shown that the blue copper is located in the coordination atmosphere of slightly distorted tetrahedrons which are formed by the coordination of the SH group of cysteine and the N of histidine imidazole. Cyclic polythiaethers are expected to provide a powerful tool for a better understanding of copper proteins as well as the structure and function of iron-sulfur proteins.

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CHAPTER 4

Applications of Crown Compounds

4.1 GENERAL ASPECTS

The creation of a new substance or the discovery of an unknown phenomenon in pure science immediately leads to a search for applications followed by development and use of the innovative product or process. Scientists throughout the world have focused considerable attention on a number of new substances called crown compounds since it was discovered that their specific characteristics may play a significant role at the interface between synthetic chemistry and life science, and many researchers have been investigating possible applications in various fields in the past few years.

Applications of crown compounds are classified according to the functions derived from their specific characteristics, as follows:

1) Applications of the capacity for selective capture, separation, and transport of cations. These include the following:
   a) Separation or concentration of alkali or alkaline earth metal ions such as Na^+–K^+ and Ca^{2+}–Sr^{2+}.
   b) Capture, recovery, removal, separation, concentration, or purification of noble or heavy metals such as Ag^+, Cd^{2+}, Hg^{2+}, and Pb^{2+}.
   c) Separation of lanthanides.
   d) Separation of isotopes.
   e) Metal assays.
   f) Ion-selective electrodes.
   g) Ion-transport membranes including liquid membranes.
   h) Applications to biochemistry and biophysics as synthetic ionophores.
   i) Applications of physiological activities to agrochemicals and drugs.
   j) Investigation of organic reaction mechanisms using masking of cations.
   k) Optical resolution using optically active crown compounds.
   l) Transition metal complex catalysts, mainly using azacrown compounds.
   m) Investigation of biochemical reactions and biophysics using azacrown or thiacrown compounds as models.
2) Applications of the capacity for solubilization of inorganic salts or alkali metals in organic solvents and for the activation of anions. A remarkably wide range of research fields utilizing these functions has already been developed, including inorganic chemistry, metallurgy, atomic energy, various kinds of organic syntheses,

polymer syntheses, analysis, environmental chemistry, biochemistry, biophysics, agrochemicals, medicines, optical resolution, and so on. Some examples of the applications are:

a) Inorganic syntheses, such as the synthesis of metal carbonyl derivatives.
b) Experiments in non-aqueous electrochemistry.
c) Use in organic syntheses such as oxidation, reduction, neutralization, saponification, nucleophilic substitution, elimination, and condensation; of particular importance is the use in homogeneous organic reactions using inorganic salts, organic syntheses under mild conditions utilizing active "naked" anions, and reactions with liquid-liquid or solid-liquid phase transfer catalysts.
d) Investigation of the mechanism or kinetics of organic reactions.

TABLE 4.1 Applications of Crown Ethers

Application Field	Utilized Function†	Examples of Applications
①Inorganic chemistry	D	Research on chemistry of alkali metal solutions.
②Inorganic syntheses	B, C	Syntheses of complexes; syntheses of metal carbonyls.
③Inorganic chemical industry	A	Purification, condensation, separation, recovery and removal of salt.
④Metallugy and metal industry	A	Purification, condensation, separation and recovery of rare metals, noble metals and heavy metals.
⑤Atomic energy industry	A	Recovery, condensation and purification of U and Th; separation of isotopes.
⑥Electrochemistry	A	Ion transport; non-aqueous electrolysis.
⑦Organic chemistry	A, B, C, D	Studies on reaction mechanisms and kinetics.
⑧Organic syntheses	B, C, D	Organic syntheses, particularly phase transfer catalysis and organic syntheses using inorganic salts.
⑨Stereochemistry	A, B, C	Optical resolution; asymmetric reaction.
⑩Polymer syntheses	C, D	Anionic polymerization using solubilized alkali metal.
⑪Analytical chemistry	A, B, C	Ion-selective electrode; polarography; metal assay; non-aqueous titration; esterification (HLC, GCL).
⑫Environmental chemistry	A	Capture and removal of harmful metal ion; metal ion assay.
⑬Biochemistry and biophysics	A	Ionophore models.
⑭Drugs and agrochemicals	A	Removal of harmful metal ions; supply of essential metal ions.

†Function: A, Selective capture, separation and transport of cation.
B, Solubilization of inorganic salt.
C, Activation of anion.
D, Solubilization of alkali metal.

e) Analytical chemistry.
f) Anionic polymerization utilizing the solubilization of alkali metals.
g) Investigation of the chemistry of alkali metal solutions.

At present, application research has made more progress with crown ethers than with other crown compounds, and some of the processes have been commercialized already. Table 4.1 summarizes the applications of crown ethers, including potential areas in which commercialization is expected.

This chapter discusses the applications of crown compounds, mainly crown ethers, in each field. Chapter 5 describes separately the epoch-making use of optically active crown compounds for optical resolution (1k), and Chapter 6 covers the polymerization or immobilization of crown compounds and the applications which are expected to be developed for practical use in various fields in the near future.

The following reviews describe the applications of crown compounds, mainly of crown ethers and cryptands:

1) General[1~4]
2) Separation of ions[5~7]
3) Ion-transport[8~10]
4) Biophysics[11]
5) Physiological activities[12,13]
6) Organic synthesis[14~26]
7) Analytical chemistry[27~31]

4.2 APPLICATIONS TO SYNTHETIC CHEMISTRY

4.2.1 Principles of Application to Organic Synthesis: Non-aqueous Homogeneous Reactions and Phase Transfer Catalysis

Among the many fields in which crown compounds have found application, organic synthesis is the area in which the most progress has been made. The reactions employing crown ethers or cryptands include various kinds of unit reactions such as neutralization, saponification, esterifiction, oxidation, reduction, nucleophilic substitution (halogenation—particularly fluorination, alkoxylation, cyanation, nitration, etc.), elimination (including carbene and nitrene formation, decarboxylation, etc.), condensation (alkylation, arylation, benzoin condensation, Darzen reactions, etc.), rearrangements (Cope rearrangements, Wagner-Meerwein rearrangements, Smiles rearrangements, Claisen rearrangements, etc.), Wittig reactions, Cannizzaro reactions, Michael additions, metalation, and anionic polymerization.

Crown compounds are useful for these organic reactions because of two specific characteristics they demonstrate in the complexation with cations: 1) solubilization of inorganic salts or alkali metals even in nonpolar solvents; 2) when inorganic salts are solubilized, the counter anion is present in the solution as an active, naked anion which is not solvated. As described in Section 3.2.4, on the mechanism of solubilization, the activated state of the naked anion is as high as the energy supplied by the stabilization which results from complexation because the anion is not solvated or is only slightly solvated in nonpolar or low-polar solvents; thus the electron-donating ability of the anion is increased, that is, the nucleophilicity and basicity of the anion are increased. In addition, because the naked anion is less bulky, it can attack the sterically hindered reaction site which the usual, solvated anion rarely contacts.

Many kinds of anions are activated during complexation of the counter cation and solubilization of the salt. In general, the degree of activation increases with decreasing ionic radius and polarization of the anion. A typical example is the fluorine-substitution reaction, which can be carried out with KF in the presence of crown ether even though KF does not act as a nucleophile in the ordinary way because F^- is strongly solvated.

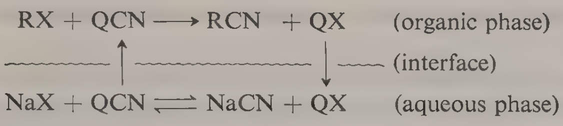
Needless to say, the degree of activation varies with the type of crown compound and the solvent. Although dipolar solvents, which stabilize the transition state in ionic reactions, are generally considered to be more effective for activation, there is no simple rule because activation is also affected by the structure and behavior of the ion pair in solution, as described in Section 3.2.2.B. As a matter of fact, while many reactions have been reported to proceed at room temperature using a dipolar aprotic solvent like acetonitrile, there are others known to proceed at room temperature even in a nonpolar solvent like benzene.

When obtaining an active naked anion by the solubilization of an inorganic salt, the counter cation may be chosen mainly on the basis of the binding ability of the crown compound to be used, that is, in terms of the stability constants mentioned in Section 3.2.3.A. Most of the reactions reported so far for applications of crown compounds to organic syntheses have used 18-crown-6 or dicyclohexyl-18-crown-6 and K salt because the crown ethers are more soluble in organic solvents and the ion size of K^+ matches nicely the cavities of 18-crown ethers. However, there are also reports of other counter cations which are more effective depending on the kind of crown compound or solvent. For example, Na salts are extracted and transported more effectively from an aqueous phase to an organic phase than K salts by octachlorodibenzo-18-crown-6, while K salts are more effectively processed by dibenzo-18-crown-6;[32)] Na^+ is more selectively coordinated by 18-crown-6 in THF than K^+.[33)]

Examples of each reaction are shown in Sections 4.2.2 ∼ 4.2.15. The specific advantages in using crown compounds are: 1) cheap inorganic salts can be used as reagents in organic syntheses; 2) non-aqueous homogeneous reactions can be achieved by solubilizing inorganic salts or alkali metals in nonpolar or low-polar solvents; 3) reactions can proceed under such mild reaction conditions as room temperature and atmospheric pressure because of the activity of the naked anions formed during the solubilization of the inorganic salts; 4) reactions with sterically hindered substrates can be carried out because the naked anion is not very bulky.

In addition to homogeneous liquid phase reactions which employ one or more equivalents of a high molecular weight crown ether to an inorganic salt, catalytic amounts of crown compounds may be used in phase transfer catalysis. This further advantage has markedly promoted the development of application research on crown compounds for organic syntheses. Of particular interest is the capacity of crown compounds to act as phase transfer catalysts not only in the usual liquid-liquid catalysis between an aqueous solution of an inorganic salt and an organic phase, but also in solid-liquid catalysis between a solid inorganic salt and an organic phase containing a catalytic amount of crown compound. Such solid-liquid phase transfer catalysis in which it is not necessary to use an aqueous solution of the inorganic salt is a specific mode of reaction which can be performed with crown compounds but not with well-known phase transfer catalysts such as quaternary ammonium salts and phosphonium salts.

Phase transfer catalysis using quaternary ammonium or phosphonium salts (QX)[23~26,34)] was first described by Starks[35,36)] in 1971, that is, shortly after the discovery of crown ethers. A typical example of such catalysis is the following. Cyanation barely proceeds when two liquid phases of NaCN aqueous solution and haloalkane (RX) are heated and stirred, but the reaction moves rapidly on the addition of small amounts of QX. The reaction can be pictured with the following scheme.



At first, most of the QX catalyst is present in the aqueous phase, and QCN is formed by the exchange of counter anions in the aqueous phase or at the interface, then the substitution reaction between QCN and RX proceeds in the organic phase. The resulting QX which is formed again contacts the aqueous phase, and these steps are repeated. Thus, the role of the onium ion (Q^+) is to form an ion pair with the CN^- of the substrate, to solubilize the ion pair in the organic phase, and to transfer the formed halogen ion (X^-) to the aqueous phase. In the overall reaction, the rate-determining step is the substitution reaction in the organic phase.

In phase transfer catalysis using QX, hydrophilic X^- and CN^- ions can be transferred to a low-polar organic phase as ion pairs with Q^+ by the aid of the lipophilicity of Q^+, and since the anion is then more active than in aqueous solution, the reaction which barely proceeds under usual conditions progresses smoothly.

Liquid-liquid phase transfer catalysis using crown ether or cryptand (L) instead of QX follows the same reaction scheme. Q^+ is replaced by LM^+ (LNa^+ in the example), which represents the cation part of the complex of ligand L, that is, a crown ether or cryptand with metal ion M^+.

In contrast to this liquid-liquid catalysis, solid-liquid phase transfer catalysis is a particular technique that skillfully utilizes the ability of a crown compound in an organic solvent to dissolve normally insoluble, solid inorganic salt in the solvent by the formation of a complex. The reaction scheme of solid-liquid phase transfer catalysis is shown in Fig. 4.1.

As solid-liquid phase transfer catalysis proceeds under absolutely anhydrous conditions, it is possible to apply the process to compounds which are hydrolized or which react with water such as benzyl halides and silane compounds. This absence of any waste water is a distinct advantage for a commercial process. Moreover, after-treatment of the reaction mixture is very simple in solid-liquid phase transfer catalysis; it may be distilled directly, or, to remove the salt product, unreacted salt, and crown compound, it may be passed through a column packed with silica or alumina gel and then distilled. By contrast, in liquid-liquid phase transfer catalysis, the after-treatment occasionally poses problems because of the difficulty in achieving complete separation of the phases. Fur-

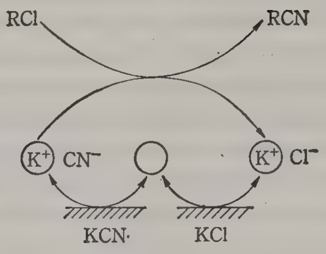


Fig. 4.1 Mechanism of solid-liquid phase transfer catalysis.

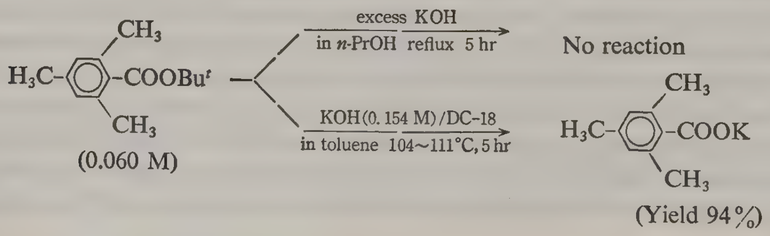
thermore, quaternary ammonium salts cannot be used in reactions that employ strong bases as reactants because the onium salts are often decomposed by the Hofman elimination reaction.

On the other hand, the disadvantages of crown compounds are that they are still more expensive than QX at the present time and that some kinds are toxic (see Chapter 7). For these reasons, the application of crown compounds to organic syntheses is still in the experimental stage, except for a few practical uses such as in the synthesis of natural products, expensive chemicals, and radioactively labeled compounds. However, it may be anticipated that commercial applications of crown compounds will be developed in the ftuure for chemical processes that will conserve resources and energy and be nonpolluting. This will come about when crown compounds become available which are low in price and toxicity and easy to handle and recover, such as the immobilized crown compounds described in Chapter 6.

Let us now turn to a more specific discussion of applications of crown compounds to synthetic chemistry, taking each type of reaction in turn.

4.2.2 Neutralization and Saponification

The first two examples of such applications employ the characteristics of crown ethers reported by Pedersen.37) The first is neutralization titration in a nonpolar solvent using a benzene or toluene solution of KOH solubilized by dicyclohexyl-18-crown-6; this is an example of a homogeneous reaction utilizing the solubilization of an inorganic salt. The second is shown in Eq. (4.1). Although sterically hindered 2, 4, 6-trimethylbenzoic acid ester cannot be saponified under conventional conditions, it can be saponified by using the dicyclohexyl-18-crown-6 complex with KOH in toluene or benzene.



(4.1)

This reaction demonstrates that naked OH^- is not only in a highly activated state with increased basicity but is also able to contact and attack the sterically hindered ester group easily because it is not solvated and therefore is less bulky.

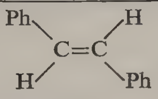
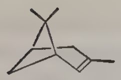
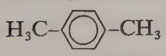
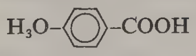
These two reactions that skillfully exploit the characteristics of crown ethers were the original applications of crown compounds to organic syntheses.

4.2.3 Oxidation

A. Oxidation with Reagents

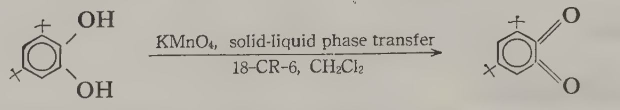
A strong oxidizing reagent, $KMnO_4$, which is insoluble in almost all kinds of organic solvents, becomes soluble even in nonpolar solvents such as benzene in the presence of crown ethers, as shown previously in Table 3.17. The reddish purple solution of $KMnO_4$ in benzene thus obtained is called "purple benzene," and it has a very strong oxidizing ability because of the naked MnO_4^- in the solution. For example, Sam and Simmons reported that the oxidation of olefin or alcohol proceeds immediately at room temperature upon addition to purple benzene, and carboxylic acid is formed in almost theoretical yield[38] (Table 4.2). In the reactions shown in Table 4.2, equimolar amounts of crown ether and $KMnO_4$ were used, but Sam and Simmons also tried solid-liquid phase transfer catalysis using catalytic amounts of crown ether. The reaction was carried out with 2.4 g (6 mmol) of dicyclohexyl-18-crown-6 for 1.0 *l* of benzene, 12.2 g (68 mmol) of *trans*-stilbene, and 28.6 g (181 mmol) of $KMnO_4$. A ball mill reactor was used in the reaction because the surface of the solid $KMnO_4$ became covered with MnO_2 when a conventional reactor with stirrer was used, and 16.0 g of benzoic acid (97% yield) was obtained after 2 hours of reaction time.

TABLE 4.2 Oxidation with "purple benzene"[38]†

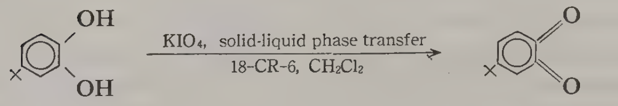
Substrate	Oxidation product	Yield(%)
	PhCOOH	100
	$HOOC(CH_2)_4COOH$	100
		90
$CH_3(CH_2)_5CHO$	$CH_2(CH_5)_3COOH$	70
$PhCH_2OH$	PhCOOH	100
$PhCH_2Ph$	PhCOPh	100
$PhCH_3$	PhCOOH	78
		100

†[Dicyclohexyl-18-Crown-6]/[$KMnO_4$] = 1, in benzene,

Recently Pannell and McIntosh performed solid-liquid phase transfer catalytic oxidation of *trans*-stilbene (3.87 g, 21.5 mmol) with $NaMnO_4$ (11.4 g, 58 mmol) instead of $KMnO_4$, 18-crown-6 (0.5 g, 1.9 mmol), and benzene (1 *l*) as a solvent, again using a ball mill reactor, and they obtained benzoic acid (2.9 g) in 56% yield after 3.5 hours.[39] Mack and Durst carried out solid-liquid phase transfer catalysis using $KMnO_4$ or KIO_4 and observed the stoichiometric formation of *o*-quinones from substituted catechols in methylene chloride (Eqs. 4.2, 4.3).[40]



(Yield 100%) (4.2)



(Yield 95%) (4.3)

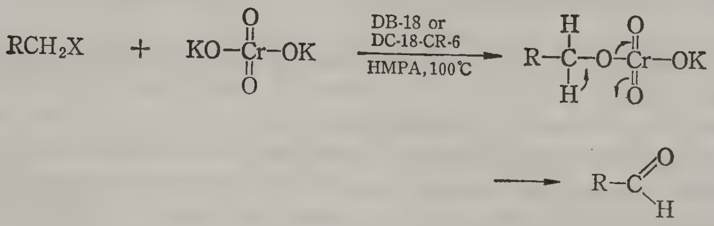
Oxidation with $KMnO_4$ by means of liquid-liquid phase transfer catalysis using catalytic amounts of crown ether was first reported by Landini *et al.*[41] Dicyclohexyl-18-crown-6 (0.05 equivalent of $KMnO_4$) was added to a benzene solution of 1-octene and a saturated aqueous solution of $KMnO_4$, and the mixture was stirred; the reaction proceeded exothermically and heptanoic acid was obtained in 80% yield after 45 minutes (Eq. 4.4).

$$CH_3(CH_2)_5CH = CH_2 \xrightarrow[\text{DC-18-CR-6, benzene}]{KMnO_4 \text{ solid-liquid phase transfer}} CH_3(CH_2)_5COOH \quad (4.4)$$

(Yield 80%)

Landini *et al.* showed that crown ethers act effectively as liquid-liquid phase transfer catalysts not only in oxidation with $KMnO_4$ but also in various other reactions such as nucleophilic substitution, alkylation, and reduction with $NaBH_4$[41] (details are given in the sections that discuss these reactions).

Cardillo *et al.* reported the preparation of aldelydes from alkyl halides in one step by using crown ether to dissolve $K_2Cr_2O_7$, which is insoluble in organic solvents, in HMPA (Eq. 4.5).[42]



$$RCH_2X + KO-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{Cr}}-OK \xrightarrow[\text{HMPA, 100℃}]{\text{DB-18 or DC-18-CR-6}} R-\overset{H}{\underset{H}{C}}-O-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{Cr}}-OK \longrightarrow R-C\overset{O}{\underset{H}{\lessdot}} \quad (4.5)$$

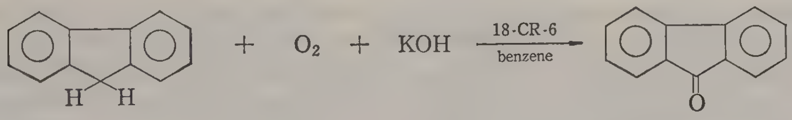
The results are summarized in Table 4.3. Compared to the conventional two-step method, which involves the conversion of halide to alcohol and then to aldehyde and which gives a low yield of aldehyde, this novel one-step synthesis of aldehyde in high yields is expected to provide a favorable method for the synthesis of fine chemicals, such as geranyl aldehyde and farnesal, though the use of $K_2Cr_2O_7$ and HMPA is disadvantageous for commercial applications.

Table 4.3 One-step synthesis of aldehydes from alkyl halides with $K_2Cr_2O_7$-crown ether/HMPA (100° C).[42)]

Alkyl halide	Reaction time (hr)	Yield of aldehyde (%)
Dimethylallyl-Br	2	78
Geranyl	2	82
Farnesyl	2	80
Benzyl-Cl	2	80
Octyl-Br	6	20

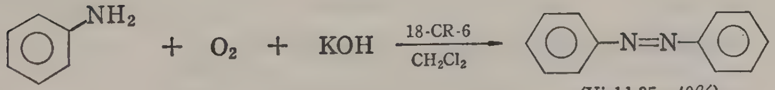
B. Oxidation with Oxygen and Singlet Oxygen

Durst has found that 18-crown-6 effectively catalyzes the air oxidation of fluorene to fluorenone in the presence of KOH (Eq. 4.6).[43)] Oxidative condensation of aniline proceeds in a similar way to give azobenzene (Eq. 4.7).[44)]



(4.6)

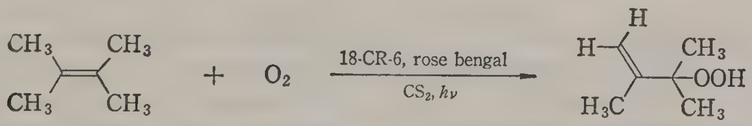
(Yield 95~100%)



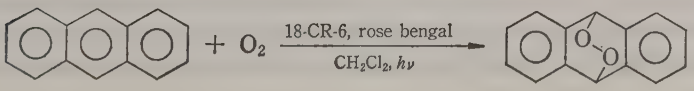
(4.7)

(Yield 35~40%)

Boden showed that the K salt of rose bengal, which is a highly effective sensitizer in photosensitized oxidation, becomes soluble even in nonpolar solvents in the presence of 18-crown-6, and described the photoaddition of singlet oxygen to tetramethylethylene and anthracene under mild conditions in CS_2 or methylene chloride (Eqs. 4.8, 4.9).[45)] It is advantageous that the singlet oxygen $^1O^2$ generated in an aprotic solvent like CS_2 has a longer life span than that in a protic solvent like methanol, which is commonly used in photosensitized oxidation.



(4.8)



(4.9)

C. Oxidation with Superoxide Anion

Superoxide anion O_2^-, one electron-reduced form of oxygen, has been detected on the surface of various heterogeneous oxidation catalysts and has been noted as the active species of biochemical oxidation accelerated by oxygenase or oxidase. These enzymes, containing metals such as Cu, Zn, Mn, and Fe, are known to disproportionate O_2^- to give molecular oxygen and hydrogen peroxide,[46] and it is necessary to understand the reaction mechanism of O_2^- with transition metal complexes in order to clarify the mode of action of such superoxide dismutase enzymes.

Though it is possible to generate O_2^- electrochemically,[47,48] Valentine and Curtis found that KO_2 is dissolved easily in DMSO in the presence of dicyclohexyl-18-crown-6 to give a solution containing the same concentration (0.15 M) of O_2^- as that of the KO_2 added.[49] The resulting pale yellow solution was positive to a qualitative test for O_2^-, which involved the deposition of a deep blue precipitate from an aqueous solution of nitroblue-tetrazolium, and it continued to be positive for one week when the solution was kept under argon at room temperature. A solution of KO_2 ranging in concentration from 10^{-3} M to 10^{-4} M gave the same esr spectrum as that of O_2^- generated electrochemically, and the addition of dilute hydrochloric acid to a 0.15 M solution of O_2^- resulted in gas evolution that was more than 90% of the calculated value and had the same spectrum as that of bleached DMSO.

Valentine and Curtis carried out the characteristic reduction of cytochrome c_{ox} to c_{red} with this solution of O_2^- and confirmed that O_2^- was the reaction species of superoxide dismutase enzyme. Then they investigated the reaction of O_2^- with Cu(II) complex using KO_2 solution, because the first step of the reaction mechanism conventionally proposed for Cu enzyme[50,51] (Eqs. 4.10 ~ 4.12) is the reaction of O_2^- with Cu(II) enzyme.

$$\text{Reduction: enz} - \text{Cu}^{\text{II}} + O_2^- \longrightarrow \text{enz} - \text{Cu}^{\text{I}} + O_2 \tag{4.10}$$

$$\text{Oxidation: enz-Cu}^{\text{I}} + 2H^+ + O_2^- \longrightarrow \text{enz-Cu}^{\text{II}} + H_2O_2 \tag{4.11}$$

$$\text{Overall reaction: } 2O_2^- + 2H^+ \longrightarrow O_2 + H_2O_2 \tag{4.12}$$

Superoxide anion O_2^- acts not only as an oxidizing agent (Eq. 4.13) but also as a reducing agent (Eq. 4.14). In the reaction shown in Eq. 4.13, a proton is necessary to stabilize the peroxide dianion O_2^{2-}. Thus, by carrying out the reaction in an aprotic solvent like DMSO, it becomes possible to examine just the first step of the enzyme system (Eq. 4.10) separately.

$$O_2^- + 2H^+ + e^- \longrightarrow H_2O_2 \tag{4.13}$$

$$O_2^- \longrightarrow O_2 + e^- \tag{4.14}$$

The Cu(II) complex $[Cu(phen)_2](ClO_4)_2$ (phen = 1, 10-phenanthroline) has a heterocyclic nitrogen ligand and is analogous to histidine-imidazol, which is thought to be present in Cu-Zn enzyme systems.[52] A DMSO solution of this complex (light blue) was converted immediately to a dark brown solution of $[Cu(phen)_2](ClO_4)$ (λ_{max} 445) by a reaction with O_2^- when a solution of KO_2 was added. In the presence of a large excess of O_2^-, a side reaction developed in which phenanthroline was attacked, but this side reaction was minimized and $[Cu(phen)_2](ClO_4)$ was obtained in 46% yield when a 0.03 M solution of the complex was added to a 2-equivalent KO_2 solution and water was added immediately to stop the reaction and to precipitate the reaction product.

The reaction of Cu(II) complex with O_2^- is the reverse of the reaction which is proposed as the first step of the autoxidation mechanism of Cu(I) complex (Eqs. 4.15, 4.16).[53)]

$$Cu^+ + O_2 \rightleftharpoons Cu^{2+}O_2^- \tag{4.15}$$

$$Cu^{2+}O_2^- + H^+ \longrightarrow Cu^{2+} + H_2O \tag{4.16}$$

As a result of the work on the oxygen oxidation of $[Cu(phen)_2]^+$, it was concluded that the equilibrium in Eqs. (4.17) and (4.18) was reversed in the presence of a proton.

$$Cu(phen)_2{}^+ + O_2 \rightleftharpoons Cu\ (phen)_2{}^{2+} + O_2^- \tag{4.17}$$

$$Cu(phen)_2{}^+ + O_2 + H^+ \rightleftharpoons Cu\ (phen)_2{}^{2+} + HO_2 \tag{4.18}$$

Because of its nucleophilicity, superoxide anion O_2^- is also useful as an organic synthetic reagent for reactions such as the S_N2 reaction, hydrogen abstraction reaction, and nucleophilic addition. Valentine *et al.* found that 18-crown-6 facilitated the solubilization of KO_2 in DMSO, and they obtained alcohols from alkyl halides or tosylates by solid-liquid phase transfer catalysis using 0.1 mole equivalent of 18-crown-6 to KO_2 in DMSO (Eqs. 4.19, 4.20).[54)] As shown in Table 4.4, C–O bond formation by S_N2 substitution was predominant and the reactivity followed the order of benzyl > primary- > secondary- > tertiary- > aryl, I > Br > Cl. In the case of secondary halides or tosylates the elimination reaction was accompanied by considerable substitution, and in the case of tertiary halides, the formation of olefins by elimination predominated; this reflected the tendency observed in reactions of alkyl halides with conventional nucleophilic reagents.

$$RX + KO_2 \xrightarrow[\text{DMSO, room temp.}]{\text{18-CR-6, solid-liquid phase transfer}} ROH \tag{4.19}$$

$$X = Cl, Br, I$$

$$ROTs + KO_2 \xrightarrow[\text{DMSO, room temp.}]{\text{18-CR-6, solid-liquid phase transfer}} ROH \tag{4.20}$$

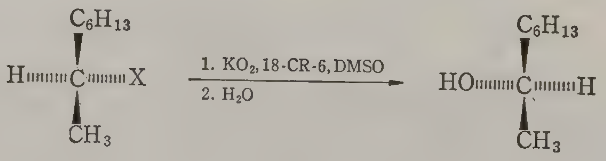
In some of the reactions with O_2^- solution, it is noteworthy that an inversion of configuration occurs. From the tosylate of (+)-(*S*)-2-octanol ($\alpha^{20}{}_{589}$ + 7.97°, optical purity 99.4%), (−)-(*R*)-2-octanol ($\alpha^{20}{}_{589}$ − 7.71°, optical purity 97%) was obtained, and (+)-(*S*)-2-octanol (optical purity 90%, 95% inversion) was obtained from (−)-(*R*)-2-bromooctane (Eq. 4.21).[54)]

Corey *et al.* found that KO_2 was dissolved not only in DMSO but also in DMF, DME, and ethyl ether in the presence of 18-crown-6, and they reported the formation of alcohols from bromides according to the S_N2 reaction shown in Eqs. (4.22) ~ (4.24).[55)]

TABLE 4.4 Reactions of KO_2 with alkyl halides and tosylates[54)] †

Substrate	Reaction time	Product	Yield (%)	Relative Reactivity (1-bromooctane = 1.0)
1-$C_8H_{17}I$	75 min	1-Octanol	46	4.5
		1-Octene	3	
		1-Octanal	11	
2-$C_8H_{17}I$	75 min	2-Octanol	48	3.3
		Octenes	48	
		2-Octanone	<1	
1-$C_8H_{17}Br$	75 min	1-Octanol	63	1.0
		1-Octene	<1	
		1-Octanal	12	
$CH_3(CH_2)_2C(CH_3)_2Br$	75 min	2-Methyl-2-pentanol	20	0.90
		2-Methylpentenone	30	
1-$C_8H_{17}Cl$	3 hr	1-Octanol	34	0.089
		1-Octene	~1	
		1-Octanal	5	
2-$C_8H_{17}Cl$	3 hr	2-Octanol	36	0.020
		Octenes	12	
		2-Octanone	<1	
1-$C_8H_{17}OT$	75 min	1-Octanol	75	
		1-Octene	<1	
		1-Octanal	1	
2-$C_8H_{17}OT$	75 min	2-Octanol	75	
		Octenes	23	
		2-Octanone	<1	
$C_6H_5CH_2Cl$	75 min	Benzyl alcohol	41	2.9
		Benzaldehyde	6	

†Substrate: 3.33 mmol; KO_2: 10.0 mmol; 18-crown-6: 1.0 mmol; DMSO: 20ml; room temp.



$$\mathrm{H}\overset{\mathrm{C_6H_{13}}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{X} \xrightarrow[\text{2. } H_2O]{\text{1. } KO_2,\text{ 18-CR-6, DMSO}} \mathrm{HO}\overset{\mathrm{C_6H_{13}}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}\mathrm{H} \qquad (4.21)$$

$$1-C_{12}H_{25}Br + KO_2 \xrightarrow[\text{DMSO, 25°C, 2 hr}]{\text{18-CR-6 (0.5 mol. eq. to } KO_2)} 1-C_{12}H_{25}OH \qquad (4.22)$$

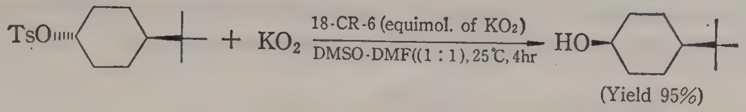
(Yield: 80%)

$$\text{geranyl} - Br + KO_2 \xrightarrow[\text{DMSO-DMF (1 : 1) 0°C, 0.5 hr}]{\text{18-CR-6 (0.5 mol. eq. to } KO_2)} \text{geraniol} \qquad (4.23)$$

(Yield: 70%)

$$C_6H_5CH_2Br + KO_2 \xrightarrow[\text{DMSO-DMF (1 : 1), 0°C, 0.5 hr}]{\text{18-CR-6 (0.5 mol. eq. to } KO_2)} C_6H_5CH_2OH \qquad (4.24)$$

They also reported that tosylate or methanesulfonate gave a configurationally inverse alcohol in high yield (Eqs. 4.25, 4.26) and that cholesterol tosylate gave 3-epicholesterol in 56% yield. The elimination reactions shown in Eqs. (4.27) and (4.28) were also facilitated by KO_2.



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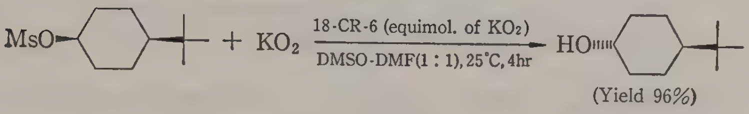
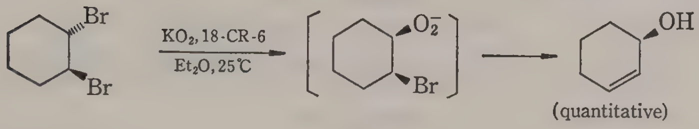
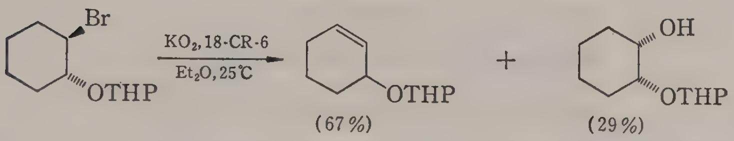


(4.26)

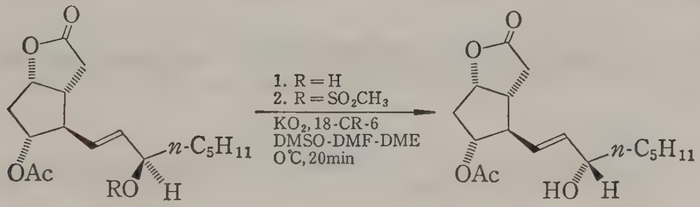


(4.27)

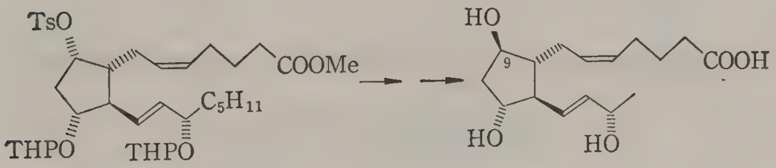


(4.28)

Corey *et al.* applied the S_N2 reaction using KO_2 to syntheses of various bioactive prostanoids and their analogues. For example, 15-*R*-prostanoid was converted to the 15-*S* form, the natural form of prostanoid, in 75% yield by the treatment of its methane-



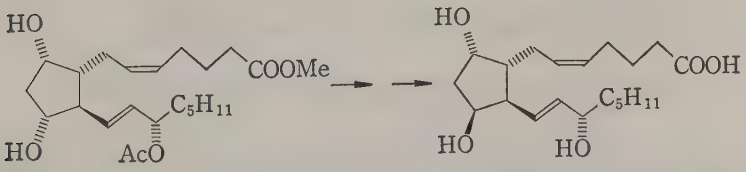
(4.29)



(4.30)

THP ether of $PGF_{2\alpha}$

9-epi-$PGF_{2\beta}$



(4.31)

11-epi-$PGF_{2\alpha}$

sulfonate with KO_2 (Eq. 4.29),[55] from prostaglandin, $F_{2\alpha}(PGF_{2\alpha})$, were derived the epimers of the 9-position, $PGF_{2\beta}$, and of the 11-position (Eqs. 4.30, 4.31).[56]

Johnson and Nidy reported a simple synthetic method for preparing dialkyl peroxide from alkyl halides, tosylates, or mesitylates using KO_2 at room temperature (Eqs. 4.32, 4.33) and proposed the reaction scheme shown in Eq. (4.34).[57]

$$RBr + KO_2 \xrightarrow[\text{benzene, room temp.}]{\text{DC-18-CR-6}} ROOR \qquad (4.32)$$

(Yield 44 ~ 77%)

$R = n\text{-}C_5H_{11} \sim n\text{-}C_{18}H_{37}$, cyclohexyl

$$ROTs\ (\text{or Ms}) + KO_2 \xrightarrow[\text{benzene, room temp.}]{\text{DC-18-CR-6}} ROOR + ROH + \text{olefin} \qquad (4.33)$$

$R = n\text{-}C_{18}H_{37}$ (46 ~ 50%) (40 ~ 42%) (—)

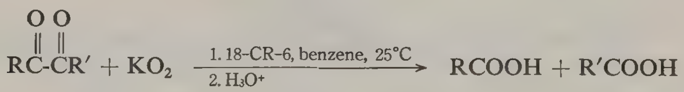
$R = sec\text{-}C_8H_{17}$ (44 ~ 52%) (13 ~ 19%) (14 ~ 16%)

$$BBr + O_2^- \longrightarrow ROO\cdot + Br^-$$
$$ROO\cdot + O_2^- \longrightarrow ROO^- + O_2$$
$$ROO^- + RBr \longrightarrow ROOR + Br^-$$

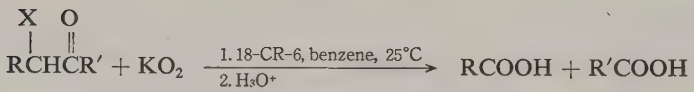
$$RBr + O_2^- \longrightarrow 1/2\ ROOR + Br^- + 1/2\ O_2 \qquad (4.34)$$

Several examples of oxidative cleavage with O_2^- (Eqs. 4.35 ~ 4.37) were described by Filippo *et al.*,[58,59] and oxidative cleavage caused by the nucleophilic addition of an enone group in the reaction of chalcone and KO_2 (Eq. 4.38) was reported by Rosenthal and Frimer.[60]

$$RCOOR' + KO_2 \xrightarrow[\text{2. } H_3O^+]{\text{1. 18-CR-6, benzene, 25°C}} RCOOH + R'OH \qquad (4.35)$$



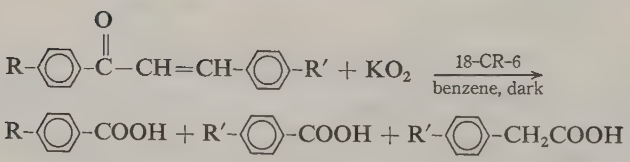
$$R\overset{O}{\overset{\|}{C}}\text{-}\overset{O}{\overset{\|}{C}}R' + KO_2 \xrightarrow[\text{2. } H_3O^+]{\text{1. 18-CR-6, benzene, 25°C}} RCOOH + R'COOH \qquad (4.36)$$



$$R\overset{X}{\overset{|}{C}}H\overset{O}{\overset{\|}{C}}R' + KO_2 \xrightarrow[\text{2. } H_3O^+]{\text{1. 18-CR-6, benzene, 25°C}} RCOOH + R'COOH \qquad (4.37)$$

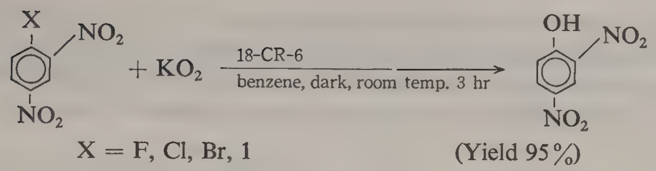
R′ = OH, OR, alkyl, aryl

X = OH, Cl, Br

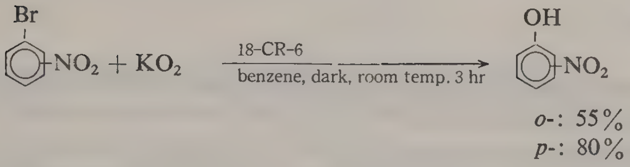


(4.38)

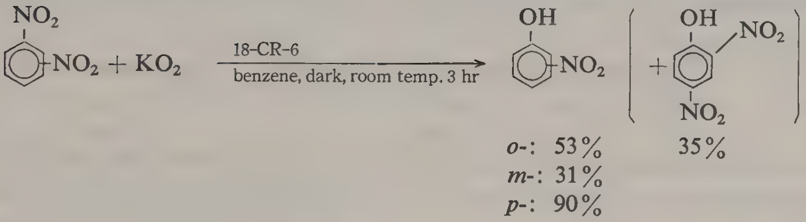
Other examples of the use of KO_2 for S_N2 substitution on aromatic compounds were reported by Frimer and Rosenthal (Eqs. 4.39 ~ 4.42).[61]



(4.39)



(4.40)



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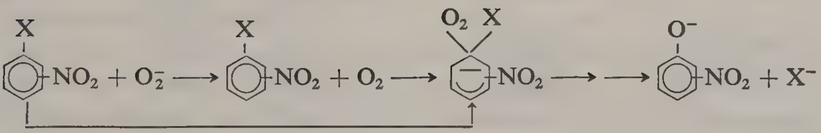
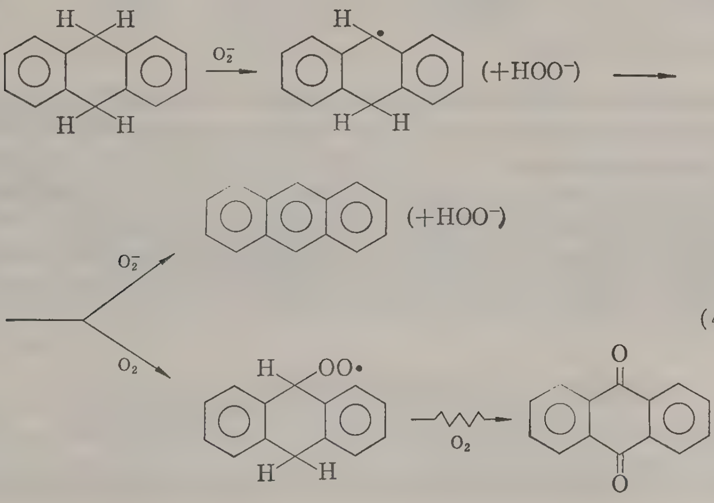


(4.42)

Several recent reports have described reactions using O_2^- solutions prepared by the solubilization of KO_2 with crown ethers. These include the oxidation of compounds

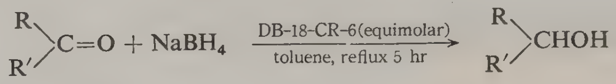


(4.43)

having labile H atoms such as dihydroanthracene, 1, 3- and 1, 4-hexadiene, anthrone, xanthene, and diphenylmethane (Eq. 4.43),[62] reactions of *tert*-butylhydroperoxide anion;[63] reactions with phenyl radicals;[64] spin trap in the formation of alkyl peroxide radicals from alkyl halides;[65] oxidation of alkyl-substituted phenols,[66] and hydrogen abstraction.[67]

4.2.4 Reduction

Matsuda and Koida reported on the effect of the addition of dibenzo-18-crown-6 on the reduction of ketones with $NaBH_4$ and compared it with the effect of adding DME or diglyme (Eq. 4.44).[68] As shown in Table 4.5, the results demonstrated a marked effect from the presence of crown ether. Furthermore, studies of the steric effects in the reduction of substituted cyclohexanone and 2-norbornanone with $NaBH_4$ in the presence of crown ether and showed that alcohols of the *trans* form were obtained from 4-methyl- and 4-*tert*-butyl-cyclohexanone with a selectivity of 74% and 77%, respectively, and alcohol of the *cis* form was predominantly produced from 3, 3, 5-trimethylcyclohexanone. The yield of *exo*-alcohol from 2-norbornanone increased up to 29 ~ 34%.



(4.44)

TABLE 4.5 Effects of the addition of ethers in the reduction of ketones with $NaBH_4$.[68]

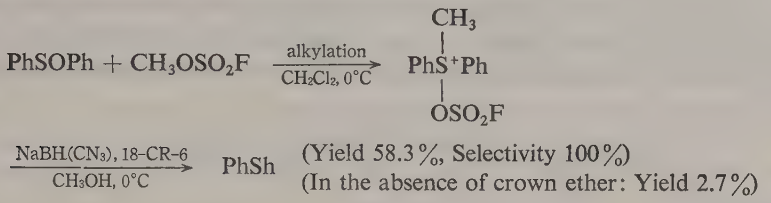
Ketone		Product (wt% of ketone)		
		DB-18-CR-6	Diglyme	DME
Acetophenone	Alcohol	49	42	23
	Ketone	0	38	40
	Others	28	12	13
Cyclohexane	Alcohol	50	28	19
	Ketone	0	32	56
	Others	37	17	8
n-Amylmethyl ketone (2-Heptanone)	Alcohol	41	27	14
	Ketone	3	9	34
	Others	29	22	18
Methylisopropyl ketone	Alcohol	23	11	0
	Ketone	63	74	78
	Others	10	6	5

Reduction of ketones with $NaBH_4$ by liquid-liquid phase transfer catalysis using catalytic amounts of dicyclohexyl-18-crown-6 (Eq. 4.45) was also reported by Landini *et al.*[41]

$$\text{2-Octanone} \xrightarrow[\text{benzene/NaBH}_4\text{-NaOH}_{\text{aq.}},\ 80^\circ\text{C, 2.5 hr}]{\text{DC-18-CR-6 (0.05 mol equiv.)}} \text{2-Octanol} \quad (4.45)$$

(Yield 92%)

Durst *et al.* carried out the reduction with Na-borocyanohydride $[NaBH(CN)_3]$ in the presence of 18-crown-6 (Eq. 4.46).[69] The yield of diphenyl sulfide increased to 58.3% (100% selectivity) from only 2.7% in the absence of crown ether.



$$\mathrm{PhSOPh} + \mathrm{CH_3OSO_2F} \xrightarrow[\mathrm{CH_2Cl_2,\ 0^\circ C}]{\text{alkylation}} \mathrm{PhS^+Ph}\ (\mathrm{CH_3}\text{ above},\ \mathrm{OSO_2F}\text{ below}) \xrightarrow[\mathrm{CH_3OH,\ 0^\circ C}]{\mathrm{NaBH(CN_3),\ 18\text{-}CR\text{-}6}} \mathrm{PhSh} \tag{4.46}$$

(Yield 58.3%, Selectivity 100%)
(In the absence of crown ether: Yield 2.7%)

Handel *et al.*[70~73] and Loupy *et al.*[74] investigated the reaction mechanism in the reduction with metal hydride by masking the alkali metal ion of $LiAlH_4$ and $NaAlH_4$ using crown ethers or cryptands. In the reduction of ketones, aldehydes, carboxylic acids, esters, acid chlorides, amides, nitriles, oximes, and epoxides with $LiAlH_4$ using diethyl ether and DMF as a solvent, it was observed that the reaction did not take place on the addition of an equimolar amount of cryptand [2, 1, 1] or [2, 2, 1], with a steric lattice in which Li^+ was enclosed. From these results, they proposed a mode of action of alkali metal ions in the reduction with metal hydride in which Li^+ as a Lewis acid was indispensable to the reaction. This is an example in which the masking of a cation was skillfully employed.

Alper *et al.* reported the reduction of aromatic nitro compounds with $Fe_3(CO)_{12}$ in benzene in the presence of an aqueous solution of 18-crown-6 and KOH (Eq. 4.47).[75] The yields of amines were as follows: 60% for aniline, 65% for *p*-toluidine, 78% for *p*-anisidine, 79% for *p*-chloroaniline, and 84% for 2-fluorenyl amine. The reduction barely proceeded in the absence of crown ether, and the yield was reduced (33% for 2-fluorenyl amine) when solid-liquid phase transfer catalysis was applied using solid KOH without water.

$$\mathrm{ArNO_2} + \mathrm{Fe_3(CO)_{12}} \xrightarrow[\mathrm{1N\ KOH_{aq}(10ml),\ Benzene(10ml),\ room\ temp.1.5\sim2.5\ hr}]{\mathrm{18\text{-}CR\text{-}6(0.1\ mmol)\ (liquid\text{-}liquid\ phase\ transfer)}} \mathrm{ArNH_2} \tag{4.47}$$

(Yield 60 ~ 84%)

4.2.5 Substitution

A. Electrophilic Substitution

Cram *et al.* used crown ethers in a series of investigations of electrophilic substitution (S_E) in optically active compounds.[76~79] The reaction rates of racemization and H-D exchange increased markedly up to $10^2 \sim 10^5$ times in the presence of dicyclohexyl-18-crown-6 in a system in which carbanion was generated in alcohol using K-alkoxide as a catalyst.

B. Nucleophilic Halogen-Substitution

There have been several reports of nucleophilic substitution reactions (S_N2) utilizing the strong nucleophilicity of naked anions generated by the action of crown ethers or cryptands in low-polar solvents.

Sam and Simmons showed that halogen-substitution of butyl brosylate could be accomplished by using the KBr or KI complex of dicyclohexyl-18-crown-6 in acetone at 25° C; they also found that the nucleophilicity of the complex was much higher than that of $Bu_4N^+X^-$.[80] Landini *et al.* carried out the halogen-substitution of octyl bromide (Eq. 4.48) by liquid-liquid phase transfer catalysis using catalytic amounts (0.01 mol/mol MI) of crown ether, as mentioned previously.[41] The results are shown in Table 4.6.

$$1\text{-}C_8H_{17}Br + MI_{aq} \xrightarrow[80^\circ C]{CR(0.01\ \text{mol equiv.})} 1\text{-}C_8H_{17}I \qquad (4.48)$$

TABLE 4.6 Liquid-liquid phase transfer catalysis by crown ethers; iodination of 1-bromoctyl with alkali iodides.[41]

Inorganic salt[†1]	Crown ether[†2]	Reaction time (hr)[†3]	Yield (%)
KI	Dibenzo-18-crown-6	40	80
NaI	Dibenzo-15-crown-5	21	80
KI	Dicyclohexyl-18-crown-6	3	100
KI	—	24	<4

[†1] Saturated aqueous solution
[†2] [CR]/[MI] molar ratio = 0.01
[†3] Reaction temp.: 80° C

When the halogenation and cyanation of alkyl mesylates was carried out with a similar method, the following observations were made, as shown in Table 4.7: the apparent nucleophilicity was in the order of $I^- > Br^- > Cl^- > F^-$; the reactivity of the secondary octyl mesylate was lower than the primary one and the elimination reaction was accompanied by substitution; among the Finkelstein reactions, Br-substitution of alkyl iodide with alkali bromide proceeded, giving alkyl bromide in 40% yield, when a crown

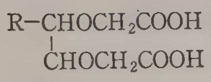
TABLE 4.7 Nucleophilic substitutions of octyl mesylates and octyl halides using dicyclohexyl-18-crown-6[†1] as a liquid-liquid phase transfer catalyst.[41]

Substrate	Reagent[†2]	Reaction Temp. (°C)	Reaction Time (hr)	Yield (%)	Product
$n\text{-}C_8H_{17}OSO_2Me$	KI	100	0.11	100	$n\text{-}C_8H_{17}I$
$n\text{-}C_8H_{17}OSO_2Me$	NaI	100	0.16	100	$n\text{-}C_8H_{17}I$
$n\text{-}C_8H_{17}OSO_2Me$	KBr	100	0.5	96	$n\text{-}C_8H_{17}Br$
$n\text{-}C_8H_{17}OSO_2Me$	NaBr	100	0.5	88	$n\text{-}C_8H_{17}Br$
$n\text{-}C_8H_{17}OSO_2Me$	KCl	100	3.0	89	$n\text{-}C_8H_{17}Cl$
$n\text{-}C_8H_{17}OSO_2Me$	NaCl	100	3.0	75	$n\text{-}C_8H_{17}Cl$
$n\text{-}C_8H_{17}OSO_2Me$	KF	115	42.0	65	$n\text{-}C_8H_{17}F$
$n\text{-}C_8H_{17}OSO_2Me$	KCN	100	0.3	90	$n\text{-}C_8H_{17}CN$
$n\text{-}C_8H_{17}Br$	KI	100	1.5	92	$n\text{-}C_8H_{17}I$
$n\text{-}C_6H_{17}I$	KBr	80	3.0	40[†3]	$n\text{-}C_8H_{17}Br$
$n\text{-}C_6H_{13}CH(OSO_2Me)Me$	KBr	100	2.5	67[†4]	$n\text{-}C_6H_{13}CHBrMe$

[†1] [CR]/[MX] molar ratio = 0.01.
[†2] Saturated oqueous Solution.
[†3] Unreacted 2-octanol: 60% same after 2 6 hr.
[†4] 2-Octanol: 16%, octenes (mixture of isomers): 16%; unreacted 2-Octyl mesylate: 1%.

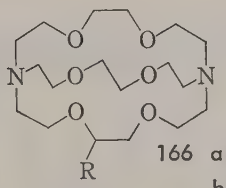
ether was used as the phase transfer catalyst, but the reaction barely advanced when quaternary ammonium salt was used as the catalyst.

Cinquini *et al.* prepared novel cryptands with side chains (**166a, b**) by the condensation of polyether dicarboxylic acids having alkyl side chains (**165a, b**) with diamino-18-crown-6 (**30**), followed by reduction.[81] The catalytic activity of these new cryptands for liquid-liquid phase transfer catalysis was compared with that of cryptand [2, 2, 2], dicyclohexyl-18-crown-6, and hexadecyltributyl-phosphonium bromide, $n\text{-}C_{16}H_{33}\overset{+}{P}Bu^{n}_{3}$ Br^-. The results are shown in Table 4.8. The catalytic activity of the cryptands having long, lipophilic, alkyl side chains was higher than the activity of long-chain alkyl phosphonium salts and crown ethers, particularly in Br–I and Cl–I substitution and in $NaBH_4$ reduction. The results of alkylation and elimination (carbene formation and addition) are also presented in Table 4.8. Cinquini and Tundo prepared crown ethers (**167a**) and azacrown ethers (**167b**) having alkyl side chains and observed that the catalytic activity in the phase transfer catalysis of nucleophilic substitution, alkylation, and ketone reduction increased with increasing lipophilicity of the alkyl side chain.[82]

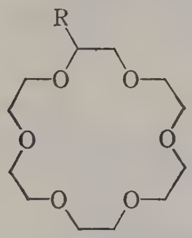


$$\begin{array}{l} R\text{-}CHOCH_2COOH \\ \quad | \\ \quad CHOCH_2COOH \end{array}$$

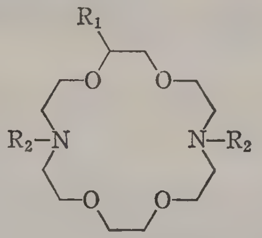
165 a $R = n\text{-}C_{14}H_{29}$
b $R = n\text{-}C_{11}H_{23}$



166 a $R = n\text{-}C_{14}H_{29}$
b $R = n\text{-}C_{11}H_{23}$



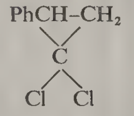
167a $R = n\text{-}C_{10}H_{21}$, $n\text{-}C_{14}H_{29}$, $n\text{-}C_{20}H_{41}$



167b $R_1, R_2 = n\text{-}C_{14}H_{29}$, H; H, $n\text{-}C_{16}H_{33}$

Because it is highly solvated to F^-, KF is not usually employed as a nucleophilic reagent, but the F-substitution reactions shown in Eqs. (4.49) ~ (4.55) were carried out by Liotta *et al.* by generating naked anions in benzene or acetonitrile using 18-crown-6 as a solid-liquid phase transfer catalyst.[83] Though the conversion was 100% in every case, the elimination reaction predominated in Eqs. (4.51) and (4.52), and only elimination took place in Eq. (4.53) because the basicity of F^- also increased. In the absence of crown ether, the conversions under the same reaction conditions were less than 5% in each reaction.

TAFLE 4.8 Liquid-liquid phase transfer catalyses by cryptands having alkyl side chains, Cryptands, Crown Ethers, and Quaternary Phosphonium Salts.[81)]

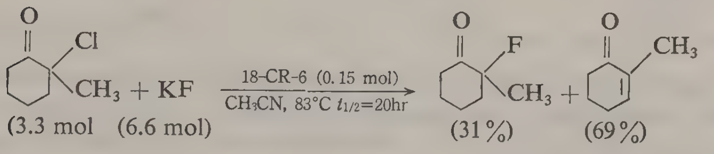
Reaction	Substrate†1	Reagent	Catalyst†7	Reaction temp. (°C)	Reaction time (hr)	Yield	Product
Br–I Substitution	n–$C_8H_{17}Br$	KI†2	C_{14}–[2, 2, 2]	60	0.2	100	n–$C_8H_{17}I$
Br–I Substitution	n–$C_8H_{17}Br$	KI†2	C_{11}–[2, 2, 2]	60	0.5	92	n–$C_8H_{17}I$
Br–I Substitution	n–$C_8H_{17}Br$	KI†2	[2, 2, 2]	60	14	90	n–$C_8H_{17}I$
Br–I Substitution	n–$C_8H_{17}Br$	KI†2	QBr†8	60	1	93	n–$C_8H_{17}I$
Br–I Substitution	n–$C_8H_{17}Br$	KI†2	DC–18–CR–6	80	3	100	n–$C_8H_{17}I$
Cl–I Substitution	n–$C_8H_{17}Cl$	KI†2	C_{14}–[2, 2, 2]	80	5	77	n–$C_8H_{17}I$
Cl–I Substitution	n–$C_8H_{17}Cl$	KI†2	C_{11}–[2, 2, 2]	80	4	85	n–$C_8H_{17}I$
Cl–I Substitution	n–$C_8H_{17}Cl$	KI†2	QBr	80	24	80	n–$C_8H_{17}I$
CN Substitution	n–$C_8H_{17}Cl$	KCN†2	C_{14}–[2, 2, 2]	80	5	93	n–$C_8H_{17}CN$
CN Substitution	n–$C_8H_{17}Cl$	KCN†2	QBr	80	5	94	n–$C_8H_{17}CN$
F Substitution	n–$C_8H_{17}OMs$	KF†2	C_{11}–[2, 2, 2]†9	120	4	85	n–$C_8H_{17}F$
F Substitution	n–$C_8H_{17}OMs$	KF†3	QBr†8	120	2	94	n–$C_8H_{17}F$
Substitution (formation of thioether)	n–$C_8H_{17}Br$	PhSNa†3	C_{14}–[2, 2, 2]	20	0.1	100	n–$C_8H_{17}SPh$
	n–$C_8H_{17}Br$	PhSNa	QBr	20	0.1	100	n–$C_8H_{17}SPh$
Sec-Br–Cl substitution	n–$C_6H_{13}CH(Br)Me$	KI†2	C_{14}–[2, 2, 2]	80	3	86	n–$C_6H_{13}CH(I)Me$
	n–$C_6H_{13}CH(Br)Me$†2	KI†2	QBr	80	6	89	n–$C_6H_{13}CH(I)Me$
Alkylation	$PhCH_2COMe$	Bu^nBr†4	C_{14}–[2, 2, 2]	20	0.75	94	$PhCH(Bu^n)COMe$
Alkylation	$PhCH_2COMe$	Bu^nBr†4	QBr	20	2.5	90	$PhCH(Bu^n)COMe$
Alkylation	$PhCH_2COMe$	Bu^nBr†4	DC–18–CR–6	80	1.5	93	$PhCH(Bu^n)COMe$
Ketone reduction	n–$C_6H_{13}COMe$	$NaBH_4$†5	C_{14}–[2, 2, 2]	20	4	97	n–$C_6H_{13}CH(OH)Me$
Ketone reduction	n–$C_6H_{13}COMe$	NaBH	QBr	20	6	78	n–C H CH(OH)Me
Ketone reduction	n–$C_6H_{13}COMe$	NaBH	DC–18–CR–6	80	2.5	92	n–C H CH(OH)Me
Elimination (carbene addition	$PhCH = CH_2$	NaOH†6 $CHCl_3$	C_{14}–[2, 2, 2]	20	24	60	

†1: Benzene was used as a solvent in the reduction with $NaBH_4$. Other reactions were carried out with no solvent. Reagents were used as saturated aqueous solutions. †2: 5 mol.; †3: 1 mol.; †4: 1.2 mol/50%NaOHaq.; †5: 1.5 mol.; †6: 2.5 mol.; †7: 0.05 mol.; †8: n-$C_{16}H_{33}P^+Bu^n_3Br^-$; †9: 0.1 mol.

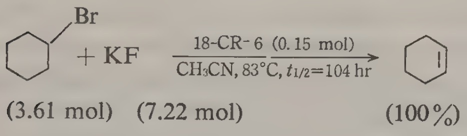
$$\underset{(2.0\ \text{mol})}{PhCH_2Br} + \underset{(4.0\ \text{mol})}{KF} \xrightarrow[\text{CH}_3\text{CN } 83°\text{C} \atop \text{half-life } t_{1/2}=11.5\ \text{hr}]{\text{18-CR-6 (0.19 mol)}} \underset{(100\%)}{PhCH_2F} \qquad (4.49)$$

$$\begin{matrix} 1\text{-}C_8H_{17}Br + KF & & 1\text{-}C_8H_{17}F + \text{1-octene} \\ \left\{\begin{matrix}(1.16\ \text{mol}) & (2.32\ \text{mol}) \\ (2.9\ \text{mol}) & (5.8\ \text{mol})\end{matrix}\right. & \xrightarrow[\substack{\text{CH}_3\text{CN: 18-CR-6 (0.19 mol)} \\ 83°\text{C, } t_{1/2}=115\ \text{hr} \\ \text{benzene: 18-CR-6 (0.68 mol)} \\ 90°\text{C, } t_{1/2}=128\ \text{hr}}]{} & \begin{matrix}(92\%) & (8\%) \\ (92\%) & (8\%)\end{matrix} \end{matrix} \qquad (4.50)$$

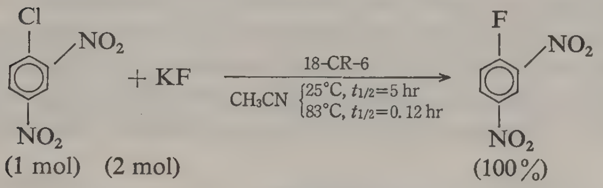
$$\underset{(2.8\ \text{mol})}{2\text{-}C_8H_{17}Br} + \underset{(5.6\ \text{mol})}{KF} \xrightarrow[\text{benzene } 90°\text{C, } t_{12/}=240\ \text{hr}]{\text{18-CR-6(0.50 mol)}} \underset{(32\%)}{2\text{-}C_8H_{17}F} + \underset{(68\%)}{\text{1-and 2-octene}} \qquad (4.51)$$



(4.52)



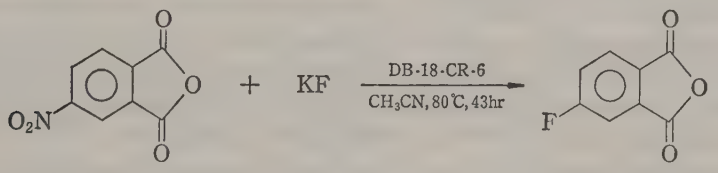
(4.53)



(4.54)

$$\underset{(7.0\ \text{mol})}{CH_3COCl} + \underset{(14.0\ \text{mol})}{KF} \xrightarrow[\text{CH}_3\text{CN, } 25°\text{C, } t_{1/2}=5.5\ \text{hr}]{\text{18-CR-6 (0.14 mol)}} \underset{(100\%)}{CH_3COF} \qquad (4.55)$$

Concerning the substitution of aromatic nitro compounds, Markezich *et al.* reported recently that the reaction in Eq. (4.56) proceeded easily in acetonitrile in the presence of dibenzo 18-crown-6.[84)]



(4.56)

Liotta *et al.* carried out the reaction of benzyl tosylate with KF, KCl, KBr, KI, KCN, KOAc, and KN_3 in acetonitrile at 30.00 ± 0.05° C in the presence of 18-crown-6, and examined the relative nucleophilicity of the naked anions by comparing the apparent first-order reaction rate constants measured by electroconductivity.[85)] The results are shown in Table 4.9. While it has been reported that, when strongly solvated, the relative nucleophilicity of I^-/F^- is 10^3 in water[86)] and 10 in DMF,[87)] the relative

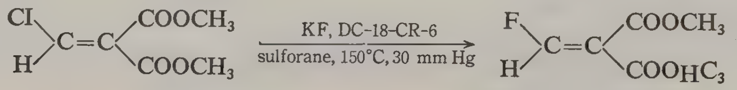
TABLE 4.9 Relative nucleophilic reactivities of naked anions to benzyl tosylate.[85]

Salt	Relative nucleophilic reactivity	
	Naked anion 18–CR–6 in CH_3CN	Solvated anion[88] in water
KF	1.4	0.2
KCl	1.3	2.0
KBr	1.3	16.0
KI	1.0	200.0
KCN	2.4	250.0
KSCN	0.3	125.0
KOAc	9.6	1.0
KN_3	10.0	20.0

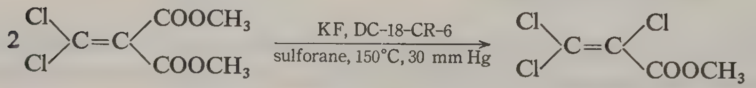
nucleophilicity of naked halogen anions is close to unity. Furthermore, OAc^-, usually very weakly nucleophilic, is very strongly nucleophilic as a naked anion; in contrast, SCN^-, which is bulky and which as a soft base displays strong nucleophilicity in water, shows very weak nucleophilicity as a naked anion. These findings indicate that naked anions are solvated to a much smaller extent in acetonitrile than in protic solvents.

Willy *et al.* also described the effects of 18-crown-6 on the halogen exchange of alkyl halides with salts of alkali metals.[89] Jeanne and Trichet carried out the fluorination of 4-nitrobenzyl bromide with KF, substitution of aryl halides (halogen: Cl, Br) with KOCN, and synthesis of Bu–O–O–Bu from BuBr and KO_2 by solid-liquid phase transfer catalysis in the presence of 18-crown-6, dibenzo-18-crown-6, and cryptand [2, 2, 2].[90]

Ykman and Hall reported an F-substitution reaction (Eq. 4.57a) and the reaction shown in Eq. (4.57b).[91] The latter reaction proceeds via elimination-substitution.



(4.57a)



(4.57b)

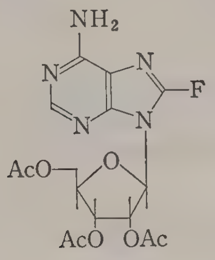
Recently Bianchi and Cate carried out the F-substitution of various alkyl and sulfonyl chlorides at room temperature in acetonitrile by solid-liquid phase transfer catalysis[92] using the acetonitrile complex[93] of 18-crown-6 (0.6 ~ 3.0 mol% of KF) (see Section 2.2.3). They obtained high yields of sulfonyl fluorides which were useful as insecticides, fungicides, and enzyme inhibitors (Eq. 4.58). Bianchi and Cate mentioned that the complex was composed of 2 moles of acetonitrile to 1 mole of 18-crown-6; this composition was confirmed recently by X-ray diffraction by Liotta *et al.* (unpublished work).

$$\underset{(1\ \mathrm{mol})}{RSO_2Cl} + \underset{(1.2 \sim 2.0\ \mathrm{mol})}{KF} \xrightarrow[\mathrm{CH_3CN\ room\ temp.} < 4\ \mathrm{hr}]{\mathrm{18\text{-}CR\text{-}6}\ (0.6 \sim 3.0\ \mathrm{mol}\%)} \underset{(\mathrm{Yield}\ 84 \sim 100\%)}{RSO_2F} \qquad (4.58)$$

R: CH_3, p-$CH_3C_6H_4$, C_6H_5, p-BrC_6H_4, p-$CH_3CONHC_6H_4$,

5-Dimethylamino-1--naphthalene (dansyl)

It is well known that 5-F-pyrimidine nucleotides display anticancer activity. Kobayashi *et al.* prepared 2′, 3′, 5′-tris-*O*-acetyl-8-fluoroadenosine (**168**), which was classified as an 8-F-purine nucleotide and was expected to have analogous activity, by the substitution of the bromide with KF in acetonitrile in the presence of 18-crown-6 in a 25% yield (120° C, 48 hours).[94]



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C. Nucleophilic Substitution with Carboxylate Anion (Acylation)

Naked carboxylate anion, $RCOO^-$, acts as a strong nucleophile in low-polar solvents as does AcO^- (Table 4.9). Liotta *et al.* carried out the acylation of alkyl bromides and ethylene dibromide with KOAc as shown in Eqs. (4.59a) and (4.59b).[95] Similar results were obtained in benzene, but the reaction rates were slower than those in acetonitrile. In the absence of crown ether, the conversion was only 5% after several days under the same conditions, even with benzyl bromide, which was the most highly reactive.

$$\underset{(1\text{ mol})}{RBr} + \underset{(2\text{ mol})}{KOAc} \xrightarrow[\text{CH}_3\text{CN or benzene}]{\text{18-CR-6 (catalytic amount)}} ROAc \qquad (4.59a)$$

R = benzyl: Yield 100% (25° C, 2 hr)
n-C_6H_{13}: Yield 100% (25° C, 150 hr)
n-C_8H_{17}: Yield 96% (83° C, 3 hr)
2-C_8H_{17}: Yield 90% (83° C, 20 hr)
[by-product: about 10% octene]

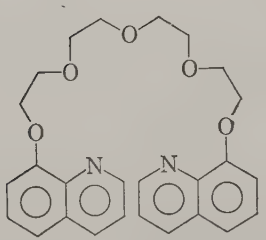
$$BrCH_2CH_2Br + 2\,KOAc \xrightarrow[\text{18-CR-6}]{\text{CH}_3\text{CN, 83°C 3 hr}} AcOCH_2CH_2OAC + BrCH_2CH_2OAc$$

$$\begin{array}{llllll} (1.3\text{ mol}) & (2.6\text{ mol}) & (0.09\text{ mol}) & (90\%) & (\text{—}) & (4.59b) \\ (1.9\text{ mol}) & (3.8\text{ mol}) & (0.06\text{ mol}) & (23\%) & (77\%) & \end{array}$$

Applying this reaction to polymers. Roovers reported the acylation of chloromethylated polystyrene with KOAc in nonpolar solvents. Dicyclohexyl-18-crown-6 was the most effective among crown ethers.[96]

Knöchel *et al.* compared the activity of various crown compounds and their analogues for solid-liquid phase transfer catalysis in the acetylation of benzyl chloride with KOAc in acetonitrile.[97] The apparent rates of the reactions catalyzed by these compounds were in the following order: dicyclohexyl-18-crown-6 ÷ cryptand [2, 2, 1]

> 18-crown-6 > [2, 2, 2] > [2, 1, 1] ≑ dibenzo-18-crown-6. Relatively lower catalytic activity was observed for diamino crown ethers having 15- ~ 24-membered rings, linear polyethers both of whose terminal groups were quinoline rings[98] (**169**), and the star polymer having 6 polyether chains (the so-called "octopus molecule")[99] (**170**). The behavior and applications of noncyclic analogues of crown compounds such as **169** and **170** are described in Section 4.2.15.



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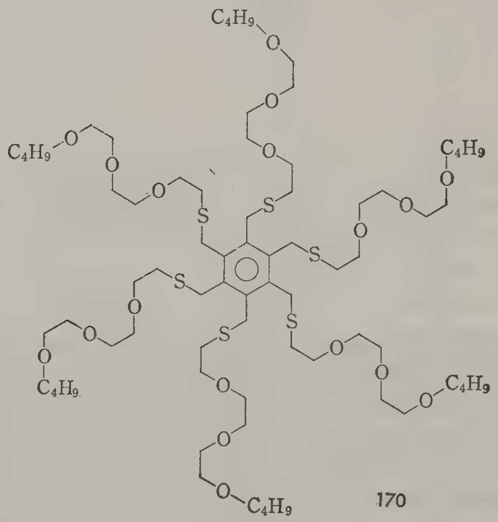
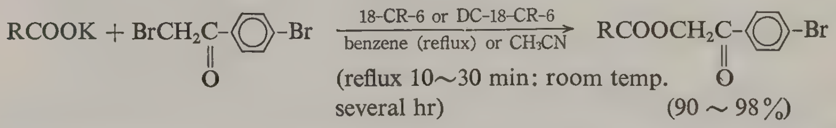


170

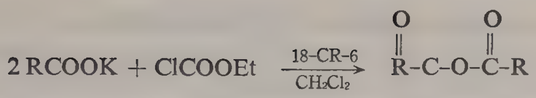
Regarding acylation other than acetylation, Durst reported the fast esterification of K salts of carboxylic acids with *p*-bromophenacyl ester in the presence of 5 mol% of 18-crown-6 or dicyclohexyl-18-crown-6 in acetonitrile or benzene (Eq. 4.60).[100] Though *p*-bromophenacyl ester has important uses in the identification and protection of carboxylic acids, the conventional method of preparation, in which the reactants are refluxed for 1 ~ 2 hours in the mixture of water and ethanol, has not yet produced the compound in adequate yields or purity. Durst *et al.* have devised a method of microquantitative analysis for a mixture of higher fatty acids that involves the stoichiometric conversion to esters utilizing their method of esterification, followed by HLC.[101,102] This analytical method is a very simple technique for HLC analyses of organic acids which have no absorption in the ultraviolet or visible region, and it may be useful for many applications other than the analytical method.



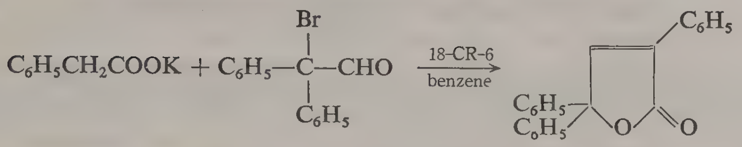
$$\mathrm{RCOOK} + \mathrm{BrCH_2}\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\text{-}\langle\bigcirc\rangle\text{-Br} \xrightarrow[\text{benzene (reflux) or } \mathrm{CH_3CN}]{\text{18-CR-6 or DC-18-CR-6}} \mathrm{RCOOCH_2}\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\text{-}\langle\bigcirc\rangle\text{-Br}$$

(reflux 10~30 min: room temp.
several hr)
(90 ~ 98%) (4.60)

Durst also reported the synthesis of acid anhydride according to Eq. (4.61),[103] and Dehm and Padwa prepared a lactone which previously had been rarely formulated by the reaction shown in Eq. (4.62).[104]



$$2\,\mathrm{RCOOK} + \mathrm{ClCOOEt} \xrightarrow[\mathrm{CH_2Cl_2}]{18\text{-CR-}6} \mathrm{R}\text{-}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\text{-}\mathrm{O}\text{-}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\text{-}\mathrm{R} \qquad (4.61)$$



(4.62)

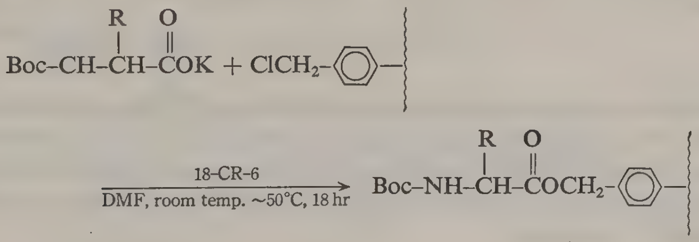
Akabori and Ohtomi carried out the esterification in Eq. (4.63) by means of solid-liquid phase transfer catalysis using cryptand [2, 2, 2].105) In the case of the disubstituent, the yield of propionic diester from dibromopropane was only 11%.

$$\mathrm{RCOOK} + \mathrm{R'Br} \xrightarrow[\text{benzene 15°C or 83°C, 3 hr}]{[2,2,2]\,\text{(about 0.1 mol equiv.)}} \mathrm{RCOOR'} \qquad (4.63)$$

$$(85 \sim 99\%)$$

$$\mathrm{R} = \mathrm{CH_3},\ \mathrm{CH_3CH_2}\ \mathrm{(CH_3)_2CH}\colon\ \mathrm{R'} = \mathrm{PhCH_2}\ n\text{-}\mathrm{C_8H_{17}}$$

A solid phase method using polystyrene as a support has been important for peptide synthesis since its invention by Merrifield.106) Roeske and Gesellchen employed a crown ether in the first step of the method, the condensation of an *N*-protected amino acid with chloromethylated polystyrene crosslinked by divinylbenzene.107) The K salts of twelve kinds of amino acids whose amino groups were protected by *tert*-butyloxycarbonyl groups were stirred together with chloromethylated polystyrene in the presence of an amount of 18-crown-6 equimolar to the amino acids in DMF at room temperature



(4.64)

or 50° C for 18 hours; the amino acids were fixed on the polymer support almost quantitively by ester bonding (Eq. 4.64). This method is noteworthy for its effective support by a polymer under mild conditions.

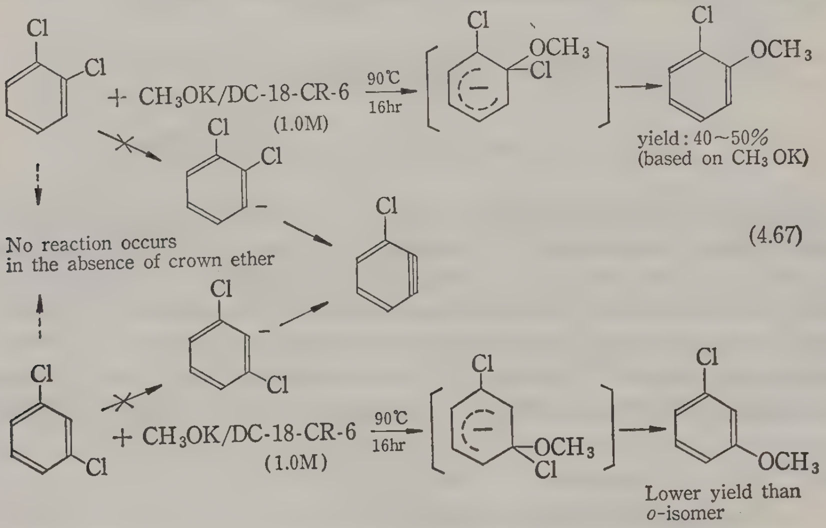
D. Alkoxy-Substitution and Phenoxy-Substitution

A markedly high nucleophilicity in the naked phenoxide anion generated by crown ethers was shown by Thomassen *et al.*108) The reaction rate of the phenoxy-substitution in Eq. (4.65) was 1.5 × 10^4 times faster than the rate without crown ether. Crown ether also had a significant effect on nucleophilic substitution with butoxide anion (Eq. 4.66).109)

$$n\text{-BuBr} + \text{PhOK} \xrightarrow[\text{dioxane}]{\text{DC-18-CR-6}} n\text{-BuOPh} \qquad k_{CR}/k_0 \sim 1.5 \times 10^4 \tag{4.65}$$

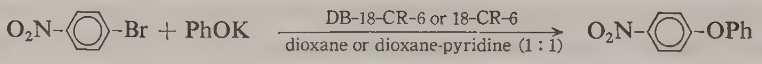
$$\text{PhCH}_2\text{Cl} + n\text{-BuONa} \xrightarrow[\text{THF, reflux}]{\text{DB-18-CR-6}} \text{PhCH}_2\text{OBu}^n \tag{4.66}$$

Sam and Simmons reported that they achieved the monomethoxylation of dichlorobenzene by nucleophilic substitution with CH_3O^- through the use of a CH_3OK-crown ether complex.[80] Though the conversion was not very high, it is interesting that this reaction does not proceed by the benzoin mechanism (Eq. 4.67) since the usual byproducts of OH^-, such as phenol, diphenyl ether, and isomers, are not obtained.



(4.67)

Nucleophilic phenoxy-substitution of aromatic bromide was also reported recently (Eq. 4.68).[110] In the absence of crown ether, the reaction rates by reaction medium were in the order of DMSO > pyridine > methanol > dioxane-pyridine (1:1) > dioxane, but, in the presence of crown ether the order was converted to dioxane ≳ dioxane-pyridine > methanol.



(4.68)

Other workers reported that methoxymethyl ether was prepared in a high yield by the reaction of PhOK with $ClCH_2OCH_3$ in the presence of crown ether in acetonitrile at room temperature, and then calcon was prepared quantitatively from the methoxymethyl ether.[111]

E. Nitrile-Substitution and Nitro-Substitution

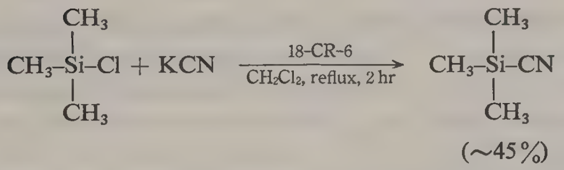
It was shown previously in Tables 4.7 and 4.8 that nitrile-substitution with KCN proceeds easily by means of liquid-liquid or solid-liquid phase transfer catalysis using crown compounds. Liotta *et al.* also reported the reactions in Eqs. (4.69) and (4.70) in which 18-crown-6 was used as a solid-liquid phase transfer catalyst.[112)] Durst *et al.* described the nitrile-substitution of benzyl chloride (Eq. 4.69), and they also prepared the nitrile easily from trimethylsilyl chloride, which was decomposed by water, by means of the same technique (Eq. 4.71).[113)] Racemic compounds of 4-(α-chlorobenzyl) anisole were converted to nitrile with the same technique and then converted to carboxylic acid.[114)]

$$RX + KCN \xrightarrow[CH_3CN,\text{ room temp. or }83^\circ C]{18\text{-CR-6}} RCN \qquad (4.69)$$

$R = 1\text{–}, 2\text{–}C_6H_{13}, 1,2\text{–}C_8H_{17}$; cyclohexyl benzyl
$X = Cl, Br$

$$X\text{–}R\text{–}Y + KCN \xrightarrow[CH_3CN,\text{ room temp. or }83^\circ C]{18\text{-CR-6}} NC\text{–}R\text{–}CN \qquad (4.70)$$

R = 1,3–propane 1,4–butane
$X = Y = Cl; X = Y = Br; X = Cl, Y = Br$



$$CH_3-\underset{CH_3}{\overset{CH_3}{Si}}-Cl + KCN \xrightarrow[CH_2Cl_2,\text{ reflux, 2 hr}]{18\text{-CR-6}} CH_3-\underset{CH_3}{\overset{CH_3}{Si}}-CN \qquad (4.71)$$

(~45%)

Rasmussen recently reported the reactions of benzaldoxime and trimethylsilyl chloride with KCN shown in Eqs. (4.72) and (4.73).[115)]

$$RCH = NOH + (CH_3)_3CiCl + KCN$$

$$\xrightarrow[CH_3CN\text{ reflux, 4 days}]{18\text{-CR-6}} PhCN + PhCH{=}NOSi(CH_3)_3 \qquad (4.72)$$

$$PhCH{=}NOH \quad \text{or} \quad PhCH{=}NOSi(CH_3)_3 + KCN$$

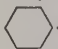
$$\xrightarrow[CH_3CN,\text{ heat}]{18\text{-CR-6}} CN + PhCONH_2 \qquad (4.73)$$

Durst *et al.* carried out nitro-substitution of haloalkane with KNO_2 by solid-liquid phase transfer catalysis (Eq. 4.74).[113)] The results are shown in Table 4.10.

$$\underset{(1\text{ mol})}{RX} + \underset{(1.1\text{ mol})}{KNO_2} \xrightarrow[CH_3CN,\ 25\sim40^\circ C]{18\text{-CR-6 (0.05 mol)}} RNO_2 \qquad (4.74)$$

Mastunaga and Yamashita carried out the reaction of $C_8H_{72}Br$ with $NaNO_2$ in the presence of catalytic amounts of 18-crown-6 and dicyclohexyl-18-crown-6 by means of 1) a homogeneous reaction using DMSO as a solvent and 2) solid-liquid phase transfer

TABLE 4.10 Nitro-substitution of haloalkanes with KNO_2 using 18-crown-6 as a solid-liquid phase transfer catalyst.[113)]

Haloalkane	Product	Yield (%)
n-$C_8H_{17}Br$	n-$C_8H_{17}NO_2$	65~70
n-$C_8H_{17}I$	n-$C_8H_{17}NO_2$	50~55
-Br	-NO_2	0~3
$PhCH_2CH_2Br$	$PhCH_2CH_2NO_2$	32
$PhCH_2CH_2CH_2Br$	$PhCH_2CH_2CH_2NO_2$	51
$PhCH_2Cl$	$PhCH_2NO_2$	34

Reaction conditions: *see* Eq. (4.74)

catalysis using CH_3CN as a solvent.[116)] Formation of nitrous acid ester, RONO, proceed together with nitration in both cases, and the formation of RONO predominated in the latter reaction system.

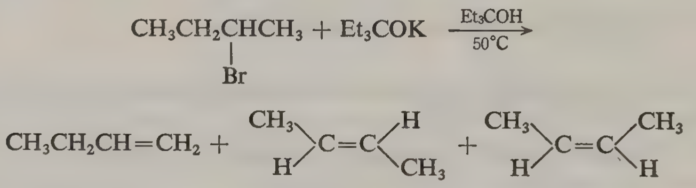
4.2.6 Elimination

A. β-Elimination

Considerable research has investigated the effects of crown ethers on β-elimination with bases such as alkoxide.[117~129)] A review by Bartsch provides a useful summary.[130)]

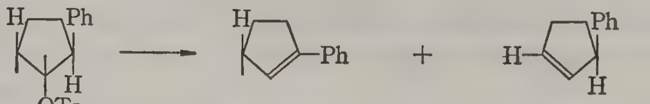
When alkoxides which are associated in solution are dissociated by crown ether, their reactivity becomes higher, and a different elimination mechanism yields products other than the usual ones.

For example, in the elimination reaction of 2-haloalkane with ROK-ROH (Eq. 4.75), the addition of dicyclohexyl-18-crown-6 caused both the selectivity for 1-alkene and the *trans* : *cis* ratio of 2-alkene to become nearly equal to those observed in dipolar aprotic solvents.[125)] In the elimination reaction of cyclopentyl-, cyclohexyl-, and norbornyl tosylate with *tert*-BuOK-*tert*-BuOH, *anti*-elimination predominated in the pres-



$$CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 + Et_3COK \xrightarrow[50°C]{Et_3COH} CH_3CH_2CH{=}CH_2 + (cis\text{-}CH_3CH{=}CHCH_3) + (trans\text{-}CH_3CH{=}CHCH_3) \qquad (4.75)$$

In the absence of crown (63.1%) (*trans*/*cis*: 1.04)
Addition of crown (equimol.) (37.3%) (*trans*/*cis*: 2.82)



(4.76)

(*syn*-elimination) (*anti*-elimination)

in the absence of crown 89%
addition of DC-18-CR-6 30%

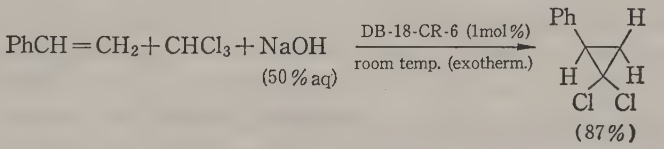
ence of crown ether while *syn*-elimination proceeded in its absence (Eq. 4.76).127) The kinetics of elimination of 1-bromo (or chloro)-2-aryl ethane were described by Alunni *et al.*131,132)

Recently Misono *et al.* reported that Cl-substitution was predominant in heterogeneous gas reactions of haloalkanes carried out over a silica gel permeated with a complex of KCl or $CaCl_2$ with dibenzo-18-crown-6, the ratio of substitution to elimination was 1— > *sec* and the relative reactivity of the haloalkanes was in the order of I > Br.133) In contrast, elimination predominated in the reactions over a silica gel bearing only KCl or $CaCl_2$. These results were apparently due to the increased nucleophilicity or basicity of the metal chloride brought about by complexation with the crown ether.

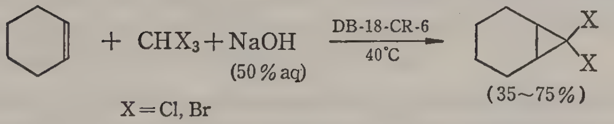
Since the basicity of the naked F^- generated by the crown ether is also increased, in some cases much more elimination occurs than substitution, as previously shown in Eqs. (4.51) ~ (4.53).83)

B. *α*-Elimination

Like quaternary ammonium and phosphonium salts, crown ether acts as a liquid-liquid phase transfer catalyst in the reaction of $CHCl_3$ with an aqueous solution of NaOH and easily generates carbene at room temperature; the carbene forms a *gem*-dihalocyclopropane ring by addition to the unsaturated bond, as shown in Eqs. (4.77)134,135) and (4.78).136)

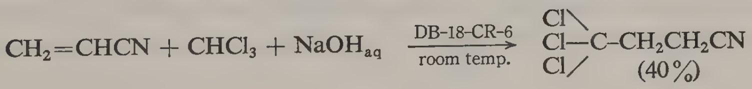


(4.77)



(4.78)

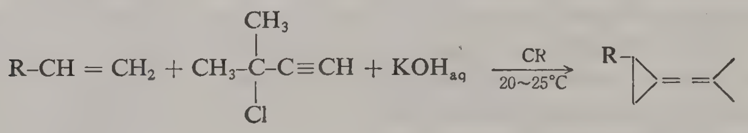
Under the same conditions, addition to acrylonitrile occurs as shown in Eq. (4.79)134,135) and diazomethane is formed from hydrazine as shown Eq. (4.80).137)



$$CH_2{=}CHCN + CHCl_3 + NaOH_{aq} \xrightarrow[\text{room temp.}]{\text{DB-18-CR-6}} Cl_3C{-}CH_2CH_2CN \quad (40\%) \qquad (4.79)$$

$$\underset{\text{(hydrate)}}{NH_2NH_2} + CHCl_3 + KOH_{aq} \xrightarrow[\text{Et}_2\text{O room temp.}]{\text{18-CR-6 (0.04 mol\%)}} \underset{(48\%)}{CH_2N_2} \qquad (4.80)$$

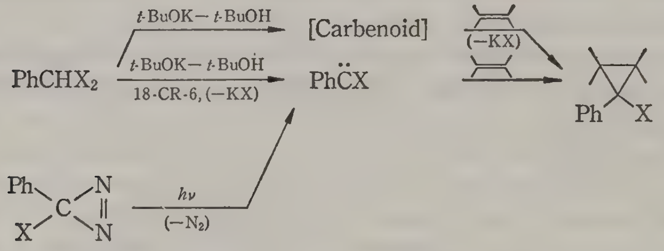
Sasaki *et al.* compared the phase transfer catalytic activities of various crown ethers with those of quaternary ammonium salts in the preparation of dimethylvinylidene cyclopropane derivative, which involves the addition to olefin of dimethylvinylidene carbene generated from 3-chloro-3-methyl-1-butyne (Eq. 4.81).138) The results showed that the catalytic activities of dibenzo-18-crown-6, dicyclohexyl-18-crown-6, and 18-crown-6 were much higher than those of quaternary ammonium salts, and that a higher yield of product was obtained with crown ethers.



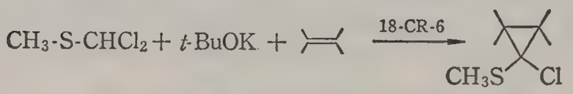
(4.81)

R = Ph: Yield 86% (2 hr)

As shown in Eqs. (4.82) and (4.83), carbenes generated by α-elimination using alkoxide usually have the reactivity of carbenoid, but they have the reactivity of free carbene in the presence of 18-crown-6.[139,140]



(4.82)

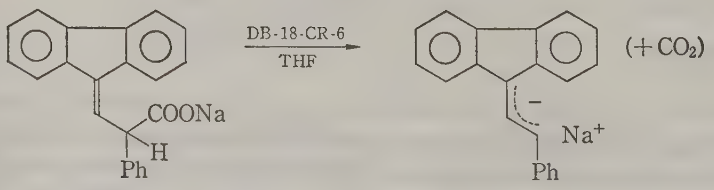


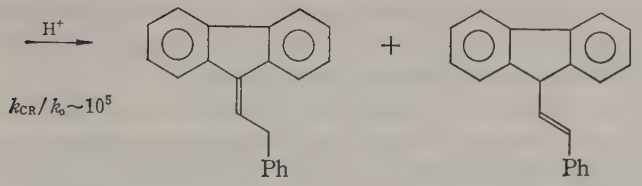
(4.83)

It was also reported that singlet carbetoxynitrene, :NCO_2Et, generated by photolysis of ethylazide formate, N_3CO_2Et, was stabilized by dibenzo-18-crown-6.[141]

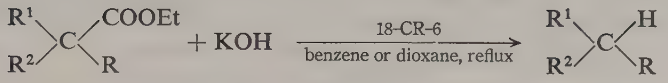
C. Other Elimination Reactions

Hunter *et al.* reported that the reaction rate of the decarboxylation shown in Eq. (4.84) increased up to 10^5 times on the addition of dibenzo-18-crown-6,[142] and they also described the hydrolysis-decarboxylation of malonic acid derivative shown in Eq. (4.85).[143]





(4.84)



(4.85)

R = COOEt, COOMe, CN (45 ~ 95%)

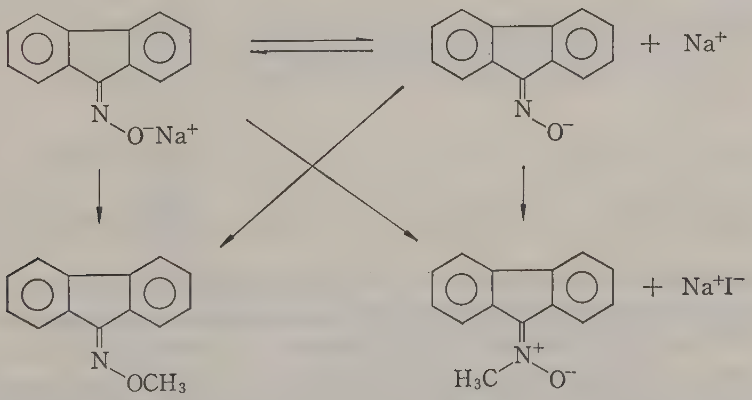
R^1 = Bu, Pr, Ph, AcNH; R^2 = H; $R^1R^2 = (CH_2)_5$

Decarboxylation with naked F^-, which is highly basic, was shown previously in Eq. (4.57b).[91)]

4.2.7 Condensation

A. Alkylation and Arylation

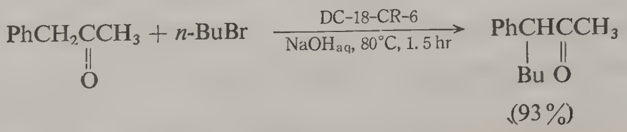
The effects of crown ethers on *O*-alkylation and *C*-alkylation have been investigated. Smith and Hanson reported that in the methylation of the Na salt of 9-fluorenone oxime with CH_3I or CH_3OTs (in a mixture of 33.5% CH_3CN and 66.5% *tert*-BuOH at 25° C), the concentration dependence of the reaction rate decreased and *O*-methylation predominated in the presence of an amount of dibenzo-18-crown-6 equimolar to the Na salt, but in the absence of crown ether, the second-order reaction rate and the ratio of *O*-alkylation/*N*-alkylation depended on concentration (Eq. 4.86).[144)] It is thought that these results are due to the increase in the dissociation of Na-oximate brought about by the crown ether, which suggests an interesting possibility for a method to control the position of alkylation of amphoteric ion compounds.



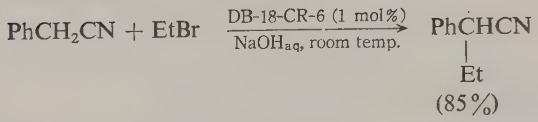
(4.86)

In the ethylation of Na, K, and Cs salts of ethyl acetoacetate enolate with EtOTs, it was found that *O*-alkylation was decreased by the addition of dibenzo-18-crown-6 or dicyclohexyl-18-crown-6, and the effect was in the order of K > Cs > Na.[145~147] Cryptands were recently found to exert a similar effect.[148]

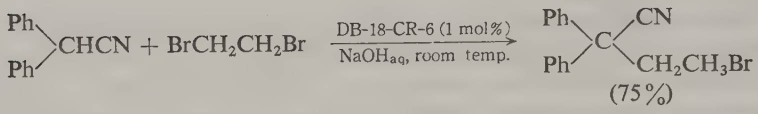
There are several reported instances of *C*-alkylation in which crown ethers were used as phase transfer catalysts. Methylbenzyl ketone was alkylated in a 83% yield at the α-methylene position according to Eq. (4.87),[41] and the α-hydrogen of nitrile was abstracted by NaOH in the presence of crown ether and then alkylated (or arylated) by alkyl (or aryl) halide (Eqs. 4.88 ~ 4.91).[134,135]



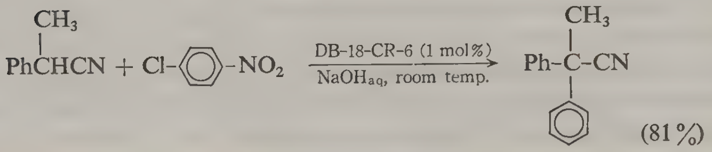
$$\underset{\overset{\|}{O}}{PhCH_2CCH_3} + n\text{-}BuBr \xrightarrow[\text{NaOH}_{aq},\ 80^\circ\text{C, 1.5 hr}]{\text{DC-18-CR-6}} \underset{\text{Bu}\ \ \text{O}}{PhCHCCH_3} \quad (93\%) \tag{4.87}$$



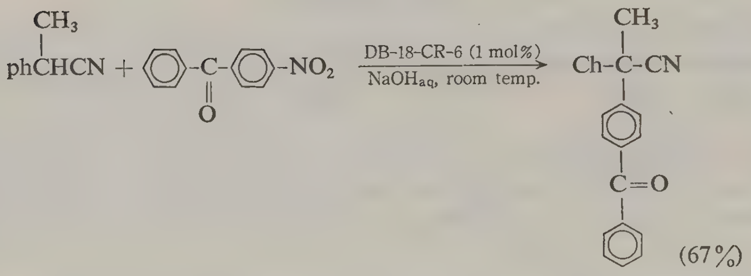
$$PhCH_2CN + EtBr \xrightarrow[\text{NaOH}_{aq},\ \text{room temp.}]{\text{DB-18-CR-6 (1 mol\%)}} \underset{\underset{Et}{|}}{PhCHCN} \quad (85\%) \tag{4.88}$$



(4.89)

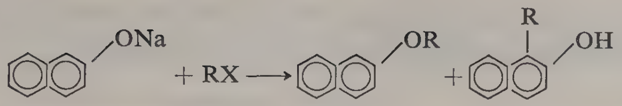


(4.90)



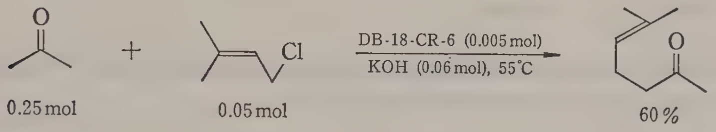
(4.91)

In the alkylation of Na-β-naphthoxide with haloalkane, it is known that *C*-alkylation proceeds in a protic solvent while *O*-alkylation proceeds in a dipolar aprotic solvent such as DMSO and DMF. However, in the presence of a catalytic amount of crown ether or cryptand, *O*-alkylation occurs predominantly (~ 90%) in a protic solvent (water), and *O*-alkylation also proceeds even in a nonpolar solvent such as benzene (yield of alkylated product: ~ 77%; selectivity of *O*-alkylation: 98%) (Eq. 4.92).[149]



(4.92)

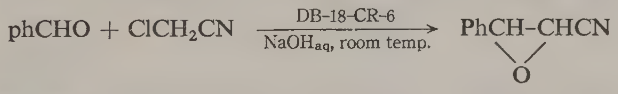
With regard to the alkylation of α, β-unsaturated ketones, Saito *et al.* reported the preparation of jasmones such as *cis*-jasmone by the alkylation of 3-methyl-2-cyclopentenone, which was barely alkylated in a nonpolar solvent, using a catalytic amount of crown ether.[150] The synthesis of methylheptenone by the alkylation of acetone with prenyl chloride (Eq. 4.93) was also reported by Saito *et al.*[151]



(4.93)

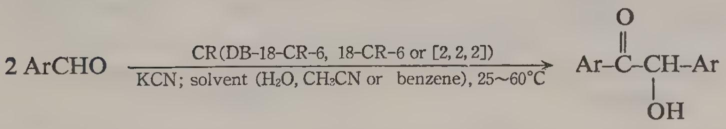
B. Other Condensation Reactions

Makosza and Ludwikow reported that dibenzo-18-crown-6 acted as a phase transfer catalyst in the Darzen reaction shown in Eq. (4.94).[134,135] Akabori *et al.* employed crown ethers and cryptand as liquid-liquid or solid-liquid phase transfer catalysts in a benzoin condensation (Eq. 4.95).[152] Nakabayashi *et al.* found that the preparation of thioether according to Eq. (4.96) was possible in the presence of crown ether and suggested that this was due to the activation of RPhS⁻ by complexation of the proton of the thiol with crown ether.[153]



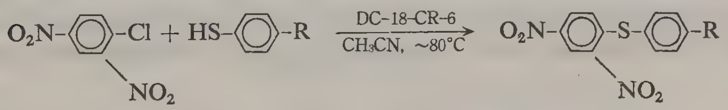
$$\mathrm{phCHO} + \mathrm{ClCH_2CN} \xrightarrow[\text{NaOH}_{\text{aq}}\text{, room temp.}]{\text{DB-18-CR-6}} \underset{\diagdown\,\mathrm{O}\,\diagup}{\mathrm{PhCH{-}CHCN}} \qquad (4.94)$$

(78 %)



$$2\,\mathrm{ArCHO} \xrightarrow[\text{KCN; solvent (H}_2\text{O, CH}_3\text{CN or benzene), }25\sim60^\circ\text{C}]{\text{CR(DB-18-CR-6, 18-CR-6 or [2, 2, 2])}} \mathrm{Ar{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\underset{\underset{\displaystyle OH}{|}}{CH}{-}Ar} \qquad (4.95)$$

Yield: Ar = Ph (74 ~ 96 %), *p*-CH_3–Ph (90 ~ 99 %), furyl (52 ~ 66 %)



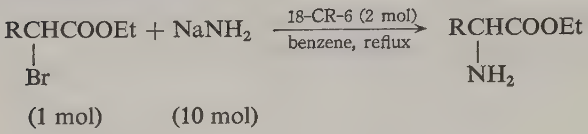
(4.96)

Yield: R = NO_2 (17 %), Br (42 %), Cl(31 %), CH_3O (13 %), H (7.9 %)

Tabushi *et al.* applied crown ether to amination and amino acid synthesis.[154] In the presence of a catalytic amount of 18-crown-6 and tetraglyme, benzyl chloride was converted to acetoamide derivative by reaction with Na-acetoamide (Eq. 4.97), and α-

halocarboxylic acid esters were aminated with $NaNH_2$ (Eq. 4.98) to give alanine from ethyl α-bromopropionate and glycine from ethyl α-bromoacetate.

$$\underset{(1\ \text{mol})}{PhCH_2Cl} + \underset{(5\ \text{mol})}{AcNHNa} \xrightarrow[CH_3CN,\ \text{reflux}]{\begin{cases}\text{18-CR-6} & (0.02\sim1\ \text{mol})\\ \text{tetraglyme} & (0\sim0.5\ \text{mol})\end{cases}} \underset{(43\sim46\%)}{PhCH_2NHAc} \qquad (4.97)$$

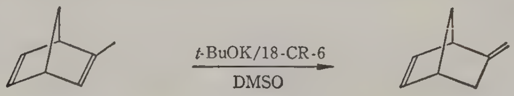


$$\underset{(1\ \text{mol})}{\underset{\displaystyle Br}{RCHCOOEt}} + \underset{(10\ \text{mol})}{NaNH_2} \xrightarrow[\text{benzene, reflux}]{\text{18-CR-6 (2 mol)}} \underset{\displaystyle NH_2}{RCHCOOEt} \qquad (4.98)$$

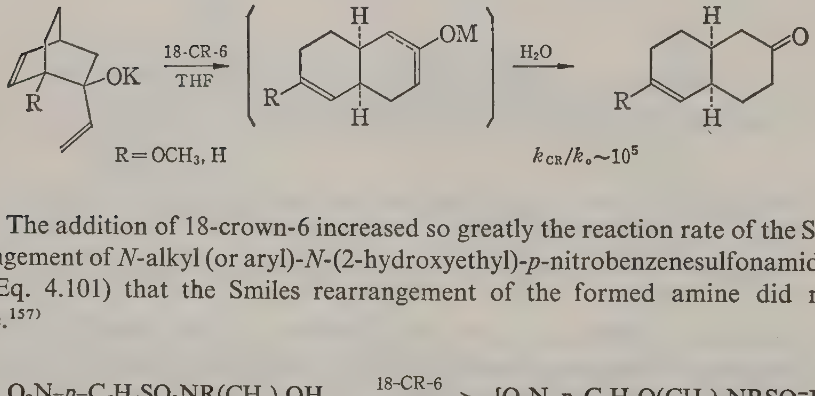
It was reported that pinacol was formed by photo-irradiation of a 1 : 1 mixture of *p*-cyanoacetophenone and 18-crown-6 in benzene.[155)]

4.2.8 Isomerization and Rearrangement

The rate of the isomerization reaction shown in Eq. (4.99) with *tert*-BuOK in DMSO was markedly increased on the addition of 18-crown-6.[120)] The addition of tetraglyme had no effect. The reaction rate of an Oxy-Cope rearrangement of 1, 5-dienealkoxide (Eq. 4.100) was also accelerated up to 10^5 times by the addition of 18-crown-6.[156)]



(4.99)



(4.100)

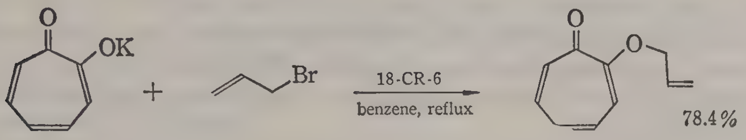
The addition of 18-crown-6 increased so greatly the reaction rate of the Smiles rearrangement of *N*-alkyl (or aryl)-*N*-(2-hydroxyethyl)-*p*-nitrobenzenesulfonamide caused by (Eq. 4.101) that the Smiles rearrangement of the formed amine did not take place.[157)]

$$O_2N\text{-}p\text{-}C_6H_4SO_2NR(CH_2)_2OH \xrightarrow[KOH,\ CH_2Cl_2]{\text{18-CR-6}} [O_2N\text{-}p\text{-}C_6H_4O(CH_2)_2NRSO^-]$$

$$\downarrow$$

$$O_2N\text{-}p\text{-}C_6H_4NR(CH_2)_2OH \dashleftarrow \times \cdots\cdots O_2N\text{-}p\text{-}C_6H_4O(CH_2)_2NHR \qquad (4.101)$$

The usual preparation of allyl ether derivatives of tropolone, which are the precursors of the Claisen rearrangement, requires the careful treatment of the Ag salt of tropolone with allyl iodide in a thoroughly dry system, but recently the ether was easily obtained in a high yield by the reaction of a K salt of tropolone with allyl bromide in the presence of 18-crown-6 in benzene (Eq. 4.102).[158] Various tropolone derivatives have been prepared with this method.

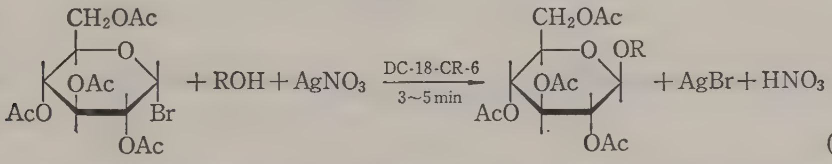


(4.102)

4.2.9 Other Reactions

A. König-Knorr Alcoholysis

König-Knorr alcoholysis of acetobromoglucose using $AgNO_3$ (Eq. 4.103) proceeds rapidly in the presence of crown ether or cryptand to give β-glucoside.[159,160]



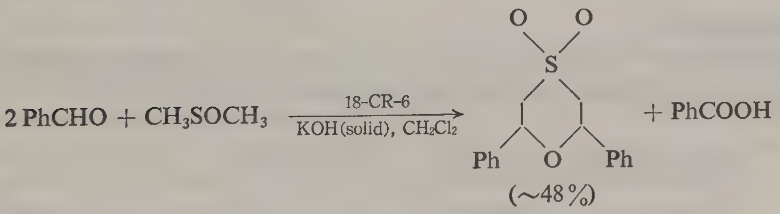
(4.103)

Yield: R = CH_3(81%), *i*-Pr (65%), *t*-Bu (51%), Cyclohexyl (43%)

B. Cannizzaro Reaction

The Cannizzaro reaction (Eq. 4.104) and the reaction of aldelyde with sulfone (Eq. 4.105) were reported to take place by liquid-liquid or solid-liquid phase transfer catalysis with 18-crown-6.[161]

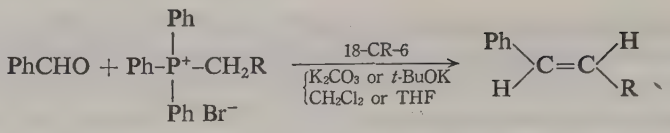
$$2PhCHO \xrightarrow[\text{benzene or } CH_2Cl_2]{\text{18-CR-6, KOH (aq. or solid)}} PhCOOH + PhCH_2OK \qquad (4.104)$$



(4.105)

C. Wittig Reaction and Horner-Wittig Reaction

In olefin synthesis by the Wittig reaction, *trans*-alkene was stereoselectively obtained under mild conditions in the presence of 18-crown-6 (Eq. 4.106).[162]



$$\mathrm{PhCHO} + \mathrm{Ph_3P^+{-}CH_2R\ Br^-} \xrightarrow[\substack{K_2CO_3 \text{ or } t\text{-BuOK} \\ CH_2Cl_2 \text{ or } THF}]{\text{18-CR-6}} \mathrm{PhCH{=}CHR} \tag{4.106}$$

R = CH_3, Ph (Yield 82 ~ 97%)

When a CH_2Cl_2 solution of α-phosphorylalkylsulfide, sulfoxide or sulfone, and aldehyde was mixed and stirred at room temperature together with a 50% aqueous solution of NaOH and crown ether as a phase transfer catalyst, the Horner-Wittig reaction proceeded and gave the corresponding α, β-unsaturated sulfides, sulfoxides, and sulfones in high yields.$^{163)}$

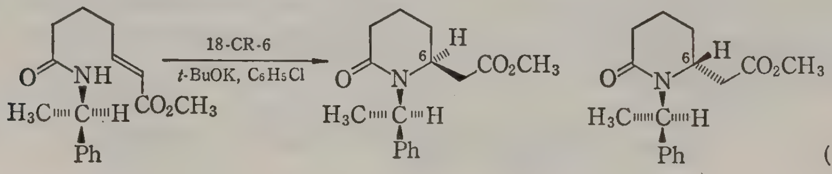
D. Michael Addition

As shown in Eqs. (4.107) and (4.108), 18-crown-6 catalyzes the Michael addition because of strong basicity of the naked F^- generated by the solubilization of KF in benzene, CH_2Cl_2, or acetonitrile.$^{164)}$

$$\mathrm{PhCH=CHCOPh + CH_3NO_2} \xrightarrow[\text{KF, CH}_3\text{CN, 81°C, 1.5 hr}]{\text{18-CR-6}} \mathrm{O_2NCH_2CH(Ph)CH_2COPh} \quad (94\%) \tag{4.107}$$

$$\mathrm{CH_2{=}CHCN + CH_3NO_2} \xrightarrow[\text{KF, CH}_3\text{CN, 81°C, 2.5 hr}]{\text{18-CR-6}} \mathrm{O_2NC(CH_2CHCN)_2} \quad (72\%) \tag{4.108}$$

Wakabayashi and Kato reported recently on the intramolecular nucleophilic Michael addition of α, β-unsaturated ester having a chiral amide using *tert*-BuOK as a catalyst in the presence of crown ether (Eq. 4.109).$^{165)}$



(4.109)

E. Photocyanation

The naked CN^- anions generated by 18-crown-6 were applied to the photocyanation of polycyclic aromatic hydrocarbons in acetonitrile (Eq. 4.110).$^{166)}$

$$\left.\begin{array}{lll}
\text{Naphthalene} & \xrightarrow[\text{KCN, CH}_3\text{CN, } h\nu]{\text{18-CR-6}} & \text{1-Cyano-(15\%)} \\
\text{Anthracene} & \xrightarrow[\text{KCN, CH}_3\text{CN, } h\nu]{\text{18-CR-6}} & \text{9-Cyano-(10\%), 9, 10-Dicyano-(10\%)} \\
\text{Phenanthrene} & \xrightarrow[\text{KCN, CH}_3\text{CN, } h\nu]{\text{18-CR-6}} & \text{9-Cyano-(25\%)} \\
\text{Biphenyl} & \xrightarrow[\text{KCN, CH}_3\text{CN, } h\nu]{\text{18-CR-6}} & \text{4-Cyano-(50\%), Dicyano-(10\%)}
\end{array}\right\} \tag{4.110}$$

F. Direct Synthesis of *α*, *β*-Unsaturated Nitriles

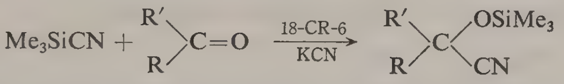
Acetonitrile reacts with ketones or aldehydes in the presence of KOH and 18-crown-6, and successive condensation-dehydration proceeds spontaneously in a short time to give *α*, *β*-unsaturated nitriles directly (Eq. 4.111).[167)]

$$CH_3CN + R\text{–}CO\text{–}R' \xrightarrow[KOH]{18\text{-}CR\text{-}6} RR'C{=}CHCN \qquad (4.111)$$

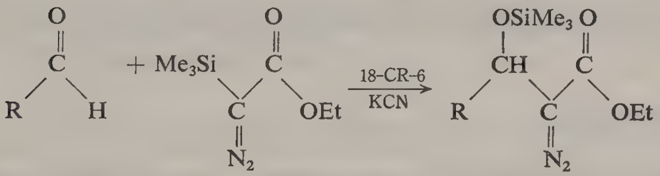
$R = Ph, 4\text{–}Me\text{–}Ph, 4\text{–}Cl\text{–}Ph, \text{–}(CH_2)_5, etc. \quad (50{\sim}88\%)$
$R' = H, Ph$

G. Reactions of Si Compounds

Substitution of $(CH_3)_3SiCl$, which decomposes in the presence of water, can be achieved by solid-liquid phase transfer catalysis using crown ether, as described previously in Section 4.2.5.E (Eqs. 4.71, 4.72). Regarding other reactions with Si compounds, Evans and Truesdale carried out the cyanosilylation of ketone (Eq. 4.112.[168)] and the reaction of aldehydes with ethyl *α*-trimethylsilyldiazoacetate (Eq. 4.113)[169)] catalyzed by KCN-crown ether complex.



(4.112)



(4.113)

H. Reactions of Diazonium Compounds

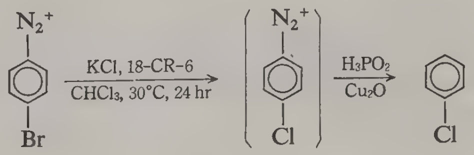
As noted in Section 3.2.1, aromatic diazonium salts form complexes with crown ethers, the proposed structure of which is shown in Fig. 3.5. Many recent studies have reported applications of the diazonium salt complexes to organic syntheses.

Bartsch *et al.* examined the thermal stability of the complexes of $ArN_2{}^+BF_4{}^-$ with various 18-crown ethers in 1, 2-dichloroethane at 50° C and found that the most stable complex was formed with 18-crown-6.[170)]

Hartman and Biffar found that diazonium $BF_4{}^-$ salt was easily reduced by copper powder (by decomposition of the diazonium group) in CH_2Cl_2 in the presence of a catalytic amount (10 mol%) of dicyclohexyl-18-crown-6,[171)] and Gokel *et al.* also reported that the diazonium group was reduced quantitatively by $H_3PO_2\text{–}Cu_2O$ (a slight amount) and 18-crown-6 (7.5 mol%) in a nonpolar solvent.[172)] Though the role of the crown ether is not clear, it is presumed that a thermal or photochemical Schieman reaction in which F-substitution occurs (Eq. 4.114) is inhibited by the crown ether,[170,173)] and in addition, diazonium salt is solubilized in nonpolar solvent by complexation with the crown ether.

$$Ph\text{–}\overset{+}{N}{\equiv}N\cdot BF_4{}^- \xrightarrow{\Delta \text{ or } h\nu} PhF + N_2 + BF_3 \qquad (4.114)$$

Gokel *et al.* experimented with halogen-substitution of 4-bromobenzene diazonium BF_4^- which was solubilized in chloroform by 18-crown-6 with KCl.[174] After treatment of the reaction mixture with H_3PO_2-Cu_2O, chlorobenzene was obtained in a 57% yield (Eq. 4.115). When KOAc was used, an acetate-substitution product was not obtained,[175] but asymmetrical biaryl was formed in benzene,[176] so the reaction mechanism shown in Eq. (4.116) was proposed.



(4.115)

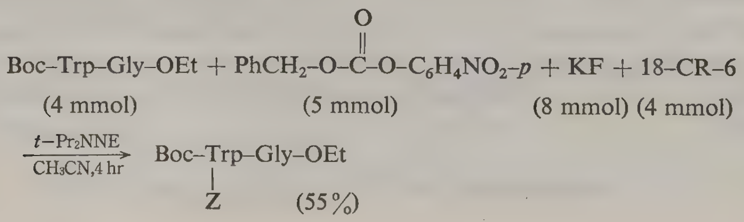
$$\left.\begin{aligned}
&\text{Ar–N}_2{}^+\text{BF}_4{}^- + (\text{K}^+)^-\text{OAc} \rightleftharpoons \text{KBF}_4 + \text{Ar–N=N–OAc}\\
&\text{Ar–N=N–OAc} + \text{AcO}^- \longrightarrow \text{Ar–N=N–O}^- + \text{Ac}_2\text{O}\\
&\text{Ar–N=N–O}^- + {}^+\text{N}_2\text{–Ar} \longrightarrow \text{Ar–N=N–O–N=N–Ar}\\
&\text{Ar–N=N–O–N=Ar} \longrightarrow \text{Ar–N=N–O}\cdot + \text{N}_2 + \text{Ar}\cdot\\
&\text{Ar}\cdot + \text{C}_6\text{H}_6 \longrightarrow \text{Ar–C}_6\text{H}_5
\end{aligned}\right\} \qquad (4.116)$$

The spectra of the diazonium ion in nonpolar solvents were reported recently by Gokel *et al.*[177]

4.2.10 Peptide Synthesis

Among the applications of crown compounds to the synthesis of nucleotides or peptides, Section 4.2.5 described the synthesis of F-substituted nucleotide **(168)**[94] and solid phase synthesis using the reaction of chloromethylated polystyrene with the K salt of Boc-amino acid (Eq. 4.64).[107]

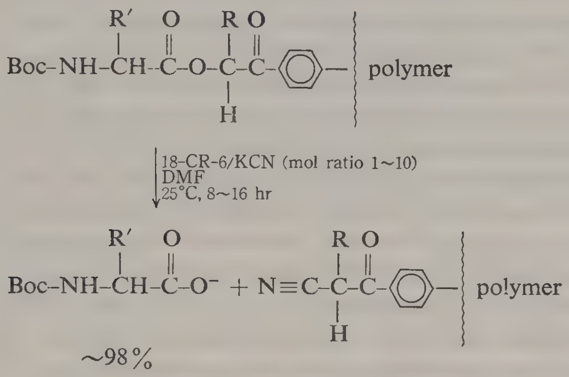
In doing benzyloxycarbonylation for the protection of the indol nitrogen of tryptophan against acid, Klausner and Chorov achieved a rapid acylation by using crown ether (18-crown-6 or dicyclohexyl-18-crown-6) and KF together with *p*-nitrophenylbenzyl carbonate as a reagent (Eq. 4.117).[178,179] Under these acylation conditions, racemization did not occur. The protective group was eliminated by catalytic reduction or treatment with hydrazine or HF. This method, based on proton abstraction from indol nitrogen by the strongly basic, naked F, exemplifies the skillful application of crown ethers.



$$\underset{(4\ \text{mmol})}{\text{Boc–Trp–Gly–OEt}} + \underset{(5\ \text{mmol})}{\text{PhCH}_2\text{–O–}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{–O–C}_6\text{H}_4\text{NO}_2\text{-}p} + \underset{(8\ \text{mmol})}{\text{KF}} + \underset{(4\ \text{mmol})}{\text{18–CR–6}}$$

$$\xrightarrow[\text{CH}_3\text{CN,4 hr}]{t\text{–Pr}_2\text{NNE}} \text{Boc–}\underset{\text{Z}}{\underset{|}{\text{Trp}}}\text{–Gly–OEt} \quad (55\%) \qquad (4.117)$$

Merrifield, the creator of solid phase synthesis of peptides, and his coworkers recently used crown ether in one of the unit operations of the synthesis, the selective elimination of protected amino acid or peptide from the polymer to which these fragments were linked by oxyacyl bonding.[180] As shown in Eq. (4.118), ester cleavage was achieved by naked CN^- generated by crown ether in the elimination reaction of Boc-amino acid from Boc-aminoacyloxyacyl-polystyrene resin. The cleavage took place quantitatively in a short time, as shown in Table 4.11, in contrast with the conventional methods such as hydrolysis with NaOH in dioxane-water (24 hours, 57% yield) or thiolysis with PhSNa in DMF (24 hours, 48 ~ 82% yield).



(4.118)

TABLE 4.11 Elimination of boc-amino acid and reptide from oxyacyl resin using KCN/18-crown-6.[180]

Oxyacyl resin	Molar ratio of KCN/CR	Time (hr)	Yield† (%)
Boc–Gly–OCH(CH_3)–CO–resin	1.0	16	94 (96)
Boc–Gly–OCH(CH_3)–CO–resin	0.4	8	92
Boc–Gly–OCH(CH_3)–CO–resin	0.2	8	95
Boc–Gly–OCH(CH_3)–CO–resin	0.1	8	90
Boc–Gly–OCH$_2$–CO–resin	1.0	16	97 (98)
Boc–Gly–OCH$_2$–CO–resin	0.4	8	93
Boc–Gly–OCH$_2$–CO–resin	0.2	8	89
Boc–Gly–OCH$_2$–CO–resin	0.1	8	89
Boc–Gly–Gly–Leu–Val–Gln–Pro–Gly–OCH(CH_3)–CO–resin	0.4	18	(93)
Boc–Gly–Gly–Leu–Val–Gln–Pro–Gly–OCH(CH_3)–CO–resin	0.2	2 × 12	86
Boc–Gly–Gly–Leu–Val–Gln–Pro–Gly–OCH(CH_3)–CO–resin	0.1	2 × 12	87

†( ): NMP solvent; others: DMF

Thus, crown ethers can be effectively applied to the protection of amino acids, immobilization onto polymer support, and elimination from polymer, all of which are the basic unit operations of the solid phase synthesis of peptides, and important developments in the use of these methods may be anticipated in the future.

4.2.11 Metalation

The capacity of crown ethers to solubilize alkali metal compounds, organoalkali metal compounds, and alkali metals in organic solvents can be applied to the metalation of organic compounds as a new technique. It is known that the metalation of $PhCH_2CPh_2CH_2Cl$ with K and Cs and the metal exchange of $PhCH_2CPh_2CH_2Li$ with *tert*-BuOk and *tert*-BuOCs both proceed smoothly in THF with 18-crown-6,181) and the metalation of 6-methyl-6-phenylcyclohexadiene with Li-, Na-, K-, and Cs-amide by using crown ether has been reported.182)

Potassium hydride is a very strong base (superbase) and may be applicable to syntheses of organometallic compounds as a strong base by which hydrocarbon can be ionized. From the results of extensive investigations by Brown,183~187) however, it had been thought that metalation of a weak "hydrocarbonic acid" such as triphenylmethane (pK_a 31.4) could not be achieved with KH, although KH is superior to LiH and NaH as a metalating reagent in general. Recently, Buncel and Menon succeeded in the metalation of triphenylmethane with KH in THF in the presence of an equimolar amount of 18-crown-6 (Eq. 4.119).188) Diphenylmethane (pK_a 33.1), di-*p*-tolylmethane (pK_a 35.1), and di-2, 4-xylylmethane (pK_a 36.3) were also metalated similarly, but weaker hydrocarbonic acids such as *p*-pheyltoluene (pK_a 38.6) and cumene (pK_a 41) were not metalated under these reaction conditions. From these results Buncel and Menon estimated the relative acidity of hydrogen in hydrocarbons.

$$PH_3CH + KH \xrightarrow[\text{THF, room temp.}]{\text{18-CR-6}} Ph_3\,CK + H_2 \qquad (4.119)$$

Sakurai *et al.* reported that hexamethyldisilane reacted with CH_3OK in the presence of 18-crown-6 in THF, benzene, and hexane to cleave the Si-Si bond, resulting in metalation and methoxylation, as shown in Eq. (4.120).189,190) The Me_3 SiK thus produced acts as strong electron transfer agent even in a low-polar solvent such as hexane. When naphthalene or benzophenone is added to this reaction mixture, a radical anion of the aromatic compound which shows a characteristic esr spectrum is formed by electron transfer.

$$Me_3SiSiMe_3 + KOMe \xrightarrow[\text{solvent}]{\text{18-CR-6}} Me_3SiK + Me_3SiOMe \qquad (4.120)$$

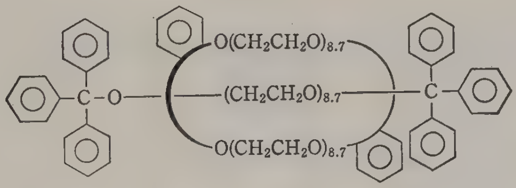
With respect to radical anions of aromatic hydrocarbons, Sections 3.2.4 and 3.3.2.C described the formation of radical anions by solubilized alkali metals using crown ethers or cryptands.191~193) Other workers have reported that the decomposition of the unstable radical anion of 4*H*-cyclopenta[*def*]phenanthrene in THF was suppressed by the addition of dibenzo-18-crown-6 because of the formation of a contact-crown separated ion pair.194) Another group found that the addition of dicyclohexyl-18-crown-6 and 18-crown-6 increased the second-order reaction rate constant in the reaction of Na-naphthalene (radical anion) complex with hexyl fluoride in which the solvent effect of THF, DMF, and others is quite small.195)

4.2.12 Oligomerization

Orvik investigated the effect that the addition of 12-crown-4, cyclic tetramer of propylene oxide (**16**), and 18-crown-6 had on the oligomerization of ethylene oxide (ring opening addition of 1 ~ 5 mol of ethylene oxide to butanol) using alkali hydroxide as a catalyst and 1-butanol as a solvent.[196)] When NaOH was used as a catalyst, the addition of 18-crown-6 caused the reaction rate to increase more than tenfold, and the molecular weight distribution was shifted to the lower molecular weight products, decreasing the formation of trimer to pentamer of ethylene oxide. It was hypothesized that, in the absence of crown ether, the chain transfer reaction was inhibited until the length of a tetramer or pentamer was reached because the propagating oligomer chain was wound around Na^+, which behaved as a template, as mentioned in Section 2.2.3. However, in the presence of crown ether, no inhibition occurred because the Na^+ was incorporated into the crown ring, so that the polymerization terminated after the formation of 1 ~ 2 mol adducts.

Recently, Dmowski *et al.* carried out oligomerization of fluoroolefins ($n = 2 \sim 3$) using as an initiator KF or CsF which was solubilized in acetonitrile or THF by 18-crown-6.[197)] In the case of $CF_2 = CFCF_3$, the rate and yield of oligomerization ($n = 2 \sim 3$) were increased by the use of crown ether, but no effect was observed in the case of $CF_2 = CF_2$.

Zilkha *et al.* prepared rotaxane (**171**), a particular type of oligomer having bulky groups at both terminals, by the oligomerization of ethylene oxide using dipotassium tetraethyleneglycolate as an initiator in the presence of 30- ~ 58-membered crown ethers, followed by termination with triphenylchloromethane.[198)] Catenane (**172**) was subsequently prepared by ring closure of the rotaxane.[199)]



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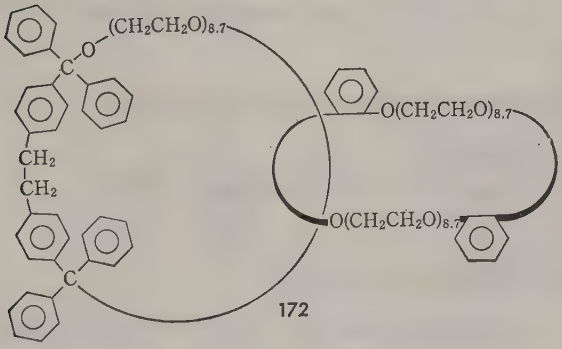

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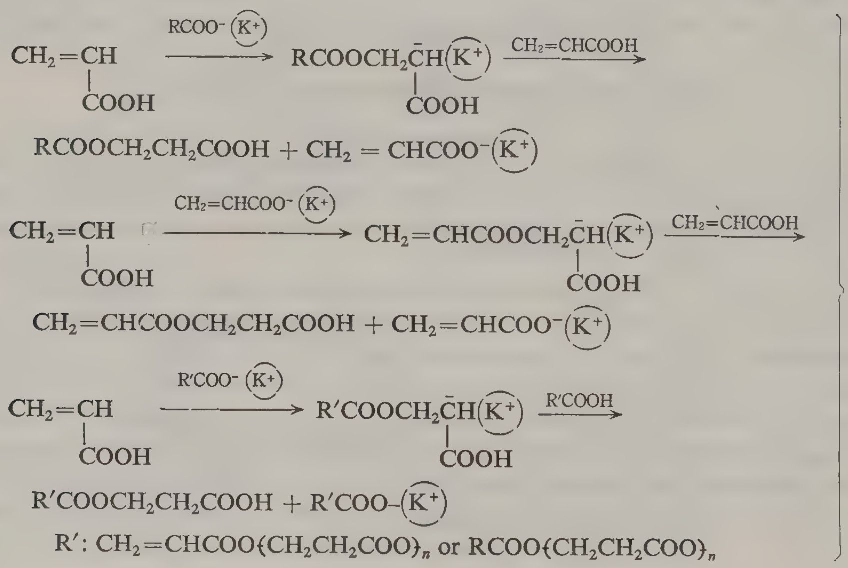
4.2.13 Polymerization

A. Addition Polymerization

There have recently been extensive investigations of anionic polymerization and its mechanism and kinetics that utilized the solubilization of organoalkali metal compounds or alkali metals in organic solvents by crown ethers or cryptands. Hogen Esch *et al.* studied the ion pairs of the complexes between 2-, 3-, or 4-vinyl pyridine carbanion and L^+-, Na^+-, Cs^+-dibenzo (or dicyclohexyl)-18-crown-6 as a part of their work on the structure and behavior of ion pairs in solution,[200)] as in Section 3.2.2.B. This was the first study of the application of crown ethers to anionic polymerization of polar vinyl monomers.

Cheng and Halasa investigated the effects of adding crown ether on the anionic polymerization of butadiene and on the anionic copolymerization of butadiene and styrene in hexane using *n*-BuNa prepared from *n*-BuCl and Na dispersion as an initiator.[201)] In the system in which was added about 0.2 molar equivalent of dicyclohexyl-18-crown-6 to Na, high molecular weight polybutadiene consisting of about 80% vinyl bonding was obtained in 95% conversion at a polymerization temperature of 30 ~ 50° C; low molecular weight polymer was obtained in low conversion in the absence of crown ether. Styrene block was not present in the butadiene-styrene copolymer.

Otsu *et al.* carried out the polymerization of acrylic acid at 80° C using KOAc-18-crown-6 complex as an initiator and obtained a polyester with polymerization degree of less than 14. It is thought that the polyester was formed by nucleophilically successive addition (Michael addition) of acrylate anion whose nucleophilicity was increased by complexation of K^+, as shown in Eq. (4.121).[202)] The polymerization did not proceed in the case of methacrylic acid.



$$\underset{\textstyle\mathrm{COOH}}{\mathrm{CH_2{=}CH}} \xrightarrow{\mathrm{RCOO^-}\,(\mathrm{K^+})} \mathrm{RCOOCH_2}\underset{\textstyle\mathrm{COOH}}{\bar{\mathrm{C}}\mathrm{H}}(\mathrm{K^+}) \xrightarrow{\mathrm{CH_2{=}CHCOOH}}$$

$$\mathrm{RCOOCH_2CH_2COOH + CH_2 = CHCOO^-}(\mathrm{K^+})$$

$$\underset{\textstyle\mathrm{COOH}}{\mathrm{CH_2{=}CH}} \xrightarrow{\mathrm{CH_2{=}CHCOO^-}\,(\mathrm{K^+})} \mathrm{CH_2{=}CHCOOCH_2}\underset{\textstyle\mathrm{COOH}}{\bar{\mathrm{C}}\mathrm{H}}(\mathrm{K^+}) \xrightarrow{\mathrm{CH_2{=}CHCOOH}} \qquad (4.121)$$

$$\mathrm{CH_2{=}CHCOOCH_2CH_2COOH + CH_2{=}CHCOO^-}(\mathrm{K^+})$$

$$\underset{\textstyle\mathrm{COOH}}{\mathrm{CH_2{=}CH}} \xrightarrow{\mathrm{R'COO^-}\,(\mathrm{K^+})} \mathrm{R'COOCH_2}\underset{\textstyle\mathrm{COOH}}{\bar{\mathrm{C}}\mathrm{H}}(\mathrm{K^+}) \xrightarrow{\mathrm{R'COOH}}$$

$$\mathrm{R'COOCH_2CH_2COOH + R'COO{-}}(\mathrm{K^+})$$

$$\mathrm{R'\!:\ CH_2{=}CHCOO\{CH_2CH_2COO\}_{\mathit{n}}\ \text{or}\ RCOO\{CH_2CH_2COO\}_{\mathit{n}}}$$

Table 4.12 Anionic polymerzation by alkali metal solutions.206)

Initiator		Solvent (ml)	Monomer (mol)	Polymerization temp. (°C)	Polymer product		
Alkali Metal	Cryptand (mol)				Yield	Molecular wt.	Microstructure
Na	[2, 2, 1] (4.7×10^{-5})	THF (30)	Isoprene (2.5×10^{-2})	−78	100	$\bar{M}_w = 1.16 \times 10^6$	Total unsaturation: 80%; 1, 4: 24%; 1, 2: 30%; 3, 4: 46%
K	[2, 2, 2] (3.2×10^{-5})	Benzene (30)	Isoprene (3×10^{-2})	25	100	—	Total unsaturation: 94%; 1, 4: 38%; 1, 2: 26%; 3, 4: 36%
K	[2, 2, 2_B](10^{-5})	THF (20)	Isoprene (2.5×10^{-2})	−78	100	$\bar{M}_w = 2.7 \times 10^6$	Total unsaturation: 94%; 1, 4: 11%; 1, 2: 28%; 3, 4: 61%
Cs	[2, 2, 2] (2.5×10^{-5})	Toluene (40)	Isoprene (2.5×10^{-2})	25	—	$\bar{M}_n \leq 3500$	
K	[2, 2, 2] (4×10^{-5})	Dioxane (40)	Styrene (2×10^{-2})	25	100	$\bar{M}_w = 10^6$	
Na	[2, 2, 1] (4.3×10^{-5})	THF (30)	Styrene (2×10^{-2})	−78	100	$\bar{M}_w = 12 \times 10^6$	
K	[2, 2,C_8] (8×10^{-5})	Toluene (40)	Styrene (2×10^{-2})	25	100	$\bar{M}_w = 10^6$	
Ca	[2, 2, 2] (4×10^{-5})	THF (40)	Styrene (2×10^{-2})	25	<50	$\bar{M}_w$ 3.8×10^6	
K	[T_2O]† (2.5×10^{-5})	Toluene (40)	2-Vinylpyridine (10^{-2})	25	<50	$\bar{M}_w = 10^6$	

†Tricyclic cryptand 42 ($n = 2$)

Takegami *et al.* prepared block copolymer of the ABA type, PMMA-PEO-PMMA, by means of polymerizing methyl methacrylate (MMA) using the Na salt of polyethylene oxide (PEO) as an initiator in the presence of dicyclohexyl-18-crown-6.[203) The content of syndiotactic structures in the polymeric chain was much higher than in the polymer prepared without using crown ether. The results of studies on the solubilization of alkali metals by crown compounds (Sections 3.2.4 and 3.3.2.C) have been applied to anionic polymerization using alkali metal as an initiator. Kaempf *et al.* carried out the homogeneous anionic polymerization of butadiene, isoprene, and MMA with solutions of Na, K, Rb, and Cs in THF and benzene by using dicyclohexyl-18-crown-6.[204) In each case, the polymerization rate was so fast that polymer was produced quantitatively in an instant. The microstructures of the polymers prepared in benzene solution at 10° C were similar to those of the polymers prepared in polar solvents. The molecular weights of the polymers were much higher than the values calculated according to the [monomer]/[initiator] ratio, and the molecular weight distributions were broad ($\bar{M}_w \bar{M}_n = 3 \sim 4$). These polymers were quite different from those obtained by the usual living polymerization technique.

Anionic polymerization initiated by alkali metals solubilized by cryptands has been studied by Kaempf and his colleagues. They have described the anionic polymerization of vinyl monomers such as styrene,[205~207) isoprene,[206) MMA,[205,206) and vinyl pyridine[206) in polar and nonpolar solvents. Some of their results are shown in Table 4.12. In almost all cases, polymerization rates were so fast that the reaction was completed in an instant and polymerization yields were quantiative; however, molecular weights of the polymers obtained were much higher than the values calculated from [monomer]/[initiator]. Their results suggested that two kinds of active species, cryptate ion pairs and free ions, were present in the polymerization system, and the rates of initiation and propagation by the former were markedly faster than those by the latter.

It is well known that Na-naphthalene complex and di-Na-*α*-methylstyrene dimer or tetramer dianion in THF act as the initiators in the living polymerization system. Consequently, Kaempf *et al.* experimented with anionic polymerization of butadiene, isoprene, styrene, MMA, and 2-vinylpyridine using Na-naphthalene, α-methylstyrene oligomer dianion, and 1, 1-diphenylethylene dianion prepared in nonpolar benzene by the use of cryptands.[206) As with solubilized alkali metals, polymerization occurred instantly, and high molecular weight polymer was obtained with a microstructure similar to that of polymers prepared in polar solvents.

Boileau *et al.* also found that the polymerization of styrene was initiated in benzene or THF even by alkali alkoxides or salts such as K-*tert*-amyl alkoxide, KOH, KSCN, CH_3COOK, and Ph_4BNa; ring opening polymerization of cyclic monomers such as hexamethylcyclotrisiloxane, propylene sulfide, and isobutylene sulfide were similarly initiated.[208) The results are shown in Table 4.13.

B. Ring Opening Polymerization

Ring opening polymerization of cyclic monomers by the use of cryptands was mentioned briefly in the preceding section. Boileau *et al.* investigated in detail the kinetics of ring opening polymerization of propylene sulfide in THF at −30° C initiated by the Na^+- and Cs^+-complexes of cryptand [2, 2, 1], [2, 2, 2], [3, 2, 2], and [2_o, 2_o, 2_s].[209)

TABLE 4.13 Anionic polymerization using alkali metal cryptate as an initiator at room temp.[208]

Initiator		Solvent	Monomer	Yield	Molecular wt. of polymer product
Alkali metal salt (mol)	Cryptand (mol)	(ml)	(mol)	(%)	
KOH (5.6×10^{-5})	[2, 2, 2] (6.1×10^{-5})	benzene (35)	Hexamethyl cyclotrisiloxane (5×10^{-2})	60 (after 5 min)	$\bar{M}_w = 7.2 \times 10^6$ $[\eta] = 11.6$ dl/g (toluene, 30° C)
tert-Amyl ONa (10^{-4})	[2, 2, 2] (10^{-4})	benzene (30)	Styrene (2×10^{-2})	100 (after 24 hr)	—
KSCN (3×10^{-5})	[2, 2, 2] (1.5×10^{-5})	THF (30)	Propylene sulfide (2.7×10^{-2})	100 (after 72 hr)	$\bar{M}_w = 1.9 \times 10^7$
CH_3COOK (2.4×10^{-6})	$[2, 2, 2_B]$ (1.7×10^{-5})	benzene (38)	Isobutylene sulfide (2.5×10^{-2})	70 (after 19 hr)	(mp = 188° C)

The results indicated that the propagation rate constant of terminal thiolate anion, which formed an ion pair with alkali metal cryptate, was larger than that of dissociated free thiolate anion, demonstrating that the structure of the ion pair and the solvent effect both contribute to ring opening polymerization of episulfide just as the nucleophilicity of the anion does.

The effects of dicyclohexyl-18-crown-6 and cryptand [2, 2, 2] on the ring opening polymerization of β-propiolactone and ε-caprolactone were also investigated by Deffieux and Boileau.[210] In the presence of crown compounds, polymerization of β-propiolactone was initiated by weak nucleophiles which usually play no role in initiation and the activity of the initiator was in the order of KOH > KSCN and CH_3COOK > KCl. The formation of oligomer increased in the homogeneous polymerization of caprolactone initiated by *tert*-BuOK in the presence of crown compounds. This finding is thought to be a result of the chain transfer of the propagating alkoxide terminals, whose activity was enhanced by complexation with crown compound just as occurred in the oligomerization of ethylene oxide described in Section 4.2.12.

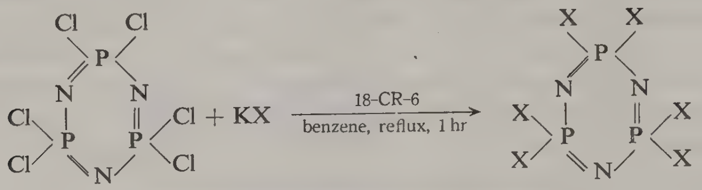
With respect to the ring opening polymerization of β-lactone, Slomkowski and Penczek also reported that the apparent propagation rate constant in the polymerization initiated by NaOAc was increased up to 100 times in the presence of dibenzo-18-crown-6 and that the polymerization proceeded in a manner similar to living polymerization.[211]

4.2.14 Applications to Inorganic Synthesis and Electrochemistry

Except for the extensive research on the applications of cyclic polyamines, which are crown compounds in a broad sense (see Sections 2.2, 3.3.3), to the syntheses of transition metal complexes and catalysts, efforts to employ crown compounds in inorganic syntheses have lagged well behind the remarkable development in applications to organic syntheses.

Acetylacetonatodicarbonyl-Ir was prepared by the carbonylation of K_2IrCl_6 in diphenylformamide in the presence of dibenzo-18-crown-6 (220° C, 9 hours),[212] and *ax*-$Mn_2(CO)_9X^-$ ($X = F, Cl, Br, I$) anion, whose counter cation was K^+-dibenzo-18-crown-6, was synthesized photochemically.[213]

Walsh *et al.* reported the formation of hexafluoro (or isothiocyanato) derivative by the nucleophilic substitution of the Cl in hexachlorotriphosphazene with KF (or KSCN) solubilized by 18-crown-6 (Eq. 4.122).[214] With KBr, the more stable linear compound NP_2Br_6 was formed.



(4.122)

X = F: 75 ~ 90%; X = NCS: 80 ~ 87%
X = CN: first produced –NC followed by conversion to –CN

Reactions of germyl- or silyl-Hg compounds with KCN (Eqs. 4.123 ~ 4.125) were reported recently.[215]

$$(Et_3Ge)_2Hg + KCN \xrightarrow[\text{THF or CH}_3\text{CN, 20°C, 23 hr}]{\text{DB-18-CR- or 18-CR-6}} \underset{(59.6\%)}{Et_6Ge_2} + \underset{(99\%)}{Hg} \tag{4.123}$$

$$Et_3(Ge)HgEt + KCN \xrightarrow[\text{THF or CH}_3\text{CN, 20°C, 23 hr}]{\text{DB-18-CR-6 or 18-CR-6}} Et_6Ge_2 + Et_2Hg + Hg \tag{4.124}$$

$$(Et_3Si)_2Hg + KCN \xrightarrow[\text{THF or CH}_3\text{CN, 20°C, 23 hr}]{\text{DB-18-CR-9 or 18-CR-6}} Et_3SiCN + (Et_3Si)_4HgK_2 + Hg \tag{4.125}$$

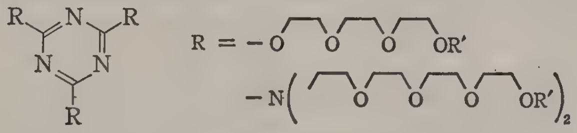
In the area of electrochemistry, there have been studies on the kinetics of rapid-charge transfer reactions[216] and on the detection of adsorption reactions[217] using the reduction of Tl(I)-dicyclohexyl-18-crown-6 in chronopotentiometry and polarography. It was also reported that the half-wave potential in the two-electron polarographic reduction of Mg^{2+}-[2, 2, 1] cryptate in propylene carbonate was more cathodic than that in the reduction of solvated Mg^{2+}.[218] Electronic switching between higher and lower impedance states was observed in a thin film of dibenzo-18-crown-6 placed between two electrodes which were coated with silver by evaporation.[219]

4.2.15 Functions and Applications of Noncyclic Analogues

The solid-liquid phase transfer catalytic action of linear polyethers with quinoline groups at both terminals (**169**) and of "octopus" molecules (**170**) were mentioned previously in Section 4.2.5.C. The functions and applications of these and other linear polyethers which are noncyclic analogues of crown compounds will be described in this section. Following the discovery of crown ethers, scientists renewed their interest in the characteristics and applications of noncyclic polyethers such as the higher glymes.

Complexation of linear polyoxyethylene derivatives with $HgCl_2$ and $CdCl_2$ was carried out by Tadokoro *et al.*[220,221] and Iwamoto and Wakano,[222,223] and the crystal structures of the complexes were analyzed. Recently, Sotobayashi *et al.*[225,225] and Okahara *et al.*[226,227] reported on the complexation and solvent extraction of alkali metals with polyoxyethylene glycol or polyoxyethylene-polyoxypropylene glycol. The present author and his coworkers observed that various inorganic salts were solubilized in nonpolar solvents by the addition of polyoxyethylene glycol, polyoxypropylene glycol, polyoxyethylene-polyoxypropylene glycol, or their methoxyethers, including linear polymers and star polymers having 3 ~ 6 chains; furthermore, these linear polyethers functioned as phase transfer catalysts in a number of organic reactions such as nucleophilic substitution and oxidations.[228] Yamazaki *et al.* described the effects of adding polyethylene oxide (viscosity-average molecular weight: 3.3×10^4) on the reduction of carbonyl compounds with $NaBH_4$ in THF[229] and on the Williamson reaction in dioxane.[230]

Akabori *et al.* investigated the phase transfer catalytic activity of "octopus" molecules in substitution reactions with a compound in which the terminal groups of compound **170** were OCH_3 groups and with another compound in which 6 chains of compound **170** consisted of polyether chains with OCH_3 or OC_6H_{13} groups at the terminals.[231,232] Montanari *et al.* prepared "octopus" molecules with a triazine nucleus and 3 or 6 polyether chains (**173**) and assessed their phase transfer catalytic action in halogen-substitution, phenylthioetheration, oxidation with $KMnO_4$, reduction with $NaBH_4$, and so on.[233]



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R′ = n-C_4H_9, n-C_8H_{17}

Like crown ethers, these functions of noncyclic polyethers are based on the ion-dipole interaction between the ether bond and the cation, but crown ethers have superior applicability because the O donors are oriented in a regular manner and maintain the same distance between the cation and each O donor in complexation; furthermore, crown ethers allow for selective complexation with a cation because of cavity size and configuration. In fact, these noncyclic polyethers and "octopus" molecules are less able to form complexes and to act as phase transfer catalysts than crown ethers, and selective complexation is not achieved.

In the case of linear polyethers, it is thought that the linear molecule is wound around one or several cations by the action of several ether linkages acting as donors (Fig. 4.2a, b). As is well known, the theory of polymer solutions holds that the higher molecular weight polyether chains are present in a form like a ball of yarn in a poor solvent, but they are loosened in a good solvent. In addition, repulsion between negatively charged O atoms also occurs in a solution. It is therefore thought that the extraction ability, catalytic activity, and the capacity of linear polyethers to form complexes with cations may depend on conditions such as the solvent, concentration, and temperature. These phenomena were observed in an investigation of the solubilization of in-

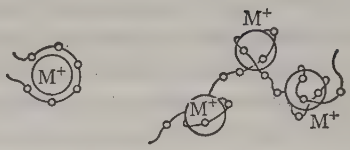


Fig. 4 2 Schematic model of cation binding by linear polyether.

organic salts in nonpolar solvents and of phase transfer catalysis with linear polyethers by the author and his coworkers;[228,234)] among the glymes with the form $CH_3O(CH_2CH_2O)_nCH_3$, the greatest ability for both was observed in the glymes with $n = 9 \sim 10$.

The octopus molecule **170** prepared by Weber and Vögtle[98)] is a viscous yellow liquid; with a CH_2Cl_2 solution of **170**, alkaline earth metal (Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) picrates can be extracted almost completely and alkali metal (Li^+, Na^+, K^+, Rb^+, Cs^+) picrates extracted completely from aqueous solutions. They hypothesized that a complex is formed by the capture of a cation with six polyether chains which act like the arms of an octopus capturing prey with its suckers, as shown in Fig. 4.3. Thus the name octopus molecule. The complexation ability diminishes with a decreasing number and length of the arms.

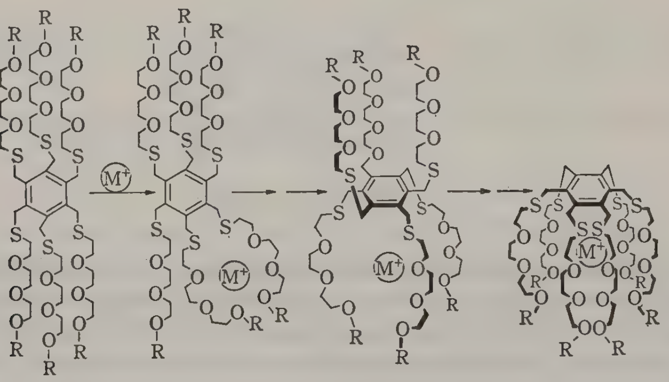


Fig. 4.3 Cation capture by an octopus molecule. (Source: Ref. 99. Reproduced by kind permission of Academic.

Generally speaking, the complexation ability of noncyclic polyethers is less than that of crown compounds and depends on conditions such as solvent and concentration. However, noncyclic polyethers such as polyetheylene glycol, polypropylene glycols including the star polymers corresponding to octopus molecules, and copolymers of ethylene oxide and propylene oxide are commercially available chemicals which are produced on a large scale and are inexpensive. Therefore, it may be possible to effectively use noncyclic polyethers for some applications such as phase transfer catalysis and extraction of cations (nonselective) by the selection of specific conditions. Noncyclic polyethers cannot be used for processes that require the selective capture of cations because they do not have selective complexation abilities. The chemistry of noncyclic compounds with analoguous functions to crown compounds was reviewed recently by Yanagida and Okahara.[235)]

4.3 APPLICATIONS TO ION SEPARATION

4.3.1 Separation of Metal Ions

A. Solvent Extraction

One of the specific characteristics of crown compounds is the ability to selectively form complexes by capturing cations with an ionic diameter fitted to the cavity size of the crown compound, and this leads to a natural application for the separation of metal ions. In fact, experiments with the solvent extraction of metal ions using crown compounds were begun shortly after the discovery of crown ethers.

Because crown ethers facilitate the solubilization of inorganic salts, as discussed in Section 3.2.4 and shown in Table 3.17, it is possible to use organic solvents containing crown ether to extract from aqueous solutions inorganic salts which form highly soluble complexes. The extraction is achieved more effectively with the salts that have bulky and highly polarized "soft" anions, such as picrates. Picrates are also used for quantitative studies on complexation[236~238)] because analysis can be easily done utilizing the strong absorption at approximately 360 nm. The results of extractions of alkali metal picrates from aqueous to CH_2Cl_2 solutions are shown in Table 4.14. It is apparent from the table

TABLE 4.14 Extraction of picrates into dichloromethane with crown ethers.[239)]†

Crown ether	Extracted picrate (%)			
	Li^+	Na^+	K^+	Cs^+
Di(*tert*-butylcyclohexyl)-14-crown-4	1.1	0	0	0
tert-Butylcyclohexyl-15-crown-5	1.6	19.7	8.7	4.0
Dibenzo-18-crown-6	0	1.6	25.2	5.8
Cyclohexyl-18-crown-6	3.3	25.6	77.8	44.2
Cyclohexyl-21-crown-7	3.1	22.6	51.3	49.7
Cyclohexyl-24-crown-8	2.9	8.9	20.1	18.1

†Extraction conditions: Alkali hydroxide 0.1 mol/*l*, alkali picrate 7 × 10^{-5} mol/*l*, CH_2Cl_2 volume equal to water.

TABLE 4.15 Equibrium constants in picrate extractions.[238)]

Crown ether	Cation	Extraction solvent	$K_E \times 10^{-3}$ (M^{-2})	$K_D \times 10^6$ (M)
Dicyclohexyl-18-crown-6				
mixture of isomers	K^+	CH_2Cl_2	2,100 ± 200	37 ± 6
isomer A	K^+	CH_2Cl_2	4,000 ± 500	25 ± 8
isomer B	K^+	CH_2Cl_2	1,100 ± 150	24 ± 8
mixture of isomers	K^+	$CFCl_2CF_2Cl$	19 ± 2	<1
mixture of isomers	K^+	n-C_6H_{14}	3.8 ± 0.2	<1
mixture of isomers	Na^+	CH_2Cl_2	15 ± 2	100 ± 20
Dibenzo-18-crown-6	K^+	CH_2Cl_2	710 ± 60	4.4 ± 2.7

that the results depend on the relationship between the cationic diameter and the cavity size of the crown ring and correspond to the stability constant, K.

Cations are extracted by crown compounds according to the distribution equilibria shown in Eqs. (4.126) and (4.127). Table 4.15 presents the extraction equilibrium constants K_E and the dissociation equilibrium constants K_D for several systems measured by Frensdorff.[238] The value of K_E depends on the stability constant, K, of the complex in aqueous solution and on the distribution coefficients of the crown ether and the complex; the most important factor is the distribution coefficient of the complex.

$$\mathrm{M_{aq}}^+ + \mathrm{A_{aq}}^- + \mathrm{L_{org}} \overset{K_E}{\rightleftharpoons} \mathrm{LMA_{org}} \tag{4.126}$$

$$\mathrm{LMA_{org}} \overset{K_D}{\rightleftharpoons} \mathrm{LM_{org}}^+ + \mathrm{A_{org}}^- \tag{4.127}$$

M^+: cation; A^-: anion; L: crown ether;
LM^+: complex cation; LMA: complex ion pair

Other than for analytical use, the technique of solvent extraction of metal ions has so far found only limited application, such as to metals employed for atomic energy. However, there has been considerable progress recently in the extraction or separation of metal ions other than actinides and lanthanides for such commercial uses as separation, recovery, condensation, and refining of metals, and much of this research has utilized the characteristics of crown ethers.

Rais *et al.* studied the extraction of Na^+, Cs^+, Ca^{2+}, Sr^{2+}, and Ba^{2+} in an ion pair with dipicrylamine anion using dibenzo-18-crown-6,[240,241] and Danesi *et al.* reported on the extraction of the complexes of Li^+-, Na^+-, K^+-, Rb^+-, and Cs^+-picrate with dibenzo-18-crown-6 in a mixture of toluene-nitrobenzene.[242~244]

One advantage in using crown ethers for the solvent extraction of metal ions is the marked selectivity resulting from the relationship between the ionic diameter and the cavity size of the crown ring, which is quite different from the extractions with other reagents. Figure 4.4 illustrates the relationship between the ionic diameter of alkali metals and the absorbence of the picrate extracted in benzene using dibenzo-18-crown-6.[245] The highest selectivity of extraction was observed with K^+, whose ionic diameter is nearest to the cavity size of the 18-crown ring. The same tendency was observed when a mixture of toluene-nitrobenzene was used as an organic phase.[243,245] These results are quite different from those of extractions with other reagents, in which the extraction increases with increasing ionic diameter of the alkali metal. In the extraction of alkaline earth metal ions in ion pairs with $(B_9C_2H_{11})_2Co^-$ anions using dibenzo-18-crown-6, the extraction was achieved in the order of $Ba^{2+} > Sr^{2+} > Ca^{2+}$ and large differences were observed between the ions.[241]

Selectivity in the extraction with crown ether is greatly influenced by the solvent.[241] The results of extracting ion pairs of Na^+- and Cs^+-dipicrylamine ion in various organic solvents using dibenzo-18-crown-6 are shown in Fig. 4.5.[241] The distribution ratio of the two metal ions was more than 10^3 in chloroform, but nearly 1 in propylene carbonate. Furthermore, the difference in the distribution ratio in chloroform compared to the ratio in propylene carbonate was more than 10^4 for the same ion and the same

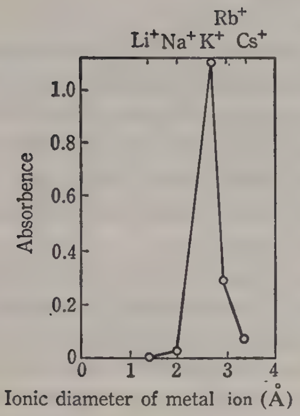


Fig 4.4 Selectivity in the extraction of alkali metal ions with crown ethers. (Source: Ref. 245. Reproduced by kind permission of the Chemical Society of Japan.)

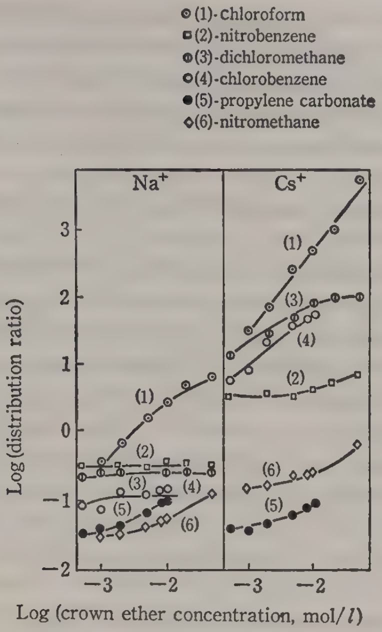


Fig. 4.5 Effect of solvent on the extraction of Na^+ and Cs^+ with crown ethers.[241)]

concentration of crown ether. It was reported that the extraction using crown ether is endothermic and is accompanied by a decrease in entropy.[245)] Solvent extractions of alkali metal picrates using 15-crown-5 and 18-crown-6,[246)] chloroform extraction of Tl(I) picrate using dibenzo-18-crown-6,[247)] and nitrobenzene extractions of alkali metal hexanitrodiphenyl amine salts using dibenzo-18-crown-6[248)] were also reported.

Regarding solvent extraction of alkaline earth metal ions, Ishimori *et al.* separated Sr^{2+} from an aqueous solution containing a small amount of Sr^{2+} (0.7 ~ 20 mg) and a large amount of Ca^{2+} (1.5 g) by means of liquid-liquid extraction using a chloroform solution of dicyclohexyl-18-crown-6.[249)] The average recovery of Sr^{2+} was 97%, and the Ca^{2+} content in the Sr^{2+} fraction was reduced to $10^{-4} \sim 10^{-5}$ after repeating the extraction four times.

Schröder-Nielsen reported extracting ion pairs composed of 2-naphthalene sulfonate and salicylate of *N*-methyl- and *N*, *N*-dimethyloctyl ammonium by the use of dibenzo-18-crown-6.[250)] The values of log K of the *sec*- and *tert*-ammonium salts thus obtained were nearly equal to or less than those of quaternary ammonium salts.

In their work on solvent extraction of metal ions, Pannell *et al.* prepared mono- and bis(chrome tricarbonyl) derivatives of dibenzo-18-crown-6 and attempted to carry out the extractions of alkali ions in organic solvents.[251)] The results showed that the derivatives had a lesser extraction capacity than the original crown ether. This diminished capacity was thought to be a product of the decrease in the electrophilicity of the

O atoms on the crown ring because of the $Cr(CO)_3$ substituent. The selectivity of extraction by the di-substituted derivative was in the order of $Na^+ > K^+$, the reverse of the order observed with dibenzo-18-crown-6.

Solvent extraction of metal ions using crown ethers is still in the experimental stage, but the development of commercial applications is expected.

B. Separation of Rare Earth Metal Ions with Crown Ethers

As mentioned in Section 3.2.2.A, King and Heckley found that the so-called "light" lanthanide ions formed stoichiometric complexes with dibenzo-18-crown-6 while the "heavy" lanthanide ions did not, so they experimented with the separation of lanthanide ions by using a column packed with a powder of dibenzo-18-crown-6 whose solubility was quite low.252) When a mixed solution of Er^{3+} and Pr^{3+} nitrates in acetone-hexane was passed through the column, Pr^{3+} was bound more tightly than Er^{3+}, and after initially eluting both Pr^{3+} and Er^{3+}, only Pr^{3+} was present in later fractions of eluent, although a complete separation was not achieved.

The earth contains rare earth metals in abundance, but their use has been limited because of the difficulties in separation and refining. The demand for these materials is now increasing for applications in electronics, atomic reactors, metallurgy, the glass industry, the ceramics industry, and so on, and King and Heckley's results suggest that the isolation or recovery of rare earth metals may be possible with a convenient apparatus and operation like column separation. In commercial techniques, the polymeric or immobilized crown compounds described in Chapter 6 may be used effectively.

4.3.2 Separation of Isotopes

It was recently reported that crown ethers may also be applicable to the separation of isotopes. Jepson and Dewitt attempted to separate $^{40}Ca^{2+}$ (concentration: 96.97%) and $^{44}Ca^{2+}$ (2.06%) by the exchange reaction shown in Eq. (4.128) using dibenzo- and dicyclohexyl-18-crown-6.253) In the liquid-liquid extraction of $CaCl_2$ using chloroform

$$^{40}Ca^{2+}{}_{(aq)} + {}^{44}CaL^{2+}{}_{(org)} \rightleftharpoons {}^{44}Ca^{2+}{}_{(aq)} + {}^{40}CaL^{2+}{}_{(org)} \qquad (4.128)$$

L: crown ether

or CH_2Cl_2 and dicyclohexyl-18-crown-6, the one-step separation coefficient of the isotopes was 1.0010 ± 0.0002 per 1 mass unit, which demonstrated that the condensation of ^{44}Ca would be possible with this method.

4.3.3 Applications for Analytical Chemistry

The specific characteristics of crown ethers can be employed for various chemical analyses. Sections 4.2.2 and 4.2.5.C mentioned neutralization titration in nonpolar solvents utilizing the solubilization of inorganic salts in organic solvents37) and bromophenacyl esterification of fatty acids to HLC with active naked anions.101,102) Other practical applications for analytical methods that exploit the selective capture of cation by crown ethers are currently being developed.

Using the liquid-liquid extraction method mentioned in Section 4.3.1 to separate ions, Ishimori *et al.* recently carried out an analysis of trace amounts (0.8 ~ 9 pCi/*l*) of radioactive ^{89}Sr and ^{90}Sr present in cow's milk using dicyclohexyl-18-crown-6.254) Sr^{2+} was separated from Ca^{2+}, Mg^{2+}, and Ba^{2+} by liquid-liquid extraction using a chloroform solution of crown ether with added Na picrate249) and applied to radiochemical analysis; the procedure was completed within 1.5 days, compared to the several days required for conventional analysis with fumic nitric acid or ion exchange resin.

Kawamura *et al.* reported that ^{85}Sr was adsorbed more selectively than ^{45}Ca from a buffer solution by a cation exchange resin permeated with dicyclohexyl-18-crown-6.255) Mitchell and Shanks carried out an ultra-micro analysis of Na (0.240 ± 0.004 and 3.81 ± 0.18 μg Na/g SiO_2) by a combined method of chloroform extraction of $NaBPh_4$ using dicyclohexyl-18-crown-6 followed by neutron irradiation.256)

Chapters 2 and 3 discuss nmr and mass spectra of crown ether complexes and cryptates. Mass spectrographic analyses of Li^+, Na^+, and K^+ using cryptands257) and measurements of free energy in the transfer of Cl^- or N_3^- from aqueous solutions of NaCl or NaN_3 to methanol258) have also been carried out.

Applications of crown ethers to ion-selective electrodes are described in Section 4.4.2.

4.4 APPLICATIONS TO ION TRANSPORT

4.4.1 Ion-Selective Transport Membrane

The structure and function of biomembranes have become salient topics in biophysics since it has been made clear that biomembranes play very important roles in the function of biological systems. A common aspect in the behavior of biomembranes is the transport of a specific ion, and almost all substances that function as selective ion carriers in biological systems are antibiotics with the structure of tetrolides or cyclic depsipeptides; they are known as ionophores and include compounds such as valinomycin and nonactin, as described in Section 1.3.

Attention has focused on crown ethers as synthetic materials with functions similar to natural ionophores, and investigations of active transport, by which ions are transported or concentrated through a membrane without the aid of pressure or electric potential, have employed crown ethers as selective ion carriers8~11) by studying selective transmission of ions through a liquid membrane containing a crown ether. The transport of the specific ion in this liquid membrane depends mainly on the distribution coefficient in the membrane. Illustrations of ion transport and concentration by ion carriers are shown in Figs. 4.6259) and 4.7.260)

The first investigation of ion transport using crown ether as a model of the selective ion carrier in living bodies261,262) was carried out by Eisenman and his coworkers,263,264) who studied the membrane potential and electroconductivity of a liquid membrane containing crown ether. Since then, other workers have examined K^+ transport in the membranes of rat liver mitochondria and cow heart mitochondria in the presence of dicyclohexyl-18-crown-6;265~267) the effects of the type of cation,

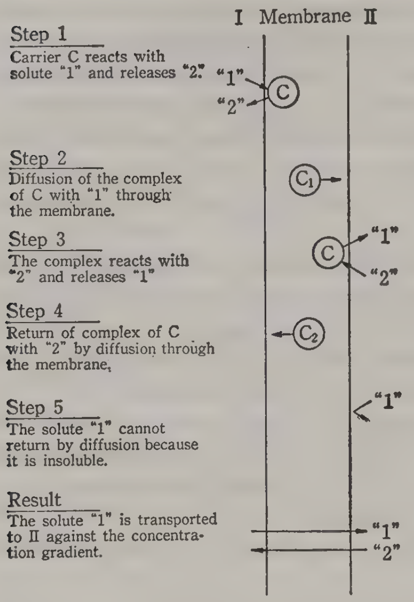


Fig. 4.6 Pumping transport of the solute in a liquid membrane by an ion carrier. (Source: Ref. 259. Reproduced by kind permission of American Institute of Chemical Engineers.)

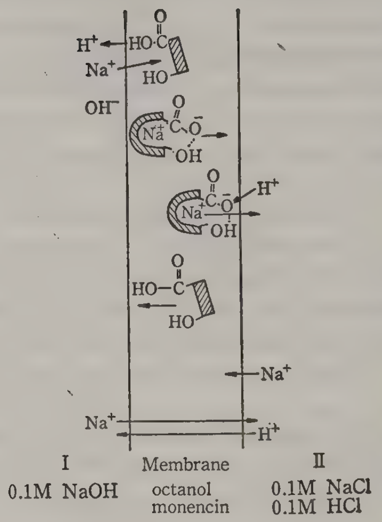


Fig. 4.7 Condensation of Na^+ with the ionophore antibiotic monencin. (Source: Ref. 260. Reproduced by kind permission of American Association for the Advancement of Science.)

concentration, and temperature on ion transport in model membrane systems consisting of dimyristoyl-α-lecitine or dipalmitoyl-α-lecitine and 18-crown-6;[268] microcalorimetric measurements of kinetic data in ion transport using bibenzo-18-crown-6;[269] the relationship between the functions of membranes containing dicyclohexyl-18-crown-6 and protein synthesis in reticulocytes;[270] ion transport in liquid membranes using 4′-methylbenzo-15-crown-5, 4′-methylbenzo-18-crown-6, and their polymers;[271] the effect of 18-crown-6 on the distribution of alkali metal ions in a liquid phase and an organic phase in comparison with the effects of valinomycin and macrotetrolides;[272] the increase in electroconductivity in the double layer of phospholipid in the presence of bis-*tert*-butylcyclohexyl-18-crown-6;[273] an *ab initio* model using Li^+–12-crown-4 complex;[274] the electron structure of the ion transport in the presence of 12-crown-4;[275] and selective ion transport of Na^+, K^+, and Cs^+ in a liquid membrane containing cryptands.[276]

Reusch and Cussler have reviewed selective ion transport membranes using crown ethers.[277]

4.4.2 Ion-Selective Electrodes

The research and development of ion-selective electrodes of the liquid membrane type in which crown ether is used as a neutral carrier have made use of the specific ability of crown ethers to transport ions selectively. Rechnitz evaluated the Na^+, Rb^+, Cs$^+$, and NH$_4^+$ selectivities of ion-selective electrodes in which nitrobenzene solutions of benzo-15-crown-5, dibenzo-18-crown-6, dicyclohexyl-18-crown-6, and dibenzo-30-crown-10 were used as liquid membranes.278)

Patranek and Ryba examined the K$^+$/Na$^+$ selectivities of ion-selective electrodes in which plasticized polyvinyl chloride containing crown ether was used as the liquid membrane.279) In this investigation with 20 kinds of crown ether, the highest selectivity was observed in the crown ethers with the ring of 18-crown-6 or 30-crown-10; they calculated the selectivity ratio $K_{K/Na}$ from the ion activities of K$^+$ and Na$^+$ (a_K, a_{Na}) which produced the same electrode potential in a mixed solution, $\leq 1.1 \times 10^{-2}$ and $\leq 2.2 \times 10^{-3}$, respectively. Mascini and Pallozzi also observed that plasticized polyvinyl chloride was the best material for a liquid membrane as a result of their work on the selectivities of ion-selective electrodes in which various polymers containing dibenzo-18-crown-6 were used as liquid membranes.280)

Ryba and Patranek also studied K$^+$-selective electrodes using dimethyldibenzo-30-crown-10 dispersed in a polyvinyl chloride matrix,281,282) and they described a miniature K$^+$-selective electrode with this membrane.283) As shown in Fig. 4.8, the miniature electrode was prepared in the following manner: 1 mg of dimethyldibenzo-30-crown-10 was dissolved in 0.1 ml of dipentyl phthalate and mixed with 1 ml of cyclohexane solution containing 5% high molecular weight polyvinyl chloride. A dry thin film was prepared from this solution, and the film was fixed at the terminal end of a glass capillary, then a 10^{-3} M solution of KCl was added. The effective membrane area of the electrode was less than 0.2 mm, and the Nernst response was observed in a concentration range of K$^+$ between 10^{-1} M and 10^{-5} M.

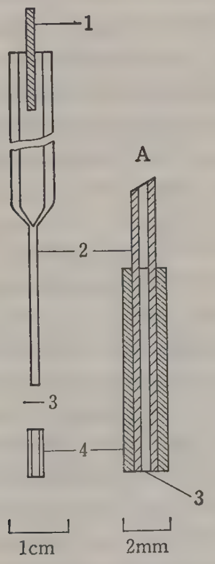


Fig. 4.8 Miniature ion-selective electrode using crown ether. (Source: Ref. 283. Reproduced by kind permission of Pergamon.)

4.4.3 Applications to Drugs and Agrochemicals

In biological systems, metal ions form complexes with the ligands having O, N, or S donor atoms, such as amino acids, peptides, proteins, enzymes, nucleic acids, carbohydrates, and lipids. Many diseases are caused by a shortage or excess of indispensable metal ions or the ingestion of harmful metals, poisons, or radioactive substances. From a biochemical standpoint, the diseases are caused by an imbalance in the metal ion-ligand interactions in the organism or by competition between the foreign substance and the normal constituents of interactions.12)

The metal ions indispensable for biological systems can be classified in the following three groups:

1) Alkali metal ions (Na^+, K^+): Na^+ is distributed mainly outside the cell and K^+ mainly inside the cell. Both ions contribute to the maintenance of osmotic pressure, the dispatch and transmission of nerve information, and the active transport of saccharides and amino acids. Na^+ and K^+, which are classified as hard acids, form complexes with the ligands having O donor atoms, which are hard bases, but these ions are transferred freely in biological systems because the interactions between the ions and the ligands are not strong *in vivo*. The role of ionophore antibiotics in active transport through cell membranes, such as the selective transmission of Na^+ and K^+ in the excitation of nerve membranes, and the function of Na^+–and K^+–ATPase are described in Sections 1.3 and 4.4.2.

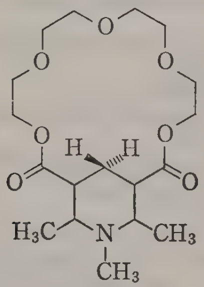
2) Alkaline earth metal ions (Mg^{2+}, Ca^{2+}): Mg^{2+} is distributed mainly inside the cell membrane and Ca^{2+} mainly outside the cell membrane. In addition to the roles of these ions in biological systems in the preservation of chemical potential and the dispatch and transmission of nerve information, they enhance such functions of the ligands as activation of enzymes and stabilization of tissue structure through complexation with ligands. This enhancement capability is due to the stronger interaction between Mg^{2+} and Ca^{2+} and the ligands of substances in biological systems which are the soft bases. Furthermore, many Ca^{2+} compounds are barely soluble in water and arteriosclerosis and chololithiasis are caused by such Ca^{2+} compounds as carbonate, oxalate, and phosphorate.

3) Transition metal ions (Mn, Fe, Co, Cu, Zn, Mo, etc.): As transition metal ions are soft acids, these ions bind tightly to the ligands in a molecule of enzyme, nucleic acid, or protein having an N or S donor, which is a soft base. They can act directly as the active center of the enzyme or protein in metabolism and can also act indirectly to multiply or enhance the activity in the maintenance of the higher structure of biopolymers.

As mentioned previously, crown compounds such as crown ethers, cryptands, cyclic polyamines, and cyclic polythiaethers are analogous to ionophore antibiotics, porphyrins, and blue-copper proteins in structure, characteristics, or mode of action. For this reason there has been considerable research on the biological activity, including toxicity, of crown compounds, as well as application research for drugs and agrochemicals. Studies using crown compounds as models of natural substances in living organisms were discussed in the preceding section. The toxicity of crown compounds is considered in Chapter 7.

Among the applications to drugs and agrochemicals, the use of crown compounds for the selective removal of harmful metal ions such as Hg^{2+} and Pb^{2+} and the addition of trace amounts of indispensable metals such as Fe and Mn is thought to have great potential.[284] The removal of ^{85}Sr from rats using cryptand [2,2,2] was reported by Müller.[285] In his experiment, four rats received a subcutaneous injection of 2.5 μ curies of 85 ^{85}Sr and 50 μ mol of the cryptand in the form of KCl-cryptate in a physiological solution. After 3 days the total body retention of ^{85}Sr was 70% in the controls, which received ^{85}Sr only, and 19% in the treated rats. In other work it was reported that diaminodibenzo-18-crown-6 and its 3,3′-bis (phenylthiourea) derivative, prepared by the reaction of the amino crown compound with isothiocyanate, have weak antitubercle activity.[286]

Pitha and Smid reported recently on the interaction between poly (vinylbenzo-18-crown-6) and polynucleotide and its effect on the DNA polymerase activity regulated by RNA.[287] Other researchers have shown that the complex of cyclic polyether ester **174** with sulfonium salt is a model for NAD(P)H, behaving as a hydride donor analogous to the enzyme.[288]



174

The removal of ^{90}Sr from a plant was reported.[289] The root of a young shoot of a shrub (*Phaseolus vulgaris* L.) was immersed in an aqueous solution containing $^{45}CaCl_2$ (50 μM), $^{90}SrCl_2$ (50 μM), and cryptand [2,2,2] (12.5 $\sim$ 150 μM) for 24 hours, then the $^{45}Ca/^{90}Sr$ was measured. The ratio was 2.1 when an equimolar amount of cryptand was added and 2.7 when 1.3 mol equivalent (150 μM) of cryptand was added; the ratio was about 1 for the control (no addition of cryptand).

Though few studies have reported applications of crown ethers and cryptands to drugs and agrochemicals, there appears to be great potential in these fields for employing such characteristics as selective complexation and selective ion transport. For this purpose, it is essential that we clarify the toxicity and metabolism of crown ethers and cryptands. The complexes of transition metals with other crown compounds, particularly the cyclic compounds having N and S donor atoms, also have great potential for such biological applications as oxygen transport, electron transport, catalysis in photochemical synthesis, and removal or supply of metals. Many books are available that discuss the bioinorganic and bioorganic chemistry of metal complexes.[290]

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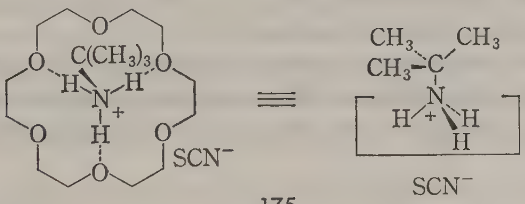
CHAPTER 5

Optically Active Crown Compounds

5.1 General Aspects

One of the most significant developments in the chemistry of crown compounds is the series of innovative studies by Cram and his coworkers on "host-guest chemistry" and its applications to the synthesis of optically active crown ethers and to optical resolution as a new method that employs the capacity of the compounds for chiral recognition.[1~11] As described in Section 3.2.1, Pedersen found that crown ethers formed complexes with both metal ions and primary ammonium salts, and he proposed that the complexes formed by ion-dipole interaction.[12] Subsequently, as mentioned in Section 3.2.3. A, Cram and his coworkers demonstrated the binding interaction between 28 kinds of monocyclic and separated polycyclic crown ethers (partially shown in Table 3.13) and primary ammonium salts, and then compared the resulting quantitative data such as the stability constants, log *K*, of the complexes. They concluded that the complexes of crown ethers with primary ammonium salts were formed by three hydrogen bonds together with three direct ion–dipole interactions combined alternately as shown in **175**.[1~4,13]



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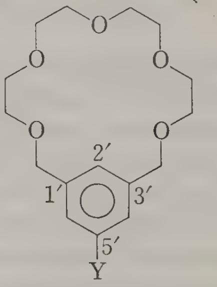
This was a very important finding. Since then, Cram *et al.* have proposed a concept of host-guest chemistry, a new system which describes the chemistry of molecular association, and they have been energetically pursuing the following studies:[14~23]

1) The capacity of separated bicyclic crown ethers (**38**) with a paracyclophane group as a structural moiety to function as host compounds.[14]
2) The ability of substituted groups directed toward the cavity of a crown ring (**127**) to act as binding sites.[15]
3) Template synthesis of benzo-27-crown-9 (**58**) using guanidium ion as a guest.[16]
4) The complexation ability of crown ethers with methoxyaryl or phenol groups.[17]

5) The concept of host-guest chemistry and Corey-Pauling-Koltum molecular models; a comparison between crown ethers and noncyclic polyether analogues as the host using ammonium, guanidium, and arenediazonium salts as the guests.[18)]
6) The effect of structural units on the association constants of the complexes between *tert*-butylammonium salts and 12 kinds of new crown ethers having pentamethylene, *m*-xylyl, *p*-phenylene, furan-2, 5-dimethyl; and tetrahydrofuran-2, 5-dimethylyl units.[19)]
7) The value of pK_a and the association constant of 6 novel azacrown ethers (e.g., **88**) having 1 ~ 4 units of 2,6-pyridinedimethylyl with *tert*-$BuNH_3^+SCN^-$.[20)]
8) Remote substituent effect on the complexation of 5-substituted 1′, 3′-xylyl-18-crown-6 (**176**) with metal and ammonium ions.[21)]



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9) Association constants for the complexation of 13 kinds of crown ethers bearing substituents directed toward the inside of the crown ether cavity (e.g., **127**) with *tert*-$BuNH_3^+SCN^-$.[22)]
10) Synthesis of 6 new separated bicyclic crown ethers having paracyclophanes unit and assessment of their function as hosts.[23)]

In the course of this work Cram *et al.* synthesized crown ether **17** with a binaphthyl group,[24)] and, using the crown ether as a host, succeeded in optical resolution of racemic primary ammonium salts and amino acid ester salts;[25)] in so doing, they

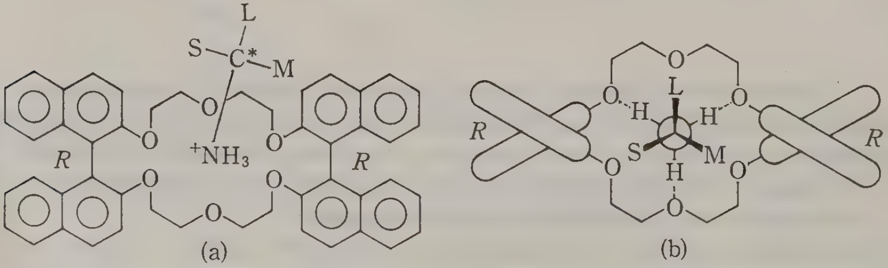


Fig. 5.1 Diastereomeric complexes formed by asymmetrical host with asymmetrical guest. (b): structure of stabler diastereomeric complex. The three groups attached to the asymmetrical center were classified as large (L), medium (M), and small (S), depending on their relative size.

skillfully utilized the optical isomerism by restricted rotation (atrop isomerism) caused by the binaphthyl group that produces a chiral cavity in the optical isomers. As Fig. 5.1 shows, in the complexation between a chiral crown ring and enantiomeric guest compounds, the stability constant is relatively larger for the complex with the diastereomer that has a more fitted configuration, and thus stereoselectivity arises. This is the principle employed for optical resolution.

Cram *et al.* subsequently synthesized a number of optically active crown compounds and carried out the optical resolution for various chiral primary ammonium salts and amino ester salts by liquid-liquid chromatography.[26~38] They also achieved optical resolution with solid-liquid chromatography using immobilized, optically active crown ethers supported on silica gel[31,39] or polystyrene.[39,39] In related research they have investigated the synthesis of enzyme models and applications to asymmetrical reactions. For example, they have designed and synthesized optically active crown compounds which model the site of substrate binding by enzymes. These compounds have additional functional groups introduced on the binaphtyhl group as the new binding site to achieve greater stereoselective binding with the guest.

The pioneering research work by Cram and his coworkers employed a unique strategy to devise an important new method for resolving enantiomers. Since then, many optically active crown compounds have been synthesized and applied to optical resolution. Cram *et al.* named the apparatus for optical resolution by liquid-liquid extraction or column chromatography using an optically active crown compound the "amino acid resolving machine," and they are developing it for practical usage. It is expected to provide a commercial process for optical resolution using an optically active crown compound prepared at low cost. Both for applications to optical resolution and as enzyme models, the optically active crown compounds which have a function closely resembling the substrate binding by enzymes are expected to be useful for asymmetrical reactions with high selectivity and high reaction rates under the mild conditions of biosynthesis, as well as for the research fields of biochemistry and biophysics.

It is also noteworthy that a series of experiments by Cram *et al.* have shown that it is possible to estimate the relative stability of a diastereomeric complex formed by a chiral host with a chiral guest by applying the CPK molecular model to a consideration of the stereochemical relationship.

5.2 Synthesis of Optically Active Crown Compounds

The cyclic oligomers of propylene oxide (**16**) described in Sections 1.3 and 2.2.3 and the cyclic oligomers of 2-substituted aziridine (**23, 76**) discussed in Section 2.3 have optical isomers due to asymmetrical carbon atoms, but the characteristics and applications based on this fact have not been investigated. In contrast, much is known about the syntheses and applications of optically active crown ethers that have a chiral cavity due to atrop isomerism of the substituent to the crown ring because of the research energetically pursued by Cram and his coworkers.

Following their discovery that the complexation of crown ethers with primary ammonium salts was due to a combination of ion-dipole interaction and hydrogen bonding and that the structural factor took part in the complexation, Cram *et al.* developed the concept of host-guest chemistry and synthesized a number of optically active crown compounds.[24~28,32~35,37~40] The principle behind these compounds is the utilization of the atrop isomerism caused by the restricted rotation of the 2,2-substituted-1,1′-binaphthyl group, whose absolute configuration has been determined by Yamada *et al.*[41], as shown in Fig. 5.2. These compounds are chiral cyclic polyethers having C_2 symmetry which form identical complexes by binding the guest molecules on either plane of the polyether ring.

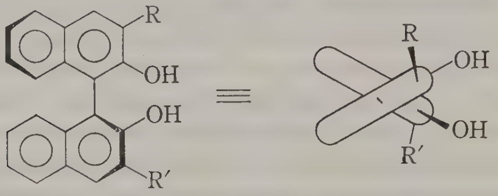
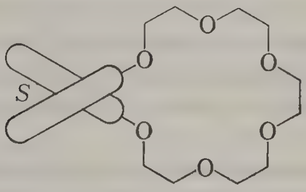


Fig. 5.2 Absolute configuration of 2,2′-substituted binaphthol.

Examples of the optically active crown ethers synthesized by Cram *et al.* are shown in formulas **177**, **178**, and **179**. They measured the stability constants of the diastereomeric complexes of these chiral hosts with various chiral guest cations, and then succeeded in the optical resolution of the enantiomeric amino acid ester salts to D and L isomers by means of liquid-liquid chromatography[25,26,28~30,32~35,37~40] (see Section 3.5.1).



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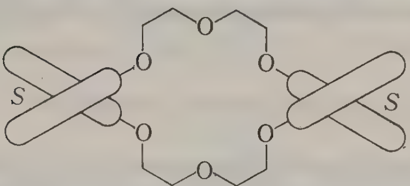

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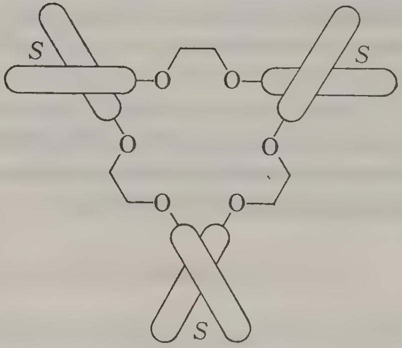
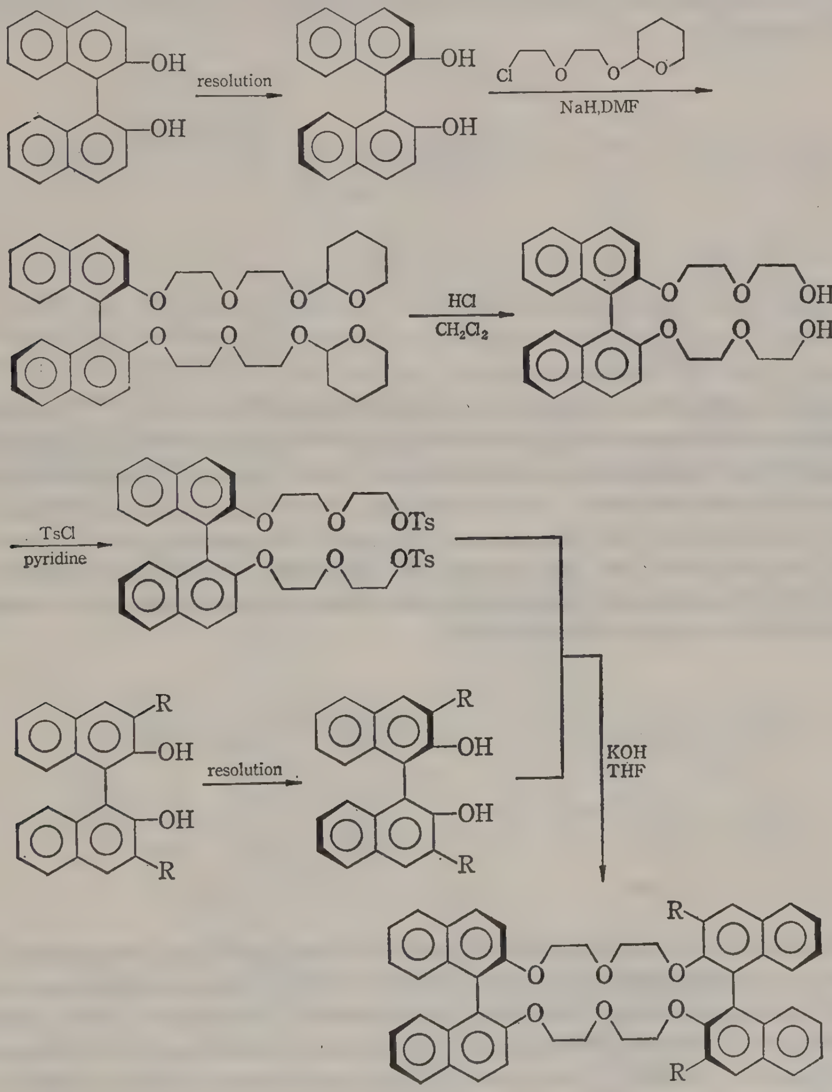


179

In addition to liquid-liquid chromatography, Cram and his group have achieved optical resolution by solid-liquid chromatography using an immobilized optically active crown ether bound to silica gel[31,39] or to polystyrene crosslinked with divinylbenzene[36 39] as a solid support. The applications of these optically active crown ethers will be discussed in Section 5.3.

In the synthesis of optically active crown ethers, 1, 1′-binaphthol is used principally as a starting material, and ring closure is carried out by a condensation reaction with polyether derivatives, as in the synthesis of aromatic crown ethers described in Section 2.2.1. There are two methods for obtaining two isomers:

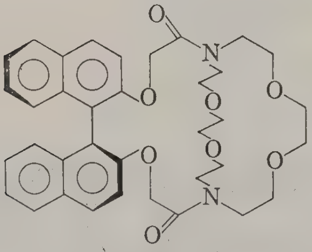
1) A racemic mixture is prepared and then optically resolved by liquid-liquid or solid-liquid chromatography based on the difference in the stability of the diastereomeric complexes, using as the guest a previously resolved D-or L-amino acid ester salt.
2) 1, 1′-Binapthyl is resolved and then condensed with a polyether derivative. Among the optically active crown ethers with two binaphthyl groups, the compounds such as **180** which have the substituents at the 3-position of one of the binaphthyl units as the



180 (5.1)

additional binding sites indicate large ability for the recognition of the enantiomers, and these compounds are synthesized only by method 2. An example of the synthesis is shown in Eq. (5.1).[39]

After the reports by Cram *et al.*, their method was used to formulate analogues of the optically active crown compounds. Lehn *et al.* prepared optically active bicyclic and tricyclic cryptands **181** and **182** with a technique similar to that used in the synthesis of usual cryptands, and reported that racemic primary ammonium salts were resolved optically in about 10% optical yield by the optically active cryptands having amide linkages.[42,43] Lehn *et al.* also reported on the synthesis of chiral 18-crown-6 having four side chains such as $-COOH$,$-CONHCH_2COOMe$, L-$CONHCH(COOMe)$, and $-CH_2$–3–indole.[44]



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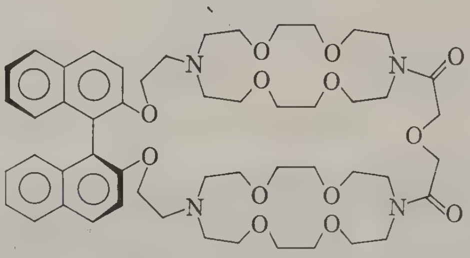
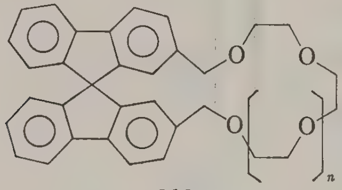


182

Other workers have synthesized chiral dicyclohexyl-18-crown-6,[45,46] chiral aza-crown ether,[47] and another kind of chiral cryptand.[48] Prelog has been also interested in the optically active crown compounds and prepared two types of 9, 9′-spiro-bifluorene-2, 2′-polyether (**183** and **183**).[49] The enantiomers were isolated and the absolute configurations were determined. Among the compounds, the one with $n = 2$ showed the highest stereoselectivity for the cations. The selectivity for the enantiomers of α-phenylalkyl ammonium and phenylglycinium derivatives was measured by means of partition and the electrochemical method.



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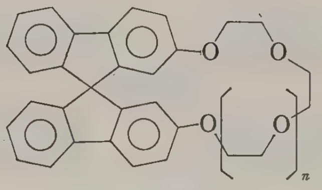
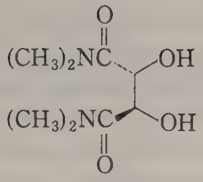


184

Optically active crown compounds have also been synthesized using natural optically active compounds as the starting materials. Lehn *et al.* prepared **186** using L-(±)-tartaric acid as the starting material by the successive condensation of its bis(N, N-dimethyl)amide derivative (**185**) and diiodoethyl ether or diethylene glycol ditosylate in the presence of Tl(I)OEt. Compound **187** was also prepared with a similar technique.[50,51]



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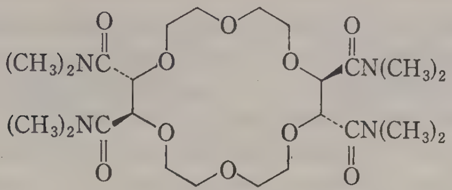

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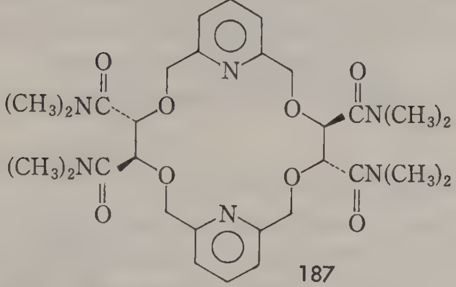
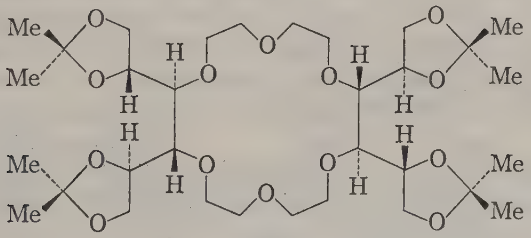


187

Stoddart *et al.* prepared chiral host compounds having 9-crown-3 and 18-crown-6 rings (**188**) using L-tartaric acid, D-mannitol, and L-threitol as the starting materials.[52~54] Compound **188** recognizes the enantiomers of primary ammonium salts, such as phenylethyl ammonium-PF_6^- salt. Stoddart *et al.* also prepared chiral azacrown ethers having a pyridine or methylamino moiety using mannitol as a starting material,[55] and chiral 18-crown-6 (**189**)[56,57] using D-glucose and D-galactose as the starting materials. These



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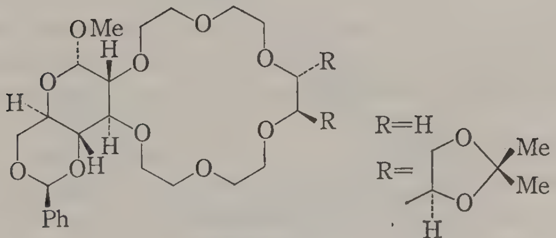

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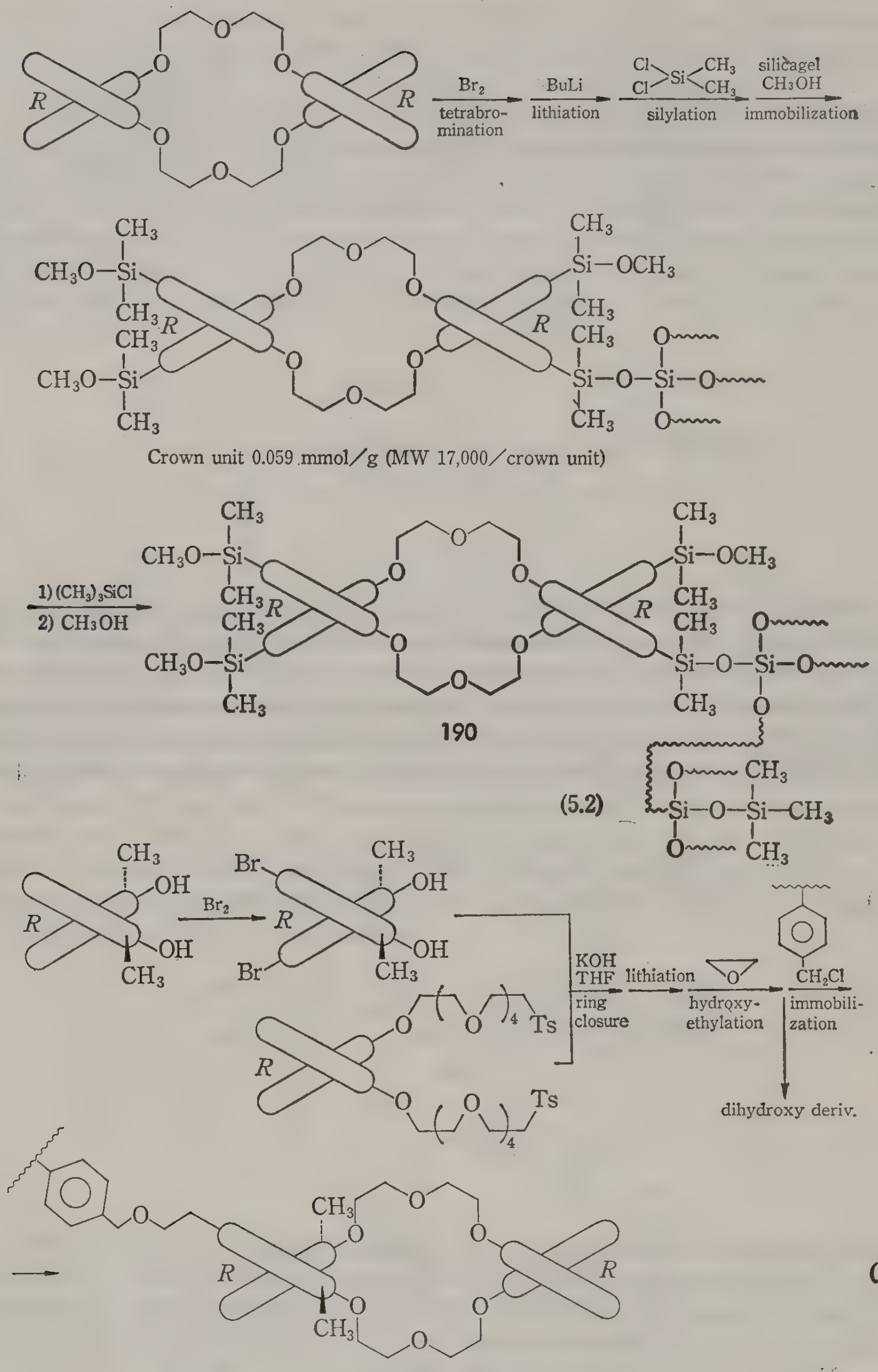


Crown unit 0.059 mmol/g (MW 17,000/crown unit)

190

(5.2)

191

(5.3)

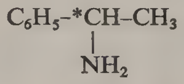
Crown unit 0.073 mmol/g (MW: ~ 14,000/Crown unit) optical isomers, whose precursors are natural carbohydrates, are cheap raw materials for the optically active crown compounds with substituted bismethylenedioxy units.

The polymers having crown ring moieties and the immobilized crown compounds which are expected to have practical applications will be discussed in detail in Chapter 6. As an example of the latter, Cram *et al.* prepared "immobilized" optically active crown compounds (**190** and **191**) by a technique in which the optically active crown compounds were supported on the surface of silica gel(31,39) or polystyrene crosslinked with divinylbenzene(36,39) by silyl ether or ether linkage, respectively, and achieved enantiomeric resolution of amino acid ester salts by solid-liquid chromatography (*see* Section 5.3.1). These methods of immobilization are demonstrated in Eqs. (5.2) and (5.3).

5.3 APPLICATIONS OF OPTICALLY ACTIVE CROWN COMPOUNDS

5.3.1 Optical Resolution

The resolution of enantiomers by Cram's optically active crown compound was achieved for the first time in the complexation of (—)-(*SS*)-dibinaptho-22-crown-6 (**178**), the (*SS*) isomer of crown ether **17**, with the PF_6^- salt of racemic α-phenethylamine (**192**),



$$C_6H_5\text{–}{}^*\underset{\displaystyle NH_2}{\underset{|}{C}}H\text{–}CH_3$$

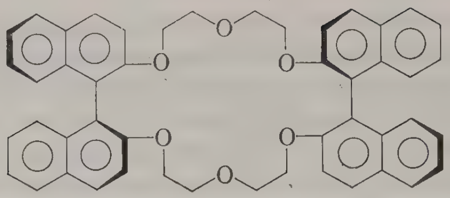
192

indicating stereoselectivity.(25) When **178** and racemic **192** in chloroform and water were shaken in the presence of $NaPF_6$, the angle of rotation of **192** bound by **178** to form a complex in the chloroform layer was $[\alpha]_{575}^{25} + 9.41°$ (CH_3Cl_3), which shows that the bound stereoisomer was (+)-(*R*)-**192**, with an optical purity of 27%. This result demonstrated that the host, (—)-(*SS*)-**178**, forms a more stable complex with (+)-(*R*)-**192** than with (—)-(*S*)-**192**, and the difference of the relative stability $\Delta(\Delta G)$ was calculated to be about 266 cal/mol at 0° C.

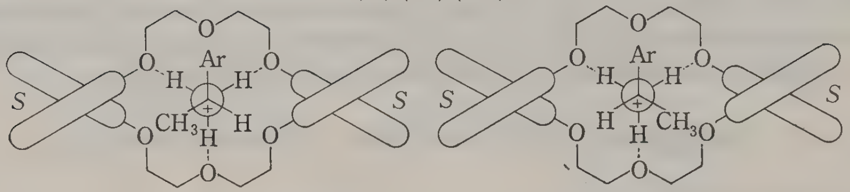
Figure 5.3 illustrates the conformation of these diastereomeric complexes. In each case, the phenyl group, which is the most bulky group, is located in the widest space in the cavity, and conformation (a) is more stable than (b) because the methyl group is less hindered sterically by the chiral barrier of the naphthyl group.

Cram *et al.* synthesized compound **193**, bearing side chains with terminal carboxyl groups at the 3, 3′-position of the binaphthyl unit, and its homologues.(27) These side chains are like tentacles and were designed to be the counter anion in the complexation and to control the freedom of the guest ion during incorporation by the host molecule, as shown in Fig. 5.4.(26)

Racemic **193** and optically pure (—)-(*R*) valine **194** were dissolved in the solvent system of D_2O-$CDCl_3$-CD_3COOD and equilibrated in the partition between the two liquid phases. Quantitative analyses were carried out with nmr, and formation of the complexes was also ascertained by the chemical shift in the nmr spectrum. The results indicated that ~ 50% of **193** and ~ 95% of valine were distributed in the D_2O layer,



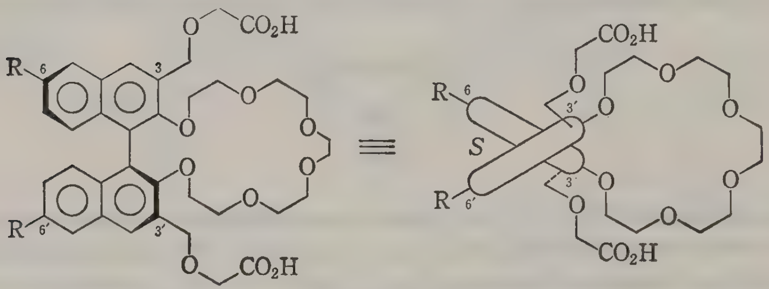
(−)-(*SS*)-(192)



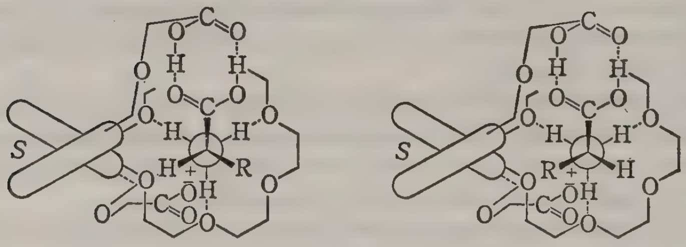
(a)
(−)-(*SS*)-(178)·(+)-(*R*)-(192)

(b)
(−)-(*SS*)-(178)·(−)-(*S*)-(192)

Fig. 5.3 **(—)-(*SS*)-178** complexes with *α*-phenethylamine **(192)**



193 (R=H)

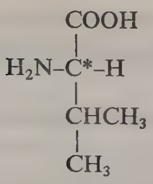


(*S*) (*S*)- configuration

(*S*) (*R*)- configuration

Fig. 5.4 Optically active crown ether having the side chains with terminal carboxyl groups and the tentacle-like action of the terminal groups in chiral recognition. (Source: Ref. 3. Reproduced by kind permission of John Wiley & Sons.)

and the **193** recovered from the D_2O layer in 44% yield showed $[\alpha]_{546}^{25}$ + 6.7° (THF). Thus, the optical purity of the recovered **193** was determined to be 27% since the maximum angle of rotation of (*S*)-**193** is 24.9° (THF). From these values, the chiral



$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H_2N{-}C^{*}{-}H} \\ | \\ \mathrm{CHCH_3} \\ | \\ \mathrm{CH_3} \end{array}$$

194

recognition factor F was calculated with Eq. (5.4), using the fact that 27% of excess R-isomer is present in addition to 37% each of R and S.

$$F = \frac{64\%\ (R)\text{-}\mathbf{193}}{37\%\ (S)\text{-}\mathbf{193}} = 1.7 \tag{5.4}$$

The largest F value was observed for **193** ($R = H$); among the homologues of **193**, the value decreased for the corresponding diesters, for the homologues having only one substituent at the 3-position, and for the homologues with a crown ether ring consisting of one less unit of ethylene oxide. It was proposed that these observations were a product of the behavior of the tentacles and the insufficient size of the cavity.

Further investigation of the recognition ability of (S)-**193** for R and S of valine demonstrated that (S)-**193** · (+)-(S) valine complex was formed predominantly since (S)-valine was obtained from the $CDCl_3$ layer in the CD_3COOD–$CDCl_3$–D_2O system. From the angle of rotation of valine, $[\alpha]_{546}^{25}$ + 32.2° (HCl), and that of the obtained valine, $[\alpha]_{546}^{25}$ + 4.0° (HCl), the chiral recognition factor was calculated to be $F = 1.3$.[26]

With these results, Cram *et al.* carried out optical resolution by liquid-liquid chromatography utilizing the difference in the stability of the complexes.[26] A solution of (S)-valine dissolved in a mixture of acetic acid and water saturated with benzene was mixed with celite and packed in a column. Then, a solution containing racemic **193** was added and eluted. Initially, (R)-**193** with the angle of rotation of $[\alpha]_{546}^{25}$ −69.2° (CH_3Cl) was eluted, and it was followed by the fraction containing (S)-**193** with the angle of rotation of $[\alpha]_{546}^{25}$ +70.0° (CH_3Cl). Optically pure (R)-**193** ($[\alpha]_{546}^{25}$ −76.5°) was obtained by repeated chromatography of the first fraction using the same column.

Since then, Cram and his coworkers have continued their research on the optical resolution of primary ammonium salts and amino acid ester salts using various optically active crown ethers which are optically pure. Cram introduced a constant named the "enantiomer distribution constant (EDC)," defined by Eq. (5.5), as a quantitative

$$\mathrm{EDC} = \frac{D_{\mathrm{A}}}{D_{\mathrm{B}}} = \frac{K_{\mathrm{A}}}{K_{\mathrm{B}}} \tag{5.5}$$

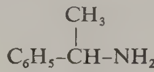
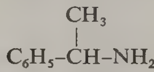
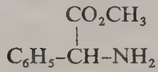
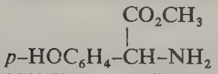
measure for chiral recognition. In Eq. (5.5), D_{A} is the distribution coefficient between the organic and aqueous phases of the enantiomer which forms the more stable complex with the host, $D_{\mathrm{A}} = [\mathrm{A}]_{\mathrm{org}}/[\mathrm{A}]_{\mathrm{aq}}$; D_{B} is the same coefficient of the enantiomer which forms the less stable complex, $D_{\mathrm{B}} = [\mathrm{B}]_{\mathrm{org}}/[\mathrm{B}]_{\mathrm{aq}}$. The ratio of D_{B} to D_{A} is equal to the ratio of the stability constants, $K_{\mathrm{A}}/K_{\mathrm{B}}$, of the complexes formed by the incorporation of A and B by the same host in the same organic solvent as the organic phase.

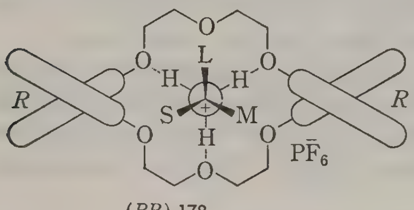
The values of EDC are in fair agreement with the separation factor α in liquid-liquid chromatography (see Eq. 5.6), and the transport rate factor k_A/k_B which will be described in Section 5.3.2.

The optical resolution of primary ammonium salts and amino acid ester salts (counter anion: PF_6^-) using optically pure crown ether as a host were carried out as follows.[2,29)] Silica gel or celite saturated with a 4 M solution of $LiPF_6$ (or $NaPF_6$) was used as the stationary phase for column chromatography. After adding the racemic guest salt dissolved in the smallest possible amount of chloroform, the racemate was eluted with a chloroform solution of optically pure crown ether host while the temperature of the column was held constant. The content of the salt in the eluent was determined by measuring the relative conductance, assuming a linear relationship between the salt concentration and relative conductance.

Table 5.1 and Fig. 5.5 illustrate the results of the optical resolution of racemic α-phenethylamine **192**, phenylglycine methyl ester, and *p*-hydroxyphenyl-glycine methyl ester by liquid-liquid chromatography using (*RR*)-**178** as a host.[29)]

TABLE 5.1 Optical resolutions of amine and amino ester salts by liquid-liquid chromatography using (*RR*)-178[25)]

No.	Amine, amino ester (HPE_6 salt)	T(°C)	EDC (D_A/D_B)	Separation factor (α)
1	 $C_6H_5\text{-}\overset{\overset{CH_3}{\vert}}{C}H\text{-}NH_2$	25°	1.5	1.5
2	 $C_6H_5\text{-}\overset{\overset{CH_3}{\vert}}{C}H\text{-}NH_2$	−21°	1.8	1.9
3	 $C_6H_5\text{-}\overset{\overset{CO_2CH_3}{\vert}}{C}H\text{-}NH_2$	−13°	2.5	2.5
4	 $p\text{-}HOC_6H_4\text{-}\overset{\overset{CO_2CH_3}{\vert}}{C}H\text{-}NH_2$	−15°	4.2	3.6



L = aryl
M=CH_3 or CO_2CH_3
S = H

(*RR*)-178
(more stable complex)

In Table 5.1, the separation factor α is defined by Eq. (5.6), in which V_{RA} is the retention volume (measured from the top of the chromatograph column to the maximum point of retention) for the faster moving (better complexed) component A; V_{RB} is the retention volume (similarly measured) for the slower moving (less well complexed) component B; and V_M is the volume of chloroform on the column at any one time. If

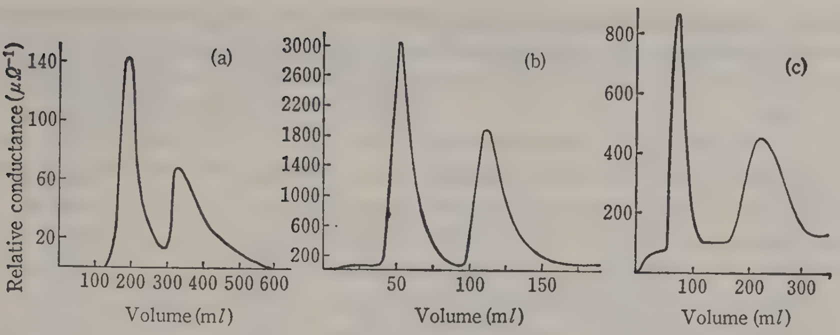


Fig. 5.5 Liquid-liquid chromatographic optical resolution by (*RR*)-**178** of (a) α-phenylethylammionium PF_6 salt (Table 5.1, No. 1), (b) methylphenylglycinate PF_6 salt (Table 5.1, No. 3), and (c) methyl *p* hydroxyphenylglycinate PF_6 salt (Table 5.1, No. 4). The stable complexes were eluted faster. In (b) and (c), ninhy drin tests of the column eluates at the base line points were negative. (Source: Ref. 29. Reproduced by kind permission of the American Chemical Society.)

equilibrium was established for distribution of the enantiomers between the two phases on the column, the column possessed the characteristics of liquid-liquid extraction and Eq. (5.7) applied.

$$\alpha = \frac{V_{RA} - V_M}{V_{RB} - V_M} \tag{5.6}$$

$$\alpha = \frac{D_A}{D_B} = \text{EDC} \tag{5.7}$$

The data of Table 5.1 indicate that the α values determined from the retention volumes were about equal to the EDC values calculated from one-plate extraction experiments. Thus, the EDC value for an amino ester will indicate whether the compound may be optically resolved by this technique.

The EDC values[2,28,29)] for a combination of amines and amino ester salts as the guest, and either (*SS*)-**178** or (*SS*)-**180** with CH_3 groups at the 3, 3′-position as the host, are shown in Table 5.2. The EDC values of (*SS*)-**180** are much larger than those of (*SS*)-**178**, and this suggests that the steric effect of the CH_3 group contributes to the chiral

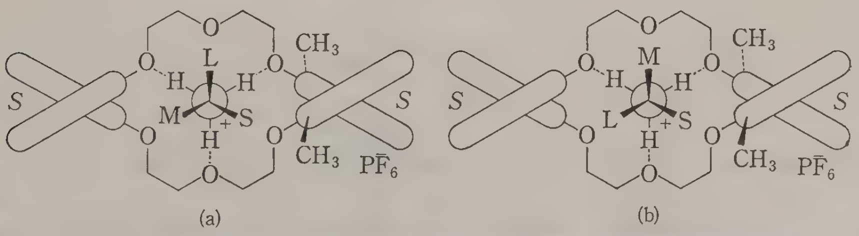


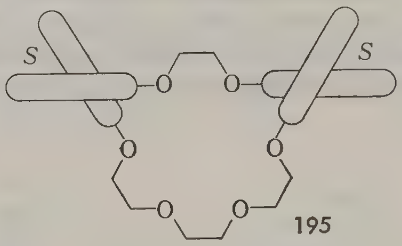
Fig. 5.6 Steric effect of the CH_3 group in (*SS*)-**180**; the (a) form is stabler.

TABLE 5.2 Enantiomer distribution constants (EDC) for amine and amino ester salts as guests.[2,28,29]

No.	Guest: $RR'CHNH_3^+PF_6^-$ R	R'	Host	Extraction temp. (°C)	EDC (D_A/D_B)	Difference of stabilities of complexes $\Delta(\Delta G)$ (cal/mol)
1	C_6H_5	CH_3	(*SS*)–178	25	1.5	240
2	C_6H_5	CH_3	(*SS*)–178	−21	1.8	300
3	C_6H_5	CO_2CH_3	(*SS*)–178	24	2.5	540
4	C_6H_5	CO_2CH_3	(*SS*)–178	−15	3.0	560
5	C_6H_5	$CO_2CH(CH_3)_2$	(*SS*)–178	25	4.0	820
6	C_6H_5	CO_2CH_3	(*SS*)–180	0	31	1,856
7	C_6H_5	CO_2CH_3	(*SS*)–180	24	12.0	1,470
8	*p*–HOC_6H_4	CO_2CH_3	(*SS*)–178	−15	5.0	830
9	*p*–HOC_6H_4	CO_2CH_3	(*SS*)–180	24	17.0	1,700
10	*p*–HOC_6H_4	CO_2CH_3	(*SS*)–180	0	38	1,966
11	$C_6H_5CH_2$	CO_2CH_3	(*SS*)–178	−1	1.8	320
12	$(CH_3)_2CH$	CO_2CH_3	(*SS*)–178	−10	1.5	240
13	$(CH_2)_2CH$	CO_2CH_3	(*SS*)–180	−10	5.3	870
14	$CH_3S(CH_2)_2$	CO_2CH_3	(*SS*)–178	−5	1.7	280
15	$CH_3S(CH_2)_2$	CO_2CH_3	(*SS*)–180	−5	2.2	420

recognition ability of a host molecule (Fig. 5.6). In the same combination of host and guest molecules, the EDC value increases at a lower temperature, and, among the esters of the same amino acid, bulky isopropyl ester gives a larger EDC value than does methyl ester.

Cram and his associates have synthesized a series of optically active crown ethers such as (*SS*)-**195**;[32] analogues of **178** in which two-$CH_2CH_2OCH_2CH_2$- units were substituted with the units of **196** ~ **199**;[33,58] **179** with three binaphthyl units;[34] analogues of **193** with such side chains (tentacles) as –SH, –CH_2SH, and –CH_2OH;[35] and separated bicyclic bis-1, 1′-(2, 3-naphtho-18-crown-6) **39**.[38] They have determined the EDC values of these crown ethers for various primary amines and amino ester salts.



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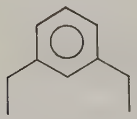

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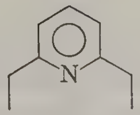


199

Optical resolution by solid-liquid chromatography has been also achieved with the immobilized optically active crown ethers **190**[31,39] and **191**[36,39] bound to a silica gel or to polystyrene crosslinked with divinylbenzene, as in Eqs. (5.2) and (5.3).

Optical resolution by solid-liquid chromatography using **190** was carried out as follows.[2,31] A 0.75 cm (internal diameter) by 56 cm column was packed with 14.0 g of **190** and equilibrated at 25°C with the elution medium, a chloroform or dichloromethane solution of an amine salt carrier (usually 18-crown-6 at concentrations of 5 $\times 10^{-3}$ to 2×10^{-6} M, 0.75% ethanol, or 5% isopropyl alcohol). The solution was passed through the column at a pressure drop of 300 ~ 975 lb/in^2, which gave a constant flow rate between 0.50 ~ 1.0 m*l*/min. Racemic amine salt (1 ~ 11 mg) was dissolved in 2 m*l* of the elution medium and introduced at the top of the column. The molar ratio of host to guest ranged from 23 to 128. The column eluate was passed through a conductivity cell attached to a recorder. The results are shown in Table 5.3 and Fig. 5.7.

TABLE 5.3 Solid-liquid chromatographic optical resolution with immobilized optically active crown ether **190** as host and primary amine salts as guests[31]

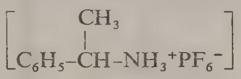
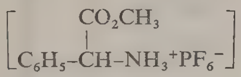
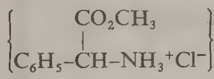
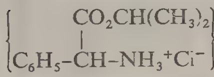
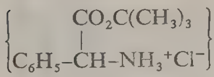
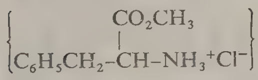
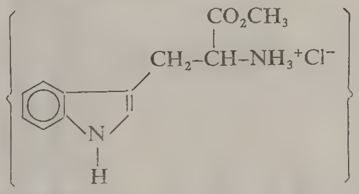
No.	Guest	Mobile phase		Separation factors (α)
		Solvent	Carrier	
1	 $\left[C_6H_5-\overset{\overset{CH_3}{\mid}}{C}H-NH_3^+PF_6^-\right]$	$CHCl_3$	18-crown-6	1.7
2		CH_2Cl_2	18-crown-6	1.5
3	 $\left[C_6H_5-\overset{\overset{CO_2CH_3}{\mid}}{C}H-NH_3^+PF_6^-\right]$	$CHCl_3$	18-crown-6	1.4
4		$CHCl_3$	0.75% C_2H_5OH	1.5
5	 $\left\{C_6H_5-\overset{\overset{CO_2CH_3}{\mid}}{C}H-NH_3^+Cl^-\right\}$	CH_2Cl_2	18-crown-6	1.2
6	 $\left\{C_6H_5-\overset{\overset{CO_2CH(CH_3)_2}{\mid}}{C}H-NH_3^+Cl^-\right\}$	CH_2CL_2	5%$(CH_3)_2CHOH$	2.9
7	 $\left\{C_6H_5-\overset{\overset{CO_2C(CH_3)_3}{\mid}}{C}H-NH_3^+Cl^-\right\}$	CH_2Cl_2	5%$(CH_3)_2CHOH$	2.2
8	 $\left\{C_6H_5CH_2-\overset{\overset{CO_2CH_3}{\mid}}{C}H-NH_3^+Cl^-\right\}$	$CHCl_2$	18-crown-6	4.4
9		$CHCl_3$	18-crown-6	6.4

Table 5.4 and Figs. 5.8 and 5.9 present the results of the optical resolution of amino ester salts (counter anion: ClO_4^-) by solid-liquid chromatography using **191** column: 9.5 g, containing 0.694 mmol of the host; elution medium: $CHCl_3$–CH_3CN).[36]

Blasius *et al.* reported the optical resolution of amino acids by solid-liquid chromatography using a column packed with a powdery polymer obtained by the additive

TABLE 5.4 Optical resolution of $RC^*H(NH_3)CO_2R'^+ClO_4^-$ guest (G) by solid-liquid chromatography on a 9.5 g column of immobilized optically active crown ether **191** (supported on polystyrene crosslinked with divinylbenzene) containing 0.694 mmol of host (H) sites.[†1,36)]

No.	Guest			H/G[†2]	CH_3CN in $CHCl_3$ (vol %)	Separation		Δ(ΔG)[†5] (cal/mol)	Resol. factor[†6] R_3	Configuration with more bound guest
	Structure R	Structure R′	W(mg)			Factor[†3] (α)	Kind[†4]			
1	C_6H_5	H	0.013	14,000	10	5.5	B.l.	926	1.99	*R*
2	C_6H_5	H	0.32	550	10	11	B.l.	1,303	2.90	*R*
3	C_6H_5	H	5.0	35	10	15	B.l.	1,471	1.13	*R*
4	C_6H_5	H	10.1	17	10	24	B.l.	1,726	0.74	*R*
5	C_6H_5	H	15.2	11	10	12	B.l.	1,350	0.76	*R*
6	C_6H_5	H	84	2	10	11	Min.	1,303	0.21	*R*
7	*p*-HOC_6H_4	H	6.6	28	10	6.1	B.l.	982	2.31	*R*
8	*p*-$HOC_6H_4CH_2$	H	5.8	36	10	1.9	Min.	349	0.42	*R*
9	$C_6H_5CH_2$	H	4.6	40	4	2.3	B.l.	453	0.97	*S*
10	$C_8H_6NCH_2$[†7]	H	2.0	104	20	6.1	B.l.	982	1.61	*R*
11	$(CH_3)_2CH$	H	1.6	97	10	2.3	Min.	452	0.45	*R*
12	$C_2H_5(CH_3)CH$	H	2.3	69	5	1.9	Min.	349	0.24	*R*
13	$(CH_3)_3C$	H	2.0	79	5	1.9	Min.	349	0.37	*R*
14	CH_3	H	1.6	82	4	1.5	Min.	220	0.21	*R*
15	$CH_3SCH_2CH_2$	H	6.6	26	4	1.4	Min.	183	0.25	*R*
16	*p*-HOC_6H_4	CH_3	9.5	50	10	26	B.l.	1,770	3.0	*R*
17	C_6H_5	CH_3	9.5	48	10	18.5	B.l.	1,585	4.5	*R*
18	*p*-$CH_3O_2CC_6H_4$	CH_3	9.5	50	10	12.6	B.l.	1,376	2.3	*R*
19	*p*-ClC_6H_4	CH_3	9.5	47	10	8.5	B.l.	1,163	2.2	*R*
20	*p*-$FC_6H_4CH_2$	CH_3	9.5	50	10	8.5	B.l.	1,163	2.7	*S*
21	$C_6H_5CH_2$	CH_3	9.5	50	10	6.4	B.l.	1,008	1.9	*S*
22	*p*-$HOC_6H_4CH_2$	CH_3	9.5	47	10	4.7	B.l.	841	1.7	*R*

[†1] Average host site ~ 14,000 mass units, or 0.073 mmol of host per gram.

[†2] Ratio of total moles of host to total moles of guest.

[†3] Separation factor (α) = (retention volume of less mobile component minus total dead volume)/(retention volume of more mobile component minus total dead volume).

[†4] B.l.: baseline separation; Min.: minimum between fractions.

[†5] $\Delta(\Delta G) = RT\ln\alpha$, and measures the free energy differences of the diastereomeric complexes.

[†6] $R_s = 2$ (retention volume of less mobile component minus that of more mobile component)/(sum of bandwidths of two peaks).

[†7] Tryptophane side chain.

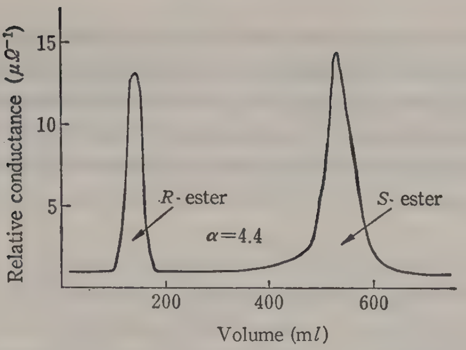


Fig. 5.7 Solid-liquid chromatographic optical resolution by **190** of methyl phenylalaninate Cl salt. (Source: Ref. 31. Reproduced by kind permission of the American Chemical Society.)

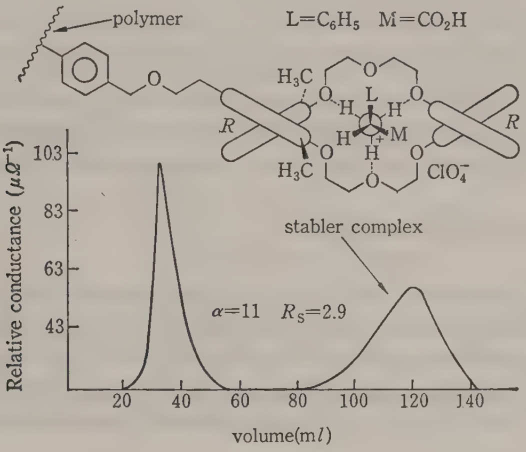


Fig. 5.8 Solid-liquid chromatographic optical resolution of phenylglycine perchlorate by **191** (Table 5.4, No. 2). (Source: Ref. 36. Reproduced by kind permission of the American Chemical Society.)

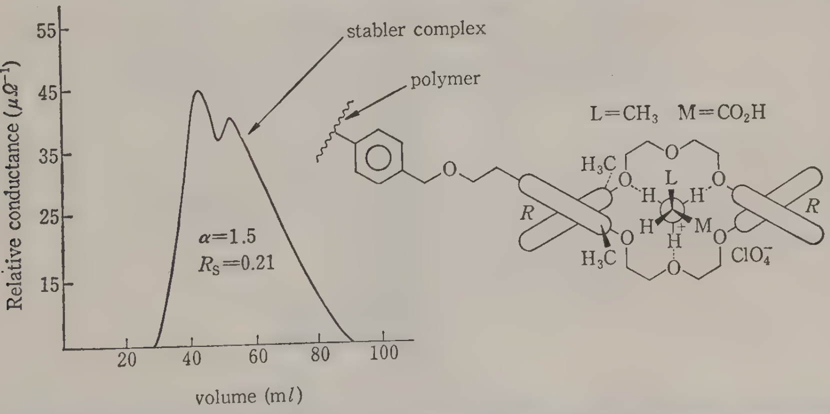
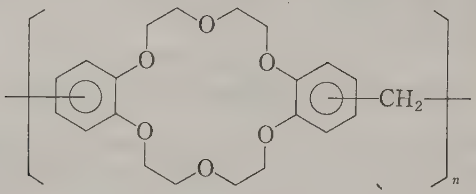


Fig. 5.9 Solid-liquid chromatographic optical resolution of alanine perchlorate by **191** (Table 5.4 No. 14). (Source: Ref. 36. Reproduced by kind permission of the American Chemical Society.)

condensation of dibenzo-18-crown-6 with formaldehyde (the proposed structure is schematically shown as **200**).[59] Though they assumed that chirality in the polymer was produced somewhere in the process of the additive condensation since the crown ring had no asymmetrical element, it would appear to be difficult to reproduce the same polymer with the same optical resolving ability because of the polymerization method.



200

It may be possible, however, to achieve optical resolution with polymers other than immobilized, optically active crown compounds; for example, polymers having chirality in the polymeric chain in the vicinity of the crown ring may be useful. Syntheses and applications of these types of polymeric crown compounds are anticipated.

5.3.2 Optically Selective Transport

The selective transport of a cation by a crown compound was described in Sections 1.3 and 1.4. In biological systems, the active transport of amino acids through lipophilic cell membranes to a higher concentration phase is linked with the passive transport of H^+, Na^+, or K^+ to the lower concentration phase.[60,61] Research is currently in progress on the transport of metal cations by means of naturally occurring ionophore antibiotics

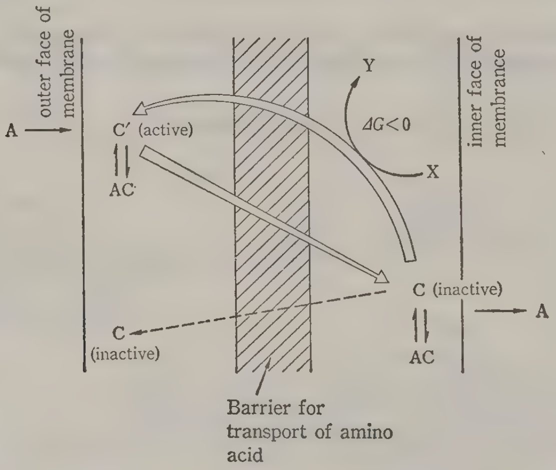


Fig. 5.10 Active transport of amino acid. X → Y: conjugate reaction advantageous in free energy; C, C′: e. g., conformer. C′ is effected allosterically by chemical activation. (Source: Ref. 66. Reproduced by kind permission of Kodansha, Japan.)

and synthetic crown compounds through artificial or liquid membrane,[62~68] as described previously. Christensen proposed a model for the active transport of amino acids through a cell membrane,[69] shown in Fig. 5.10,[66] and Lehn et al. carried out experiments with transport of amino acids and dipeptides from one aqueous phase to another through a liquid membrane of toluene.[70] The amount of amino acid transported through the liquid membrane was controlled by the change in cation concentration.

Cram *et al.* applied the results of their research on the optical resolution of amino acids (Section 5.3.1) to the transport of amino acids[3,30] and obtained the resolution of amino ester and primary ammonium salts by stereoselective passive transport of their HCl, HBr, or HPF_6 salts from one aqueous phase to another through a liquid membrane of chloroform using optically active crown compounds. The method is schematically shown in Fig. 5.11.[66] Cram *et al.* suggested that the thermodynamic driving force for the transport was the entropy of dilution (driving force from the chloroform layer in the direction of the black arrow) and the changes in solvation energy associated

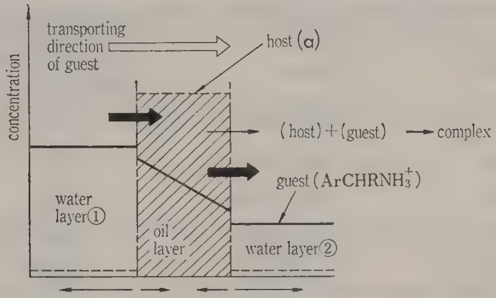


Fig. 5.11 Passive transport of primary ammonium salt (guest) by crown ether (host). (Source: Ref. 66. Reproduced by kind permission of Kodansha, Japan.)

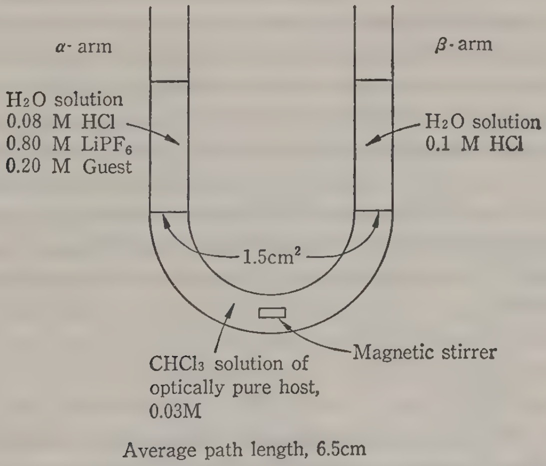
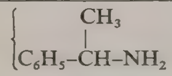
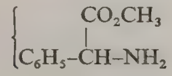
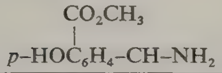


Fig. 5.12 Apparatus for chiral recognition in transport. (Source: Ref. 3. Reproduced by kind permission of John Wiley & Sons.)

with the inorganic salt "salting out" the organic salt from its original solution (driving force through the interface between the water layer ① and chloroform in the direction of the black arrow).

Figure 5.12 is a diagram of the apparatus used by Cram *et al.* for the investigation of optically selective transport. The host compounds were (*RR*)-**178** and (*RR*)-**180**, and the guest compounds were the PF_6 salts of α-phenylethylamine, methyl phenylglycinate, and methyl *p*-hydroxyphenylglycinate. Table 5.5 present the results.[3,30] For each of the guest compounds, (*RR*)-**180** with two methyl groups demonstrated higher chiral recognition and transported the guest more rapidly than did (*RR*)-**178** without the methyl groups. Apparently the methyl groups sterically inhibit electron delocalization into the aromatic rings, in addition to their effect on steric hindrance during complexation described in Section 5.3.1. Furthermore, the inductive effect of the methyl groups makes the aryl oxygen of (*RR*)-**180** more basic than that of (*RR*)-**178**, so the former is a better binder for the cations.[3]

TABLE 5.5 Optically selective transport by optically active crown ethers[3,30]

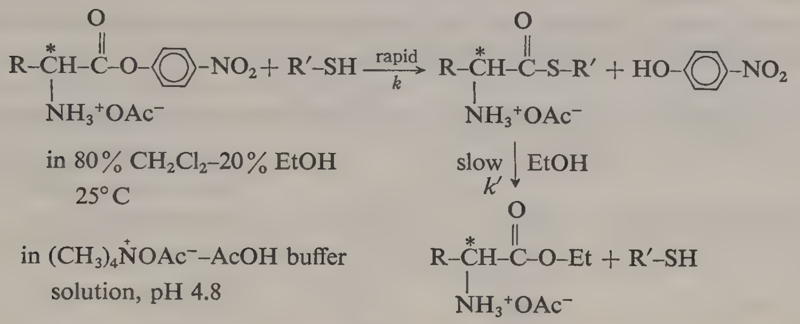
No.	Guest (HPF_6 salt)	Host	Ratio of transport rates (k_A/k_B)	EDC(D_A/D_B)
1	 $\left\{\begin{array}{c}CH_3\\ \vert\\ C_6H_5\text{–}CH\text{–}NH_2\end{array}\right.$	(*RR*)–**178**	1.5	1.5
2		(*RR*)–**180**	2.3	—
3	 $\left\{\begin{array}{c}CO_2CH_3\\ \vert\\ C_6H_5\text{–}CH\text{–}NH_2\end{array}\right.$	(*RR*)–**178**	2.2	2.5
4		(*RR*)–**180**	10.0	12.0
5	 $\begin{array}{c}CO_2CH_3\\ \vert\\ p\text{–}HOC_6H_4\text{–}CH\text{–}NH_2\end{array}$	(*RR*)–**180**	14.0	17.0

These experimental methods of passive transport can be used effectively to estimate the EDC values and the separation factors (α) in optical resolution by liquid-liquid chromatography described in Section 5.3.1, particularly in cases where the D_A and D_B values are small. Moreover, optically selective transport based on the principle and method of chiral recognition will provide an important technique for investigations in biophysics as a transport model for essential organic substances in biological systems, as well as for medical applications such as artificial membrane. In addition, the "optical resoluting machine" devised by Cram will be further developed for practical use in the near future as a significant new method for the optical resolution of various enantiomers including amino acids.[71] Cram and his associates are continuing their work on optically selective active transport.

5.3.3 Asymmetrical Reactions

It is well known that, in enzyme systems, intermolecular association occurs prior to the catalytic reaction. That is, a complex is formed between the enzyme and the substrate, then the reaction proceeds with the cooperation of neighboring groups at the catalytic site on the enzyme, and finally, the reaction product is liberated from the enzyme. Using optically active compounds bearing reactive functional groups, Cram *et al.* experimented with asymmetrical reactions involving the formation and cleavage of the covalent bonds in an intermolecular complex in an effort to reproduce the systematic ordering of an enzyme system.[4,35)]

The thioester formation reaction in which an SH group acts as a nucleophile was chosen as a model for the simulation of protease, in which an SH group is the nucleophilic site. The reaction scheme and the reaction conditions are shown in Eq. (5.8). Amino ester acetate was used as a guest and a *p*-nitrophenoxy group as a leaving group; the latter is often employed for model reactions in biochemistry because its concentration is easily determined by uv.



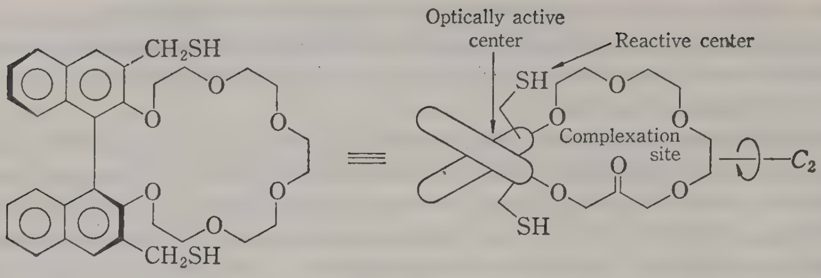
(5.8)

Whereas formation of the thioester is a rapid reaction, the second step, solvolysis (alcoholysis) of the thioester, is slow. Although the overall reaction is a transesterification, the SH group plays the role of a leaving group in the intermediate process because the sulfur atom is a stronger nucleophile than the oxygen atom.

The reaction rate was determined by uv measurement of the amount of liberated *p*-nitrophenol and by following the optical rotation of the amino ester. This reaction obeys first-order kinetics for the concentration of the base when R′-SH is $HOCH_2CH_2SH$, but is independent of the concentration of the buffer solution. Therefore, when the concentration of $R'–S^-$ is low, R′–SH acts as a nucleophile and the reaction is not subject to an acid-base catalysis. When an optically active crown ether having SH groups (**201**) was used as R′-SH, the ratio of k/k' reached as high as 10^4 when R = $C_6H_5CH_2$ in the amino acid.

This reaction is analogous to the reaction of trypsin in the sense that a bond is formed between the host (enzyme) and the guest (substrate), and the guest is an ammonium salt. The reaction also resembles the reaction of chymotrypsin where fast transacylation of the enzyme by the substrate occurs in the hydrolysis of an ester, followed by slow deacylation of the acylated enzyme. Furthermore, it is like acyl rearrangement by papain in that an SH group acts as a nucleophile.

Figure 5.13 shows the optically active crown ether (*S*)-**201** which was used as R′SH by Cram *et al.* Since the host (*S*)-**201** has a C_2 symmetry axis, the same complex can be formed whether a guest molecule approaches from the top or bottom of the crown ring. In the complex, the acyl group in the guest molecule transfers to the host molecule; Table 5.6 compares the rates of the transfer reactions for *l*-amino ester salts with the



(a) (b)

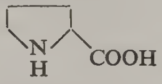
(S)-201

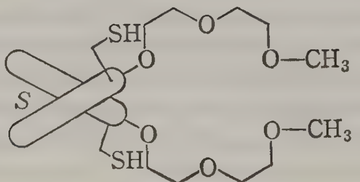
Fig. 5.13 Optically active crown compound used in asymmetrical reaction. (Source: Ref. 4. Reproduced by kind permission of Kagakudojin, Kyoto.)

TABLE 5.6 Reactivities of optically active crown ether (*S*)-**201** and moncyclic polyethor homologue (*S*)-**202** with *l*-amino acid ester salts.[35)]

R in RCH $(\overset{+}{N}H_3)CO_2Ar$	$k \times 10^8$ (sec^{-1})		Relative rates of reaction
	(*S*)–**201**	(*S*)–**202**	(*S*)–**201**/(*S*)–**202**
prolyl†	16	21	0.8
H	>700	5.4	>130
CH_3	≳700	5.4	≳130
$(CH_3)_2CH$	13	0.08	160
$C_6H_5CH_2$	200	0.41	500
$(CH_3)_2CHCH_2$	≳700	0.6	≳1,100

†prolyne





(S)-202

rates observed with the noncyclic polyether analogue (*S*)-**202**. Table 5.6 gives the apparent first-order rate constants *k* and the relative rates for the liberation of *p*-nitrophenol due to transacylation in the presence of (*S*)-**201** or (*S*)-**202**. When *R* was a prolyl group, the relative rate was 0.8, indicating a nearly identical reaction rate for both cyclic and noncyclic polyethers having SH groups. These similar rates were thought to result because proline is a secondary amine and its ammonium salt has only two hydrogen atoms available for hydrogen bonding; thus the complex with *l*-proline ester ammonium salt is less stable because three hydrogen bonds are known to be necessary to form a stable complex (see Section 5.1, **175**).

In contrast, with *l*-amino ester salts having primary ammonium ions such as glycine, alanine, and valine ester salts, the reaction rate with the cyclic polyether having SH groups was about 100 times faster than that with the noncyclic analogue, and with phenylalanine and leucine salts the rates were 500 times and over 1000 times faster, respectively. These results reflect the more highly ordered configurations in the complexes of cyclic crown ethers compared to the noncyclic polyether complexes. These results also demonstrate that, just as the rate of reaction can be enhanced by the intramolecular neighboring groups, the intermolecular configuration in the complexation of compounds which do not have such neighboring groups may also affect the rate.

Cram and his associates compared the rates of the reactions of (*S*)-**201** with *l*- and *d*-amino ester salts in order to evaluate the effect of the chiral recognition ability of (*S*)-**201** and (*R*)-**201** for these salts on the rate of the transesterification reaction. Some of their results are shown in Table 5.7. Although the chirality of alanine was not recognized, with leucine ester salt the *l*-isomer reacted 6 times faster than the *d*-isomer, and with phenylalanine ester salt and valine ester salt the *l*-isomer reacted about 8 times and 9 times faster, respectively.

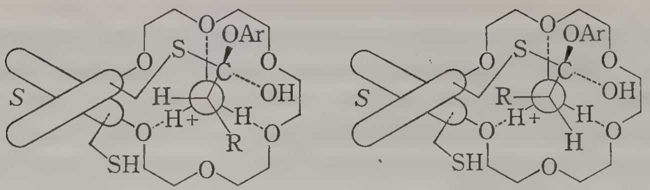
TABLE 5.7 Reactivity of optically active crown ether **201** with *l*-amino ester salts.[35)]

	$k \times 10^8$ (sec^{-1})		Relative rates of reaction
R in *l*-RCH(NH$_3$) CO$_2$Ar	(*S*)–**201**	(*R*)–**201**	(*S*)–**201**/(*R*)–**201**
CH$_3$	70	70	1
(CH$_3$)$_2$CHCH$_2$	~70	11	~6
C$_6$H$_5$CH$_2$	340	41	8.3
C$_6$H$_5$CH$_2$†[1]	42	340	8.1†[2]
(CH$_3$)$_2$CH	22	2.4	9.2

†[1] *d*-Amino ester salt was used.
†[2] Value of (*R*)–**201**/(*S*)–**201**

These are striking results because the optically active crown ether demonstrated chiral recognition through designed complexation, and also because it simulated the stereoselective function in an enzyme system. It is particularly noteworthy that, the larger the size of the *R* group situated in the vicinity of the asymmerical center of the amino ester, the greater was the chiral recognition ability of (*S*)-**201**. The same phenomenon is seen in hydrolysis by chymotrypsin, in which the steroselectivity for amino ester increases from about 20 times with the alanine ester having a smaller *R* group up to about 500 times with the tryptophan ester having a large *R* group.

Figure 5.14 illustrates the configurations of complexes of (*S*)-**201** with an *l*-amino ester salt (more stable) and a *d*-amino ester salt in Newman's projection. In these figures, the acyl carbon atom, assumed to be a tetrahedral intermediate in the transition state, is an optically active center with the *p*-nitrophenoxy group directed upward from the paper and the hydroxyl group directed downward from the paper. These directions of the substituents should be understood from the other stereochemical relationships. Comparing the structures of complexes (a) and (b), it can be seen that the relatively large *R* group is directed toward a larger space in (a), whereas the *R* group is directed toward the steric barrier in (b). This difference should be observed with *l*- and *d*-amino



(a) (b)

Fig. 5.14 Complexes of (*S*)-**201** with (a) *l*-amino ester salt (more stable) and (b) *d*-amino ester salt (less stable). (Source: Ref. 35. Reproduced by kind permission of the American Chemical Society.)

acids since the center of the Newman's projection is an asymmetrical carbon of the amino acid, and the host (*S*)-**201** more easily forms a stable complex with *l*-amino acid, as shown in (a). The host (*R*)-**201**, whose two naphthyl groups rotate in the reverse direction, of course shows the opposite stereoselectivity.

Among the recent efforts to study enzyme reactions, the investigations by Cram and his associates are significant in the discovery of a novel catalyst with a function analogous to that of enzyme. Whereas the artificial reactions employed previously were based on the random collision of the reactant molecules, the asymmetrical reactions using optically active crown ethers with both binding ability and chiral recognition ability are expected to permit the development of processes that mimic biochemical reactions.

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CHAPTER 6

Polymeric Crown Compounds and Immobilized Crown Compounds

6.1 General Aspects

Preceding chapters have discussed specific characteristics of crown compounds as well as the research and development of the compounds for a wide range of applications in both basic science and practical fields of fine chemical synthesis and analytical chemistry. However, some problems remain to be clarified, such as high solubility, biological action, and toxicity, and in addition, the compounds are very expensive for commercial use in the chemical, metallurgical, and atomic power industries, in environmental engineering, and so on.

Though several kinds of crown compounds have been on the market as chemical reagents, they are still expensive at the present time. It is well known that a commercial product has a life cycle that includes conception (research stage), birth (commercialization stage), growth maturation (saturation stage), and decline just as human life does. The relationship between production and price in the life cycle of a commercial product is illustrated schematically in Fig. 6.1.1) Only 14 years have passed since the discovery of crown ethers, and crown compounds are now at the beginning of the birth phase in commercial terms because of the rapid development of research work in recent years. It is a common pattern in the commercialization of new products that the results of research on synthesis, characteristics, and applications mutually feed back to develop the market, the price lowers with increasing demand, and that lower price leads to a further expansion of applications. As mentioned in Chapter 2, production costs at the same level as the usual industrial materials will be achieved when the expansion of demand permits large-scale commercial production because specific raw materials and special processes are not necessary in the manufacture. It is also anticipated that crown compounds will be employed in another mode of usage in the near future as immobilized crown compounds, which are prepared by supporting a small amount of the compound on the surface of an inexpensive carrier.

The generally high solubility of crown compounds in water and organic solvents limits their use and requires a process for recovery.

The toxicity of various crown compounds has not yet been fully elucidated, as discussed in Chapter 7. Generally speaking, the crown compounds which are highly soluble (and/or whose complexes are highly soluble) in water and which have relatively large vapor pressures, such as dicyclohexyl-18-crown-6 and 12-crown-4, have greater

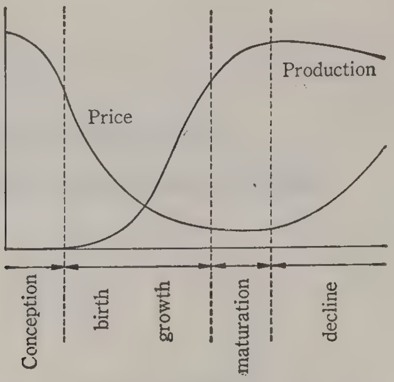


Fig. 6.1 Life cycle of a commercial product. (Source: Ref. 1. Reproduced by kind permission of Nihon Keizai Shimbun (in Japanese).

oral, skin, and inhalation toxicity. In contrast, the crown compounds that are slightly water soluble and have low vapor pressures are less toxic.[2] There should be continued investigation of the biological action and toxicity of crown compounds because such assessment and safety data are indispensable prior to the practical use of a new material.

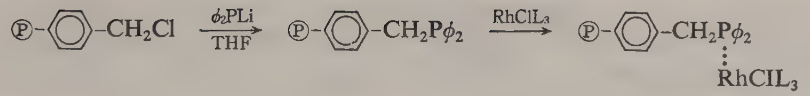
In terms of these problems, polymeric crown compounds (polymers having crown moieties) and immobilized crown compounds on solid support, both of which are insoluble, may be desirable for industrial usage because they offer advantageous forms for easy treatment, recovery, and reuse such as membranes or columns for ion-selective separation and powders or granules for catalysts, as described in Section 2.7. In addition, it is expected that they will be less expensive and much less toxic than "monomeric" crown compounds. For these reasons, polymeric and immobilized crown compounds are current subjects of research and significant developments in industrial applications are anticipated.

There are two methods for the polymerization of crown compounds:

1) Vinyl polymerization or copolymerization of the vinyl derivatives of crown compounds by a radical or ionic polymerization mechanism.
2) Utilization of the reactions of crown compounds with functional groups, in particular, additive-condensation, polycondensation, and polyaddition of crown compounds with two or more functional groups.

Section 2.7 described the syntheses of crown compounds having functional groups, such as vinyl, amino, hydroxyl, and carboxyl groups, and their precursors, such as crown compounds with halogen, nitro, and nitrile groups.

It is well known that a technique that employs an "immobilized enzyme," an enzyme supported on the surface of a natural or synthetic polymer such as cellulose and polystyrene or an inorganic solid, has been developed and used recently in practice as a new tool for the industrial application of enzymes.[3] Equation (6.1) is an example of the insolubilization of a transition metal complex catalyst soluble in organic solvent by support on polystyrene; this technique has become one of the research trends in the field of transition metal complex catalysts.[4]



(6.1)

The same concept has been applied to crown compounds, and "immobilized" crown compounds have been prepared by the following methods:

1) Chemical bond formation by the reaction between a crown compound derivative having a functional group and a functional polymer or silica gel as a solid support.
2) Impregnation of a porous solid support with a crown compound.
3) Coating the surface of a polymer or an inorganic solid support with a polymeric crown compound.

Some of the methods of preparation, their characteristics such as the complexation with cations, uses in solid-liquid phase transfer catalysis, and applications as catalysts for gas phase reactions, ion separation, and optical resolution have been described previously in Sections 2.7, 4.2.6.A, 4.3.3, 5.2 and 5.3.1.

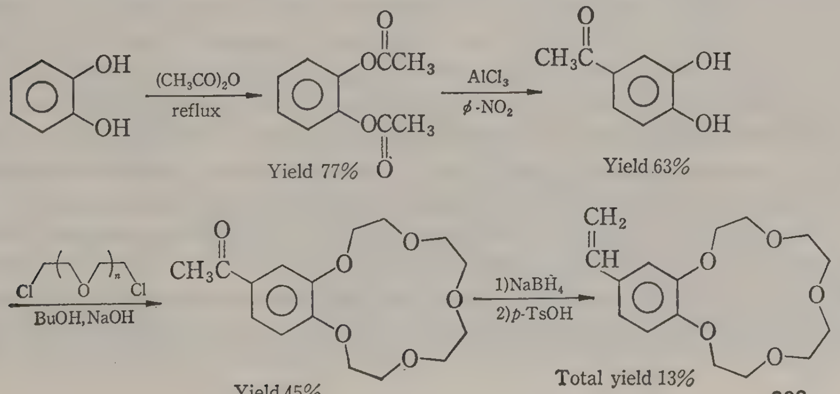
This chapter will discuss further the preparation methods, the characteristics, and applications of polymeric and immobilized crown compounds which have been reported so far. Polymeric crown compounds have been reviewed recently by Shono *et al.*[5]

6.2 POLYMERIC CROWN COMPOUNDS

6.2.1 Poly(Vinyl Crown Compounds)

Poly(vinyl crown compounds) have been prepared by the synthesis of monomeric crown compounds having vinyl groups followed either by radical or anionic polymerization of the monomers to give homopolymers or by copolymerization with a comonomer such as styrene to give the copolymers.

Smid *et al.* synthesized the vinyl derivatives of benzo-15-crown-5 (**203**), dibenzo-15-crown-5, and dibenzo-18-crown-6 (**204**) as in Eqs. (6.2) and (6.3),[6,7] and prepared the polymers by homopolymerization of the vinyl monomer and copolymerization with styrene using a radical initiator of α-methylstyrene tetramer dianion (counter cation: Na^+).[8~10] Equation (6.4) illustrates the radical and anionic homopolymerization.



(6.2)

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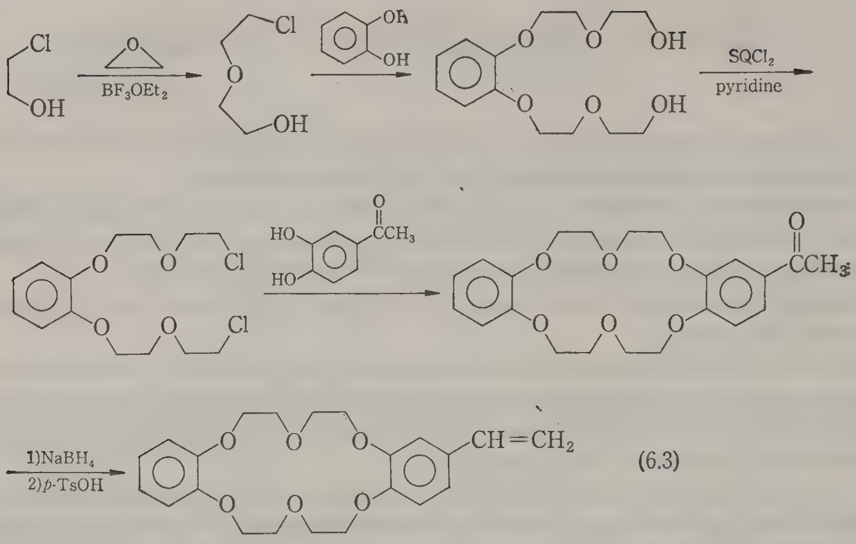

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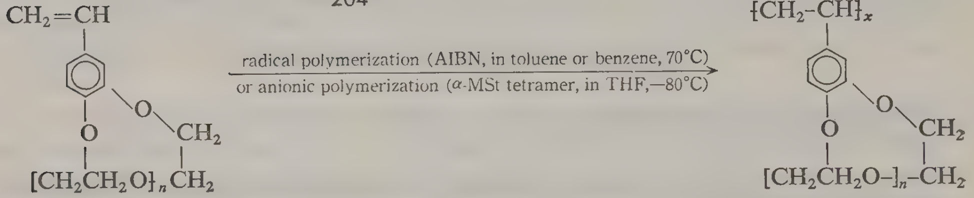
(6.3)



$\bar{M}_n$ 18,000 ~ 119,000

205

(6.4)

The poly(vinyl crown ethers) (**205**) thus obtained were soluble in organic solvents, even the polymer with the high average molecular weight of 10^4. The solubilities and the intrinsic viscosities $[\eta]_0$ of the polymers are shown in Table 6.1.

The results of the extraction of alkali metal picrates (*see* Section 4.3.1.A) using dichloromethane solutions of poly(vinylbenzo-15-crown-5) [abbreviated as P15C5] and poly(vinylbenzo-18-crown-6) [abbreviated as P18C6] showed that the complexation ability of P15C5 was larger than that of "monomeric" benzo-15-crown-5 [15C5] not only with large alkali metal ions such as K^+, but also with small ions such as Na^+ and Li^+, as summarized in Table 6.2. Like the formation of the 2 : 1 complex of two molecules of 15C5 with K^+ described in Sections 3.2.2.A and B, the results here were explained by a similar neighboring group effect of the polymer that caused a 2 : 1 complex to be formed by the neighboring two crown moieties on the polymeric chain. The superior complexation ability of 18C6 with the larger alkali metal ions compared to 15C 5 was explained by the difference in the cavity diameters.

The polymer P18C6 was better able to form complexes with the larger alkali metal ions than was 18C6, but the difference was not so marked as that between P15C5 and 15C5.

TABLE 6.1 Solubility at 25°C (S, g/100 m*l*) and intrinsic viscosity $[\eta]_0$ of poly (vinyl crown ethers).6)

Solvent	P 15C5†[1]		P18 C6†[2]		PVDB 18C6†[3]
	S	$[\eta]_0$	S	$[\eta]_0$	S
Acetone	2.6		0.3		Barely soluble
Methanol	0.34		0.73		Barely soluble
Water	0.095		8.1	0.107	Barely soluble
Hexane	0.09		0.06		Barely soluble
Benzene	Very soluble		Very soluble		Soluble
Toluene	Very soluble		Very soluble		Soluble
Chloroform	Very soluble	0.41	Very soluble	0.37	Fairly soluble
Dichloromethane	Very soluble		Very soluble		Fairly soluble
THF	Very soluble	0.27	Very soluble	0.24	Soluble
Nitrobenzene	Very soluble		Very soluble		Fairly soluble

†[1] Poly(vinylbenzo-15-crown-5) $\bar{M}_n = 116{,}000$
†[2] Poly(vinylbenzo-18-crown-6) $\bar{M}_n = 106{,}000$
†[3] Poly(vinyldibenzo-18-crown-6) $\bar{M}_n = 18{,}000$

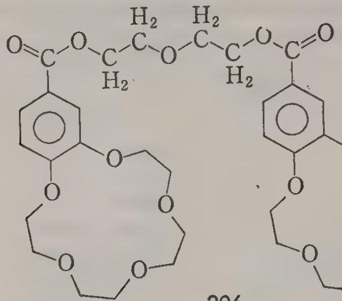
TABLE 6.2 Alkali metal ion-capturing ability of poly(vinylbenzo-15-crown-5), poly(vinylbenzo-18-crown-6), and monomeric crown ethers.6,8)†[1]

Cation	Captured alkali metal ion (%)†[2]					
	15C5	P15C5†[3]	(Polymer/ monomer)	18C6	P18C6†[3]	(Polymer/ monomer)
Li^+	<1	10.0	(>10)	1.01	6.3	(6.2)
Na^+	10.6	24.7	(2.3)	13.1	20.7	(1.6)
K^+	22.3	85.2	(3.8)	85.6	90.2	(1.1)
Rb^+	13.0	83.7	(6.4)	74.0	84.2	(1.1)
Cs^+	3.5	68.8	(19.7)	71.0	87.9	(1.2)

†[1] Determined by the extraction of picrate in aqueous solution by dichloromethane solution of crown polymer or monomer. Concn. of picric acid: 7×10^{-5} M; crown: 35×10^{-5} M; alkali hydroxide: 0.1 M.
†[2] Based on total picric acid.
†[3] $\bar{M}n \doteqdot 10^5$, same concentration of crown unit as that of monomer (35×10^{-5} M).

Smid *et al.* studied the behavior of ion pairs9) and the conductivity of an acetone or MEK solution of Ph_4B^- salts11) using these poly(vinyl crown ether)s. They also prepared the dimeric model (**206**) and studied the complexation with K^+, Na^+, and NH_4^+.12) Dimer **206** formed a 2 : 1 complex (crown unit: cation) with K^+, and a value of log *K* much larger than that of the monomeric 15C5 was observed. The complexation ability was also affected by the type and length of the chain linking two crown rings; for example, the substitution of O with CH_2 reduced complexation because the chain became more rigid.

Wong and Smid recently reported that poly(vinylbenzo-18-crown-6) behaved as a neutral polysoap in an aqueous solution and captured organic solutes such as Na-picrate and methyl orange to form stable complexes with higher stability constants than those of the complexes of polyvinylpyrrolidone and bovine serum albumin.13) They also reported that poly(vinylbenzo-18-crown-6) formed a water-insoluble polysalt complex with Na-carboxymethyl cellulose (CMC) in an aqueous solution in the presence of



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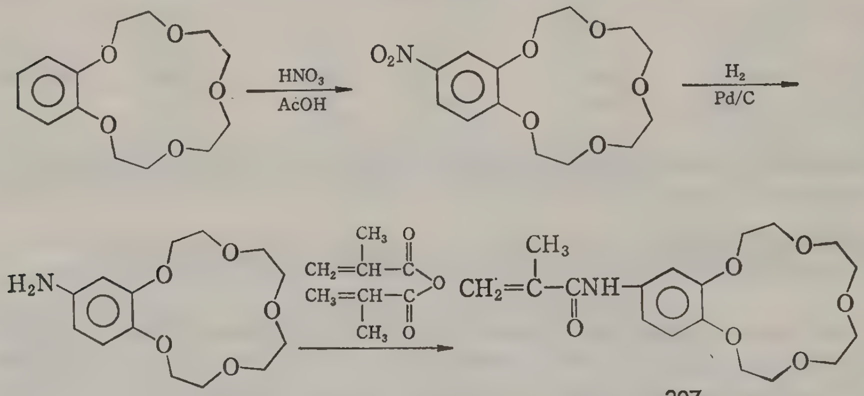
NaCl, KCl, and CsCl.[14] A recent review summarizes the investigations of the characteristics of poly(vinyl crown ether)s by Smid and his coworkers.[15]

The synthesis employed by Smid *et al.* for preparing monomeric vinyl derivatives of crown ethers followed Eqs. (6.2) and (6.3), required many reaction steps, produced a rather low total yield. Shono *et al.* synthesized monomeric methacrylamide derivative (**207**) by the reaction of metacrylic acid anhydride with 4′-aminobenzo-15-crown-5, which was prepared by nitration of benzo-15-crown-5 followed by reduction, as shown in Eq. (6.5).[16] Monomer **207** was dissolved in toluene and polymerized by using AIBN as an initiator. The copolymer was also prepared by copolymerization with methyl metacrylate. The complexation ability of these polymeric crown ethers was measured with Smid's method, using the extraction of alkali metal picrates.[17] The polymers had a greater ability to capture alkali metal ions than did monomer **207**, and in particular, marked differences were observed between the polymer and the monomer for the combinations of K^+ with 15-crown and Cs^+ or Rb^+ with 18-crown, which was prepared in a manner similar to 15-crown. Shono *et al.* also experimented with passive transport of cations using a liquid membrane composed of a chloroform solution of these polymeric crown ethers. The results indicated that the rates of transport by the polymer were



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(6.5)

slower than those by the monomer, while the polymer showed a superior ion-selective transport ability for Na^+/K^+.

Akabori and Miyamoto reported the formation of naked phenolate anion in the condensation reaction (solution reaction) of Na-phenolate with allyl chloride in the presence of poly(vinylbenzo-18-crown-6).[18]

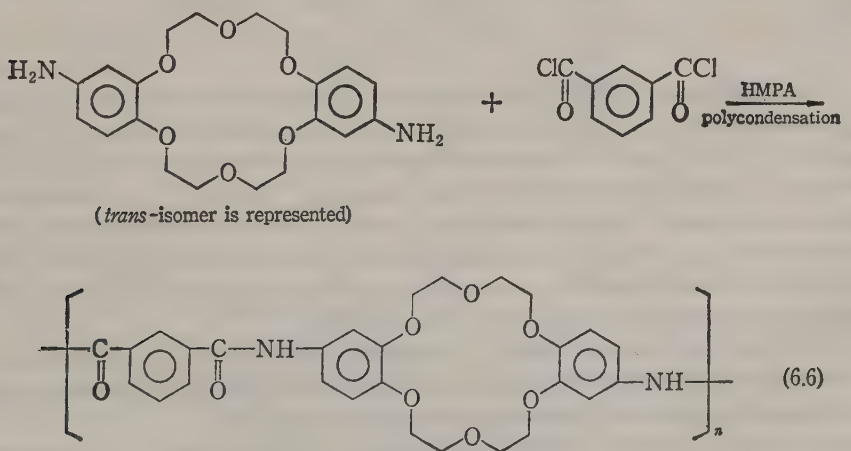
Another synthetic method for 4′-vinylbenzo-15-crown-5 that was reported recently by Matsuda *et al.*[19] was described in Section 2.7 [Eq. (2.36)].

The method for the preparation polymeric crown ethers reported by Shono *et al.* is simpler than Smid's method. However, the applications of the polymeric crown ethers prepared by the two methods may be limited to the situations in which the specific merit of a solid polymer can be effectively utilized because both polymeric crown ethers are soluble in common organic solvents whereas the complexation ability of a polymer is superior to that of the corresponding monomer in the solution.

6.2.2 Polymeric Crown Compounds Prepared by Polycondensation

A. Polyamide Type

Feigenbaum and Michel prepared polyamide **208**, with crown ring moieties in the polymeric chain.[20] Compound **130**, 4, 4′-diaminodibenzo-18-crown-6, was synthesized by the nitration of dibenzo-18-crown-6 followed by reduction and was then used in a polycondensation reaction with an equimolar amount of isophthaloyl chloride or terephthaloyl chloride in HMPA or dimethylacetamide (DMAC). A higher molecular weight polymer was obtained in a higher yield with a combination of *trans*-diamino crown ether-isophthaloyl chloride-HMPA [Eq. (6.6)] than with the other combinations.



(*trans*-isomer is represented)

(6.6)

[η]=0.9~1.1g⁻¹dl(HMPA,30°C)
white fibrous, mp > 220 °C(decomposed)
yield 97 %(based on amine)

208

This crown polyamide (**208**) is insoluble in the solvent that is effective for common polyamides, but a fairly tough film was formed by the cast method using hexafluoroisopropyl alcohol (HFIP). The mechanical and electrical properties of the film thus obtained are shown in Table 6.3. The film that was formed after complexation with K^+ showed nearly the same properties, and because little change was observed in the value of electrical resistance, this was taken as evidence of complexation between the crown polyamide and the cation.

TABLE 6.3 Mechanical and electrical properties of the film of polyamide prepared from *trans*-diaminodibenzo-18-crown-6 and isophthaloyl chloride.[20]

	Tensile modulus (kpsi)	Tenacity (kpsi)	Elongation (%)	Dielectric constant (10^3Hz)	Dissipation factor (10^3 Hz)	Resistance (ohm cm)
I	286	9.9	12	3.86	0.013	2.3×10^{14}
II	346	11.2	12	3.82	0.013	2.8×10^{14}

I: Film formed by casting of crown polyamide.
II: Film formed by casting of crown polyamide after complexation with 52 mol% of K^+.
Film thickness: 1 ~ 2 mil (1 mil = 10^{-3} in); all properties were measured at 23°C.

TABLE 6.4 Complexation ability of polyamide film having 18-crown-6 moiety (in hot 20% solution of metal chloride.[20]

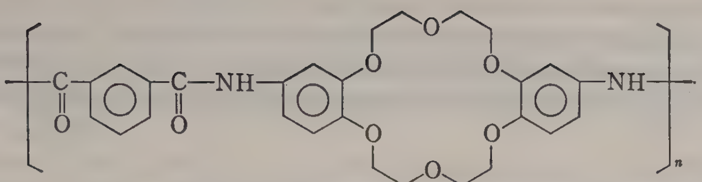
Cation	Ionic diameter (Å)	Captured cation (mol %)
Li^+	1.20	24
Na^+	1.90	54
Ca^{2+}	1.98	0
K^+	2.66	64
Ba^{2+}	2.70	0
Cs^+	3.34	0

The complexation ability of the crown polyamide film was assessed by dipping it into a hot 20% solution of metal chlorides. The results are shown in Table 6.4. The film captured $Li^+ > Na^+$, and K^+, and ion-selectivity was in the order of $Li^+ > Na^+ > K^+$, which was the same order as the 18-crown ethers. Ca^{2+} and Ba^{2+}, which are bound by dibenzo-18-crown-6 to form complexes, were not captured, nor was Cs^+, whose ionic diameter is large. Hydration of these ions in the aqueous solution and less freedom for a conformational change by the crown ring during complexation because of immobilization seem to be the reasons for these findings.

The pioneering research work by Feigenbaum and Michel on polymeric crown ethers was significant because it suggested the possibility of practical applications of film formation and the capture of cations from aqueous solutions.

Based on this research, Shchori and Jagur-Grodzinski prepared a reverse osmosis membrane utilizing the ion-selective transport function of crown ethers.[21,22] Polyamide **209** (PC-6) with a high molecular weight ($[\eta] = 7.5 g^{-1}$ dl in HMPA at 30°C, Tg = 216° C) was synthesized by one type of interfacial polycondensation that involved slow agitation of a chilled mixture of an HMPA solution of *cis*-4, 4′-diaminodibenzo-18-crown-6 and crystalline isophthalyl chloride in an atmosphere of argon.

PC-6 was dissolved in DMF containing hexafluoroisopropyl alcohol (HFIP) or NaSCN (an amount equimolar to the crown moiety in the polyamide), then a film with



209

a thickness of 25 ~ 50 μm was formed by the casting method. Polymer alloy film was also prepared by dissolving a mixture of PC-6 and polyvinylpyrrolidone (PVP) with a molecular weight of about 360,000 in the same way, followed by casting.

A film of the crown polyamide with a relatively low molecular weight ($[\eta] = 0.7 \sim 0.8$ g^{-1}dl), prepared by Feigenbaum's method, became brittle and cracked when it was kept standing in a wet state, whereas a tough film with an excellent capacity for elongation and superior water and solvent resistance was obtained from PC-6. Table 6.5 compares the mechanical properties of the films prepared from PC-6 and the polymer alloy of PC-6 with PVP to the data on crown polyamide fiilm **208** ($[\eta] = 0.9 \sim 1.1$ g^{-1}dl) reported by Feigenbaum and Michel[20] and to the data on the commercial aromatic polyamide film for reverse osomosis membranes sold by the Chemstrand Company.[23]

TABLE 6.5 Mechanical properties of crown-polyamide membranes.[21]

Film	Method of preparation†[3]	Tensile strength (kg/cm²) ultimate	Tensile strength (kg/cm²) at yield	Modulus of elasticity (kg/cm²)	Elongation (%) at yield	Elongation (%) at break
PC-6	1	580	585	22,700	3.6	135
	2	650	608	23,250	4.1	175
	3	525	515	19,700	4.2	153
Polymeric alloy of PC-6 and PVP (20 wt%)	2	470	510	22,000	3.3	180
	3	535	488	19,400	3.7	150
Low molecular weight crown-polyamide†[1]	—	700	—	20,000	—	12
Aromatic polyamide†[2]	—	640	—	22,600	—	—

†[1] Values reported by Feigenbraum and Michel.[20]

†[2] Chemstrand aromatic polyamide used for reverse osmosis. Values taken from McKinney's report.[23]

†[3] 1: Cast from HFIP; 2: cast from DMF + NaSCN and rinsed with water for 24 hr; 3: cast as 2 and rinsed with 1 M NaSCN.

The film of the polymer alloy of PC-6 with PVP (≤ 30 wt%) was transparent and had approximately the same mechanical properties as PC-6 film. The thermal stability of the polymer alloy film observed by TGA and DSC was superior to that of PC-6 film (exotherm peak in DSC at 275° C) and nearly equal to or greater than that of PVP film (exotherm peak in DSC at 350° C). As PVP is a water-soluble polymer, the polymer alloy film was hygroscopic, but substantially no elution of PVP into water was observed in an immersion test at room temperature for 720 hours.

Table 6.6 gives the distribution coefficients of alkali metal salts into PC-6 films which have been equilibrated with aqueous solutions of the salts.[22)] As can be seen, the film had a large capturing ability for NaSCN, whereas the capture decreased to about 1/3 for NaCl. The capture of Li^+, with a small ionic diameter, was only about 1/10 that of Na^+.

TABLE 6.6 Distribution of sodium and lithium salts in PC-6 membranes equilibrated with aqueous solutions.[22)]

Equilibrating solution		Membrane cast from DMF + NaSCN (water content f_w = 0.20 vol)		Membrane cast from HFIP (f_w = 0.20 vol)	
		$\bar{C}_s$ (mmol/ml)	α_s(mmol/ml)	$\bar{C}_s$ (mmol/ml)	α_s(mmol/ml)
NaCl	0.1 M	0.43	4.27		
NaSCN	0.02 M	0.48	24.0		
	0. 1M	1.15	11.5	0.91	9.1
	0.5 M	1.35	2.7		
	1.0 M	1.92†	1.92		
LiSCN	0.1 M	0.095	0.95	0.10	1.0

†A value of $\bar{C}_s$ = 1.97 is calculated for the 1 : 1 molar ratio between the bound salt and the crown ring.

Release of the captured Na^+ from the film was examined by measuring the diffusion coefficients. The coefficients were 5×10^{-12} cm²/sec for PC-6 film and 1.7×10^{-9} dm²/sec for the PC-6—PVP polymer alloy film. From these small values it is thought

TABLE 6.7 Osmotic characteristics of crown-polyamide membranes.[22)]

		PC-6-PVP (20%)[†1]	PC-6-PVP (30%)	PC′-6[†2]	2.5-Cellulose acetate[†3]	Aromatic polyamide (Chemstrand Co.)[†3]
RO	Rate of permeation of water $P_w = 10^7$(cm²/sec)	3.6	6.3 6.1[†4]	6.0	2.6	0.1 ~ 0.8
	Salt rejection $\left(1 - \frac{J_s}{J_w \Delta C}\right) \times 100(\%)$	98.0[†5]	95 99.7[†4]	99.4	99.8	99.8
Direct osmosis	Salt rejection $(1 - J_s/_w\Delta JC) \times 100$ (%)	97.8	88.3	97.5	99.7[†6]	—
	$P_w \times 10^7$ (cm²/sec)	3.6	7.3	6.0	2.5[†6]	—

RO experiments were conducted at 95 ~ 98 atm; 0.1 N NaCl feed solutions were used except [†4]. ΔC = 2.9 N NaCl in direct osmosis.

[†1] Polymeric alloy; 20 ~ 30 μ thickness.

[†2] Cast from 0.1 M $Ba(SCN)_2$–DMF.

[†3] Values quoted by Lonsdale.[24)]

[†4] 0.1 M $MgCl_2$ was used as feed solution.

[†5] Tests with rhodamine B indicated presence of some imperfection in the membrane. Higher than 99 % of the limiting salt rejection was estimated.

[†6] Results obtained by Shchori *et al.*[22)]

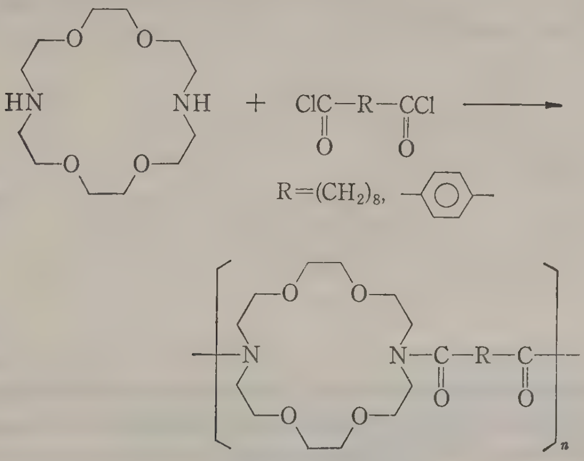
that Na^+ may transfer in a hop-step-jump fashion from one crown ring to another in the polymeric chain. The diffusion coefficient of water into the polymer alloy film was $2 \sim 5$ x 10^{-7} cm /sec. The apparent activation energy of the diffusion of Na^+ was ~ 12 kcal/mol, which was equal to the activation energy of dissociation of the Na^+-dibenzo-18-crown-6 complex.

Desalting of an aqueous solution of NaCl was assessed by using PC-6 film as a reverse osmosis membrane.[22) The results are shown in Table 6.7. The salt rejection was as high as $95 \sim 99.4\%$, substantially the same capability as the commercial cellulose acetate and aromatic polyamide membrane used in practice. The rate of permeation of water into the PC-6 film was one order faster than that in the aromatic polyamide membrane.

These results provide fundamental data for the application of crown polyamide to desalting by dialysis or reverse osmosis and to ion separation, and commercialization of the process is expected once answers are found to the remaining problems such as degradation in the properties of the film.

A patent has been issued for the ultrafiltration membrane and the reverse osmosis membrane prepared from polyamide or polyimide, which is obtained by polycondensation of diaminodibenzo-18-crown-6 with pyromellitic anhydride or trimellitic anhydride.[25) Ion-selective permeation membranes have been reviewed by Ueno *et al.*[26)

As to other polyamide type polymeric crown compounds, Lehn *et al.* synthesized polyamides **210** by the polycondensation of diazacrown ether **30** with dibasic carboxylic acid chlorides according to Eq. (6.7) and studied their capacity for cation capture.[27)

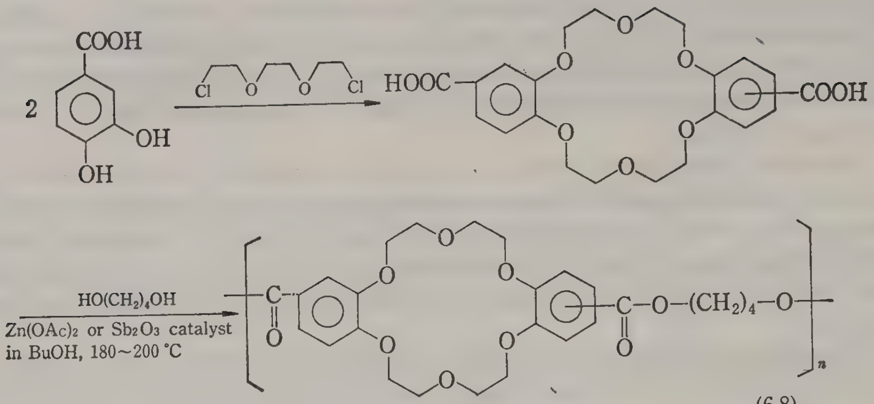


210

(6.7)

B. Polyester Type

A patent related to polyester **211** has been applied.[28) A dicarboxylic acid derivative of dibenzo-18-crown-6 was synthesized from 3,4-dihydroxybenzoic acid and triethylene glycol, then polycondensation of the crown dicarboxylic acid with a diol was carried out as shown in Eq. (6.8).

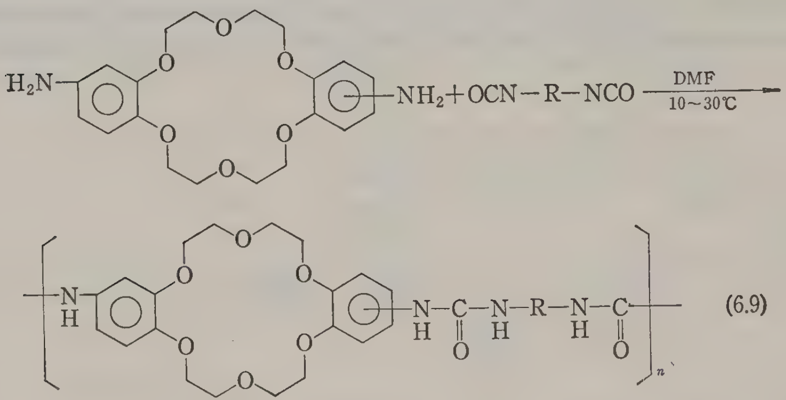


211

(6.8)

6.2.3 Polymeric Crown Compounds Prepared by Polyaddition

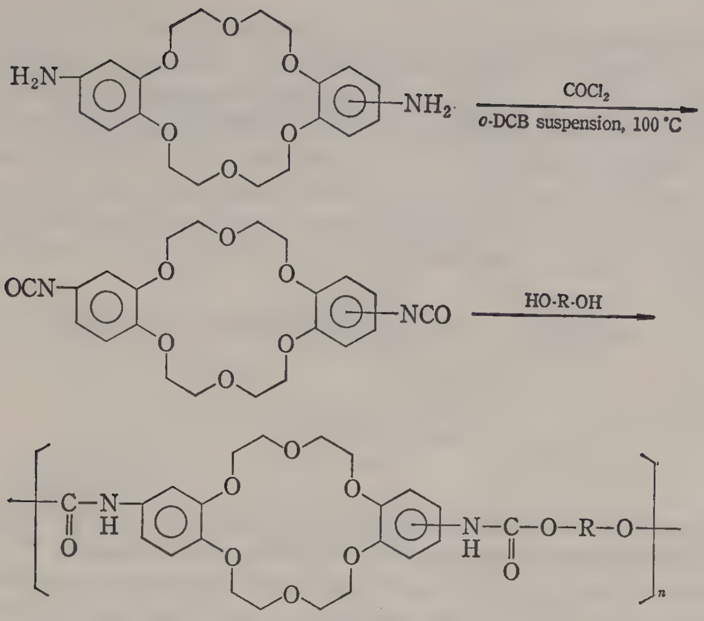
Polyurea **212**, with crown moieties in the polymeric chain, was prepared by the polyaddition of a diisocyanate such as tolylene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), or hexamethylene diisocyanate (HMDI) to a diaminodibenzo-crown ether according to Eq. (6.9).[29] The complexation ability of the polyurea with cations was larger than that of the monomeric diaminodibenzo-crown ether.



212

(6.9)

When phosgene is blown through a suspension of diaminodibenzo-crown ether in *o*-dichlorobenzene at 100° C, the diamino derivative is easily converted to diisocyanate derivative. The diisocyanate derivative reacts with polyhydric alcohols, dibasic acids, and diamines to give polyaddition polymers. When polyurethane **213** is prepared by the reaction with polypropylene glycol according to Eq. (6.10), both soft and rigid polyurethane foams can be obtained,[30] as with the usual polyurethane foam.

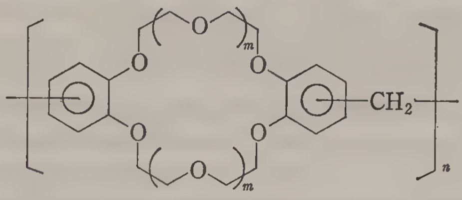


(6.10)

213

6.2.4 Polymeric Crown Compounds Prepared by Additive Condensation

Blasius *et al.* prepared thermosetting resins (**214**) with a three-dimensional network structure from dibenzo-18-crown-6 and dibenzo-24-crown-8 by the reaction with formaldehyde in the presence or absence of phenol, using HCOOH as a solvent.[31,32]



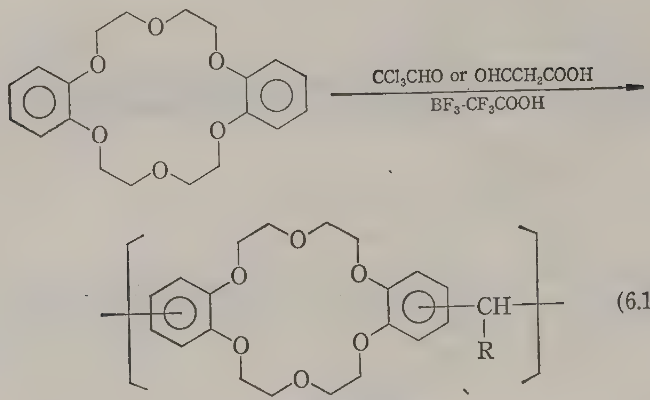
$m = 1$ or 2

214

These polymers captured alkali metal, alkaline earth metal, and ammonium ions from water-methanol or methanol solutions. Though the capturing capacity and the distribution coefficient of a cation in the resin were dependent on the type of counter anion and the solvent, the polymer having an 18-crown ring ($m = 1$) selectively captured K^+ and Cs^+, and the polymer having a 24-crown ring ($m = 2$) selectively captured Rb^+ and Cs^+ and thus separated these ions from others.

The use of these polymers for the optical resolution of amino acids[33] and a proposed explanation for this function were described previously in Section 5.3.1.

Davydova *et al.* also prepared a gelated polymer by the reaction of dibenzo-18-crown-6 with formaldehyde in chloroform using sulfuric acid as a catalyst.[34] A structure similar to **214** was estimated to be the structure of the gel. A patent related to



(6.11)

R=CCl_3,COOH

215

polymer **215**, prepared by the additive condensation of dibenzo-18-crown-6 with chloral or glutaric acid in CF_3COOH containing BF_3 (Eq. 6.11), has been issued.[35)]

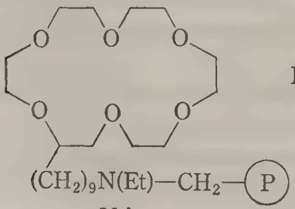
These polymers can be easily prepared by additive condensation polymerization from inexpensive raw meterials and are presumed to have the property of good resistance to solvents and chemicals because of their three-dimensional structure. It can thus be anticipated that the polymers will find practical applications in powder or granular form to ion-selective capture or separation and to catalysis in organic syntheses.

6.3 IMMOBILIZED CROWN COMPOUNDS

6.3.1 Immobilized Crown Compounds Bound to Solid Surfaces Having Functional Groups

Section 5.2 described the methods for preparing two immobilized optically active crown ethers: **190**,[36,37)] immobilized on silica gel by utilizing the reactivity of silanol groups on the surface of the gel, and **191**,[37,38)] immobilized on polystyrene crosslinked with divinyl benzene (Eqs. 5.2 and 5.3). Applications of these compounds to the optical resolution of amino ester salts using solid-liquid chromatography was mentioned in Section 5.3.1.

Montanari *et al.* prepared immobilized crown ether **216** and cryptand **217** on polystyrene[39)] and compared their activity in phase transfer catalysis to that of immobilized quaternary ammonium salts **218** and phosphonium salt **219** as part of a series.



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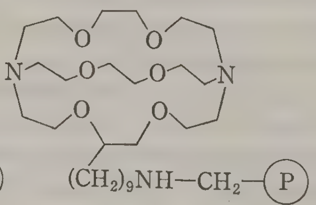

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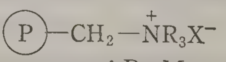
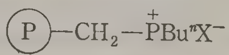


$\text{(P)}-CH_2-\overset{+}{N}R_3X^-$

a : R=Me
218 b : R=Bu^n
c : R=Oct^n

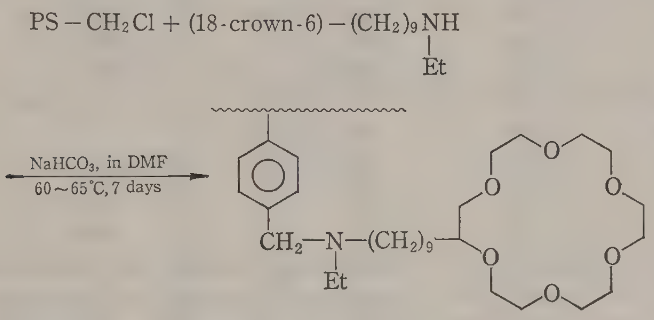


$\text{(P)}-CH_2-\overset{+}{P}Bu^n_3X^-$

219

of experiments$^{40\sim42)}$ on nucleophilic substitution reactions, using crown ethers, azacrown ethers, cryptands, and their derivatives with side chains as phase transfer catalysts, as described in Section 4.2.5.B.

The immobilization of the crown compounds on polystyrene was carried out as illustrated in Eq. (6.12). Chloromethylated polystyrene (crosslinked with *p*-divinyl benzene (2 ~ 4 wt%) containing 0.7 ~ 3.7 meq/g polymer of Cl) was reacted with a derivative of crown ether **132** or cryptand **133** having an ω-ethylaminononyl group as a side chain group which had been prepared according to Eq. (2.37) in Section 2.7.



$$\mathrm{PS-CH_2Cl + (18\text{-}crown\text{-}6)-(CH_2)_9\underset{\displaystyle Et}{N H}}$$

(6.12)

Table 6.8 shows the results of a triphase transfer catalysis of *n*-octyl bromide (toluene solution) with a saturated aqueous solution of KI and KSCN using **216** ~ **219** as catalysts. These results indicated that triphase catalyses using immobilized crown compounds could be characterized as follows:

1) The catalytic activity was in the order of immobilized cryptand **217** ≳ immobilized crown ether **216** > immobilized phosphonium salt **219** ≫ immobilized ammonium salts **218**. Some of the **218** salts were decomposed in reactions between 80 and 90° C.

2) Although the rates of reactions catalyzed by the immobilized catalysts **216** ~ **219** were slower than those catalyzed by corresponding free crown compounds or onium salts,$^{339\sim40,43\sim48)}$ the order of catalytic activity in the former group agreed with the order in the latter.

3) It has been suggested that a sufficiently lypophilic alkyl substituent is necessary to produce an active catalyst because of the poor catalytic activity shown by **218a** as well as the reduced lypophilicity of $Me_4N^+X^-$.$^{43\sim45,48)}$

4) In these experiments the frequency of the active species in the polymeric chain did not notably affect the rate of reaction.

5) In contrast to the findings with free onium salts,$^{49\sim51)}$ no correlation was observed between the concentration of the immobilized catalyst (1 ~ 10% of the substrate) and the conversion time. The large amount of solvent absorbed in the presence of higher concentrations of immobilized catalyst may be one explanation for this difference.

6) The catalytic activity of immobilized phosphonium salt **219** is lost when the crosslinking density of the polymer is increased by elevating the amount of divinylbenzene from 2% to 4%, but the crosslinking density has little effect on the catalytic activity of immobilized crown compounds **216** and **217**.

TABLE 6.8 Triphase transfer catalysis with immobilized crown compounds and immobilized onium salts (n–$C_8H_{17}Br_{org}$ †[1] + $KX_{aq} \rightarrow n$–$C_8H_{17}X$ + KBr).[42]

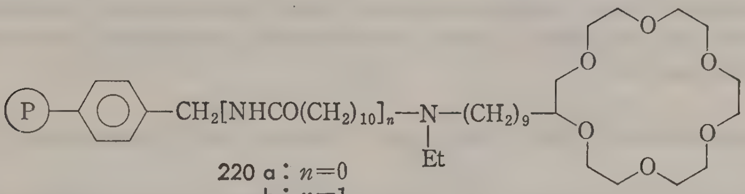
	Catalyst	Frequency of functionalized monomeric units (apoximate values; 2% divinylbenzene)	Mol. equiv. of catalyst	Reaction temp. (°C)	KI†[2]		KCN†[2]	
					Time (hr)	Yield (%)†[3]	Time (hr)	Yield (%)†[3]
Immobilized crown compound	216	1 : 20	0.01	90	5	≥95		
	216	1 : 10	0.01	90	3	≥95		
	216	1 : 3	0.01	90	5.5	≥95	8	≥95
	216	1 : 5†[5]	0.01	90	6	≥95	7	≥95
	217	1 : 40	0.01	90	3.5	≥95	2	≥95
	217	1 : 20	0.01		3	≥95		
Immobilized onium salt	218 a†[4]	1 : 2	0.1	90	16	—	16	19
	218 b	1 : 15	0.1	60	5	76		
	218 c	1 : 10	0.1	60	6.5	73		
	219	1 : 10	0.1	60	5	77		
	219	1 : 15	0.1	90	1.5	90	1.5	68
	219	1 : 10	0.1	90	1.5	90	1	86
	219	1 : 2	0.1	90	2.5	73		
	219	1 : 2†[5]	0.1	90	16	—		
	219	1 : 10	0.01	90	5.5	89	3.5	90
	219	1 : 2	0.01	90	7	85	4	95
	219	1 : 2†[5]	0.01	90	5	—		

†[1] In toluene (1 : 3 vol/vol).
†[2] Saturated aqueous solution, 2.5 mol. equiv.
†[3] By glc analysis.
†[4] AG 1–X2 (Bio-Rad).
†[5] 4 % Divinylbenzene.

7) After completion of the reaction, the immobilized catalyst can be used for the next reaction without any treatment except filtration. The catalytic activity did not decrease after repeating the same reaction five times.

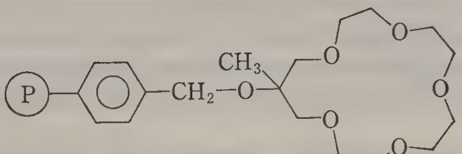
This triphase transfer catalysis between an organic phase, a solid phase, and an aqueous phase using a solid catalyst was named "triphase catalysis" by Regen,[52,53] who used a quaternary ammonium salt bound to chloromethylated polystyrene, PS–CH_2–$N^+Me_2Bu^nCl^-$, as a solid catalyst. It is a significant process because it offers ease of catalyst recovery and reuse and of product separation, as well as possible applications to a flow system. The advantage of the method is that the crown compound is immobilized by covalent bonding to the surface of the solid support, but the disadvantage is that the crown compound derivatives with functional groups for immobilization are not usually synthesized easily, so for practical uses will be necessary to develop economical methods for introducing the functional groups.

Montanari *et al.* prepared immobilized crown ether **220** and phosphonium salt, both of which have long chains to the polystyrene support, and examined the effect of triphase catalysis on the nucleophilic substitution reactions of n-octylbromide with KI and PhSK (catalyst: 0.01 mol equivalent).[54] The half-lives of the conversion of octylbromide to octyliodide (toluene solution, 90° C) were 53 min for **220a**, 45 min for **220b**, and 42 min for **220c**, and the half-lives of the conversion of octylbromide to phenyloctylsulfide were 70 min for **220a**, 45 min for **220b**, and 39 min for **220c**; it took 33 min for *n*-decyl-18-crown-6. The effect of the chain length on the reaction rate depended on the polarity of solvent used. A large effect was observed in low-polar *n*-heptane, while no significant effect was seen in *m*-dichlorobenzene. For a catalyst immobilized on the surface of a solid support with a short chain, the reaction rate increased with the increasing polarity of the solvent.



220 a: $n=0$
b: $n=1$
c: $n=2$

Kakiuchi *et al.* prepared immobilized crown ether **221** by a reaction between chloromethylated polystyrene (Cl: 4.6 mmol/g polymer) and the Na alkoxide of **142**, which was synthesized according to Eqs. (2.38) and (2.40), and examined the triphase catalysis of *n*-octylbromide with KI.[55] When [catalyst]/[Br] = 0.081, *n*-octyliodide was formed in yields of 80% (1 hour) and more than 95% (2 hours).



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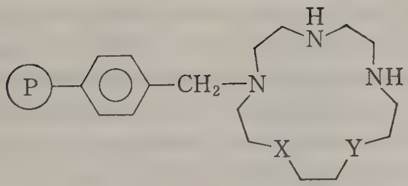
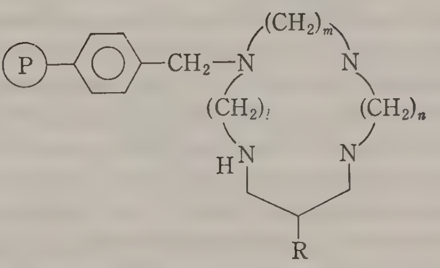


$X=Y=O$
$X=Y=S$
$X=O, Y=NH$
$X=S, Y=NH$
$X=Y=NH$

222



$l=m=n=2, R=CH_2CH_2OH$
$l=n=2, m=3, R=CH_2CH_2CH_2CH_2NH_2$
$l=n=3, m=2, R=CH_2CH_2CH_2CH_2NH_2$

223

Tabushi *et al.* prepared immobilized azacrown compounds and azathiacrown compounds **222** by the nucleophilic substitution of chloromethylated polystyrene with cyclic polyamides followed by reduction with B_2H_6.[56~58)] They also prepared immobilized azacrown compounds **223** by the following procedure:[59)] 1, 3-diketo cyclic polyamine was prepared from substituted malonic acid ester and linear polyamine according to Eq. (2.19) and was then immobilized through a C–N linkage by a reaction with chloromethylated polystyrene (MW 1,600 ~ 1,800, 60% chloromethylated) in chloroform at room temperature for 24 hours, followed by the reduction of the carbonyl group with B_2H_6 in THF. These immobilized crown compounds captured Ni^{2+}, Co^{2+}, and Cu^{2+}, and both adsorption and desorption of these transition metal ions were accomplished more easily by **223** with substituents than by the immobilized crown compounds without substituents.

6.3.2 Immobilized Crown Compounds Infused into Porous Solid Carriers

The research by Misono *et al.* on the elimination of haloalkanes by the heterogeneous catalytic gas phase reaction using a catalyst consisting of silica gel impregnated with KCl and $CaCl_2$ complexes with dibenzo-18-crown-6[60)] was previously described in Section 4.2.6.A, and the study by Kawamura *et al.* which found that an ion-exchange resin impregnated with dicyclohexyl-18-crown-6 adsorbed ^{85}Sr more selectively than ^{48}Ca from the buffer solution[61)] was mentioned in Section 4.3.3.

These immobilization methods by impregnation are very easy, but the applications are limited because there is no bonding between the solid carrier and the crown compound, so that the crown compound is eluted by solvents and stripped by mechanical force. Despite of this weak point, the technique may be used as a simple tool for basic research on catalytic gas phase reactions by using a solid carrier impregnated with crown compounds having very low vapor pressure, and porous solids impregnated with crown compounds having very low solubility may also be applicable to ion-separation.

6.3.3 Immobilized Crown Compounds Film-Coated on Solid Surfaces

The polymeric crown compounds and immobilized crown compounds which have been discussed so far are still unsatisfactory for practical uses because they are uneconomical. In the case of polymeric crown compounds, many steps are needed to synthesize the monomers which are the derivatives of crown compounds bearing functional groups, and the yields of the monomers are usually very low. Among the monomers, diaminocrown ethers can be prepared by a relatively simple method in a relatively high yield, but a special solvent is needed to make the film of the polyamides derived from diaminocrown ethers. The polymeric crown compounds prepared by additive condensation are considered to be comparatively inexpensive, but all the polymeric crown compounds have the following disadvantage. The utilization efficiency of the crown compound that serves as a raw material is very low because only the crown moieties present on the surface of the polymer can make contact with the substrate.

In contrast, a much higher utilization efficiency of the crown compound is achieved with immobilized crown compounds bound chemically to the surface of a solid support. However, many steps are needed to synthesize the derivatives of crown

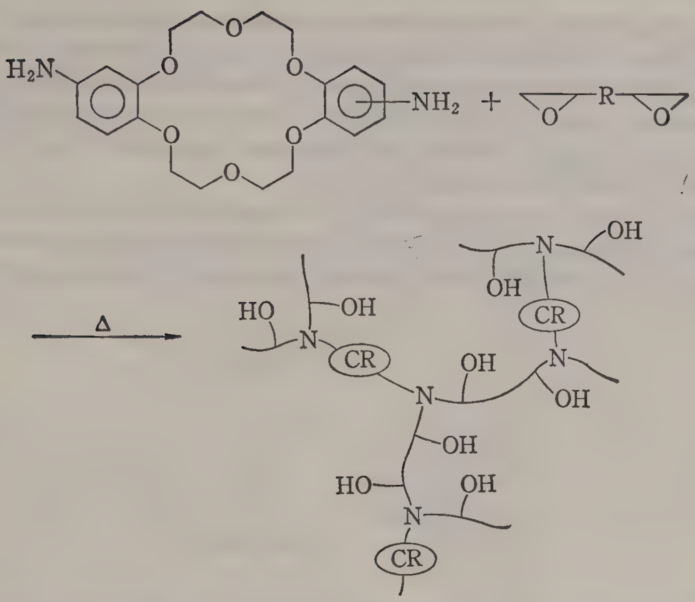


Fig. 6.2 Schematic presentation of a curing reaction of diepoxide with diaminocrown ether.

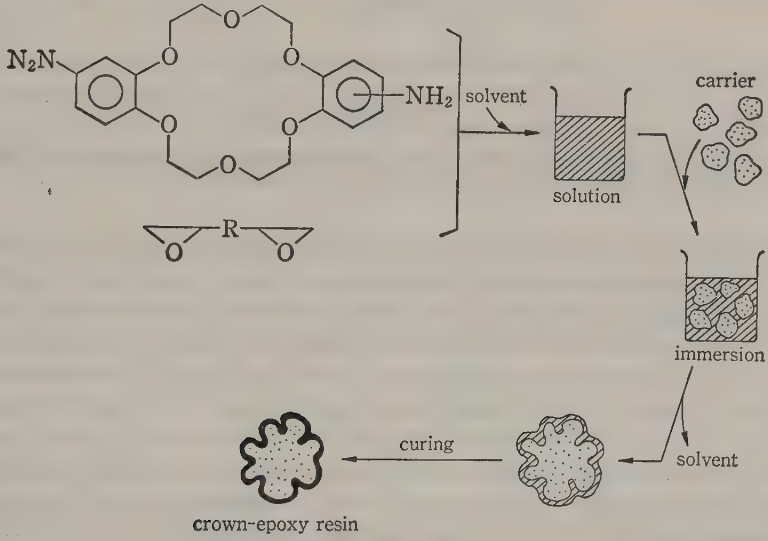


Fig. 6.3 Immobilization by formation of a crown-epoxy resin.

compounds for immobilization, and, when an organic polymer such as polystyrene is used as the solid support, problems may sometimes remain in the resistance to solvents and chemicals and in mechanical properties.

In an attempt to overcome these disadvantages, Hiraoka *et al.* prepared a new type of immobilized crown ether.[62~64] Compound **130**, 4, 4′-diaminodibenzo-18-crown-

6, which can be obtained in approximately quantitative yield by nitration followed by reduction of dibenzo-18-crown-6, was reacted with an epoxy compound on the surface of a solid carrier to form thin coating film of "crown-epoxy" resin that strongly adhered to the solid carrier. The curing reaction of the epoxy resin using diaminocrown ether as a crosslinking agent (curing agent) is shown schematically in Fig. 6.2, and the immobilization method is illustrated in Fig. 6.3.

A plot of the cation-capturing ability of the crushed powder of crown-epoxy resin vs. the relative surface area of the powder gave a straight line, as shown in Fig. 6.4, which suggested that only the crown moieties present on the surface act effectively.

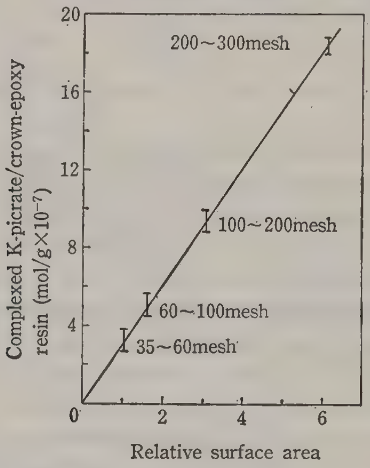


Fig. 6.4 Particle size of crown-epoxy resin vs. binding ability for K^+. Crown-epoxy resin: 500 mg; 0.1 mol/*l* aqueous KOH solution containing 6.5×10^{-5} mol/*l* of picric acid: 25 m*l*.

An example of the method for preparing the immobilizing crown-epoxy resin is as follows.[63,64] A solid carrier such as alumina, silica gel, diatomaceous earth, glass beads, glass wool, metal wire, metal plate, fiber, cloth, or plastic film is immersed in a DMF solution of diaminodibenzo-18-crown-6 (a mixture of *cis* and *trans* isomers) and bisphenol-type epoxy compound (Epikote 828, MW 355), then the solvent is removed and the solid is heated to form a cured, thin, coating film of crown-epoxy resin on the surface of the solid carrier. The adhesion of the crown-epoxy resin to glass, metal, and fiber is very strong, and the resin is very stable in organic solvents, acids, and alkalis.

The selective capture of alkali metal ions was examined using an immobilized crown-epoxy resin (CE-B18: 4.3 wt% as diaminocrown ether) coated on the surface of porous diatomaceous earth (Celite 545, 100 ~ 200 mesh). The results are shown in Fig. 6.5. The amounts of captured ions were in the order of $K^+ > Rb^+ > Ca^+ \gg Li^+$; the maximum value was observed for K^+, with an ion size nearest to the cavity size. These results agreed with the results of solvent extraction which were described in Section 3.2.1.

For alkaline earth metal ions, no marked selectivity was observed, though some tendency was found, as shown in Fig. 6.6. The observation that a larger amount of Mg^{2+},

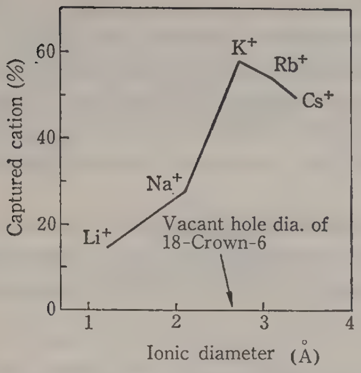


Fig. 6.5 Selective binding of alkali metal ions by crown-epoxy immobilized crown ether CE-B18 (carrier: Celite 545, 100 ~ 200 mesh).
To 25 m*l* of a mixed solution of 0.1 N aqueous solution of alkali metal hydroxide and 4.0 × 10^{-5} mol/*l* solution of picric acid was added 0.5 g of CE-B18 containing 4.3 wt% of diamino-dibenzo-18-crown-6 moiety. After stirring for 4 hr at 25° C, the solution was filtered. Amount of captured cation was calculated from the absorbance at 357 nm of the filtrate.

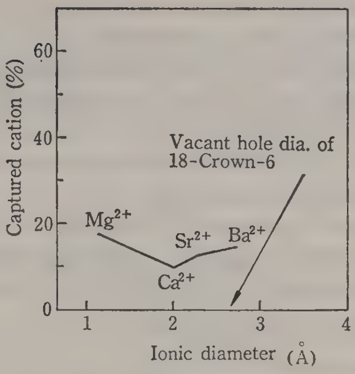


Fig. 6.6 Selective binding of alkaline earth metal ions by crown-epoxy immobilized crown ether CE-B18 (carrier: Celite 545, 100 ~ 200 mesh).
Test solutions: 0.01 mol/*l* aqueous $M(OH)_2$ solution + 4.0 × 10^{-5} mol/*l* picric acid.

with a small ionic diameter, was captured than the other alkaline earth metal ions may be explained by the binding of two Mg^{2+} into the cavity, but this has not yet been proven.

Figures 6.7 and 6.8 show the results of ion separation by a mixed solution of NaCl-KCl (solvent: water, methanol) using a column packed with immobilized crown-

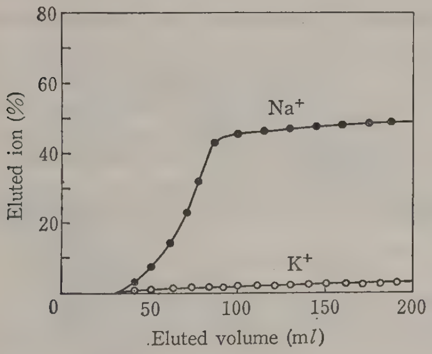


Fig. 6.7 Column separation of K⁺ and Na⁺ by crown-epoxy immobilized crown ether SG-B18 (carrier: silica gel). (1) Aqueous solution.
Column: 2 cm I.D. × 13.5 cm; SG-B18: 16.9 g.
Solution: 50 m*l* of 5.0 × 10^{-3} mol/*l* aq. MCl solution + 150 m*l* of distilled water.
SV: 0.2

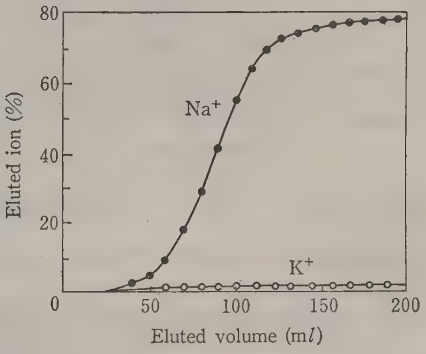


Fig. 6.8 Column sepraation of K⁺ and Na⁺ by crown-epoxy immobilized crown ether SG-B18 (carrier: silica gel). (2) Methanol solution.
Column: 1.2 cm I.D. × 17.5 cm; SG-B18: 10.0 g.
Solution: 25 m*l* of 1.0 × 10^{-2} mol/*l* MCl methanol solution + 175 m*l* of methanol.
SV: 0.8

epoxy resin SG-B18 on silica gel (Fuji ID, 200 ~ 300 mesh). The content of each ion in the eluate was analyzed quantitatively by ion-selective electrodes. More than 98 % of K^+ was captured from both aqueous and methanol solutions. The finding that a larger selectivity ratio of K^+/Na^+ was observed in a methanol solution than in an aqueous solution agreed with the previously known larger stability constants of crown ether complexes and the larger selectivity ratio of K^+/Na^+ for complexation in methanol than in water, described in Section 3.2.2.

Figure 6.9 presents the results of a column separation of Ca^{2+} and Sr^{2+} in an aqueous solution using the same immobilized crown-epoxy resin. Although the one-path ion separation was incomplete in comparison with the K^+–Na^+ separation, fairly good separation was achieved.

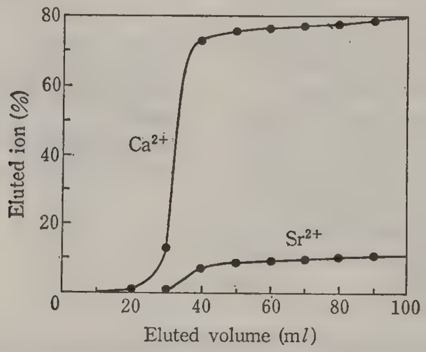


Fig. 6.9 Column separation of Ca^{2+} and Sr^{2+} in aqueous solution by crown-epoxy immobilized crown ether SG-B18 (carrier: silica gel).
Column: 1.2 cm I.D. × 27.3 cm; SG-B18: 21.0 g
Solution: 1.0×10^{-2} mol/l aq. $CaCl_2$ solution + 1.6×10^{-3} mol/l aq. $SrCl_2$ solution.

TABLE 6.9 Catalytic activity of crown ethers and crown-epoxy immobilized crown ether for phase transfer catalysis.[63]

	Reaction equation (6.13)			Reaction equation (6.14)		
Catalyst	Molar ratio of [crown]/[BuBr]	Yield (%)	Reaction conditions	Molar ratio of [crown]/[$C_8H_{17}Br$]	Yield (%)	Reaction conditions
None	—	3.9	BuBr/benzene: 2.7 mol/l	—	0	$C_8H_{17}Br$/toluene: 2.0 mol/l
Dibenzo-18-crown-6	0.07	39.6	KI/H_2O: 8.3 mol/l	0.1	0	KCN/H_2O: 5.0 mol/l
Dicyclohexyl-18-crown-6	0.07	91.6	[BuBr]/[KI]: 1/5	0.1	2.4	[$C_8H_{17}Br$]/[KCN]: 1/10
18-Crown-6	—	—	80°C, 6 hr	0.1	0	90°C, 6 hr
Immobilized crown ether (CE–B18)†1	0.07	77.5		0.1	82.3	
Celite 545	†2	10.6		†2	0	

†1 Carrier: Celite 545, 100 ~ 200 mesh
†2 Carrier only. Same amount (wt) as CE–B18.

The immobilized crown epoxy resin also acted as a triphase transfer catalyst. Table 6.9 compares the results of phase transfer catalysis between an organic phase containing alkyl halide and an aqueous solution of KI or KCN (Eqs. 6.13 and 6.14) using CE-B18 (carrier: diatomaceous earth) as a catalyst with the results of catalysis using free crown ether.

$$n\text{–BuBr}_{\text{org}} + \text{KI}_{\text{aq}} \longrightarrow n\text{–BuI}_{\text{org}} + \text{KBr}_{\text{aq}} \tag{6.13}$$

$$n\text{-C}_8\text{H}_{17}\text{Br}_{\text{org}} + \text{KCN}_{\text{aq}} \longrightarrow n\text{–C}_8\text{H}_{17}\text{CN}_{\text{org}} + \text{KBr}_{\text{aq}} \tag{6.14}$$

The immobilized crown-epoxy resin CE-B18 showed a high catalytic activity, particularly the specific activity shown in Eq. (6.14). The catalyst can be recovered from the reaction system by filtration only and reused. The catalytic activity did not decrease after repeating the same reaction five times.

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CHAPTER 7

Toxicity of Crown Compounds and Handling Precautions

7.1 GENERAL ASPECTS

Since the characteristics of crown compounds are due to the binding of cations into the cavity, it is natural that the compounds will display certain biological activities. It is, of course, essential that the toxicity, biodegradability, and cumulative properties should be well understood before a crown compound is put into practical use. However, there have been only a few reports so far on the toxicological properties of crown compounds. Pedersen discussed the toxicity of dicyclohexyl-18-crown-6,$^{1,2)}$ and Leong *et al.* noted the toxicity of 12-crown-4 and called attention to the possible toxicity of other crown ethers.$^{3,4)}$ Other reports have provided toxicity data on ethylene oxide cyclic oligomers, including the oral toxicity of 12-crown-4,$^{5)}$ 15-crown-5,$^{5)}$ and 18-crown-5$^{5,6)}$ and the neuropharmacological toxicology of 18-crown-6.$^{7)}$ The present author and his coworkers have also been carrying out various toxicological tests for the six types of crown ether shown in Table 2.1 which have been put on the market.

This chapter will discuss the data presently available on the toxicological properties of crown ethers and analogous compounds, noncyclic polyethers. Table 7.1 summarizes this data and presents for comparison similar information on low molecular weight glycols and glycol ethers.

These data show that the toxicity of dibenzo-18-crown-6 is much less than that of other crown ethers, and that the LD_{50} (oral) value for dibenzo-18-crown-6 is less than that of glyme, ethylene glycol, and ethylene glycol monoether. These findings may reflect the low solubility of dibenzo-18-crown-6 in water.$^{8)}$ If so, it may be expected that the polymeric and immobilized crown ethers described in Chapter 6 will exhibit quite low toxicity in practical use. It is well known that the biological activity and toxicity of a chemical compound can be markedly changed by modifications of the structure such as varying the substituent groups, so toxicological investigations should be extended to modified derivatives of the crown ethers in order to find compounds of very low toxicity.

The toxicological properties of crown ethers have been reviewed by Hiraoka,$^{13,14)}$ and the biological activity of general metal complexes have been discussed by Kimura.$^{15)}$ Kimura has also reviewed recently the biological activity and toxicity of ionophores, which are compounds related to crown compounds.$^{16)}$

TABLE 7.1 Toxicological data on crown ethers and their analogues

		Acute oral toxicity	Acute skin toxicity	Other effects
Crown ethers	Dibenzo-18-crown-6	LD$_{50}$ (rat): 11 g/kg[8] LD$_{50}$ (mouse): > 300 mg/kg[9]	ALD (guinea pig): 7.500 mg/kg[8]	*See* 7.2.1
	Dicyclohexyl-18-crown-6	ALD (rat): 300 mg/kg[1,2,10] LD$_{50}$ (mouse): > 300 mg/kg[9]	ALD (rabbit): 130 mg/kg[1,2]	*See* 7.2.2
	Dibenzo-24 crown-8	LD$_{50}$ (mouse): > 300 mg/kg[9]		*See* 7.2.3
	12-Crown-4	LD$_{50}$ (mouse): 3.15 ± 0.06 g/kg[5]		*See* 7.2.4
	15-Crown-5	LD$_{50}$ (mouse): 1.02 ± 0.1 g/kg[5]		*See* 7.2.5
	18-Crown-6	LD$_{50}$ (mouse): 0.705 ± 0.08 g/kg[5]		*See* 7.2.6
Noncyclic polyethers	1, 2-Dimethoxyethane (glyme)[11]	LD$_{50}$ (rat): 7 g/kg		*See* 7.2.7. Threshold limit value (TLV) for continuous handling: 120 ppm
	Dithylene glycol diethyl ether[11]	LD$_{50}$ (rat): 4.79 g/kg	LD$_{50}$ (rabbit): 6.70 g/kg	
	Polyethylene glycol[12] MW 200	LD$_{50}$ (rat): 28.9 ml/kg		
	300	LD$_{50}$ (rat): 31.7 ml/kg		
	400	LD$_{50}$ (rat): 43.6 ml/kg		
	600	LD$_{50}$ (rat): 38.1 ml/kg		
	1000	LD$_{50}$ (rat): 42 ml/kg		
	1500	LD$_{50}$ (rat): 44.2 ml/kg		
	4000	LD$_{50}$ (rat): 50 ml/kg		
	6000	LD$_{50}$ (rat): 50 ml/kg		
	Polypropylene glycol (diol)[12] MW 400	LD$_{50}$ (rat): 0.7 ~ 1.2 g/kg		
	1200	LD$_{50}$ (rat): 0.6 g/kg		
	2000	LD$_{50}$ (rat): 5 ~ 10 g/kg		
Low mol. wt. glycols, glycol ethers	Ethylene glycol[12]	LD$_{50}$ (rat): 5.5 ~ 5.8 ml/kg LD$_{50}$ (mouse): 13.1 ~ 13.8 ml/kg		Larger doses cause central nervous system effects, vomiting, lethargy, coma, difficulty in breathing, tremor, congestion and bleeding in the kidneys, fatty degradation in the liver, anuria, bronchitis, pneumonia, and death, depending on the dose.
	Diethylene glycol[12]	LD$_{50}$ (rat): 20.76 ml/kg	LD$_{50}$ (rabbit): 11.9 ml/kg	Toxic symptoms caused by oral ingestion.
	2-Methoxyethanol[12]	LD$_{50}$ (rat): 2.46 g/kg	LD$_{50}$ (rabbit): 1.34 ml/kg	Ingestion or inhalation causes acute or chronic toxic symp-

TABLE 7.1—*Continued*

		Acute oral toxicity	Acute skin toxicity	Other effects
				toms. TLV for continuous handling: 25 vol ppm.
	2-Ethoxyethanol[12]	LD$_{50}$ (rat): 3.0 g/kg	LD$_{50}$ (rabbit): 3.5 m*l*/kg	Oral ingestion causes toxic symptoms. TLV for continuous handling: 2,000 vol ppm, 0.73 m*l*/*l*
	Diethylene glycol monomethyl ether[12]	LD$_{50}$ (rat): 9.21 g/kg	LD$_{50}$ (rabbit): 6.54 m*l*/kg	TLV: 25 ppm
	Diethylene glycol monoethyl ether[12]	LD$_{50}$ (rat): 9.05 g/kg	LD$_{50}$ (rabbit): 16.5 m*l*/kg	
Low mol. wt. cyclic ethers	1, 4-Dioxane[11]	LD$_{50}$ (rat): 6.0 g/kg		Lethal concentration (rat, air): 5,000 ppm. TLV: 100 ppm, 360 mg/m^3. Continuous inhalation irritates eyes and respiratory organs, causes impediments in the liver and kidney, and causes acute hydrops in the brain or foot. Giddiness, headache, and stomach-ache appear at concentrations of more than 200 ppm. Safe at 100 ppm for 30 min.
	Tetrahydrofuran[11]			TLV: 200 ppm, 590 mg/m^3 Irritates skin, eyes, nose, and mucous membranes of the throat. Vapor exhibits an anesthetic effect. Inhalation of vapor in high concentrations for long periods causes retching, giddiness, and headache. These effects are promoted by the formation of perioxide.

7.2 TOXICOLOGICAL DATA ON CROWN ETHERS

7.2.1 Dibenzo-18-crown-6

The toxicity of dibenzo-18-crown-6, an aromatic crown ether, is much less than that of dicyclohexyl-18-crown-6, which is the corresponding alicyclic crown ether. In an acute oral toxicity test in mice, dibenzo-18-crown-6 did not exhibit any effect at a level of 300 mg/kg.[9]

The toxicity tests done at the du Pont company showed that the lethal oral dose (LD$_{50}$) for rats was 11 g/kg of body weight.[8] Exposure of guinea pig skin to a 1-butanol paste of dibenzo-18-crown-6 indicated an approximate lethal dose (ALD) for skin absorption of 7,500 mg/kg. Mild skin irritation was noted. Eye exposure to the compound produced temporary, mild, conjunctival irritation with no corneal or iritic change.[8]

7.2.2 Dicyclohexyl-18-crown-6

Dicyclohexyl-18-crown-6 is a chemical that possesses unusual physiological properties which necessitate significant care in its handling. It is toxic by ingestion or absorption. It is very injurious to the eyes and skin. Inhalation and eye and skin contact must be avoided.

A. Oral Toxicity

The results of a preliminary test for acute oral toxicity in mice showed the LD_{50} value was more than 300 mg/kg.[9)] The approximate lethal dose (ALD) for ingestion in rats was 300 mg/kg.[1,2,10)] In a 10-day, subacute oral test, the compound did not exhibit any cumulative oral toxicity when administered to male rats at a dose level of 60 mg/kg/day.[1,2,10)] It should be noted that a dose at the ALD level caused death in 11 minutes, but a dose of 200 mg/kg was not lethal in 14 days.[1,2)]

B. Eye Irritations

Dicyclohexyl-18-crown-6 produced some generalized corneal injury, some iritic injury and conjunctivitis when introduced into a rabbit's eye as a solid or in a 10% solution in propylene glycol.[1,2,10)] Prompt washing of the eyes with water did not prevent eye injury and some of the injury produced was permanent.[1,2,10)]

C. Skin Toxicity

Primary skin irritation tests run on dicyclohexyl-18-crown-6 indicated that the compound should be considered a very irritating substance.[1,2)] The compound was very readily absorbed through the skin of test animals (rabbits) when applied in a 1-butanol solution, and it was lethal when absorbed at the level of 130 mg/kg.[1,2)] The ALD value varied with the solvent and method of exposure. If covered with a clothing, the rate of absorption was much higher.[10)]

Clinical signs of toxicity were observed at skin dose levels above 60 mg/kg. These included rapid breathing, apparent tenseness, lack of coordination, and lethargy, which suggested an effect on the central nervous system.[10)] The histopathology noted was congestion of the kidney, liver, spleen, and thymus.[10)] The lack of specificity in the target organs may be related to the ability of the compound to bind with the metal ions normally present; the result is probably a generalized interference with cellular activity.

7.2.3 Dibenzo-24-crown-8

A preliminary acute oral toxicity test in mice did not reveal any effect at a level of 300 mg/kg.[9)]

7.2.4 12-Crown-4

The toxicological properties of the cyclic tetramer of ethylene oxide (12-crown-4) have been evaluated and reported in detail by Leong *et al.*[4)] Based on their evaluation, Leong noted that chemists should pay close attention to the toxicological effects of the compound in order to handle it safely.[3)]

Although the cavity diameter of 12-crown-4 is less than 1.2 Å, which is nearly equal to the ionic diameter of Li^+ (1.2 Å), and although the complexation ability of the compound with cations having an ionic diameter larger than Na^+ (1.90 Å) is much smaller than that of 15-crown-5 (cavity diameter: 1.7 ~ 2.2 Å) and 18-crown-6 (cavity diameter: 2.6 ~ 3.2 Å), the inhalation toxicity of 12-crown-4 vapor is high, according to Leong. It is thought that the toxicity of 12-crown-4 may be explained by the fact that the compound, which is liquid at room temperature and which has a small molecular weight (176), has a vapor pressure of 0.03 mm Hg, even at room temperature (bp: 238° C/760 mm Hg).

The results of the toxicological evaluation by Leong *et al.* are as follows. In a series of preliminary inhalation experiments, rats exposed to the vapors for 6 hours daily for 6 ~ 8 days exhibited extreme anorexia, loss of body weight, asthenia, lack of hind-quarter coordination, testicular atrophy, auditory hypersensitivity, tremors, convulsions, a moribund condition, and death, depending on the exposure concentration, which ranged from 1.2 to 63.8 ppm in air. The survivors recovered slowly from all the adverse effects except for testicular atrophy, which persisted as long as 4 months after exposure.

One of the earliest observable changes in the animals was the shift in the color of the blood to "cherry-red." The *in vivo* reaction product(s) of 12-crown-4 vapor and hemoglobin exhibited a Mössbauer spectrum of carboxyhemoglobin. The mechanism for the formation of carboxyhemoglobin has not been elucidated.

Repeated inhalation exposure of rats to as low as 0.5 to 1 ppm of 12-crown-4 vapor in air for 7 hours per day, 5 days per week for 3 weeks, resulted in a degradation of conditioned behavioral performance during the 3 weeks of exposure and a long-lasting testicular atrophy after the exposure.

Toxicological studies indicated that central nervous system effects and testicular atrophy could be produced in rats by 12-crown-4 via oral administration of a single dose in the range of 100 mg/kg body weight.

Leong *et al.* also evaluated the acute oral toxicity of ethylene oxide cyclic pentamers (15-crown-5), hexamers (18-crown-6), and heptamers (21-crown-7) and propylene oxide cyclic tetra- and pentamers.[3)] The studies showed that these compounds also cause central nervous system effects in rats. The dosages required to produce the effects were 1 to 10 times higher than that for 12-crown-4.

The acute and chronic oral toxicities of 12-crown-4, 15-crown-5, and 18-crown-6 in mice have been studied recently by Hendrixon *et al.*[5)] The values for the acute oral lethality of 12-crown-4 in mice were determined to be: LD_{16}, 2.97 ± 0.06 g/kg; LD_{50}, 3.15 ± 0.06 g/kg; and LD_{80}: 3.22 ± 0.06 g/kg. The LD_{50} values for 15-crown-5 and 18-crown-6 were 1.02 ± 0.1 g/kg and 0.705 ± 0.08 g/kg, respectively. The compounds follow a general trend of increasing toxicity with increasing ring size and water solubility.

In the case of 12-crown-4, the mice receiving the larger doses developed body tremors less than 5 minutes after administration of the compound. The tremors became more pronounced, and over a period of approximately 10 minutes motor activity increased, with alternating periods of hopping and shaking. Eventually, the mice stopped and shook in place. Death, preceded by intense respiratory effort, usually occurred within 15 minutes, with contraction of the dorsal muscles causing piloerection.

As for the chronic effects in mice, there appeared to be no cumulative effect of daily ingestion of one-half the LD_{50} value of the compound over a 2-week period.

Acute skin absorption studies on rabbits by Leong revealed that 12-crown-4 could be absorbed in acutely toxic amounts to produce central nervous system effects, whereas the other crown ethers caused no more than a slight redness of the skin.3)

Leong *et al.* also noted the relatively slight toxic effect of the smallest member of the series of ethylene oxide cyclic oligomers, dioxane.4) Inhalation of the vapor at a concentration of approximately 100 ppm for 2 years resulted in no compound-related effects.

7.2.5 15-Crown-5

The acute oral toxicity tests in rats by Leong *et al.* indicated that 15-crown-5 produced central nervous system effects.4) Acute skin absorption studies on rabbits showed that the compound caused no more than a slight redness of the skin.

A preliminary acute oral toxicity test in mice did not reveal any effect at a level of 300 mg/kg.9)

Hendrixon *et al.* reported the acute oral lethality of 15-crown-5 in mice.5) They determined the following values: LD_{16}, 0.785 ± 0.1 g/kg; LD_{50}, 1.02 ± 0.1 g/kg; LD_{80}, 1.26 ± 0.1 g/kg. In a test of the chronic effects in mice, there appeared to be no cumulative effect of daily ingestion of one-third the LD_{50} value of the compound over a 2-week period.

7.2.6 18-Crown-6

The acute oral toxicity tests in rats by Leong *et al.* showed that 18-crown-6 produced the same central nervous system effects as 15-crown-5.4) Acute skin absorption studies on rabbits revealed that the compound caused no more than a slight redness of the skin. Preliminary acute oral toxicity tests in mice did not reveal any effect at a level of 300 mg/kg.9)

Hendrixon *et al.* reported on the acute oral lethality of 18-crown-6 in mice.5) They obtained the following LD values: LD_{16}, 0.348 ± 0.08 g/kg; LD_{50}, 0.705 ± 0.08 g/kg; LD_{80}, 1.06 ± 0.08 g/kg. As to the chronic effects in mice, there appeared to be no cumulative effect of daily ingestion of one-half the LD_{50} value of the compound over a 2-week period.

Takayama *et al.* reported an apparent oral toxicity of 18-crown-6 and its complex with sulfamonomethoxine in dogs. 6) Six beagles weighing about 10 kg each were orally given 499.2 mg of the solid complex of 18-crown-6 with sulfamonomethoxine in a powder form wrapped in 2 pieces of wafer. Here, the dose corresponded to 199.2 mg of 18-crown-6 and 300 mg of sulfamonomethoxine. Another group of dogs was similarly given 200 mg of 18-crown-6 alone, and a third group received a physical mixture of 300 mg of sulfamonomethoxine and 200 g of 18-crown-6. The following symptoms appeared more or less in all cases: tremulous movement, salivation, and paralysis of the hind legs

2 ~ 12 hours after administration of the compounds. These symptoms disappeared around 24 hours after administration.

Behaivoral and neuropharmacological toxicology of 18-crown-6 was reported recently by Grad *et al.*7) The compound was assessed for neurologic effects in rats, mice, and rabbits by intravenous and intraperitoneal routes of administration. Male rats and mice exhibited no effect with intraveneous doses up to 20 mg/kg/day. Given intraperitoneal doses of 20 to 160 mg/kg/day, rats and mice displayed numerous symptoms, including aggression, tremors, muscle weakness, and a degradation of some reflexes. When the dosage levels were doubled, all signs faded after 4 days, and all signs disappeared upon termination of exposure. Treatment with *p*-chlorophenylalanine or dibenzyline caused most signs to disappear. Rabbits given 6.0 mg/kg/day intravenously displayed tremors, hyperactivity, unsteady gait, and stereotypic behavior, with acclimation as in rats and mice.

Isolated tissue preparations were not affected by 18-crown-6 unless it was first incubated with the tissues. Both *p*-chlorophenylalanine and dibenzyline reversibly blocked the action of incubated 18-crown-6 on isolated tissue. It has been hypothesized that 18-crown-6 is metabolized to become a serotonergic antagonist.

7.2.7 Noncyclic Polyethers

As mentioned in Section 4.2.15, some noncylic polyethers which are the analogues of crown ethers also have a complexation ability with cations because of the donor O atoms in the ether linkages, and they exhibit such action analogous to crown ethers as binding of cations, solubilization of inorganic salts, and phase transfer catalysis though the action is weaker than that of crown ethers.

Among these noncyclic polyethers, glymes are commercially employed in solvents; polyethylene glycols are widely used for nonionic surface-active agents, textile auxiliaries, cellophane, wetting agents, toiletries, binders for medicines, bases for ointments and suppositories, and so on; and large amounts of polypropylene glycols provide the raw materials of polyurethane, paints, printing inks, lubricants, and toiletries.

The LD_{50} values (oral and skin) for these noncyclic polyethers are shown in Table 7.1 together with toxicological data on crown ethers and low molecular weight glycols and glycol ethers.11,12)

It was reported that glymes did not cause hydropsy in the skin,11) and the oral toxicity of glymes did not proportionally increase on repeated administration, although the toxicity was higher than that of glycols. Inhalation of glyme vapor in high concentrations caused injuries to the lung, liver, and kidney. For 1, 2-diethoxyethane, the concentration limit for continuous handling has been fixed at 120 ppm or 600 mg/m^3.11)

Polyethylene glycols are used for medicines and toiletries because of their low toxicity; they produced no effect by skin absorption and no eye irritation.12)

7.3 HANDLING PRECAUTIONS

As mentioned earlier, the toxicity of crown compounds has not yet been fully delineated, but dicyclohexyl-18-crown-6 and a number of ethylene oxide cyclic oligomers exhibit high oral and skin toxicity. Since other crown compounds also form complexes with metal ions, they, too, should be handled carefully.

In general, all contact with crown compounds or their solutions should be avoided. If the possibility of spills or splashes is present, it is important to wear protective equipment and use shields. A "Chem-Proof" air suit should be worn when handling any appreciable quantity of crown compounds or their solutions. Rubber gloves, apron, and acid goggles or tight monogoggles may be worn when handling small quantities. In the event of skin or eye contact, the affected area should be immediately washed copiously with soap and water, contaminated clothing removed, and the individual should receive medical attention.$^{10)}$

The physical constants and properties of typical crown compounds are described in Chapter 2, but the properties of other crown compounds should also be fully understood before handling. Crown compounds having ether linkages must not be allowed to come into contact with air at higher temperatures in the molten state to avoid the formation of peroxides. It is recommended that crown compounds be stored under nitrogen.

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Since the discovery of crown ether by Mr. C. J. Pedersen in 1962, the chemistry and applications of crown compounds, including crown ethers and their analogues have been developed rapidly as a tool for studying the interface between chemistry and biology.

The aim of this book is to review and systematize the current knowledge about the chemistry of crown compounds and to provide useful information on the synthetic methods and characteristics of a large number of crown compounds and a wide variety of application research. It also discusses current topics including optically active crown compounds, the immobilized crown compounds, and toxicological data. This book should contribute to a more widespread recognition of the potential of crown compounds and stimulate further research and utilization.

Michio Hiraoka graduated in 1949 from the Department of Applied Chemistry at the University of Tokyo. He won his master's degree from the same institution in 1951 and subsequently entered Nippon Soda Co. Ltd., where he carried out research on, and was engaged in commercialization of, a wide variety of organic syntheses. He was awarded the degree of Doctor of Engineering from the University of Tokyo in 1965. He was appointed Director of the Synthetic Chemistry Research Laboratory at Nippon Soda in 1972 and was promoted to Counselor and Director of the Department of Science Investigation, Technology Division, in 1978. He is an active member of several chemical societies in Japan and received an award from the Society of Polymer Science, Japan, in 1970. He holds over forty patents, and has published more than fifty scientific papers and eight books. His main interest is research and development in the field of biomimetic chemistry.

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