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Macrocyclic Polyethers and Their Complexes[***]

By C. J. Pedersen and H. K. Frensdorff[*]

The most important, and almost unique, property of the macrocyclic polyethers ("crown compounds") is their tendency to form complexes with alkali metal salts and salts with similar cations. Such complexes are held together by electrostatic attraction between the cation and the negative end of the C—O dipoles. The stability of the polyether complexes depends primarily upon how well the cation fits into the polyether ring; other factors are the charge density of the cation and—in solution—the solvating power of the medium. Cyclic polyethers have been successfully employed, inter alia, in experiments with ionic compounds in organic solvents and in studies of ion transport in biological systems.

1. Introduction

Complexing of sodium, potassium, and related cations by neutral molecules is an uncommon phenomenon. Strong stoichiometric complexes have been observed only in the last decade[1, 2], and then only with biological materials (see Section 1.3).

Hence some of the recently synthesized macrocyclic polyethers[3, 4] have aroused considerable interest in several divisions of chemistry because they form stable complexes, both in solution and in the crystalline form, with salts of alkali and other metals.

More than sixty macrocyclic polyethers have been synthesized. They are neutral compounds containing four to twenty oxygen atoms each separated from the next by two or more carbon atoms, but the most effective complexing agents are found among those containing five to ten oxygen atoms each separated from the next by two carbon atoms. These compounds form 1:1 salt-polyether complexes in which the cation is encircled by the oxygen atoms of the polyether ring, being held there by the elec-

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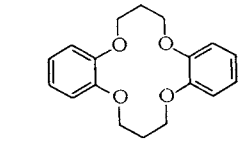
trostatic attraction between the negatively charged oxygens of the C—O dipoles and the cation. In some cases, 2:1 and even 3:2 polyether : salt complexes are found[5]. The following cations have so far been observed to form complexes with cyclic polyethers: Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, RNH_3^+, Ag^+, Au^+, Ca^{2+}, Sr^{2+}, Ba^{2+}, Ra^{2+}, Zn^{2+}, Cd^{2+}, Hg^+, Hg^{2+}, La^{3+}, Tl^+, Ce^{3+}, and Pb^{2+}[3]. Only a few complexes of transition metals have been reported[6].

This review will deal mainly with the preparation, the chemical and physical properties, the structures, and the stabilities of these macrocyclic polyethers and their salt complexes.



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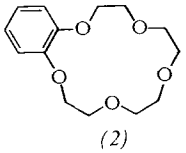

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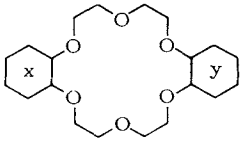

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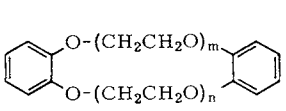

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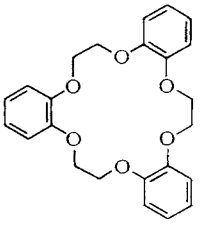

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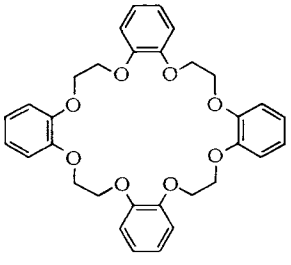

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1.1. Nomenclature

The macrocyclic polyethers ("crown compounds") can be assigned unique but very cumbersome names by application of the IUPAC rules for bridged hydrocarbons (rules A-31 and A-32). Thus compound *(3f)* [*(3)*, $x = y = C_6H_{10}$] is called 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0^{9,14}]hexacosane, and compound *(5)* 2,5,12,15,22,25-hexaoxatetracyclo[24.4.0.0^{6,11}.0^{16,21}]triaconta-6(11),7,9,16(21),17,19,26(1),27,29-nonaene. The rules for fused polycyclic compounds (A-21 to A-23) likewise give unequivocal but most complicated names. A system of *ad hoc* names was therefore devised solely for the ready identification of these compounds[3]. The examples in Table 1 illustrate how these names are made up of the side-ring substituents, the total number of atoms in the polyether ring, the "crown", and the number of oxygen atoms in the main ring. The "crown names" are simple but should only be used in conjunction with formulas since they are not unambiguous. Cyclohexane rings fused to the polyether ring, as in compound *(3c)*, are termed "perhydrobenzene" in the present report; the more common, but ambiguous, term is cyclohexyl.

1.2. History

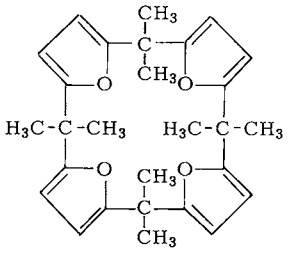
The pre-1967 literature on macrocyclic polyethers is meager and, above all, the possibility of their being complexing agents was not recognized. Among the previously reported compounds related to the crown polyethers are *(7)*[7], *(8)*[8], and *(9)*[8], as well as the cyclic tetramers of ethylene oxide[9] and propylene oxide[10].

The first crown compound, dibenzo[18]crown-6 *(3d)*, was formed as an unexpected by-product during a preparation of bis[2-(*o*-hydroxyphenoxy)ethyl] ether from bis(2-

Table 1. Some representative macrocyclic polyethers with their "crown" names, methods of preparation, and melting points (see Section 2.1 for an account of synthetic methods).

Compound	Crown name	Synthesis eq.	Synthesis yield (%)	M.p. (°C)
(1)	dibenzo[14]crown-4	(3)	27	150–152
(2)	benzo[15]crown-5	(1)	62	79–79.5
(3a), x = nil, y = nil	[18]crown-6			39–40
(3b), $x = C_6H_4$, y = nil	benzo[18]crown-6	(1)	60	43–44
(3c), $x = C_6H_{10}$, y = nil	perhydrobenzo[18]crown-6			<25
(3d) ≡ *(4a)*, $x = C_6H_4$, $y = C_6H_4$	dibenzo[18]crown-6	(2)	45	164
(3e), $x = C_6H_{10}$, $y = C_6H_4$	benzoperhydrobenzo[18]crown-6			<25
(3f), $x = C_6H_{10}$, $y = C_6H_{10}$	perhydrodibenzo[18]crown-6			A: 61–62.5 B: 69–70
(4a) ≡ *(3d)*, $m = 2$, $n = 2$	dibenzo[18]crown-6	(2)	45	164
(4b), $m = 2$, $n = 3$	dibenzo[21]crown-7	(3)	36	106.5–107.5
(4c), $m = 3$, $n = 3$	dibenzo[24]crown-8	(2)	38	113–114
(4d), $m = 4$, $n = 4$	dibenzo[30]crown-10	(2)	>6	106–107.5
(4e), $m = 5$, $n = 9$	dibenzo[48]crown-16	(3)	32	<25
(4f), $m = 9$, $n = 9$	dibenzo[60]crown-20	(3)	41	<25
(5)	tribenzo[18]crown-6	(3)	28	190–192
(6)	tetrabenzo[24]crown-8	(2)	18	150–152

chloroethyl) ether and the sodium salt of 2-(*o*-hydroxyphenoxy)tetrahydropyran which contained a small quantity of catechol[3,4]. It was recovered from the reaction products



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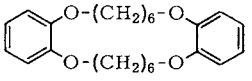

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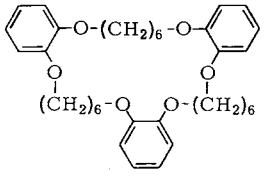


(9)

as a very minor component in the form of white fibrous crystals, which were quite insoluble in methanol itself but became readily soluble in it on addition of sodium salts. This observation led to the discovery of the complexing power of the crown compounds and to the synthesis of other macrocyclic polyethers.

1.3. Macrocyclic Antibiotics

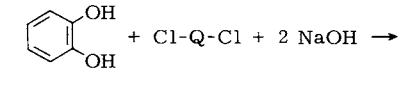
A number of antibiotics, such as valinomycin and nonactin, which contain ether, ester, and amide bonds in 32- to 36-membered rings exert interesting biological effects[11], which are related to the way in which these substances influence transport of Na^+ and K^+ across cell membranes[12]—one of the fundamental processes of living systems. Complexing of these cations by the macrocyclic antibiotics appears to be responsible for their effects on ionic transport across natural and synthetic membranes[1,2,13]. Reports on the solution properties of such complexes[1,2,14] and X-ray structural studies[15,16] have appeared recently. It will become evident in this review that the complexing properties of these biogenic macrocyclic compounds resemble those of the crown polyethers in many respects.

2. Preparation and Properties

2.1. Synthetic Methods

The aromatic crown polyethers are prepared by straightforward condensation methods[3,4] exemplified by the stoichiometric equations (1) to (3), in which Q and T represent divalent organic groups, generally of the type $-(CH_2CH_2O)_nCH_2CH_2-$.

The condensations are typically run in 2-butanol under reflux for 12 to 24 hours. Method (1) can be used to prepare, *e.g.*, benzo[12]crown-4 (yield 4%). Method (2) gives, for instance, dibenzo[18]crown-6 *(3d)* (see Table 1). The starting



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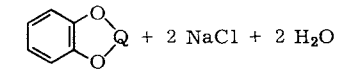

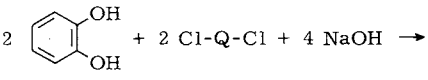

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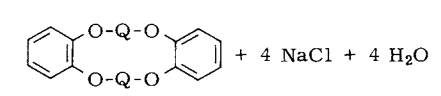

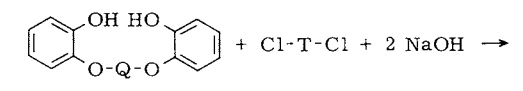

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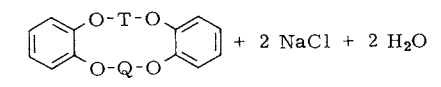


material for method (3) is made by attaching a base-stable protecting group, *e.g.* benzyl or tetrahydropyranyl, to one of the hydroxyls of catechol; two moles of this compound are then condensed with Cl—Q—Cl, and the protecting group is subsequently removed. Eq. (3) is most convenient for synthesis of uneven-numbered polyether rings, *e.g.* dibenzo[21]crown-7 *(4b)* (see Table 1).

Aromatic macrocyclic polyethers containing neutral substituents, such as alkyl or chloro, may be prepared by using suitably substituted aromatic vicinal diols. Of course, the substituents must be inert toward sodium hydroxide and the open-chain dichloropolyether.

Saturated polyethers are prepared from the corresponding aromatic ones by catalytic hydrogenation, typically in 2-butanol at 100 °C and 7—10 atm over a ruthenium catalyst[3]. Recovery of the product is best done by column chromatography on alumina, and the yields are almost quantitative.

2.2. Properties

The macrocyclic polyethers with aromatic side rings are colorless crystalline compounds. For a given polyether ring the melting point rises with the number of benzo groups (see Table 1). These compounds, particularly those containing more than one benzo group, are nearly insoluble in water and sparsely soluble in alcohols and many other common solvents at room temperature. They are readily soluble, however, in methylene chloride and chloroform[3].

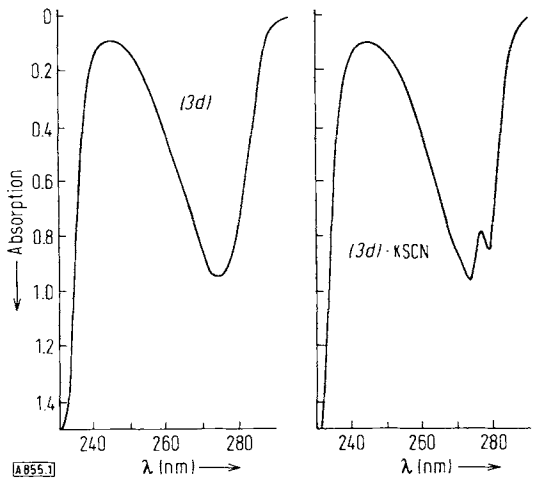


Fig. 1. Ultraviolet spectra of dibenzo[18]crown-6 *(3d)* and its KSCN complex (1.8×10^{-4} mol/l in methanol, 1 cm cell).

The saturated polyethers are colorless, viscous liquids or solids of low melting point. They are very much more soluble in all solvents than their aromatic precursors. Most of them dissolve even in petroleum ether and yet display appreciable water solubility.

While the saturated compounds do not show any absorption above 220 nm, the aromatic ones show absorption bands (in methanol) near 275 nm, which are characteristic for catechol and its ethers, with extinction coefficients of about 2200 per benzene ring (see Fig. 1). Saturated cyclic polyethers show an IR band near 1100 cm^{-1} (aliphatic ether), which is also shown by the aromatic ones in addition to another near 1230 cm^{-1} (aromatic-aliphatic ether).

Aliphatic crown compounds with two or more cyclohexane rings fused to the main ring show bridge-bond isomerism. For example, perhydrodibenzo[18]crown-6 *(3f)*, obtained by hydrogenation of dibenzo[18]crown-6 *(3d)*, can be separated into two isomers (A m.p. 61—62.5 °C; B m.p. 69—70 °C) by chromatography[17]. NMR studies[18] have shown that the bridge bonds of both isomers are *trans*, as are those of several other analogs[*].

The macrocyclic polyethers are thermally stable; for instance, dibenzo[18]crown-6 *(3d)* can be distilled at 380 °C. They must be protected from oxygen, however, at elevated temperatures. The aromatic crown compounds react like anisole or veratrole; for example, they can be halogenated, nitrated, or condensed with formaldehyde to give resins containing polyether rings.

3. Complexing of Salts and Other Compounds

Their ability to form complexes with salts and certain other compounds is the most remarkable property of the cyclic polyethers. In this section we shall discuss a number of different ways in which this complex formation manifests itself.

[*] Recent X-ray structural investigations of complexes of these isomers have led to apparently conflicting conclusions: *M. R. Truter* (personal communication) finds that isomer B in its $NaBr \cdot 2H_2O$ complex has a centrosymmetrical *trans* conformation, while *N. K. Dalley, D. E. Smith, R. M. Izatt*, and *J. J. Christensen* (Chem. Commun., in press) conclude that isomer A in its $Ba(SCN)_2$ complex is *cis-syn-cis*.

3.1. Complexing in Solution

3.1.1. Solubility Effects

The simplest, often spectacular, and potentially most useful way in which complexing by cyclic polyethers manifests itself is the solubilization of ionic compounds in organic solvents. In many cases addition of polyether causes dissolution of salts and related compounds in solvents in which they are otherwise substantially insoluble[3]. For instance, crystals of $KMnO_4$, *tert*-C_4H_9OK, or K_2PdCl_4 can be made to dissolve in aromatic hydrocarbons merely by the addition of perhydrodibenzo[18]-crown-6 *(3f)*.

In early experiments it was found that direct addition of salt and polyether to solvent was frequently not very effective, and that much more concentrated solutions could be prepared by solvent exchange: dissolving the ingredients in methanol, removing this solvent by evaporation *in vacuo*, and then redissolving in the final solvent. It later became apparent that the methanol is frequently not removed completely by this procedure, since it is often very tenaciously held by the complex and probably forms an integral part of it. The finding that addition of quite small concentrations of methanol greatly increases the quantities of salt which dissolve directly in solvents containing cyclic polyether (see Table 2) obviates the need for the solvent-exchange procedure and provides further evidence that methanol, or some analogous compound, may take part in the complex, possibly serving to complete the solvation sphere of the cation or to solvate the anion.

Table 2. Solubilization of alkali-metal halides in organic solvents by addition of 50 mmol/l of perhydrodibenzo[18]crown-6 *(3f)* [a].

Solvent	Methanol (mmol/l)	Solubility (mmol) [b] NaCl	NaBr	KCl	KBr	KI
C_6H_6	0	0.01	1.8	0.03	2.3	9.2
	250	0.48	24	8.7	30	46
CCl_4	0	0.03	2.7	0.6	4.1	0.8
	250	1.1	28	8.8	34	15
$CHCl_3$	0	1.8	37	21	41	43
	250	5.7	41	34	44	44
CH_2Cl_2	0	1.8	35	17	41	43
	250	5.8	42	33	42	44
Tetrahydro-	0	0.02	1.2	0.1	3.6	45
furan	250	0.04	5	0.4	13	50

[a] *H. K. Frensdorff*, unpublished data.
[b] Salt concentration after agitation of the polyether solution with enough salt to give 50 mmol/l solution.

While complexing of the cation is an obvious prerequisite for solubilization, the anion also plays an important role, as illustrated by the increase in solubility with anionic size (Table 2). The complexed cation is surrounded by organophilic groups and thus can be more or less easily accommodated in a nonpolar environment. However, interaction between the anion and a nonpolar solvent is much less favorable, especially for small anions of high charge density and low polarizability. Accordingly, salts of such "hard"[19] anions as fluoride or sulfate are often not solubilized appreciably by cyclic polyethers, while those of "soft" anions, *e.g.* iodide, thiocyanate, picrate, and fatty acid anions, are solubilized more easily.

Potassium and sodium hydroxide can be solubilized in benzene with perhydrodibenzo[18]crown-6 *(3f)* either by solvent exchange or by direct addition of 1% methanol to give solutions which are as much as 1 N in base. These solutions, which appear to contain methoxide as well as hydroxide anions, are capable, for instance, of readily saponifying esters of 2,4,6-trimethylbenzoic acid which are resistant to ordinary saponifying agents.

Solubilization by polyether is not a simple function of solvent polarity (cf. low solubility in tetrahydrofuran, Table 2). Specific interactions, such as solvation of the anion or competition between solvent and polyether, evidently overcome more general polarity effects in some cases.

3.1.2. Changes in Ultraviolet Spectra

All the cyclic polyethers containing benzo groups have a characteristic absorption maximum at 275 nm (in methanol). Complexing with a cation brings about distinctive changes in this band, generally by appearance of a second peak at about 280 nm (see Fig. 1), at other times by a hypsochromic shift and changed absorbance of the main band. Since the new peak is not clearly separated from the main one, it is not suitable for precise quantitative measurements. However, it has been used extensively for qualitative detection of complexing[3, 20].

3.1.3. Conductivity Changes

The existence and stoichiometry of the complexes are demonstrated simply and convincingly by conductance measurements[17]. The results in Fig. 2 clearly show the 1:1 stoichiometry of the complex formed from potassium chloride and perhydrodibenzo[18]crown-6 *(3f)*. This figure illustrates two contrasting cases: (a) in methanol the dissociation of KCl is essentially complete, and complexing, by increasing the size and thus decreasing the mobility of the cation, reduces the conductance; (b) in chloroform/methanol (90:10) KCl is largely undissociated, but complexing, by surrounding the cation with the polyether ring, shields its charge and thus greatly increases dissociation of the ion pairs, which results in an appreciable conductance increase.

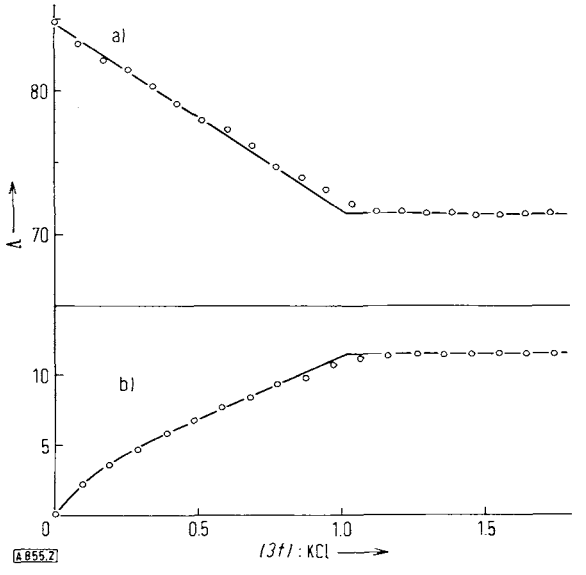


Fig. 2. Conductometric titration of KCl with perhydrodibenzo[18]-crown-6 *(3f)* a) in methanol and b) in chloroform/methanol (90:10). KCl concentration 10^{-3} mol/l [17].

3.2. Crystalline Complexes

3.2.1. Preparation

Numerous well-defined, sharp-melting, crystalline complexes of salts and cyclic polyethers have been prepared by straightforward methods, *i.e.* by bringing together the ingredients in a common solvent, in two immiscible solvents, in a medium which dissolves one of them, or in the dry state[3, 5]. Although salts with high lattice energy, such as fluorides, nitrates, and carbonates, form complexes with the cyclic polyethers in alcoholic solution, they cannot be isolated in the solid state because one or the other of the uncomplexed components precipitates when the solution is concentrated. Some typical crystalline complexes are shown in Table 3.

Table 3. Typical crystalline polyether-salt complexes [1, 5] (see Table 1 for formulas).

Polyether	m.p. (°C)	Salt	m.p. (°C)	Polyether: Salt (mol/mol)	Complex, m.p. (°C)
(1)	150–152	LiSCN	—	1:1	300
(2)	79–79.5	$AgNO_3$	210	1:1	134–135
(2)	79–79.5	NaSCN	323	1:1	162–165
(2)	79–79.5	KSCN	175	2:1	176
(2)	79–79.5	NH_4SCN	149	2:1	131–132
(3c)	<25	$Ba(SCN)_2$	—	1:1	282
(3d)	164	$NaNO_2$	271	1:1	154–157
(3d)	164	KI	685	1:1	232–234
(3d)	164	RbSCN	195	1:1	184–185
(3d)	164	RbSCN	195	2:1	175–176
(3d)	164	CsSCN	—	2:1	146–147
(3d)	164	CsSCN	—	3:2	145–146
(4d)	106–107.5	KSCN	175	1:1	176–178

As shown by several of the examples in Table 3, the complexes are not always of 1:1 stoichiometry, some polyether-cation combinations having a tendency to form 2:1, or even 3:2, complexes. As a rule, this occurs when the cation is too large to fit into the hole of the polyether ring (see Table 4), which suggests a "sandwich" structure[5].

Like most of the complexes, that formed by KSCN and dibenzo[18]crown-6 *(3d)* is stable in water containing an excess of the salt but decomposes in pure water. However, some of the complexes are stable in the presence of water, *e.g.* KI_3-perhydrodibenzo[18]crown-6.

Table 4. Polyether ring sizes and ionic diameters.

Polyether ring	Hole diameter (Å) [a]	Ion	Ionic diameter in crystal (Å)
[14]Crown-4	1.2–1.5	Li^+	1.36
[15]Crown-5	1.7–2.2	Na^+	1.94
[18]Crown-6	2.6–3.2	K^+	2.66
[21]Crown-7	3.4–4.3	Rb^+	2.94
		Cs^+	3.34
		NH_4^+	2.86
		Ag^+	2.52
		Ba^{2+}	2.68

[a] From ref. [5]; lower values estimated from Corey-Pauling-Koltun atomic models, higher values from Fisher-Hirschfelder-Taylor models.

3.2.2. Structure

The structures of four crystalline complexes have been determined by X-ray diffraction by *Truter et al.*[21,22]: NaBr-$(H_2O)_2$-dibenzo[18]crown-6; NaI-H_2O-benzo[15]-crown-5; $(RbSCN)_2$-(dibenzo[18]crown-6)$_3$; and KI-dibenzo[30]crown-10. The two sodium complexes contained water of crystallization though no water was deliberately added to the methanol in which they were prepared[22]. This observation confirms the strong propensity of Na^+ to complete its entire solvation shell (cf. Section 3.1.1).

In both of the sodium complexes the cation is located in the center of the very nearly coplanar ether oxygens. Water and bromide coordinate with the sodium in the direction perpendicular to the polyether ring, though the iodide anion does not interact directly with its sodium.

The 3:2 RbSCN complex has a very interesting structure, though not the postulated sandwich[21]. The unit cell contains four molecules of a 1:1 RbSCN-dibenzo[18]-crown-6 complex and two uncomplexed polyether molecules of crystallization. The Rb^+ is centrally located and approximately 1 Å below the plane of the ether oxygens (see Fig. 3), and the SCN group sticks out approximately perpendicular to the ether ring. In the uncomplexed molecules of polyether the O atoms are not quite coplanar.

No X-ray structure of any complex of the 2:1 polyether-cation type has been published so far. However, since these invariably involve a cation too large to fit into the hole of the polyether, they may be expected to have a structure with the cation "sandwiched" between two parallel polyether rings.

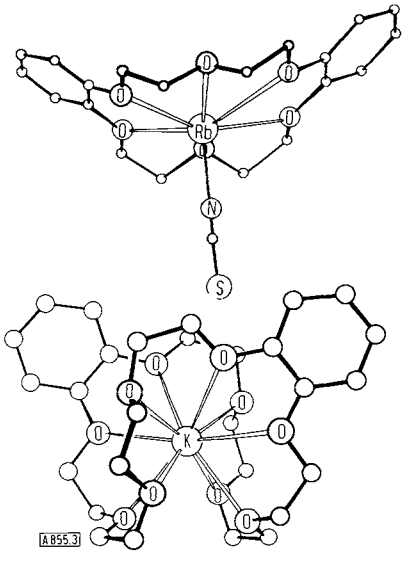


Fig. 3. Structures of typical complexes. Rubidium thiocyanate: dibenzo[18]crown-6 (above, free polyether molecule not shown), potassium iodide: dibenzo[30]crown-10 (below, anion not shown), according to *Truter et. al.* [21, 22].

Special interest resides in the complexes of much larger rings which, since they are more flexible and have enough oxygen atoms, may envelop the cations completely, as do the macrocyclic antibiotics in their complexes[14–16]. X-Ray analysis of one such complex, KI-dibenzo[30]-crown-10, has been accomplished recently[22]. It was found that this complex indeed possesses a wrap-around structure having all ten oxygen atoms coordinated with the central cation (see Fig. 3).

3.3. Complexes of Amino Compounds and Thioureas

Since ammonium ion resembles K^+ with respect to charge and size, it is not surprising that it forms similar complexes with the cyclic polyethers (see Table 3). Ammonia and unionized ammonium hydroxide, on the other hand, are not complexed because they do not carry a charge. In general, NH_3^+-substituted compounds form complexes, while those containing NH_2^+ and NH^+ groups, and quaternary ammonium ions do not[3]. Apparently the NH_3^+ group can intrude sufficiently into the polyether ring, but the others are too large to do so.

Thiourea and related compounds, such as thiosemicarbazide, as well as some of their derivatives have been found to form sharp-melting crystalline complexes with cyclic polyethers[23]. The stoichiometry of these complexes is unpredictable (from 1:1 to 6:1 thio compound : polyether), and their nature has not yet been elucidated. Inclusion complexes seem to be ruled out by the small ratios. One possibility is that at least one molecule of the sulfur compound is complexed in the zwitterion form, $^-S-C=NH_2^+$, while the others merely fill up the crystal lattice.

4. Complexing Equilibria in Solution

4.1. Stability Constants

The stability constants for the polyether-cation complexes are the most straightforward measure of the strength of complexing in solution. They are defined as the equilibrium constants (in l/mol) for reactions (4) and (5) where M^+ and P represent uncomplexed cation and polyether; PM^+ and P_2M^+ 1:1 and 2:1 complex, respectively.

$$M^+ + P \underset{}{\overset{K_1}{\rightleftharpoons}} PM^+ \quad (4)$$

$$PM^+ + P \overset{K_2}{\rightleftharpoons} P_2M^+ \quad (5)$$

Such stability constants have been measured by a calorimetric titration technique[24], by potentiometric measurements with ion-selective electrodes[25], and by spectroscopic methods[26], besides being deduced indirectly from conductance and potential measurements on phospholipid bilayers[27].

4.1.1. Complexing in Aqueous Solutions

Stability constants for several cyclic polyethers with various cations are collected in Table 5. No data on benzo-substituted polyethers are available because of their generally low water solubility.

The stability constants for the [18]crown-6 polyethers with the alkali-metal cations go through a maximum at K^+ as the cationic size increases. This can be explained in terms of competition between hydration and complexing,

since at least some of the water of hydration must be stripped off the cation to accommodate it in the hole of the polyether ring. Though the smaller cations, with their high electric charge density, greatly attract both water and polyether, their tendency to undergo hydration is too strong for the polyether to compete successfully. On the other hand, the larger cations have comparatively low charge densities and, hence, low attraction for either polyether or water. Moreover, Rb^+ and Cs^+ are too large to fit into the hole of the [18]crown-6 ring, hence the complexing tendency is reduced by their inability to attain the position of maximum charge density in the plane of the ether oxygens. The comparatively high stability constants for the divalent cations Sr^{2+} and Ba^{2+} reflect their high charge densities, while those for Ag^+ are a consequence of its slight hydration tendency.

Table 5. Stability constants of polyether-cation complexes in water at 25°, based on K_1 in l/mol [a]; cf. eq. (4).

Polyether	$\log_{10} K_1$								
	Li^+	Na^+	K^+	Rb^+	Cs^+	NH_4^+	Ag^+	Sr^{2+}	Ba^{2+}
Perhydrobenzo[15]crown-5	<1.0	<0.3	0.6	—	—	—	—	—	—
Perhydrobenzo[18]crown-6 *(3c)*	<0.7	0.8	1.9	—	0.8	1.1	1.8	—	—
Perhydrodibenzo[18]crown-6 *(3f)* (isomer A)	0.6	1.7	2.2	1.5 [b]	1.2	1.4	2.3	3.2 [b]	3.6 [b]
Perhydrodibenzo[18]crown-6 *(3f)* (isomer B)	—	1.4	1.8	0.9 [b]	0.9	0.8	1.8	2.6 [b]	3.3 [b]
Perhydrodibenzo[21]crown-7	—	—	—	—	1.9	—	—	—	—

[a] Values from ref. [25], unless marked otherwise.
[b] Values from ref. [24].

Enthalpy changes on complexing in water, as measured calorimetrically by *Izatt et al.*[24], are small. They amount to −2 to −6 kcal/mol for reaction (4). They might be even closer to zero for some ions, *e.g.* Na^+, for which these authors found no measurable heat change[24], though potentiometry indicated measurable complexing[25].

4.1.2. Complexing in Methanol

Methanol is a particularly convenient solvent for complexing measurement and permits comprehensive study of the effect of polyether ring size and substituents on the strength of complexing[25] (see Table 6). Comparison between Tables 5 and 6 reveals that the stability constants are three to four decades higher in methanol than in water, evidently because methanol is a much weaker solvating medium and thus competes less with the polyether for the cations (cf. Section 4.1.1).

Table 6. Stability constants of polyether-cation complexes in methanol at 25°, based on K_1 in l/mol [25]; cf. eq. (4) and (5).

Polyether	$\log_{10} K_1$		
	Na^+	K^+	Cs^+
Tetramethyl[12]crown-4	1.4	—	—
Perhydrodibenzo[14]crown-4	2.2	1.3	—
Perhydrobenzo[15]crown-5	3.7	3.6 [a]	2.8 [a]
[18]Crown-6 *(3a)*	4.3	6.1	4.6
Perhydrobenzo[18]crown-6 *(3c)*	4.1	5.9	4.3
Perhydrodibenzo[18]crown-6 (isomer A) *(3f)*	4.1	6.0	4.6
Perhydrodibenzo[18]crown-6 (isomer B) *(3f)*	3.7	5.4	3.5
Dibenzo[18]crown-6 *(3d)*	4.4	5.0	3.6 [b]
Dibenzo[21]crown-7 *(4b)*	2.4	4.3	4.2
Dibenzo[24]crown-8 *(4c)*	—	3.5	3.8
Dibenzo[30]crown-10 *(4d)*	2.0	4.6	—
$CH_3(OCH_2CH_2)_5OCH_3$	1.5	2.2	—

[a] Polyether : cation = 2:1; $\log K_2 = 1.9$.
[b] Polyether : cation = 2:1; $\log K_2 = 2.9$.

The stability constant for each cation goes through a maximum with increasing polyether ring size: between-[15]crown-5 and [18]crown-6 for Na^+; at [18]crown-6 for K^+; and between[18]crown-6 and [21]crown-7 for Cs^+. These optimum ring sizes are exactly those which provide the closest fit between the cation and the "hole" (see Table 4). Table 6 also indicates the three systems in which clear evidence of 2:1 complexing in solution was found: perhydrobenzo[15]crown-5 with K^+ and Cs^+, as well as dibenzo[18]crown-6 with Cs^+. These are all cases of the cation's being too large to fit into the hole and represent combinations of cation and polyether ring of which crystalline 2:1 complexes have been found.

Comparison of the various [18]crown-6 derivatives in Table 6 shows that the effects of substitution on the polyether ring are relatively small and difficult to systematize. For instance, dibenzo[18]crown-6 complexes Na^+ more strongly than the unsubstituted parent ring or hydrogenated analogs, but the reverse is true for K^+ and Cs^+.

As illustrated by the last entry in Table 6, the stability constants of an open-chain polyether are three to four decades lower than those of its cyclic analog([18]crown-6). Evidently entropic forces work against complete envelopment of the cation by the non-cyclic polyether.

4.1.3. Complexing in Other Solvents

Very few data are available for solvents less polar than methanol. Since competition by solvation would become less significant, one expects stability constants to be higher, especially for the smallest cations. However, the results will be complicated by more or less extensive ion-pair formation, so that anion effects will become appreciable.

Wong, Konizer, and *Smid*[26] have reported some stability constants for alkali metal fluorenyl compounds in tetrahydrofuran as determined by spectroscopic methods. These authors found the stability constants for the fluorenylsodium ion pair to be above 10^6 l/mol with perhydrodibenzo[18]crown-6 *(3f)* and di(methylbenzo)[18]-crown-6 compared to 150 l/mol for dibenzo[14]crown-4 *(1)* and 450 l/mol for $CH_3(OCH_2CH_2)_5OCH_3$. They

found fluorenylsodium to be more strongly complexed in tetrahydrofuran than its potassium analog, while the reverse was true in oxetane.

4.2. Distribution between Phases

Since the polyether complexes display appreciable solubility in certain organic solvents, salts can often be extracted from aqueous solutions into organic solvents containing polyethers. Extraction is efficient only if the anion is large and highly polarizable, as for instance picrate, which has the additional advantage of an absorption near 360 nm for easy analysis. Accordingly, picrate extraction has been used extensively for quantitative determination of relative complexing power[4, 20]. The typical results in Table 7 show how extraction of any given cation is most efficient with polyethers of the ring size for which the stability constant indicates optimum strength of complexing.

Table 7. Extraction of picrates into methylene chloride containing polyether [20]. Initial concentrations: alkali hydroxide 0.1 mol/l; alkali picrate 7×10^{-5} mol/l; polyether 7×10^{-5} mol/l. Equal volumes of water and CH_2Cl_2. No measurable extraction of cation takes place in the absence of either picrate or polyether.

Polyether	Picrate extracted (%)			
	Li^+	Na^+	K^+	Cs^+
Di(*tert*-butylperhydrobenzo)[14]crown-4	1.1	0	0	0
tert-Butylperhydrobenzo[15]crown-5	1.6	19.7	8.7	4.0
Dibenzo[18]crown-6	0	1.6	25.2	5.8
Perhydrodibenzo[18]crown-6	3.3	25.6	77.8	44.2
Perhydrodibenzo[21]crown-7	3.1	22.6	51.3	49.7
Perhydrodibenzo[24]crown-8	2.9	8.9	20.1	18.1

When extraction results are available over wide concentration ranges, they can be analyzed in terms of the following equilibria[17]:

$$M^+_{aq} + A^-_{aq} + P_{org} \overset{K_E}{\rightleftharpoons} PMA_{org} \quad (6)$$

$$PMA_{org} \overset{K_D}{\rightleftharpoons} PM^+_{org} + A^-_{org} \quad (7)$$

where M^+ is the cation, A^- the extractable anion, P the polyether, PM^+ the complex cation, and PMA the complex ion pair, while the subscripts refer to the phases. Equilibrium constants for several systems are shown in Table 8. Under the conditions of Table 7 extraction of the cation is not very efficient, since the low concentrations of picrate and polyether are limiting. The equilibrium constants can be used to predict how much greater the extraction efficiency will be at higher concentrations. It is interesting to note that these extraction measurements permit evaluation of dissociation constants, K_D, and that the results indicate appreciable dissociation of the complex ion pairs in methylene chloride at submillimolar concentrations, in agreement with the conductance results (see Section 3.1.3) in similar solvents.

That extraction efficiency depends not only on strength of complexing but also on the solubilities of all the species in both phases is indicated by the lower extraction of sodium picrate by dibenzo[18]crown-6 *(3d)* compared to perhydrodibenzo[18]crown-6 *(3f)* (Table 7), even though the stability constant of the aromatic polyether is higher, at least in methanol (Table 6). In order to make these solubility effects more explicit, the extraction equilibrium constant K_E was analyzed in terms of the aqueous stability constant and the partition coefficients for polyether and for complex[17]. This analysis showed that the latter partition coefficient is a most important factor and varies through many orders of magnitude.

Table 8. Equilibrium constants for picrate extraction with polyether-containing organic solvents [17]; see eq. (6) and (7).

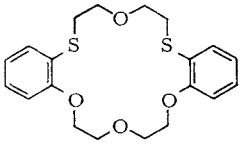
Polyether	Cation	Solvent	K_E (l/mol)^2	K_D (mol/l)
Perhydrodibenzo[18]crown-6 *(3f)*	K^+	CH_2Cl_2	2×10^6	4×10^{-5}
Perhydrodibenzo[18]crown-6 *(3f)*	K^+	n-C_6H_{14}	4×10^3	$< 1 \times 10^{-6}$
Dibenzo[18]crown-6 *(3d)*	K^+	CH_2Cl_2	7×10^5	4×10^{-6}
Perhydrodibenzo[18]crown-6 *(3f)*	Na^+	CH_2Cl_2	1.5×10^4	1×10^{-4}

5. Polyethers Containing Other Heteroatoms

5.1. Monocyclic Polyethers Containing Nitrogen and Sulfur

5.1.1. Preparation

More than a dozen cyclic polyethers have been reported in which one or more sulfur atoms have been substituted for oxygen[28–30]. They are prepared by condensation methods similar to those used for the ordinary polyethers. The synthesis is, in many cases, facilitated by the greater reactivity of thiol groups compared to phenol.



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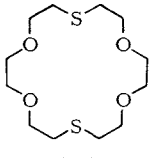

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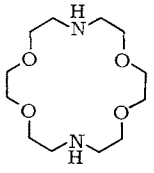
Mention has also been made of several cyclic polyethers in which one or two NH or NR groups replace oxygen[25, 31]. Synthesis of these compounds is accomplished typically by reaction of a diamine (*e.g.* $(CH_2OCH_2CH_2NH_2)_2$) with a diacid chloride (*e.g.* $(CH_2OCH_2COCl)_2$) and subsequent reduction of the resulting cyclic diamide[32].



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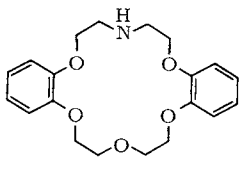

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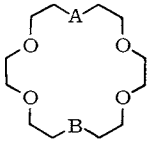
5.1.2. Complexing Properties

As judged by the effect of salts on the UV spectra and by the picrate extraction method, complexing of alkali and alkaline earth cations is greatly decreased by substitution of S for O in the polyether ring, while complexing of Ag^+ is either increased or unaffected[30]. These conclusions were confirmed by the formation of crystalline silver nitrate complexes and the failure of attempts to prepare such complexes of KSCN with sulfur-containing polyethers.

Similar effects are observed when one or two nitrogens are substituted for oxygen, as shown quantitatively by the K^+ stability constants (see Table 9), which decrease in the



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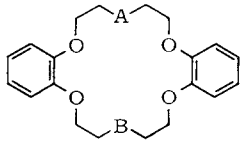

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Table 9. Effect of nitrogen and sulfur substitution in the polyether ring on the complexing properties, based on K_1 in l/mol [25].

Type	Polyether A	B	Formula	log K_1 K^+ in methanol	Ag^+ in water
I	0	0	*(3a)*	6.1	1.6
II	0	0	*(3d)*	5.0	—
II	NR [a]	0		4.1	—
I	NH	0		3.9	3.3
II	NH	0	*(13)*	3.2	—
I	NH	NH	*(12)*	2.0	7.8
II	NH	NH		1.6	—
I	S	S	*(11)*	1.2	4.3

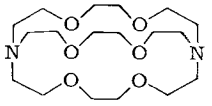
[a] $R = n\text{-}C_8H_{17}$.

same order as the electronegativities, O > NR > NH > S[25]. In other words, the electrostatic attraction between the cation and the heteroatoms diminishes with the negative charge on the latter.

Nitrogen substitution greatly enhances Ag^+ complexing (see Table 9), just as sulfur was noted to do. Evidently the principal forces involved here are not simple electrostatic ones, but rather covalent bonding analogous to that present in the numerous well-known complexes of Ag^+ with amines and other nitrogen-containing compounds. Indeed some open-chain amine compounds have Ag^+ stability constants of the same order of magnitude as the corresponding cyclic amino polyethers[33].

5.2. Bicyclic Amine Polyethers

Preliminary reports have started to appear of bicyclic polyethers *(14)* containing amine bridge atoms[31]. They are made by an extension of the method used for the preparation of monocyclic amine polyethers[31] (see Section 5.1.1) in analogy to the preparation of bicyclic amines by *Simmons* and *Park*[34].



(14)

These bicyclic compounds have remarkable complexing properties, as demonstrated by their aqueous stability constants. Preliminary results[31, 35] obtained by a "pH-metric" method for compound *(14)* are Ba^{2+} (log K_1 9.5), Sr^{2+} (8.0), K^+ (5.4), Ca^{2+} (4.4), Rb^+ (4.4), Na^+ (3.9), *i.e.* two or more decades above the [18]crown-6 derivatives, in spite of the nitrogen atoms in the rings. Evidence of complexing was also obtained by NMR, solubilization in chloroform, and formation of crystalline complexes[31, 35, 36].

Bicyclic amine polyethers form complexes with the same cations as the cyclic polyethers. The complexes, which are termed "cryptates"[31], are formed by "encapsulation" of the cation within the cavity of the compound, as demonstrated by X-ray analysis of the crystalline KSCN complex[36]. Evidently the cation is held in the cavity under the influence of the negative charges of the six oxygen and two nitrogen atoms. Complexation in solution is pH sensitive, since protonation of the amino nitrogens prevents complex formation, apparently because of repulsion between the two positively charged nitrogen atoms and the cation. It is interesting to note that encapsulation of cations by the bicyclic polyether amines has a parallel in the encapsulation of anions by bicyclic amines which contain no oxygen atoms[37].

6. Applications

6.1. Organic Chemistry

Many salts or salt-like compounds of alkali and alkaline earth metals are used in organic synthesis, frequently under inefficient conditions, *i.e.* low concentrations or two-phase operation, because of their limited solubility in organic solvents. It is evident that the crown polyethers can help to overcome such difficulties in many cases, not only by solubilizing the salts but also by increasing the dissociation of ion pairs (cf. Section 3.1.3) to provide highly reactive, unsolvated anions. A related effect, more subtle than complete dissociation of ion pairs, is the conversion of contact ion pairs into solvent-separated ones. It has been demonstrated convincingly that this can be brought about by crown polyethers[26, 38].

Examples of such organic applications of crown polyethers based on solubilization and enhanced reactivity are sa-

ponifications by KOH in benzene (cf. Section 3.1.1) and oxidations by $KMnO_4$ in benzene[3, 39]. The cyclic polyethers have also been found to exert profound effects on the course of a number of different reactions involving alkali-metal cation-carbanion ion pairs[40–43].

A related development of great significance is the dissolution of potassium and cesium metal in tetrahydrofuran and diethyl ether by perhydrodibenzo[18]crown-6[44], which promises to extend greatly the range of solvents in which solvated electrons and related species can be obtained.

These examples, all published very recently, are just a hint of the impact which the crown polyethers will assuredly have on organic chemistry in studies of reaction mechanism and in syntheses involving such reagents as alkyllithium compounds, Grignard reagents, alkali salts of carbanions, and alkali metals.

6.2. Biophysics

The discovery of the complexing properties of the crown polyethers aroused much interest among the investigators of ionic transport phenomena because of the similar properties of the macrocyclic antibiotics (see Section 1.3). For the first time synthetic materials were available for systematic study of structural effects. Crown polyethers have indeed been found to affect cationic transport across bilayer membranes[13], though these effects are somewhat different from those of the antibiotics. Moreover, methods developed for studying the cyclic polyethers in solution, *i.e.* picrate extraction (see Section 4.2), have been profitably applied to the antibiotics[45].

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