Crown Ethers and Analogs
Edited by Saul Patai and Zvi Rappoport

Crown ethers and analogs

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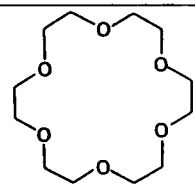

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Foreword

This is the third volume published in the new series entitled 'Updates from the Chemistry of the Functional Groups'.

The main volume on *The ether linkage* in the Functional Groups series appeared in 1967. This book did not even mention crown ethers, while *Supplement E* which appeared in 1980 already contained three full chapters (a total 174 pages) on crown ethers, while a fourth chapter also dealt mainly with the structural aspects of the same class of compounds. Now, less than ten years after the appearance of *Supplement E*, the present volume again contains a very substantial part describing material which was unknown or at least unpublished ten years ago. Indeed, the four updated chapters in the present volume deal not only with new material in the field of crown ethers, but with a variety of analogous types of compounds which were developed and for which important new uses were found only recently.

Chapters 1,2,4 and 6 were originally published in *Supplement E* (1980), while Chapter 8 is reprinted from *Supplement C* (1983). Chapters 7 and 9 are essentially updates of some of the reprinted chapters although they too contain much novel material. Chapter 5 is almost wholly devoted to new types of complexes and, finally, Chapter 3 is a review emphasizing modern methods of molecular modelling as applied to host–guest chemistry.

As always, the editors will be grateful to readers who would call their attention to mistakes or omissions in this volume as well as in other volumes of the series.

SAUL PATAI
ZVI RAPPOPORT

JERUSALEM
March 1989

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Crown Ethers and Analogs
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CHAPTER **1**

Synthesis of crown ethers and analogues

DALE A. LAIDLER and J. FRASER STODDART
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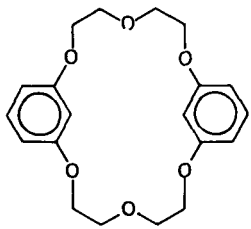
I. HISTORICAL BACKGROUND

It is interesting to reflect upon the fact that, although linear compounds containing sequential ether linkages[1-3] have occupied an important position in chemistry for many years, it is only during the last decade or so that macrocyclic polyethers and their analogues have made their major impact upon the scientific community. Alas, the fascinating complexing properties of macrocyclic polyethers were not anticipated from the comparatively mundane chemical behaviour of cyclic ethers containing up to seven atoms in their rings[4,5]. Indeed, as often happens in science, serendipity played[6] an important role in the discovery of the so-called crown ethers and the appreciation of their somewhat intriguing characteristics. Although the early literature was not devoid of reports on the synthesis of macrocyclic polyethers, their value and potential was not realized by those involved. It is easy to feel with hindsight that it should have been; but it is difficult to envisage how it could have been!

The first macrocyclic polyethers were reported by Lüttringhaus[7] in 1937 as part of an investigation of medium- and large-sized rings. For example, he obtained the 20-membered ring compound **1** in low yield after reaction of the monosubstituted resorcinol derivative **2** with potassium carbonate in pentan-1-ol. Later, the tetrafuranyl derivative **3** was isolated[8] after acid-catalysed condensation of furan with acetone and the cyclic tetramers **4** and **5** of ethylene[9] and propylene[10] oxides, respectively, were reported.



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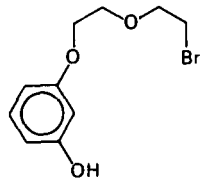

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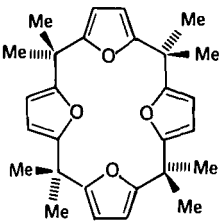

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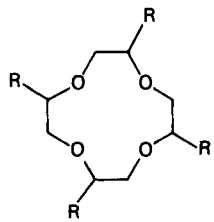
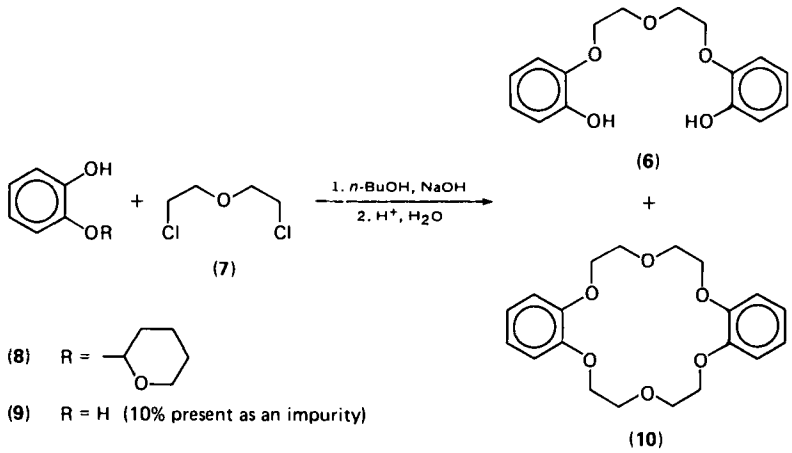


(4) R = H

(5) R = Me

Several acyclic polyethers, as well as compound (5), were found[10] to dissolve small quantities of potassium metal and sodium–potassium alloy giving unstable blue solutions of solvated electrons and solvated cations. However, it was not until 1967 that Pedersen[11] reported on the formation of stable complexes between macrocyclic polyethers and salts of alkali and alkaline earth metals. During an attempted preparation of the diphenol 6 from the dichloride 7 and the mono-protected catechol derivative 8, the presence of 10% of catechol (9) as an impurity led[6] to the isolation (see Scheme 1) of the unexpected by-product which was identified as the macrocyclic polyether **10**. Given the trivial name dibenzo-18-crown-6 by Pedersen[6,12], it was found to be insoluble in methanol by itself, but became readily soluble on the addition of sodium salts. Furthermore, it was obtained in 45% yield when pure catechol (9) was employed[6,12] in its synthesis.



SCHEME 1.

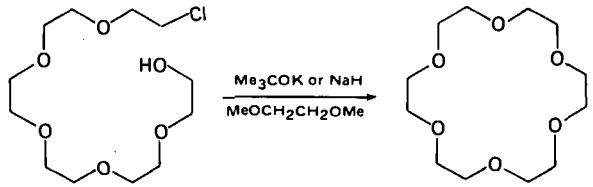
This amazingly high yield for a macrocycle obtained on condensation of four molecules raises questions of fundamental importance which will be discussed in Section II. Following upon his initial discoveries, Pedersen[12] prepared more than 60 compounds in order to ascertain the optimum ring size and the preferred constitutional arrangement of oxygen atoms in the macrocycles for them to complex with a wide variety of cationic species. Those compounds which contain between five and ten oxygen atoms, each separated from its nearest neighbour by two carbon bridges, were found to be the most effective complexing agents. These observations have led to the synthesis of many crown ethers and analogues. This chapter is devoted to a review of the general principles and fundamental concepts governing this kind of macrocyclic ring formation as well as to a summary of the methodology and reaction types employed in the synthesis of these macrocycles.

II. FACTORS INFLUENCING YIELDS IN SYNTHESIS

A. The Template Effect

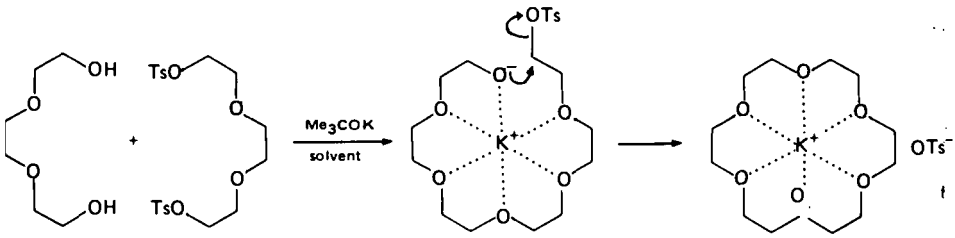
The isolation of dibenzo-18-crown-6 (**10**) in 45% yield under the conditions given in Scheme 1 prompted Pedersen[6] to observe that 'the ring-closing step, either by a second molecule of catechol or a second molecule of bis(2-chloroethyl) ether,

was facilitated by the sodium ion, which, by ion–dipole interaction 'wrapped' the three-molecule intermediates around itself in a three-quarter circle and disposed them to ring-closure'. The isolation of numerous other macrocyclic polyethers in synthetically attractive yields by Williamson ether syntheses, as well as by other approaches, has led to the recognition of a template effect involving the cationic species present in the reaction mixture. Such a phenomenon is, of course, not unique to the synthesis of macrocyclic polyethers. Transition metal template-controlled reactions have been used extensively in the synthesis of (*a*) porphyrins from suitably substituted pyrroles[13,14], (*b*) corrin ring systems[15] leading to vitamin B_{12}, and more recently (*c*) large-ring lactones[16]. Evidence for the operation of a template effect in crown ether synthesis comes from a consideration of the published procedures for the preparation of 18-crown-6. Somewhat surprisingly, base-promoted cyclization of hexaethyleneglycol monochloride (**11**) in $MeOCH_2CH_2OMe$ using either Me_3COK or NaH as base led (equation 1) to very low (ca. 2% in each case) isolated yields of **12** in the first synthesis to be reported



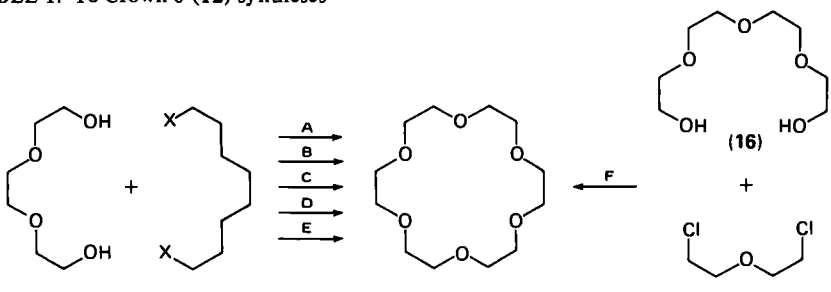
(11) (12) (1)

by Pedersen[12]. Consequently, improved procedures were sought; these are summarized in Table 1. Depending upon the nature of the solvent, 18-crown-6 (**12**) can be obtained[17,18] in 33–93% yields from reaction of triethyleneglycol (**13**) with its ditosylate (**14**) in the presence of Me_3COK. By employing less expensive reagents, e.g. triethyleneglycol (**13**), its dichloride (**15**), and KOH in aqueous tetrahydrofuran[19] or tetraethyleneglycol (**16**), diethyleneglycol dichloride (**7**), and KOH in dry tetrahydrofuran[20] yields of 30–60% can be attained. In all these synthetic approaches to 18-crown-6 (**12**), a template effect involving the K^+ ion is an attractive proposition as, at least, a partial explanation for the high yields. In the reactions of **13** with **14** employing methods B–D in Table 1, a mechanism for cyclization (see equation 2) involving formation of an intermediate acyclic complex is envisaged[18]. The observations that (*a*) the macrocycle **12** can be isolated[17,18] as its potassium tosylate complex **12**·KOTs, (*b*) doubling the concentration of reactants in method C resulted[18] only in a decrease in the yield from 84 to 75%, and (*c*) when tetra-*n*-butylammonium hydroxide was used as the base the yield of



(13) (14) (12·KOTs)

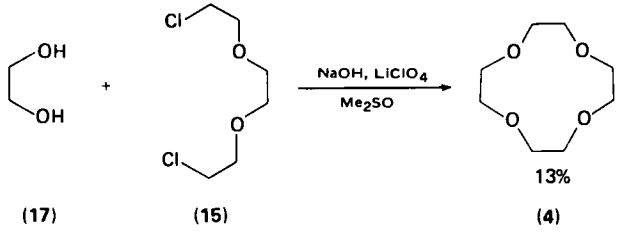
TABLE 1. 18-Crown-6 (12) syntheses



Method	X	Base	Solvent	Yield (%)	Reference
A	OTs	Me_3COK	Me_3COH/C_6H_6	33	17
B	OTs	Me_3COK	THF[a]	30–60	18
C	OTs	Me_3COK	DMSO[b]	84	18
D	OTs	Me_3COK	DME[c]	93	18
E	Cl	KOH	THF^a/H_2O	40–60	19
F	Cl	KOH	THF[a]	30	20

[a]Tetrahydrofuran.
[b]Dimethyl sulphoxide.
[c]1,2-Dimethoxyethane.

12 was reduced drastically[18], all support the operation of a template effect in the formation of 18-crown-6. The effect has generality. In reactions of ethyleneglycol (17) and diethyleneglycol (18) with 15 (equations 3 and 4, respectively), Li^+ and Na^+ ions have been shown[21] to template the formation of 12-crown-4 (4) and 15-crown-5 (19), respectively.



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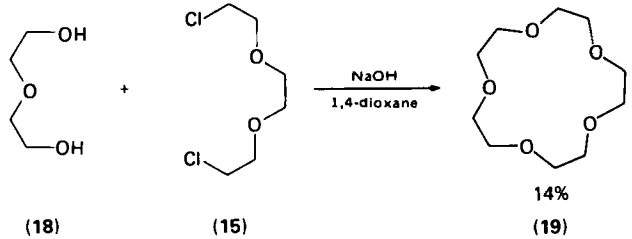
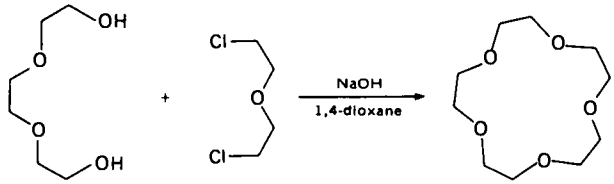


(4)

Interestingly, however, a better yield of **19** is reported[20] for condensation (equation 5) of the diol **13** with the dichloride **7** under the same conditions as those employed in equation (4). It would be unwise to read too much into situations of this kind; isolated yields often reflect the skills of the experimentalist!

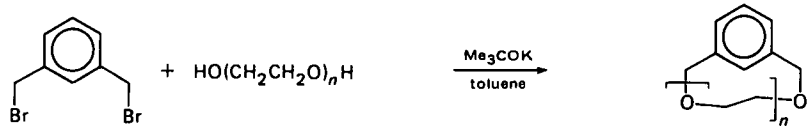


(5)

(13) (7) (19)

The optimization of template effects is probably achieved when the diameter of the cation corresponds most closely to the cavity diameter of the macrocycle being formed. Thus, for simple crown ethers, Li^+, Na^+ and K^+ ions are clearly suited to templating the syntheses of 12-crown-4 (**4**), 15-crown-5 (**19**) and 18-crown-6 (**12**), respectively. However, the effect is quite general. For example, in the acid-catalysed cyclic cooligomerization of furan and acetone to form the 16-crown-4 derivative (**3**), the addition of $LiClO_4$ to the reaction mixture increased[22] the yield of **3** from 18–20 to 40–45%. Also, large variations in yields (see Table 2) of the cyclic monomers **25**–**31** were observed[23] in condensations between the dibromide **20** and the dipotassium salts of $HO(CH_2CH_2O)_nH$ (n = 2–8). Significantly, the maximum yield (67%) occurred with the *meta*-xylyl-18-crown-5 derivative (**27**) and was virtually insensitive to variations in the rate of addition of the dibromide **20** to the glycolate derived from tetraethyleneglycol (**16**). This latter observation suggests that during the second stage of the reaction, intramolecular displacement of bromide ion to give **27** is very much faster than the competing intermolecular

TABLE 2. The dependence of isolated yields on ring size

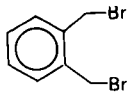


(20)

	n	Yield(%)	
(18)	2	2[a]	(25)
(13)	3	16[b]	(26)
(16)	4	67	(27)
(21)	5	49	(28)
(22)	6	18	(29)
(23)	7	21	(30)
(24)	8	21	(31)

[a]The cyclic dimer was isolated in 30% yield.
[b]The cyclic dimer was isolated in 9% yield.

reaction. A related investigation[24] on the cyclization of 1,2-bis(bromomethyl)-benzene (32) with polyethyleneglycolates revealed that the yields of cyclic monomers were not only dependent upon the chain length of the glycol but also on the nature of the cation present in the reaction mixture. For the 14-crown-4 (33), 17-crown-5 (34) and 20-crown-6 (35) derivatives, the optimum yields were



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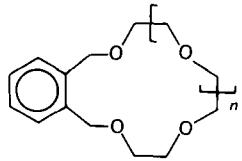
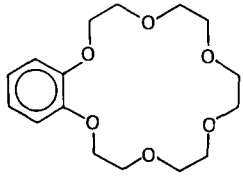


(33) $n = 1$
(34) $n = 2$
(35) $n = 3$

obtained when Li^+, Na^+ and K^+ ions, respectively, were present with the appropriate polyethyleneglycolate. If a template effect operates in these reactions, then the comparative yields of crown ethers will reflect the relative stabilities of the cationic transition states leading to them. Perhaps, it is not surprising that, in competitive experiments, comparative yields of crown ethers reflect[24] their complexing ability towards the cation in question!

Kinetic evidence[25] for a template effect has also been presented recently. The influence of added Group IA and IIA metal ions upon the rate of formation of benzo-18-crown-6 (36) from the crown's precursor (37) in aqueous solution at



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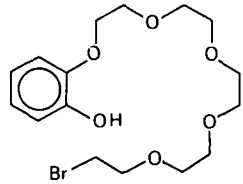
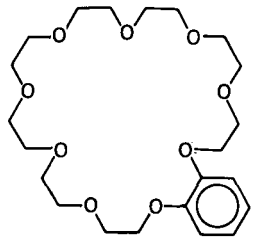


(37)

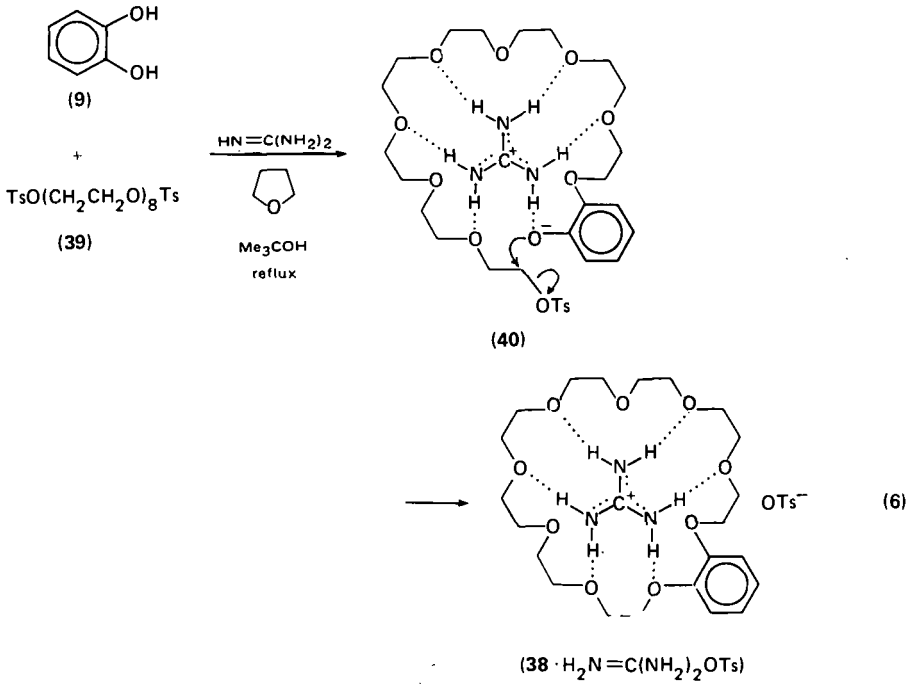
+50°C was investigated with Et_4N^+ ions as the reference. The initial concentration (ca. 2×10^{-4} M) of 37 was made sufficiently dilute to make any contribution from second-order dimerization negligible. When the kinetics were followed spectrophotometrically by monitoring the disappearance of phenoxide ions, first-order behaviour was observed in all cases. Although Li^+ ions had a negligible effect upon the cyclization rate, significant rate enhancements were observed when Na^+ and K^+ ions were present at concentrations between ca. 0.1 and 1.0 M. Most strikingly, there were dramatic increases in cyclization rates when Ba^{2+} and Sr^{2+} ions were present in low concentrations (<0.1 M) indicating the remarkable templating properties of these Group IIA metal ions. Thus, it would appear that rates of cyclization reflect a close correspondence between the catalytic effect and the relative complexing ability of crown ethers towards the cations used in their synthesis.

Organic cations can also act as templates for crown ether syntheses. The bases, Me_3COK, $HN{=}C(NH_2)_2$ and $HN{=}C(NMe_2)_2$ have all been examined[26,27] under similar reaction conditions for their comparative abilities to template the synthesis of benzo-27-crown-9 (38) from catechol (9) and octaethyleneglycol ditosylate (39).



(38)

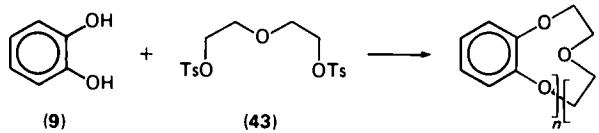
Yields of **38** of 59, 23 and 2%, respectively, indicate that K^+ ion > $H_2N{=}C(NH_2)_2^+$ ion > $H_2N{=}C(NMe_2)_2^+$ ion in bringing together the reacting centres of the acyclic intermediate during the final cyclization step. In particular, the ten fold difference in yields between the condensations employing $HN{=}C(NH_2)_2$ and $HN{=}C(NMe_2)_2$ as bases suggests that in the former case an intermediate acyclic complex (**40**) involving six hydrogen bonds might stabilize the transition state leading to the complex **38** $\cdot H_2N{=}C(NH_2)_2OTs$ of benzo-27-crown-9 as shown in equation (6).



(6)

The abilities of Me_3COK, $HN{=}C(NH_2)_2$, $HN{=}(NMe_2)_2$ and $(MeCH_2CH_2CH_2)_4N^+OH^-$ to produce benzo-9-crown-3 (**41**), dibenzo-18-crown-6 (**10**) and tribenzo-27-crown-9 (**42**) from catechol (**9**) and diethyleneglycol ditosylate (**43**) were also compared[27]. The results recorded in Table 3 show that the large nontemplating $H_2N{=}C(NMe_2)_2^+$ and $(MeCH_2CH_2CH_2)_4N^+$ ions favour the formation of **41** while K^+ ion > $H_2N{=}C(NH_2)_2^+$ ion > $(MeCH_2CH_2CH_2)_4N^+$ ion > $H_2N{=}C(NMe_2)_2^+$ ion in

TABLE 3. Effect of base on yields of crown ethers when catechol (9) was reacted with diethyleneglycol ditosylate (43) in tetrahydrofuran–Me_3COH under reflux[217]



(9) (43)

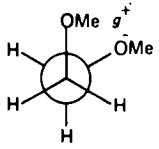
(41) $n = 1$
(10) $n = 2$
(42) $n = 3$

Base	Percentage yields based on catechol (41)	(10)	(42)
Me_3COK	5	44	20
$HN{=}C(NH_2)_2$	4	25	11
$HN{=}C(NMe_2)_2$	11	6	0
$(MeCH_2CH_2CH_2)_4N^+OH^-$	15	23	5.5

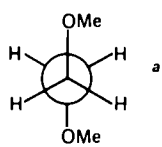
assembling four molecules to produce **10** and six molecules to produce **42**. The ability of the $H_2N{=}C(NH_2)_2^+$ ion to favour the formation of **10** and **42** suggests that it acts as a template during the final unimolecular reactions which produce dibenzo-18-crown-6 (**10**) and tribenzo-27-crown-9 (**42**) although it does so less effectively than K^+ ion.

B. The Gauche Effect

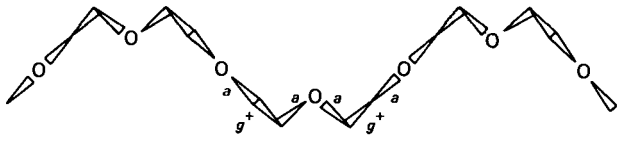
There is overwhelming physical and chemical evidence[28-31] that the C—C bond in $-OCH_2CH_2O-$ units prefers to adopt the *gauche* conformation. Infrared spectroscopy indicates[32] that, although the simplest model compound, 1,2-dimethoxyethane, comprises a range of conformationl isomers including both *gauche* (**44a**) and *anti* (**44b**) conformations in the liquid phase at +25°C, it adopts only the *gauche* conformation in the crystal at −195°C. (The descriptors *g* and *a* are employed here beside formulae to denote *gauche* and *anti* torsional angles, respectively. In addition, *gauche* torsional angles are described as g^+ or g^- according as to whether they exhibit positive or negative helicities.) In the crystal, polyoxyethylene adopts[33] only *gauche* conformations about the C—C bonds with the expected *anti* preferences for the C—O bonds. A helical conformation (**45**) results. Comparisons between empirical and calculated physical properties indicate[34] that this is also the preferred conformation in solution.



(44a)

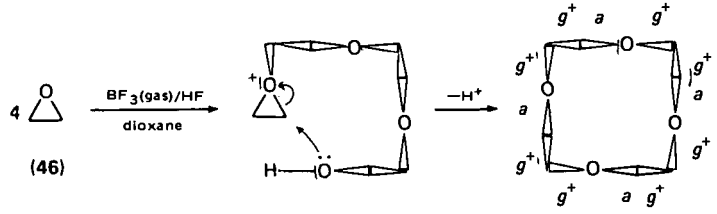


(44b)



(45)

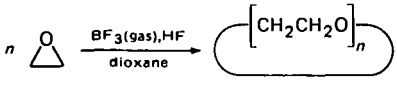
The *gauche* effect would appear to play a significant role in crown ether syntheses in appropriate situations. For example, even though it is not the most stable product thermodynamically, 12-crown-4 (**4**) is the major product formed[35] from the cyclooligomerization of ethylene oxide (**46**) using BF_3 as catalyst and HF as cocatalyst. Crown ethers up to the undecamer (33-crown-11) have been separated and identified by gas–liquid chromatography. The product distribution recorded in Table 4 is not influenced markedly by changes in temperature or reactant concentrations. These observations suggest a mechanism for cyclooligomerization compatible with a helical shape for the growing oligooxyethylene chain (**47**), which brings the reactive centres, as shown in equation (7), into a good relative disposition for cyclization after addition of the fourth ethylene oxide residue.



(46) (47) (4) (7)

Template effects can operate in conjunction with the *gauche* effect. Thus, the presence of certain suspended metal salts during BF_3-catalysed cyclooligomerization of **46** leads[35,36] to the exclusive production of 12-crown-4 (**4**), 15-crown-5 (**19**) and 18-crown-6 (**12**). In addition to other factors, the product distribution depends (see Table 5) upon the nature of the cation. The experimental procedure, which now forms the basis of a successful commercial route to crown ethers, involves the addition of **46** to a cold suspension of the insoluble metal salt in dioxane containing the catalyst (e.g. BF_3, PF_5 or SbF_5). As the salt dissolves, the metal ion–crown complexes either precipitate or afford a separate liquid phase. The complexes may be separated without prior neutralization leaving the mother liquors

TABLE 4. Product distribution[35] from the acid-catalysed oligomerization of ethylene oxide (**46**)



(46)

n	2	3	4	5	6	7	8	9	10	11	>11
Percentage yield	40	1	15	5	4	3	2	2	1	1	25

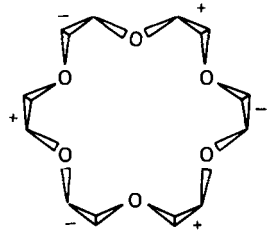
TABLE 5. The product distribution of crown ethers resulting from polymerization of ethylene oxide (46) by BF_3 as catalyst in 1,4-dioxane in the presence of suspended anhydrous salts[36]

Salt	Ionic diameter of cation (A)[b]	Cavity diameter (A)[a] and product distribution (%) 12-Crown-4 (4) 1.2–1.4	15-Crown-5 (19) 1.7–2.2	18-Crown-6 (12) 2.6–3.2
$LiBF_4$	1.36	30	70	0
$NaBF_4$	1.94	25	50	25
KBF_4	2.66	0	50	50
KPF_6	2.66	20	40	40
$KSbF_6$	2.66	40	20	40
$RbBF_4$	2.94	0	0	100
$CsBF_4$	3.34	0	0	100
$Ca(BF_4)_2$	1.98	50	50	0
$Sr(BF_4)_2$	2.24	10	45	45
$Ba(BF_4)_2$	2.68	10	30	60
$AgBF_4$	2.52	35	30	35
$Hg(BF_4)_2$	2.20	20	70	10
$Ni(BF_4)_2$	1.38	20	80	0
$Cu(BF_4)_2$	1.44	5	90	5
$Zn(BF_4)_2$	1.48	5	90	5

[a]Estimated from Corey–Pauling–Koltun molecular models.
[b]Values taken from *Handbook of Chemistry and Physics* (Ed. R. C. Weast), 56th ed., Chemical Rubber Co., Cleveland, Ohio, 1975.

for use in further reactions. The crown ethers are most simply liberated from their complexes by pyrolysis under reduced pressure. The salt which remains behind may be reused without purification. The crown ethers are obtained pure (*a*) by fractional distillation, or alternatively (*b*) by fractional crystallization of their complexes prior to pyrolysis. The results in Table 5 show that, for the Group IA and IIA metal ions at least, the relative yield of a particular crown ether is highest when its cavity diameter corresponds most closely to the ionic diameter of the metal ion present during its synthesis. The cation seems to mediate the reaction by promoting appropriate folding of the growing polymer chain prior to cyclization (i.e. the *gauche* and template effects are operating in unison) as well as by protecting the crown ethers which are formed from subsequent degradation. The positive charge on the metal in the complex prevents the formation of the oxonium salt which would initiate degradation.

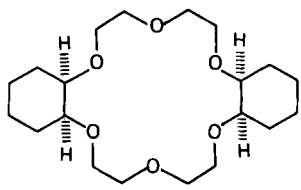
So far, we have seen that the *gauche* and template effects can operate together to increase the rate of cyclization by raising the probabilities that molecules are in favourable conformations and dispositions relative to each other to react. However, the implications of stereochemical control appear to go deeper than the *gauche* effect alone in the templated reactions of oligooxyethylene fragments to give crown ethers. The complete stereochemistry of the acyclic precursor can become important. In order to examine this claim, consider what is known about the structures of complexes of 18-crown-6 (12). There is evidence that they adopt the 'all-*gauche*-OCH_2CH_2O' conformation (12a) with D_{3d} symmetry in solution [37] as well as in the crystalline state[38–41]. Moreover, the association constants (K_a) and the corresponding free energies of association (ΔG) for the 1 : 1 complexes formed[42–44] between Na^+Cl^- and K^+Cl^- in MeOH and 18-crown-6 (12) are considerably greater (see Table 6) than the corresponding K_a and ΔG values for the



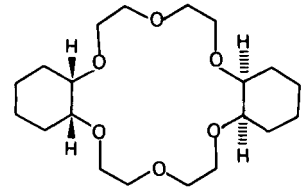
$g^+g^-g^+g^-g^+g^-$

(12a)

isomeric[43] dicyclohexano-18-crown-6 derivatives (48–51). Figure 1 shows that the *cis–cisoid–cis* (48a) and *cis–transoid–cis* (49a) isomers (*a*) can attain an 'ideal' complexing conformation and (*b*) are 'flexible' to the extent that the 18-membered ring can undergo inversion ($g^+g^-g^+g^-g^+g^- \rightleftharpoons g^-g^+g^-g^+g^-g^+$); the *trans–cisoid–trans* (50a) and *trans–transoid–trans* (51a) isomers are 'rigid' to the extent that the 18-membered ring cannot undergo inversion and, whilst 50 can attain an 'ideal'



(48)

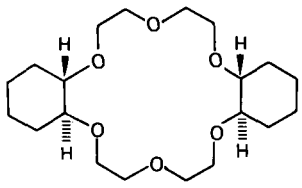


(49)

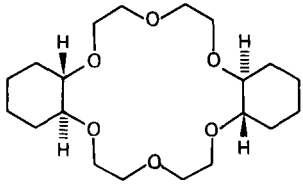
TABLE 6. The log K_a (based on K_a in M^{-1}) and ΔG values for the formation of 1:1 complexes with Na^+Cl^- and K^+Cl^- in MeOH

	Na^+			K^+		
Crown ether	log K_a^b	ΔG^c	$\Delta\Delta G^c$	log K_a^b	ΔG^c	$\Delta\Delta G^c$
18-Crown-6 (12)	4.32[d,e]	−5.9[e]	–	6.10[d,f]	−8.3[f]	–
cis–cisoid–cis-DCH-18-6[a] (48)	4.08[d]	−5.5	0.4	6.01[d]	−8.2	0.1
cis–transoid–cis-DCH-18-C-6[a] (49)	3.68[d]	−5.0	0.9	5.38[d]	−7.3	1.0
trans–cisoid–trans-DCH-18-C-6[a] (50)	2.99[g]	−4.0	1.9	4.14[g]	−5.6	2.7
trans–transoid–trans-DCH-18-C-6[a] (51)	2.52[g]	−3.4	2.5	3.26[g]	−4.3	4.0

[a]DCH-18-C-6 ≡ Dicyclohexano-18-crown-6.
[b]Obtained for the equilibrium, M^+ *n*MeOH + Crown ⇌ M Crown$^+$ + *n*MeOH, at 20–25°C by potentiometry with ion selective electrodes.
[c]In kcal/mol. The $\Delta\Delta G$ values correspond to the differences in the ΔG values between the particular crown ether and 18-crown-6 (12).
[d]Values from Reference 42.
[e]Values for log K_a, ΔG, ΔH (kcal/mol), and $T\Delta S$ (kcal/mol) determined calorimetrically (Reference 44) at 25°C are 4.36, −6.0, −8.4 and −2.4, respectively.
[f]Values for log K_a, ΔG, ΔH and $T\Delta S$ determined calorimetrically (Reference 44) at 25°C are 6.05, −8.2, −13.4 and −5.2, respectively.
[g]Values from Reference 43.

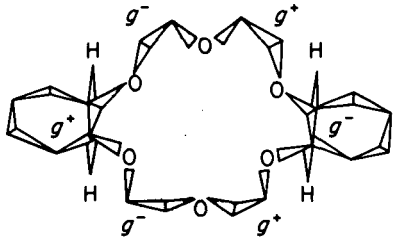


(50)



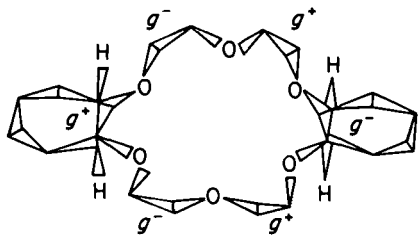
(51)

$g^+g^-g^+g^-g^+g^-$ conformation (50a), **51** is unable to adopt this 'ideal' complexing conformation. In view of the fact that it is a racemic modification[43], it has a $g^+g^-g^-g^+g^-g^+/g^-g^+g^+g^-g^+g^-$ conformation (**51a**). It is clear from the results in Table 6 and the stereochemical features highlighted in Figure 1 that a qualitative correlation exists[31,45,46] between the $\Delta\Delta G$ values and the conformation of the 18-crown-6 ring in **48**–**51**. Fine stereochemical differences involving only conformational features and gross stereochemical differences involving both configurational and conformational features can be differentiated. An example of gross stereochemical control in synthesis appears to be operative during the attempted preparation[47] as shown in Scheme 2 of **50** and **51** by condensation of (±)-*trans*-2,2′-(1,2-cyclohexylidene)dioxyethanol (**52**) with its ditosylate (**53**) in benzene in the presence of Me_3COK. Only **50** was isolated with a comment[47] about 'the marked tendency for pairing of (+) with (−) in the cyclization to give the *meso* form'. On formation of



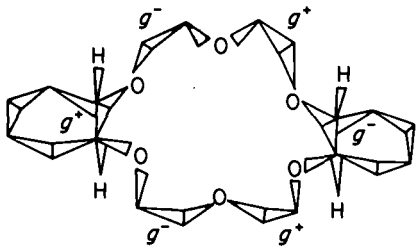
$g^+g^-g^+g^-g^+g^- \rightleftharpoons g^-g^+g^-g^+g^-g^+$

(**48a**)



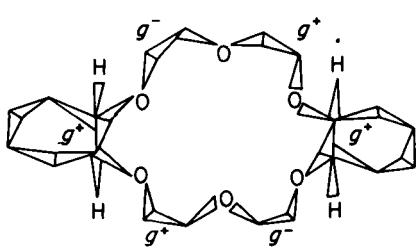
$g^+g^-g^+g^-g^+g^- \rightleftharpoons g^-g^+g^-g^+g^-g^+$

(**49a**)



$g^+g^-g^+g^-g^+g^-$

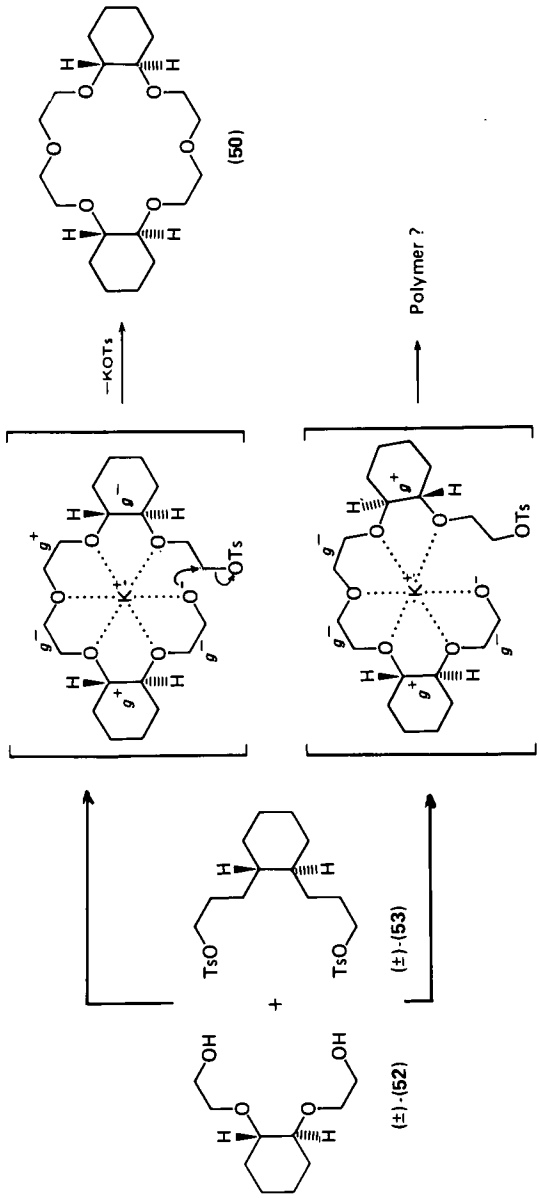
(**50a**)



$g^+g^-g^-g^+g^-g^+/g^-g^+g^+g^-g^+g^-$

(**51a**)

FIGURE 1. The designations of conformational types for the di-*cis* (48a) and (49a) and di-*trans* (50a) and (51a) isomers of dicyclohexano-18-crown-6.



SCHEME 2.

the first C—O bond in both of the intermediates in Scheme 2, the relative configurations of the products are established. The observed steroselectivity ensues from the greater stabilization through efficient templating action of K^+ ions on the transition state leading to **50** than on the transition state leading to **51**. In the second instance, intermolecular reaction to give polymer is probably competing successfully with the intramolecular reaction. Thus, it would even seem to be possible to control diastereoisomeric ratios during cation-templated syntheses of chiral crown ethers. This possibility, which relates to the principle[31,45] that noncovalent bonds are highly directional in character, is capable of considerable exploitation.

C. Other Effects

The synthesis of medium- and large-sized ring compounds is usually a highly inefficient process. As we have seen in Sections II.A and II.B, success in crown ether syntheses depends strongly upon preorganized reactants being brought together under some external influence and then the acyclic precursor having the 'correct' stereochemical orientation in the final cyclization step. The operation of template and/or *gauche* effects helps to overcome unfavourable entropic factors which mitigate against the formation of highly ordered species. Rigid groups (e.g. benzo groups) can also increase[48] the rate of cyclization by reducing the number of conformational possibilities for the reactants and providing favourable stereochemistries for both inter- and intra-molecular reactions. Historically, reactions to form macrocyclic compounds have often been performed[49] under high dilution conditions. This meant that all reactions including cyclizations had to be fast in order to maintain very low concentrations of reactants and so suppress the formation of acyclic oligomers with respect to cyclic products. Although it is seldom possible to employ fast reactions to prepare crown ethers because C—O bond formation is relatively slow, it often proves[48] worthwhile to use high dilution conditions in the syntheses of aza- and thia-crown ethers. The ease of forming C—N and C—S bonds relative to forming C—O bonds makes the use of high dilution technology attractive from the point of view of obtaining higher yields for these derivatives than could be obtained by conventional means.

In this section on factors influencing yields in synthesis we have tried to highlight those areas which have particular relevance to crown ether syntheses. It is obvious that other factors such as (*a*) the nature of the leaving group in displacement reactions, (*b*) the solvent in which the reaction is conducted, (*c*) the temperature of the reaction mixture etc. will all have a bearing on the outcome of a particular synthetic step. Also, particular reaction conditions often pertain to the more specialized approaches to crown ether synthesis. These will be discussed as and when necessary in Section IV on syntheses exemplified.

III. DESIGN AND STRATEGY

The well-known receptor properties of crown ethers and their analogues provide one of the main incentives for their synthesis. Indeed, the design of receptor molecules for appropriate substrates is becoming more of a science than an art every day. During the embryonic phase of development of this science, the use of space-filling molecular models has become an indispensable adjunct and activity in the design stage and has generated a lot of new synthetic strategies and goals in different laboratories around the world. Nonetheless, it should be pointed out that, as far as molecular models are concerned, the framework variety have an important

role to play in highlighting subtle stereochemical features such as those discussed in Section II.B. However, there is little doubt that design and strategy is going to rely more and more in future upon model building with the aid of high-speed electronic computers.

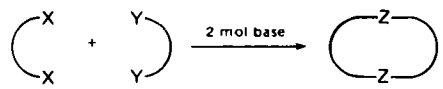
The design of synthetic receptor molecules which complex with (*a*) metal and other inorganic (e.g. H^+, NH_4^+ and H_3O^+ ions) cations and (*b*) inorganic anions (e.g. Cl^-, Br^- and N_3^-) has been extensively reviewed by Lehn[48,50,51]. Recommended strategies to be adopted in synthesis have also been outlined[48] in considerable detail. In several reviews[52-55], Cram has discussed the design of achiral and chiral crown ethers which complex with organic cations (e.g. RNH_3^+, RN_2^+ and $H_2N{=}C(NH_2)_2^+$ ions). He has appealed to axial chirality in the shape of resolved binaphthyl units in the elaboration of chiral crown ethers as synthetic analogues to Nature's enzymes and other receptor molecules. The attractions of utilizing natural products – and particularly carbohydrates – as sources of inexpensive chirality is one that the present authors[31,45,56] have championed.

IV. SYNTHESES EXEMPLIFIED

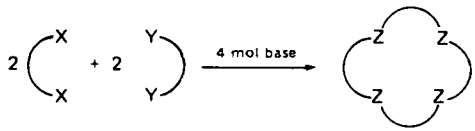
In this section, we shall deal with synthetic methods for preparing achiral crown compounds, chiral crown compounds, and macro-bi-, -tri- and -poly-cyclic ligands. We shall also include a brief mention of 'acyclic crown compounds'. Our treatment overall will be far from exhaustive! Fortunately, a number of lengthy reviews[57-60] have appeared which are highly comprehensive in their coverage of the literature.

A. Monocyclic Multidentate Ligands

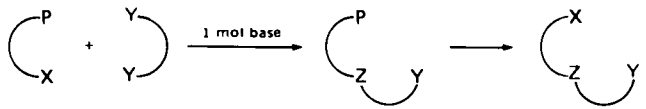
Equations (8)–(11) illustrate the most common approaches (cf. Reference 48) employed in the preparation of monocyclic multidentate ligands. Experimentally, the approaches illustrated in equations (8) and (9) represent the most facile 'one-pot' methods. Depending upon the nature of X–X and Y–Y, two-molecule (equation 8) and four-molecule (equation 9) condensations may compete. The approach indicated in equation (10) suffers from the disadvantage that the intermediate X–Z–Y may undergo intramolecular cyclization as well as intermolecular

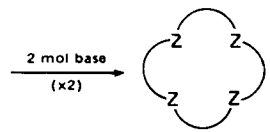


(8)

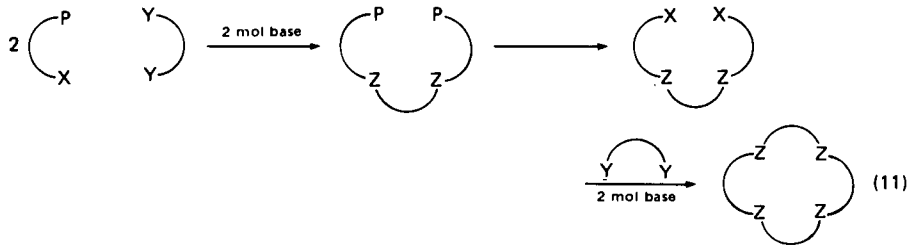


(9)





(10)

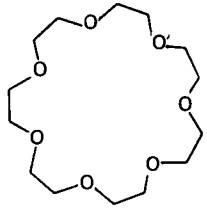


(11)

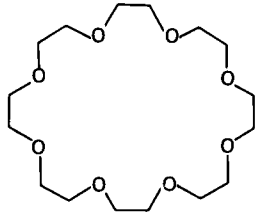
cyclization. The stepwise approach outlined in equation (11) is a versatile one and usually affords good yields of macrocyclic ligands. Despite the low yields in general, the approaches depicted in equations (8) and (9) are preferable for the synthesis of 'simple' monocyclic multidentate ligands. The approaches depicted in equations (10) and (11) are important in preparing macrocyclic ligands incorporating a variety of different structural features.

1. All-oxygen systems

The general method for preparing macrocyclic polyethers is the Williamson ether synthesis[61] which involves the displacement of halide ions from a dihaloalkane by the dianion derived from a diol. Common adaptions of this reaction utilize sulphonate esters – usually toluene-*p*-sulphonates – as leaving groups. Equations (8)–(11) illustrate (where —— = a carbon chain, X = a leaving group, Y = OH, Z = a heteroatom and P = a base-stable protecting group) the general approaches employed in the assembly of macrocyclic compounds. The base employed is typically NaH, NaOH, KOH or Me_3COK. The solvent is typically $Me(CH_2)_3OH$, Me_3COH, $MeOCH_2CH_2OMe$, Me_2SO or tetrahydrofuran. Reactions are usually conducted at room temperature or just above. The synthesis of 12-crown-4 (**4**), 15-crown-5 (**19**) and 18-crown-6 (**12**) have been discussed in considerable detail already in Section II.A. 21-Crown-7 (**54**) was obtained[17] in 26% yield when triethyleneglycol (**13**) was reacted with the ditosylate of tetraethyleneglycol (**16**) and Me_3COK in benzene. Using similar conditions, 24-crown-8 (**55**) was isolated[17] in 15% yield from

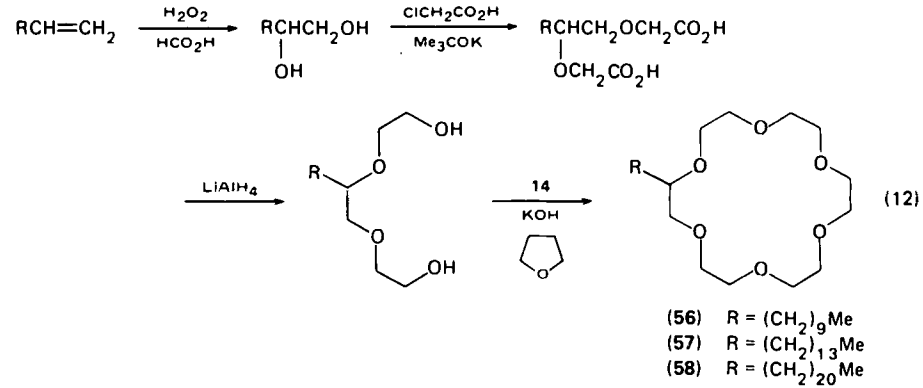


(54)

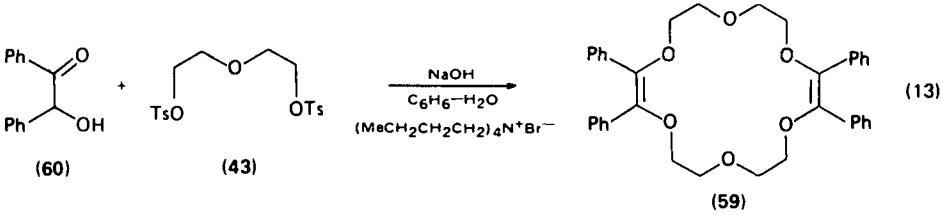


(55)

condensation of tetraethyleneglycol (**16**) with its ditosylate. In tetrahydrofuran, reaction between tetraethyleneglycol (**16**) and triethyleneglycol ditosylate (**14**) in the presence of Me_3COK gave[18] **54** in 18% yield. Substituents can, of course, be introduced into the polyether ring with little difficulty. For example, the long-chain alkyl-substituted 18-crown-6 derivatives **56**–**58** can be obtained[62] in four steps from the corresponding alkenes as depicted in equation (12). This reaction sequence illustrates one method of preparing substituted 'half-crown' diols for use in crown ether syntheses. Double bonds can also be introduced into polyether rings. The stilbenediol dianion can be generated[63] by reaction of benzoin with NaOH in

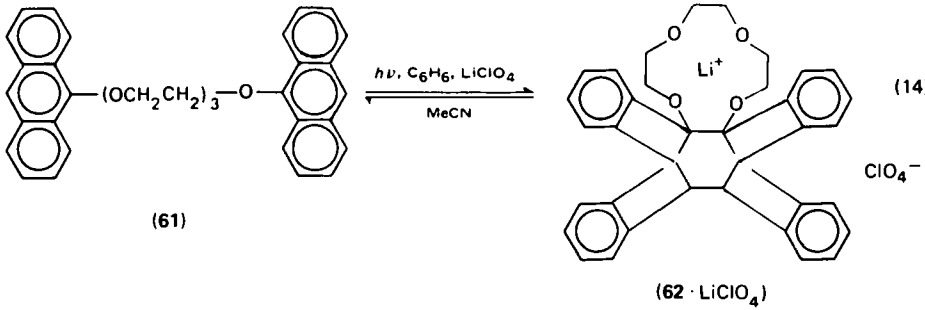


water under phase-transfer conditions. Subsequent reaction of the dianion with difunctional alkylating reagents gives cyclic derivatives in which the double bonds have (*Z*) configurations. The 18-crown-6 derivative (**59**) has been prepared[63] (equation 13) in 19.5% yield by reaction of benzoin (**60**), NaOH and diethyleneglycol ditosylate (**43**) in a C_6H_6–H_2O two-phase system using $(MeCH_2CH_2CH_2)_4N^+Br^-$ as a phase-transfer catalyst. The accessibility of the unsaturated 18-crown-6



derivative (**59**) and the possibility of chemical modification of the prochiral C=C double bonds could prove valuable in the synthesis of substituted 18-crown-6 derivatives.

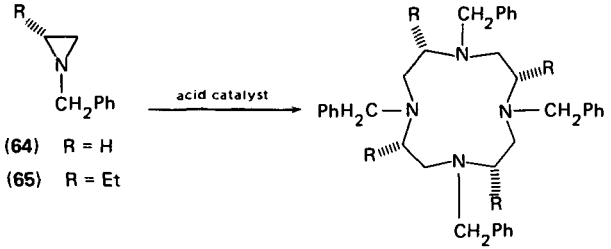
Although alkylations to give macrocyclic polyethers provide the most important synthetic routes to the compounds, other approaches are available. As we have seen already in Section II.B, the acid-catalysed cyclooligomerization of ethylene oxide (**46**) is important[35,36] from a commercial angle. One report[30] of a photochemically generated, Li^+ ion-locked 12-crown-4 derivative is intriguing. Irradation of the bisanthracene **61** in benzene in the presence of $Li^+ClO_4^-$ yields the complex **62**·$LiClO_4$ which is thermally stable but dissociates easily on addition of MeCN



(equation 14). Finally, a method[64] of synthesizing macrocyclic polyethers by acid-catalysed insertion of an olefin into cyclic acetals in a one-step process lacks wide appeal because of (*a*) the mixtures of compounds which can result, and (*b*) the presence of three carbon units – which is generally detrimental to good complexing ability – in the products.

2. *All-nitrogen systems*

A wide variety of cyclic polyamines have been synthesized and listings of those prepared up to mid-1975 have been produced[57,59]. Several reviews have been published describing their synthesis[13,65,66] and the distinctive coordination chemistry and biological significance of their complexes[67]. Since cyclic polyamines are only distantly related to crown ethers, a detailed discussion is outside the scope of this review. A few examples will be cited, however. The tetraaza-12-crown-4 derivative **63** can be isolated[68] (see equation 15) in 96% yield from the reaction between *N*-benzylaziridine (**64**) and toluene-*p*-sulphonic acid in refluxing aqueous ethanol. It appears to be a unique reaction for **64** since aziridine itself and other *N*-substituted derivatives give only high molecular weight polymers. Chiral 1-benzyl-

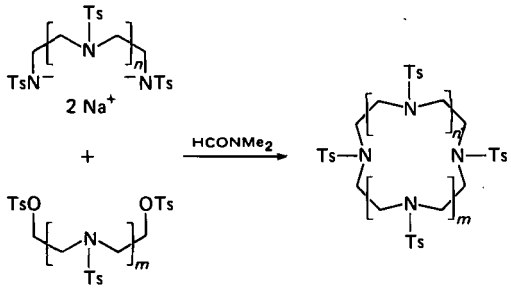


(64) R = H
(65) R = Et

(63) R = H
(66) R = Et

(15)

2-(*R*)-ethylaziridine (**65**) ring-opens[69] in the presence of BF_3-Et_2O at room temperature to give **66**. As a result of ring-opening exclusively at the primary centre only one constitutional isomer is produced (equation 15) in which the configurations at the chiral centres are preserved. A more general method of preparing aza-analogues of crown ethers has appeared[70]. The compounds **67**–**70** were synthesized by condensation of α,ω-ditosylates with the preformed sodium salts of appropriate α,ω-bissulphonamides in $HCONMe_2$ as shown in equation (16). The

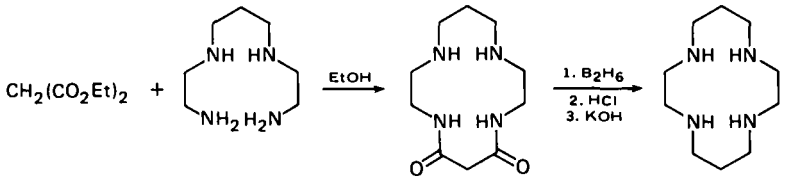


	n	*m*	Yield (%)
(67)	1	1	80
(68)	1	2	83
(69)	1	3	75
(70)	2	3	45

(16)

free amines can be obtained by acid-catalysed hydrolysis of the cyclic sulphonamides, followed by treatment of the salts with base. It does not appear that Na^+ ions act as templates since their replacement with Me_4N^+ ions did not lead to a

significant decrease in the yield of the cyclic tetramer. Macrocyclic polyamines can be obtained as shown in equation (17) by reduction of bislactam precursors which are readily available from the condensations of α,ω-diamines with diesters. For example, reaction of **71** with diethyl malonate (**72**) in ethanol under reflux gave[71] the cyclic bislactam (**73**) (30%) which afforded the tetraaza-14-crown-4 derivative (**74**) on diborane reduction.

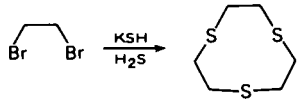


(17)

(72) (71) (73) (74)

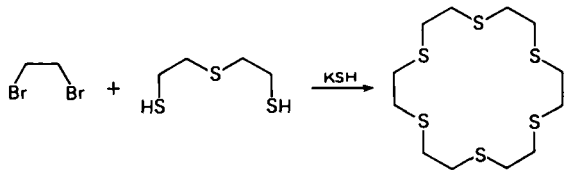
3. *All-sulphur systems*

The synthesis of polythiaethers is of interest in many areas of chemistry and has been the subject of an extensive review[72]. The first perthiacrown compounds were described over 40 years ago, some 30 years before the preparation of the oxygen analogues by Pedersen. The synthesis of trithia-9-crown-3 (**75**) as shown in equation (18) from $BrCH_2CH_2Br$ (**76**) and alcoholic KSH saturated with H_2S was described[73] in 1920. The isolation of hexathia-18-crown-6 (**77**) in very low yield (<2%) from the reaction (see equation 19) between the dimercaptan (**78**) and $BrCH_2CH_2Br$



(18)

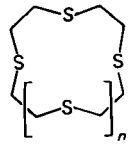
(76) (75)



(19)

(76) (78) (77)

(**76**) in the presence of KSH was reported[74] in 1934. More recently, **77**, as well as tetrathia-12-crown-4 (**79**) and pentathia-15-crown-5 (**80**) were prepared[75] by

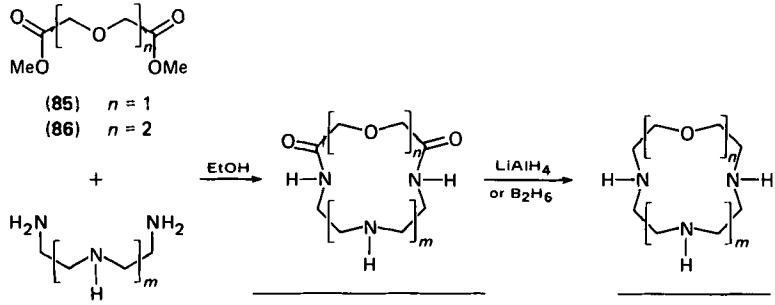


(**79**) $n = 1$
(**80**) $n = 2$

reaction of the appropriate α,ω-dimercaptans with α,ω-dihalopolythiaethers in yields of 25–35, ca. 6 and 11%, respectively. Yields can be improved[76] by resorting to the use of high-dilution techniques.

4. *Oxygen and nitrogen systems*

The variety and number of mixed heteroatom macrocycles that have been synthesized to date is immense. Fortunately, lists of mixed heteroatom macrocycles reported in the literature up to mid-1977 have been compiled[57,59]. These reviews also serve as excellent reference sources for their syntheses and properties. Macrocyclic aza polyethers have been prepared in good yields under high-dilution conditions by condensation of α,ω-diamines with α,ω-diacid dichlorides followed by hydride or diborane reduction of the key macrocyclic bislactam intermediates. The method has been exploited *par excellence* by Lehn[48,50,51] in the synthesis of macrobicyclic systems with nitrogen bridgeheads (see Section IV.G). An efficient flow synthesis of macrocyclic bislactams has also been developed[77]. However, a convenient synthesis of the aza polyethers **81**–**84** by cyclization of the readily available dimethyl esters of the α,ω-dicarboxylic acids **85** and **86** with the commercially available polyethylenepolyamines **87**–**89** in refluxing ethanol followed by reduction of the resulting cyclic amides **90**–**93** has been reported[78], which requires neither high-dilution techniques nor protection of the secondary amine functions in the starting polyethylenepolyamines. Although the yields recorded in equation (20)

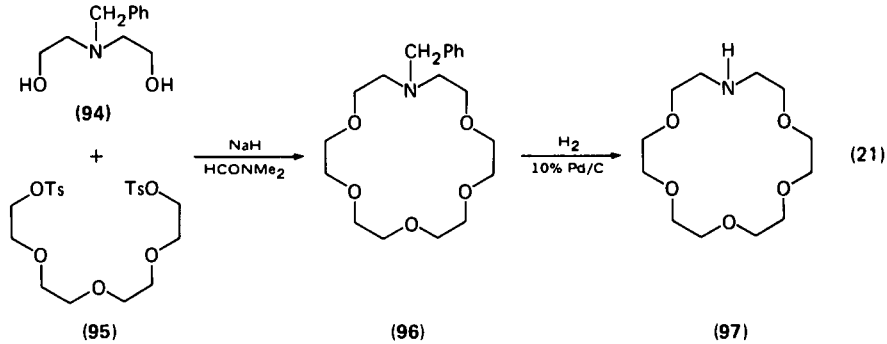


	n	m	Yield (%)
(90)	1	2	12
(91)	1	3	12
(92)	2	1	32
(93)	2	2	67

	n	m
(81)	1	2
(82)	1	3
(83)	2	1
(84)	2	2

(20)

are lower than those obtained using high-dilution techniques, the method is much more convenient experimentally. Other researchers have prepared macrocyclic aza polyethers by alkylation. For example, reaction between *N*-benzyldiethanolamine (**94**) and tetraethyleneglycol ditosylate (**95**), followed by hydrogenolysis of the resulting *N*-benzylazacrown (**96**) gives[79] monoaza-18-crown-6 (**97**) as shown in equation (21). The diaza-12-crown-4 (**98**) and 18-crown-6 (**99**) derivatives have been prepared[70] in 80% yields by reaction of the **100** and **101** dianions derived from the appropriate α,ω-bissulphonamides with diethyleneglycol ditosylate (**43**) and triethyleneglycol ditosylate (**14**), respectively, in $HCONMe_2$. The corresponding free amines **102** and **103** were obtained (see equation 22) by acid-catalysed hydrolysis of the cyclic bissulphonamides followed by treatment of the salts with base. The diaza-18-crown-6 (**103**) was obtained[80] (see equation 23) in much lower yield by (*a*) reacting triethyleneglycol ditosylate (**14**) with the dianion derived from the α,ω-bistrifluoroacetamide (**104**) followed by alkaline hydrolysis of the trifluoroacetyl groups and (*b*) reacting the α,ω-dichloride (**15**) with excess of NH_3.



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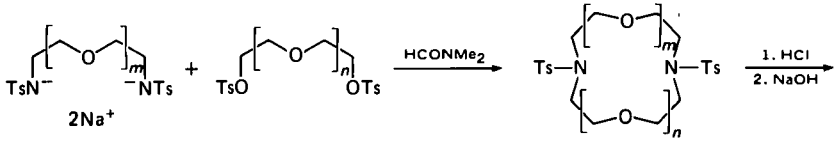
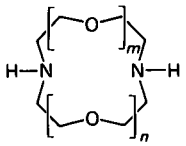
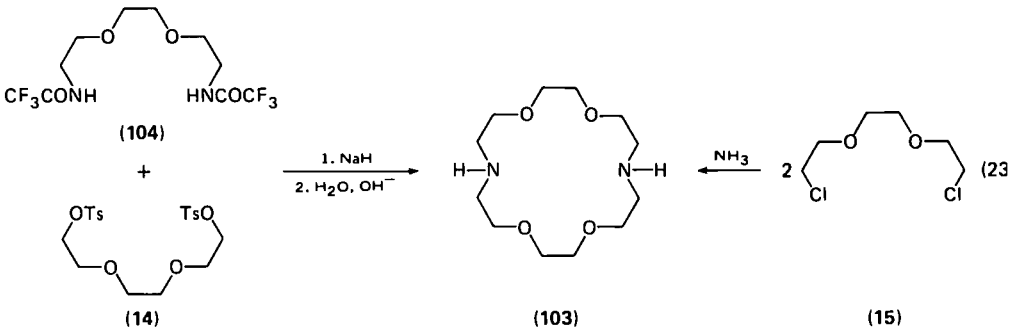


(100) $m = 1$ (43) $n = 1$ (98) $m = n = 1$
(101) $m = 2$ (14) $n = 2$ (99) $m = n = 2$

(22)



(102) $m = n = 1$
(103) $m = n = 2$

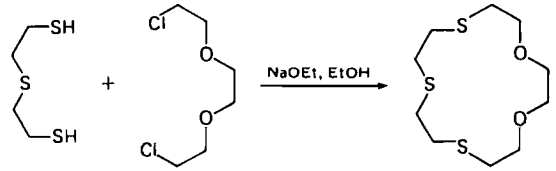


(23

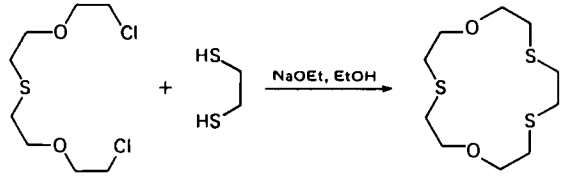
5. *Oxygen and sulphur systems*

Since the early reports[73,74] of macrocyclic compounds containing oxygen and sulphur atoms, a large number of simple thia polyethers have been synthesized[76,81-84]. Those reported in the literature up to mid-1975 have been the subject of two extensive reviews[59,72]. The most convenient method of synthesizing thiacrown ethers involves reaction of an appropriate α,ω-oligoethyleneglycol

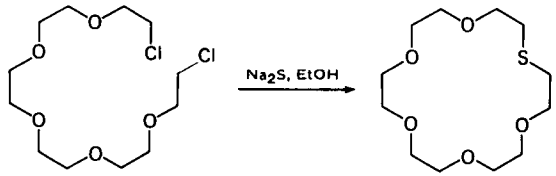
dichloride with either an α,ω-dimercaptan or sodium sulphide. These methods are illustrated by the preparations[83] of (*a*) 1,4,7-trithia-15-crown-5 (**105**) from the α,ω-dichloride (**15**) and the dithiol (**106**) (see equation 24), (*b*) 1,4,10-trithia-15-crown-5 (**107**) from the α,ω-dichloride (**108**) and ethanedithiol (**109**) (see equation 25), and (*c*) thia-18-crown-6 (**110**) from the α,ω-dichloride (**111**) and sodium sulphide (see equation 26).



(106) (15) (105) (24)



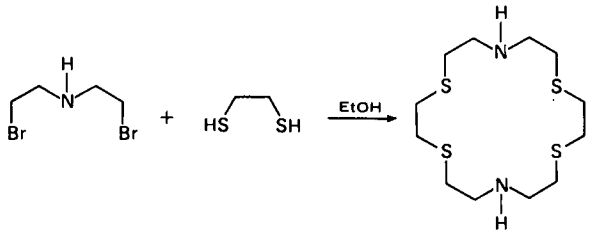
(108) (109) (107) (25)



(111) (110) (26)

6. *Nitrogen and sulphur systems*

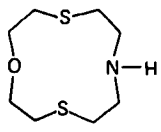
Approaches involving both (*a*) alkylation and (*b*) acylation, followed by amide reduction, have been employed to obtain this series of crown compounds. The diazatetrathia-18-crown-6 derivative (**112**) has been isolated[85] from the reaction shown in equation (27) between the dibromide (**113**) and ethanedithiol (**109**) in ethanol under high dilution conditions. More recently, however, an acylation–reduction sequence has afforded better overall yields of **112**[86] and related crown compounds[78,87].



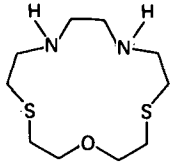
(113) (109) (112) (27)

7. Oxygen, nitrogen and sulphur systems

Systems such as **114**–**116** have been synthesized using (*a*) the alkylation approach[85] and (*b*) the acylation–reduction sequence[86,87].



(114)



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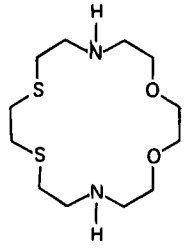
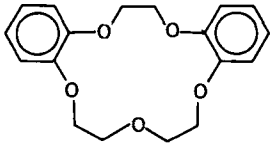


(116)

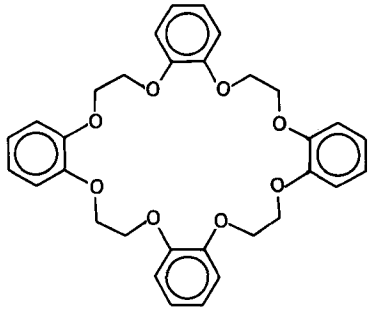
B. Crown Compounds Incorporating Aromatic Residues

1. Systems fused to benzene rings

Subsequent to his report of the accidental synthesis of dibenzo-18-crown-6 (**10**) in 1967, Pedersen[11,12] described the preparation of numerous other crown ethers, e.g. **117** and **118**, incorporating *ortho*-disubstituted benzene rings with both symmetrical and asymmetrical deployments around the polyether ring and with up to

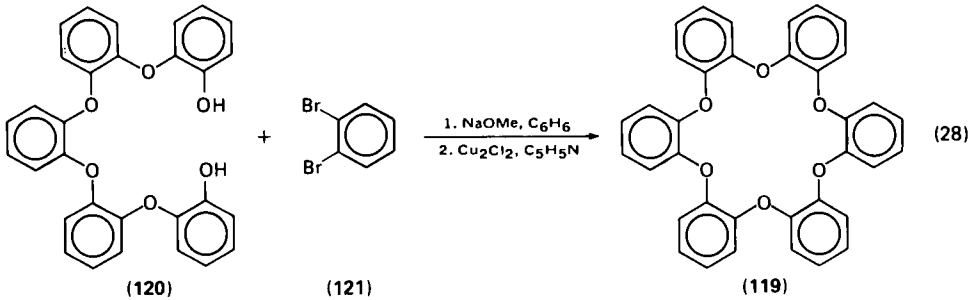


(117)

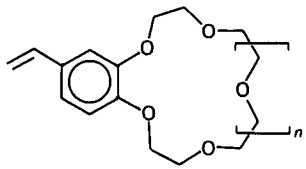


(118)

four aromatic rings fused to the macrocycle. More recently, the synthesis of hexabenzo-18-crown-6 (**119**) has been described[88]. A series of Ullmann-type condensations and de-*O*-methylations starting from 2,2′-oxydiphenol and *o*-bromoanisole afforded the diphenol (**120**) which was condensed with *o*-dibromobenzene (**121**) to give **119** (see equation 28). Alas, it does not complex with Group IA and IIA metal ions! Benzocrown ethers incorporating 4-methyl[89] and 4-*t*-butyl[12] substituents have been reported. 4-Vinyl-benzo-18-crown-6 (**122**) and -15-crown-5 (**123**) have been obtained[90] by cyclization of 3,4-dihydroxybenzaldehyde with the appropriate α,ω-dichloropolyethyleneglycol followed by reaction of the formyl group with a methyl Grignard reagent and dehydration of the resulting alcohol. The vinyl benzocrown ethers serve as important intermediates in the synthesis of polymer-supported crown ethers. A series of 4,4′-disubstituted dibenzo crown ethers have been prepared[91] from the constitutionally isomeric 4,4′-diaminodibenzo-18-crown-6 derivatives by condensation with aldehydes and isothiocyanates.

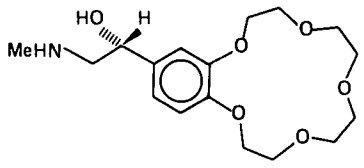


(120) (121) (119)

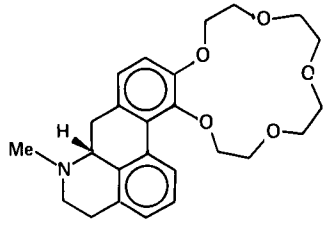


(122) $n = 2$
(123) $n = 1$

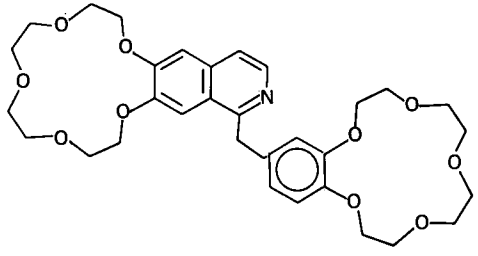
A diaminodibenzo crown ether was obtained by nitration of dibenzo-18-crown-6 (**10**) followed by reduction of the aromatic nitro groups to amino groups. Other interesting benzocrown ethers in which the aromatic ring carries functionality have been prepared. The 15-crown-5 derivatives (**124**) and (**125**) of adrenaline and apomorphine, respectively, were obtained[92] in one step from their physiologically active precursors. The bis-15-crown-5 derivative (**126**) incorporating a fully de-*O*-methylated papaverine residue has been reported[93]. Nitrogen atoms have been



(124)



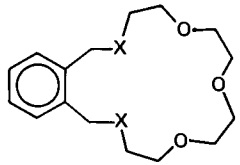
(125)



(126)

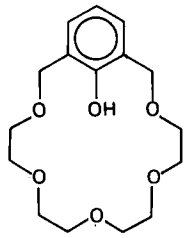
incorporated into the polyether rings of benzo and dibenzo crown ethers by employing (*a*) *o*-aminophenol[94,95] (*b*) *o*-amino aniline[94,95] and (*c*) *o*-nitrophenol[95] as readily available precursors. The syntheses[24] and detailed mass spectral analyses[96] of numerous crown ethers, e.g. **127**, containing one or two *ortho*-xylyl

residues have been reported. The derivatives were obtained by reaction of *o*-xylylene dibromide with polyethyleneglycols in the presence of Me_3COK or NaH as base. *Ortho*-xylyldithiacrown ethers, e.g. **128**, are also known[97,98].



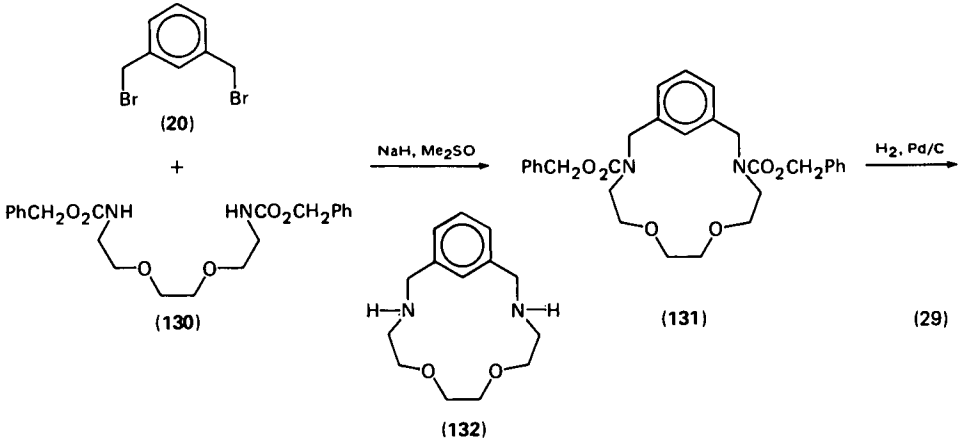
(127) X = O
(128) X = S

We have already discussed the synthesis of *meta*-xylyl crown ethers, i.e. **25**–**31**, in Section II.A. In addition to these investigations by Reinhoudt and his collaborators[23], Cram and his associates[99] have prepared numerous *meta*-xylyl-18-crown-6 derivatives with substituents at $C_{(2)}$ and $C_{(5)}$. Recently, phenolic crown ethers, such as **129**, have been obtained[100] in greater than 90% yield by de-*O*-methylation



(129)

of the corresponding methyl ethers upon exposure to anhydrous LiI in dry C_5H_5N at 100° for 10 h followed by acidification. The success of these deetherifications has been attributed to intramolecular crown ether catalysis, as neither anisole nor 2,6-dimethylanisole furnish the corresponding phenol when subjected to similar treatment. *Meta*-xylyl-diaza-15-crown-5 derivatives have been synthesized[101] by reaction of *m*-xylylene dibromide with dianions generated from α,ω-bisurethanes on treatment with base. For example, when the α,ω-bis-*N*-benzyloxycarbonyl derivative (**130**) was treated with NaH in Me_2SO and *m*-xylylene dibromide (**20**) added, the macrocyclic bisurethane (**131**) was obtained as shown in equation (29).

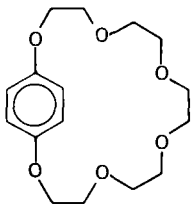


(20) + (130) → (131) (29)

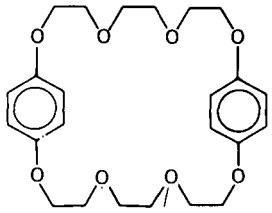
(132)

Removal of the benzyloxycarbonyl protecting groups affords the free amine (**132**) which is a useful synthetic intermediate. *Meta*-xylyl-18-crown-5 derivatives containing sulphur atoms have also been reported[97,98].

para-Phenylene units have been incorporated into a wide range of crown compounds. Standard synthetic approaches have led to the preparation of (*a*) **133** and **134** from *p*-hydroquinone and the appropriate polyethyleneglycol ditosylate[102], (*b*) **135** and **136** from *p*-xylylene dibromide and the appropriate diol[23] or dithiol[98], and (*c*) **137** from *p*-phenylene-β,β'-diethylamine and triethylene glycol ditolsylate[103]. Recently, the synthesis of some anion receptor molecules incorporating *para*-phenylene units and guanidinium groups has been described[104]. For



(133)



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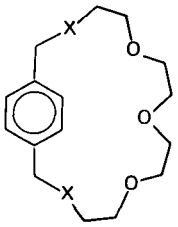
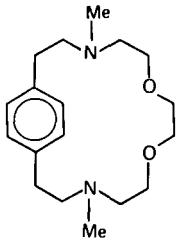


(135) X = O
(136) X = S



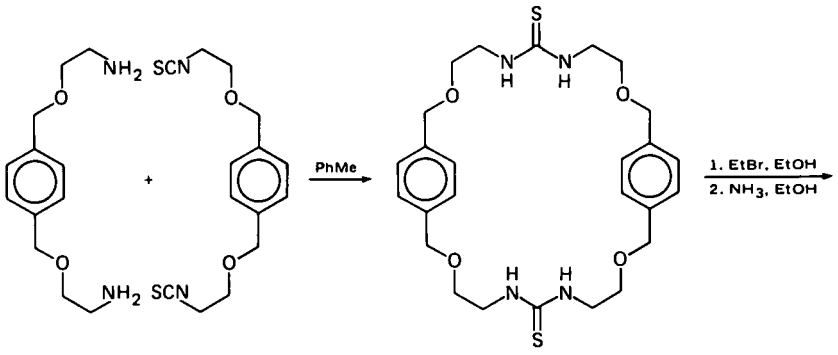
(137)

example, reaction of the diamine (**138**) with the bisisothiocyanate (**139**) affords the macrocyclic bisthiourea (**140**), which can be converted (see equation 30) into the bisguanidinium bromide, **141**·2Br$^-$, by treatment with EtBr in EtOH followed by reaction of the bis-*S*-ethyl thiouronium derivative with NH_3 in EtOH.

Polycyclic compounds which incorporate (*a*) aryl groups of the [2.2]-paracyclophane nucleus[102] and (*b*) naphthalene-1,5, -1,8 and -2,3-dimethylyl[105] units into crown-6 macrocycles have also been reported. Finally, biphenyl residues have been included[106] as aromatic subunits – exhibiting both 2,2′ and 3,3′ substitution patterns – in various macrocyclic compounds.

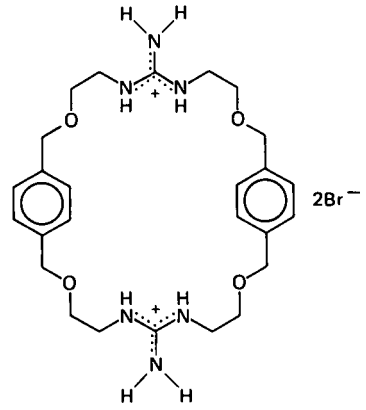
2. *Systems fused to furan rings*

Furan-2,5- and -3,4-dimethylyl units have been incorporated[23,24] into crown ethers by at least two groups of investigators. A series of 18-crown-6 derivatives, e.g. **142**–**144**, containing one, two and three furano residues deployed around the macrocyclic ring have been reported[107]. The key starting material in their synthesis is 5-hydroxymethyl-2-furaldehyde which can be obtained[108] from sucrose. This hydroxy aldehyde (**145**) can be converted into the diol (**146**), the dichloride (**147**), the extended diol (**148**) and chloro alcohol (**149**), and the bisfuran diol (**150**) and

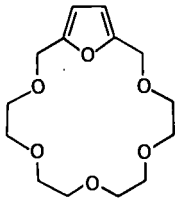


(138) (139) (140)

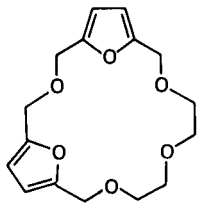
(30)



(141.2Br)



(142)



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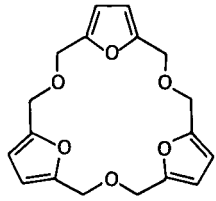
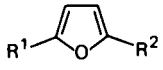
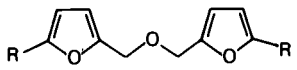


(144)

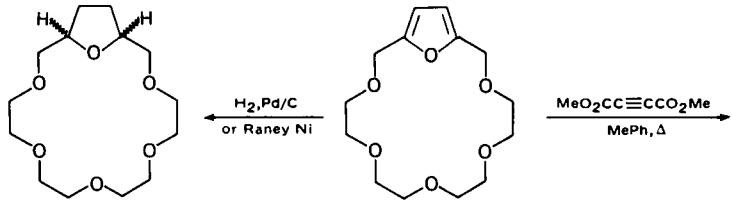




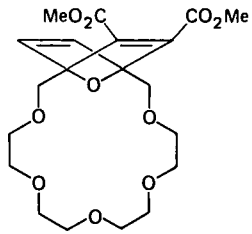
(145) $R^1 = CH_2OH$; $R^2 = CHO$
(146) $R^1 = R^2 = CH_2OH$
(147) $R^1 = R^2 = CH_2Cl$
(148) $R^1 = R^2 = CH_2OCH_2CH_2OH$
(149) $R^1 = CH_2OH$; $R^2 = CH_2OCH_2CH_2Cl$

(150) $R = CH_2OH$
(151) $R = CH_2Cl$

dichloride (**151**) by conventional methods. The compounds can then be employed as immediate precursors to **142**–**144** and other furan-containing cycles. Since furan rings lend themselves to chemical modification, macrocycles containing them have the potential to serve as precursors in the synthesis of receptor molecules whose perimeters are lined with a variety of shaping and binding residues. The monotetrahydrofuranyl-18-crown-6 derivative **152**, for example, is obtained on catalytic hydrogenation of **142** (see equation 31). When Pd on C was used as catalyst, **152** was obtained as a 1 : 1 mixture of *cis* and *trans* isomers; however, in the presence of Raney nickel as catalyst, only the *cis* isomer was isolated. When **142** was heated in refluxing toluene with an excess of $MeO_2CC{\equiv}CCO_2Me$, the [4 + 2] cycloaddition product (**153**) was obtained (see equation 31) in virtually quantitative yield. In

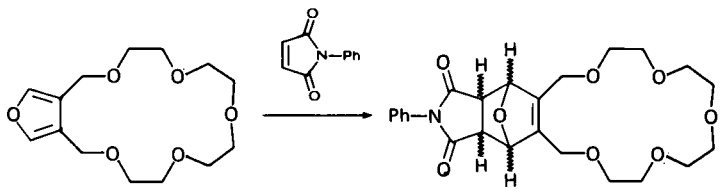


(**152**) (**142**)



(**153**) (31)

addition to forming an adduct with $MeO_2CC{\equiv}CCO_2Me$, the monofuranyl-17-crown-6 derivative (**154**) incorporating a furan-3,4-dimethylyl unit undergoes[34,96] a Diels–Alder reaction with *N*-phenylmaleimide to form the adduct **155** as shown in equation (32).

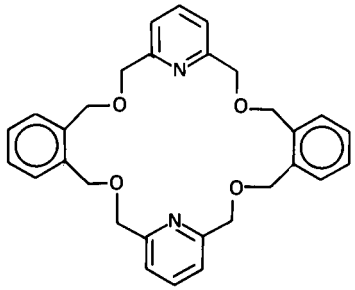


(**154**) (**155**) (32)

3. Systems fused to pyridine rings

The pyridine-2,6-dimethylyl unit is another one which has been widely employed as a heterocyclic subunit in crown compounds. In this work, the key starting material has been 2,6-bis(bromomethyl)pyridine. In 1973, Newkome and Robinson[109] isolated 22-, 33-, 44-, and 55-membered ring compounds after re-

action of this dibromide with 1,2-di(hydroxymethyl)benzene in $MeOCH_2CH_2OMe$ with NaH as base. An example of the smallest kind of macrocycle is provided by **156**. A series of crown compounds, e.g. **157**–**159**, containing between 12 and 24 atoms in the macroring and incorporating between 1 and 4 pyridine-2,6-dimethylyl units have been synthesized[110] by conventional means. Diaza, e.g. **160**, and dithia, e.g. **161**, derivatives have also been reported[97,98,111], and, in some cases, e.g. **161**,



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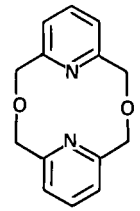

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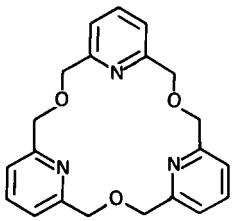
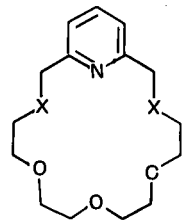
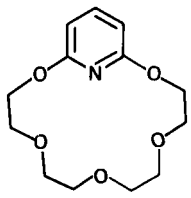


(158)



(159) X = O
(160) X = NTs
(161) X = S

the preparation of the *N*-oxide has been accomplished. The pyridine ring is found in other guises in a few macrocycles reported in the literature. Base-promoted reaction of 2,6-bisbromopyridine with the appropriate polyethyleneglycol has yielded[112] **162** and **163**, for example, whilst incorporation of the 2,2′-bipyridyl unit into heteroatom-containing macrocycles through its 3,3′- and 6,6′-positions has been achieved[58,113].



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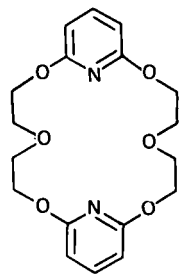


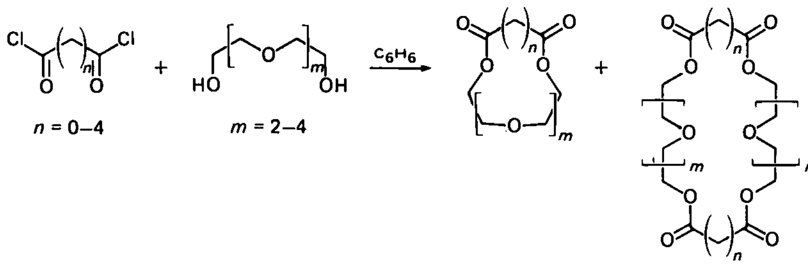
(163)

4. Systems fused to thiophene rings

Both thiophene-2,5- and -3,4-dimethylyl units have been incorporated[24,96,97,111] into crown compounds.

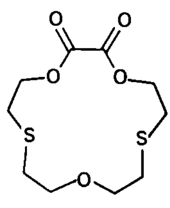
C. Macrocyclic Diester, Dithioester and Diamide Compounds

Macrocyclic diesters have been synthesized by condensation of α,ω-diacid dichlorides and polyethyleneglycols in benzene using high-dilution techniques. Using this simple procedure without the addition of any base, macrocycles containing between 4 and 6 ether oxygen atoms and incorporating 1 or 2 residues derived from oxalic[114], malonic[115–118], succinic[116,117,119], glutaric[114,117] and adipic[117] acids have been prepared in good yields according to equation (33). Several



(33)

methyl-, phenyl- and perfluoro-substituted diester crown compounds have also been reported[117] as well as macrocycles incorporating fumaric[117] and maleic[119] acids. The syntheses of several macrocyclic thia polyether diesters[114,116], e.g. **164**, aza polyether diesters[119] e.g. **165**, polyether dithioesters[114,116] e.g. **166** and thia polyether dithioesters[114] e.g. **167** derived from oxalyl, malonyl, succinyl and



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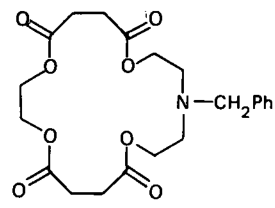

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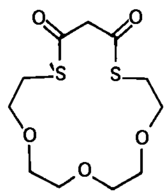

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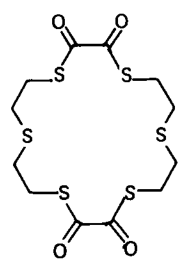
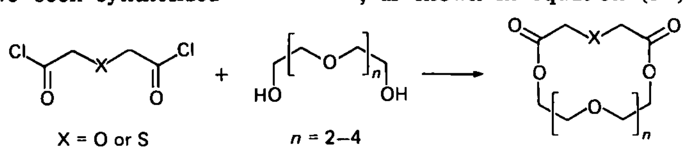


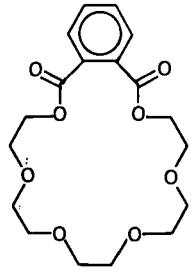
(167)

glutaryl dichlorides have also been described. In addition, a series of macrocyclic diesters have been synthesized[118,120,121], as shown in equation (34), by the

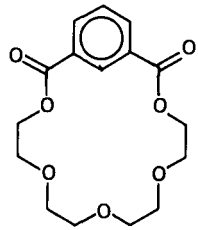


(34)

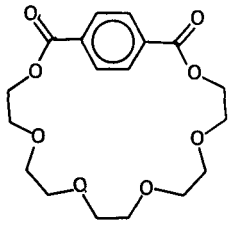
condensation of α,ω-diglycolic acid dichloride and α,ω-thiodiglycolic acid dichloride with various polyethyleneglycols. Macrocyclic diesters e.g. **168**–**171**, incorporating aromatic diacids have also been prepared[122,123]. In particular, 2,6- and 3,5-pyridine dicarboxylate residues have been introduced[123–125] into a variety



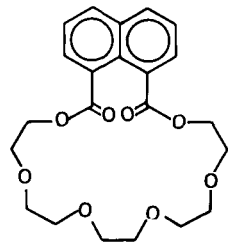
(168)



(169)

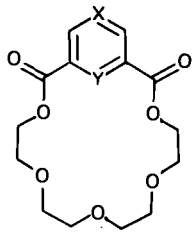


(170)



(171)

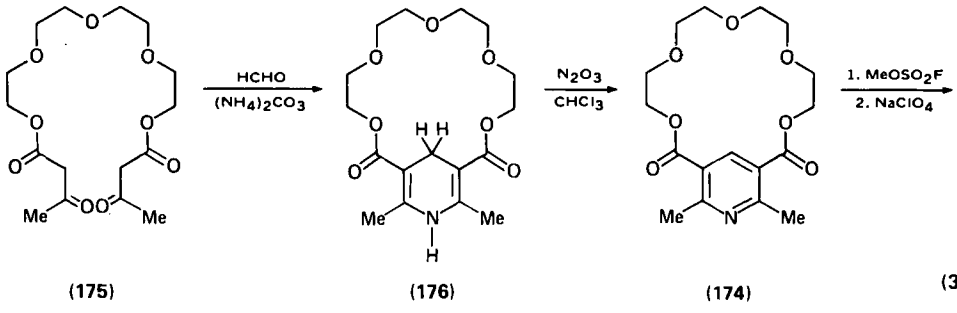
of macrocyclic compounds, e.g. **172** and **173**, by reaction of the diacid dichlorides derived from the pyridine dicarboxylates with polyethyleneglycols. In the case of **172**, a high yield (78%) was obtained from the reaction despite the absence of



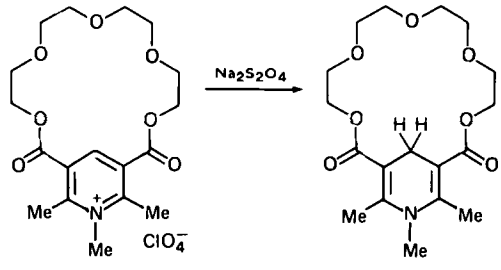
(172) X =CH; Y = N
(173) X = N; Y = CH

metal ions. It has been suggested[124] that the high yield could arise from protonation of the nitrogen atom by HCl and the consequent ability of the pyridinium ion to act as a template for ring-closure.

Several new crown ethers, e.g. **174**, containing the 3,5-di(alkoxycarbonyl)-pyridine ring system have been prepared[126] by an approach which is novel to crown ether synthesis. It relies upon a Hantzsch-type condensation of the α,ω-bis(acetoacetic ester) (**175**) of tetraethyleneglycol with HCHO and an excess of $(NH_4)_2CO_3$ in an aqueous medium followed by dehydrogenation of the intermediate 1,4-dihydropyridine derivative **176** as shown in equation (35). The macrocyclic and heterocyclic rings are thought to be generated simultaneously during the

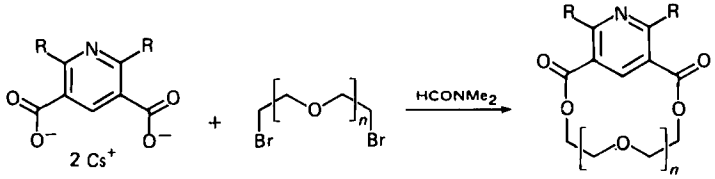


(175) (176) (174) (35)



(178) (177)

course of this reaction. The pyridyl derivative **174** by methylation affords the pyridinium salt **178** which in turn can be converted into the *N*-methylhydropyridine derivative **177** by reduction with $Na_2S_2O_4$. The potential of **177** as a model for NAD(P)H has been demonstrated[127] by its ability to transfer hydride readily to sulphonium salts. Attempts to extend this type of synthesis to systems other than **174** have met with only limited success and alternative procedures have been sought. Reaction of the dicesium salts of 3,5-pyridinedicarboxylic acid (**179**) (R = H or Me) with α,ω-polyethyleneglycol dibromides in $HCONMe_2$ gives (see equation 36) cyclic 3,5-di(alkoxycarbonyl)pydridine derivatives (**180**) (R = H or



(179) (180) (36)

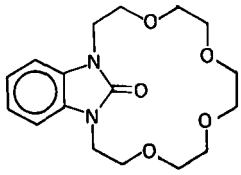
R = H or Me n = 2–5

Me) in yields of between 20 and 90% depending upon the chain length of the glycol. Cs^+ ions play a virtually irreplaceable role in the formation of **180** (R = H, n = 3) since the yield of macrocycle decreases drastically when Cs^+ ions are replaced by Rb^+, K^+ or Na^+ ions. It has been suggested that the Cs^+ ion acts as a template during the early stages of the reaction.

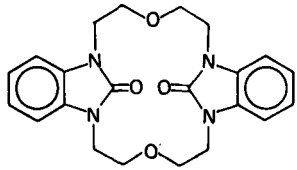
Several groups of investigators have prepared macrocyclic compounds incorporating the ubiquitous amide functional group. For example, macrocyclic peptides have been synthesized and investigated[128] for their cationic binding properties. In

addition, macrocyclic diamides prepared by the approaches outlined in Section IV.A.4 have served as important intermediates in the synthesis of macrobiocyclic diaza polyethers (see Section IV.G). The preparation of several macrocyclic diamides incorporating 2,6-disubstituted pyridine bridges have also been reported[98,111].

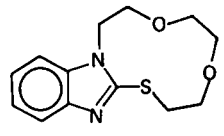
Benzimidazolone has been reacted[129] with α,ω-polyethyleneglycol dichlorides in $HCONMe_2$ in the presence of LiH or NaH to afford a series of novel monomeric and dimeric derivatives, e.g. **181** and **182**. Interestingly, benzimidazolethione



(181)



(182)



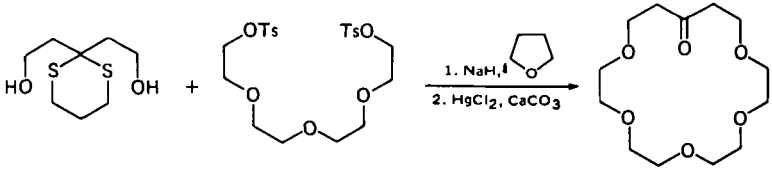
(183)

undergoes[129] alkylation firstly at sulphur and then at nitrogen to yield nitrogen–sulphur-bridged compounds, e.g. **183**. Quinoxaldione and 5-methyluracil have also been incorporated[129] into macrocyclic polyethers.

D. Crown Compounds Containing Carbonyl Groups

1. Oxocrown ethers

The carbonyl group has been introduced into crown ethers both as a direct replacement for an ether oxygen atom and as a formal insertion into an OCH_2CH_2O fragment. The oxo-18-crown-5 derivative **184** has been prepared[130] by base-promoted condensation of the dithiane **185** with tetraethyleneglycol ditosylate (**95**) followed by regeneration of the masked carbonyl group from the spiro intermediate as shown in equation (37). Reaction of tetraethyleneglycol (**16**)

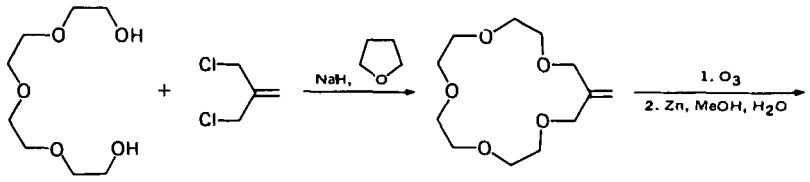


(185) (95) (184) (37)

with NaH and 1,1-bis(chloromethyl)ethylene (**186**) gave[131] the methylene-16-crown-5 derivative **187**, which, on ozonolysis and decomposition of the ozonide, afforded (see equation 38) the oxo-16-crown-5 derivative **188** in nearly quantitative yield. Oxocrown ethers promise to be valuable synthetic intermediates. The novel dioxodithia-18-crown-6 derivative **189** has been obtained[132] recently from reaction of 1,9-dichloroanthraquinone with the appropriate polyethyleneglycol dithiol.

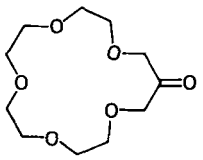
2. Crown ethers incorporating β-diketone residues

Since enolizable β-diketonates, such as acetylacetone, form stable complexes with both metal ions[133] and nonmetallic[134] elements, it is of interest to incorporate them into macrocyclic polyethers. Macrocyclic polyethers, e.g. **190**–

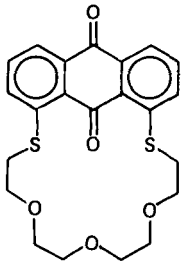


(16) (186) (187)

(38)

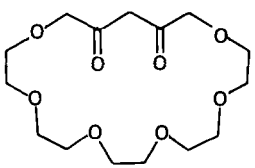


(188)

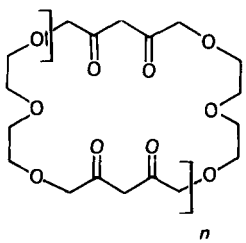


(189)

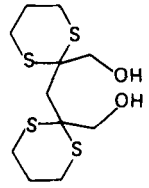
192, which contain 1,2 and 3 β-diketone units in the ring have been made[135] from reaction of the key starting material (193) with NaH and (*a*) pentaethyleneglycol ditosylate – to give the β-diketone **190** after regeneration of the carbonyl groups – or (*b*) diethyleneglycol ditosylate – to give a mixture of the bis(β-diketone) (**191**) and the tris(β-diketone) (**192**) after regeneration of the carbonyl groups. The templated syntheses of acyclic and cyclic acetylacetone derivatives have been investigated[136] as well. The macrocycle **194** was produced in 13% yield from the reaction of the magnesium salt – but not the calcium salt – of **195** with bis(bromomethyl)benzene (**20**) under similar reaction conditions (see equation 39). In addition, the disodium salt of **195** was noted to give only polymer when cyclization



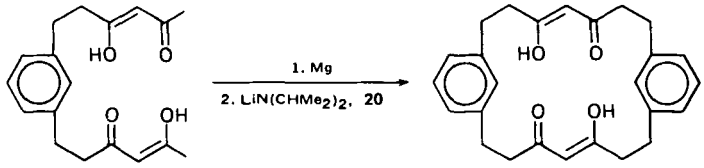
(190)



(191) $n = 1$
(192) $n = 2$



(193)



(195) (194) (39)

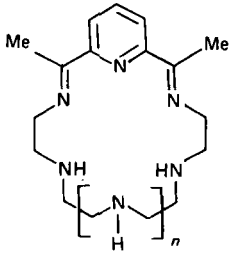
with the dibromide **20** was attempted. These experimental observations demonstrate that the cyclizations are templated selectively by metal ions.

E. Crown Compounds Incorporating Imine and Oxime Functions

1. Macrocycles from Schiff-base condensations

The Schiff-base condensation between a CO and an NH_2 group to form a C=N linkage forms the basis of many successful macrocyclic ligand syntheses. The use of alkaline earth and transition metal ions to control cyclizations and form *in situ* Schiff-base complexes is well established[137]. Two types of template effect have been recognized[13,66] in this area. According as to whether the metal ion lowers the free energy of (*a*) the transition state in an irreversible reaction or (*b*) the product in a reversible reaction, a 'kinetic' or 'thermodynamic' template effect is operative[138]. Although a 'kinetic' template effect clearly operates (see Section II.A) during the irreversible crown ether syntheses, many of the templated reactions involving the formation of imine functions probably rely upon[138] a 'thermodynamic' template effect.

The 2,6-diiminopyridyl moiety has enjoyed popular application in the *in situ* synthesis of metal complexes of both macrocyclic polyamines and aza polyethers. The isolation of crystalline iron (III) complexes of the pentadentate 15-membered ring (**196**) and hexadentate 18-membered ring (**197**) compounds after Schiff-base

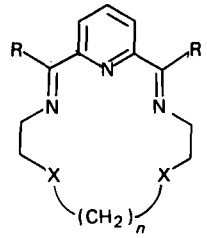


(196) $n = 0$
(197) $n = 1$

condensation of 2,6-diacetylpyridine with the appropriate polyamine in the presence or iron (II) salts has been reported[139]. Other investigators[140–142] have

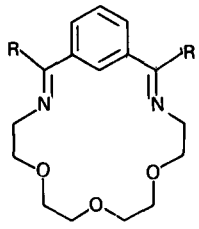
prepared similar types of complexes *in situ*. They have varied the nature of the coordinated metal ion, the size of the macrocycle and the nature (O, N and S) of the heteroatoms in the rings. In some instances, benzene rings have also been fused on to the macrocycle.

In view of the relatively high abundance of Mg^{2+} ions in Nature – and particularly their occurrence in chlorophylls – the effectiveness of Mg^{2+} as a templating ion in the synthesis of planar nitrogen-donor macrocyles is of considerable biological interest. The Mg^{2+} ion-templated syntheses of the macrocycles **198** and **199** and their isolation as hydrated $MgCl_2$ complexes has been reported[143]. More recently, the magnesium (II) complexes of the 2,6-diiminopyridyl polyethers **200** and **201** have been prepared[144]. A Group IV.B cation has been utilized[145] in the



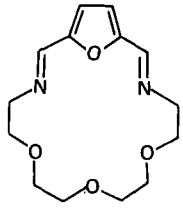
	R	X	*n*
(198)	Me	NH	2
(199)	Me	NH	3
(200)	Me	O	2
(201)	H	O	2

templated Schiff-base condensation of 2,6-pyridinedicarbonyl derivatives with α,ω-diamines and lead (II) thiocyanate complexes of the macrocyclic imino polyethers **202** and **203** have been isolated.

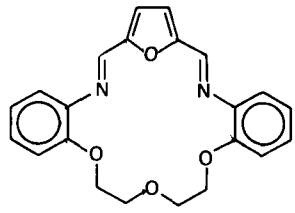


(202) R = H
(203) R = Me

Recently, the first reported syntheses of alkaline earth metal complexes of macrocycles containing 2,5-diiminofuranyl units have appeared[146] in the literature. Schiff-base condensation of furan-2,5-dicarboxaldehyde with the appropriate α,ω-diamino polyethers in the presence of either Ca, Sr of Ba thiocyanates as templates led to the isolation of the metal ion thiocyanate complexes of **204** and **205**.



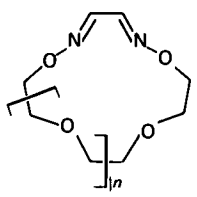
(204)



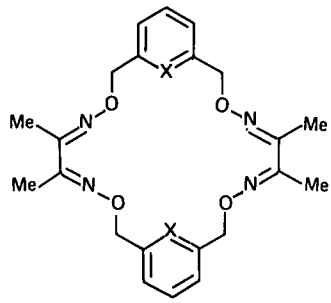
(205)

2. *Oxime linkages in macrocycles*

Oxime functions have recently been incorporated into multiheteromacrocyclic structures. The syntheses of the dioximes **206** and **207** and the tetraoximes **208** and **209** have been accomplished[147] by reaction of diacetyldioxime with either the

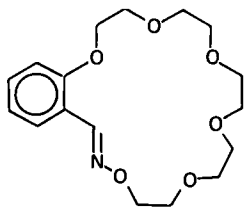


(206) $n = 1$
(207) $n = 2$



(208) X = N
(209) X = CH

appropriate polyethylene glycol ditosylate, 2,6-bis(bromomethyl)pyridine or 1,3-bis(bromomethyl)benzene in anhydrous $HCONMe_2$. In addition, the cyclic oxime **210** was prepared in ca. 28% yield from salicylaldoxime and pentaethyleneglycol dibromide. In all these macrocycles, the oxime linkage has the (*E*)-configuration. Novel multiheteromacrocycles, e.g. **211**, have been isolated[148] by polymerization



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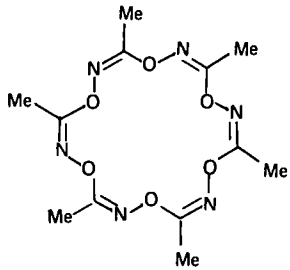


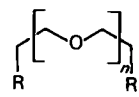
(211)

of acetonitrile oxide in the presence of nucleophilic catalysts. Several of the compounds, including **211**, form crystalline complexes with KSCN.

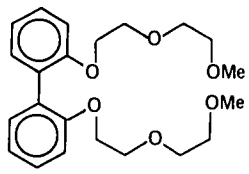
F. Acyclic Crown Compounds

The solvating power of polyethyleneglycol ethers (glymes) toward alkali metals and their salts was first recognized by Wilkinson and his collaborators[10] in 1959. They investigated the solubility of sodium and its potassium alloy in various glymes and observed that the intensities of the blue-coloured metal solutions increased with the number of oxygen atoms in the glyme. Since Pedersen's discovery[11,12] of cyclic crown compounds in 1967, there have been numerous reports of 'acyclic crown compounds'. We shall limit our brief discussion of these compounds to those examples where the $-OCH_2CH_2O-$ repeating unit is the predominant constitutional feature. For the most part, they have been synthesized by alkylations involving monoprotected polyethyleneglycol derivatives. The terminal residues in

these so-called 'octopus' molecules may be introduced in the form of the original blocking group or they may be inserted in the final step of the synthesis with the penultimate step involving the removal of a temporary protecting group. Examples (*a*) based on polyethylene glycol chains, e.g. **212–216**, (*b*) emanating from aromatic rings, e.g. **217–221** and (*c*) emanating from nitrogen atoms, e.g. **222–224**, have been reported[149] in the literature. The triethanolamine tripod ligands can be viewed as analogues of the diazamacrobicyclic polyethers (see Section IV.E).

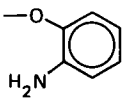


(212) R = OMe; *n* = 4
(213) R = $CONH_2$; *n* = 5
(214) R = CO_2Et; *n* = 5

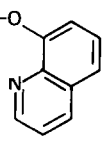


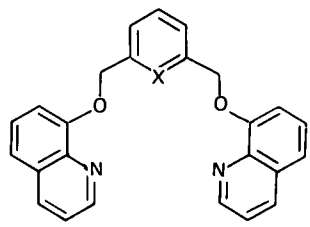
(217)

(215) R = —O— ; *n* = 5

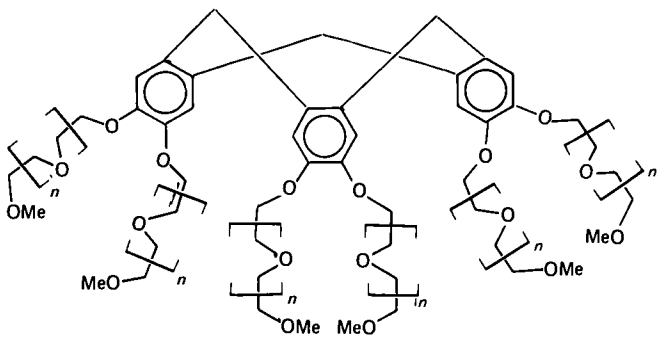


(216) R = —O— ; *n* = 3



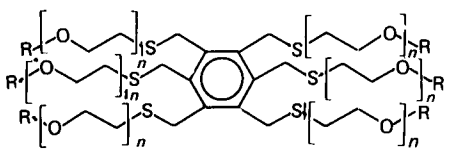


(218) X = COMe
(219) X = N

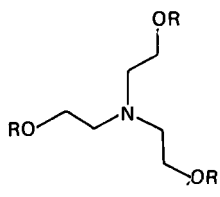


n = 3

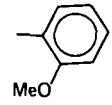
(220)

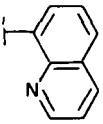


(221) R = $Me(CH_2)_3$; *n* = 2



(222) R = Me

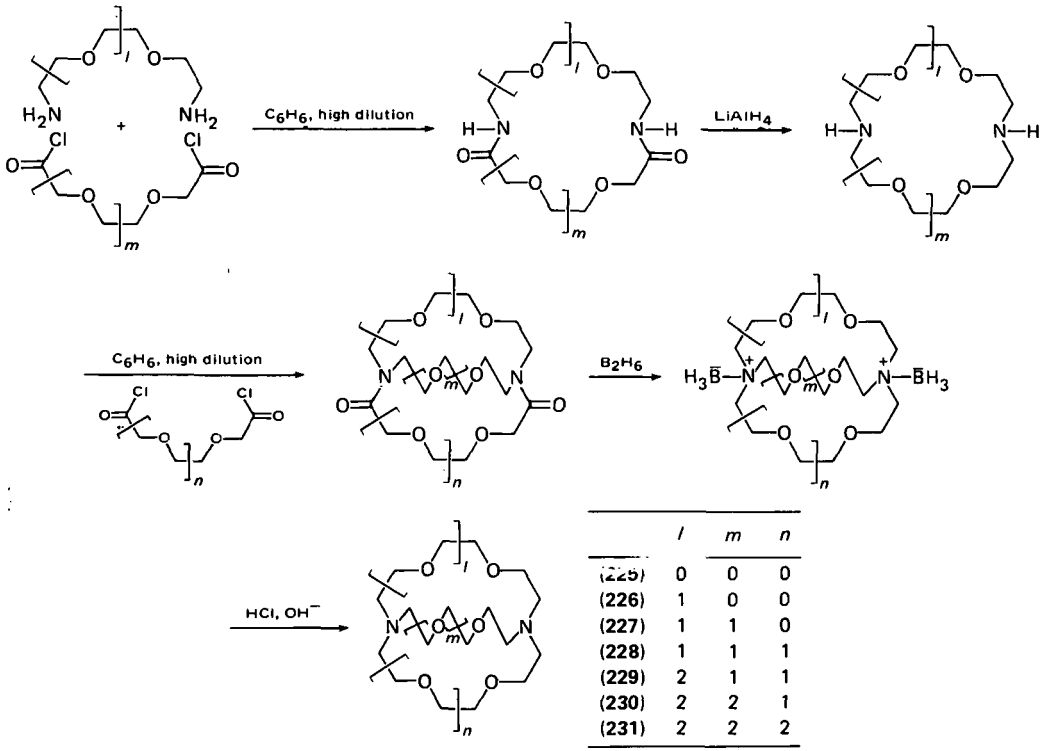
(223) R = 

(224) R = 

G. Macrobicyclic, Macrotricyclic and Macropolycyclic Ligands

1. Systems with nitrogen bridgeheads

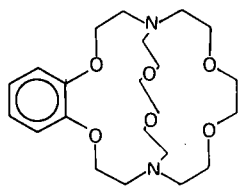
The inspired association by Lehn and his collaborators[48,50,51,150] of the synthetic accomplishments of Pedersen[6,11,12] on crown ethers and Simmons and Park[151] on macrobicyclic diamines led to the realization of diaza macrobicyclic polyethers in 1969. These ligands which can *encapsulate* metal cations in spherical holes usually form very strong complexes. A generalized scheme of reactions employed[150] in the synthesis of the macrobicyclic ligands 225–231 is portrayed in



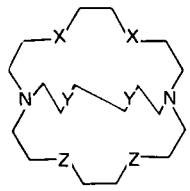
	l	*m*	*n*
(225)	0	0	0
(226)	1	0	0
(227)	1	1	0
(228)	1	1	1
(229)	2	1	1
(230)	2	2	1
(231)	2	2	2

SCHEME 3.

Scheme 3. Reaction of an α,ω-diamino polyether with an α,ω-diacid dichloride ($l = m$ or $l \neq m$) under high-dilution conditions (cf. Section IV.A.4) gives a macrocyclic diamide which can be reduced to the corresponding diamine. Condensation of this macrocycle with the same (i.e. $m = n$) or a different (i.e. $m \neq n$) α,ω-diacid dichloride under high-dilution conditions gives a bicyclic diamide which can be reduced with B_2H_6 to afford the corresponding bis(boraneamine). Acid-catalysed hydrolysis followed by passage of the bishydrochloride salts through an anion-exchange resin affords the diaza macrobicyclic polyethers. As part of an investigation into the factors that control the selectivity of macrobicyclic ligands toward binding of various metal ions, the Strasbourg group have synthesized compounds, e.g. 232–237, in which (*a*) *ortho*-disubstituted benzene rings have been incorporated[152] and (*b*) the ether oxygen atoms have been replaced progressively either

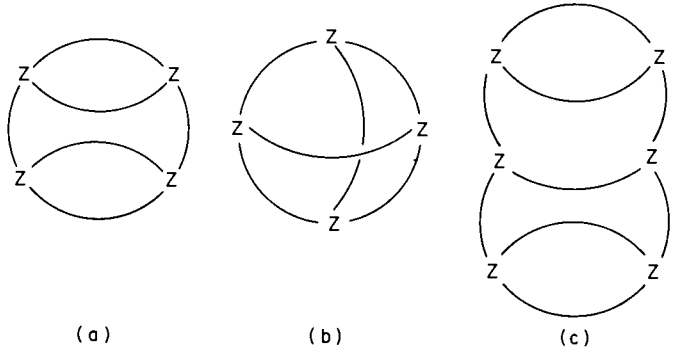


(232)



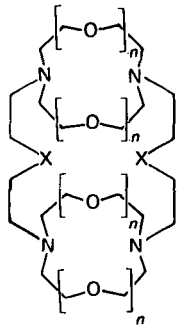
	X	Y	Z
(233)	NMe	O	O
(234)	NMe	NMe	O
(235)	S	O	O
(236)	S	S	O
(237)	S	S	S

by secondary and tertiary amine groups[153] or by sulphur atoms[86]. More recently, *meta*-xylyl, pyridyl, and 1,1′-bipyridyl residues have been introduced into the side-arms. Finally, macrobicyclic polyethers have also been covalently bound[155] to a polystyrene support. Macrotricyclic ligands can assume[48,50,51] at least two types of topology – identified by (a) and (b) in Figure 2 – which are distinct. Type (a) ligands may be considered to be cylindrical and are formed when two monocycles are linked by two bridges. A synthetic approach – involving the established routine of sequential condensations and reductions – which allows[154,156] construction of cylindrical macrotricyclic ligands, e.g. 238–242, with the same or different sizes of monocycles and the same or different lengths of bridges between them is based upon the following three-stage strategy: (*a*) the synthesis of a monocyclic diaza crown ether which is then monoprotected at nitrogen before (*b*) forming a bis-(monocyclic) crown ether and removing the protecting groups on the nitrogens and

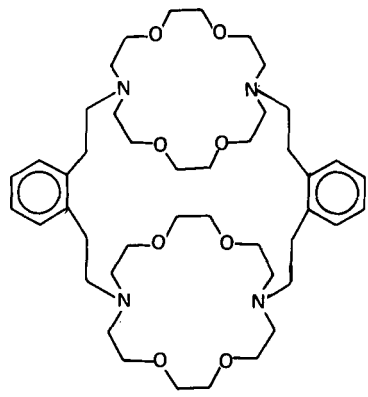


(a) (b) (c)

FIGURE 2. Topological representations of (a) cylindrical macrotricyclic, (b) spheroidal macrotricyclic, and (c) cylindrical macrotetracyclic ligands.

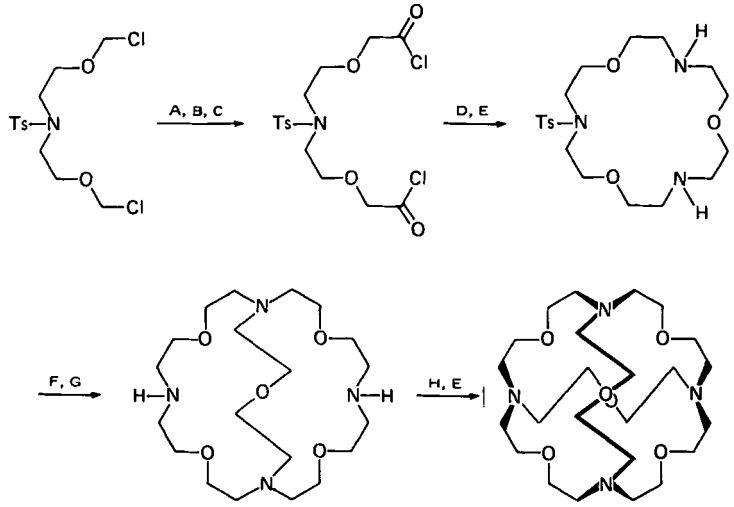


(238) X = O; n = 1
(239) X = O; n = 2
(240) X = NH; n = 2
(241) X = CH_2; n = 2



(242)

(*c*) inserting the second bridge to afford the macrotricyclic ligand. If the bridging units are chosen to incorporate nitrogen atoms, then a third bridge can be introduced[156] to give a macrotetracyclic ligand with the topology represented under type (c) in Figure 2. Returning to macrotricyclic ligands, the spheroidal topology belonging to type (b) in Figure 2 has also been realized[157] (see Scheme 4) in the



(243)

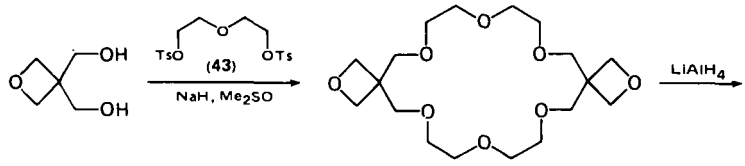
Reagents A: NaCN, $HCONMe_2$; B: $Ba(OH)_2$, H_2O then HCl; C: $(COCl)_2$, C_6H_6; D: $H_2NCH_2CH_2OCH_2CH_2NH_2$, C_6H_6; E: B_2H_6; F: $TsN(CH_2CH_2OCH_2COCl)_2$, C_6H_6; G: $LiAlH_4$; H: $ClCOCH_2OCH_2COCl$, C_6H_6

SCHEME 4.

shape of **243** with four identical faces. The use of the protected tosylamides is the key to this elegant synthesis conceived and accomplished by Graf and Lehn[157].

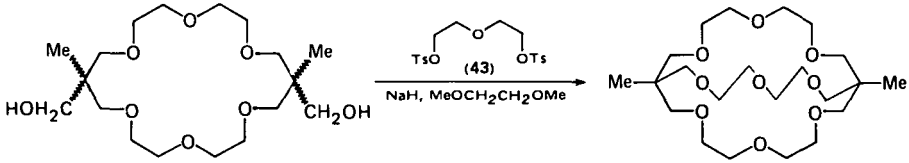
2. *Systems with carbon bridgeheads*

In principle, any atom of valency three or higher can occupy the bridgehead positions. Macrobicyclic polyethers with bridgehead carbon atoms have been synthesized[158] in a number of different ways from diethyleneglycol ditosylate (**43**) and either pentaerythritol or 1,1,1-tris(hydroxymethyl)ethane. For example, pentaerythritol can be converted[158] into the oxetanediol **244** by known reaction procedures. Reaction of **244** with NaH and **43** in Me_2SO afforded the dispiro-20-crown-6 derivative[159] (**245**) as shown in equation (40). The diastereoisomeric diols **246**, obtained on reductive ring-opening of the oxetane rings in **245**, gave the macrobicyclic polyether **247** on reaction with NaH and **43** in $MeOCH_2CH_2OMe$.



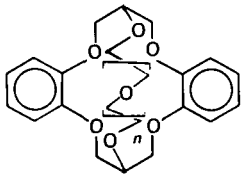
(244) (245)

(40)



(246) (247)

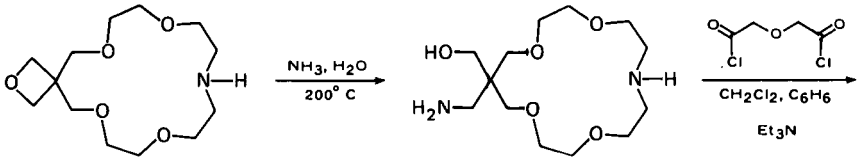
This ligand forms extemely weak complexes with alkali metal cations! More recently, 1,3-dichloropropan-2-ol has been employed[160] as the source of bridgehead carbon atoms in a four-step synthesis of the macrobicyclic polyethers **248** and **249**. These derivatives of glycerol preserve the –O–C–C–O– unit throughout their constitution and hence it is not surprising that they bind Group IA metal cations strongly.



(**248**) $n = 2$
(**249**) $n = 3$

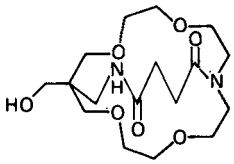
3. *A system with nitrogen and carbon bridgeheads*

A novel macrobicyclic polyether diamide (**250**) containing both nitrogen and carbon bridgehead atoms has been prepared[161] from the spiro compound **251** by opening of the oxetane ring with NH_3 to give the amino alcohol **252** which was then condensed with diglycolyl dichloride as shown in equation (41).



(251) (252)

(41)

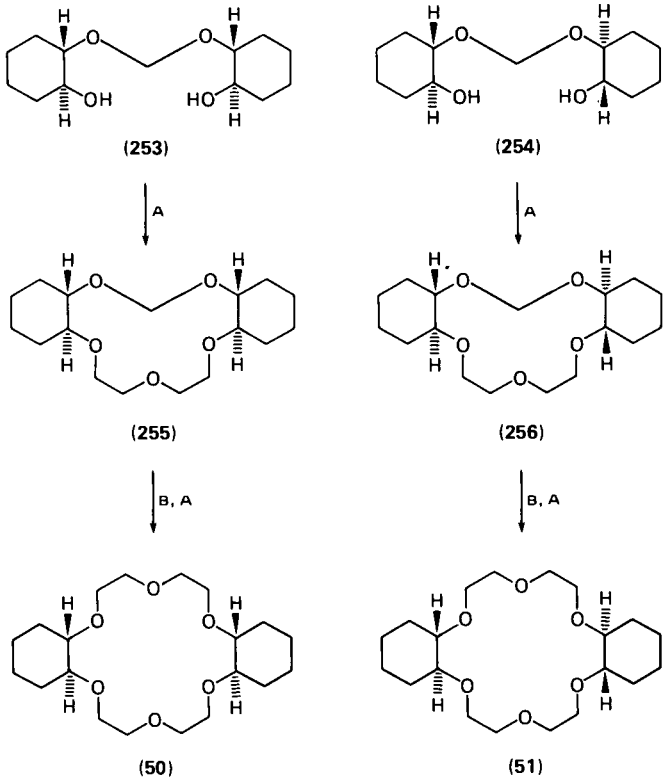


(250)

H. Chiral Crown Ethers

1. Meso *compounds and racemic modifications*

Four, namely **48**–**51**, of the five possible configurational diastereoisomers of dicyclohexano-18-crown-6 are known. The two di-*cis* isomers **48** and **49** and the *trans–cisoid–trans* isomer (**50**) are *meso* compounds; the *trans–transoid–trans* isomer (**51**) belongs to a chiral point group (D_2) and so can be obtained optically active or as a racemic modification. Pedersen[12,162,163] isolated two crystalline isomers of dicyclohexano-18-crown-6 after hydrogenation of dibenzo-18-crown-6 (**10**) over a ruthenium on alumina catalyst followed by chromatographic separation on alumina[42,163,164]. They were designated[42,163,164] as Isomer A (m.p. 61–62°C) and Isomer B (m.p. 69–70°C). After a period of some confusion in the literature (cf. Reference 43), Isomer A was identified as the *cis–cisoid–cis* isomer (**48**) on the basis of an X-ray crystal structure analysis[165] of its barium thiocyanate complex. Similarly, an X-ray crystal structure determination of the sodium bromide dihydrate complex of Isomer B established[166] that it is the *cis–transoid–cis* isomer (**49**). More recently, X-ray crystallographic data on the uncomplexed ligand has confirmed that Isomer A is the *cis–cisoid–cis* isomer (**48**). Isomer B exists[164] in a second crystalline form, Isomer B′, with m.p. 83–84°C. In solution, the two forms are identical. A ready separation of Isomer B′ from Isomer A takes[168] advantage of the large differences in solubility in water between the lead and oxonium perchlorate complexes of the two isomers. X-ray crystallography has revealed[167] that Isomer B′ like Isomer B has the *cis–transoid–cis* configuration. Whilst it is generally believed[164] that Isomers B and B′ in the crystalline states are polymorphs, it is possible (cf. Reference 43) that they are conformational isomers differing in the relative conformations of the cyclohexane rings fused to the 18-membered ring. The stereospecific synthesis of the *trans–cisoid–trans* (**50**) and *trans–transoid–trans* (**51**) isomers from the methylenedioxydicyclohexanols[169] has been achieved[43,170]. Scheme 5 illustrates the synthetic route employed. Treatment of **253** and **254** in turn with diethyleneglycol ditosylate (**43**) under basic conditions gave the cyclic acetals **255** and **256**, respectively. Acid-catalysed hydrolysis afforded diols, which following further base-promoted condensations with **43** gave the two di-*trans* isomers **50** and **51** stereospecifically. A one-step synthesis

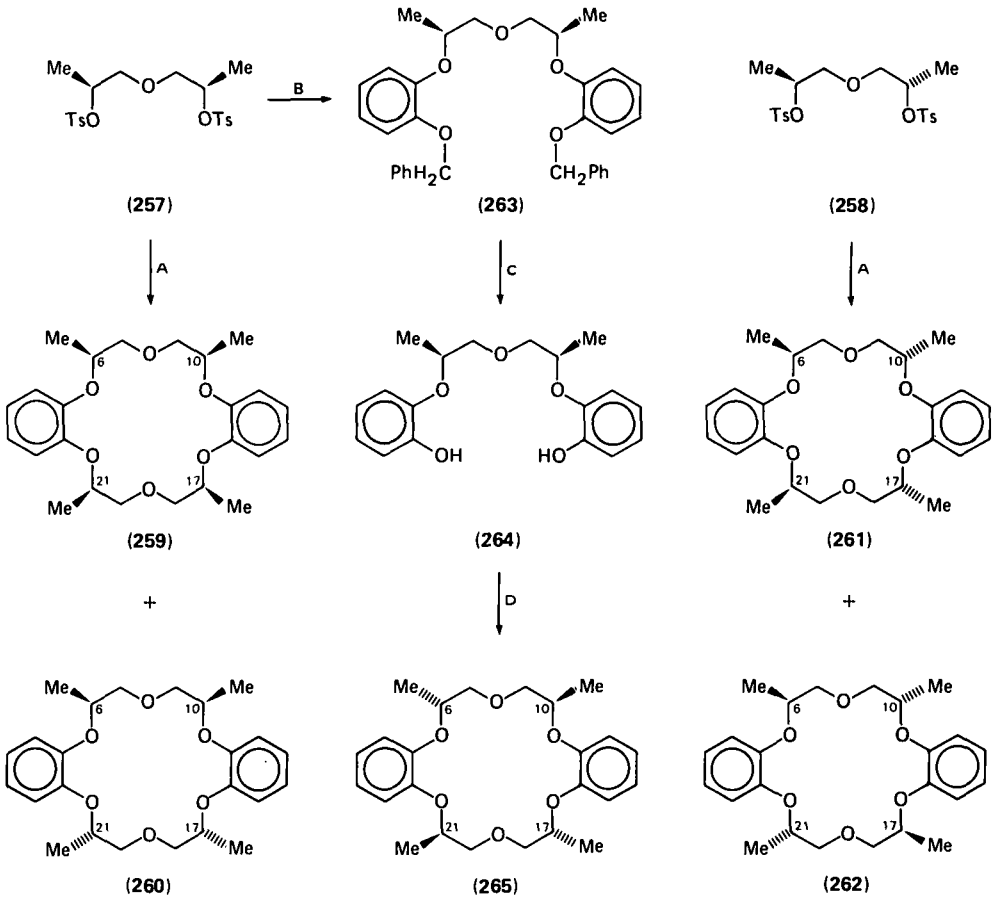


Reagents A: $TsOCH_2CH_2OCH_2CH_2OTs$, NaH, $Me_2SO/(MeOCH_2)_2$; B: H^+/H_2O

SCHEME 5.

of **50** and **51** from (±)-cyclohexane-*trans*-1,2-diol was accompanied by the formation of some (±)-*trans*-cyclohexano-9-crown-3.

The formal location of four constitutionally equivalent chiral centres at either $C_{(6)}$, $C_{(10)}$, $C_{(17)}$ and $C_{(21)}$, or $C_{(7)}$, $C_{(9)}$, $C_{(18)}$, and $C_{(20)}$ on the macrocyclic framework of dibenzo-18-crown-6 (**10**) generates five possible diastereoisomers in each series. The synthesis and separation of all ten configurational isomers of the constitutionally symmetrical tetramethyldibenzo-18-crown-6 derivatives have been described[171]. On the basis of stereochemically-controlled reactions and X-ray crystal structure analyses relative configurations have been assigned[171,172] to four of them. Scheme 6 outlines the preparation of the five diastereoisomers of the 6,10,17,21-tetramethyl derivative. A mixture of *meso*- and (±)-1,1′-oxydipropan-2-ol was prepared by reacting propylene oxide with (±)-propan-1,2-diol. The *meso*-isomer can be fractionally crystallized from the (±)-isomer. Tosylation of both the *meso*- and (±)-diols in turn afforded the *meso*-**257** and (±)-**258** ditosylates. Base-promoted condensation of **257** with catechol (**9**) gave a mixture of diastereoisomers **259** and **260**, which were separated by fractional crystallization. Similarly, reaction of the racemic ditosylate **258** with catechol (**9**) under basic conditions led



Reagents A: *o*-$C_6H_4(OH)_2$ (**9**), NaOH, $Me(CH_2)_3OH$; B: *o*-$PhCH_2OC_6H_4OH$, NaOH, $Me(CH_2)_3OH$; C: H_2, Pd; D: **258**, NaOH, $Me(CH_2)_3OH$

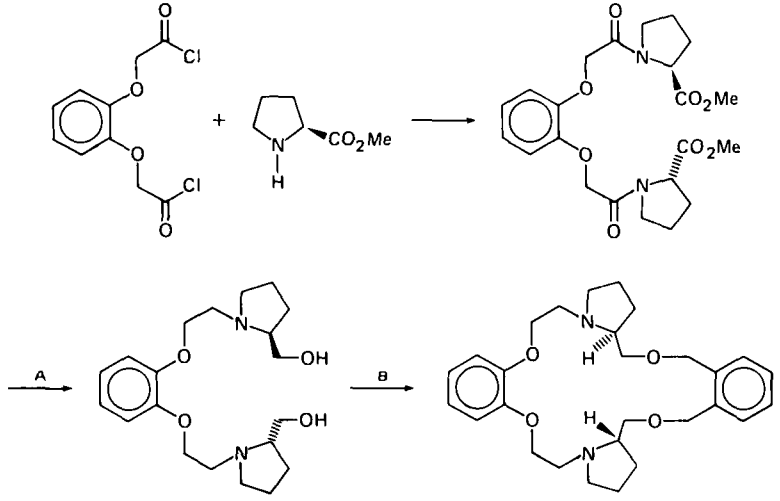
SCHEME 6.

to the isolation of a pair of diastereoisomers **261** and **262** which were separated by solvent extraction. The final diastereoisomer (**265**) was obtained by a three-stage procedure. The monobenzyl ether of catechol was condensed with **257** to give the dibenzyl ether **263**. After removal of the protecting groups to afford the diol **264** condensation with **258** led to ring-closure and isolation of **265**. The configuration of **265** follows from its mode of synthesis. The relative configurations of **259** and **260**, and **261** and **262**, have not been determined.

Catalytic hydrogenation of macrocyclic polyethers containing furan residues has led[107,173] in most cases to mixtures of diastereoisomers which have not been separated.

2. *Optically-active crown ethers from natural products*

The first crowns incorporating optically-active residues were described by Wüdl and Gaeta[174] in 1972. L-Proline was introduced into the macrocyclic diaza polyether LL-**266** by the procedure outlined in Scheme 7. D-ψ-Ephedrine was

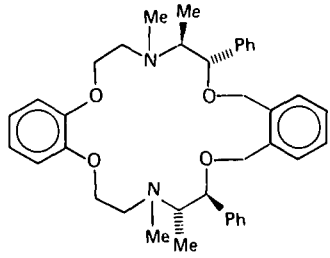


(LL-**266**)

Reagents A: $LiAlH_4$ B: o-$C_6H_4(CH_2Br)_2$ (**32**), NaOH, Me_2SO

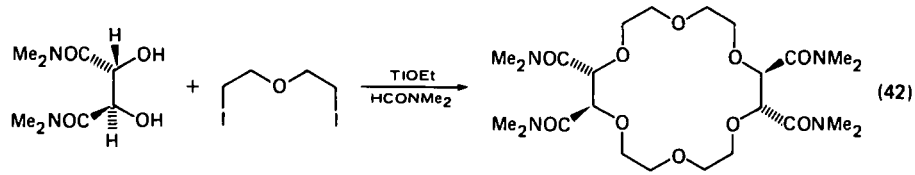
SCHEME 7.

incorporated into DD-**267** by a similar approach. In principle, a whole range of natural products including alkaloids, amino acids, carbohydrates, steroids and terpenes can be viewed[56] as chiral precursors. In practice, carbohydrates lend[31]



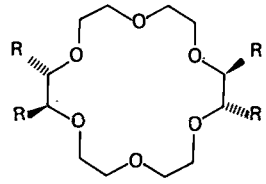
(DD-**267**)

themselves to the most detailed exploitation. For example, treatment of the bis(*N,N'*-dimethylamide) (L-**268**) of L-tartaric acid with two equivalents of thallium (I) ethoxide in anhydrous $OHCNMe_2$, followed by an excess of diethyleneglycol diiodide (**269**) in a modification[175] of the Williamson ether synthesis, afforded[176] (see equation 42) the tetracarboxamide 18-crown-6 derivative LL-**270**. This compound can be hydrolysed to the tetracarboxylate which can be converted into the tetraacid chloride, a key compound[177] in the preparation of derivatives with a

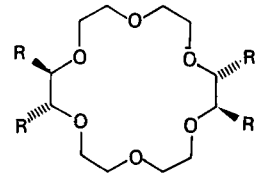


(L-268) (269) (LL-270) (42)

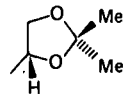
whole range of side-chains where the functionality has catalytic potential. The synthesis of LL-270 illustrates the attractions of employing chiral sources with C_2 symmetry. *Two* such residues are incorporated into *one* macrocycle which has D_2 symmetry. The same principle was relied upon in the synthesis of chiral 18-crown-6 derivatives, e.g. LL-271, LL-272, DD-273 and DD-274, incorporating L-threitol[178],

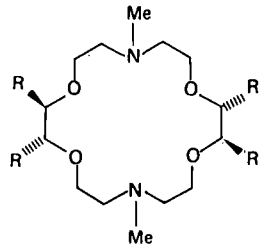


(LL-271) R = CH_2OH

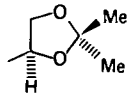


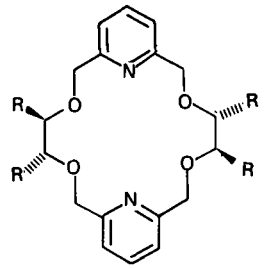
(LL-272) R =



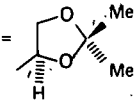


(DD-273) R =

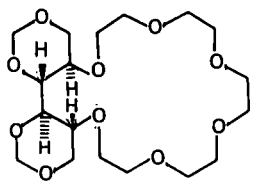




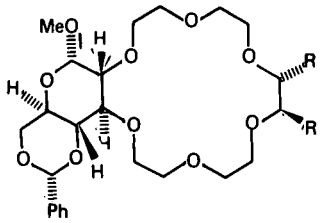
(DD-274) R =



L-iditol[179], and D-mannitol[178,180], all of which have C_2 symmetry. The key diols employed in these preparations were 1,4-di-*O*-benzyl-L-threitol and the 1,2:5,6-di-*O*-isopropylidene derivatives of L-iditol and D-mannitol. More recently, 1,3:4,6-di-*O*-methylene-D-mannitol has been incorporated[181] into a 20-crown-6 derivative D-275. Chiral asymmetric 18-crown-6 derivatives, e.g. D-276 and DD-277 have also been synthesized with D-glucose[182], D-galactose[182], D-mannose[183], and D-altrose[183] as the sources of asymmetry. In these cases, chain-extensions to give 'half-crown' diols through the sequence[47] of reactions, (*a*) allylation, (*b*) ozonolysis and (*c*) reduction, on the 4,6-*O*-benzylidene derivatives of methyl glycosides proved invaluable. Although only one compound results from condensations involving two chiral precursors, one with C_1 and the other with C_2 symmetry, two constitutional isomers, e.g. DD-278 and DD-279 result[184,185] when two asymmetric residues are incorporated into an 18-crown-6 derivative.

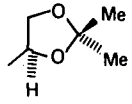


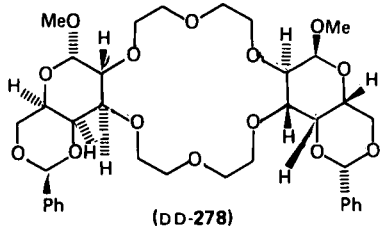
(D-275)



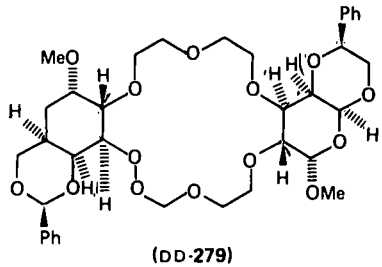
(D-276) R = H

(DD-277) R =



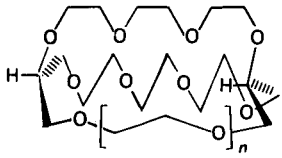


(DD-278)



(DD-279)

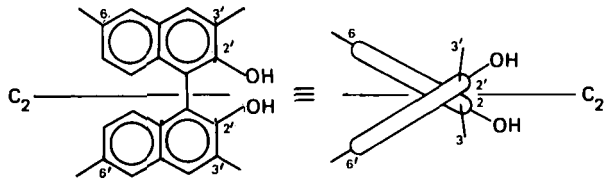
Finally, 2,3-*O*-isopropylidene-D-glycerol has been utilized[186] in an elegant synthesis of the chiral macrobicyclic polyethers DD-280 and DD-281. One of the novelties of the preparative route is that it affords a stereospecific synthesis of *in–out* isomers of bicyclic systems.



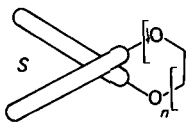
(DD-280) $n = 2$
(DD-281) $n = 3$

3. Optically active crown ethers from resolved precursors

The syntheses of (+)-(*SSSS*)-*trans–transoid–trans*-dicyclohexano-18-crown-6 as well as (+)-(*SS*)-*trans*-cyclohexano-15-crown-5 and (+)-(*SS*)-*trans*-cyclohexano-18-crown-6 have been reported[47] starting from optically pure (+)-(1*S*,2*S*)-cyclohexane-*trans*-1,2-diol resolved via the strychnine salts of the hemisulphate diester. However, it is the 1,1′-binaphthyl residue with axial chirality which has been utilized so elegantly by Cram and his associates[52–55,106,187–189] that has found its way into a whole host of optically active crown ethers! 2,2′-Dihydroxy-1,1′-binaphthyl is the key starting material in the syntheses. The fact that this diol is easily accessible from 2-naphthol and can then be resolved readily through either its monomenthoxyacetic ester or through the cinchonine salt of its phosphate ester to give, for example, (−)-(*S*)-**282** with C_2 symmetry accounts for its unique status. A range of macrocycles incorporating one, e.g. (+)-(*S*)-**283** to (−)-(*S*)-**287**, two, e.g.

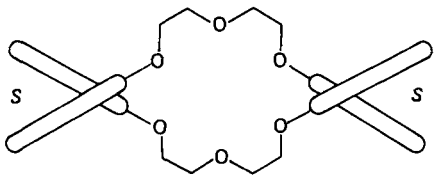


[(−)-(*S*)-**282**]

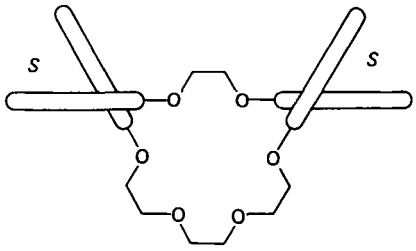


	n	Yield (%)
(+)-(*S*)-**283**	1	23
(+)-(*S*)-**284**	2	2
(−)-(*S*)-**285**	2	65
(−)-(*S*)-**286**	4	52
(−)-(*S*)-**287**	5	64

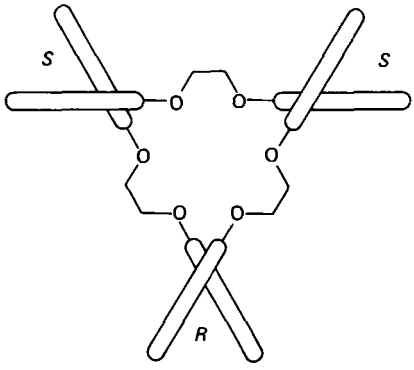
(−)-(*SS*)-**288** and (−)-(*SS*)-**289**, and three, e.g. (−)-(*RSS*)-**290**, binaphthyl moieties have been synthesized by reactions involving base-promoted substitutions on RCl,



[(−)-(*SS*)-**288**]

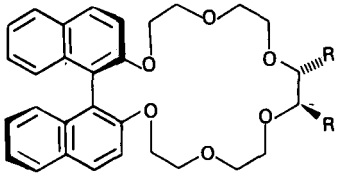


[(−)-(*SS*)-**289**]

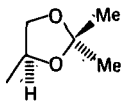


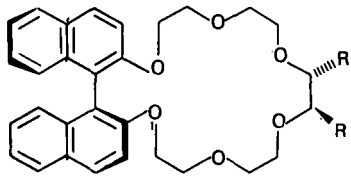
[(−)-(*RSS*)-**290**]

RBr or ROTs. Substituents, some containing functional groups have been incorporated at positions 3, 3′, 6, and 6′, and other residues and heteroatoms have been built into the macrocyclic ring. 'Resolution' of the 1,1′-binaphthyl unit has also been achieved[190] by employing (*RS*)-binaphthol, (*RS*)-**282**, and 1,2:5,6-di-*O*-isopropylidene-D-mannitol in the syntheses of the diastereoisomeric macrocyclic

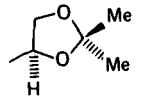


[(*R*)-D-291] R =

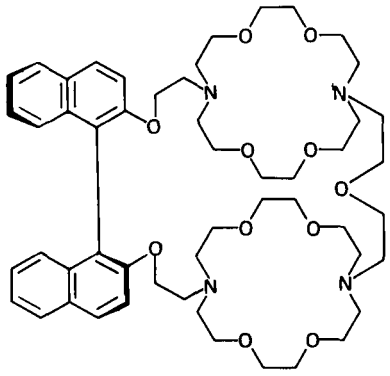




[(*S*)-D-292] R =



polyethers (*R*)-D-291 and (*S*)-D-292. Finally, it should be mentioned that (*S*)-282 has been incorporated[191] into the chiral macropolycyclic ligand (*S*)-293.



[(*S*)-293]

V. TOXICITY AND HAZARDS

Despite the large number of crown compounds synthesized during the past decade, comparatively little information is available in the open literature relating to their physiological properties. In his early papers, Pedersen[6,12,163] reported that dicyclohexano-18-crown-6 is toxic towards rats. The lethal dose for ingestion of this crown ether was found to be approximately 300 mg/kg of body weight. In ten-day subacute oral tests, the compound did not exhibit any cumulative toxicity when administered to male rats at a dose level of 60 mg/kg/day. Dicyclohexano-18-crown-6 was also found to be a skin irritant and generalized corneal injury, some iritic injury and conjunctivitis occurred when it was introduced into the eyes of rats as a 10% solution in propyleneglycol. Leong and his associates[192] have published toxicological data for 12-crown-4 (4) and other simple crown ethers. Rats exposed to 4 at concentrations between 1·2 and 63·8 p.p.m. in air suffered loss of body weight. They also developed anorexia, asthenia, hindquarter incoordination, testicular atrophy, auditory hypersensitivity, tremors, convulsions and moribund conditions. Oral adminstration of 4 to rats in a single dose of 100 mg/kg of body weight produces effects upon the central nervous system in addition to causing testicular atrophy. Acute oral toxicity investigations on 15-crown-5 (19), 18-crown-6 (12) and 21-crown-7 (54) revealed that these compounds also produce effects upon the central nervous system of rats although higher dosages were needed than those required with 4. It is clear that crown ethers should be handled with caution and respect!

There has been a report[193] of an explosion during one particular experimental manipulation[19] to obtain pure 18-crown-6 (12) from a reaction mixture. In one step of the isolation procedure, it is necessary to decompose thermally under reduced pressure the 18-crown-6-KCl complex formed during the reaction. However, at the temperatures of 100–200°C necessary to decompose the complex, decomposition may occur at the distillation head with the production of 1,4-dioxane. Breaking of the vacuum at >100°C can lead to autoignition of air–1,4-dioxane mixtures and hence explosions. Experimental procedures have been suggested[194] to reduce the risk of these as a result of distilling 18-crown-6 (12) from its KCl complex at high temperatures. Constant vigilence is essential!

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Crown Ethers and Analogs
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CHAPTER **2**

Organic transformations mediated by macrocyclic multidentate ligands

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I.	INTRODUCTION	59
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I. INTRODUCTION

With the advent of crown ethers and related macrocyclic and macrobicyclic multidentate compounds[1-4], simple and efficient means have become available for solubilizing metal salts in nonpolar and dipolar organic solvents where solvation of the anionic portion of the salt should be minimal[1,5-8]. Anions, unencumbered by strong solvation forces, should prove to be potent nucleophiles and potent bases and should provide the basis for the development of new and valuable reagents for organic synthesis. These weakly solvated anionic species have been termed naked anions[5-7].

Figure 1 illustrates the structures and names of some synthetically useful crowns. The estimated cavity diameters of the crowns and the ionic diameters of some alkali metal ions are also included[6]. It is apparent that the potassium ion has an ionic diameter which will enable it to fit inside the cavity of 18-crown-6 while the sodium ion and the lithium ion have ionic dimensions which are compatible with 15-crown-5 and 12-crown-4, respectively. While this specificity has been experimentally demonstrated, it must be emphasized that 18-crown-6 will also complex sodium and caesium ions. In the application of crowns to organic transformations, exact correspondence between cavity diameter and ionic diameter is not always a critical factor.

The following four points will be addressed at this juncture:

(1) The effect of a given crown in solubilizing metal salts (with a common cation) in nonpolar and dipolar aprotic media.
(2) The effect of various crowns in solubilizing a particular metal salt.

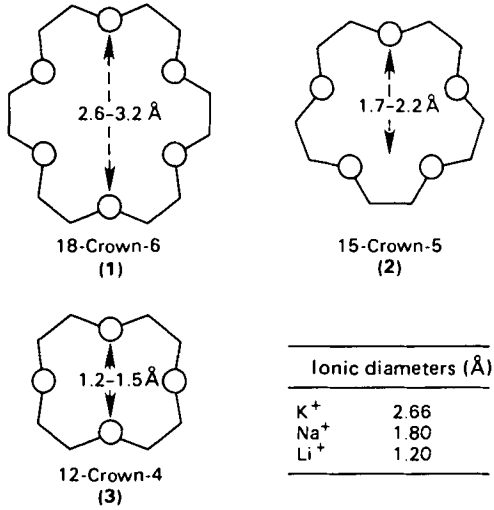


FIGURE 1.

(3) The reactivity of anions solubilized as their metal salts by crowns.
(4) The reactivity of a particular anion solubilized as its metal salt by a variety of macrocyclic and macrobicyclic ligands.

Table 1 summarizes the solubilities of a wide variety of potassium salts in acetonitrile at 25°C in the presence and in the absence of 18-crown-6 (0.15M)[6]. The concentrations of potassium ion were determined using flame photometric techniques. Excellent solubility enhancements are achieved for all salts except for potassium chloride and potassium fluoride whose crystal lattice free energies are quite high. The concentration of potassium acetate in acetonitrile-d_3 and benzene has been determined from ^{1}H-NMR analysis as a function of 18-crown-6 concentration (Table 2)[9]. At least 80% of the crown was complexed with the potassium acetate. The solubility of potassium fluoride in acetonitrile has also been determined at various crown concentrations (Table 3) using flame photometry[5].

TABLE 1. Solubilities of potassium salts (M) in acetonitrile at 25°C in the presence and absence of 18-crown-6

Potassium salt	Sol. in 0.15M crown in acetonitrile	Sol. in acetonitrile	Solubility enhancement
KF	4.3×10^{-3}	3.18×10^{-4}	0.004
KCl	5.55×10^{-2}	2.43×10^{-4}	0.055
KBr	1.35×10^{-1}	2.08×10^{-3}	0.133
KI	2.02×10^{-1}	1.05×10^{-1}	0.097
KCN	1.29×10^{-1}	1.19×10^{-3}	0.128
KOAc	1.02×10^{-1}	5.00×10^{-5}	0.102
KN_3	1.38×10^{-1}	2.41×10^{-3}	0.136
KSCN	8.50×10^{-1}	7.55×10^{-1}	0.095

TABLE 2. Solubility of potassium acetate in solvents containing 18-crown-6

	18-Crown-6 (M)	Potassium acetate (M)
Benzene	0.55	0.4
	1.0	0.8
Acetonitrile-d_3	0.14	0.1

TABLE 3. Concentration of potassium fluoride at various crown concentrations at 25°C by flame photometry

	KF concentration (M)
1.01M 18-Crown-6-benzene	5.2×10^{-2}
0.34M 18-Crown-6-benzene	1.4×10^{-2}
0.16M 18-Crown-6-CH_3CN	3.5×10^{-3}

The solubility of potassium acetate in the presence of a variety of macrocyclic and macrobicyclic multidentate ligands has been reported. The following order of solubilization effectiveness was found[10]:

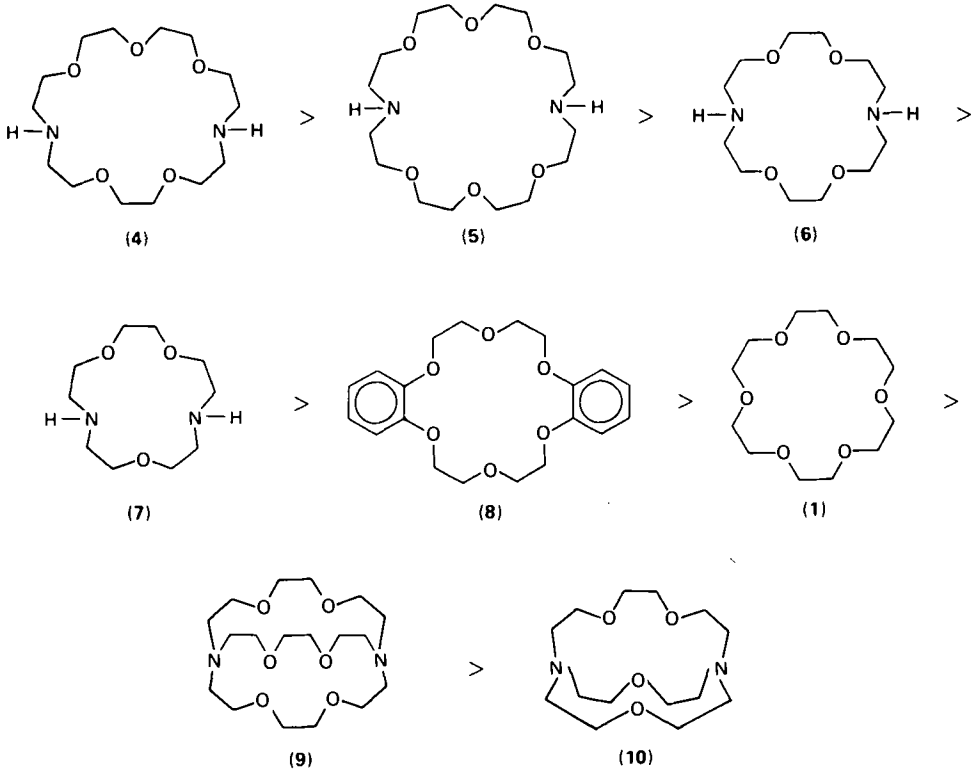


TABLE 4. Relative nucleophilicities of naked anions

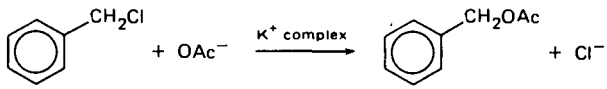
	Acetonitrile				Benzene		
Nucleophile	k_{PhCH_2OTs} ($M^{-1}s^{-1}$)	Rel. rates	$k_{n\text{-}C_5H_{11}Br}$ ($M^{-1}s^{-1}$)	Rel. rates	$k_{n\text{-}C_5H_{11}Br}$ ($M^{-1}s^{-1}$)	Rel. rates	Rel. rates in protic media
N_3^-	1.02	10.0	4.90×10^{-3}	7.5	1.04×10^{-4}	7.5	100
$CH_3CO_2^-$	0.95	9.6	1.66×10^{-3}	2.5	5.10×10^{-5}	3.7	5
CN^-	0.23	2.4	3.58×10^{-3}	5.5	3.12×10^{-5}	2.2	1250
Br^-	0.12	1.3	–	–	–	–	80
Cl^-	0.12	1.3	–	–	–	–	10
I^-	0.09	1.0	6.52×10^{-4}	1.0	1.39×10^{-5}	1.0	1000
F^-	0.14	1.4	–	–	–	–	1
SCN^-	0.02	0.3	3.28×10^{-5}	0.05	1.06×10^{-5}	0.76	625

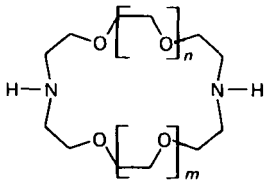
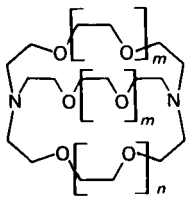
Arguments based upon cavity diameter, lipophilicity and rigidity of the macrocycle or macrobicycle were advanced to explain the observed order.

Studies related to the relative nucleophilicities of a series of naked anions toward benzyl tosylate in acetonitrile ($\epsilon = 37$) at 30°C[11] and toward 1-bromopentane in acetonitrile ($\epsilon = 37$) and benzene ($\epsilon = 2$) at 20°C[12] are summarized in Table 4. It is interesting to note that there appears to be a marked levelling effect in the nucleophilicities of naked anions toward a particular substrate in a particular solvent. The results are in direct contrast to the previously observed nucleophilicities in protic media[13]. Under naked anion conditions, nucleophiles which were considered poor (under protic conditions) become as active as nucleophiles which were considered excellent. This appears to be true irrespective of the substrate or solvent. Some recent evidence indicates that the superoxide radical anion is more nucleophilic than the anions in Table 4 by several orders of magnitude[14].

The effect of a wide variety of macrocyclic multidentate ligands on the activation of acetate (dissolved in acetonitrile as its potassium salt) toward benzyl chloride has been reported (Table 5). The characteristics of the ligand which influenced the rate were suggested to be (*a*) the stability of the metal–ligand complex, (*b*) the lipophilicity of the ligand, (*c*) the rigidity of the ligand, and (*d*) the reactivity of the ligand toward the substrate (aza crowns)[10].

TABLE 5. Effect of macrocyclic polydentate ligand on rate of reaction of potassium acetate with benzyl chloride in acetonitrile



Ligand		Approx. half-life (h)
None		685
18-Crown-6 (1)		3.5
Dibenzo-18-crown-6 (8)		9.5
Dicyclohexo-18-crown-6 (12)		1.5
	[2.1] (7)	700
	[2.2] (6)	65
	[3.2] (4)	75
	[3.3] (5)	100
	[2.1.1] (10)	8
	[2.2.1] (13)	0.8
	[2.2.2] (9)	5.5

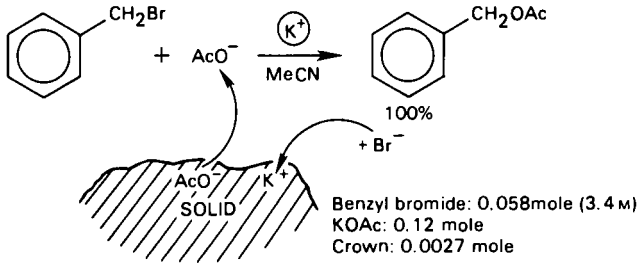
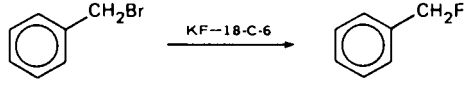


FIGURE 2.

The use of crowns to enhance the solubility of metal salts in nonpolar and dipolar aprotic solvents augmenting the reactivity of the anionic portions of the salts (naked anions) has prompted many investigators to use these novel ligands in catalysing organic reactions and in probing reaction mechanisms[6]. Reactions carried out under homogeneous conditions as well as those carried out under solid–liquid and liquid–liquid phase-transfer catalytic conditions have been reported[7]. To illustrate this latter technique, consider the reaction between benzyl bromide (0.058 mole) and potassium acetate (0.12 mole) in acetonitrile containing only catalytic quantities (0.0027 mole) of 18-crown-6 (Figure 2). Since there is not enough crown present to dissolve all the potassium acetate present the reaction mixture is a two-phase system. Nevertheless, the reaction proceeds quantitatively to benzyl acetate. This result indicates that in priniciple the crown acts as a carrier of potassium acetate reactant from the solid phase to the liquid phase and also as a carrier of potassium bromide product from the liquid phase to the solid phase. In the absence of crown little reaction takes place during a comparable period of time. This technique of performing organic transformations has also been accomplished between two liquid phases[7]. Representative examples of crown-mediated reactions will be explored in the following sections. No attempt will be made to present an exhaustive survey. Only the general scope and flavour of this subject will be addressed.

II. ORGANIC REACTIONS MEDIATED BY MACROCYCLIC AND MACROBICYCLIC MULTIDENTATE LIGANDS

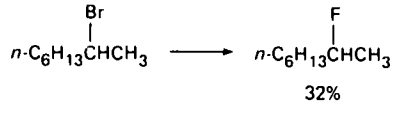
In spite of the marginal solubilization of potassium fluoride by 18-crown-6 in actonitrile and benzene[5], enough anion is present in solution, even in the presence of catalytic quantities of crown, to allow facile transformations which introduce fluorine into organic molecules by simple displacement processes (reactions 1–8).



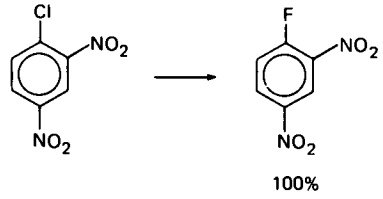
(1)

$$n\text{-}C_6H_{13}CH_2CH_2Br \longrightarrow n\text{-}C_6H_{13}CH_2CH_2F \quad 92\%$$
$$+\ n\text{-}C_6H_{13}CH{=}CH_2 \quad 8\%$$

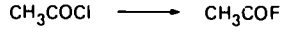
(2)



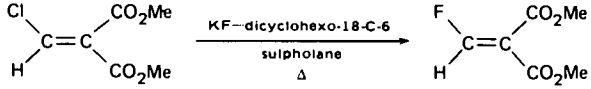
(3)



(4)

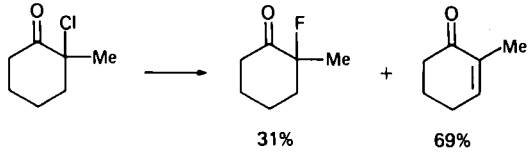


(5)



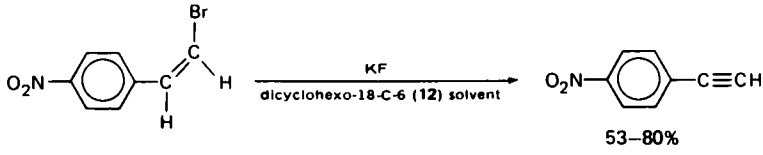
(Ref. 15) (6)

(Ref. 16) (7)

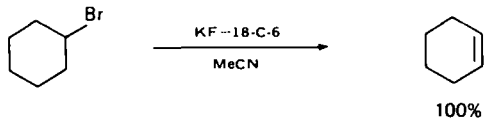


(8)

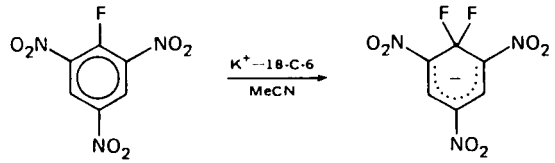
It is interesting to note that fluoride ion behaves as a dehydrohalogenating agent with certain substrates (reactions 2, 3, 8–10). The *gem* difluoro σ-anionic complex (reaction 11) was observed by means of ^{1}H- and ^{19}F-NMR spectroscopy. Naked fluoride has been reported to be an effective base catalyst in the deprotonation of the indole ring of tryptophan in the formation of *N*-benzyloxycarbonyl and *N*-2,4-dichlorobenzyloxycarbonyl derivatives[19].



(Ref. 17) (9)

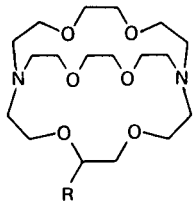


(Ref. 5) (10)



(Ref. 18) (11)

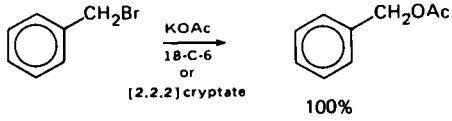
Nucleophilic substitution and elimination processes have been reported for chloride[15], bromide[20] and iodide[20] under solid–liquid phase-transfer catalytic conditions using dicyclohexo-18-crown-6 (12) and under liquid–liquid phase-transfer catalytic conditions using dicyclohexo-18-crown-6 (12), benzo-15-crown-5 (11), dibenzo-18-crown-6 (8), 1,10-diaza-4,7,13, 16-tetraoxacyclooctadecane (6) and **9a**, **b** and **c**[21,22].



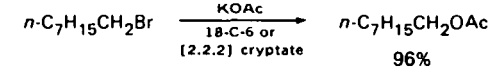
(a) R = H
(b) R = n-$C_{11}H_{23}$
(c) R = n-$C_{14}H_{29}$

(9)

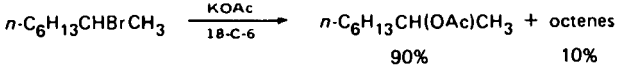
Acetate ion has always been considered a marginal to poor nucleophile in protic media (see Table 4). Nevertheless, when solubilized as its potassium salt in acetonitrile and benzene, it becomes an active nucleophilic species. Reactions of naked acetate with a wide variety of organic substrates (Figure 2, reaction 12; reactions 13–17)[19,23]. Indeed, carboxylate ions in general become quite reactive under naked anion conditions (reactions 18–21). It is interesting to note that acetate



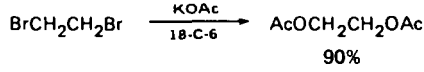
(Refs. 9, 30) (12)



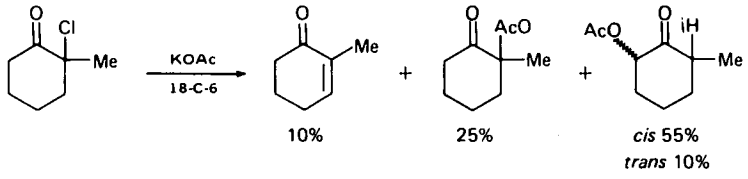
(Refs. 9, 30) (13)



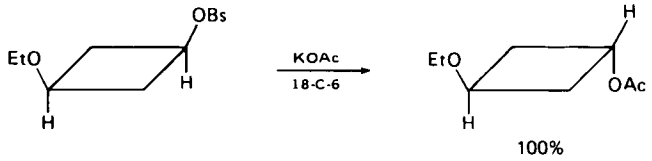
(Ref. 9) (14)



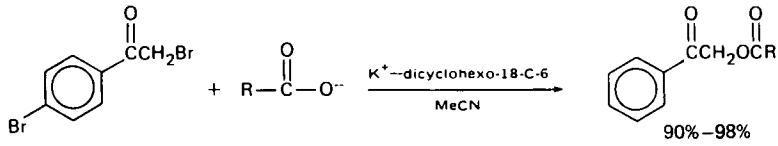
(Ref. 9) (15)



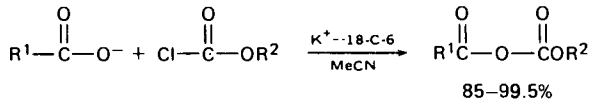
(Ref. 9) (16)



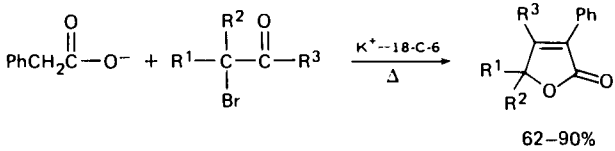
(Ref. 23) (17)



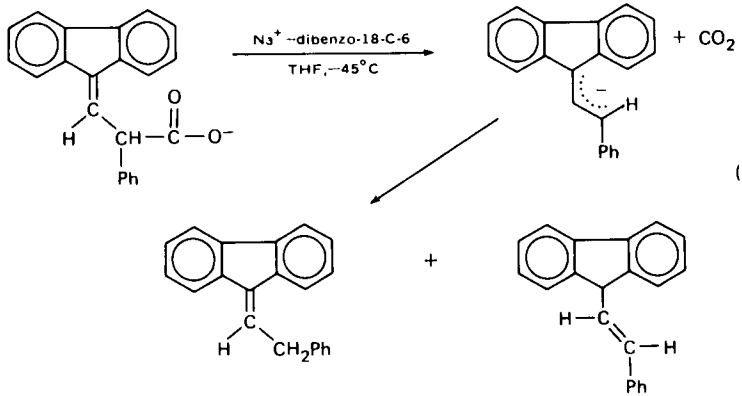
(Ref. 24) (18)



(Ref. 25) (19)



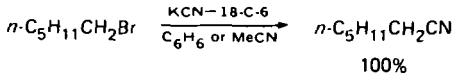
(Ref. 26) (20)



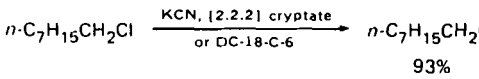
(Ref. 27) (21)

promotes less dehydrohalogenation compared to fluoride under comparable reaction conditions. The reaction of chloromethylated resin with the potassium salts of boc-amino acids in dimethyl formamide solution was shown to be facilitated by the presence of 18-crown-6[28] and the polymerization of acrylic acid has been reported to be initiated by potassium acetate complexed with crown[29].

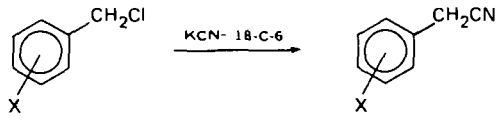
Cyanide ion, generated under solid–liquid and liquid–liquid phase-transfer catalytic conditions using crowns and cryptates, has been demonstrated to be a useful reagent in a wide variety of substitution, elimination and addition processes (reactions 22–35). It is interesting to note that in displacement reactions by



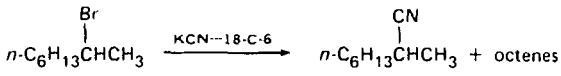
(22)



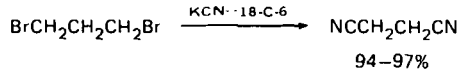
(Ref. 22) (23)



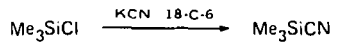
(Refs. 31, 32) (24)



(Ref. 31) (25)



(Ref. 31) (26)



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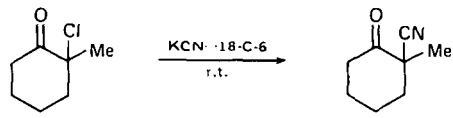

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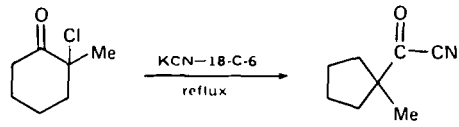
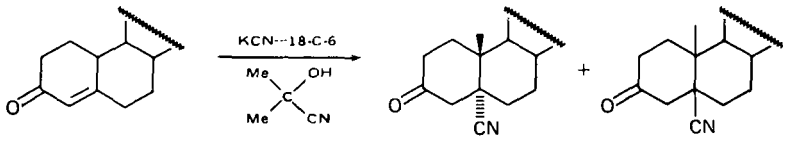


(Ref. 6) (29)



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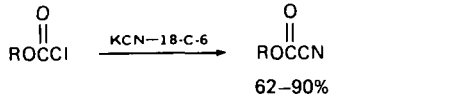
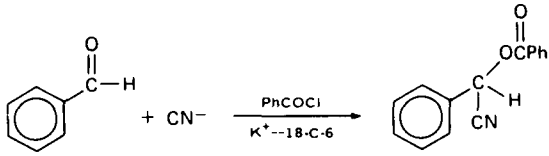
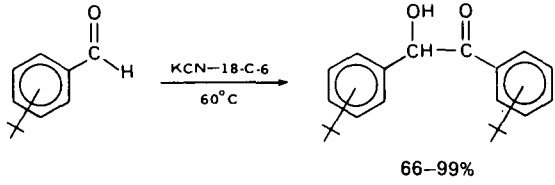


(31)



(Ref. 35) (32)



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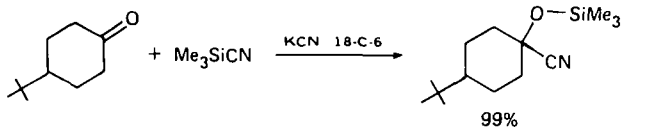
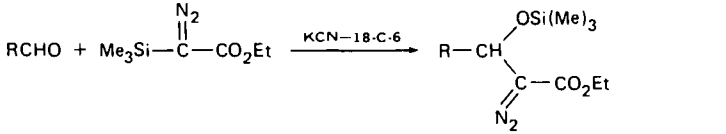


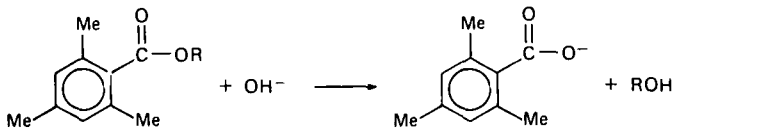
(Ref. 37) (34)



(Ref. 39) (35)

cyanide under solid–liquid conditions, primary chlorides react faster than primary bromides while secondary bromides react faster than secondary chlorides. 18-Crown-6 has been shown to facilitate the photochemical aromatic substitution by potassium cyanide in anhydrous media[40] and to enhance the nucleophilic displacement by cyanide on hexachlorocyclotriphosphazene[41].

Kinetic studies have shown that the presence of macrocyclic multidentate ligands increases the solubility and alters the ionic association of metal hydroxides and alkoxides in relatively nonpolar media and greatly increases the nucleophilic and basic strength of the oxy anions[42-44]. For instance, sterically hindered esters of 2,4,6-trimethylbenzoic acids easily undergo acyl-oxygen cleavage by potassium hydroxide in toluene containing dicyclohexo-18-crown-6 or the [2.2.2] cryptate (reaction 36)[45], chlorine attached to a nonactivated aromatic ring is readily displaced by methoxide ion dissolved as its potassium salt in toluene containing crown



(Refs. 1, 45) (36)

by an addition–elimination mechanism (reaction 37), and carbanions are generated from weak carbon acids by hydroxide and alkoxide in nonpolar solvents containing

(Ref. 20) (37)

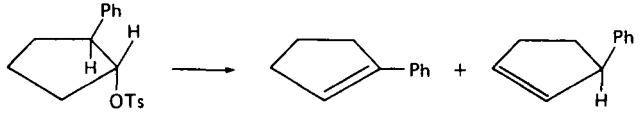
crowns and cryptates (reactions 38–40)[45]. Indeed, the regiochemical and stereochemical course of reaction in both substitution and elimination processes is

(38)

$$Ph_3CH \longrightarrow Ph_3C^- \quad (39)$$

$$Ph_2CH_2 \longrightarrow Ph_2CH^- \quad (40)$$

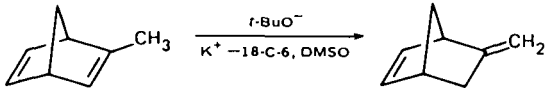
markedly altered by the presence of crown[46–50]. Reaction of 2-phenylcyclopentyl tosylate (reaction 41) with potassium *t*-butoxide in *t*-butyl alcohol produces two isomeric cycloalkene products[46]. In the presence of dicyclohexo-18-crown-6, 3-phenylcyclopentene is produced in greatest quantity while in its absence 1-phenylcyclopentene is the major product. This and other studies indicate that in nonpolar



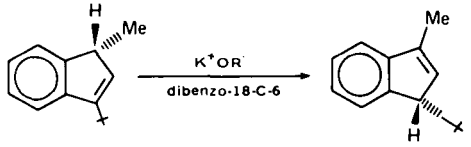
(Ref. 46) (41)

media metal alkoxides react as ion aggregates and promote elimination reactions via a *syn* pathway, while in the presence of a macrocyclic multidentate ligand, the aggregate is disrupted and the *anti* elimination pathway becomes dominant.

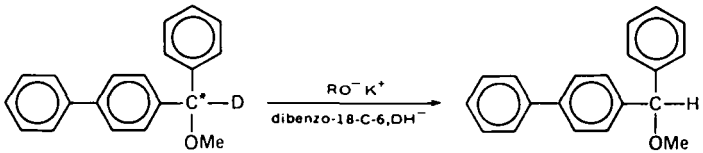
Isomerization reactions, reactions involving stereochemical course of isotope exchange, and fragmentation reactions promoted by metal alkoxides and rearrangements of metal alkoxides in the presence and in the absence of crowns have been reported (reactions 42–47). Enolates and related species and halomethylenes and



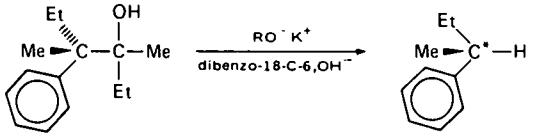
(Ref. 51) (42)



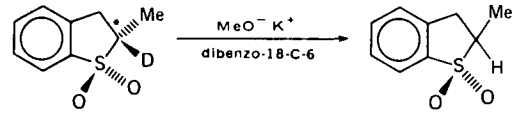
(Ref. 52) (43)



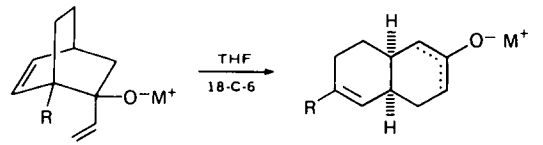
(Ref. 53) (44)



(Ref. 53) (45)



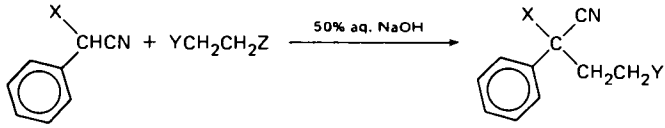
(Ref. 53) (46)



(Ref. 54) (47)

their carbanion precursors have been generated under liquid–liquid phase-transfer catalytic conditions using crowns and cryptates and effectively used in synthetic transformations (reactions 48–54)[55a–c]. Ambient ions such as 9-fluorenone oximate (**14**), and the enolates of ethyl malonate (**15**) and ethyl acetoacetate (**16**) have been generated in the presence of macrocyclic multidentate ligands in a variety of solvents. It has been demonstrated that the presence of a metal ion complexing agent greatly effects the rate of alkylation as well as the ratio of N/O and C/O allylation[6–60].

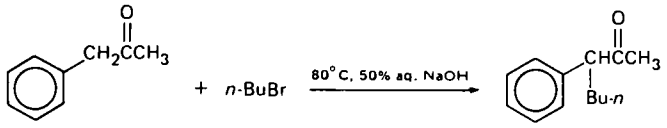
Potassium superoxide has been successfully solubilized in dimethyl sulphoxide, benzene, tetrahydrofuran and dimethylformamide containing 18-crown-6 and effectively used as a nucleophilic reagent for the preparation of dialkyl and diacyl



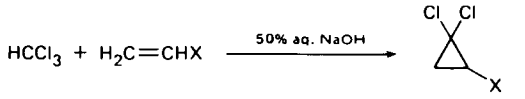
(Ref. 55a) (48)

X = H, Ph
Y = H, Br
Z = Br, Cl

Y = H 85%
Y = Br 75%

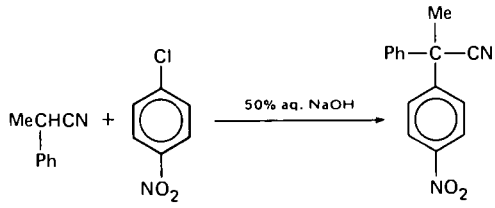


(Ref. 22) (49)

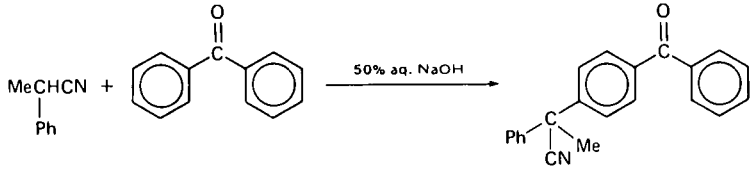


(Ref. 55a) (50)

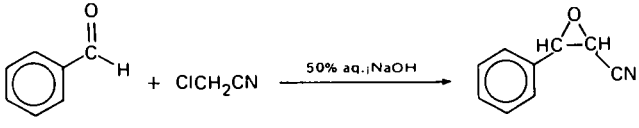
X = Ph 87%
X = CN 40%



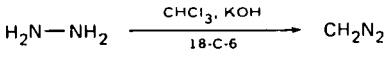
81% (Ref. 55a) (51)



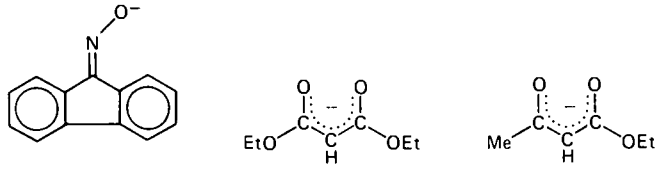
67% (Ref. 55a) (52)



78% (Ref. 55a) (53)



48% (Ref. 55b) (54)

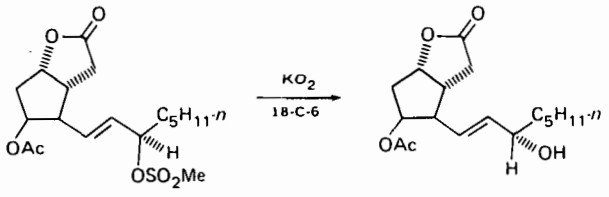


(14) (15) (16)

peroxides and alcohols (reactions 55 and 56)[14,60-64]. It has also been demonstrated that superoxide in benzene is an efficient reagent for cleavage of carboxylic esters[62,63] and for promoting the oxidative cleavage of α-keto, α-hydroxy and α-halo ketones, esters and carboxylic acids[65] and α,β-unsaturated carbonyl compounds[66] (reactions 57 and 58).

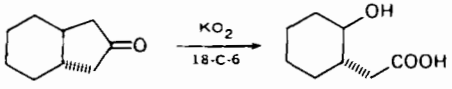
It has been demonstrated that potassium permanganate solubilized in benzene with crown provides a convenient, mild and efficient oxidant for a large number of

55% (Ref. 61) (55)



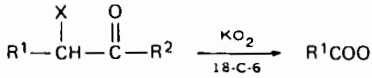
75%

(Ref. 62) (56)



85%

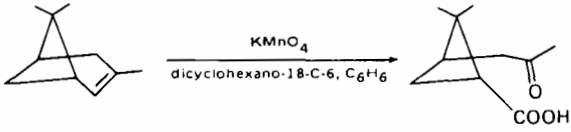
(Ref. 64) (57)



50–98%

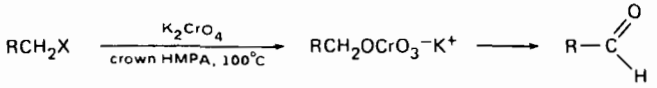
(Ref. 65) (58)

organic reactions (reaction 59)[20], while potassium chromate has been reported to react with primary alkyl halides at 100°C in hexamethylphosphoramide containing



(59)

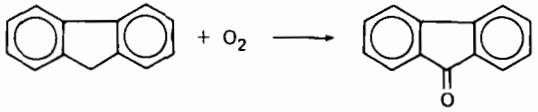
crown to produce good yields of aldehydes (reaction 60)[67]. Carbanions formed from reaction of weak carbon acids with potassium hydroxide in toluene containing



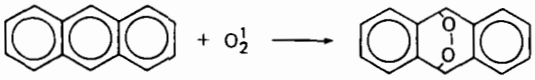
78%–82%

(60)

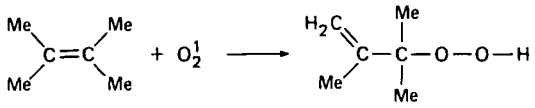
crowns or cryptates are readily oxidized by molecular oxygen (reaction 61)[45] and the homogeneous photosensitization of oxygen by solubilizing the anionic dyes Rose Bengal and Eosin Y in methylene chloride and carbon disulphide using crown is reported to produce singlet oxygen (reactions 62 and 63)[68].



(61)

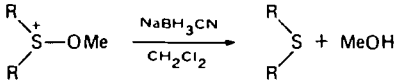


(62)



(63)

The action of reducing agents such as lithium aluminium hydride, sodium borohydride and sodium cyanoborohydride on organic substrates has been explored in the presence of macrocyclic and macrobicyclic polydentate ligands under homogeneous, solid–liquid and liquid–liquid phase-transfer catalytic conditions[22,69-72]. In the former cases, crowns and cryptates were used to elucidate the role of the metal cation as an electrophilic catalyst. Sodium cyanoborohydride in the presence of crown has been reported to reduce alkoxysulphonium salts to sulphides (reaction 64)[72].



(64)

71–91%

Sodium, potassium and caesium anions have been generated in ether and amine solvents in the presence of crowns and cryptates[73] and sodium, potassium, caesium and rubidium have been reported to dissolve in benzene and toluene and in cyclic ethers containing these hydrocarbons in the presence of crowns and cryptates to produce the corresponding anion radicals[74].

Finally, macrocyclic multidentate ligands have been found to be a sensitive tool for exploring the mechanistic details in the reactions and rearrangements of carbanions[52-54,75-78] and in substitution and elimination processes[46-50]. Indeed, any reaction involving metal ion anion intermediates is, in principle, subject to mechanistic surgery with the aid of crowns and cryptates. It must be remembered that these macrocyclic and macrobicyclic species can be designed and synthesized specifically for a particular metal ion. Herein lies their potential power.

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Crown Ethers and Analogs
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CHAPTER **3**

Modern aspects of host–guest chemistry: molecular modeling and conformationally restricted hosts

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Pleasantest of all ties is the tie of host and guest—Aeschylus

I. INTRODUCTION

It is particularly appropriate, having concluded the 20th anniversary of the first paper[1a] in the field of crown ether chemistry, in a year which has seen the award of the Nobel Prize for Chemistry to the founders of this field, to consider the present status of aspects of what is now variously known as host–guest chemistry, supramolecular chemistry or molecular recognition chemistry. All three appellations will be used, but host–guest chemistry will be emphasized as the description of choice for the field which has grown from Pedersen's initial studies, because of its pre-eminence in the literature of this discipline. In addition, both 'supramolecular' and 'molecular recognition chemistry' are terms with associations in other fields, whereas 'host–guest chemistry' is particularly conjoined with the field of synthetic molecular complexation chemistry.

That the field has undergone rapid growth can easily be seen by considering Figure 1, which contains three graphs relating host–guest publications and total publications in chemistry by year. The data were obtained from a computer search of the *Chemical Abstracts* database from 1967 to May 1988, with various permutations of the following terms: host–guest chemistry, supramolecular chemistry, molecular recognition chemistry, crown ether, crown compounds, cyclic polyether, lariat ether, macrocyclic polyether, coronand, cryptand, cryptate, speleand, hemispherand, spherand, macrocyclic receptor, macropolycyclic ether, podand, open-chain polyether, acyclic crown ether, cryptophane, cavitand, carcerand, synthetic receptor, molecular cleft and calixarene. Including primary journal papers, reviews, books and patents, the total number of host–guest publications in

the search from 1967 through 1986 was 5075. Approximately 75% of the publications for 1987 had been added to the *Chemical Abstracts* database, and are only reflected in the graph of host–guest publications as a fraction of total publications. Between the years 1967 and 1986, host–guest publications per year increased from 2 to 639 while the total number of publications increased from 239 000 to 474 000. Interestingly, in the search period the Nobel Laureates Pedersen, Cram and Lehn had published 22, 107 and 121 publications, respectively, in host–guest chemistry. To emphasize further the powerful impact of Pedersen's pioneering work, of his 22 publications during the search period only seven[1] are primary research papers. The rest are divided between four reviews[2], ten patents and one *Organic Synthesis* preparation.

Did host–guest chemistry reach its zenith in 1985? The graph of host–guest publications as a fraction of total publications certainly suggests this possibility. An alternative explanation is that the proliferation of new sections of host–guest chemistry has made it progressively more difficult for a search to be comprehensive. It will be necessary to examine the data for the next few years before conclusions can be drawn. The degree of stimulus provided by the awarding of the Nobel Prize should be very interesting to follow.

Regardless of the future of host–guest chemistry, the past, especially since the last update in this series contained references up to 1979[3], makes a comprehensive review difficult owing to the enormous number of papers published in the intervening years. An attempt has been made to highlight recent advances in host–guest chemistry by reviewing areas which are currently under active investigation and which are particularly interesting to the author. Areas which will not be covered, except for occasional comparisons, include cyclodextrin chemistry[4], naturally occurring ionophores[5], siderophores and synthetic analogs[6], complexones[7], calixarenes[8], electrides[9], polymeric hosts[10], podands[11], Schiff base-derived macrocycles[12] and hosts as anion activators[13]. The particular emphases in this chapter will be on modern methods of molecular modeling as applied to host–guest chemistry and on conformationally restricted hosts. Coverage of the conformationally mobile hosts and the cyclophane hosts will be predominantly limited to the section on molecular modeling and to various comparisons with the conformationally restricted hosts.

The photographs that appear in this chapter were taken with a Nikon 35 mm camera with a 50 mm lens in the existing light from an Evans & Sutherland PS 390 terminal using Biograf Version 1.40. Kodak VGR 100 print film was used at *f*/8, and an exposure series of 2, 4, 8 and 16 s was shot for each picture. The best negative was then printed.

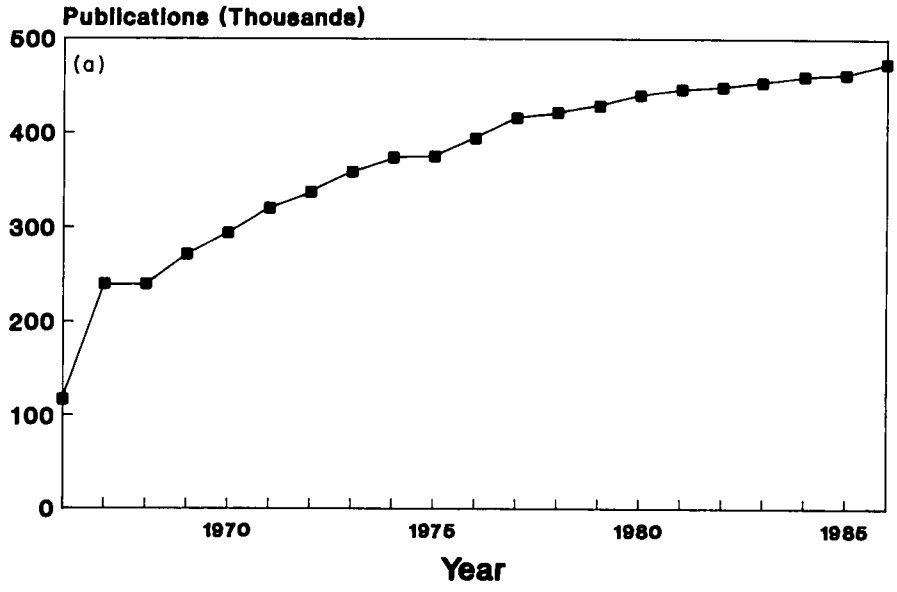
II. GENERAL CONCEPTS

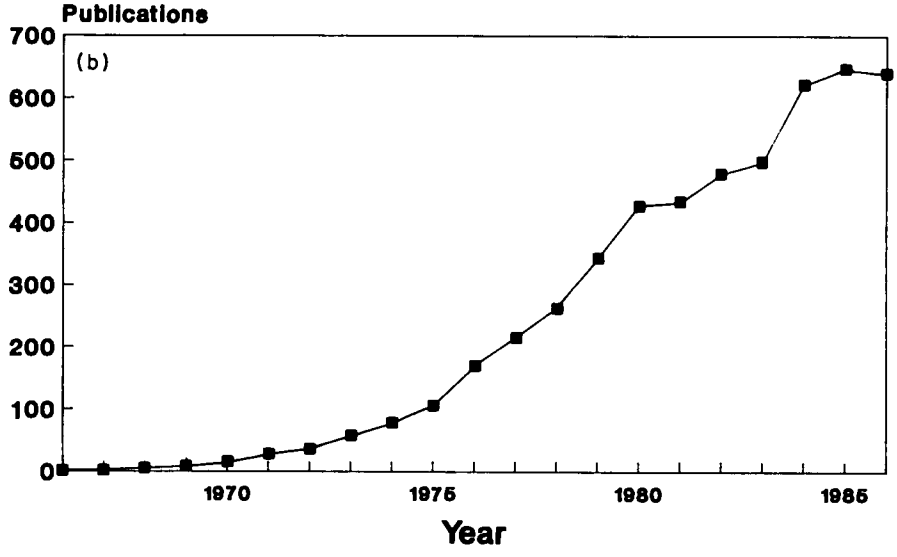
A. Definitions

Although host–guest interactions had been considered in clathrates[14] and energy transfer processes[15] prior to 1974, it was then that Cram coined the use of the term 'host–guest chemistry'[16] to describe the then relatively new field of synthetic complexation chemistry exemplified by the crown ethers and cryptands. Host–guest chemistry is primarily concerned with elucidating the 'rules of non-covalency'[17] involved in the recognition and binding of a guest by a synthetic receptor, much as earlier investigators focused on thoroughly exploring covalent interactions.

A host is a molecule which can non-covalently interact with and bind a guest. Hosts may be acyclic, macrocyclic or oligomeric, and possess cavities or clefts into which the guest fits. The host's recognition site or sites for the guest may be present continuously or may be organized during interaction with the guest. Hosts are generally large compared with guests, or at least with the actual portion of the guest bound. The term 'epitope' will be used to refer to the part of the guest actually complexed by the host, an extension of the use of

the term in immunology, where the epitope is the portion of the antigen actually recognized by an antibody. Hosts possess binding sites which tend to converge upon the guest. The binding sites may interact with guests by combinations of all non-covalent interactions available including hydrogen-bonding, ion–dipole, ion–ion, π, van der Waals, electron donor–acceptor and hydrophobic interactions. Figure 2 lists some representative hosts.





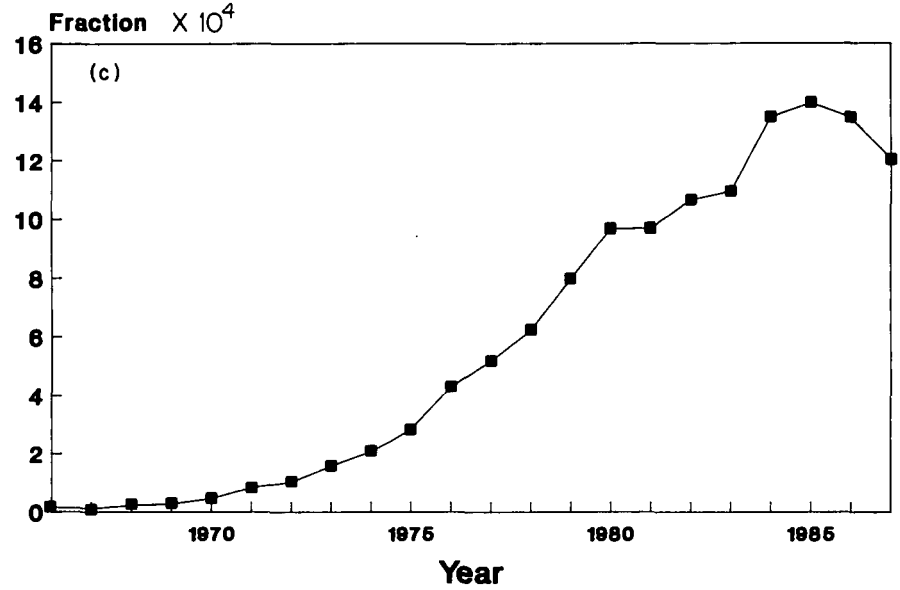


FIGURE 1. (a) Total chemistry publications by year. (b) Host–guest chemistry publications by year. (c) Host–guest publications as a fraction of total publications by year

Guests are molecules or atoms which may be ionic or neutral and whose epitopes present divergent binding sites complementary in charge and steric requirements to the host. Typical guests include metal ions, ammonium ions, polar neutral species such as acetonitrile, hydrogen-bonding compounds, aromatic substrates, diazonium salts, halides and many others. The interaction of host and guest produces a complex. An example is shown in Plate 1, which is a computer-generated space-filling representation of the crystal structure of host **1** complexed with Na^+.[18]

Striking parallels exist by design between host–guest chemistry and molecular cell biology. Examples of biological host–guest interactions include enzymatic processes, typified by the hydrolysis of peptides by chymotrypsin and DNA cleavage by restriction endonucleases; cell surface receptor binding, exemplified by the recognition of low-density lipoprotein by the LDL receptor; symport, antiport and uniport transport mechanisms; and neurotransmitter receptors in impulse transmission[19]. As will be seen, attempts to mimic or surpass biological host–guest interactions with synthetic hosts form the basis for many of the elegant studies in host–guest chemistry.

B. Nomenclature

As with many rapidly developing areas, nomenclature in host–guest chemistry is a fluid matter, with much variability among authors. One problem is that for the practicing chemist the systematic nomenclature for most hosts is nearly worthless. Consequently, trivial and semi-trivial schemes crop up to name every new type of molecule produced. As an example of trivial nomenclature, the host in Plate 1 is often referred to as dibenzo-18-crown-6[2d], with the prefix denoting the major substituents on the host macroring, the first

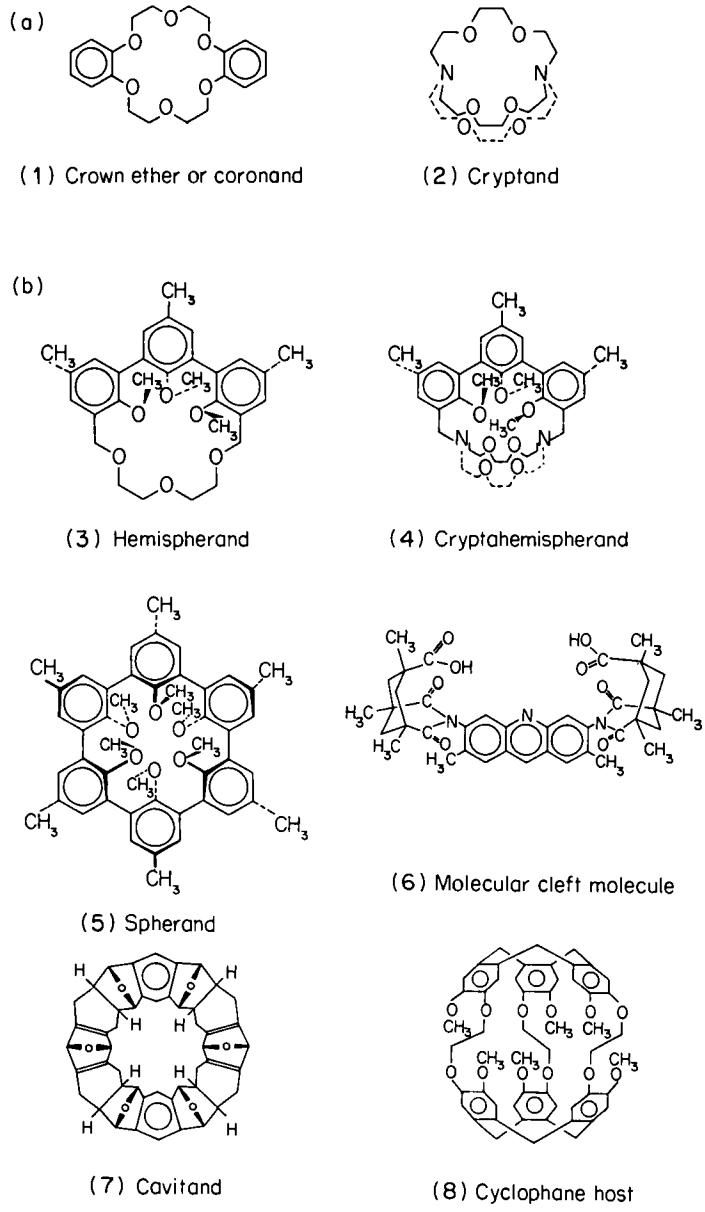


FIGURE 2. Host classes and representative members. (a) Conformationally mobile hosts. (b) Conformationally restricted hosts

number delineating the macroring size, the word 'crown' to identify the compound as a crown ether and the final number to specify the total number of heteroatoms in the macroring. However, other suggestions for the compound type include coronands[20], chorands[21] or corands[22]. In this chapter the terms 'crown ether' and 'coronand' will be used interchangeably. Use of the newer Weber and Vögtle semi-systematic nomenclature[11b] for host **1** yields 18⟨O_6(1,2)benzeno.2_2.(1,2)benzeno.2_2coronand-6⟩. This is difficult to decipher, but certainly an improvement over the IUPAC designation, 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.$0^{9,14}$]hexacosa-1(22),8,11,13,23,24-hexaene.

Bicyclic versions of coronands with bridgehead nitrogens were invented by Lehn *et al.*[23], who called the hosts 'cryptands' after the Greek word *cryptos* meaning 'cave'. The name describes the host's topology, especially when complexed. Cryptands are trivially named with the numbers of heteroatoms in the bridges within brackets, followed by the class designator 'cryptand'; hence compound **2** is [2.2.2]cryptand or, in recent years with the trend toward space conservation, [222]cryptand. There is also a semi-systematic nomenclature for cryptands[11b]. Complexes of cryptands are called cryptates.

This suggested to Weber and Vögtle that trivial host names which end in the suffix 'and' (from lig*and*) should have that ending replaced with 'ate' upon complexation[24]. Thus a coronand becomes a coronate and a podand (open-chain complexing agent) becomes a podate when complexed. However, Cram[22] pointed out the unfortunate association that 'ate' suffixes have to most chemists, namely that compounds ending in 'ate' are often anions, such as phosph*ate* and perchlor*ate*. Therefore, host **5**, which is a spherand, upon complexation becomes a spheraplex and hemispherand **3** becomes a hemispheraplex. The suffix 'plex' is derived from the Latin word *plexus*, meaning an 'interwoven arrangement of parts'. Precedence is a powerful force, as the Brontosaurus found out when metamorphosed into the Apatosaurus. Consequently, the earlier 'ate' suffixes are likely to continue in use indefinitely in host–guest chemistry.

A problem with nomenclature in supramolecular chemistry is that the simpler systems provide less information but are easy to use, whereas the names approaching the systematic level are information rich but very difficult to interpret. Also, as substituents are added, even the most trivial of names becomes difficult to identify with its corresponding structure. In the final analysis, this is a structurally intense science, and without structures little information is conveyed. The best solution outside of archival purposes is probably to give a new type of host a trivial name and refer to a structure with the name and a number. Probably no Greek or Latin name, prefix, or suffix denoting in any fashion a hole or cavity or the ability to grip tightly will remain unused in the years to come.

Host–guest chemistry has rapidly passed through the stage where a simple name was sufficient for the reader to visualize a host, to the point where a two-dimensional diagram is barely adequate. Already, some sort of three-dimensional representation of the more elaborate hosts is necessary to appreciate their structural features completely. In this chapter trivial names are used, linked with drawings for most structures, interspersed with photographs of space-filling representations of parent compounds for each class of host and for hosts which cannot otherwise be easily visualized.

C. Synthesis

The synthesis of macrocyclic hosts has been reviewed extensively[25]. Specific instances will be covered in the sections on particular host types.

D. Complexation Kinetics and Thermodynamics[26]

The central purpose of synthesizing most hosts is to determine how they associate with guests. Consequently, the quantification of the kinetics and thermodynamics of host–

guest interactions is pivotal to the discipline of host–guest chemistry and has received appropriate attention[27]. Most physical techniques for the determination of association constants and the elucidation of kinetics have been applied to supramolecular chemistry, including the use of ion-selective electrodes[28], extraction of colorimetric and other active species[29], NMR spectroscopy[30], microcalorimetry[31], equilibrium perturbation methods[32], polarography[33], fluorescence spectroscopy[30d,34], pH-metric methods[35] and others.

The equilibrium expression for complexation of a guest (G) by a host (H) is deceptively simple, as many factors influence the outcome:

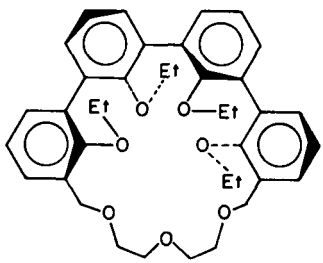
$$H_{(solv)} + G_{(solv)} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} (H{:}G)_{solv} \tag{1}$$

$$K_a = \frac{k_1}{k_{-1}} \tag{2}$$

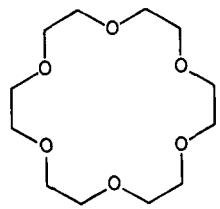
These factors include conformational changes in both host and guest before and during the complexation event and the reorganization of solvent throughout the binding process. Specific examples of complexation data will be cited later. However, for alkali metal and ammonium cations, trends in order of increasing complexing ability among hosts in Figure 2 are coronands < hemispherands < cryptands < cryptahemispherands < spherands[20]. The order of the forward rate constants, k_1 is the reverse of the order of binding. As an example, for most simple coronands k_1 approaches the diffusion-controlled limit for complexation of alkali metal and ammonium cations[26]. As the host becomes more sterically hindered and desolvation of the guest by the host becomes more difficult, k_1 decreases. Consequently, k_1 for the complexation of [211]cryptand with Na^+ is 3.1×10^6 $l\,mol^{-1}\,s^{-1}$ in MeOH[36]. Complexation is relatively unhindered in the quateraryl hemispherand **9** where k_1 for the complexation of potassium picrate (K^+Pic^-) in $CDCl_3$ is $2 \times 10^8\,l\,mol^{-1}\,s^{-1}$.[22] Spherand **5**, however, is extremely hindered to the approach of solvated cation and shows a consequent dramatic decrease in k_1 to $4.1 \times 10^5\,l\,mol^{-1}\,s^{-1}$ for the complexation of Na^+Pic^- in $CDCl_3$. The binding order is produced by an even more precipitous decrease in k_{-1}.

E. The Macrocyclic Effect

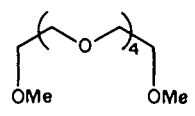
A significant increase in binding ability is usually seen for a macrocycle in comparison with its acyclic analog. This is the macrocyclic effect[37], which together with complementarity and preorganization is one of the key contributing factors in determining the overall binding ability of a host. Figure 3 compares the relative free energies and enthalpies for the binding of three cations by 18-crown-6 (**10**) and its podand analog, pentaglyme (**10a**), in MeOH[38]. A general conclusion drawn from this and other data is that as long as there is



(9)



(10)



(10a)

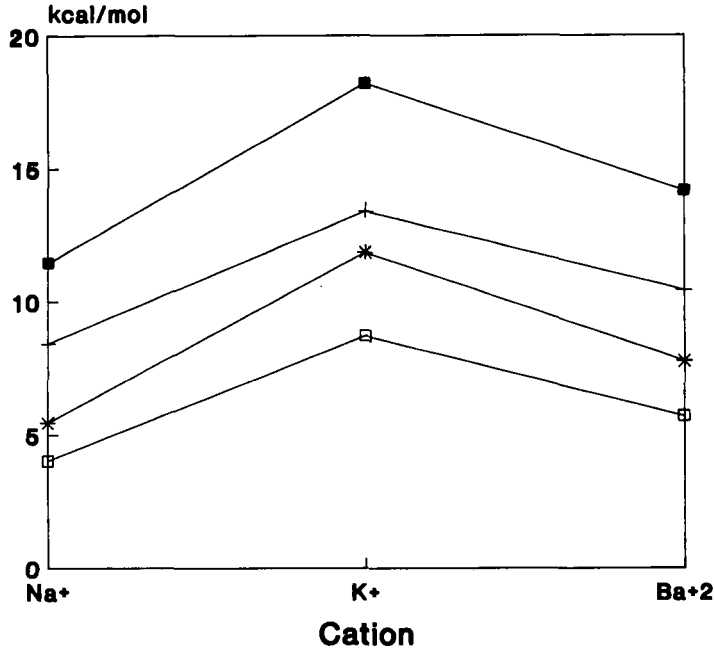
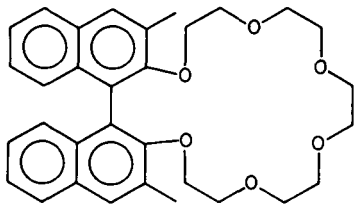


FIGURE 3. Comparison of cation binding by 18-crown-6 and pentaglyme. ■, ΔG (crown); *, ΔG (acyclic); +, ΔH (crown); □, ΔH (acyclic)

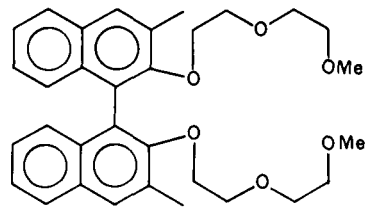
not a serious discrepancy between the cavity size of the host and the size of the guest, enthalpy will play the major role in the macrocyclic effect, with entropy contributing to a lesser degree[37b].

Other examples of the importance of the macrocyclic effect include the $-\Delta G^0$ value of 1.6 kcal mol^{-1} between the dibinaphthyl coronand **11** and its open-chain counterpart **12** for complexation of *t*-butylammonium isothiocyanate in $CDCl_3$[39]. Partial preorganization of podand **12** by the dibinaphthyl unit probably accounts for the relatively small difference in free energies for complexing the ammonium salt between the podand and coronand **11**. The largest free energy difference for alkali metal complexation between macrocyclic and acyclic hosts is that between spherand **5** and the acyclic analog **13** of > 17 kcal mol^{-1} for the binding of Li^+Pic^- in $CDCl_3$[22].



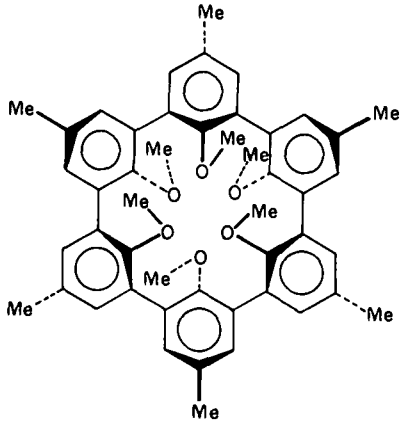
(11)

$\Delta G^\circ(RNH_3^+) = 6.4$ kcal mol^{-1}



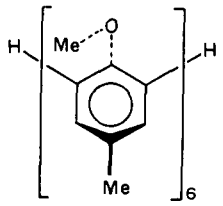
(12)

$\Delta G^\circ(RNH_3^+) = 4.8$ kcal mol^{-1}



(5)

$\Delta G°(Li^+) > 23$ kcal mol^{-1}



(13)

$\Delta G°(Li^+) < 6$ kcal mol^{-1}

Suggestions for the origin of the enthalpic contribution to the macrocyclic effect include the greater dipole–dipole repulsion in a macrocycle versus its acyclic correspondent[40], the more extensive solvation of the acyclic analog[37b,41] and the availability of low-energy conformations for the acyclic counterpart not available for the macrocycle[42,43]. Each plays a role which differs according to the host and solvent. All contribute to a higher relative energy for the macrocycle which may be partially relieved by complexation.

F. Complementarity

The concept of complementarity states that for optimum binding, the epitope of a guest must fit in the recognition site of a host as exactly as possible in terms of size, electronic match and steric compatibility with nearby groups. The host must provide the guest with the correct number and type of binding sites. Plates 2a, b show top and side views of the X-ray crystal structure conformations of 18-crown-6 with its ideal guest, K^+ [18a,44a]. Plate 3 is a side view of 18-crown-6 complexed with Cs^+ [18a,45]. It is clear that Cs^+ does not exemplify the complementarity principle owing to its large size relative to the dimensions of the binding cavity. The cation can still bind, but must 'perch' on the host instead of 'nesting' in its cavity[46]. The differences in compatibility between K^+ and Cs^+ for 1:1 complexation by 18-crown-6 are reflected in the free energies for binding in MeOH of -8.2 and -6.5 kcal mol^{-1}, respectively[47].

The electrostatic potential surface dot picture[48] (Plate 4) nicely visualizes the electronic complementarity between host and guest for the 18-crown-6 complex with K^+. Negative partial charge is shown in red and positive charge in blue. The power of complementary electrostatic interactions between host and guest is further illustrated by the change in the electrostatic contribution to the total strain energy in molecular mechanics calculations[49] of the 18-crown-6:K^+ complex of from -35.2 to $+86.6$ kcal mol^{-1} if the guest charge is arbitrarily changed from $+1$ to -1.

The ideal of steric compatibility of a guest with the groups surrounding the binding cavity of a host is elucidated by the recognition of the preferred amino acid enantiomer by chiral host **14** to give complex **15** (Figure 4). The ammonium group of the guest forms a tripodal array of hydrogen bonds to alternating oxygens of the host. Then the large R group extends over the least hindered portion of the macroring. The carboxyl group

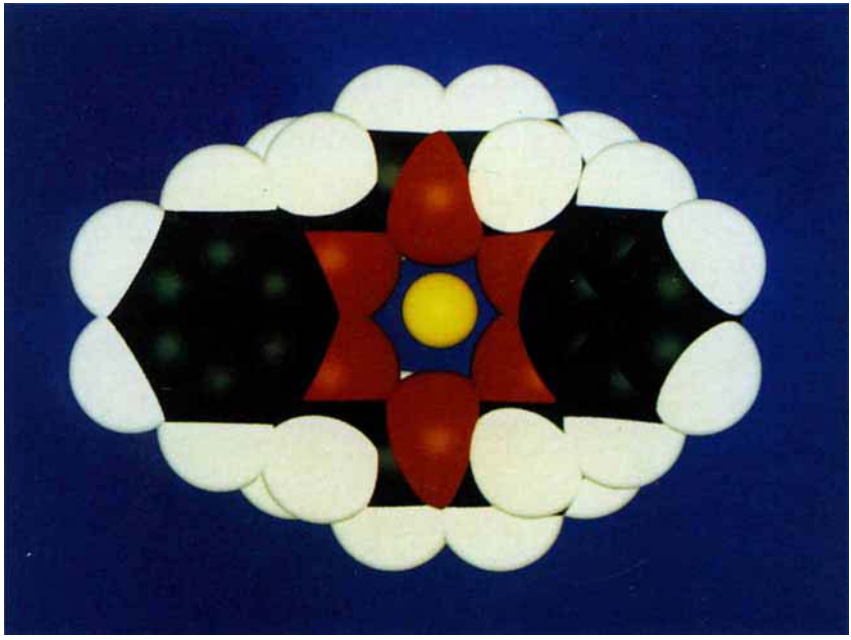
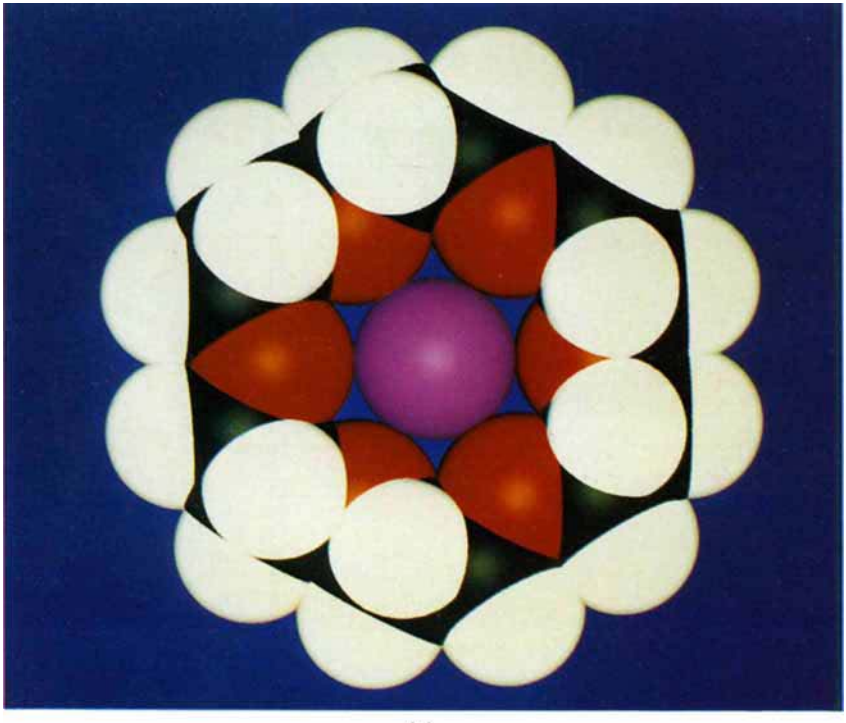
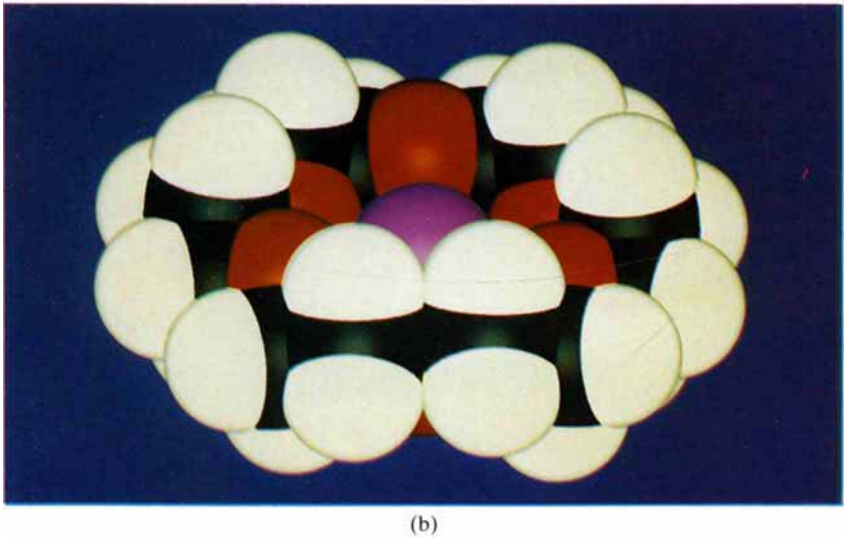


PLATE 1. Space-filling representation of the X-ray crystal structure of the dibenzo-18-crown-6. Na^+ complex. Space-filling at 0.89 × Van der Waals radius for all such representations unless noted



(a)



(b)

PLATE 2a, b. Top (a) and side (b) views of the X-ray crystal structure conformation of the 18-crown-6: K^+ complex

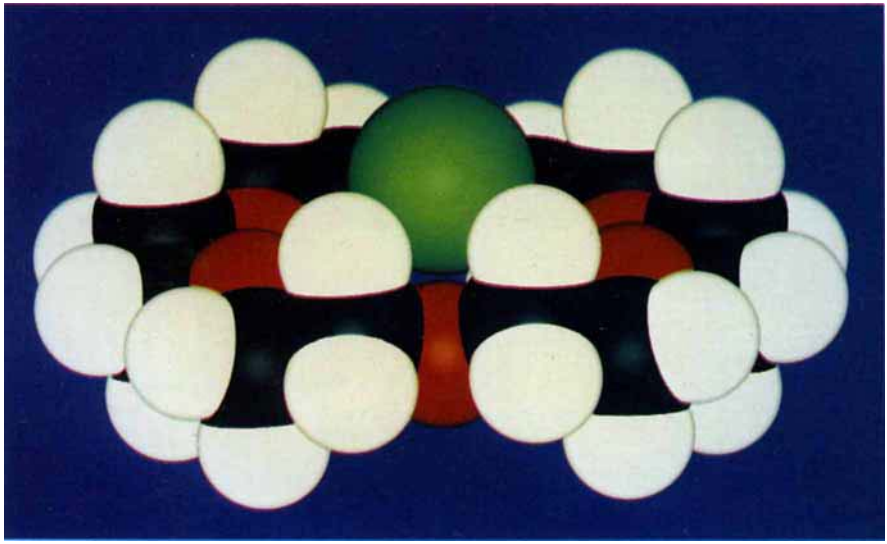


PLATE 3. Side view of the X-ray crystal structure conformation of the 18-crown-6: Cs^+ complex. Space-filling at 0.63 × Van der Waals radius

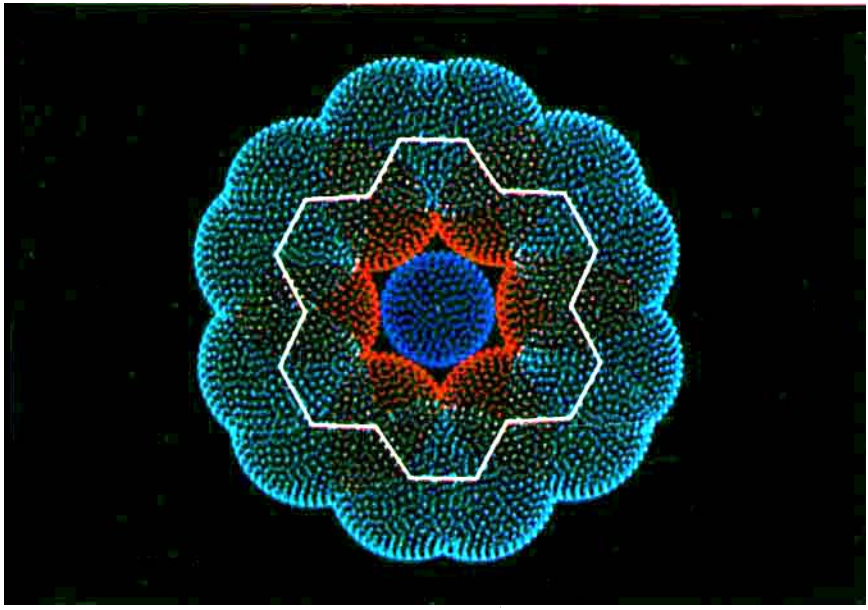


PLATE 4. Surface dot picture of the electrostatic potential of the 18-crown-6: K^+ complex. Charge is graded from red for negative to blue for positive

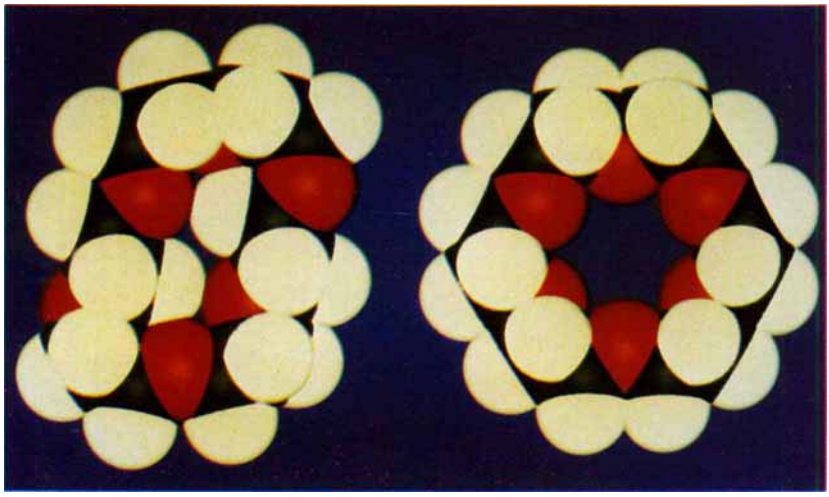


PLATE 5. Space-filling models of conformations of 18-crown-6. Left structure is uncomplexed *Ci* conformer. Right structure is the D_{3d} host conformation from the K^+ complex

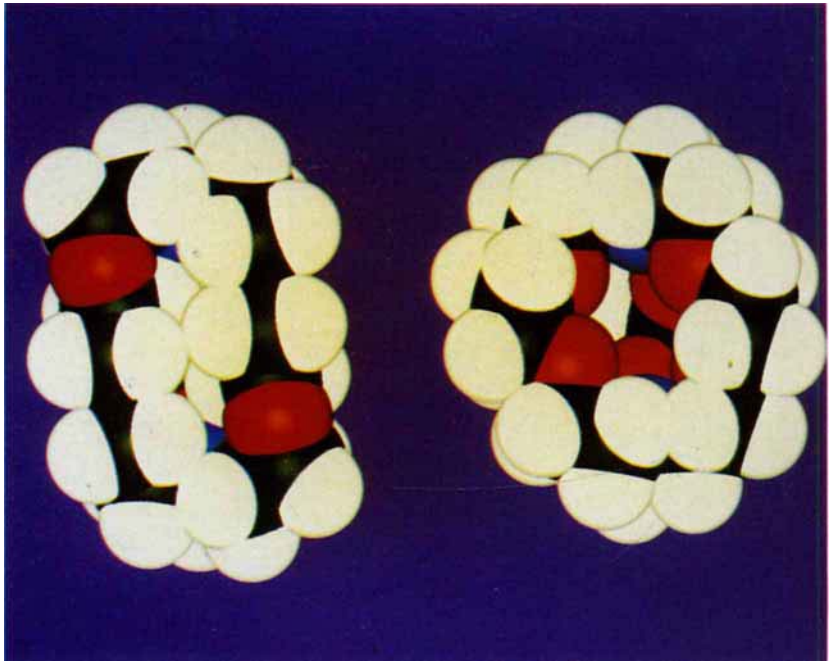


PLATE 6. Conformations of [222]cryptand and cryptate. Left structure is the crystal structure conformation of [222]cryptand. Right structure is the host conformer from the K^+ complex

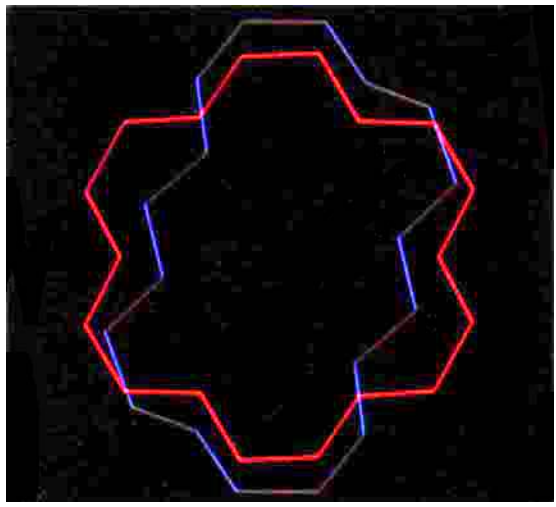


PLATE 7. Least-squares fit of host conformers from complexed and uncomplexed 18-crown-6. The K^+ complexed host conformer is in red and the uncomplexed in blue

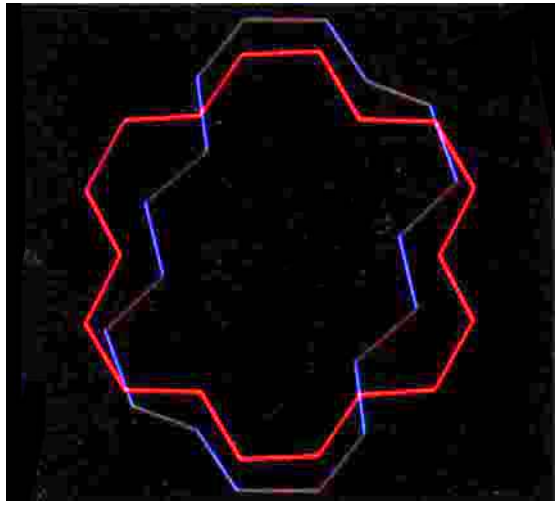


PLATE 8. Least-squares fit of conformers of [222]cryptand and the K^+ cryptate. The K^+ complexed host conformer is in red and the uncomplexed in blue

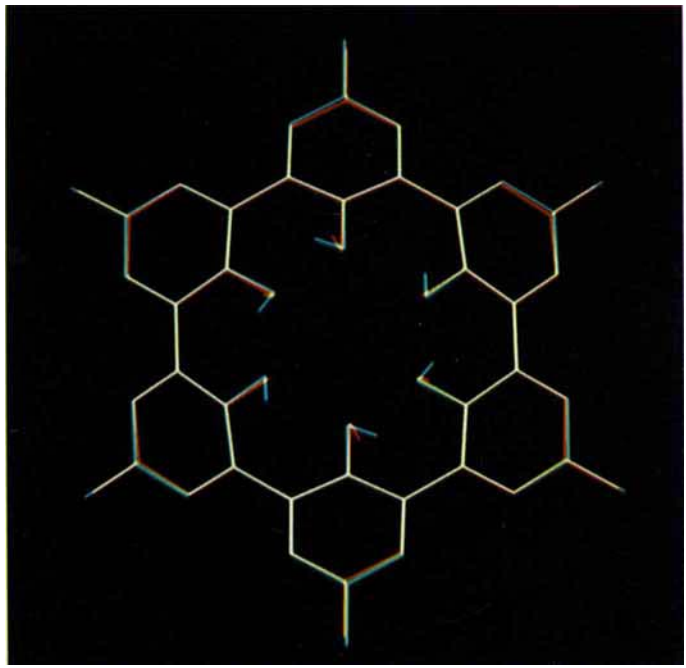


PLATE 9. Least-squares fit of spherand **5** and the host conformer of the Li^+ speraplex. The Li^+ complexed host conformer is in red and the uncomplexed is in cyan. The overlap region appears yellow

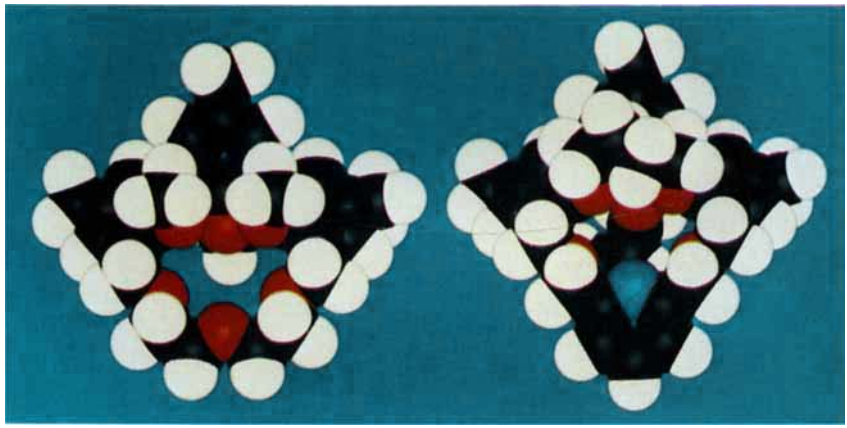


PLATE 10. Space-filling models of hemispherands **3** and **84** showing the effect of constriction on the binding cavity

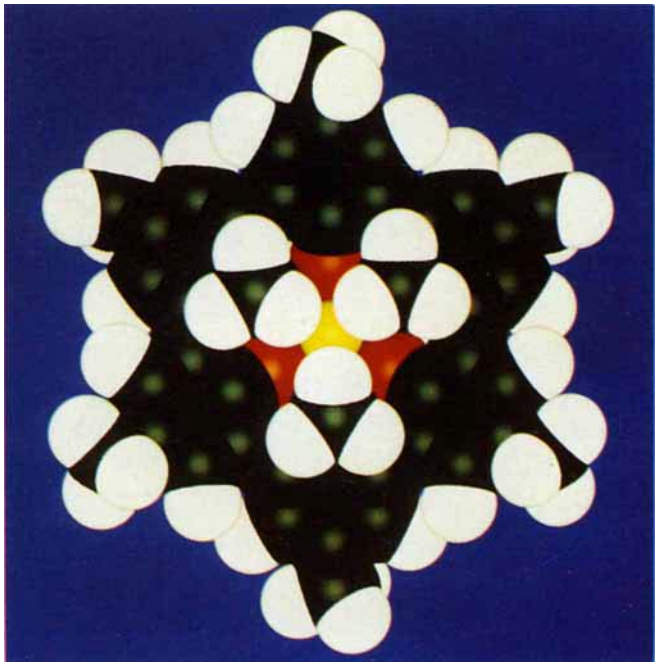


PLATE 11. Space-filling representation of Li^+ spheraplex **5**. Space-filling at 0.63 × Van der Waals radius

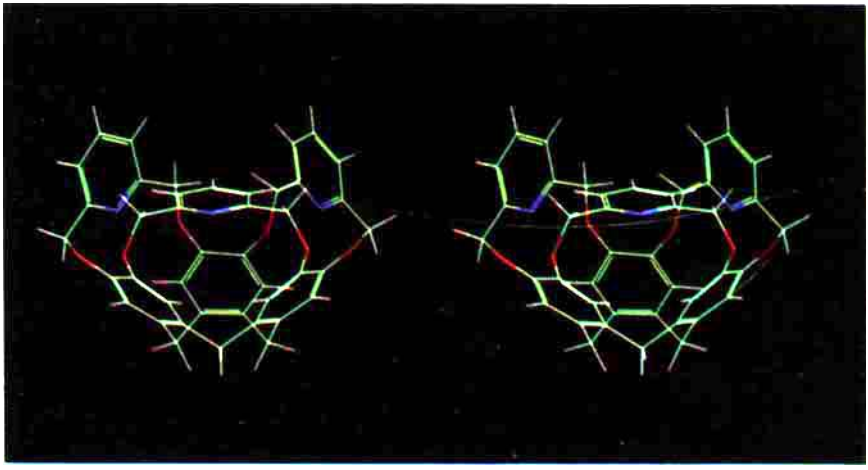


PLATE 12. Stereoview of the energy-minimized conformer for cavitand **292**

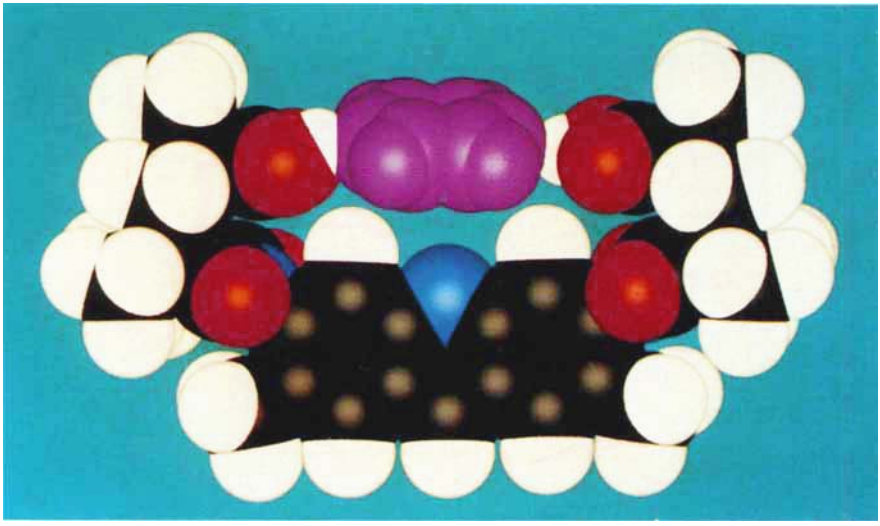
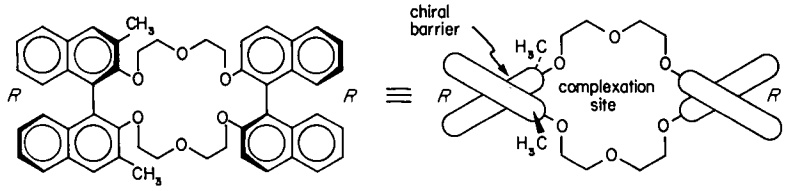
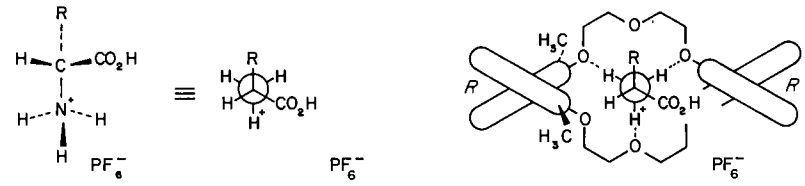


PLATE 13. Space-filling model of complex **312**. Pyrazine guest is magenta. Space-filling is at 0.73 × Van der Waals radius



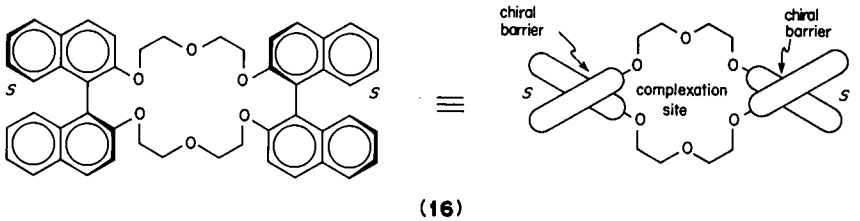
(14)



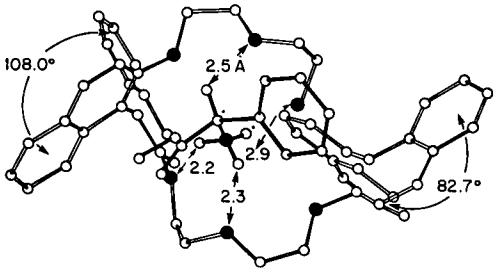
(15)

More stable complex

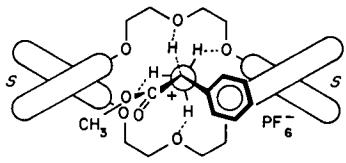
FIGURE 4. Preferred complex between chiral host **14** and guest amino acid



(16)



(17)



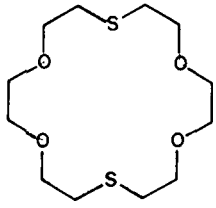
(18)

FIGURE 5. Disfavored complex between chiral dibinaphthyl host **16** and guest amino acid

projects along one side of a naphthalene ring and the α-hydrogen pokes into the side of the opposite naphthalene ring[50]. The binding of the guest enantiomer does not occur by the same method owing to the implicit projection of the carboxyl into a naphthalene face. The X-ray crystal structure (**17**) of demethylated host **16** shows that a new form of binding occurs which minimizes such an unfavorable interaction (Figure 5) at the expense of considerable strain in the host[50,51].

What are the correct number and type of binding sites for a given guest? There are considerable variations in the literature but, as a rough generality, alkali metal ions complex with 4–8 sites in a host depending on ionic diameter. The guest may also fill additional coordination sites with solvent. Alkaline earth cations complex with at least eight binding sites if available, presumably owing to the need to overcome their enormous hydration energies[52]. It is advantageous with other more elaborate guests to design into a host as many points of complementary contact as possible, drawing from the full range of non-covalent interactions. Expanding the epitope should increase selectivity in binding.

Clearly, to be complementary a host must also provide its guest with the appropriate type of binding sites. As an example, complexation by 18-crown-6 (**10**), with relatively hard oxygen heteroatoms, is 2 kcal mol^{-1} more favorable for K^+ than for Ag^+.[47] Conversely, dithia-18-crown-6 (**19**) binds Ag^+ with $-\Delta G^0 = 13.1$ kcal mol^{-1} in water[53a]. Complexation of K^+ by host **19** was measured in MeOH ($-\Delta G^0 = 1.6$ kcal mol^{-1})[53b]. In general, neutral hosts are much poorer cation binders in water than in the less polar solvent MeOH[47]. Host **19** is a superior Ag^+ complexor because of the favorable interaction between the metal and the 'soft' sulphurs.

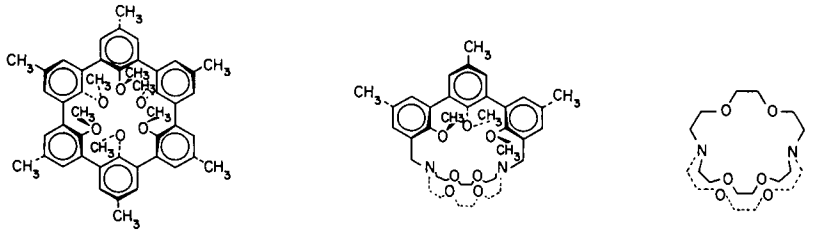


(19)

G. Preorganization

A host is said to be preorganized if its bound and unbound conformations closely resemble each other[22]. The more highly the hosts are organized for binding and low solvation during synthesis rather than during complexation, the higher is the resultant binding constant for interaction with a guest. Preorganization is distinct from but complementary to the macrocyclic effect, in that there are acyclic hosts which are preorganized and macrocyclic hosts which are not. Although the macrocyclic effect and complementarity are important to the binding ability of a host, the degree of preorganization must also be considered as an important contributing factor to the major differences in binding ability seen between host classes. Figure 6 gives a list of several predominantly cation binding hosts, their class names and the best complexed guest and its binding energy from picrate extractions[22]. It is clear that the class differences are not due solely to either macrocyclization or numbers of binding sites, although those are important. The most powerful binder, spherand **5**, has fewer binding sites than two of the other examples and the same number of binding sites as the other three hosts. These hosts differ fundamentally in their degree of preorganization.

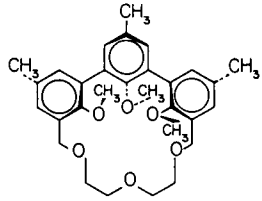
Plate 5 shows space-filling representations of the conformations of complexed and



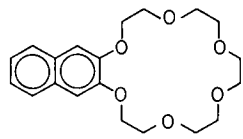
Spherand[a] 5
Li^{+b} (>23)[c]

Cryptahemispherand 4
Na^+ (21.0)

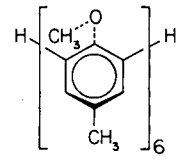
Cryptand 2
K^+ (18.0)



Hemispherand 3
Na^+ (12.2)



Coronand 20
K^+ (10.8)

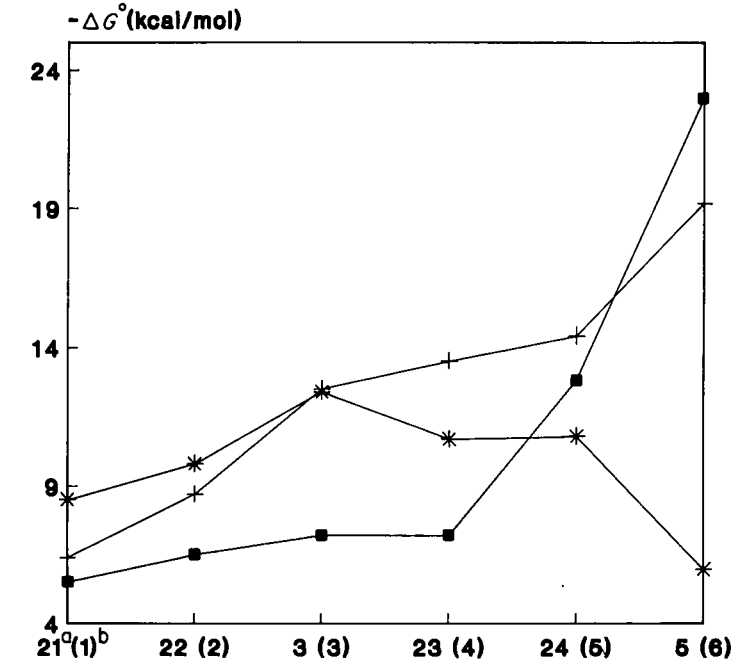


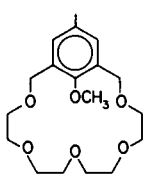
Podand 13
K^+ (< 6)

FIGURE 6. Cation complexing hosts arranged according to binding ability. [a]Class name. [b]Most preferred guest. [c] $-\Delta G°$ for best complexed guest (kcal mol^{-1})

uncomplexed 18-crown-6 obtained from the X-ray crystallographic studies[18a,44]. Plate 6 provides analogous data for [222]cryptand[18a,54]. The free ligands have inwardly turned methylenes with hydrogens occupying the binding cavities in the crystalline state. In order to complex, the host must undergo an energy-expensive conformational reorganization to attain the binding conformation. In stark contrast, spherand **5** undergoes very little conformational rearrangement upon complexation with Li^+ or Na^+[55]. It was considered that least-squares fitting of the coordinates obtained from crystal structure studies of complexed and uncomplexed hosts might quantitate the degree of preorganization of a given host. Plates 7–9 are the results of least-squares fits of the atomic coordinates of three hosts, each overlaid with its best complex[49]. For 18-crown-6 and its K^+ complex, the root mean squared (RMS) difference for all carbons and heteroatoms was 0.82 Å. The analogous RMS difference for [222]cryptand and its K^+ complex was 1.01 Å. A considerably lower value was obtained for spherand **5** and its Li^+ complex. For these hosts, the RMS difference for overlapping the two structures was only 0.21 Å.

By the quantitative criteria of the least-squares fitting of bound and unbound host conformations, it is clear that [222]cryptand is less preorganized than coronand **10**. Analogous evaluation of the rest of the hosts in Figure 6 by least-squares fitting was not directly possible because the coordinates of relevant crystal structures were not available in the Cambridge database[18a]. However, in the case of hemispherand **3** an approximate idea of the degree of preorganization was obtained by first minimizing the computer-generated Na^+ complex using molecular mechanics with parameters similar to those of Kollman and coworkers[42,56]. A very reasonable structure resulted, similar in host conformation to the published complex with *t*-butylammonium perchlorate[39]. Least-

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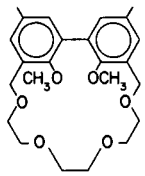
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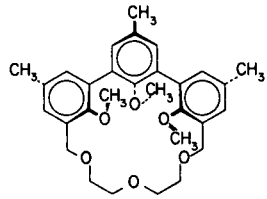
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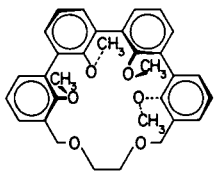
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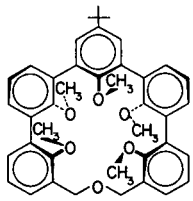
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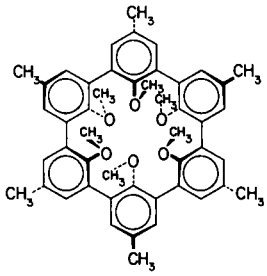

(5)[c]

FIGURE 7. Alkali metal picrate complexation by hosts with 1–6 anisyl groups in 18-membered macrorings. [a]Structure number. [b]Number of anisyl groups. [c]Host **5** binds Li^+ with $-\Delta G° > 23\,kcal\,mol^{-1}$ and K^+ with $-\Delta G° < 6\,kcal\,mol^{-1}$ in $CDCl_3$. ■, Li^+; +, Na^+; *, K^+

squares fitting of the carbons and oxygens of this minimized structure with the structure from the crystallographic analysis of the uncomplexed hemispherand[158] gave a RMS difference of 0.65 Å. For cryptahemispherand **4** the coordinates for neither the bound nor free host are in the Cambridge database. However, the structure resulting from the X-ray crystallographic analysis of the Na^+ complex has been published[39]. Minimizations of free host and host complexed with Na^+ were carried out as for hemispherand **3**. The calculated conformation for the minimized complex compared well with the actual crystal structure. The lowest energy conformers for complexed and uncomplexed hosts were fitted by least-squares methods. The RMS difference was 0.69 Å.

This preliminary evaluation suggests that the degree of preorganization for the studied hosts is spherands $\gg$ cryptahemispherands = hemispherands > coronands > cryptands. This is considerably different from their relative binding abilities (Figure 6). What is the contribution of preorganization to binding? It appears significant predominantly for the hosts with contiguous rigid units. The conformationally locked anisyl units are the preorganizational members of their hosts. In addition, the anisyl units provide stable platforms from which to append binding sites. Removing the binding sites from being a part of the structural framework of the macroring in the anisyl hosts in Figure 6 frees them to focus their electron pairs in the most ideal fashion to accommodate appropriate guests[56]. A significant proportion of the difference in binding between [222]cryptand and 18-crown-6 is probably due to the greater number of binding sites and the fact that the binding sites of the cryptand are structurally disposed in an ideal fashion around a guest, not to cryptands being more preorganized than coronands.

Spherands are at the pinnacle of both binding and selectivity among alkali metal cation complexing agents. Here the reason seems clearly to be preorganization. Figure 7 lists $-\Delta G^0$ values from picrate extractions for the complexation of Li^+, Na^+ and K^+ by the series of 18-membered macrocycles with 1–6 anisyl units in the macroring[22,39,57]. This provides a clear demonstration of the effects of preorganization.

Both experimental evidence[152] and calculations[151] suggest that uncomplexed 18-crown-6 shifts its conformation in polar solvents from the C_i conformer found in the crystal structure[44b] and in apolar solvents to the D_{3d} conformer which is the K^+ binding conformation[44a]. Hence, in polar solvents, host **10** could be said to be preorganized with an intact binding cavity. However, the intrinsically higher energy D_{3d} conformer apparently forms because it is better solvated in polar solvents than the C_i conformer[151]. Consequently, although the unbound D_{3d} conformer appears ready to receive a guest, the host must still be desolvated at a considerable energy cost in order to bind. Conversely, spherand **5** is organized in such a fashion that its oxygens cannot be effectively solvated. The avoidance with spherands of host desolvation during complexation must surely be one of the major reasons for their high binding abilities[39].

III. MOLECULAR MODELING

A. Space-filling Molecular Models

Researchers in host–guest chemistry have made extensive use of Corey–Pauling–Koltun (CPK) space-filling molecular models to aid in the design of hosts. As considered in the previous section, the complexity of hosts is such that without three-dimensional representation it is difficult to visualize many systems. It is even more difficult to design a host for a new purpose without the aid of models. Properties such as selectivity between various ions[22,39], selectivity between pairs of enantiomers by a chiral host[39,58], enantioselective reactions[59], allosteric effects[60] and features of many crystal structures[39] have been successfully predicted using space-filling models. The occasional failure in correct prediction (Figure 5) is often the fault of conformations of the host and guest not

properly accounted for during model building. At best, space-filling models give a 'feel' for expected properties in a new host, which must be coupled with chemical intuition and experimentation to realize particular objectives. No quantitative predictions can be made.

B. Computational Chemistry

1. *Introduction*

Attempts to supply quantitative information in the design of new hosts or the interpretation of properties of existing hosts are the province of studies in computational chemistry[61]. Computational methods divide between model building and energy calculations. The use of sophisticated graphics workstations with appropriate software packages allows model building and manipulation, notably allowing direct importation of structures from crystallography databases or structure entry using templates and builders followed by docking operations for the manipulation of intermolecular positioning. Calculation techniques encompass molecular orbital calculations including *ab initio*[62], semiempirical[61] and molecular mechanics techniques[61,63].

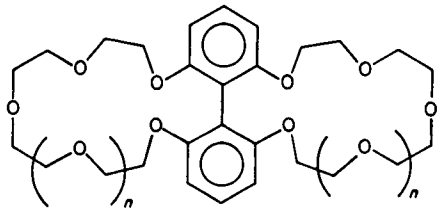
2. Ab initio *and semiempirical methods*

The predominant current use for both *ab initio* and semiempirical calculations in host–guest chemistry is to determine parameters such as partial charges on relevant atoms using model calculations for subsequent use in other computational methods such as molecular mechanics. An example is the use of dimethyl ether as a model for the ethylene glycol oxygens so prevalent in crown ethers and other hosts. *Ab initio* calculations also allow the modeling of metal–ligand interactions and the generation of parameters for subsequent use in molecular mechanics programs[42]. High-quality *ab initio* calculations are more reliable than semiempirical calculations in these model studies because semiempirical programs tend to give the wrong geometries, to yield unrealistic interaction energies and to overemphasize greatly the importance of charge-transfer in binding[64].

Another powerful technique is the use of a molecular mechanics program to generate a minimized conformation of a host as input into a semiempirical program. Table 1 compares observed versus calculated UV transitions for hosts **25**, **26** and model tetramethoxybiphenyl **27**. In this study[65] the minimized geometries of the biphenyl derivatives **25–27** were obtained using the molecular mechanics program MMP1[66]. The biphenyl dihedral angles for the minimized hosts were transferred to the model tetramethoxybiphenyl **27**. The resulting geometries of the biphenyl model were used to simulate the UV transitions of the hosts and model using CNDO/S[67] calculations. The combination of molecular mechanics, semiempirical calculations and observed spectral behavior visualized the clear relationship between the hosts' biphenyl dihedral angles and UV transitions and lent support to the assertion that their minimized structures are an accurate reflection of the average solution conformations.

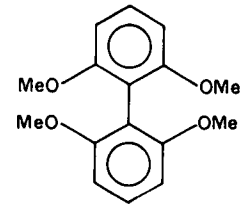
Table 1. CNDO/S calculated UV transitions for **25–27** from dihedral angles obtained from model biphenyl **27**[65]

Biphenyl	$\lambda_{obs.}$(nm)	$\lambda_{calc.}$(nm)	$\theta_{calc.}$(°)
25	259	258	60
26	246	244	67
27	246	230	90



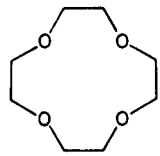
(25) $n=1$

(26) $n=2$



(27)

Some studies have appeared in which *ab initio* or semiempirical programs have been used as the sole calculation technique to study hosts and their complexes. An early *ab initio* study on 12-crown-4 (**28**) and its Li^+ complex reproduced qualitatively the binding features even though cation binding energies computed with the STO-3G basis set are overemphasized and the approach distances calculated were too small[68]. Recently, simulated *ab initio* molecular orbital calculations have been applied to 12-crown-4[69].



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The pair potential procedure has been used by Simon and coworkers[93] to generate a series of isoenergy contour diagrams for various coronands complexed with alkali metal cations or ammonium salts (Figure 8). The conformations of the crown ethers and any

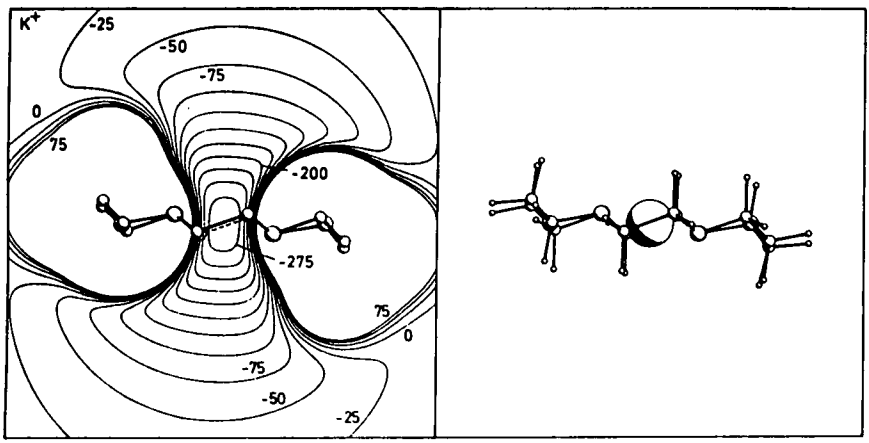


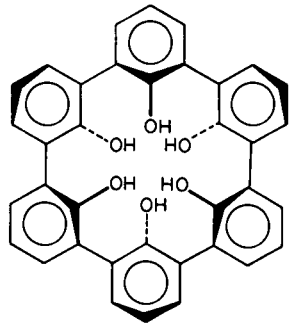
FIGURE 8. Left: isoenergy contour diagram (energies in kJ mol^{-1}) for the interaction of K^+ with 18-crown-6. Right: Structure of the K^+ complex with 18-crown-6 as determined by X-ray crystallography

waters involved in the complexes were fixed as found experimentally. The pair potential approach describes the interaction energies of two molecules as the sum of pairwise interactions, with the assumption that each atom of the host interacts independently with each atom of the guest. A large number of *ab initio* calculations are first performed on models which exemplify the various features of the host–guest interaction to be studied. The host–guest interaction energy is then rapidly calculated with surprisingly good correspondence with experiment. For the above study, the calculated minimum energy contours for the guest ions varied from the experimental ion positions by 0–0.5 Å.

The electronic structures of lanthanide complexes of crown ethers have been studied utilizing an INDO method[70]. In addition, arenediazonium interactions with crown ethers have been modeled with the CNDO/2 program by the unusual expedient of replacing the host with three dimethyl ether molecules[71]. 12-Crown-4 (**28**) has been examined by semiempirical techniques in a series of papers[72]. Yamabe *et al.*[73] have utilized the semiempirical program CNDO/2 in a study of the complexes of 18-crown-6 (**10**) and 12-crown-4 (**28**) with Na^+, K^+ and NH_4^+, and concluded that cation selectivity is strongly influenced by both the relative hydration energies of the cations and their interaction energies with the coronands. The photoelectron spectra of these two hosts were described well by the MO calculations. In addition, the importance of charge-transfer interactions between the crown ligand and the guest cation was concluded from the extent of the orbital interactions in the calculations, a conclusion contested by others[42].

Ab initio energy component calculations on alkali metal cation–oxygen complexes suggest that the main attractive forces are electrostatic and polarization, the charge-transfer actually being smaller than second-order exchange[74]. Later work by Yamabe and coworkers[75] using *ab initio* calculations with the STO-3G basis set again stressed the importance of charge-transfer interactions in host complexation of alkali metal cations. However, it has been stated that the STO-3G basis set is too small to allow reliable calculation of ion–ligand interaction energies[64], and that it produces overestimates of the contribution of charge-transfer interactions[76].

Finally, a CNDO/2 study of cyclosexiphenol spherand **29** and its complexes with Li^+ and Na^+ was recently published[77]. The Na^+ complex was calculated to be unstable whereas the Li^+ complex was predicted to be stable. The spherand has not been synthesized yet, so this constitutes a predictive rather than a retrospective study.



(**29**)

3. *Molecular mechanics*

a. Introduction. A major problem with using both *ab initio* and semiempirical techniques in host–guest chemistry is the time involved in calculations for such large

Table 2. CYBER 845 computer run times and results for calculating the properties of propane using various calculational methods[61]

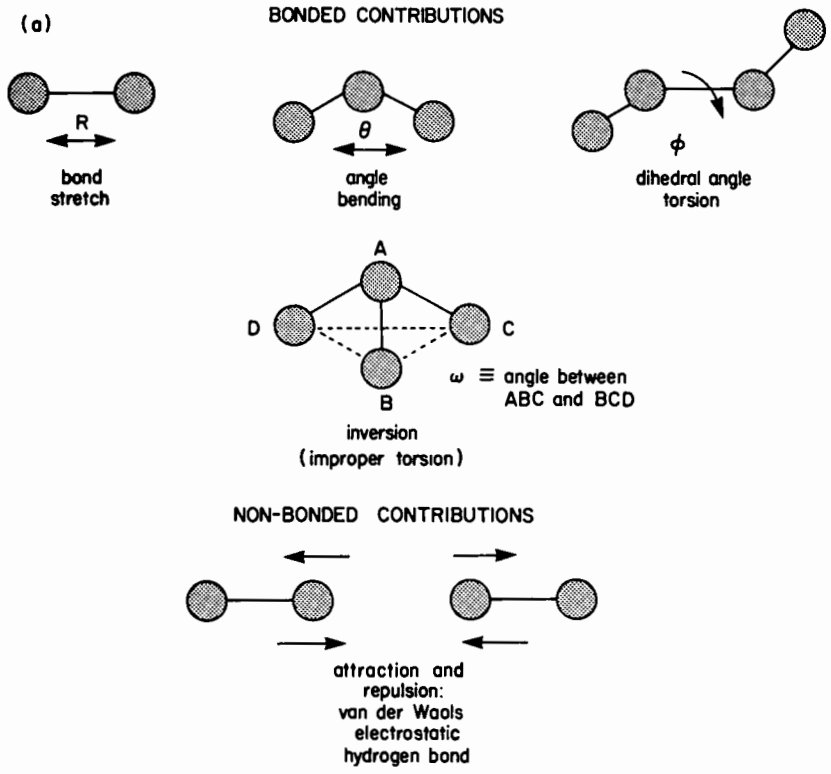
Program	CPU time (s)	r_{CC}(Å)	$\langle_{CCC}$(°)	ΔH_f° (kcal mol^{-1})
MM2	0.83	1.534	111.7	−24.8
MINDO/3	9.75	1.495	121.5	−26.5
MNDO	10.32	1.530	115.4	−24.9
3-21G	550	1.541	111.6	—
6-31G*	4702	1.528	112.7	—
Exp.	—	1.526	112.4	−25.0

molecules. The computer time required for *ab initio* calculations is roughly proportional to the fourth power of the number of atomic basis functions used, which renders studies on host–guest systems with more than 150–200 electrons problematic[64]. Table 2 relates the CPU time for various popular calculation programs in the optimization of propane from the same starting geometry with a CYBER 845 computer[78]. Propane is a member of the parametrization sets for MM2, MINDO/3 and MNDO, so agreement with the experimentally determined heat of formation was expected. The calculation times vary by a factor of over 5000, which would increase dramatically for the larger host molecules.

Molecular mechanics programs generally give minimized geometries with hosts in a fraction of the time needed for either semiempirical or *ab initio* calculations. The major drawbacks to molecular mechanics remain the difficulty in isolating relevant conformational energy minima, often from many possibilities, handling solvation effects appropriately and correctly representing the electrostatic properties of atoms in molecules and the induced polarization on complexation. Methods for compensating for these shortcomings have been developed, and molecular mechanics studies have appeared which have correctly reproduced many of the properties of both complexed and uncomplexed hosts.

Molecular mechanics approaches include energy minimization programs, molecular dynamics[79] and Monte Carlo simulations[80]. Molecular mechanics, or force field, calculations involve the treatment of molecules as an assemblage of atoms governed by a set of classical mechanical potential functions. Among these functions are terms for bond stretching, angle bending, dihedral angle torsion and inversion, which form the bonded contribution, and steric/dispersion, electrostatic and hydrogen-bonding terms, which account for the non-bonded interactions (Figure 9). Molecular graphics software packages which allow structure entry, manipulation and performing molecular mechanics include BIOGRAF[81], CHEM-X[82], CHARMM[83], MACROMODEL[84], SYBYL[85] and CHEMLAB[86].

In general, host–guest chemistry provides excellent substrates for the use of molecular mechanics. The molecules are too large for routine handling by *ab initio* or semiempirical techniques and are much smaller than many of the biological macromolecules which are the frequent subjects of molecular mechanics studies. In addition, hosts normally have built-in conformational restrictions as a function of their design which further simplifies treating them with molecular mechanics techniques. Most molecular mechanics studies involving host–guest chemistry have used energy minimization programs. Such programs have in common the following steps: selection of a starting conformation, calculation of the conformational energy using the potential energy expression, modification of the independent variables using an appropriate algorithm, recalculation of the conformational energy, determination of the direction toward lower energy, adjustment of the independent variables in the direction of lower energy and repetition of the last three steps until a minimum energy structure is obtained[87].



(b)

$$E = (1/2)\, k_b\, (R - R_0)^2 \qquad \textit{(bond stretch)}$$

$$+ (1/2)\, k_\theta\, (\theta - \theta_0)^2 \qquad \textit{(angle bending)}$$

$$+ \Sigma\, k_f \left[1 + \cos\left(n\phi + \delta_n\right)\right] \qquad \textit{(dihedral angle torsion)}$$

$$+ k_\omega\, (\omega - \omega_0)^2 \qquad \textit{(inversion)}$$

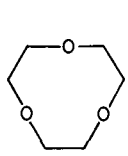
$$+ \Sigma\, (Q_i\, Q_j / 4\pi\epsilon_0\, R_{ij}) \qquad \textit{(electrostatic)}$$

$$+ \Sigma\, (D_0)_{ij} \left\{ \left[(R_0)_{ij} / R_{ij}\right]^{12} - 2\left[(R_0)_{ij} / R_{ij}\right]^{6} \right\} \qquad \textit{(van der Waals)}$$

$$+ \Sigma\, (D_0)_{ij} \left\{ 5\left[(R_0)_{ij} / R_{ij}\right]^{12} - 6\left[(R_0)_{ij} / R_{ij}\right]^{10} \right\} \qquad \textit{(hydrogen bond)}$$

FIGURE 9. (a) Components of the potential energy expression. (b) The potential energy expression

b. Energy minimization. Pioneering work by Sutherland and coworkers[40] on the structural flexibility of coronands and by Truter[88] on 18-crown-6 and other crown ethers, and work by Hancock and McDougall[89] on the macrocyclic effect in several polyamines and their transition metal complexes, laid the foundation for later molecular mechanics studies in host–guest chemistry. Sutherland and coworkers[40] examined the calculated properties of known or speculated conformations of 9-crown-3 (**30**), 12-crown-4 (**28**), 14-crown-4 (**31**) and 18-crown-6 (**10**) using the molecular mechanics program WBFF2, which had been specifically modified to allow optimized calculation of properties of ethers and compounds with the 1,4-dioxa unit.



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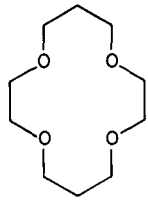


(31)

For 12-crown-4 (**28**), the global minimum was shown to be the so-called 'square' conformation, which has four identical *gauche, gauche, anti*-conformations for the individual O—C—C—O groups, in agreement with solution IR spectroscopy and ^{13}C NMR results. The global minimum conformation was 2.9 kcal mol^{-1} lower in energy than the conformation adopted in the crystal structure, largely owing to lower torsion angle strain.

In 18-crown-6 (**10**) and comparisons with the crystal structure of its benzylammonium thiocyanate complex, it was calculated that the minimum energy conformation, which has the cavity occupied by CH_2 hydrogens, is 7.84 kcal mol^{-1} lower in energy than the binding conformation seen in complexes with K^+, Rb^+ and Cs^+ (Figure 10). The binding conformation would be the lowest energy conformation except for the unfavorable electrostatic repulsions between the oxygens. These unfavorable interactions are partially compensated for by complexation.

A study of 18-crown-6 and its complexes with alkali metals by Wipff *et al.*[42] focused on structural flexibility, which is the tendency of coronands to adopt different conformations under different conditions, on cation selectivity, which is the preference of the host in binding certain cations, and on the macrocyclic effect, which pertains to the greater host–guest binding energies seen with coronands than with acyclic models. Using the molecular mechanics software package AMBER[90], they were able to demonstrate that the various conformations from X-ray crystal structure studies represent minima in the potential energy surface. The absolute energy differences between conformations of uncomplexed host differed from those previously determined by Sutherland and coworkers[40], which is not surprising because the total energies in these calculations depend dramatically on the partial charges used. In addition, Wipff *et al.*[42] did not use a specifically optimized program for their calculations. Both studies reproduced the C_i symmetry conformation from the X-ray crystallography study of Dunitz *et al.*[44b] as the lowest energy conformation for uncomplexed 18-crown-6. However, in the study by Wipff *et al.*, the D_{3d} conformation, which is the binding conformation with K^+, Rb^+ and Cs^+[44a,45,91], was lower in energy than the C_i conformation from the Na^+ complex[92]. This is the reverse of the order found by Sutherland and coworkers. Of further interest concerning host flexibility was the calculation by Wipff *et al.* that the transformation of 18-crown-6 with C_i symmetry to the

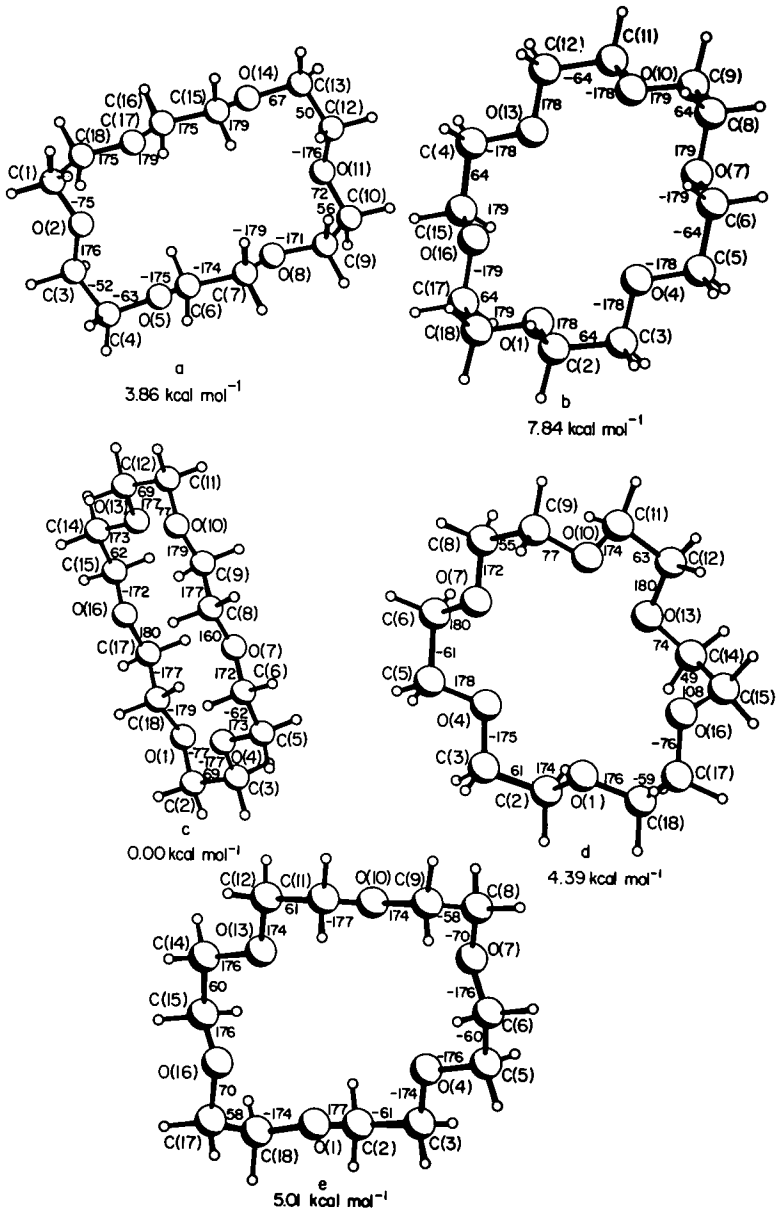


FIGURE 10. Calculated mimima in the potential energy surface for 18-crown-6. From Ref. 40. (a) Analogous to the conformation adopted by crystalline cyclooctadecane. (b) Corresponds with the D_{3d} conformer from the K^+ complex. (c) Like the C_i conformer for the uncomplexed host. (d) Similar to C_i conformation found in the Na^+ complex. (e) Low-energy minimum conformation

D_{3d} conformation has a barrier of 7.6 kcal mol^{-1}. In addition, a low-energy non-centrosymmetric 18-crown-6 conformation was found which has not been seen in X-ray crystallographic studies and which may contribute to the solution properties of uncomplexed 18-crown-6 and explain its significant temperature-dependent dipole moment.

Cation-selective binding was modeled by first comparing the total calculated gas-phase binding energies of the Na^+, K^+, Rb^+ and Cs^+ complexes of five conformations of 18-crown-6. In each case, the lowest energy conformation for the complex was in good qualitative agreement with the observed conformation in the X-ray crystal structure. In addition, the perching conformation of Cs^+ seen in the X-ray structure of a Cs^+–crown complex[45] was reproduced by the minimization program. Utilizing the calculated energies for the best complexes for each cation and the hydration energies of the cations allowed the estimation of cation selectivities in water. The calculations correctly predicted K^+ to form a more stable complex with 18-crown-6 than Na^+ but incorrectly predicted the Rb^+ complex to be even better. The K^+ complex appears to be more stable than the Na^+ complex because the difference between the hydration energies of Na^+ and K^+ is greater than the difference in their interaction energies with 18-crown-6, in agreement with the semiempirical calculations of Yamabe *et al.*[73].

Finally, the macrocyclic effect was studied by comparison of the alkali metal complexes of 18-crown-6 and its acyclic analog pentaglyme. A significant enthalpic contribution to the relative cation affinities between macrocyclic and acyclic hosts was predicted owing to the greater stability in pentaglyme of conformations which cannot interact favorably with the cation to form a complex.

Using the minimization program WMIN[94] with parameters chosen to be consistent with those of the previously discussed study of Wipff *et al.*[42], Burns and Kessler[95] were able to calculate the minimized structures for 18-crown-6 and for its complexes with Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+} and Ra^{2+}. The conformations calculated for the free ligand and the Sr^{2+} and Ba^{2+} complexes compared well with the experimental results from X-ray crystallography studies. Following the approach used by Wipff *et al.*[42], the preference of the crown ether for binding the cations in water was modeled and found to decrease in the order $Ba^{2+} > Sr^{2+} > Ca^{2+} > Ra^{2+} \gg Mg^{2+}$, which is the experimentally determined order for Ba^{2+}, Sr^{2+} and Ca^{2+}.[96]

Using ^{13}C spin–lattice relaxation time measurements, Grootenhuis *et al.*[97] demonstrated that 2,6-pyrido and benzo but not 1,3-xyleno crown ethers (hosts **32**, **33** and **34**, respectively) with at least 24-membered macrorings can adopt conformations in which the

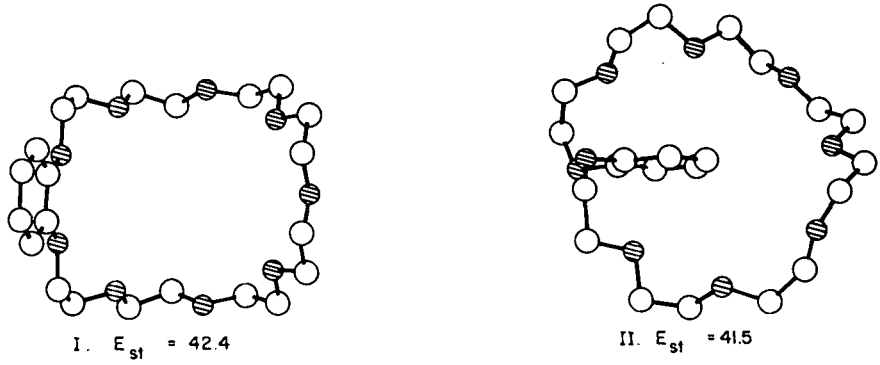
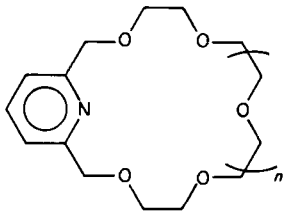
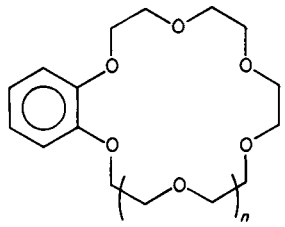


FIGURE 11. Minimized structures for benzo-27-crown-9 demonstrating the potential for self-complexation. Steric energies in kcal mol^{-1}. Oxygen atoms are shaded

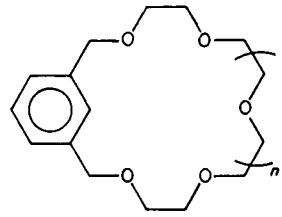
aromatic group is encapsulated by the polyether portion of the macroring (Figure 11). This intramolecular self-complexation was studied by molecular mechanics using MM2 and MMP2. The global minima were not determined for the various hosts because crown ethers with greater than 18-membered macrorings have hundreds of local minima to sort through. However, representative low-energy self-complexed conformations for the benzo crown ethers indicated that self-complexation was driven predominantly by van der Waals forces, with some attendant contribution from electrostatic interactions. Analogous treatment of the pyrido crowns showed that self-complexation is due largely to electrostatic interactions with a substantial contribution from van der Waals interactions. For the 1,3-xyleno hosts, lower energy conformations could always be found for the hosts with the xyleno group outside of the polyether cavity than for self-complexed conformations, although for 1,3-xyleno-27-crown-8 the difference was miniscule.



(32) $n=0-6$

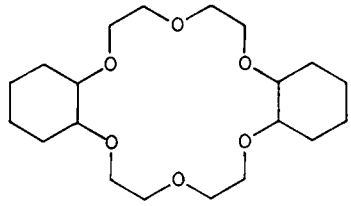


(33) $n=0-6$



(34) $n=0-6$

Complexation of the neutral guest malononitrile by the *cis–syn–cis* and *cis–anti–cis* isomers of dicyclohexano-18-crown-6 (**35**) was the subject of a recent study[98]. The *cis–syn–cis* isomer crystallizes as the 1:1 complex with malononitrile whereas the *cis–anti–cis* isomer gives the 2:1 (guest:host) complex. Molecular mechanics studies with the MM2 program using a series of parameter sets allowed generation of fully optimized conformations starting from the X-ray crystal structure coordinates, which related very well to the crystal forms for both isomer complexes (Figure 12). The calculated binding enthalpies for 1:1 complexation of malononitrile by both isomers of dicyclohexano-18-crown-6 agreed very well with the experimental value for the complexation enthalpy measured in benzene[99]. However, the minimization program predicted that both crown isomers would form facile 2:1 complexes with malononitrile whereas only the *cis–anti–cis* isomer does so experimentally. The authors invoked crystal packing as an explanation for the observed results.



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A recent extensive study of 18-crown-6 (**10**) using the MM2 program and more than 190 host starting conformations led to the conclusion that the host has a potential energy surface with many minima separated by small energy differences[100]. Large electrostatic

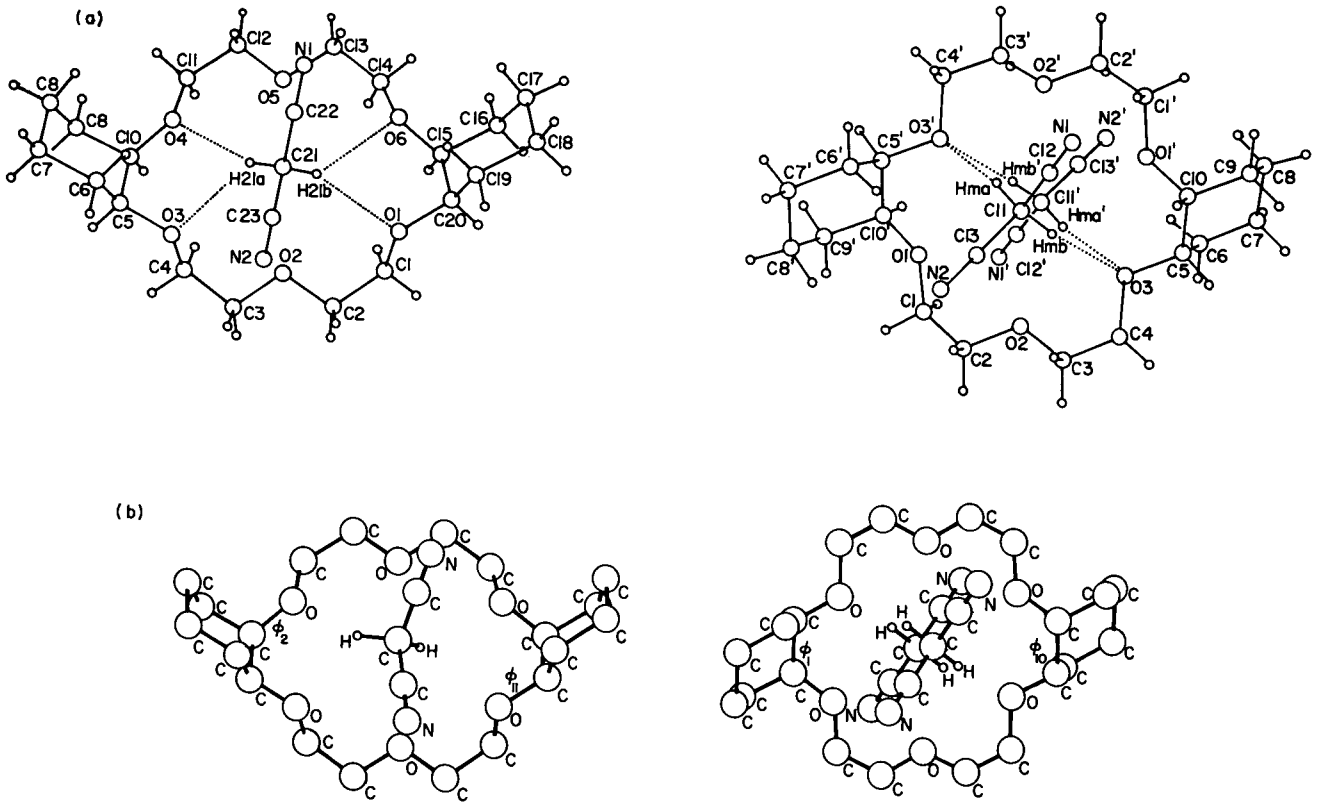


FIGURE 12. (a) X-ray crystal structures of malononitrile complexed with *cis–syn–cis* (left) and *cis–anti–cis* (right) isomers of dicyclohexano-18-crown-6. (b) Analogous views of the energy-minimized structures of the malononitrile complexes

contributions give the conformation of uncomplexed 18-crown-6 in the crystal state, whereas the absence of electrostatic interactions favors conformations such as those seen in complexes of the host. Complexes with urea and formamide were studied by both the MM2 and MM2HB force fields. The MM2HB force field, which is a modified version of MM2 including an empirical N—H···O hydrogen-bond potential, gave superior results in calculations with interactions between the host and neutral guests. Agreement between calculations and the experimental data[101] for complexes of 18-crown-6 with both formamide and urea was excellent. Other minimization studies of simple crown ethers are included in Refs. 102–104.

Because they are the best studied systems with the most available experimental data, the simple crown ethers have been the subjects of the majority of the molecular mechanics investigations in host–guest chemistry to date. However, some publications have appeared on other types of hosts. Wipff and Kollman[105] performed molecular mechanics calculations on [222]cryptand (**2**) beginning with thirteen conformations from various crystal structure studies and with eleven generated conformations using two force fields and two sets of constraints with each. The crystal structures were of both cryptand and cryptates and included the BH_3 complex in which both nitrogen lone pairs are oriented out (*exo–exo*). Each of the starting conformations was decomplexed and minimized. The lowest energy conformation corresponded to the crystal structure obtained for the uncomplexed cryptand. The force field with the best fit with experiment reproduced the [222]cryptand structure with an RMS deviation between calculated and observed structures of 0.19 Å. The average deviation in 33 dihedral angles was 4.6°. The calculated N···N distance was 7.0 Å, compared with 6.9 Å for the experimental value[106]. The nitrogen lone pairs were in the *endo–endo* orientation for both calculated and experimental conformations.

When the various cations were replaced in the different starting conformations and minimizations were carried out, some fascinating insights were obtained. The larger cations, which would be expected to fit well in the cavity of [222]cryptand, minimized to the same general structure regardless of starting conformation. For the FF1 force field, where the rotational barriers were smaller, even the Na^+ and K^+ complexes begun in the *exo–exo* conformation obtained from the crystal structure of the borane complex were able in the minimization process to revert to the true structures for their complexes as seen in the X-ray crystal structures in which the nitrogen lone pairs are in the *endo–endo* orientation. The smaller cation Na^+, however, gives a minimized structure starting from the conformation initially obtained from the Ag^+ complex which is lower in energy than the minimized conformation obtained when starting from the Na^+ crystal structure conformation. This may be due to [222]cryptand being too small for Na^+ to fit effectively in the cavity and undergo ion–ligand interactions with all the donor groups of the cryptand without forming a highly strained structure.

The intrinsic gas phase selectivity of the host followed the order $Na^+ > K^+ > Rb^+ > Cs^+$. When the hydration energies were accounted for, the order was $K^+ > Rb^+ > Na^+ > Cs^+$. Although the experimentally determined enthalpies[107] peak at Rb^+ instead of K^+, the calculations do give a peak in selectivity in the center of the alkali metals and fairly close values for the calculated enthalpies of complexation to experiment.

The total energies for the minimized *exo–exo* and *endo–endo* conformations with the FF2 force field were 123.7 and 114.9 kcal mol^{-1}, respectively. No crystal structure existed for a cryptand in the *exo–endo* conformation to use as a starting point in the minimization process. Instead, template-built structures were minimized. The best *exo–endo* conformation had a total energy of 125.7 kcal mol^{-1}, which is not excessively greater than that for the *exo–exo* ligand.

In a similar, virtually simultaneous study, Geue *et al.*[108] also examined [222]cryptand (**2**) by molecular mechanics, in this case using the MM2 program[109]. They added the

analysis of [111]cryptand (**36**) and performed semiempirical molecular orbital calculations (CNDO/2)[110] on the minimized structures which they obtained from molecular mechanics. Generated conformations had to be used for the [111]cryptand, because at the time no X-ray studies had been published. With [111]cryptand, regardless of the starting conformation, *endo–endo* and *exo–endo* conformations minimized to the same *endo–endo* structure (Figure 13). Various *exo–exo* starting conformations all minimized to yield the same *exo–exo* conformation of [111]cryptand (Figure 14). Table 3 summarizes the

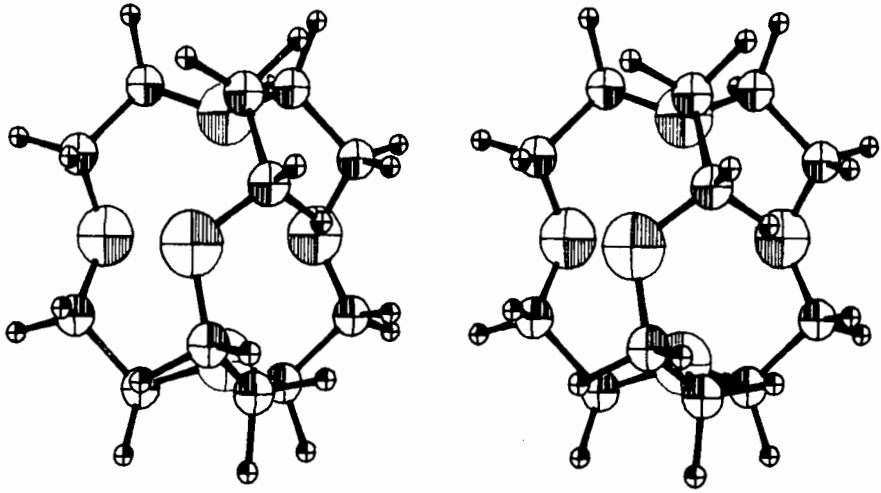


FIGURE 13. Stereoview of the minimized *endo–endo* conformer of [111]cryptand (**36**)

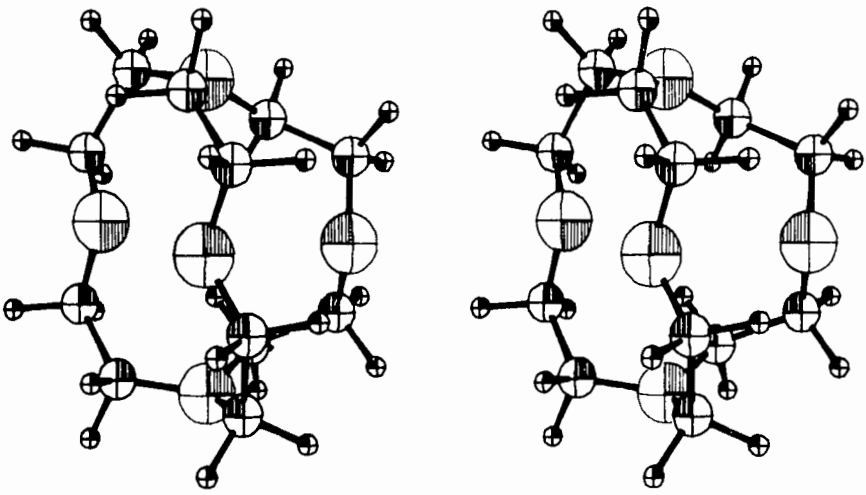
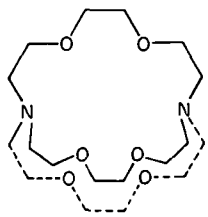


FIGURE 14. Stereoview of the minimized *exo–exo* conformation of [111]cryptand (**36**)

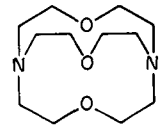
Table 3. Strain energy (kcal mol^{-1}) of [111]cryptand (**36**) calculated by MM2

	endo–endo	*exo–exo*
Compression	3.0	3.4
Bending	12.9	32.0
Stretch–bend	1.3	2.3
Non-bonded interaction	17.9	23.2
Torsion	20.4	19.9
Dipole	3.6	0.6
Total strain energy	59.1	81.4

strain energies for *exo–exo* and *endo–endo* [111]cryptand. The large energy difference between the two conformations is in accord with several experiments, which uniformly demonstrate the free [111]cryptand ligand to be *endo–endo*[111].



(**2**)



(**36**)

The input conformations for the study of [222]cryptand were acquired from crystal structure studies[112]. Minimized conformations were similar to those obtained by Wipff and Kollman[105]. The [222] structure was shown to be much more conformationally flexible than the [111] structure. In addition, finding three low-energy conformations differing primarily in nitrogen inversion suggested the potential for facile *exo–endo* conversion in solution, in agreement both with the earlier postulate of Lehn[113] and with several experiments[114]. Figure 15 presents three stereoviews of the minimized *endo–endo* (I) structure which had the crystal structure of uncomplexed [222]cryptand as a starting conformation. Interestingly, the *endo–endo* (I) structure is much more elongated than the *exo–exo* structure, owing to the conformational reorganization of the bridges between nitrogens. The suggestion was made that the *endo–endo* conformation is preferred in complexes of [222]cryptand primarily because the more elongated structure brings the oxygens into closer contact with the guest than would be possible with an *exo–exo* conformation. This is in agreement with the experimental result that the average metal–oxygen distance in cryptates is less than the average metal–nitrogen distance[112,115].

The authors considered the distance between the two planes defined by the CH_2 groups attached to the nitrogens (R_{CP}) as an indication of the elongation of the cryptand. The postulate is that only structures with small R_{CP} values would be kinetically reactive with cations (Figure 16). The preference in solution for the elongated *endo–endo* (I) form would help to explain the fact that rate constants for metal complexation are low compared with the predictions of a simple dissociative interchange mechanism[114g,116]. Additionally, the observation that decomplexation of cryptates is often acid catalyzed[114g,116d,117] might be explained by a protonated *exo*-nitrogen lone pair allowing the retention of a more spherical conformation (smaller R_{CP} value), which would allow

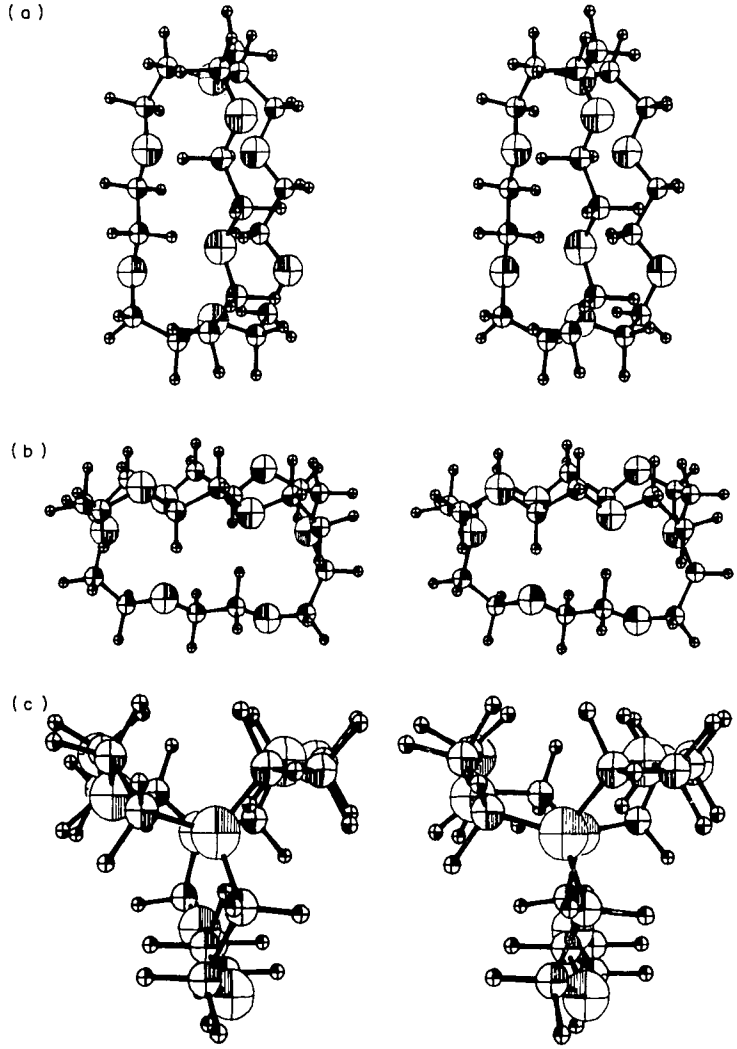


FIGURE 15. Stereoviews of the energy-minimized *endo–endo* (I) conformer for [222]cryptand (**2**). (a) [222]*endo–endo* (I) conformation; (b) alternative view; (c) alternative view

facile decomplexation. For complexes with smaller cations, direct protonation of the *endo–endo* conformation might lead to the more spherical *endo–endo* (II) conformation (Table 4), which could decomplex more easily.

No explicit treatments of metal complexes of either [111]- or [222]-cryptands were considered in the above study. After the paper had been submitted, a report of the crystal structure of [111]cryptand appeared[118]. It is comforting to note that the agreement between the calculated conformation and the crystal structure is good, although the host is disordered in the crystal (Figure 17). Although not explicitly covered in this review, cyclams have also been studied by molecular mechanics techniques[119].

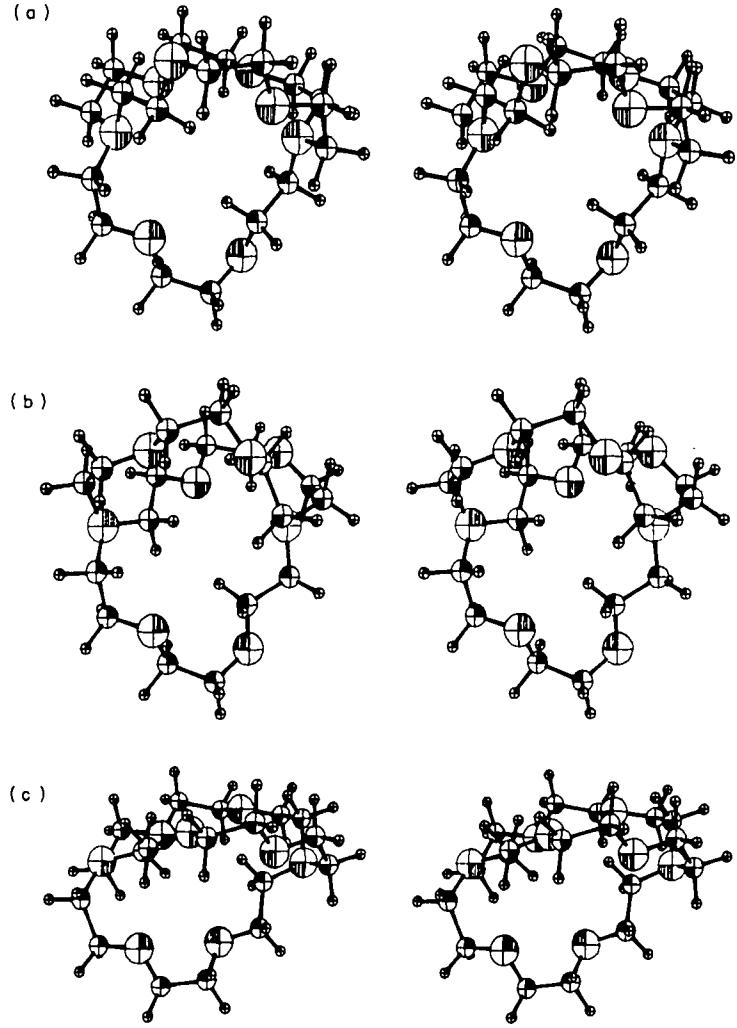


FIGURE 16. Stereoviews of conformational minima of [222]cryptand (**2**). (a) [222]cryptand *endo–endo* (II) conformer; (b) [222] *endo–exo* conformation; (c) [222] *exo–exo* conformation

Table 4. Relative strain energies (kcal mol^{-1}) and geometries of [222]cryptand (**2**) conformations

			Strain energy	
Conformation	R_N(Å)	R_{CP}(Å)	MM2	CNDO2
endo–endo (I)	6.77	7.64	0	0
endo–endo (II)	5.27	6.17	−0.4	−2.6
endo–exo	5.50	5.54	3.6	1.7
exo–exo	6.71	5.89	−1.2	0.2

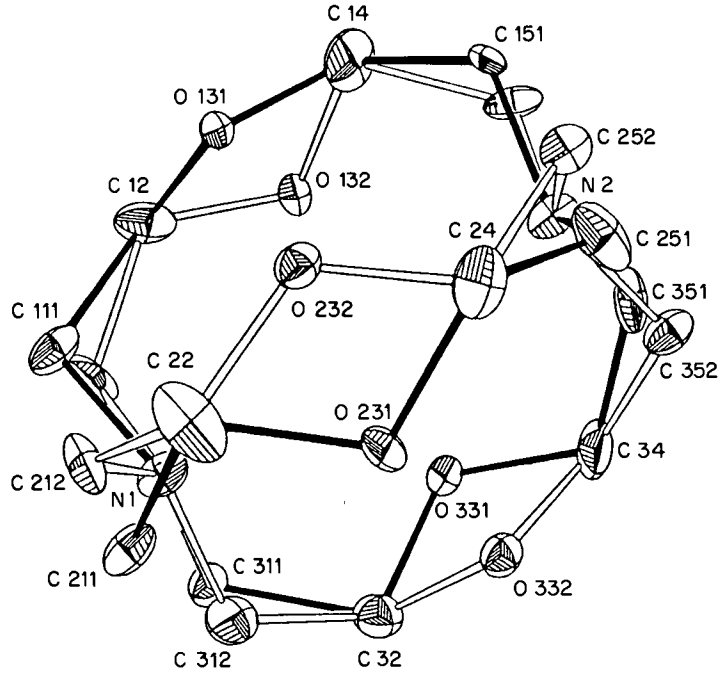


FIGURE 17. Crystal structure of disordered [111]cryptand

Using an 'interactive theoretical–experimental approach', which describes the process of feeding information back and forth between theoretical predictions and experimental validation to optimize desired parameters, a series of ionophores were designed and synthesized. Lifson and coworkers first examined the naturally occurring ionophores enniatin B[120] and valinomycin[121] using the empirical force field (EEF)[122] method for minimization. Agreement between calculated conformations and data from crystal structures of complexed and uncomplexed valinomycin was excellent, confirming the belief that the belt of hydrogen bonds gives valinomycin its distinctive cavity. Also, the calculations confirm that the ester carbonyl groups are inwardly directed, and little conformational reorganization of the host is necessary to bind the larger alkali metal cations (Figure 18). The known preference[123] of valinomycin for the larger alkali metal cations over Li^+ and Na^+ was also confirmed by calculations, in which it was demonstrated that the host cannot adequately deform to allow optimal contact distances between the smaller cations and the ester carbonyls.

The low cation selectivity of enniatin B has been attributed to the high flexibility of its cavity[123,124]. Calculations do not confirm a highly flexible molecule. Rather, the alternating carbonyls directed above and below the best plane of the macroring (Figure 19) appear ideally situated for 2:1 (host:guest) binding. The force field minimization results support the hypothesis that 2:1 binding becomes progressively more important in enniatin B as the alkali metal cation becomes larger.

Application of the EEF method to previously synthesized ref-lactones and rotolactones allowed an explanation of the observed ionophoric behavior[125]. The ref-lactones were shown to be poor ionophores. The minimized structures showed the macrocycles to be

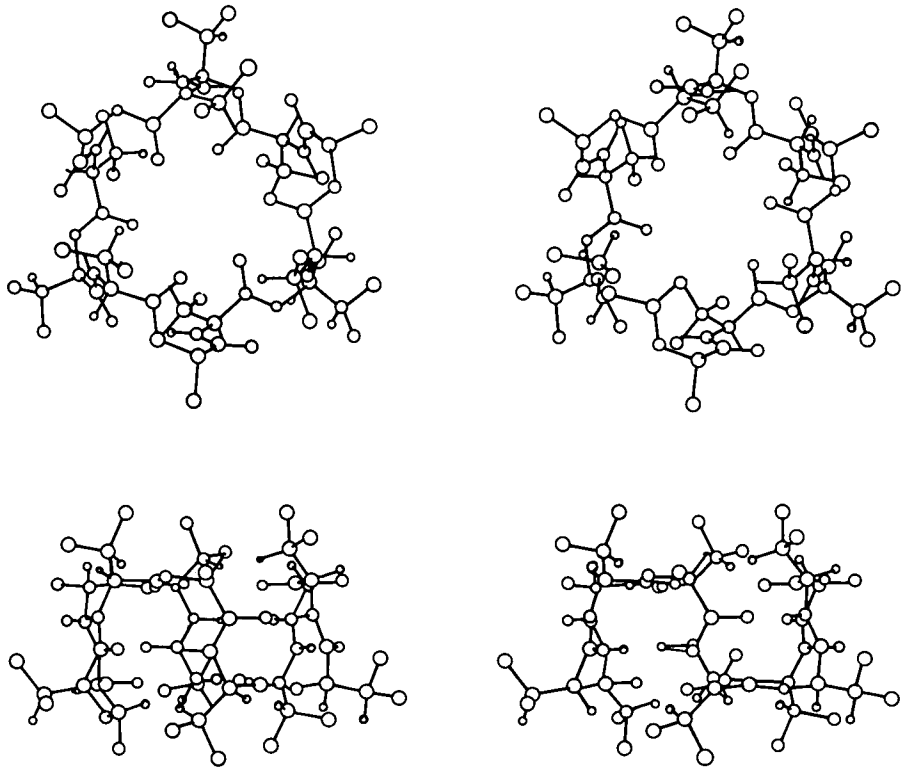


FIGURE 18. Alternative stereoviews of a calculated conformation of valinomycin

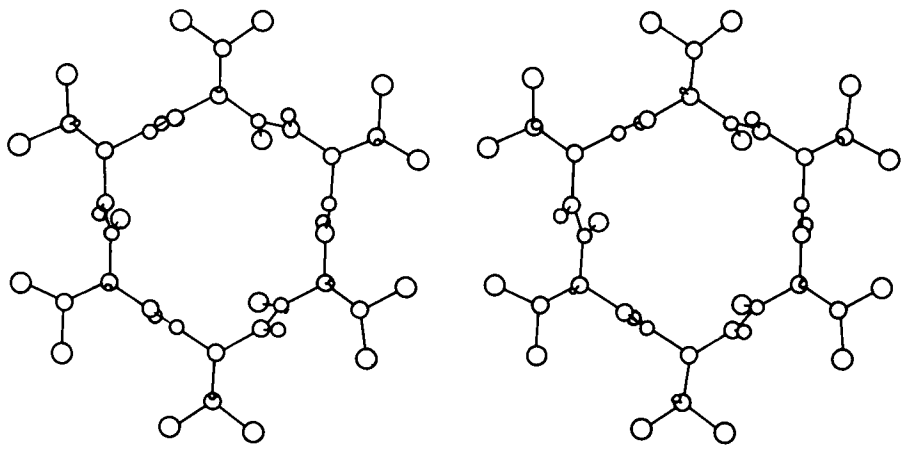
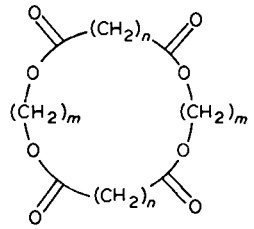
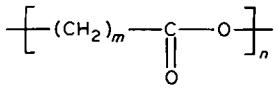


FIGURE 19. Stereoview of a minimized conformer of enniatin B

flexible but largely incapable of focusing their carbonyl groups toward the inside of the cavity.



Ref-lactones



Rotolactones

The tripropiorotolactones ($n = m = 3$) with isopropyl side-chains have been studied with the EEF methodology, and the prediction has been made that the dimer should show some selectivity for Li^+ or Na^+[126]. No experimental data have yet appeared to corroborate this prediction. The tetrarotolactones in calculations possess minima with the four carbonyl oxygens defining a tetrahedron, but oriented extra-annularly. In order to bind a cation inside the macroring, the carbonyls must bend inwards at the expense of considerable strain energy (Figure 20). Complexation experiments revealed only weak binding of $LiClO_4$.

Finally, the methyl analog of LD-cyclohexahydroxyisovaleryl (LD-Hylv6) has been shown to have a low-energy conformation with beautiful S_6 symmetry (Figure 21) in which the carbonyl groups form an octahedral array for binding[125,126]. The prediction of some Na^+ selectivity in the 1:1 complex was partially validated by experiment. The cation selectivity of LD-Hylv6 was shown to be $Li^+ \ll Na^+ < K^+ = Rb^+ = Cs^+$[127]. The cations K^+, Rb^+ and Cs^+ were proved to bind externally in a sandwhich complex between two ionophores[123].

A fascinating group of hosts, the hemispherands, have at least three contiguous binding sites preorganized in a conformation predisposed toward complexation and requiring little conformational reorganization to bind a guest. A recent study has considered both uncomplexed hosts and their complexes with the neutral guest malononitrile by X-ray

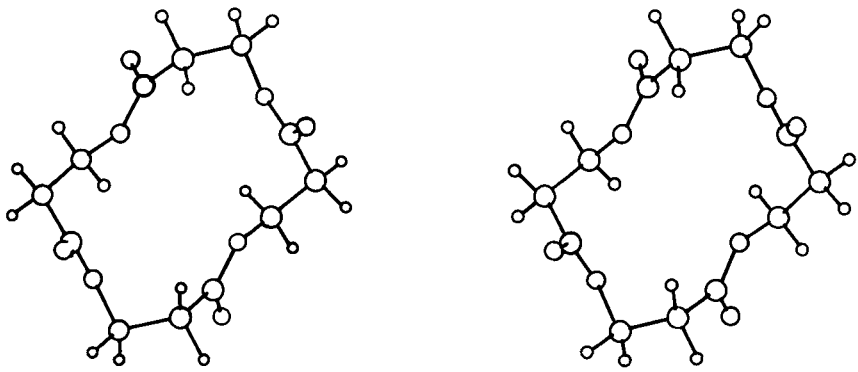


FIGURE 20. Stereoview of minimized conformation of a tetrarotolactone

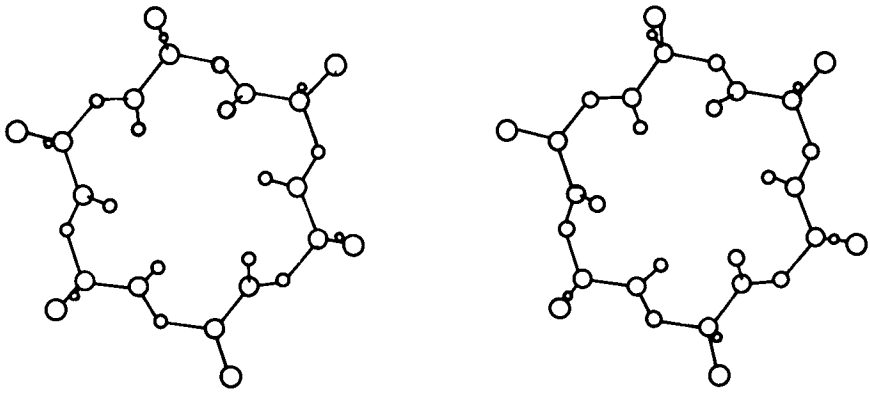
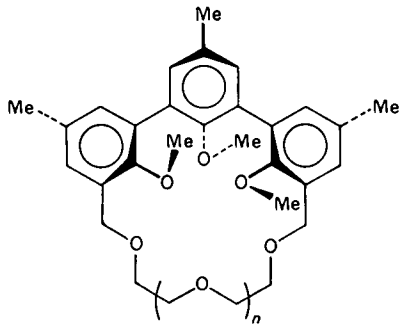


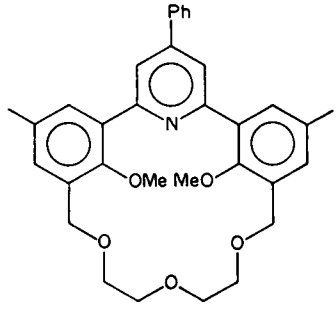
FIGURE 21. Minimized conformation for the methyl analog of LD-Hylv6

crystallographic analysis, by ^{13}C T_1 relaxation times and by molecular mechanics[128]. In contrast with a flexible host like 18-crown-6 (**10**), which has at least 190 conformations available[100] within an energy range of 20 kcal mol^{-1}, various starting conformations of hemispherands **3**, **37** and **38** yielded less than ten low-energy conformations each after minimization using the MMP2 molecular mechanics program[63a,129]. One effect of preorganization is to place a small number of available conformers near the bottom of a steep energy well. Interestingly, for the more rigid hosts **3** and **38**, the conformers obtained after minimization of starting host conformations from the crystal structures of the free hosts and the structures of the malononitrile complexed ligands with the guest removed prior to minimization differ by only 2.4 and 1.2 kcal mol^{-1}, respectively. The more flexible hemispherand **37** has an analogous calculated energy difference of 7.9 kcal mol^{-1}. The global minimum conformer for each of these hemispherands approximates the crystal structure of the uncomplexed host. As we have previously seen for coronands and cryptands, even when the guest is removed from complexes with these hemispherands the bound conformation represents a local energy minimum. The energy differences between free and bound calculated structures were due predominantly to increased electrostatic interactions in the bound conformers.



(**3**) $n=1$

(**37**) $n=2$



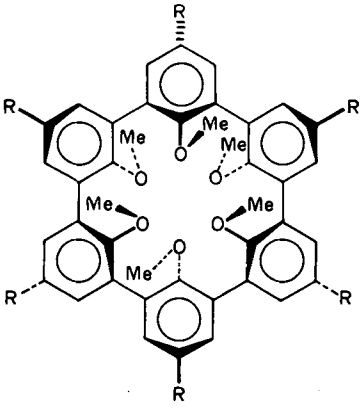
(**38**)

In addition, the *meso* form of host **3**, which is the only form detected experimentally to date, was found to be 16.7 kcal mol^{-1} more stable than the D, L-isomers. The *meso* isomer has the alternating anisole groups in the up-down-up orientation, whereas the D, L-isomers have the anisole units in the up-up-down or down-down-up configurations.

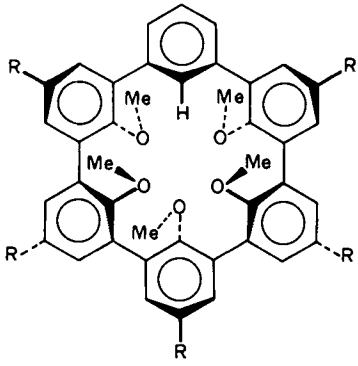
From the study of ^{13}C T_1 relaxation times it appears that the central methoxy groups of the hosts studied are less mobile than the flanking methoxy groups. For host **3**, the dihedral driver option of the MMP2 program was used to rotate around the O—CH_3 and Ar—O bonds while the rest of the structure was optimized. The minima in the potential energy surfaces as a function of the two dihedral angles were in a much steeper potential well for the central methoxy group than for the flanking ones, in agreement with the results of the ^{13}C T_1 relaxation time experiments. No explicit treatment of the host–malononitrile complexes was undertaken in this study.

Currently, the ultimate lipophilic alkali metal complexing agents are the spherands, in term of both selectivity and high binding affinities[39]. Spherand **5** and similar structures cannot be considered as ionophores because the requirements for an effective ionophore include turnover after transport of a guest across a lipophilic membrane between aqueous phases. Many of the spherands complex prodigiously, but do not release their guests except under extreme conditions. Spherand **5**, a cyclosexianisole, binds Na^+ with $-\Delta G^0 = 19.2$ kcal mol^{-1} and Li^+ with a higher negative free energy than can be measured, but which is estimated to be $\geqslant 23$ kcal mol^{-1} in $CDCl_3$[39]. Spherand **5** has no measurable affinity for K^+, the larger alkali metal cations or the alkaline earth metal dications. In fact, the host will extract trace amounts of Li^+ and Na^+ from reagent-grade KOH[130a]. The cyclosexianisole structure is so preorganized that few conformational options exist. Consequently, the crystal structures of the complexed and uncomplexed spherands appear very similar as far as the hosts are concerned.

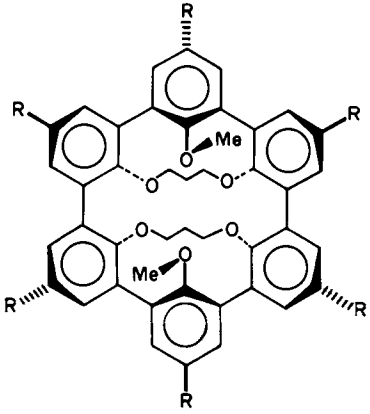
Recently, an elegant study of spherands using the AMBER molecular mechanics program appeared[56]. For simplicity, most of the calculations were carried out on the demethylated spherands **39**, **41**, **43** and **45**, whereas the experimental work utilized hosts **5**, **40**, **42** and **44**[39,130,55]. For crucial calculations, results were checked with appropriate methylated hosts. In addition, the hydrogens were not explicitly considered except for the central hydrogen of host **41**. A unified atom force field was used. The simple assignments of



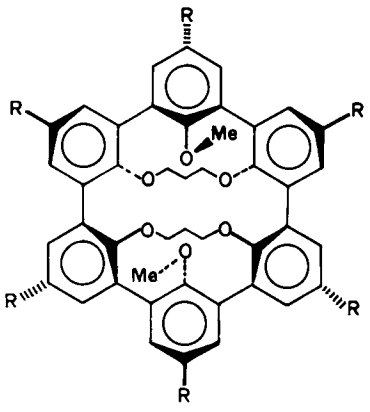
(**5**) R=Me
(**39**) R=H



(**40**) R=Me
(**41**) R=H



(42) R=Me
(43) R=H



(44) R=Me
(45) R=H

partial charges to oxygen ($q_O = -0.6$) and adjacent carbons ($q_C = +0.3$) were made for the spherands. Even with this relatively simple model, several of the experimental characteristics of the spherands were reproduced fairly well by the minimization procedure. For example, the binding order $Li^+ > Na^+ \gg K^+$ seen experimentally for spherand **5**[130a,b] was reproduced in minimizations of the model host **39**. In addition, the calculations gave a $-\Delta E$ between the Na^+ and K^+ complexes of host **39** of 40.6 kcal mol^{-1}, in line with the inability experimentally to detect binding of K^+ with spherand **5**.

The dramatic decrease in the affinity of host **40** for Li^+ and Na^+ in comparison with host **5** due to the removal of one methoxy group[130a,b] was also duplicated in calculations on model spherand **41**. The ability to calculate the normal modes of vibration allowed the estimations of entropy and hence the gas-phase free energies for the complexation of the various model spherands and Li^+, Na^+ and K^+, although a referee criticized the use of AMBER for calculation of vibrational modes because it has not been specifically calibrated for that purpose. The calculated differences in the free energy of hosts **39** and **41** with Li^+ and Na^+ were -13.6 and -15.6 kcal mol^{-1}, respectively. This is in reasonable agreement with the experimental values for the analogous differences in binding free energies for hosts **5** and **40** of > -12.6 and -12.6 kcal mol^{-1}, respectively[130a,b].

Simulations of the reaction pathway for cations associating with host **39** were performed by moving Li^+, Na^+ and K^+ along the threefold axis away from the center of the binding cavity to a point ca 2.05 Å from the three nearest oxygens and ca 3.05 Å from the furthest oxygens. Restraining the $M^+ \cdots O$ distances at these values and minimizing gave almost equivalent energy costs for Li^+ and Na^+ of 25.4 and 25.8 kcal mol^{-1}, respectively, and a much higher energy cost for K^+ of 55.4 kcal mol^{-1}. Removal of the restraints followed by minimization resulted in structures in which all three cations had returned to the center of the binding cavity. Starting with geometries in which the cations were completely outside the binding cavity led to minimized structures in which Li^+ and Na^+ had returned to the center of the cavity, whereas K^+ was still on the outside (Table 5).

The minimized structures for the Li^+ and Na^+ complexes of spherand **39** corresponded very well with the crystal structures of complexes of **5**[55], whereas the calculated structure for the uncomplexed host differed substantially from the crystal structure of uncomplexed **5**[55]. The Ar–Ar dihedral angles for the calculated uncomplexed spherand **39** are about 22° too large (Table 6). A possible reason for this is the use of the unified atom force field in this

Table 5. Total energies for 'reaction' pathway calculations for M^+–**39** complexes[56]

Complex	E_r(center)[a]	E_r(3-fold)[b]	E_r(3-fold, relax)[c]	E_r(outside)[d]
Li^+–**39**	−68.6	−43.2	−68.6	−68.6
Na^+–**39**	−45.7	−19.8	−45.7	−45.7
K^+–**39**	−5.1	50.3	−5.1	32.2

[a]Optimized energy for M^+ in the center of the host. All energies in kcal mol^{-1}.
[b]M^+ restrained 0.5 Å from center along 3-fold axis of host during minimization.
[c]Starting with geometry as in footnote *b*, then restraint removed and optimized. All three metals refined to the original central position.
[d]Starting with M^+ 1 Å outside the binding cavity along the 3-fold axis and refining with no restraint. Note that Li^+ and Na^+ return to the center of the binding cavity; K^+ does not.

study, which neglects the explicit contributions of the hydrogens. It may be especially important to include the aryl hydrogens in the spherands to obtain reasonable aryl–aryl dihedral angles for the uncomplexed hosts. Using the Dreiding force field, a part of the BIOGRAF molecular modeling program[81], the author was able to calculate the minimum energy conformation of uncomplexed spherand **5** with all hydrogens explicitly included[131]. The average of the absolute values of the six Ar–Ar dihedral angles was 53.3°, in excellent agreement with the experimental value of 52°[55]. The analogous approach with the Na^+ complex of spherand **5** gave a minimized structure with an average Ar–Ar dihedral angle of 63.6° in comparison with the experimental value of 61°. By way of a timing comparison, the complete minimization of the uncomplexed spherand **5** with explicit hydrogens took 3.3 min of CPU time on a VAX 8800, while minimization using the unified atom approach took 1.5 min.

For the bridged spherand **43**, minimization again led to the calculated ion selectivities in the experimental order, $Li^+ > Na^+ > K^+$.[56] However, gas-phase calculated binding energies from molecular mechanics for hosts and alkali metals may intrinsically favor that order. For instance, before solvation effects were considered, the calculated order of binding for 18-crown-6 was $Na^+ > K^+$. Taking solvation into account for the spherands by the hybrid approach using the calculated intrinsic free energies for complexation and the experimental hydration energies for the cations, in analogy to Wipff *et al.*'s earlier work with 18-crown-6[42], leads to the prediction that spherand **39** should favor Na^+/Li^+ by 4.6 kcal mol^{-1} and Na^+/K^+ by 20.4 kcal mol^{-1}. Host **41** would be predicted to favor Na^+/Li^+ by 2.6 kcal mol^{-1} and Na^+/K^+ by 19.3 kcal mol^{-1}. Only the calculated free energies for Li^+ and Na^+ were given for bridged spherand **43**. Considering cation solvation for this host leads to the prediction that it should favor Na^+/Li^+ by 3.0 kcal mol^{-1}. The experimental findings for spherands **5**, **40** and **42** are that Li^+ is selected over Na^+, sometimes by a substantial amount[130a,b]. However, these results are not unreasonable considering the crudity of the hybrid approach, and that K^+ binding is correctly predicted to be much less favorable than either Li^+ or Na^+ complexation.

A rare prediction in advance of experimental discovery was made after comparison of complexes of hosts **43** and **45** by molecular mechanics. The highly strained spherand **42** with both bridges on the same side of the molecule is the experimentally obtained conformation[130e]. Calculations showed spherand **45**, which has the bridges on opposite sides of the molecule, to have a higher Li^+ affinity than any other spherand considered. Subsequently, Cram and Helgeson[132] isolated host **44** and showed that it is a better Li^+ complexing agent even than spherand **5**. It is intriguing that when structures for the Li^+ complex of spherand **43** were minimized with the Li^+ in a starting position approximately in the center of the binding cavity, the resulting structure had five $Li^+ \cdots O$ distances which

Table 6. Calculated and experimental geometrical parameters for **39** and **41** and their M^+ inclusion complexes[a]

Molecule	$R(O\cdots O)^b_{ortho}$	$R(O\cdots O)^c_{meta}$	$R(O\cdots O)^d_{para}$	$\phi(Ar\cdots Ar)^e$	$\phi(OCH_3)^f$	$\phi(COCH_3)^g$	$R(M^+\cdots O)^h$
39	3.55(2.92)	3.89(3.32)	5.24(4.42)	73.6(52)	84.2(62)	116.5(115)	
Li^+–**39**	2.74(2.78)	3.21(3.24)	4.22(4.28)	55.1(56)	87.1(85)	112.6(112)	2.11(2.14)
Na^+–**39**	3.02(3.00)	3.44(3.43)	4.66(4.55)	62.3(61)	86.9(84)	114.0(113)	2.33(2.28)
K^+–**39**	3.57	3.88	5.31	83.4	86.3	114.6	2.66
41	3.51	4.03	5.22	80.9	81.6	116.4	
Li^+–**41**	2.74	3.20	4.06	63.1	85.7	112.2	2.05
Na^+–**41**	3.03	3.47	4.48	68.2	86.8	113.6	2.30
K^+–**41**	3.49	4.01	5.22	79.8	86.4	114.2	2.61

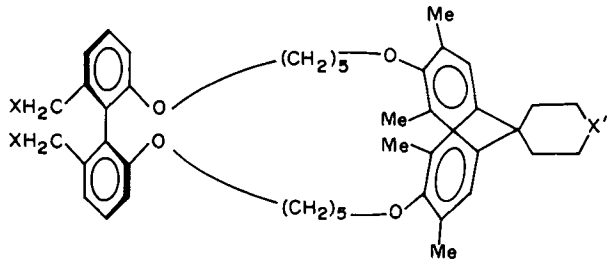
[a] Experimental values (where available) from Ref. 55 in parentheses; calculations on **39** and its complexes; experiments on **5** and its complexes.
[b] Average distance between pseudo-*ortho* oxygens (Å).
[c] Average distance between pseudo-*meta* oxygens (Å).
[d] Average distance between pseudo-*para* oxygens (Å).
[e] Average dihedral angle of aryl groups (°).
[f] Average dihedral angle of OCH_3 with respect to aryl (°).
[g] Average Ar–O–CH_3 angle (°).
[h] Average $M^+\cdots O$ distance (Å).

averaged 2.05 Å and one long $Li^+ \cdots O$ distance of 2.60 Å. The crystal structure of host **42** has five $Li^+ \cdots O$ distances between 2.00 and 2.09 Å and one longer distance of 2.99 Å [130b].

Calculations suggested that there is a minimum intrinsic barrier of 18 kcal mol^{-1} to entry of K^+ into the binding cavity of spherand **39**, as well as the need to desolvate the cation, which K^+ has in common with other guests. The authors found that K^+ is not poorly bound by spherands simply because of its size. In fact, Na^+ induces about 7 kcal mol^{-1} more strain energy in host **39** than does K^+. Both Na^+ and K^+ interact in calculations with spherand **39** about six times better than with one dimethyl ether molecule. Since the calculated $Na^+ \cdots O(CH_3)$ interaction energy is 7.4 kcal mol^{-1} more favorable than the K^+ interaction, the source of the calculated Na^+/K^+ preference in spherands is clear. An apparent key to the powerful binding of the spherands is the ability to focus the appended oxygens optimally toward a complexed guest, an arrangement unlike that found for the simple coronands.

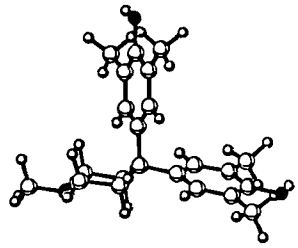
Most of the previous examples have dealt with the use of molecular mechanics in the reproduction and interpretation of experimental findings. A particularly fascinating example of the predictive use of molecular modeling in the area of cyclophane macrocycles has recently been published[133]. The approach taken was first to design spacer units with a modified MM2 molecular mechanics program. Then the appropriate macrocycles were synthesized and their complexation behavior was examined. Finally, molecular mechanics and computer graphics studies were implemented on the resultant macrocycles.

The authors were impelled to examine new chiral spacer units using molecular mechanics after the use of CPK space-filling molecular models had led to the erroneous prediction that macrocycle **46** should be an enantiodiscriminatory host in acidic water for various racemic aromatic guests. Complexation studies showed that macrocycle **46** does not act as a host at all[134]. With molecular mechanics, the energetics of a flexible macrocycle could be evaluated, thus adding a new dimension to the design of chiral building blocks. Figure 22 shows the minimum energy conformations for a series of aromatic spacer units to be incorporated in cyclophane macrocycles.



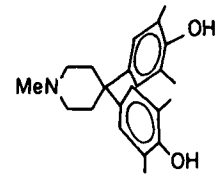
(46) $X = NMe_2$, $X' = NMe$

The problem with the biphenyl unit **48** is the short distance between oxygens of only 4.10 Å. This results in a closed macrocycle with no well defined cleft for complexation. In CPK models, manipulation resulted easily in open conformations in which the oxygens were further apart, but there was no way to tell if they were energetically feasible. On the other hand, both the achiral diphenylmethane unit **47** and the chiral 4-phenyltetrahydroisoquinoline spacer **49** give minimized conformations in which the oxygens are much further apart. It had previously been shown that achiral cyclophane macrocycles with two diphenylmethane groups function as efficient hosts for aromatic guests[135]. It was believed that substitution of a chiral unit for one of the diphenylmethane units would result in a host capable of chiral recognition in complexation if the substituted chiral building block

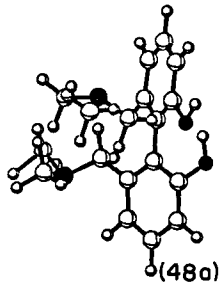


(47a)

8.91Å

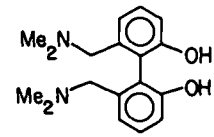


(47)

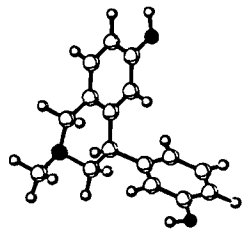


(48a)

4.10Å

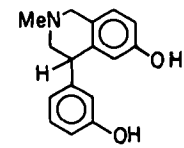


(48)

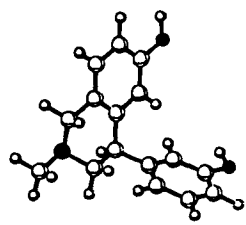


(49a)

7.58Å



(49)



(49b)

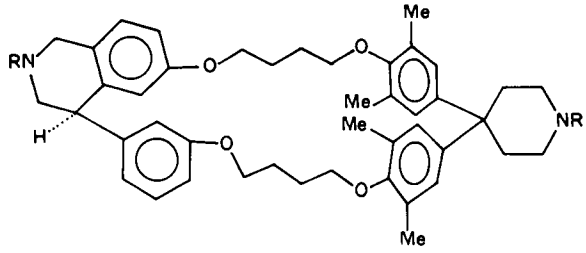
6.33Å

FIGURE 22. Minimum energy conformers for spacers in cyclophane hosts and oxygen–oxygen distances

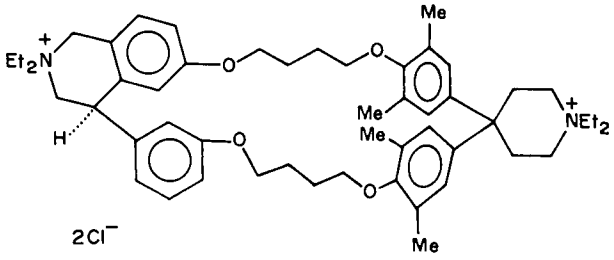
maintained the same degree of openness in the macrocycle obtained with the diphenylmethane unit **47**.

Incorporation of chiral unit **49** and the diphenylmethane spacer **47** into a macrocycle resulted in hosts **50** and **51**. Both of these hosts complexed with 2,6-disubstituted

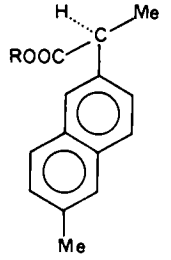
naphthalenes with a high degree of selectivity toward other aromatic guests such as quinine, tryptophan and 2,6-naphthalenedisulfonate, which were not bound. The association constant between host **50** and 6-methoxy-2-naphthonitrile in 0.5 M KD_2PO_4–CD_3OD (60:40) was 336 l mol^{-1}. Both hosts also formed diastereomeric complexes with the enantiomers of naproxen **52** and its methyl ester **53**. The methyl ester was bound more tightly, possibly owing to easier desolvation and to π–π interactions between the ester carbonyl and the aromatic ring of the 4-phenyltetrahydroisoquinoline residue. Severe signal overlap in the ^{1}H NMR spectra of these complexes prevented the quantitative analysis of binding constants or the degree of chiral recognition.



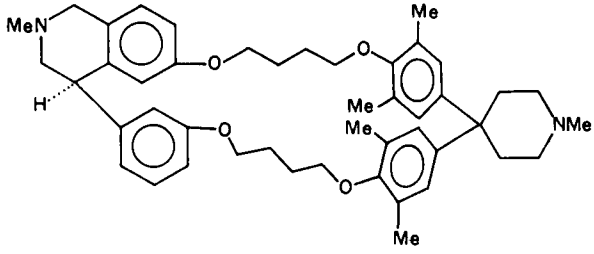
[(+)-**50**] R = Et



[(+)-**51**]



[(*S*)-**52**] R = H
[(*S*)-**53**] R = CH_3

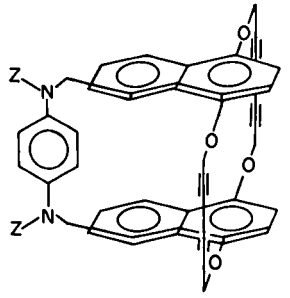


(**54**)

Minimization studies with macrocycle **54** indicated that 2,6-disubstituted naphthalenes bind inside the cavity with a nearly perfect pseudo-axial orientation, which is the same geometry previously deduced from NMR studies of the complexes of related hosts[135,136]. Minimization of host **46** with the biphenyl spacer led to a structure without a cleft, explaining the failure to detect binding of aromatic guests experimentally[134].

Optimization of the structure of the *N*-methyl derivative of host **50** with the 4-phenyltetrahydroisoquinoline unit started from the two orientations shown in Figure 22 resulted in four conformers, which differed in energy across a range of about 6 kcal mol^{-1}. All the conformers possessed a large enough cavity to accommodate 2,6-disubstituted naphthalenes in the pseudo-axial orientation, although the best fit was with the highest energy conformer and the worst with the lowest energy conformer.

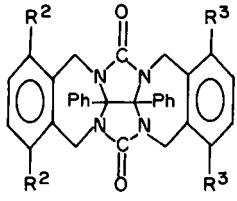
Masck *et al.*[137] have also examined cyclophane macrocycles with molecular mechanics, although not in complexing systems. Miller and Whitlock[138] used molecular mechanics to provide part of the justification for the predominant formation of racemic **55b** instead of its *meso* isomer. In addition, they calculated a gas-phase enthalpy bias of -6.9 kcal mol^{-1} toward complexation of benzene by host **55a**, although solvation was completely neglected (Figure 23). Finally, use of the MM2 program has aided in the conformational analysis of the novel concave building block **56**, which was subsequently used in the construction of three new hosts[139].



(55)

(a) Z = Me

(b) Z = $COCH_2CH_2CO_2Me$



(56)

(a) $R^2 = R^3 = H$

(b) $R^2 = R^3 = OH$

(c) $R^2 = R^3 = OMe$

(d) $R^2 = R^3 = O(CH_2)_6O$

The cited molecular mechanics studies were fairly successful in reproducing the gross trends in conformations of hosts and complexation selectivities. Molecular mechanics should find a place in the arsenal of the host–guest chemist interested in adding to the

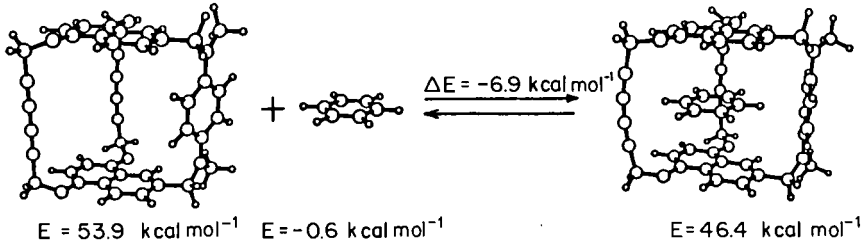


FIGURE 23. Calculated complexation of benzene by host **55a**

value of traditional space-filling models as predictive and explanatory tools. At the present stage of development, the use of molecular mechanics allows the likely properties of new host systems to be probed in a broad sense with a reasonable probability of success.

However, the existing approaches do not do particularly well in reproducing quantitative data on intermolecular associations such as binding energies or precise selectivities. This is at least partly due to one of the major drawbacks with molecular mechanics, which is the difficulty in correctly accounting for solvation effects. Other computational techniques which will surely become of increasing inportance in host–guest chemistry allow more precise handling of the effects of solvation[140] and may have other advantages lacking in molecular mechanics. Among these techniques are molecular dynamics[79] and Monte Carlo simulations[80].

c. Molecular dynamics. Molecular dynamics provides a means of simulating molecular motion[79a,141]. Atoms are treated as Newtonian particles which are subjected to accelerations over a series of discrete steps about 0.001 ps in duration. The forces on each atom are estimated from a previously calculated potential function according to the equation

$$F_i = -\sum_j \nabla U_{ij} \tag{3}$$

where U_{ij} is the potential of interaction between atoms i and j. According to Newton's third law of motion, a force acting on an atom of mass m_i produces an acceleration a_i:

$$F_i = m_i a_i \tag{4}$$

By solving these equations simultaneously for all atoms in a molecule, the position of each atom in a molecule can be recalculated after each discrete step, and a new structure can be generated from the resulting coordinates or used in the next step. Records of the internal motion of a molecule over lengthy periods (100 ps) can be obtained. An option with some molecular modelling packages is animation of the resulting dynamics trajectory allowing observation of the molecular motion[81]. Fesik *et al.*[142] examined various computational methods for the generation of peptide structures and found that constrained molecular dynamics was the method of choice because it consumed less user or computer time and was less sensitive to the starting conformation. Also tested were molecular mechanics minimizations, distance geometry methods and fitting distances obtained from NOE experiments graphically.

Also available are quenched and annealing dynamics methods[143], which provide opportunities to overcome energy barriers to local minima in the search for low-energy conformations. Quenched dynamics allows the user to sample a dynamics trajectory at specified intervals and energy minimize the resulting structures. In annealing dynamics, new minima are generated by subjecting the atomic coordinates of a starting structure to successive cycles of heating and cooling. Resulting conformations are saved if lower in energy than previous ones.

One technique utilizing molecular dynamics for quantitatively calculating host–guest binding selectivities in solvent involves the use of thermodynamic cycle-perturbation simulations[144]. Equations 5 and 6 describe a typical experiment where a host, H, complexes with two guests, G_1 or G_2:

$$H + G_1 \xrightarrow{\Delta A_1} H{:}G_1 \tag{5}$$

$$H + G_2 \xrightarrow{\Delta A_2} H{:}G_2 \tag{6}$$

where ΔA is the Helmholtz free energy of binding given the use of the canonical ensemble of constant temperature, volume and number of particles. The binding process is obviously complicated, involving conformational changes, potentially of both host and guest, desolvation and the formation of complementary interactions between the associating species. In practice, it is difficult to assess computationally the free energy for complexation in a solvent[145]. Desolvation steps may be very slow to occur during the calculation, and conformational changes associated with binding may also be slow. In addition, to determine each ΔA value requires a sequence of long simulations, yielding an imprecise value. Consequently, $\Delta\Delta A$, representing the selectivity, is statistically even more uncertain because it is the difference between two large, imprecise numbers. A thermodynamic cycle can be generated by incorporating equations 7 and 8 with equations 5 and 6:

$$H + G_1 \xrightarrow{\Delta A_3} H + G_2 \tag{7}$$

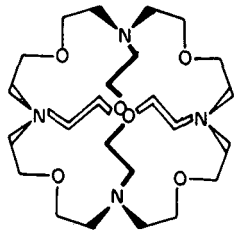
$$H{:}G_1 \xrightarrow{\Delta A_4} H{:}G_2 \tag{8}$$

The cycle is then given by

$$\begin{array}{ccc} H + G_1 & \xrightarrow{\Delta A_1} & H{:}G_1 \\ \downarrow \Delta A_3 & & \downarrow \Delta A_4 \\ H + G_2 & \xrightarrow{\Delta A_2} & H{:}G_2 \end{array} \tag{9}$$

where $\Delta\Delta A = \Delta A_2 - \Delta A_1 = \Delta A_4 - \Delta A_3$, since A is a thermodynamic state function. The transformations of $H + G_1$ to $H + G_2$ and of $H{:}G_1$ to $H{:}G_2$ can be modeled in solvent by employing a perturbation technique[145,146] involving the use of constant-temperature molecular dynamics[147]. For the complexation by the Lehn macrotricyclic receptor SC24 (**57**) of Cl^- and Br^- in water, the calculated $\Delta\Delta A$ value[144] was -4.15 ± 0.35 kcal mol^{-1}, in excellent agreement with the experimental value[148] of about -4.3 kcal mol^{-1}. The drawbacks to thermodynamic cycle-perturbation methodologies are the need for substantial amounts of computer time and the difficulty in transmuting G_1 into G_2 for other than simple guests. The potential for molecular dynamics to investigate the kinetic and thermodynamic features of host–guest interactions is in its infancy.

d. Monte Carlo simulations. Monte Carlo simulations are statistical mechanics simulations typically performed on solutes in 100–300 solvent molecules[140,149]. An entire



(**57**)

molecule in the ensemble is chosen and translated in all three Cartesian directions and rotated about a randomly chosen axis. Solvent bond lengths and bond angles are usually fixed. Solute geometries may also be fixed. Use of the Metropolis algorithm[150] allows the computation of the probability that a move should be made from configuration i to j. If the probability is expressed as p, than for $p \geqslant 1$, which for the canonical ensemble means $U_j \leqslant U_i$, the move is accepted by the program. If $p < 1$, p is compared with a random number, x, between 0 and 1. If $p \geqslant x$ the move is also accepted, otherwise configuration j is rejected and i repeats. The random aspect of the calculations provided impetus for the name 'Monte Carlo' simulations.

Use of the Metropolis algorithm concentrates the sampling on configurations with low energy. Nevertheless, convergence of the calculations normally takes of the order of 10^6 configurations for pure solvent systems alone. Addition of the solute requires the use of preferential and umbrella sampling to allow convergence after 1.5–2 million configurations with one solute in 125 solvent molecules[140].

Runghino *et al.*[151] performed Monte Carlo simulations on the C_i, D_{3d} and C_1 conformers of 18-crown-6. Coordinates for the C_i conformer were obtained from the crystal structure of the uncomplexed host, and the D_{3d} and C_1 conformers were obtained by removal of the K^+ and Na^+ from the respective coordinates of the crystal structures. Each conformer was considered in a cubic box of 32 Å on a side surrounded by only 100 water molecules to avoid prohibitive computer times. The host was kept rigid, and the water molecules were allowed to move randomly. For each 18-crown-6 conformer, 600 000 moves were performed at 300 K. The results indicate that the C_i conformer, which in the gas phase is the most energetically favorable conformation in the absence of a guest[40,42], is the most poorly hydrated in water. This is apparently because the C_i conformation does not have the hydrophilic oxygens exposed as well to the solvent as the other conformers. The D_{3d} and C_1 conformers are quite close in solute–water energies (Table 7). The prediction was that in water the C_i conformer which cannot bind will reorganize to yield the C_1 and D_{3d} conformers, both of which are in binding conformations.

Some molecular mechanics calculations have suggested[42] that the D_{3d} conformation is intrinsically more stable than the C_1 conformer by about 9 kcal mol^{-1}. Because of the close similarity in their solute–water interaction energies, these conformers are unlikely to have their intrinsic stability difference compensated for by water. Therefore, the D_{3d} conformer was predicted to be the preferred conformation in water, which would give it a preformed cavity for cation binding. This prediction is consistent with the observation of a D_{3d} structure for the 18-crown-6 molecule in crystals where it is surrounded by N—H^+, O—H^+ or even weakly polar C—H bonds and with the crystal structure of the water–dinitrophenol–18-crown-6 complex[152]. However, the C_1 conformation was calculated to be lower in energy than the D_{3d} conformer by 3.4 kcal mol^{-1} in the gas phase by

Table 7. Monte Carlo results: average water–water (E_{ww}) and solute–water (E_{sw}) interaction energies[a]

	Conformation		
	C_i	D_{3d}	C_1
E^b_{ww}	−5.9	−6.0	−5.4
E_{sw}	−29.4	−52.4	−54.3

[a] Energies in kcal mol^{-1}.
[b] E_{ww} for bulk water, calculated with the same potentials, is 8.5 kcal mol^{-1} [G. C. Lye, E. Clementi and M. Yoshimine, *J. Chem. Phys.*, **64**, 2314 (1976)].

Sutherland and coworkers[40]. Probably the best conclusion that can be drawn from this study is that solvent effects cannot by ignored even when comparing relative conformations of the same host.

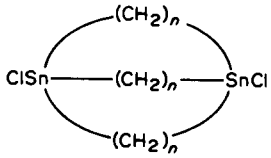
Monte Carlo techniques have also been used to consider macrocyclizations to form crown ethers. In the unsubstituted coronands, cyclizations of poly(oxyethylene) molecules with various chain lengths were predicted to be most favorable for the formation of 18-crown-6[153], a result in harmony with experiment[154]. The D_{3d} conformation seen in the K^+ complex of 18-crown-6 was calculated to be among the most stable. In contrast, the C_i conformer was predicted to make up only about 1% of the macrocycles in the unperturbed state. For cyclizations of open-chain benzo derivatives[155] and poly(thiaethylene) molecules[156], the special ease of formation of the 18-membered macroring was calculated to be abolished. Cyclization probabilities from the Monte Carlo simulations correlated well with the kinetic data of Illuminati *et al.*[157] for formation of benzo crown ethers.

Monte Carlo simulations can also be used as the perturbation method in thermodynamic cycle-perturbation calculations[144]. In conclusion, molecular mechanics is already a powerful technique in host–guest chemistry with greater potential for further development. The use of molecular dynamics is in an early stage in complexation chemistry although already used extensively in modeling biomolecules[79a,141]. It shows great promise in modeling of solvent effects. In addition, the ability to examine kinetics is one of the more appealing aspects of molecular dynamics which will surely be of value in future analyses of host–guest interactions. Finally, Monte Carlo simulations offer particular advantages in the modeling of solvent effects but are computationally intense, requiring great amounts of computer time.

IV. CONFORMATIONALLY RESTRICTED HOSTS

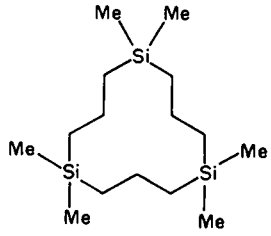
A. Introduction

As previously mentioned, the emphasis of this review is on conformationally restricted macrocylic hosts. Extensive reviews of the conformationally mobile macrocycles, the coronands and cryptands, have appeared[3,159], including exhaustive lists of most of the hosts synthesized in these classes[11b,25c]. The recent fascinating advances in the complexation of anions with macrobicyclic Lewis acids such as host **58**[160] and anion transport with the silacrown **59**[161] and the beautiful catenates (**60**) of Dietrich-Buchecker *et al.*[162] are highlighted in passing. Previous reviews including some mention of conformationally restricted hosts include Refs 22, 30f, 39, 159a and 163.

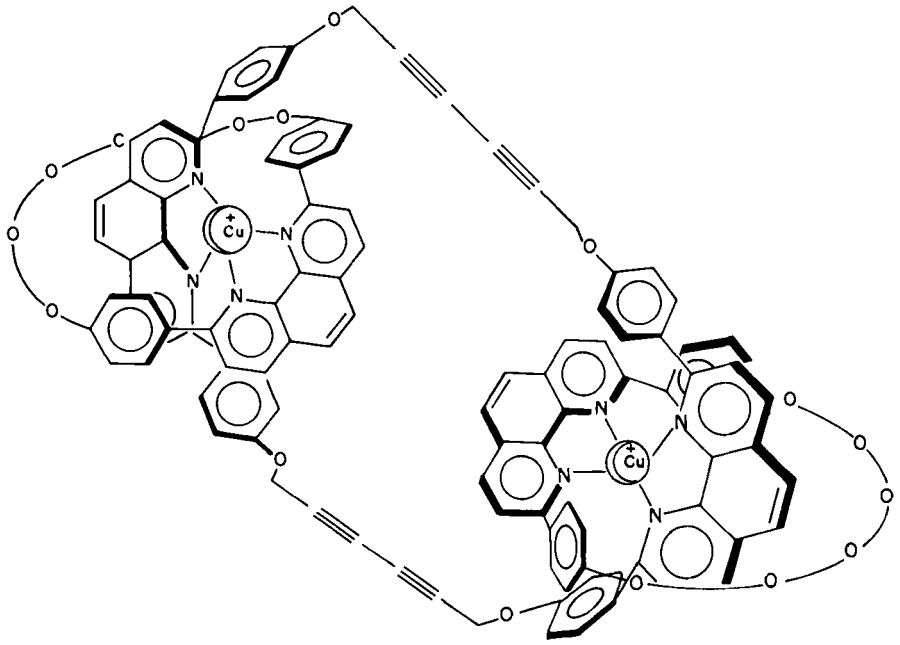


(58)

(a) $n=8$
(b) $n=10$
(c) $n=12$



(59)



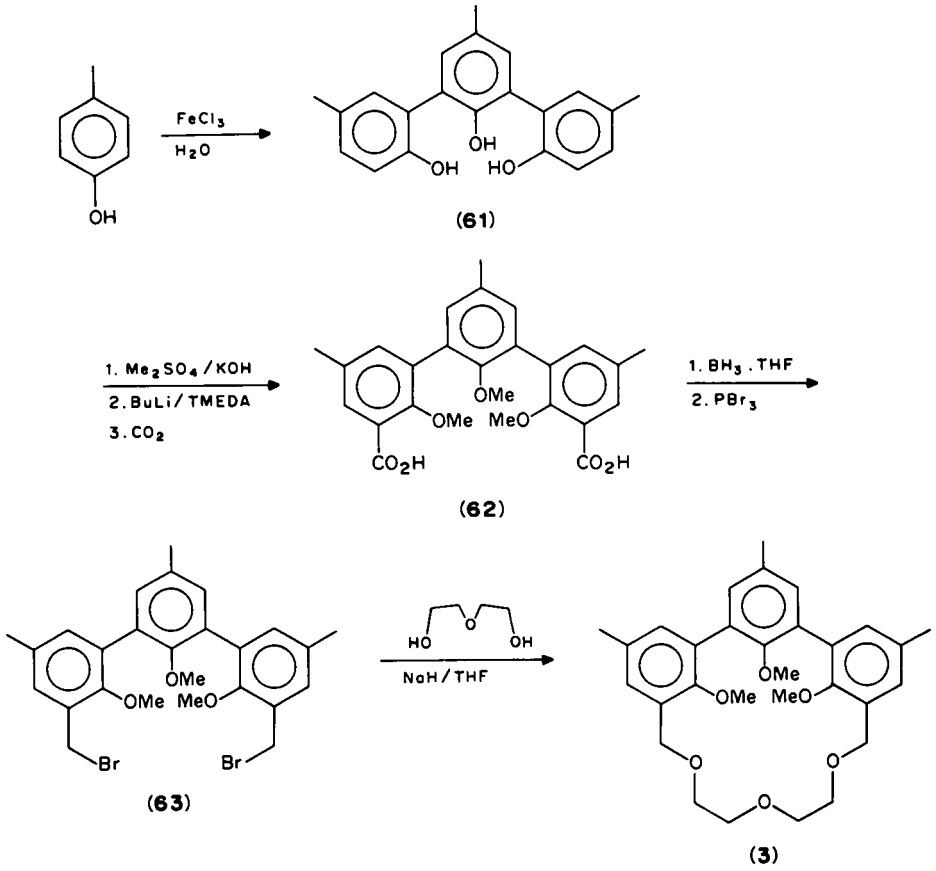
(60)

B. Hemispherands

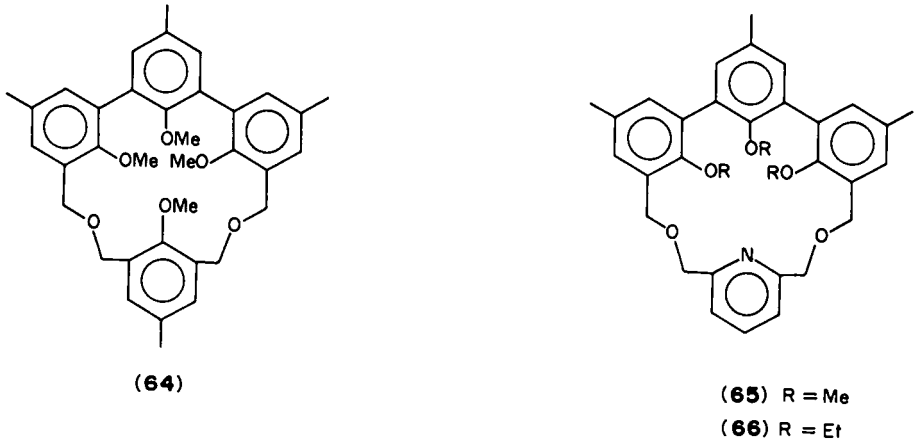
For the purpose of this review, hemispherands are defined as macrocyclic hosts with three or more contiguous rigid structural groups such as aryl units making up a portion of the macroring. The rigid units have potential binding groups appended to them which project into the binding cavity. The binding groups are not a part of the structural framework of the macroring. The remainder of the macroring consists of flexible units such as ethylene glycols. Host **3** is the parent hemispherand. Hemispherands synthesized to date include three to six rigid groups. As has been discussed, the effect of the rigid structural units is partially to preorganize the binding cavity prior to complexation. Therefore, the hemispherands are intermediate between the coronands and spherands in terms of preorganization. In the following discussion, the hemispherands will be categorized according to the number of contiguous rigid groups present, as ter-, quater-, quinque- and sexi-hemispherands.

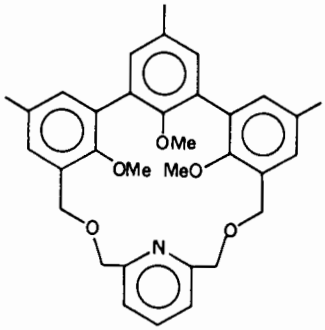
1. Ter-hemispherands

a. Synthesis. The first terphenyl hemispherands (**3** and **64**) were reported in 1979 by Cram *et al.*[164]. They were interested in exploring the effects of incorporation of the anisyl unit into coronands. The synthesis is outlined in Scheme 1, the key steps being the interesting oxidation of *p*-cresol to terphenol **61** with $FeCl_3$[165] and the final high dilution closure with dibromide **63** and diethylene glycol in reasonable yield (49%) to give hemispherand **3**. Following similar methodology, Cram and coworkers synthesized hosts **64**, **65**[166] and **67**[167]. Toner and coworkers[168] prepared the simple alkoxy hemispherands **66**, **68**, **71** and **72**. The observation that terphenol **61** could be selectively monoalkylated at the center phenol[166,167] and later alkylated at the outer phenols with simple alkyl halides

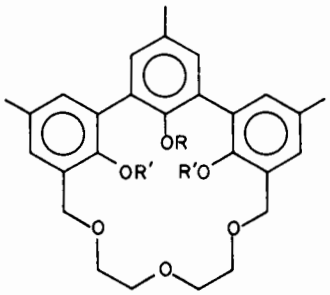

FeCl3
H2O
OH
OH
OH
HO
(61)
1. Me2SO4/KOH
2. BuLi/TMEDA
3. CO2
OMe
OMe MeO
CO2H
CO2H
(62)
1. BH3.THF
2. PBr3
OMe
OMe MeO
Br
Br
(63)
HO
O
OH
NaH/THF
OMe
OMe MeO
O
O
O
(3)

SCHEME 1

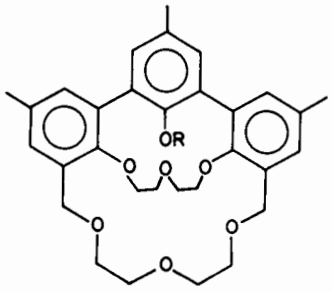

OMe
OMe MeO
OMe
O
O
(64)
OR
OR
RO
O
N
O
(65) R = Me
(66) R = Et



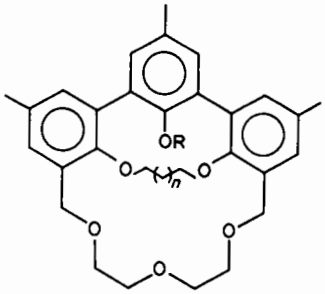
(67)



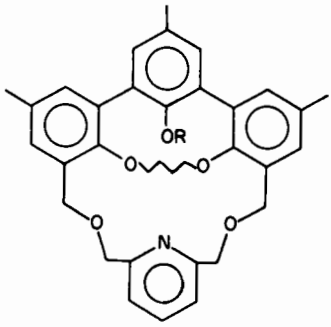
(3) R = R′ = Me
(66) R = R′ = Et
(68) R = Pr, R′ = Et
(70) R = Et, R′ = Pr
(71) R = R′ = Pr
(72) R = R′ = *i*-Pr
(73) R = H, R′ = Me
(74) R = $CH_2CH{=}CH_2$, R′ = Me



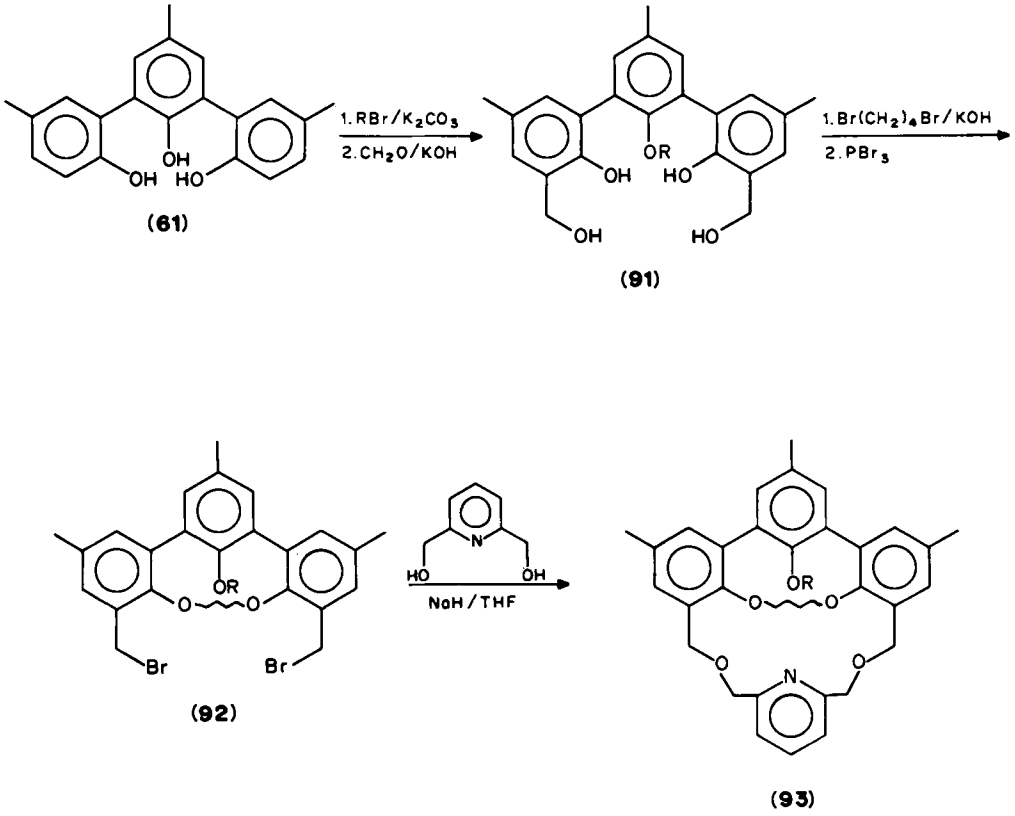
(80) R = H
(81) R = Me
(82) R = $CH_2CH{=}CH_2$



(75) R = Me, *n* = 1
(76) R = Pr, *n* = 2
(77) R = $CH_2CH{=}CH_2$, *n* = 2
(78) R = CH_2Ph, *n* = 2
(79) R = $CH_2CH{=}CH_2$, *n* = 3

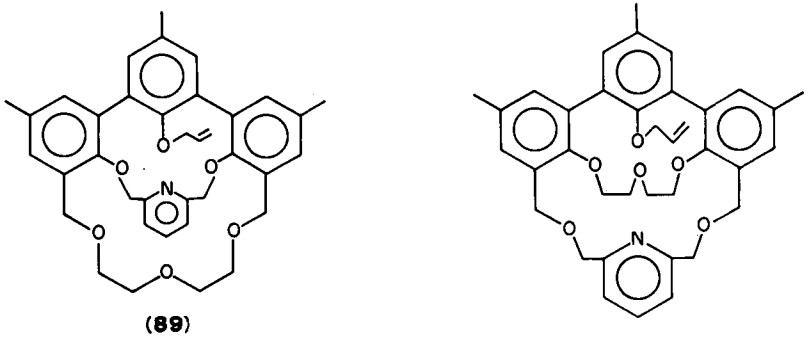


(83) R = H
(84) R = $CH_2CH{=}CH_2$
(85) R = CH_2Ph
(86) R = $CH_2C_6H_4OCH_3$-*p*
(87) R = $CH_2C_6H_4Cl$-*p*
(88) R = $CH_2C_6H_4I$-*p*

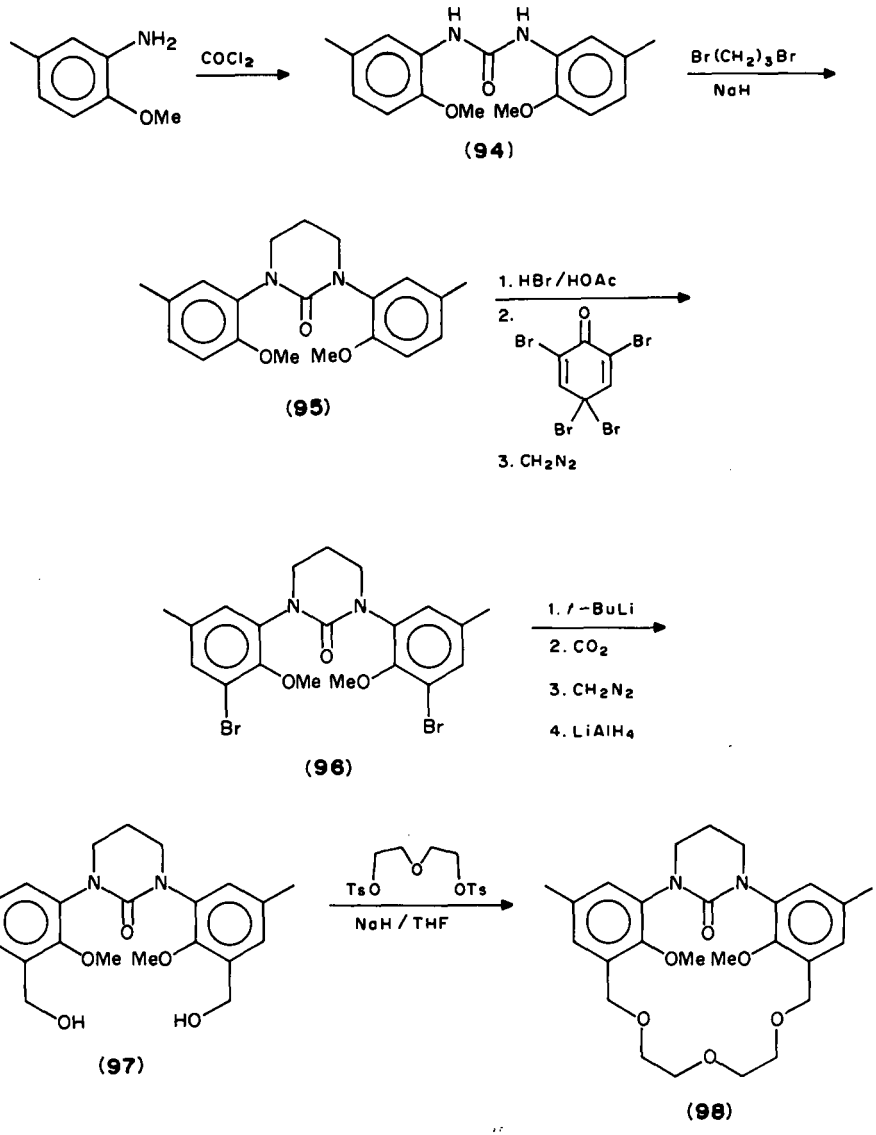


(61) (91) (92) (93)

SCHEME 2

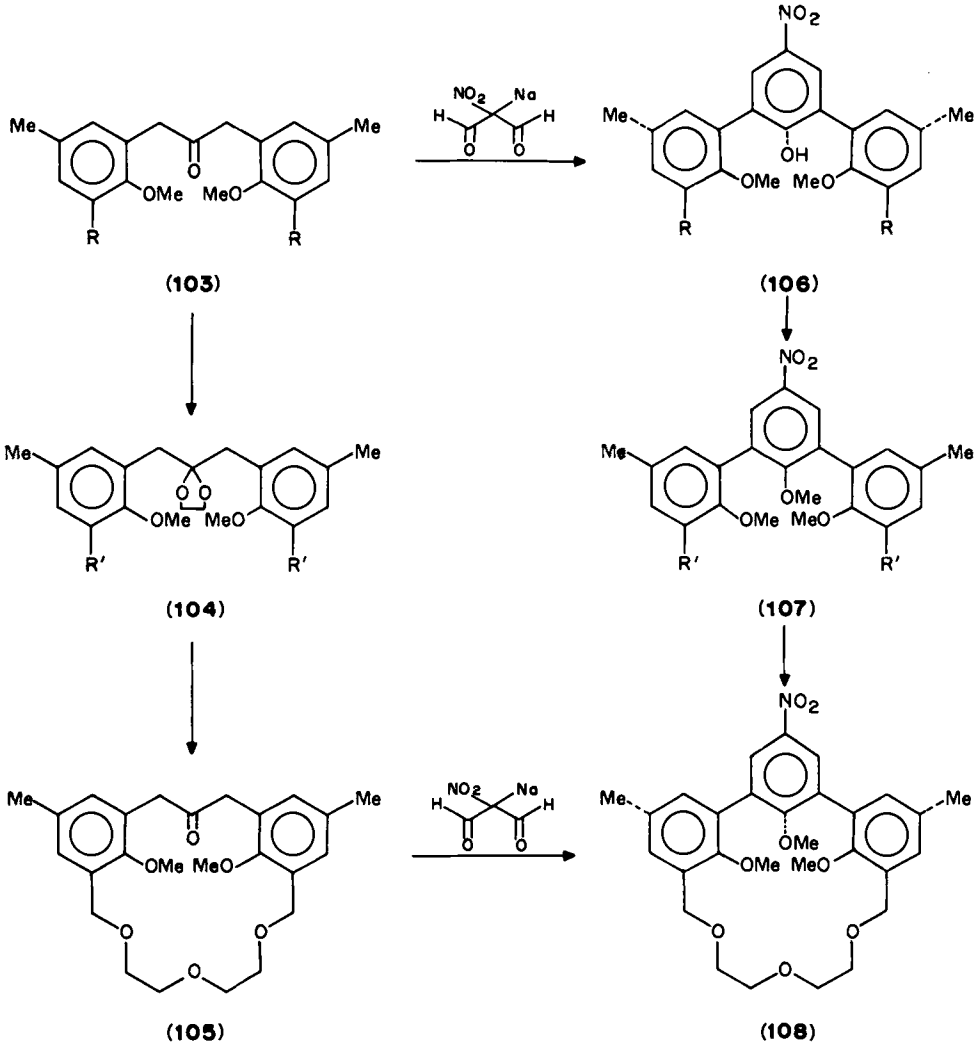


(89) (90)



SCHEME 3

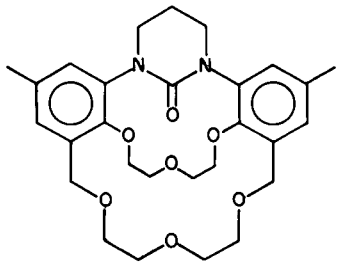
or bridged with bis-alkylating agents allowed the synthesis of hosts **69**, **70**, **75**, **76** and **78** by Toner and coworkers and hosts **74**, **77**, **79–82**, **89** and **90** by Lein and Cram[167]. Macrocyclization of the conformationally flexible bisbromomethyl precursor to host **3** without high dilution conditions gave the host in 17% yield versus 47% with high dilution[163]. Toner and coworkers found that precursor **92** is already preorganized to some extent by the bridge. Macrocyclization without high dilution conditions gave doubly organized hosts **84–87** in an average yield of about 50% (Scheme 2)[168b].



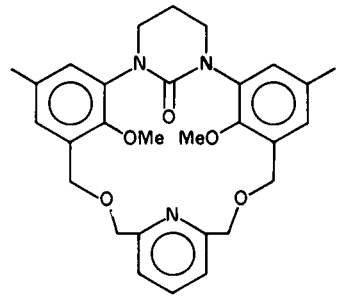
SCHEME 4

Center phenol **73** was synthesized by deprotection of center allyoxy host **74** with Pd–TsOH. Center phenol **83** was secured either by removal of the *p*-methoxybenzyl group of hemispherand **86** in CF_3CO_2H or by treatment of benzyl hemispherand **85** with $Pd/C/NH_2NH_2$. Elaboration of the center phenol was easily accomplished with a wide variety of alkylating agents to produce highly constricted hemispherands such as **88**[168b].

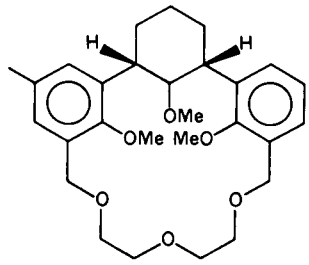
Interest in the effects of substituting other donor groups for the anisyl units of the previously described hemispherands led Cram and coworkers to replace the central anisyl



(99)



(100)



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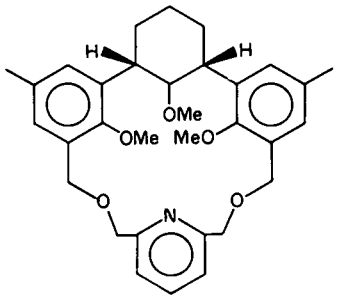

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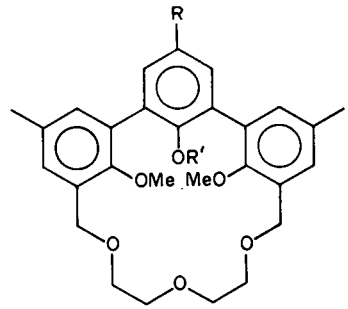
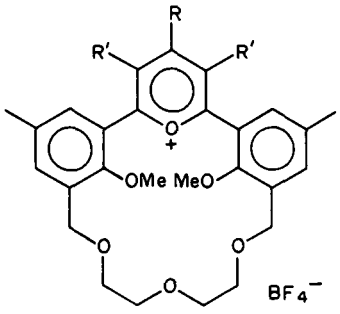
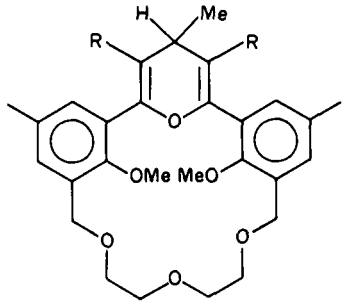


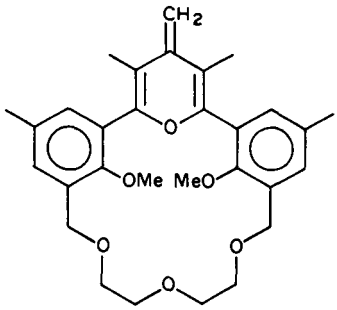
(108) R = NO_2, R′ = Me
(109) R = NO_2, R′ = H
(110) R = Br, R′ = Me
(111) R = $COCH_3$, R′ = Me



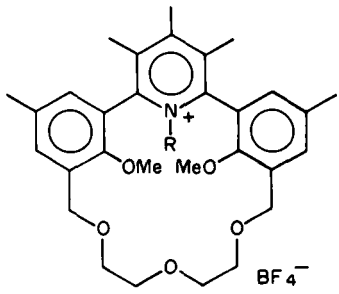
(112) R = Me, R' = H
(113) R = Me, R' = Me
(114) R = CH=CHPh, R' = Me



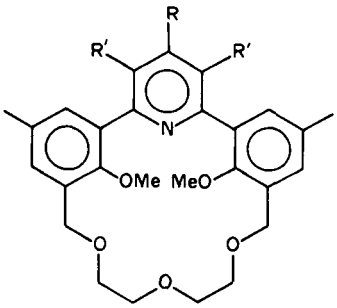
(115) R = H
(116) R = Me



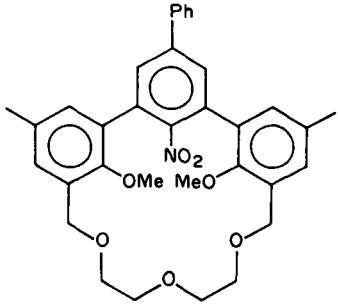
(117)



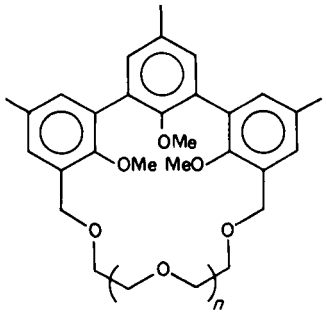
(118) R = Me
(119) R = Ph



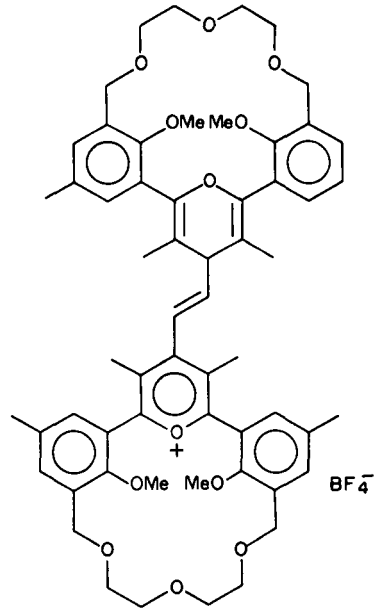
(38) R = Ph, R' = H
(120) R = H, R' = H
(121) R = H, R' = Me
(122) R = CH=CHPh, R' = Me



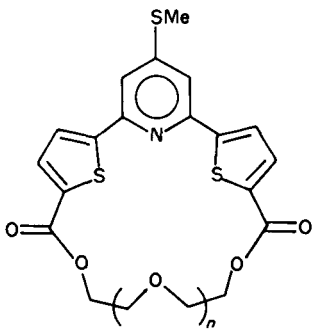
(123)



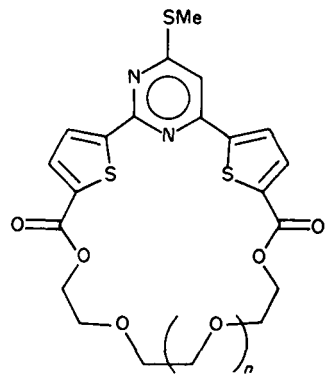
(37) $n = 2$



(124)



(125) $n = 2$
(126) $n = 3$
(127) $n = 4$

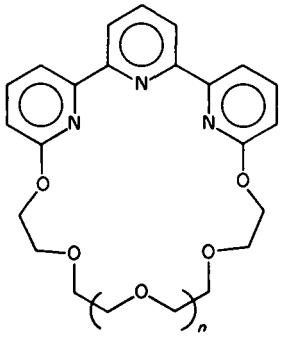


(128) $n = 1$
(129) $n = 2$
(130) $n = 3$

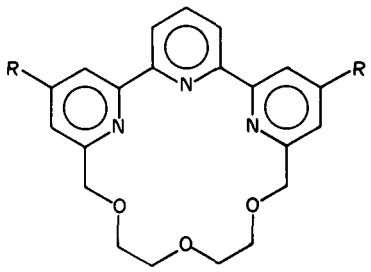
group of host **3** with a cyclic urea unit, following the procedure outlined in Scheme 3 to obtain host **98**[166,169]. By similar methodology, hosts **99** and **100** were synthesized. Also synthesized were hosts **101** and **102**, in which the center anisyl unit of hemispherand **3** has been formally replaced with a methoxycyclohexane group[170].

Two new approaches to the construction of ter-hemispherands have come from Reinhoudt's group[128a,b,171], again primarily involving replacement of the center ring of the teranisyl unit in earlier hemispherands. Scheme 4 summarizes the steps in the synthesis of host **108** involving an aromatization reaction as the key step[171c]. By the same method, hosts **109–111** were prepared. Using pyrylium chemistry, hosts **112–124** were synthesized[171a,b,d]. The 21-membered macroring host **37** was also synthesized[171b] by an extension of the method used for host **3**[165].

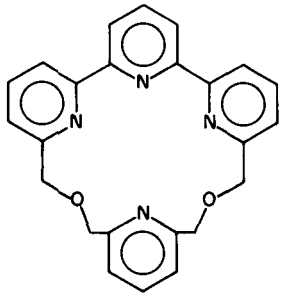
The teranisyl group has been completely replaced in work by four research groups. Potts and Cipullo[172] produced hemispherands **125–130** which do not bind alkali metal cations, probably owing to the presence of the thiophene rings which are poor ligands for these cations. Newkome and coworkers[173,174] synthesized terpyridine hemispherands **131**, **132** and **136** using methods similar to those used for the synthesis of cyclosexipyridine, which will be covered later.



(131) $n=3$

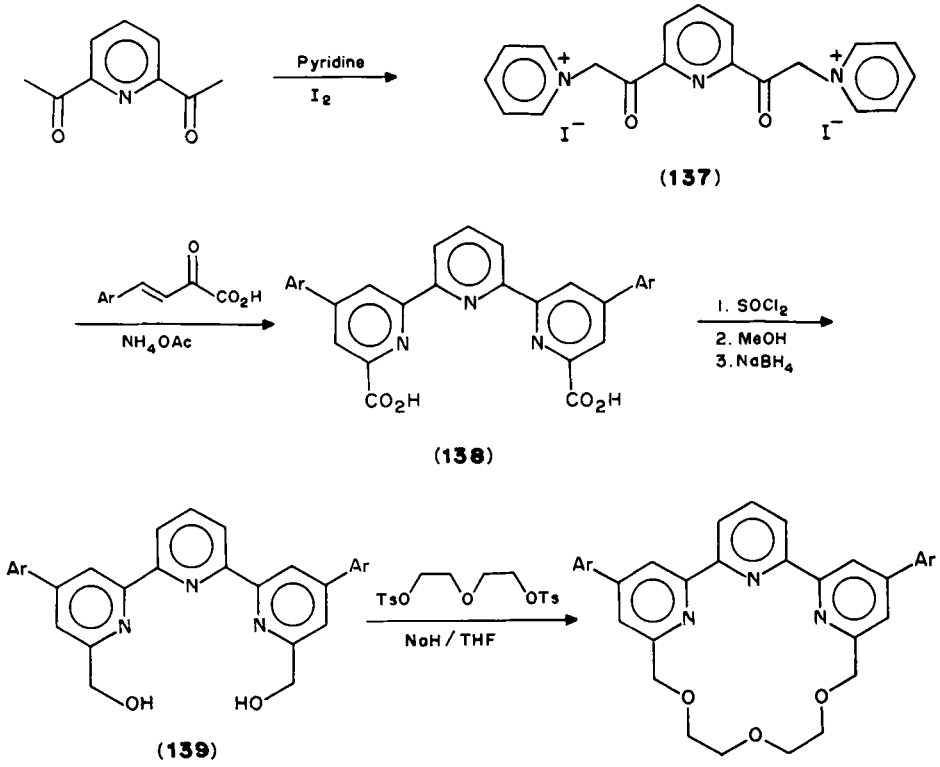


(132) R=H
(133) R=Ph
(134) R=C_6H_4Me-p
(135) R=C_6H_4OMe-p



(136)

Substituted terpyridine hemispherands **133–135** were prepared by Toner *et al.*[175] by the procedure given in Scheme 5, using the Kröhnke reaction[176] to form the key terpyridine diacid **138** (30–95% yield, depending on the nature of the aryl group). Attempts to prepare the analogous compounds with 15-membered macrorings have resulted in only low yields to date. Novel terpyridine hemispherands with 15-membered macrorings were produced by the methodology shown in Scheme 6 by Lewis and coworkers[177]. The final ring closure could be templated only by relatively few transition metals. Use of Me_2SnCl_2

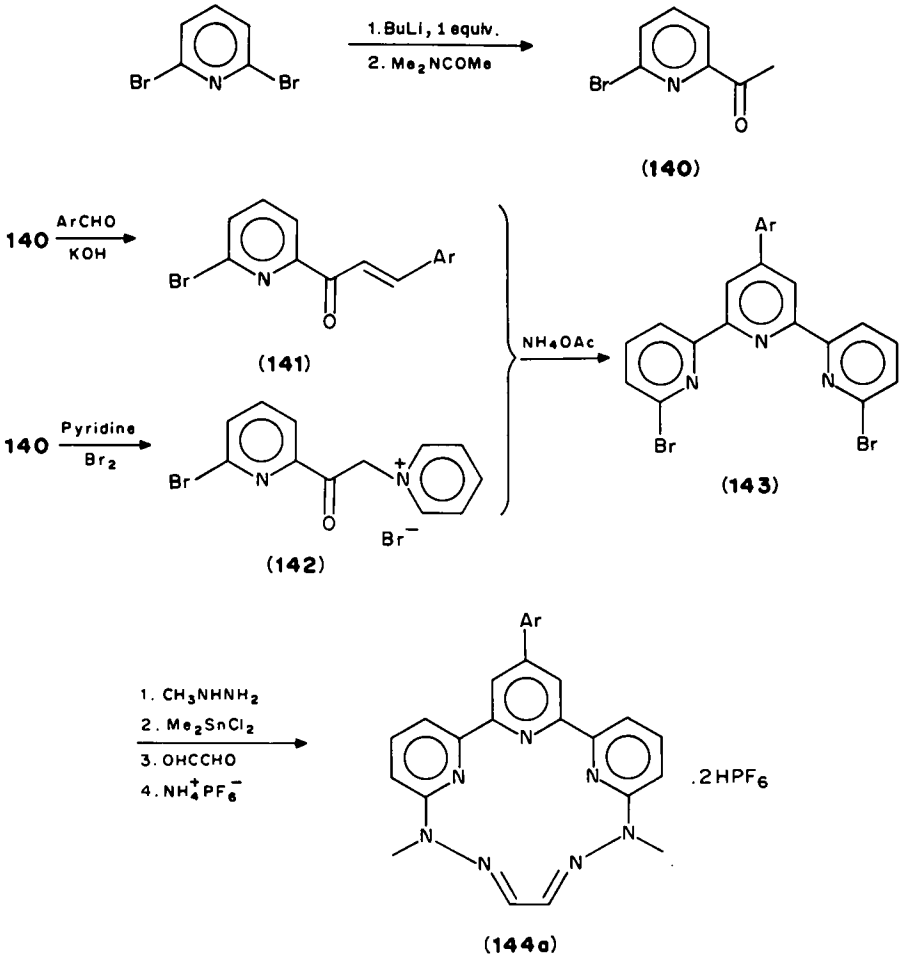


SCHEME 5

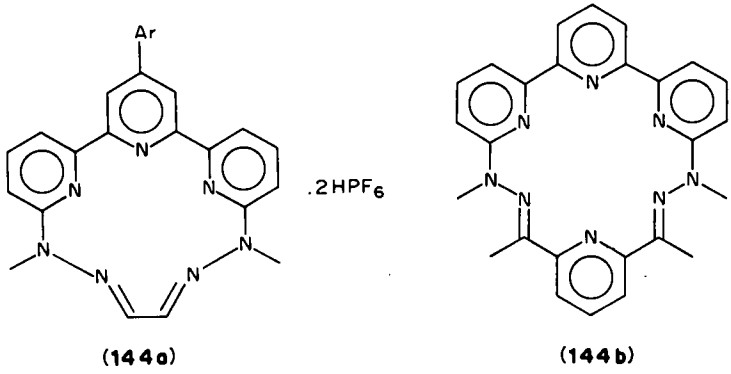
or $CrCl_3$ allowed the formation of host **144a** with the metals acting as transient templating agents. The uncomplexed ligand was easily obtained after treatment of the complexes with NH_4^+ PF_6^- [177c]. By similar methodology, sexidentate ligand **144b** was also synthesized[177c].

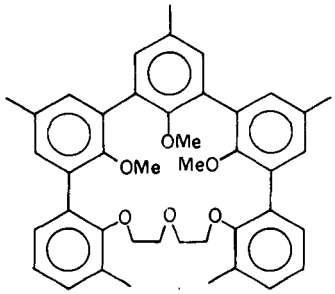
Because of the provision that the binding groups projecting from the rigid units of hemispherands not should be a part of the structural makeup of the macroring, hosts **145–149** are included as ter-hemispherands. Also included here are the hosts obtained by joining two ter-units with flexible linking groups (**150–153**). Finally, ter-hemispherands with odd-sized macrorings, unusual linking groups or chiral units are given in structures **154–158**.

b. Complexation. Most of the hemispherands were synthesized with the particular purpose of determining how incorporation of the preorganizational unit would effect guest recognition. Representative examples of the ter-hemispherands will be chosen to illustrate their binding properties and selectivities. The association constants for guest binding for most of the ter-hemispherands have been determined using the picrate extraction method[29a]. Complete lists of binding constants are available in the references cited. Figure 24 summarizes the general distinctions in complexing ability between teranisyl hemispherands and the other types of ter-hemispherands, with naphtho-18-crown-6 (**20**) as a reference coronand.

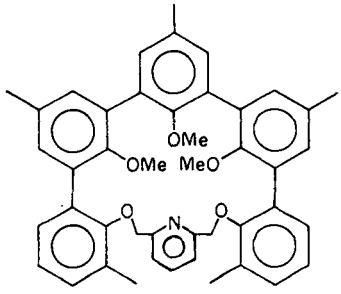

1. BuLi, 1 equiv.
2. Me2NCOMe
(140)
ArCHO
KOH
(141)
Pyridine
Br2
(142)
NH4OAc
(143)
1. CH3NHNH2
2. Me2SnCl2
3. OHCCHO
4. NH4+PF6−
.2HPF6
(144a)

SCHEME 6

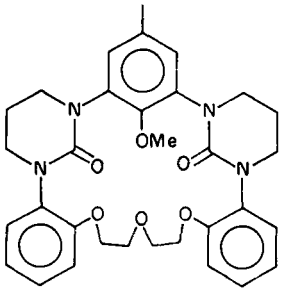

.2HPF6
(144a)
(144b)



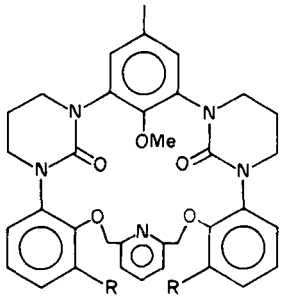
(145)



(146)



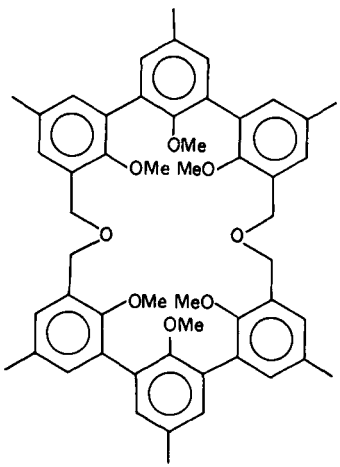
(147)



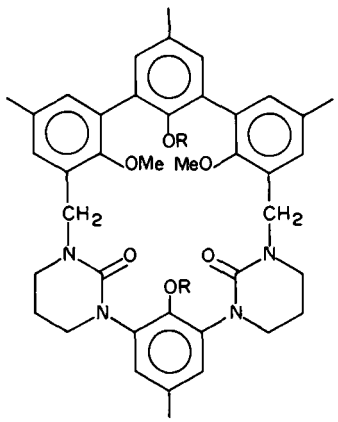
(148) R = Me

(149 a) R = CH_2OMe

(149 b) R = CH_2OH

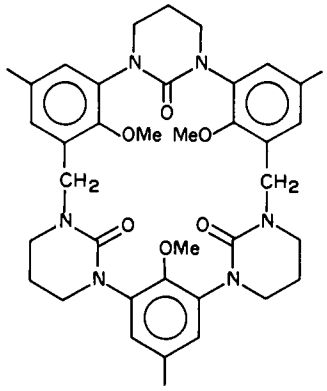


(150)

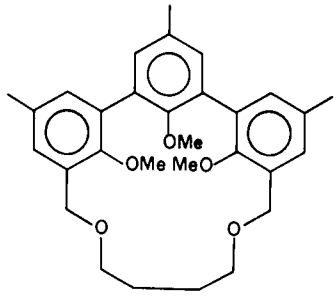


(151) R = Me

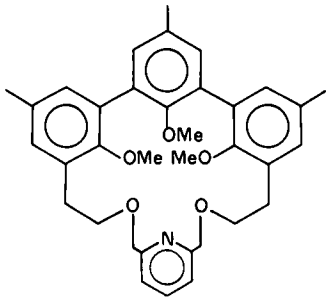
(152) R = CH_2Ph



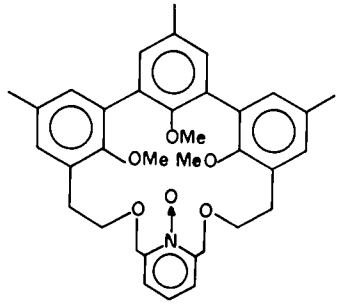
(153)



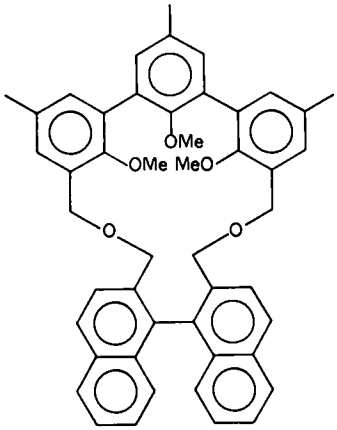
(154)



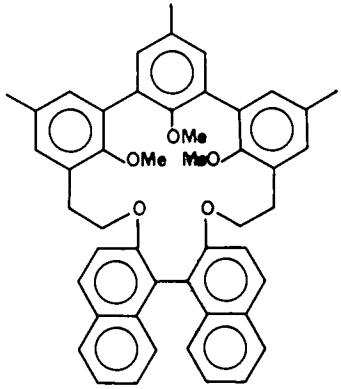
(155)



(156)



(157)



(158)

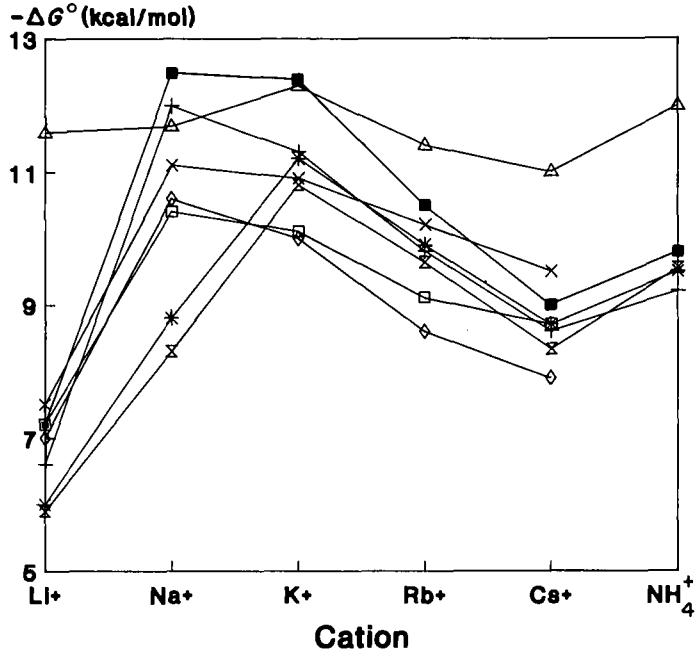


FIGURE 24. Trends in binding between ter-hemispherands. ■, Host **3**; ×, **38**; +, **98**; ◇, **123**; *, **101**; Δ, **135**; □, **116**; ⧖, naphtho-18-crown (**20**)

Methoxycyclohexane hemispherand **101** shows similar binding to the reference coronand. The crystal structure of the similar methoxycyclohexane host **102** shows that the methyl group of the central methoxy turns in the uncomplexed form and occupies the binding cavity[170]. Presumably, the same holds true for host **101** as the binding trends for these hosts are similar, and different from those of teranisyl hemispherand **3**. The energy cost of reorganizing host **101** to attain a binding conformation is apparently the reason for its marked change in binding versus host **3**. In host **3**, the anisyl groups are similar in conformation in both the complexed and uncomplexed forms[39].

Most of the remaining hosts in Figure 24 have similar patterns of binding with differences in degree. Characteristic is the profound change in Na^+ and K^+ recognition seen for these hemispherands versus coronands such as host **20**. Not surprisingly, nitrophenyl host **123** is not particularly good as a binder. The nitrophenyl group apparently preserves the up-down-up arrangement of rigid groups seen for host **3**. Consequently, the binding pattern is similar to that of hemispherand **3** but is shifted to lower values. The nitro group is probably not involved in binding Na^+, as is known to be the case for center pyridyl host **38** and 4*H*-pyran hemispherand **117**[171d]. Figure 25 shows the X-ray crystal structure for the Na^+ Pic^- complex of **38**[171d].

Center urea host **98** is the closest in binding to host **3**. From the X-ray crystal structure of its *t*-butylammonium perchlorate complex, it is clear that all host oxygens are involved in binding[169]. Remarkable is the lack of specificity of terpyridyl hemispherand **135**. The terpyridyl unit is conformationally flexible and probably accommodates any size of cation by opening the aryl–aryl dihedral angles. Toner *et al.*[175] synthesized hosts **133–135** because pyridine is such a good ligand in its own right, as opposed to anisole. We were

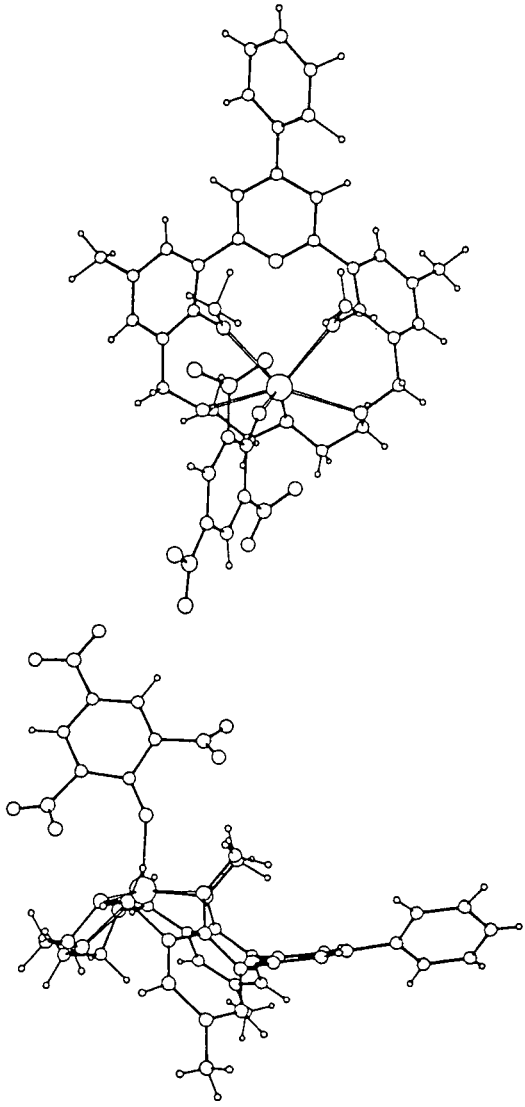
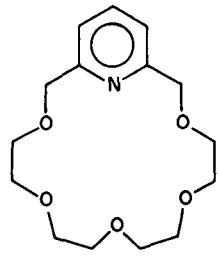


FIGURE 25. Two views of the X-ray crystal structure of the complex between pyrido hemispherand **38** and Na^+Pic^-

intrigued to see the effect of the organization of three or more contiguous pyridines in hemispherands, given that host **159** is so similar in complexation properties to normal coronands[22]. Comparisons of space-filling molecular models of hosts **3** and **135** suggested the greater conformational flexibility of the terpyridyl unit when incorporated into a macrocycle. This host demonstrates that the binding increase gained by having three,



(159)

contiguous rigid units in a macrocycle is not limited to conformationally locked units such as teranisyls; however, selectivity apparently is. Attempts to synthesize analogous terpyridyl hemispherands with 15-membered macrorings are in progress because of the excellent Li^+ binding of the 18-membered hosts.

The effects of additional donor groups on complexation[167] are seen in Figure 26 with host **3** as the reference. The general effect is an increase in overall binding without much change in selectivity.

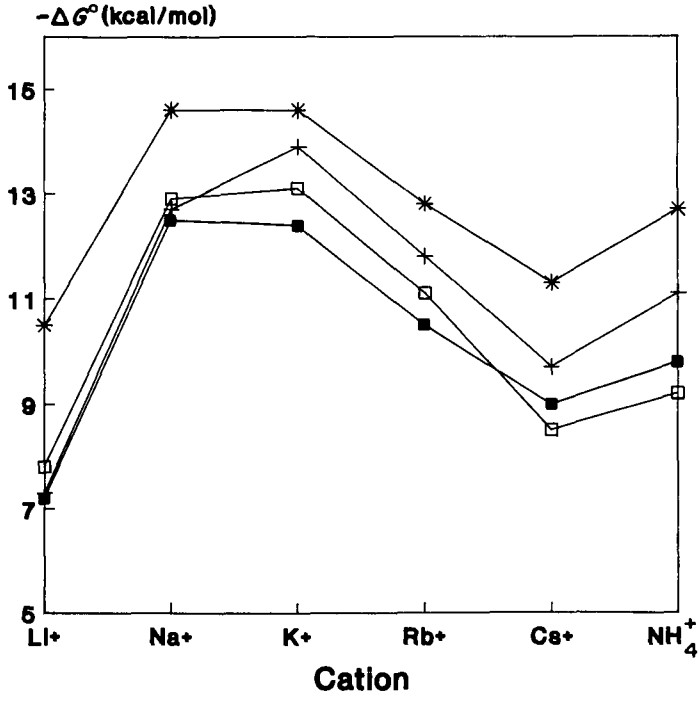


FIGURE 26. Effects of additional donor groups on ter-hemispherand complexation of M^+Pic^-. ■, Host **3**; +, **81**; *, **89**; □, **99**

Binding by hosts **145–148**[178] is highlighted in Figure 27, again with host **3** for comparison. The teranisyl hosts **145** and **146** are comparable in binding to host **3**, whereas the bis-urea hosts **147** and **148** show poorer binding.

The desire to design a truly Na^+-specific ionophore led us to examine teranisyl hemispherands as candidates. Host **3** is reasonably selective for Na^+ against cations other than K^+. Our feeling, based on models and early complexation data with the first hemispherands, led us to believe that constriction of the binding cavity of host **3** might produce the Na^+/K^+ selectivity we desired by favoring the smaller Na^+ at the expense of K^+. In essence, we wanted to preorganize the hemispherand binding cavity powerfully without moving out of the hemispherand class. Unfortunately for the design of an ionophore, Cram[22] has shown that, in general, powerful preorganization brings attendant high binding constants. An ionophore must rapidly complex and release its guest in order to function, especially in ion-selective electrodes. At some point the binding is so good that a host does not release its guest at a reasonable rate. Spherand **5** ($k_{-1} \approx 10^{-9}\,s^{-1}$) was examined, and it was shown that it does not function as an ionophore, being effectively an irreversible binder of Na^+ and Li^+ [168b].

We constricted the binding cavities of hemispherands by three techniques, using host **3** as a point of departure and benchmark. Included were alkoxy substitution of the methoxy groups of host **3**, bridging and inclusion of pyrido and anisyl rings. Initial efforts with simple alkoxy group replacements led to the synthesis of hosts **68–72**, which form a nice

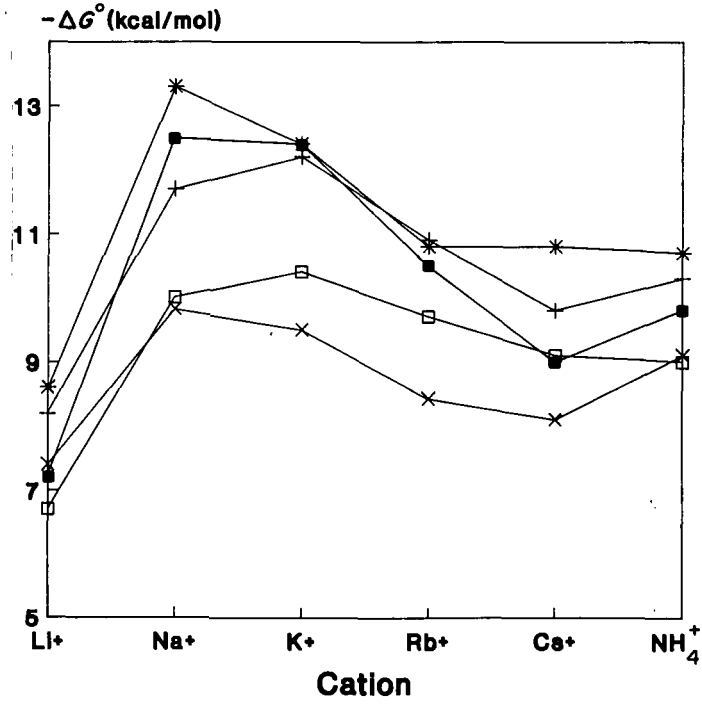


FIGURE 27. Picrate binding by hosts **145–148**. ■, Host **3**; +, **145**; *, **146**; □, **147**; ×, **148**

steric series. The negative logarithm of their potentiometrically determined Na^+ selectivities is shown in Figure 28, which came as dismal news at the time. Examination of solution behavior and solid-state conformations of hosts **3**[39], **68** and **72** confirmed that far from better preorganizing the hemispherand cavity, we had succeeded with trisisopropoxy hemispherand **72** in distorting it greatly. The center isopropoxy groups force themselves

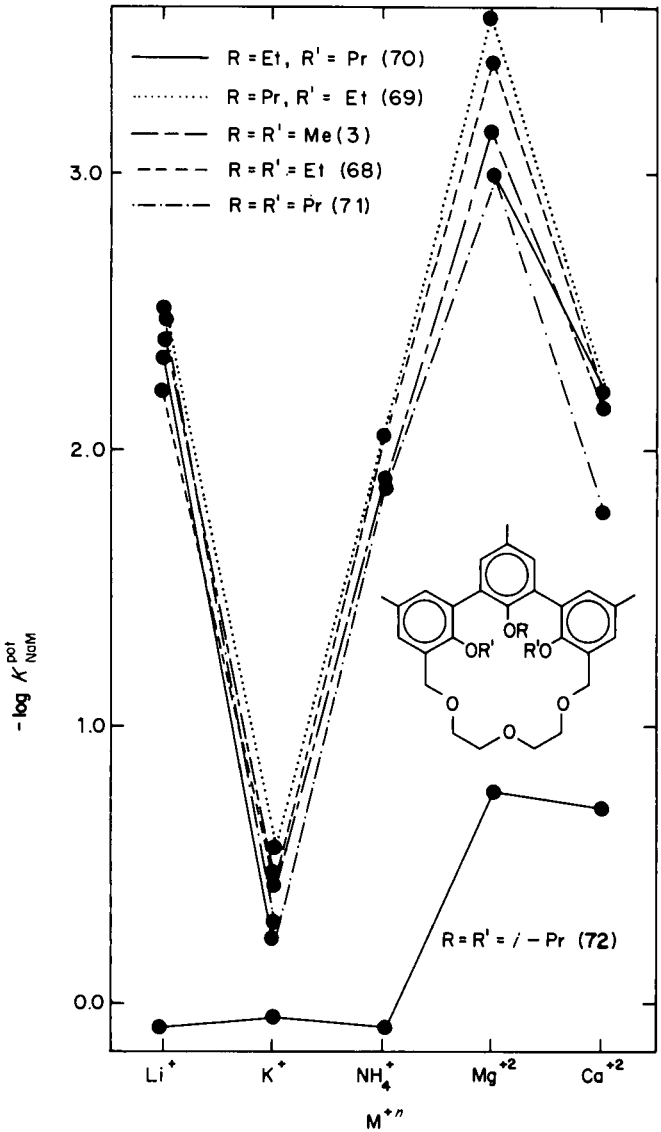


FIGURE 28. Potentiometric $-\log K$ values for Na^+ selectivities toward mono- and di-cations in a hemispherand steric series

away from contact with each other. The aryl–aryl dihedral angles for host **3** are both 58° whereas for host **72** they are 78° and 49°. Bridging and inclusion of pyrido and anisyl groups were more successful, as expected from examination of the picrate-based K_a values (Figure 29)[165–167]. Combinations of all three constriction methodologies led to synthesis of hosts **84–88** and many others after the formation and alkylation of phenol **83** had been perfected. Figure 30 indicates progress toward the initial vision of constructing an Na^+-specific complexing agent which still remained an ionophore. Coumarin hemispherand **160** is at present the most Na^+-selective ionophore that we have been able to synthesize.

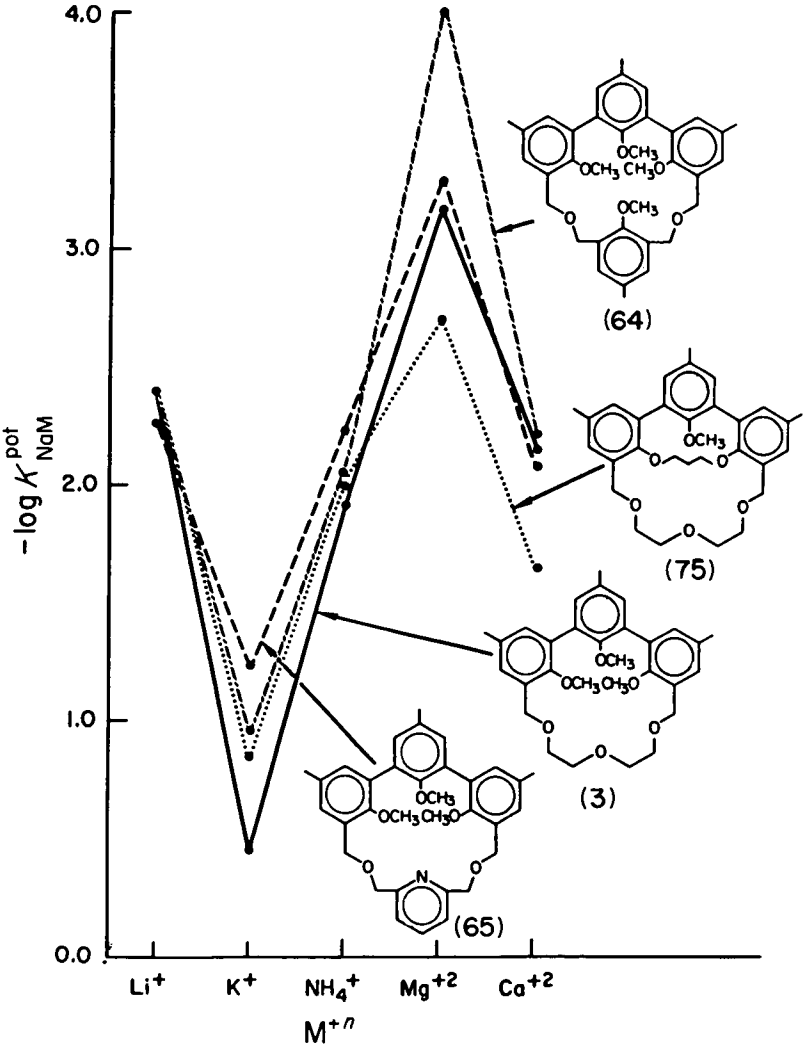


FIGURE 29. Potentiometric Na^+ selectivities for ter-hemispherands with one binding cavity constricting feature

Returning to M^+Pic^- derived binding constants, examination of Figure 31 makes it clear that the reason for the high Na^+/K^+ selectivity seen with these constricted hosts is selective exclusion of K^+. The effect on the binding cavity dimensions in progressing from host **3** to the highly constricted hemispherands can be seen in Plate 10. Consequently, these constricted hemispherands have the novel virtue of greater preorganization with lower overall binding, but with higher Na^+ selectivity than host **3**. Molecular mechanics minimizations of uncomplexed and Na^+-complexed benzyl hemispherand **85** followed by

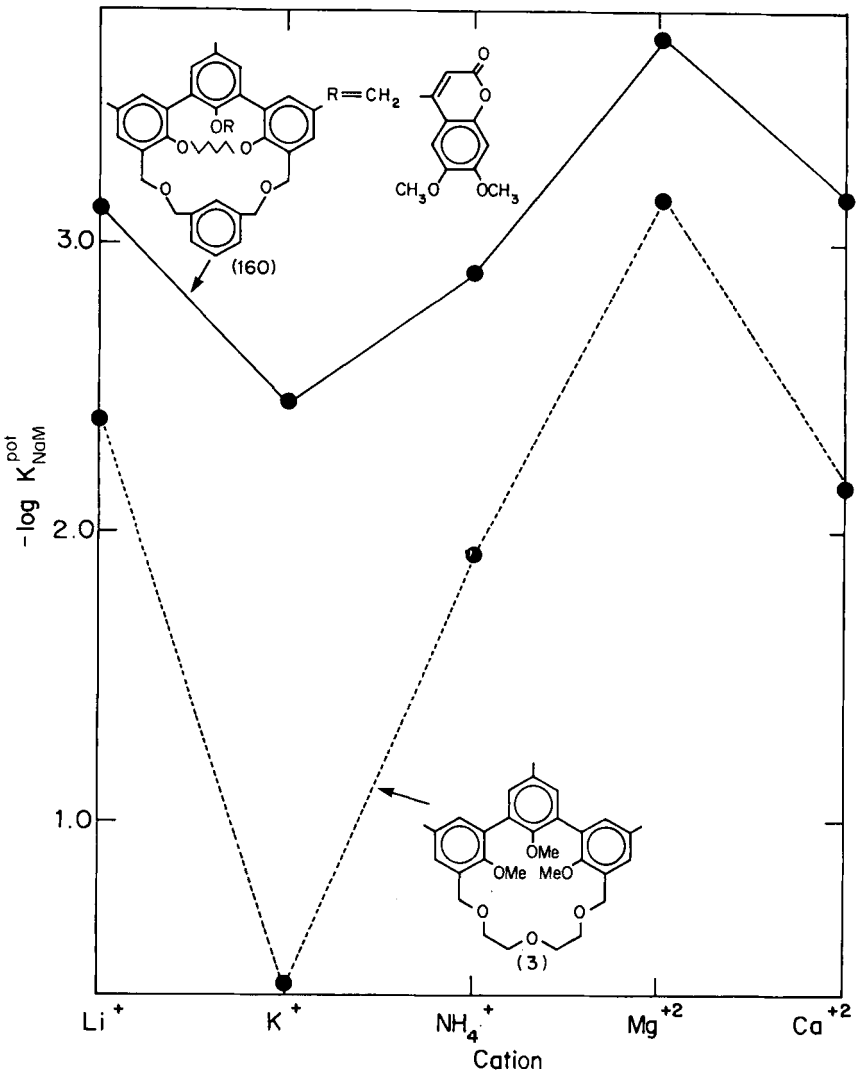


FIGURE 30. Progress toward an Na^+ specific ionophore. Numbers on the ordinate are potentiometrically determined values.

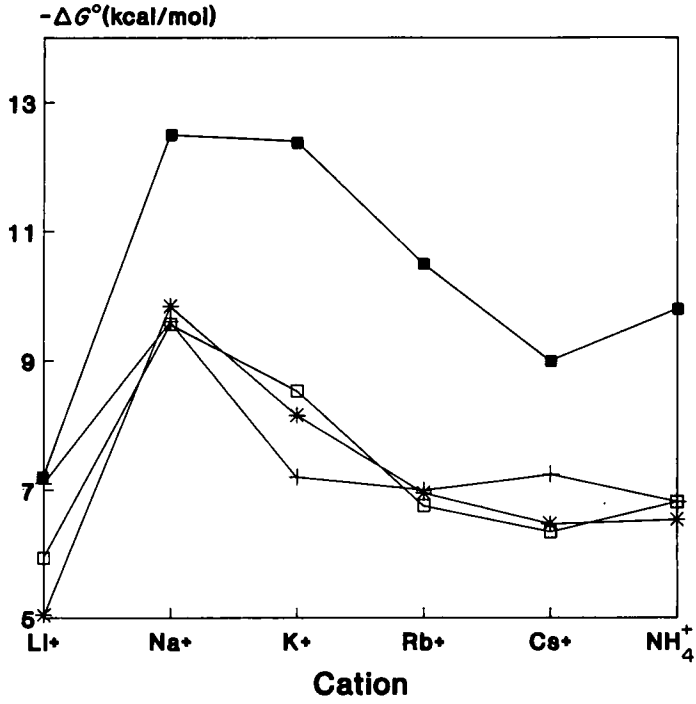


FIGURE 31. Effects of ring constriction on ter-hemispherand complexation of M^+Pic^-. ■, Host **3**; +, **85**; *, **78**; □, **76**

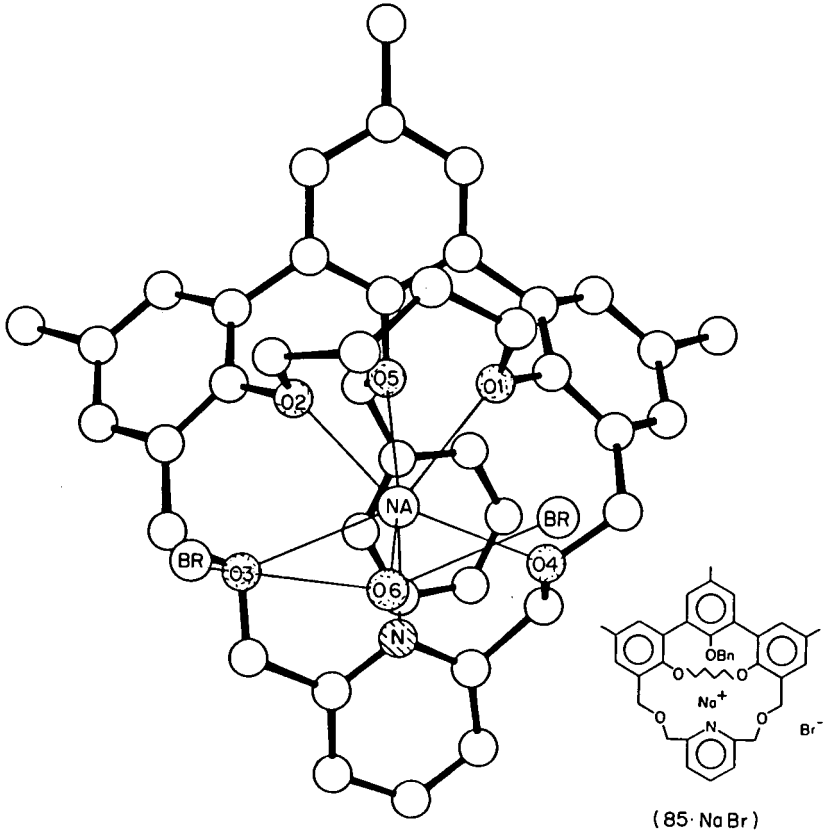
least-squares fitting of the resulting structures with a methyl group in place of the benzyl group gave an RMS difference of 0.34 Å, well below the value of 0.65 Å for host **3**, indicating that greater preorganization was achieved for the constricted hosts.

Figures 32 and 33 are drawings of the crystal structures of host **85** complexed with NaBr and uncomplexed, respectively. In the NaBr complex, the Na^+ has one water molecule as an additional ligand, hydrogen-bonded to two Br^- ions. Uncomplexed hemispherand **85** crystallizes in two conformations, one of which is shown in Figure 33.

2. *Quater-hemispherands*

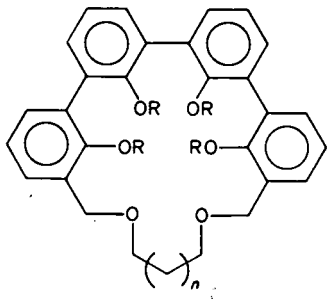
a. Synthesis. Hosts **161–176** were synthesized by an interesting route shown for host **23**, which involves the opening of bisdibenzofuran diacid **178** with fused NaOH–KOH to produce the key quaterphenyl diacid **179** in 95% yield (Scheme 7)[181].

b. Complexation. The quater-hemispherands present an intriguing series for a number of reasons. They are chiral and potentially resolvable, depending on the rate of inversion of the alkoxyphenyl groups through the macroring. In addition, the hosts with 18-membered macrorings are more Na^+-selective than unconstricted ter-hemispherands (Figure 34). Formation of 21-membered quater-hemispherands led to an interesting reversal in selectivity, now favoring K^+/Na^+ by as high as 4.5 kcal mol^{-1} for host **174**. This trend is

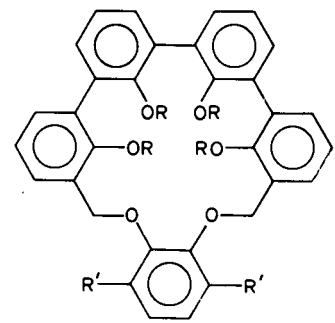


(85·NaBr)

FIGURE 32. X-ray crystal structure of benzyl hemispherand **85** complexed with NaBr



(23) R=Me, n=0
(161) R=Me, n=1
(162) R=Et, n=1



(163) R=Me, R'=H
(164) R=Me, R'=Me
(165) R=Et, R'=H

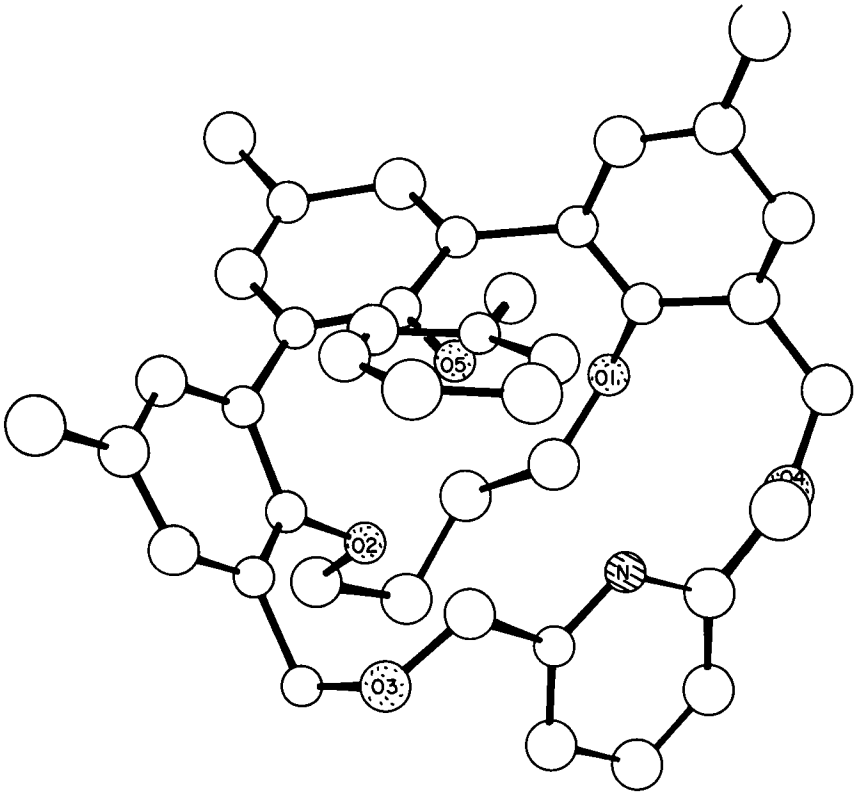
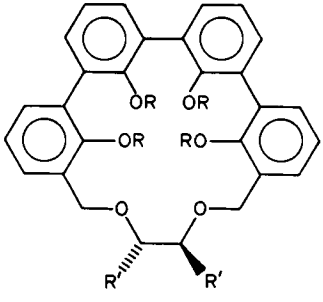
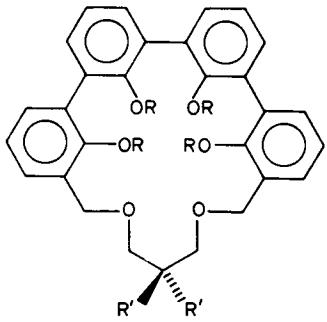


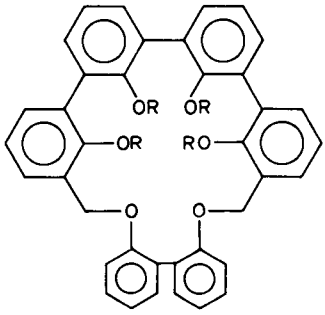
FIGURE 33. Crystal structure of uncomplexed benzyl hemispherand **85**



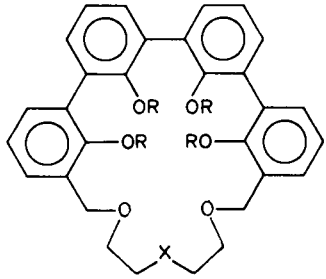
(166) R=Me, R'=CH_2OCH_2Ph



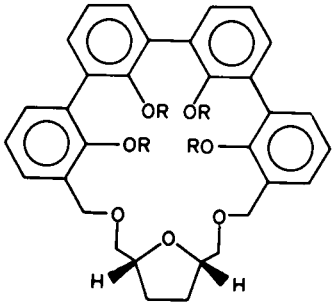
(167) R=Me, R'=CH_2OMe



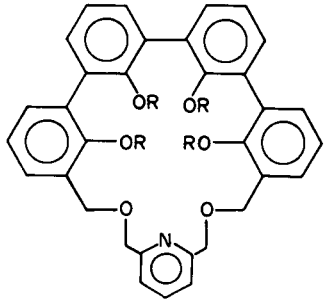
(168) R=Me



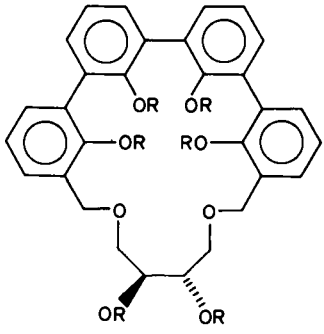
(169) R=Me, X=O
(9) R=Et, X=O
(170) R=Me, X=S
(171) R=Me, X=S(O)
(172) R=Me, X=SO_2



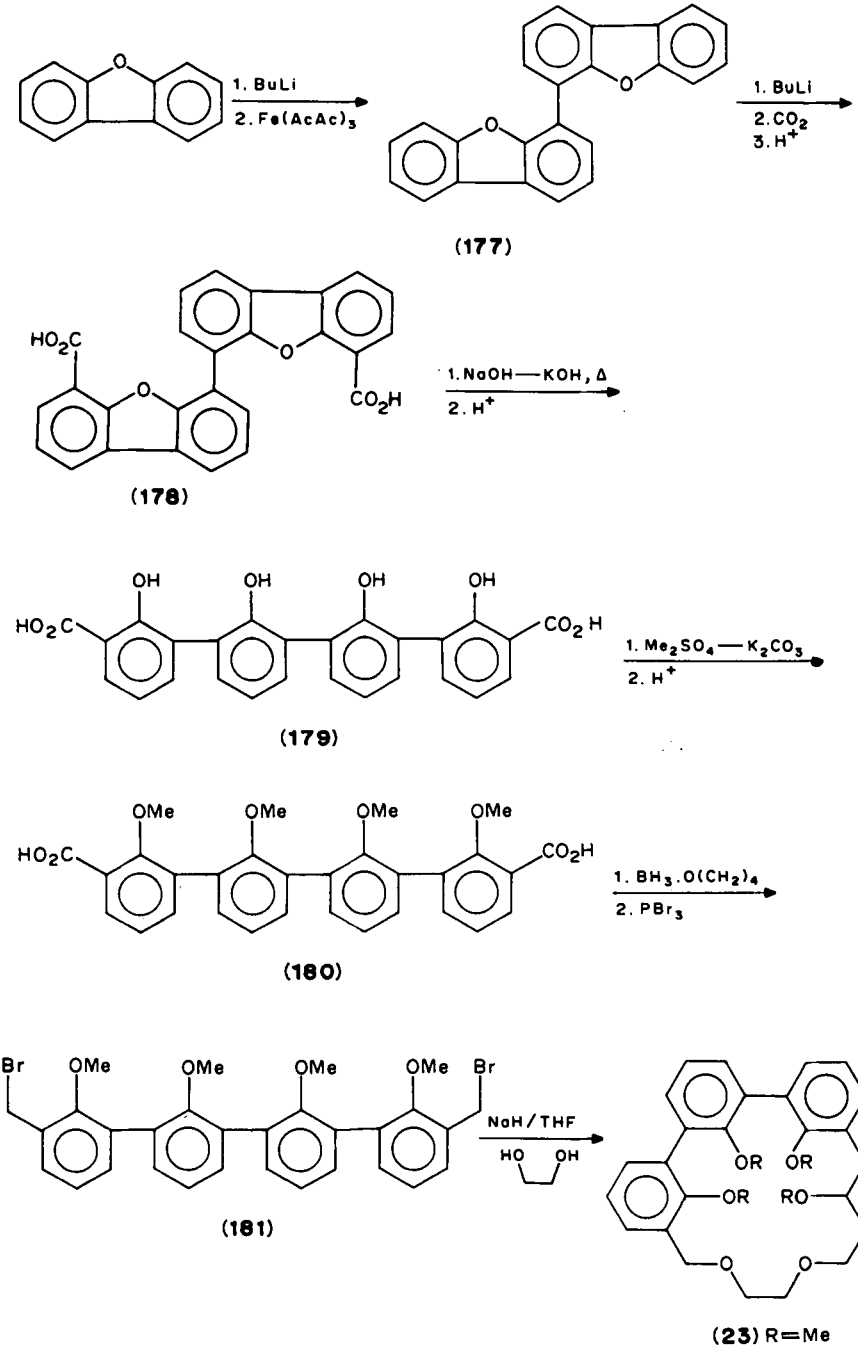
(173) R=Me
(174) R=Et



(175) R=Me



(176) R=Me


1. BuLi
2. Fe(AcAc)3
1. BuLi
2. CO2
3. H+
(177)
HO2C
CO2H
1. NaOH—KOH, Δ
2. H+
(178)
OH
HO2C
CO2H
1. Me2SO4—K2CO3
2. H+
(179)
OMe
HO2C
CO2H
1. BH3.O(CH2)4
2. PBr3
(180)
Br
OMe
Br
NaH/THF
HO
OH
(181)
OR
RO
(23) R=Me

SCHEME 7

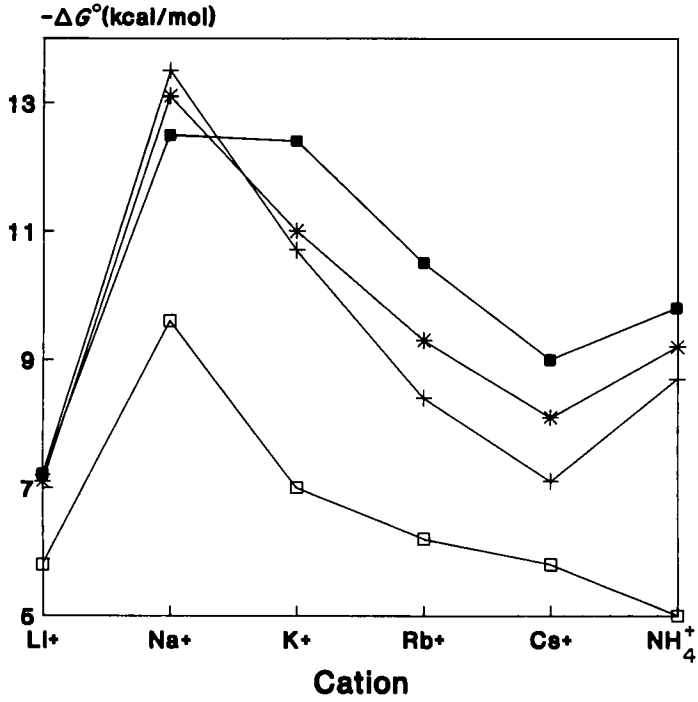


FIGURE 34. M^+Pic^- binding by 18-membered quater-hemispherands. ■, Host **3**; +, **23**; *, **163**; □, **164**

also seen in teranisyl hemispherands (Figure 35). It is noteworthy that switching Et for Me in hosts **174** and **173** and in hosts **9** and **169** led to increases in K^+/Na^+ of 1.6 and 1.4 kcal mol^{-1}, respectively, although the steric effect would, if anything, have predicted favoring the smaller Na^+. Artz and Cram[181] have also studied the kinetics of K^+ decomplexation for four of the quaterphenyl hemispherands and found the rate constants to vary from 4 to 27 s^{-1}.

3. *Quinque-hemispherands*

a. Synthesis. The quinque-hemispherands[182] represent the second most populous group of hemispherands (**182–206**). As a representative example, Scheme 8 outlines the synthesis of hosts **182** and **183**, once again relying on the opening of a dibenzofuran with fused NaOH–KOH. Formation of the bis-cyclic urea precursor **211** led to the final ring closures to give **182** and **183** in 3.5 and 30% yields, respectively[179].

b. Complexation. Several of the quinque-hemispherands are extremely powerful binders. They also reach equilibrium very rapidly[182d] with k_1 measured in $CDCl_3$ for hosts **191**, **192** and **205** ranging between 10^{11} and 10^{12} $l mol^{-1} s^{-1}$. The fast complexation rates are due to the presence of the urea groups, which do not present the steric impedance to complexation found with the anisyl hosts. Figure 36 presents binding data for five representative quinque-hemispherands. Figure 37 shows three crystal structures of the

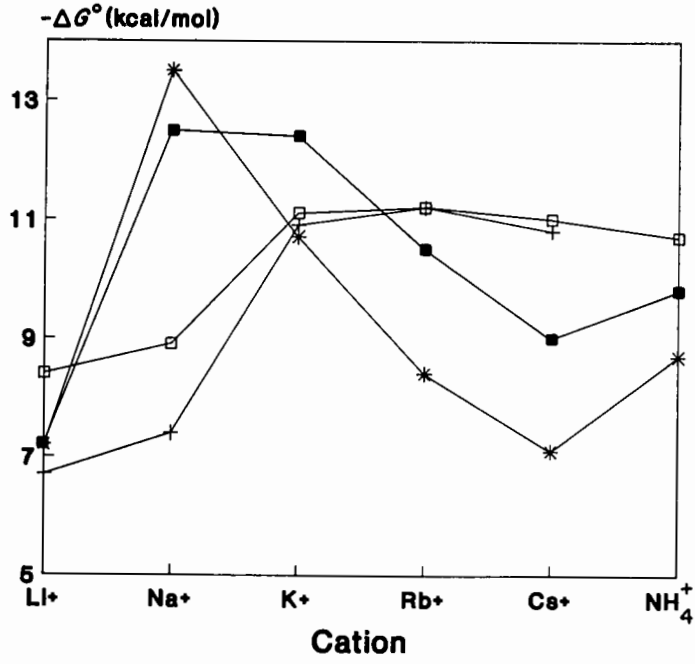
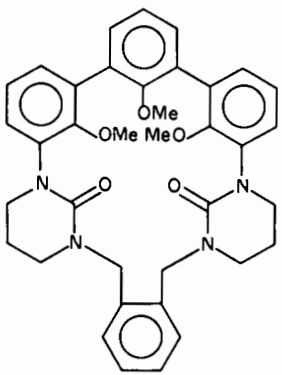
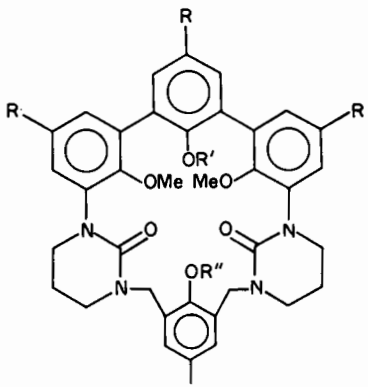


FIGURE 35. Complexation trends between hemispherands with 18- and 21-membered macrorings toward M^+Pic^-. ■, Host **3** (18-ter); *, **23**, (18-quat), +, **37** (21-ter); □, **169** (21-quat)



(**182**)

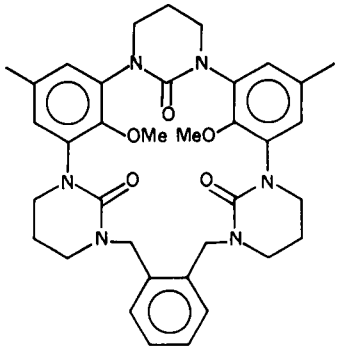


(**183**) R = H, R′ = Me, R″ = Me

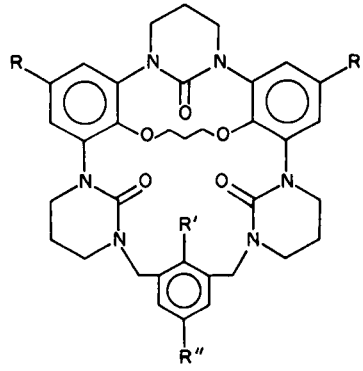
(**184**) R = Me, R′ = CH_2Ph, R″ = $CH_2CH{=}CH_2$

(**185**) R = Me, R′ = CH_2Ph, R″ = H

(**186**) R = Me, R′ = H, R″ = H

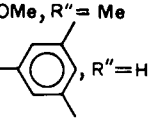


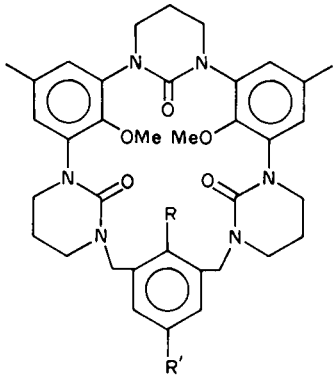
(187)



(188) R = Me, R′ = OMe, R″ = Me

(189) R = H, R′ = OMe, R″ = Me

(190) R = H, R′ =  , R″ = H



(191) R = H, R′ = Me

(192) R = OMe, R′ = Me

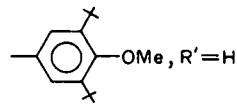
(193) R = H, R′ = H

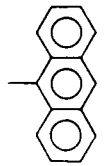
(194) R = Br, R′ = H

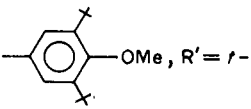
(195) R = CO_2Me, R′ = H

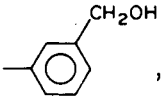
(196) R = H, R′ = *t*-Bu

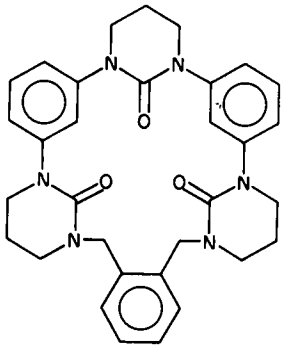
(197) R = Br, R′ = *t*-Bu

(198) R =  , R′ = H

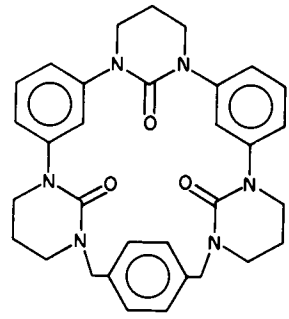
(199) R =  , R′ = H

(200) R =  , R′ = *t*-Bu

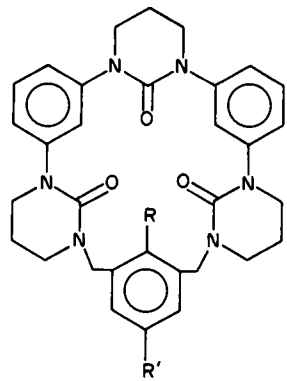
(201) R =  , R′ = H



(202)

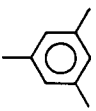


(203)



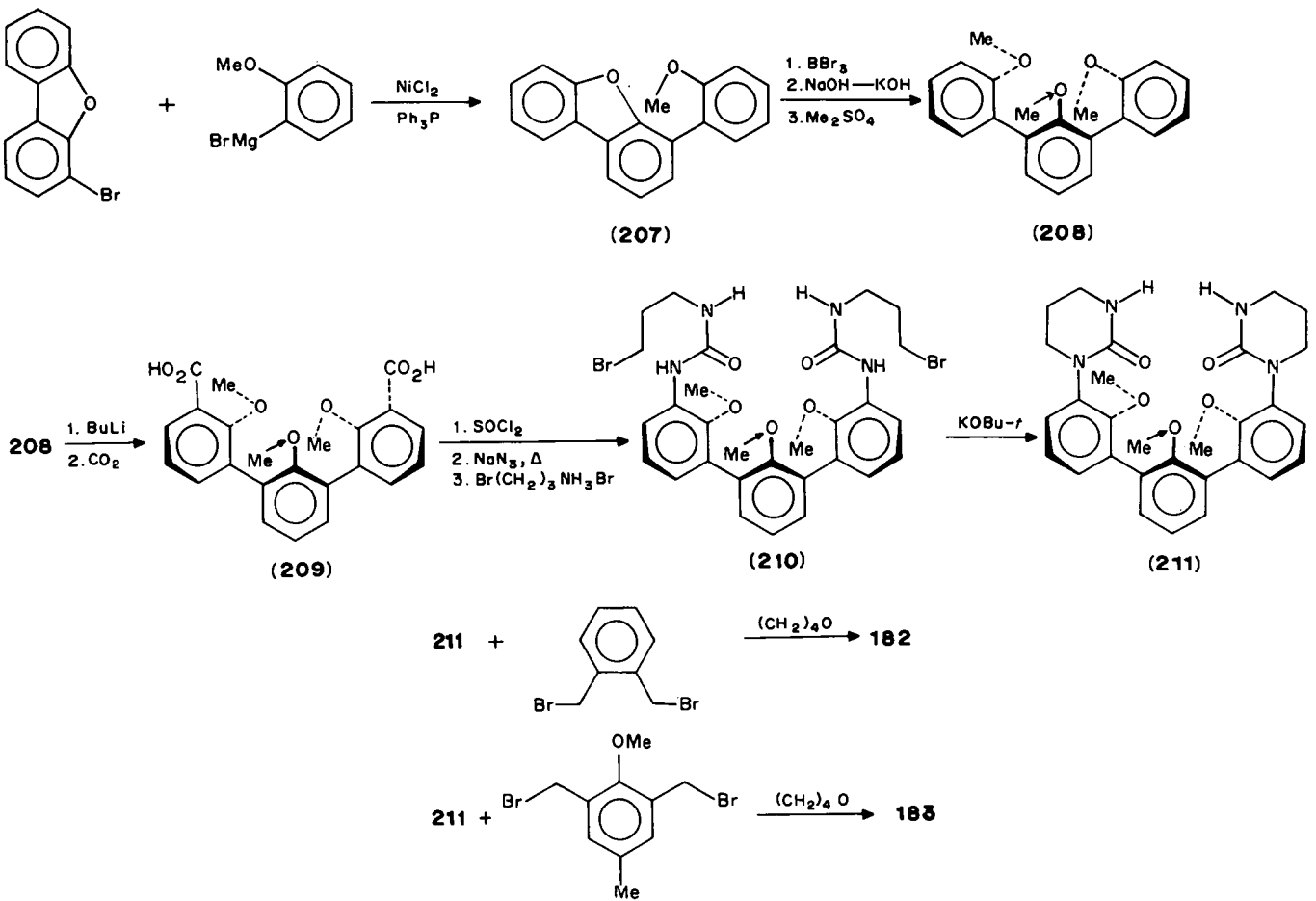
(204) R=H, R'=H

(205) R=OMe, R'=Me

(206) R=  , R'=H

quinque-hemispherands **183**, **192** and **195** complexed with Na^+ and *t*-butylammonium[182d]. Because of the tripodal arrangement of cyclic urea carbonyls possible in several of these hosts, complexation of ammonium salts is exceptionally facile. Incorporation of a steric blocking group in host **200** led to discrimination between $MeNH_3^+$ and *t*-$BuNH_3^+$ of 2.5 kcal mol^{-1}[182e].

Cram and Doxsee[183] showed that host **190** binds aryldiazonium salts more powerfully than 18-crown-6 and offers a higher degree of stabilization toward thermal decomposition and azo dye formation. Hemispherand **190** binds *p*-Me_3 $CC_6H_4N_2BF_4$ with a free energy of about -5.9 kcal mol^{-1} compared with -3.6 kcal mol^{-1} for 18-crown-6 and the same guest. In essence the host is a non-covalent protective group. When Na^+ was added to a stable colorless solution of the complex between host **190** and *p*-$Me_3CC_6H_4N_2BF_4$ with $C_6H_5NMe_2$ present, instantaneous dye formation resulted. The Na^+ ion acts as a 'trigger'


MeO
BrMg
NiCl2
Ph3P
Br
(207)
1. BBr3
2.NaOH—KOH
3.Me2SO4
(208)
208
1. BuLi
2.CO2
(209)
1. SOCl2
2. NaN3, Δ
3. Br(CH2)3NH3Br
(210)
KOBu-t
(211)
211 +
(CH2)4O
182
211 +
(CH2)4O
183

SCHEME 8

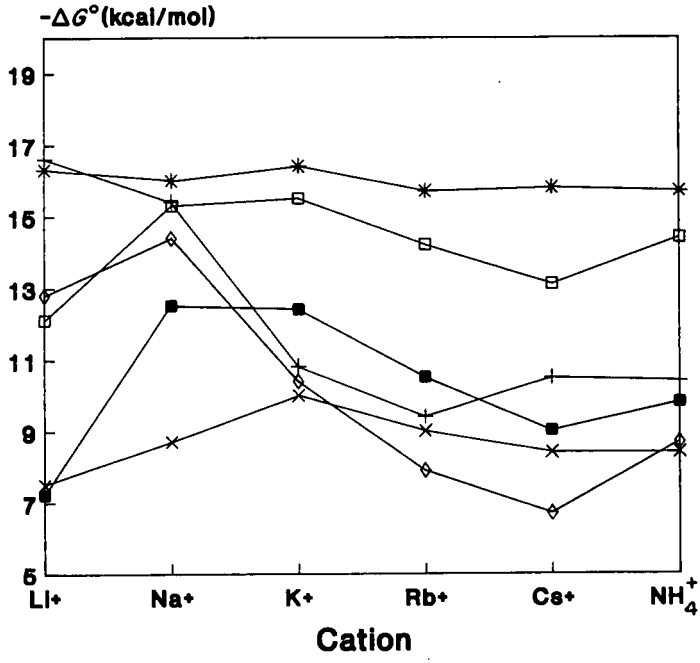
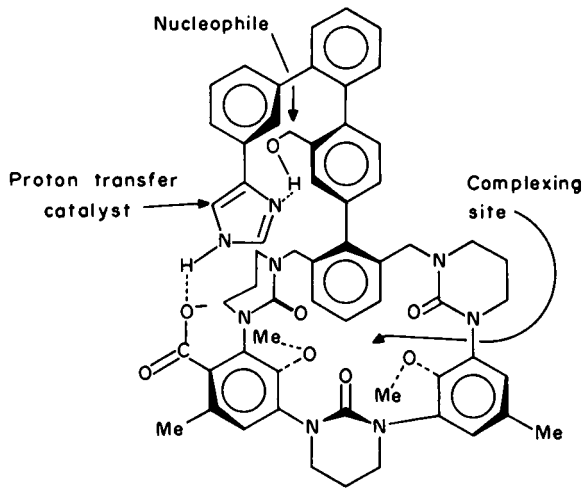


FIGURE 36. Complexation of M^+Pic^- by quinque-hemispherands. ■, Host **3**; +, **182**; *, **188**; □, **192**; ×, **205**; ◇, **24**

for the dye reaction because it has a much higher binding constant with host **190** than the diazonium salt.



(214)

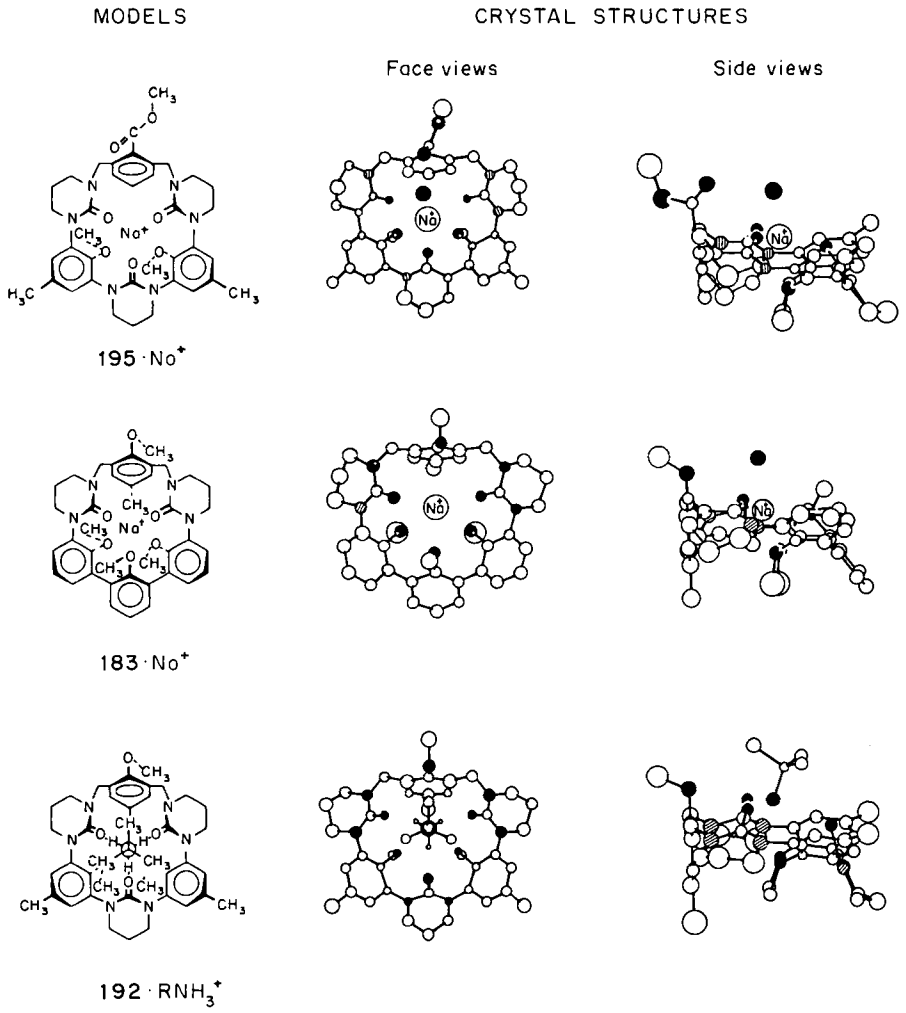
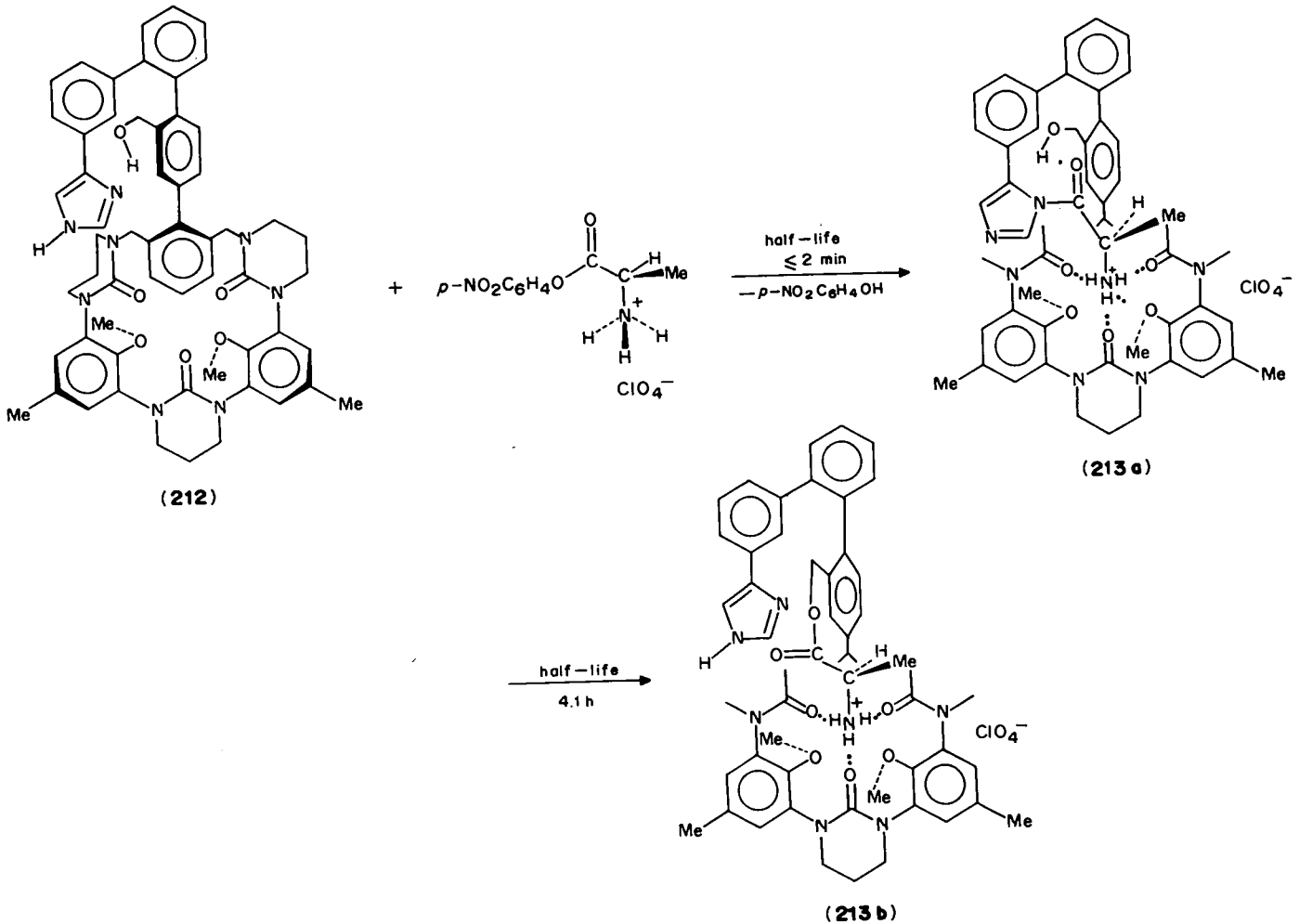


FIGURE 37. Crystal structures of quinque-hemispherands

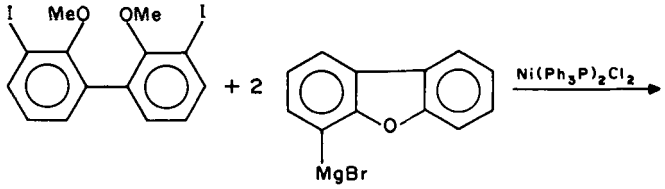
The serine protease mimics of Cram and coworkers[29c,184] are a special subdivision of quinque-hemispherands. The transacylase partial mimic **212** was obtained after a 30-step synthesis. The host rapidly binds and reacts with amino acid ester salts, acylating the imidazole group to give **213a** (Scheme 9). The intermediate **213a** slowly converts to **213b** with a half-life of 4 h. Host **214** is a potential complete transacylase mimic.

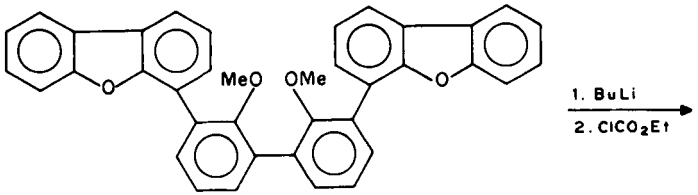
4. *Sexi-hemispherands*

a. Synthesis. The four sexi-hemispherands **215–218** were reported by Cram *et al.* in 1984[185a]. Scheme 10 depicts the synthesis of host **215**, from which were synthesized **216**

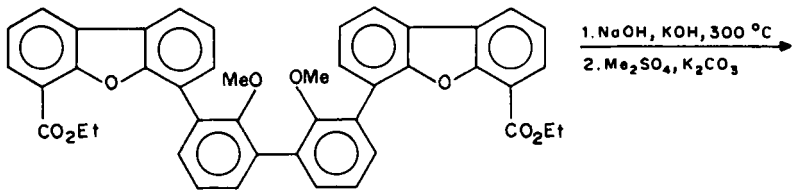

(212)
+
p-NO2C6H4O
Me
ClO4−
half−life
≤ 2 min
−p-NO2C6H4OH
(213a)
half−life
4.1 h
(213b)

SCHEME 9

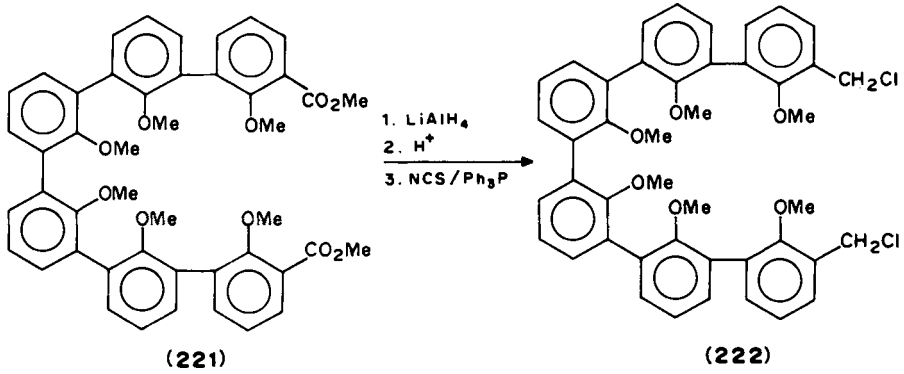




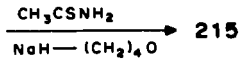
(219)



(220)



(221) (222)



SCHEME 10

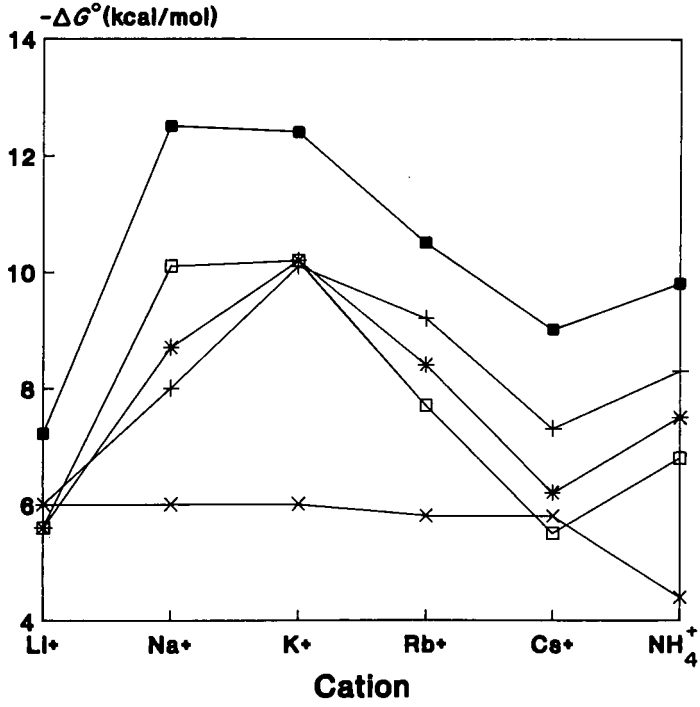


FIGURE 38. Complexation of M^+Pic^- by sexi-hemispherands. ■, Host 3; +, 215; *, 216; □, 217; ×, 218

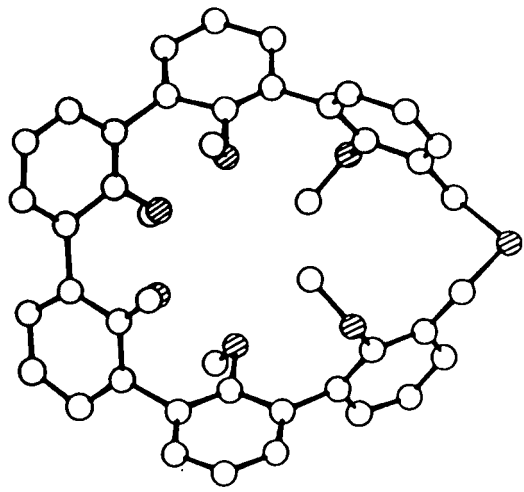
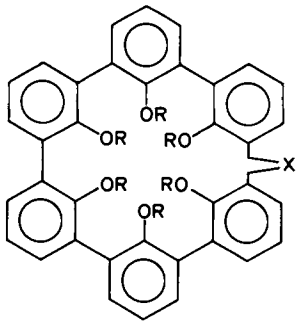


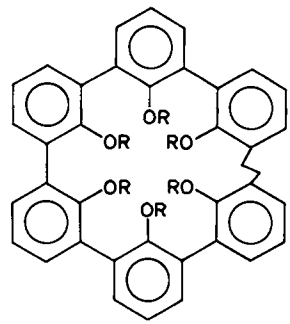
FIGURE 39. X-ray crystal structure of sexi-hemispherand 215

and **217**. Formation of the critical sexianisyl unit **221** required treatment of bis-dibenzofuranylbiphenyl **220** with fused NaOH–KOH. Final macrocyclization was effected by treatment of **222** with thioacetamide–NaH in 75% yield.

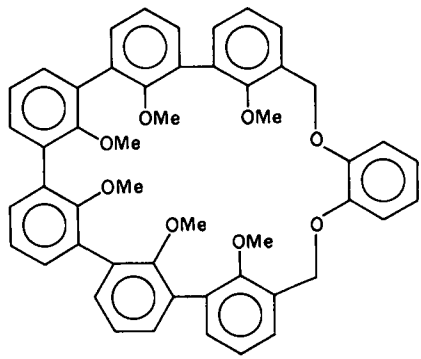
b. Complexation. The binding of these hosts is poor (Figure 38). This is presumably due to two of the anisyl methyl groups in the uncomplexed hosts occupying the binding cavity, as can be seen in the crystal structure of host **215** (Figure 39)[185].



(215) R=Me, X=S
(216) R=Me, X=SO_2



(217) R=Me



(218)

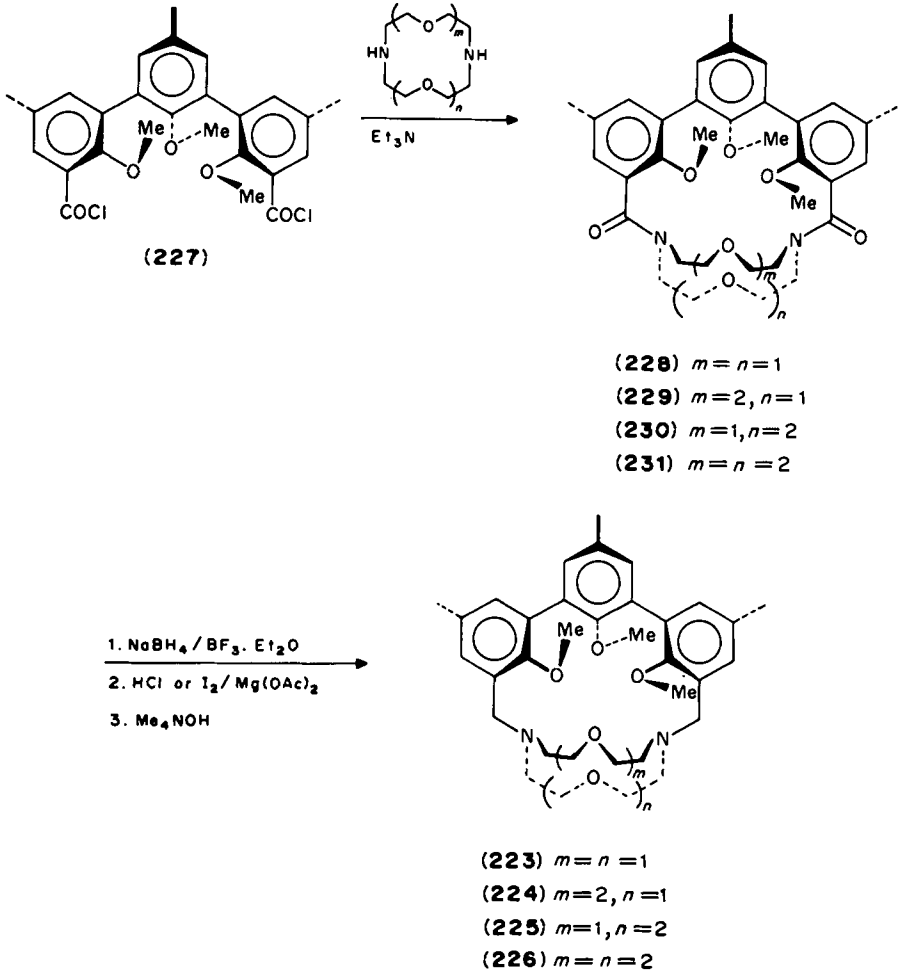
C. Cryptahemispherands

1. Introduction

The cryptahemispherands were recently reviewed[22] but are included here for completeness and for comparison purposes with the hemispherands and spherands. Strictly speaking, cryptahemispherands are ter-hemispherands. However, their prowess as complexing agents, in terms of both high negative free energies for complexation and selectivity, sets them apart as a separate class. As the name implies, they have macrorings which are cryptand–hemispherand composites.

2. Synthesis

Cryptahemispherands **223–226** were synthesized from diacyl chloride **227** by the procedure shown in Scheme 11[186a]. The free cryptahemispherands slowly decompose on keeping and are usually stored as their borane complexes. Hosts **224** and **225** sluggishly interconvert at room temperature. Addition of KSCN gave complete conversion to **224**. KSCN from the original mixture of isomers.



(227)

(228) $m = n = 1$
(229) $m = 2, n = 1$
(230) $m = 1, n = 2$
(231) $m = n = 2$

(223) $m = n = 1$
(224) $m = 2, n = 1$
(225) $m = 1, n = 2$
(226) $m = n = 2$

SCHEME 11

3. Complexation

The normal picrate extraction technique could not be used to determine the binding constants of cryptahemispherands **223–226** because of their basicity, the water solubility

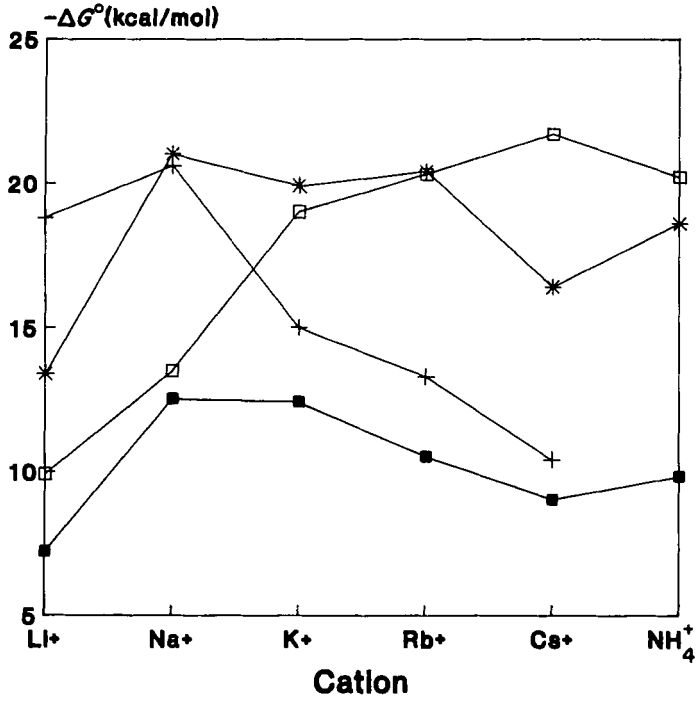


FIGURE 40. Complexation of M^+Pic^- by cryptahemispherands. ■, Host 3; +, **233**; *, **224**; □, **226**

of their complexes and their high association constants[186b]. Consequently, NMR competition experiments with guest cations between hosts **223–226** and other hosts whose binding abilities were known gave the desired free energies for complexation (Figure 40). Crystal structures of complexes of the cryptahemispherands **224** and **226** are shown in Figure 41[186a].

The cryptahemispherands are more powerful binders than cryptands[186b]. Their selectivities are also better than the cryptands on comparing some nearest neighbor cations (Na^+/K^+, K^+/Rb^+, etc.) and worse on comparing others. For example, [222]cryptand binds K^+ with $\Delta G° = -18.0\,kcal\,mol^{-1}$ vs $-19.0\,kcal\,mol^{-1}$ for the cryptahemispherand **226**. Similarly, cryptahemispherand **224** binds Na^+ $3.3\,kcal\,mol^{-1}$ more strongly than [221]cryptand.

In comparisons of nearest neighbor cation selectivities between cryptands and cryptahemispherands, [221]cryptand prefers Na^+/K^+ by $2.4\,kcal\,mol^{-1}$ whereas host **223** selects Na^+/K^+ by $5.6\,kcal\,mol^{-1}$. [222]Cryptand selects K^+/Na^+ by $3.6\,kcal\,mol^{-1}$ in comparison with $5.5\,kcal\,mol^{-1}$ with cryptahemispherand **226**. On the other hand, [222]cryptand selects Rb^+/Cs^+ by $6.8\,kcal\,mol^{-1}$ with the best comparable cryptahemispherand value of $4.0\,kcal\,mol^1$ with host **224**. [221]Cryptand prefers K^+/Rb^+ by $2.6\,kcal\,mol^{-1}$ vs $1.7\,kcal\,mol^{-1}$ for host **223**.

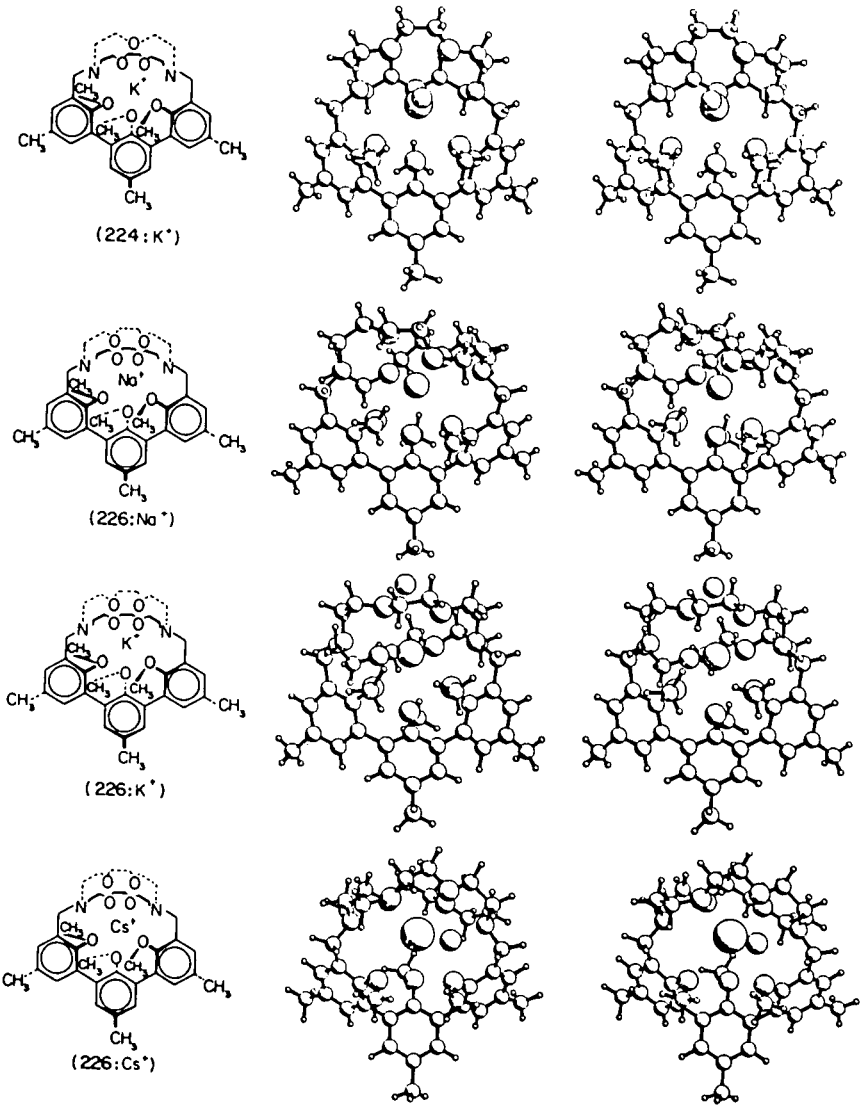


FIGURE 41. Crystal structures of cryptahemispherands

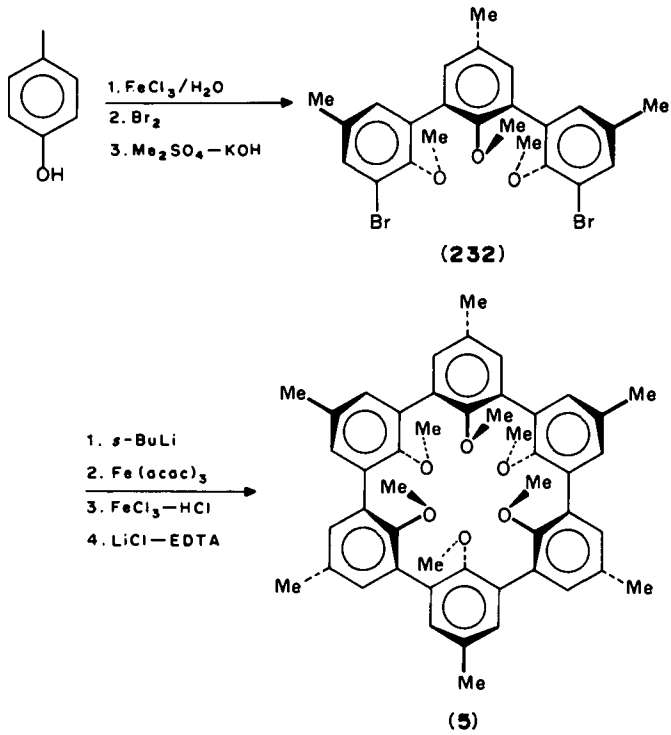
D. Spherands

1. Introduction

Spherands are hosts in which the macroring is composed completely of contiguous rigid units. Binding groups are appended to the rigid units and converge on the binding cavity. Spherand **5** is the prototype. Analogous to the treatment of hemispherands, spherands will be considered according to the number of rigid units making up the macroring.

2. Sexi-spherands

a. Synthesis. The sexi-anisyl spherands form a group which are almost completely preorganized for complexation during synthesis rather than during binding. The key step in the synthesis of the sexi-spherands was the oxidative coupling of teranisyl dibromide **232**. Scheme 12 outlines the procedure for the synthesis of spherand **5**. After much experimentation, the invention of a new use for $Fe(acac)_3$ as an agent in aryl–aryl oxidative coupling reactions was accomplished[130a]. Optimizing the process improved the yield of the coupling step to 28% for formation of the Li^+ spheraplex. Figure 42 shows the lithium complex of spherand **5**. Plate 11 is a computer-generated space-filling model of the Li^+ complex of spherand **5**. Decomplexation was accomplished with difficulty in comparison with most other hosts. The spheraplex as the LiCl complex was heated in



SCHEME 12

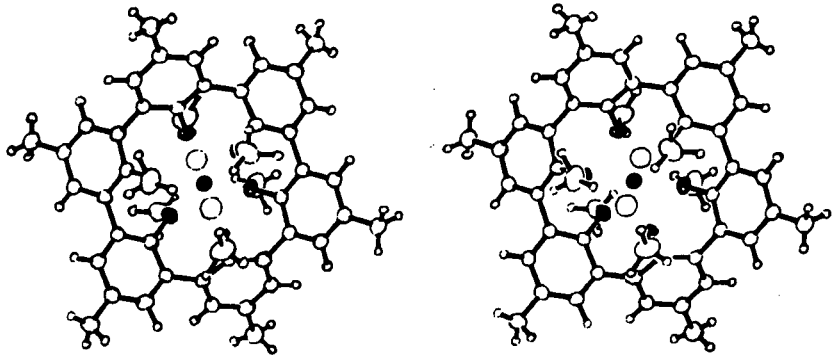


FIGURE 42. Stereoview of the crystal structure of Li^+ spheraplex **5**

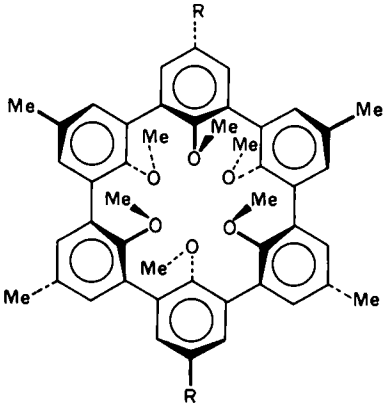
MeOH–H_2O in a sealed tube at 125 °C for 20 days (84% yield). The decomplexation was driven by precipitation of the insoluble free host **5**[130d]. Structures **5**, **40**, **42**, **237–242**, and **245–249** depict sexi-spherands synthesized by similar methods by Cram and coworkers.

Bridged spherands **42** and **238** were synthesized from the appropriate bridged terphenyl precursors by the method used for spherand **5**. It was initially believed that the bridges were on opposite sides of the macroring, a relatively strain-free conformation in CPK models. However, the X-ray analysis revealed that with both hosts the bridges were *syn* to each other (Figure 43)[188]. It is only by the expedient of shaving the CPK models that **42** and **238** can be constructed. The reason for this unusual result is still unknown. However, as previously mentioned, molecular mechanics calculations on **44**, the *anti*-isomer of **42**, predicted it to be a more powerful Li^+ binder than the parent spherand **5**[56]. Subsequently, Cram and Helgeson[132] isolated the *anti*-isomer **44** and showed that its Li^+ complex is more stable than that of host **5** based on the relative difficulties in decomplexing the two hosts.

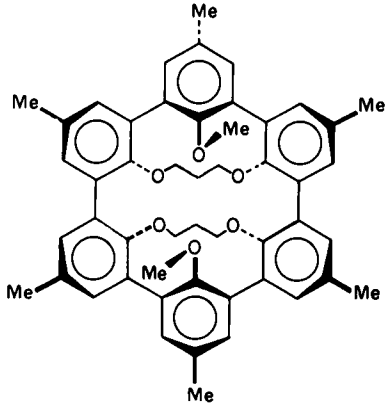
Chiral host **240** was formed by the oxidative coupling of (*R*)-dibromide **243** under the conditions used for spherand **5**. Monodemethylation and decomplexation occurred. After realkylation, spherand **240** was obtained in 2.6% yield. The perfluoro macrocycle **241** was designed to see how far the concept of focusing a poor ligand perfectly for binding could be extended[190].

Spherand **242** was obtained in 26–28% yield by the direct metalation of teranisyl **244** followed by oxidation coupling with $Fe(acac)_3$. Monodemethylation was accomplished by heating the Li^+ spheraplex in pyridine–water (1:6) at 200 °C to give, after acidification, phenol **246** (98%). Oxidation of **246** with thallium nitrate to quinone **247** followed by condensation with 2, 4-dinitrophenylhydrazine gave the chromogenic ion-selective spherand **248** in good yield[191]. The bis(methoxycyclohexyl) spherand **249** was also synthesized. The X-ray crystal structure shows that the methoxy methyl groups of the cyclohexanes fill the cavity in the absence of a guest, similar to the situation with hemispherand **102**[192].

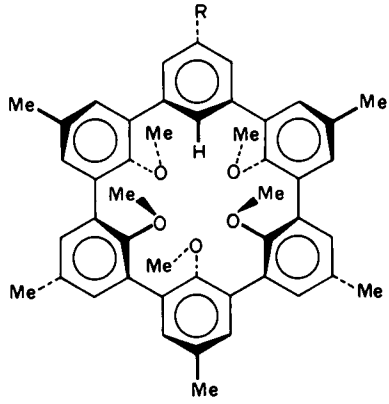
Reinhoudt and coworkers[193] accomplished the synthesis of spherands **233–236** as the LiCl complexes by forming substituted terphenyls using the methodology cited for their hemispherand synthesis, followed by oxidative coupling with $Fe(acac)_3$. Spherand **236**, unfortunately, was formed in extremely low yields and was characterized only by mass spectrometry. Hosts **234** and **235** will be very interesting to compare with spherand **5** in terms of complexation kinetics. The *p*-OMe and *p*-OCH_2OMe groups of spherands **234** and **235** might aid the desolvation of cations during binding.



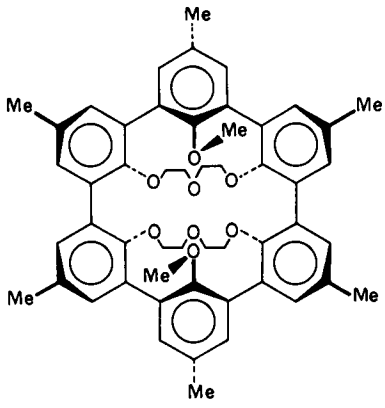
(5) R = Me
(233) R = H
(234) R = OMe
(235) R = OCH_2OMe
(236) R = $N(CH_2Ph)_2$



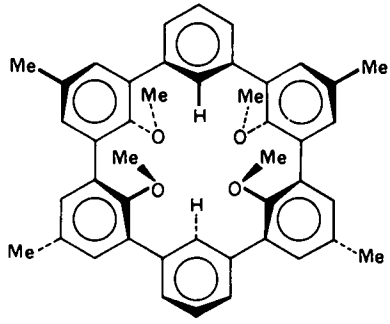
(42)



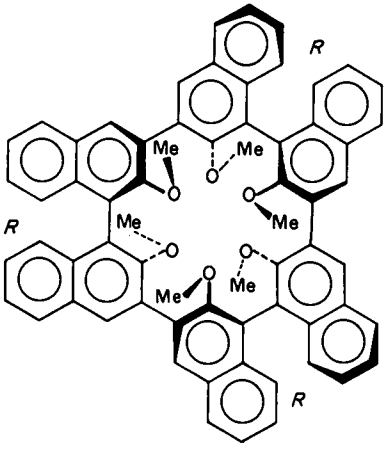
(40) R = H
(237) R = Me



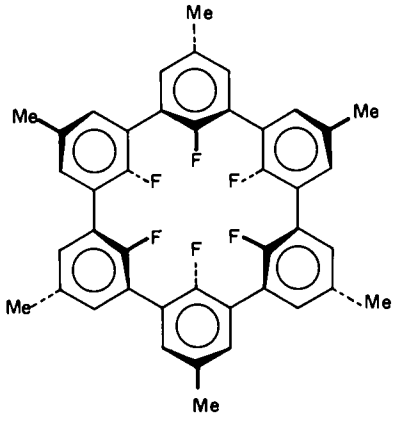
(238)



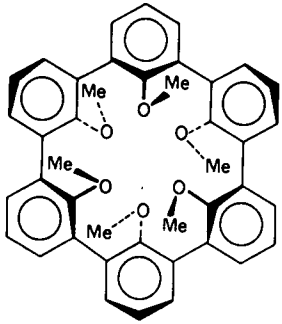
(239)



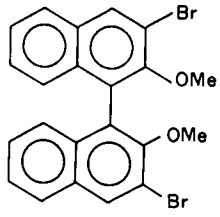
(240)



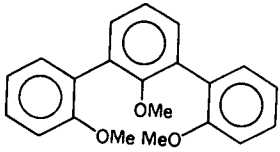
(241)



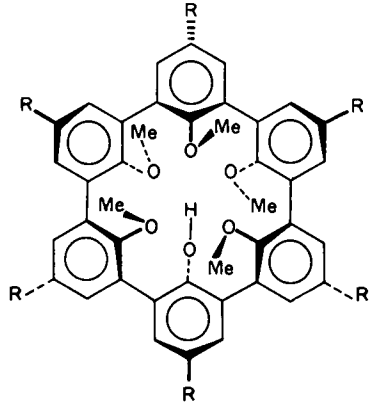
(242)



(243)

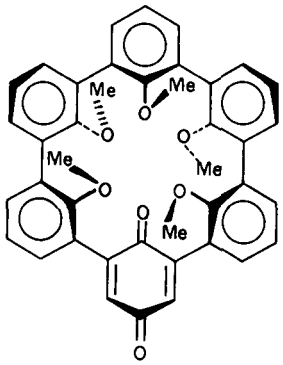


(244)

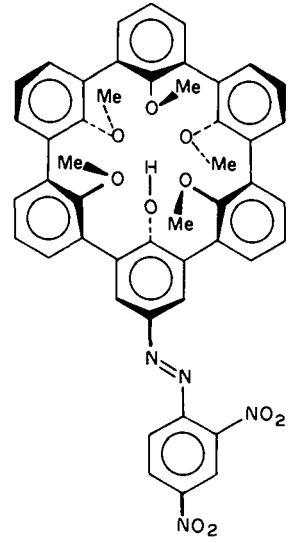


(245) R = Me

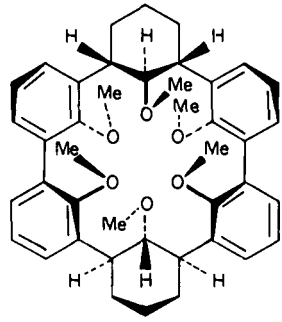
(246) R = H



(247)

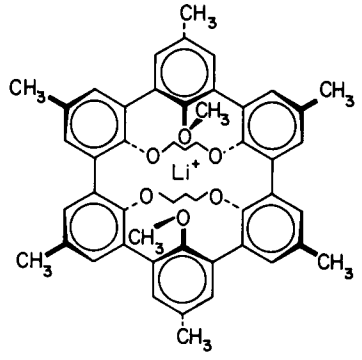


(248)

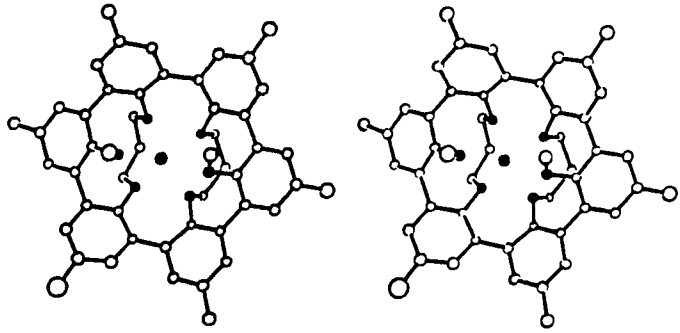


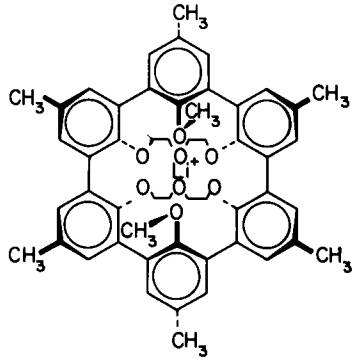
(249)

Interest in the replacement of the anisyl units of spherand **5** with intrinsically more powerful ligands led to the synthesis of the first aza spherands, cyclosexipyridines **250–252**, by Toner[194] and Newkome and Lee[195] by the methodologies outlined in Schemes 13 and 14, respectively. The cyclosexipyridines formed were highly insoluble, which precluded examination of their complexation chemistry. Efforts on our part to synthesize more soluble cyclosexipyridines have not yet been successful. Cyclosexipyridine **250** was obtained as the free ligand, whereas **251** and **252** both analyze as the Na^+OAc^- complexes. Na^+ was scavenged either as an impurity or perhaps removed from glass. Molecular modeling calculations on cyclosexipyridines in comparison with spherand **5** indicate that the cyclosexipyridines should complex tenaciously and essentially non-selectively[196].



(42. Li^+)





(238. Li^+)

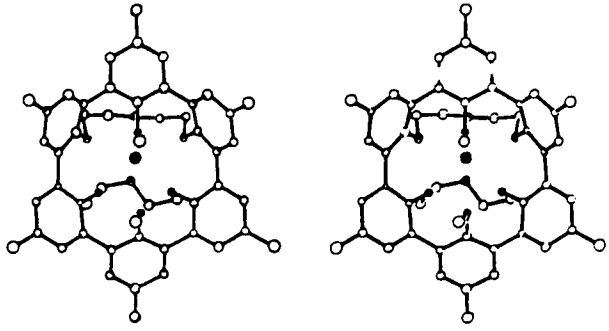
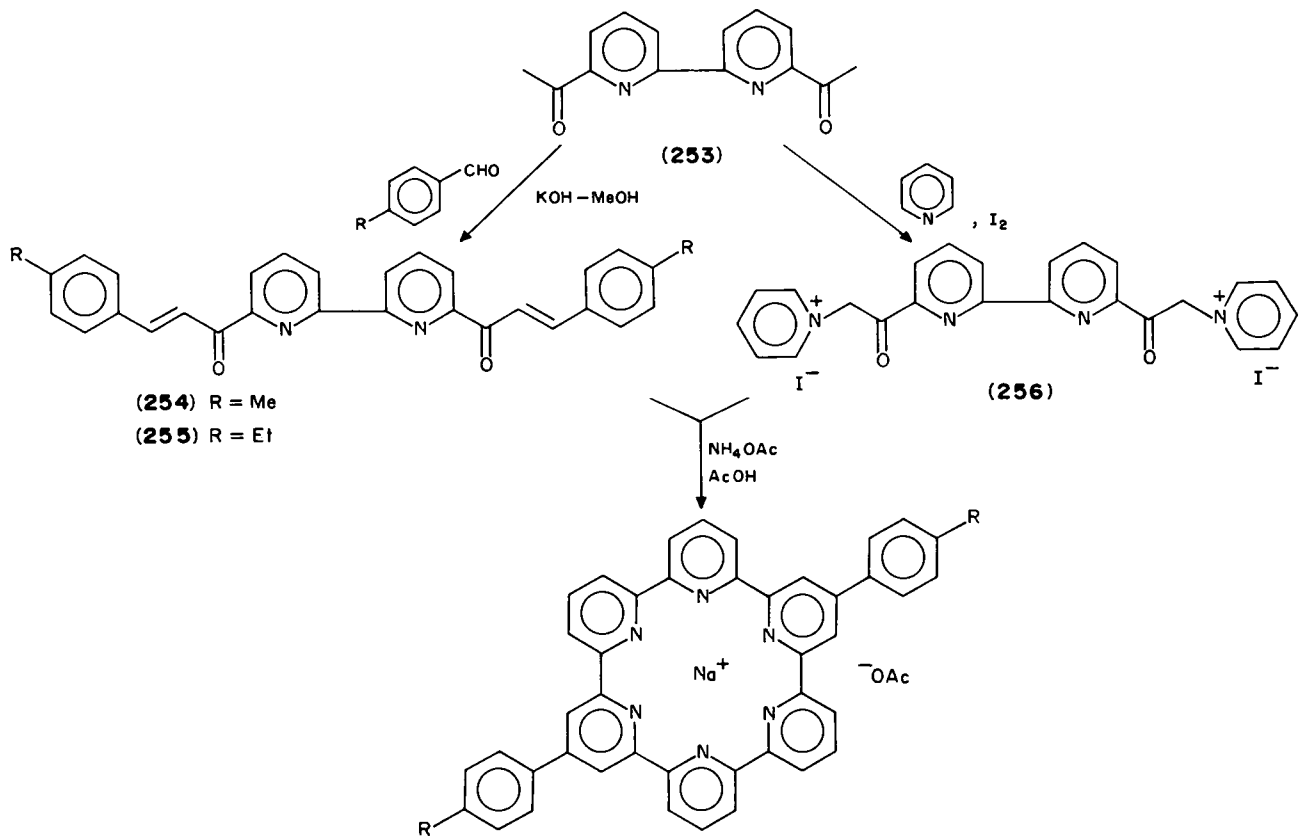
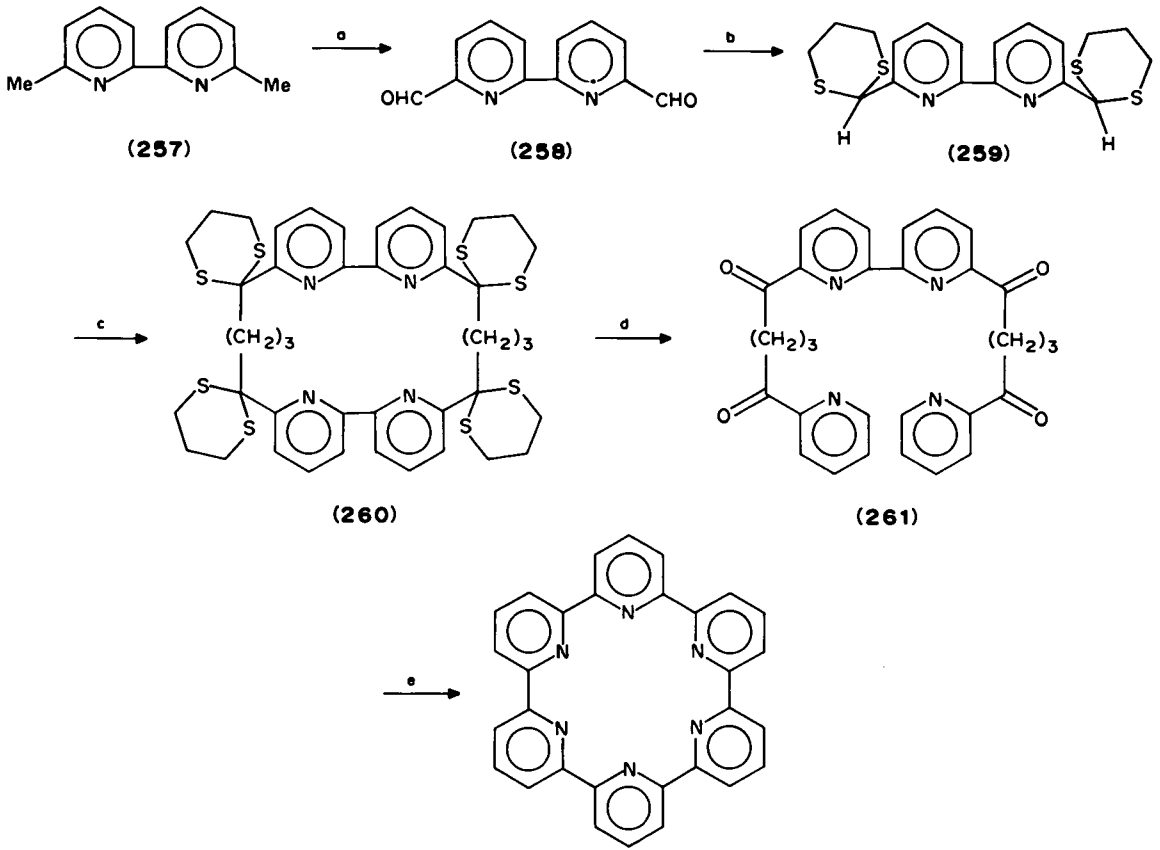


FIGURE 43. Stereoviews of the X-ray crystal structures of bridged spherand:Li^+ complexes


(253)
KOH – MeOH
CHO
R
, I_2
(254) R = Me
(255) R = Et
(256)
I^-
NH_4OAc
AcOH
Na^+
^-OAc
(251) R = Me
(252) R = Et

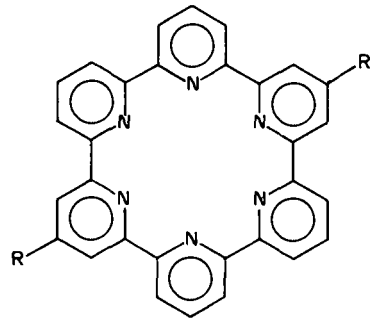
SCHEME 13



(257) (258) (259) (260) (261) (250)

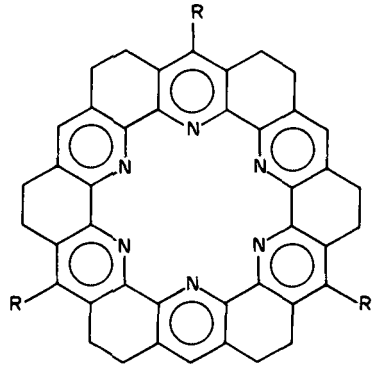
SCHEME 14

(a) SeO_2, AcOH, 24 h, reflux. (b) $CH_2(CH_2SH)_2$, PhMe, *p*-TsOH, 5 h, reflux.
(c) BuLi, THF, $CH_2(CH_2Br)_2$, 3 days, −45 °C. (d) NBS, THF, MeOH. (e) $H_2NOH \cdot HCl$, AcOH.



(250) R = H
(251) R = C_6H_4Me-*p*
(252) R = C_6H_4Et-*p*

An extreme example of preorganization in spherands is the synthesis of the elegant dodecahydrohexaazakekulenes **262** and **263** by Ransohoff and Staab[197] and by Bell and Firestone[198], respectively. Compound **262** has been characterized by NMR and mass spectrometry. Its properties await further investigation. Host **263** was named a torand



(262) R = H
(263) R = Bu

because of the toroidal shape of the compound in space-filling models. It forms as the calcium triflate salt during synthesis. The Ca^{2+} was scavenged as a 0.3% impurity in triflic acid. The complex survives chromatography intact. Further investigation of the complexation properties of torands should be fascinating, considering the highly focused nature of the nitrogen lone pairs.

b. Complexation. The sexi-spherands are the best and most selective alkali metal complexing agents known. Spherand **5** binds Li^+Pic^- with $-\Delta G^\circ > 23$ kcal mol^{-1} and Na^+Pic^- with $-\Delta G^\circ = 19.2$ kcal mol^{-1}. It completely rejects K^+, larger monovalent and all divalent cations. The minimum Na^+/K^+ selectivity ratio is 10^{10}, with $Li^+/Na^+ > 600$. Both the host and its Li^+ spheraplex have D_{3d} symmetry in which the Li^+ is suspended perfectly in a hole surrounded by the oxygen electron pairs[130d]. The negative free energies

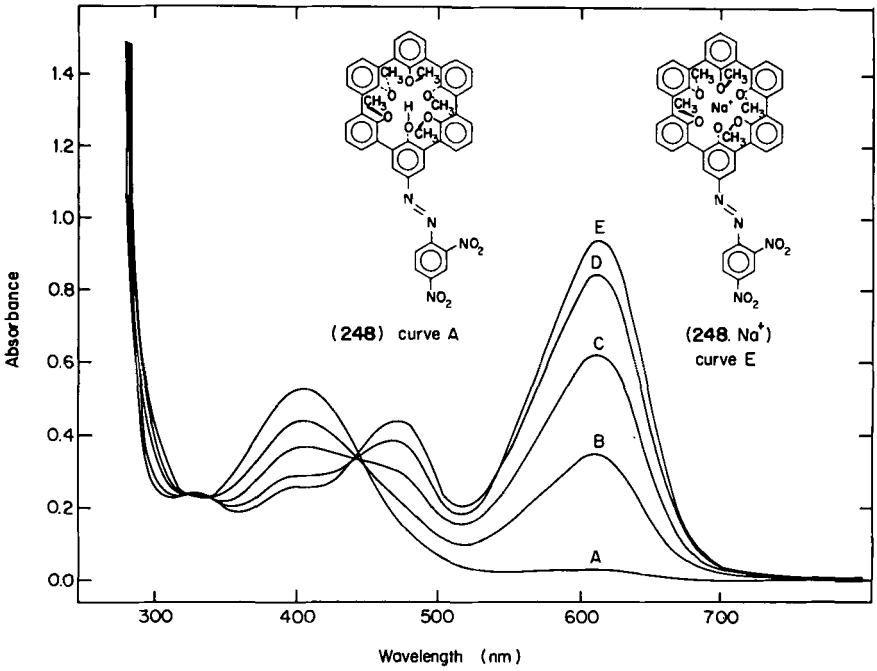


FIGURE 44. Colorimetric response of azophenol spherand **248** to added $NaClO_4$. All curves, 1 equiv. of pyridine present. (A) No added salt; (B) 0.25 equiv. of salt; (C) 0.50 equiv. of salt; (D) 0.75 equiv. of salt; (E) 1.0 equiv. (or more) of salt

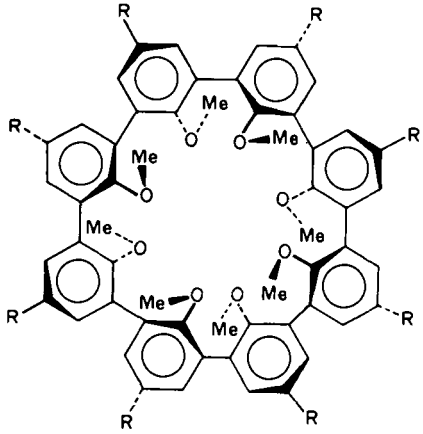
of binding[130e] are as follows: for propylene bridged spherand **42**, Li^+ 16.8, Na^+ 13.3; for diethyleneoxy bridged host **238**, Li^+ 15.9, Na^+ 18.7; for center hydrogen spherand **40**, Li^+ 10.4, Na^+ 6.6; and for spherand **239** with two center hydrogens[130b], $Li^+ < 6$, $Na^+ < 6$ kcal mol^{-1}.

It is interesting to note the dramatic decrease in binding which occurs when first one methoxy unit, then two, are removed from spherand **5**. Also, bridging with ethyleneoxy units decreases the Li^+ binding dramatically, but preserves Na^+ binding. The hexafluoro derivative **241** did not complex alkali metal cations at all. Some kinetics of complexation and decomplexation have been measured for spherands **5**, **42** and **238**[130c,e]. Complexation rates for Li^+ and Na^+ Pic^- ranged from 10^5 to 10^6 l mol^{-1} s^{-1}. The decomplexation rates obviously varied dramatically. With spherand **5**, k_{-1} was $< 10^{-12}$ s^{-1} for Li^+ and 3.4×10^{-9} s^{-1} for Na^+ at, or extrapolated to, 25 °C. For propylene bridged host **42**, k_{-1} for Li^+ was 1.9×10^{-7} s^{-1} and for Na^+ it was 2.2×10^{-4} s^{-1}. Finally, the analogous k_{-1} value for host **238** with Li^+ was 6.7×10^{-7} s^{-1} and with Na^+ it was 1.6×10^{-9} s^{-1}.

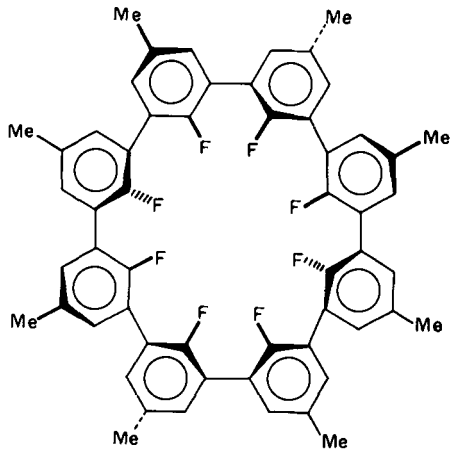
The chromogenic spherand **248** is an ion-selective indicator which undergoes the spectral change from faint yellow to deep blue as shown in Figure 44 on treatment with Li^+ and Na^+ plus pyridine as a base. Other cations did not produce the bathochromic shift in absorption[191]. Spherand **248** is capable of detecting Li^+ and Na^+ at concentrations as low as 10^{-8} M in the presence of other ions. The pK_a of spherand **248** changes from about 13 to 5.9 when complexed with Li^+ and to 6.9 when complexed with Na^+ in dioxane–water (8:2, v/v). Spherand **248** is a powerful enough Na^+ scavenger to colorize in contact with Pyrex.

3. Octi- and deci-spherands

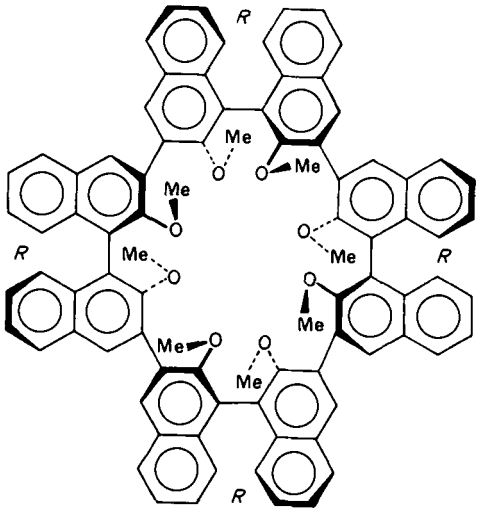
a. Synthesis. Spherands **266** and **268** were by-products in the synthesis of chiral host **240**, obtained in 7 and 1.6% yields, respectively[189]. Octafluoro macrocycle **265** was prepared in the same study as **241**, by cyclization of the linear octamer of *p*-methylfluorobenzene (9%)[190]. Finally, cyclooctianisyl **264a** was synthesized by the oxidative coupling of 3,3'-dilithio-2,2'-dimethoxybiphenyl with $Fe(acac)_3$ in 1.4% yield. Ring closure of the appropriate linear octamer to form **264b** was found to be improved by Cs^+, from 2.9% without the cation to 4.7% upon Cs^+ addition.



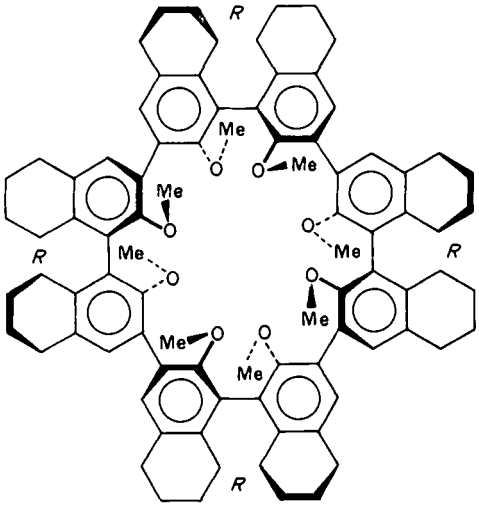
(**264a**) R=H
(**264b**) R=Me



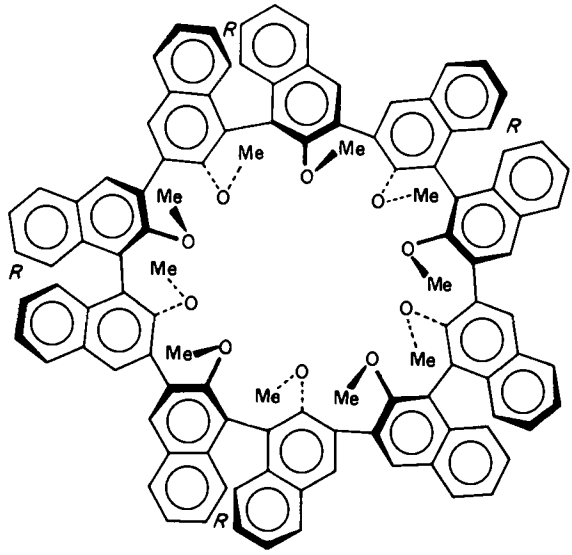
(**265**)



(**266**)



(**267**)



(268)

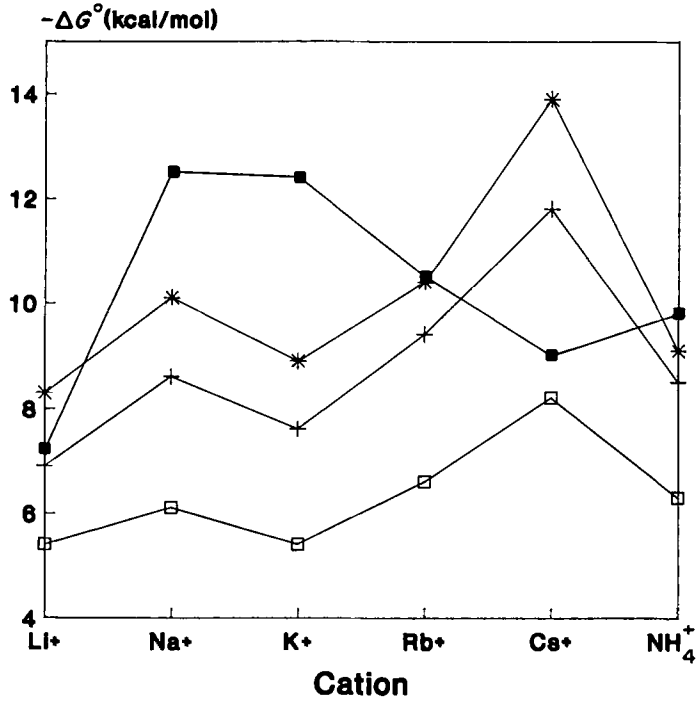


FIGURE 45. Complexation of M^+Pic^- by octi-spherands. ■, Host **3**; +, **264a**; *, **264b**; □, **266**

b. Complexation. Figure 45 shows the association constants of spherands **264a**, **264b** and **266** toward metal picrates. Noteworthy is the Cs^+ binding of hosts **264a** and **264b** and especially the Cs^+ selectivity of host **264b**, which favors Cs^+ by 3.5 kcal mol^{-1} over Rb^+.

E. Overview

The hemispherands, cryptahemispherands and spherands take their places in the hierarchy of host–guest complexation in the order spherands > cryptahemispherands > cryptands > hemispherands > coronands > podands. As previously noted from least-squares analysis, the preorganization trend for unmodified members of each class is probably spherands > cryptahemispherands = hemispherands > coronands > cryptands > podands. Within a host class, modifications can dramatically alter the degree of preorganization and in the case of the constricted hemispherands can impact both binding ability and selectivity. Within the ranks of the restricted hosts so far considered are examples with excellent selectivity for Li^+ (host **5**), Na^+ (**23** and **160**), K^+ (**174**), Cs^+ (**264b**) and $MeNH_3^+$ (**200**). Between classes, increasing the number of rigid units in 18-membered macrorings has a profound impact on both cation association constants and selectivities (Figure 46).

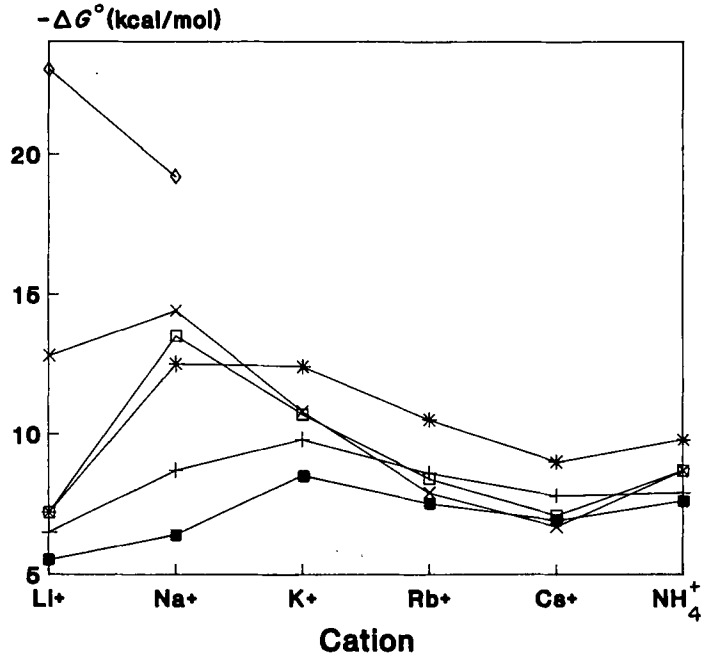


FIGURE 46. Complexation of M^+Pic^- by 18-membered macroring anisyl hosts. ■, **21**(1);[a] +, **22**(2); *, **3**(3); □, **23**(4); ×, **24**(5); ◇, **5**(6)
[a]Host (number of anisyls)

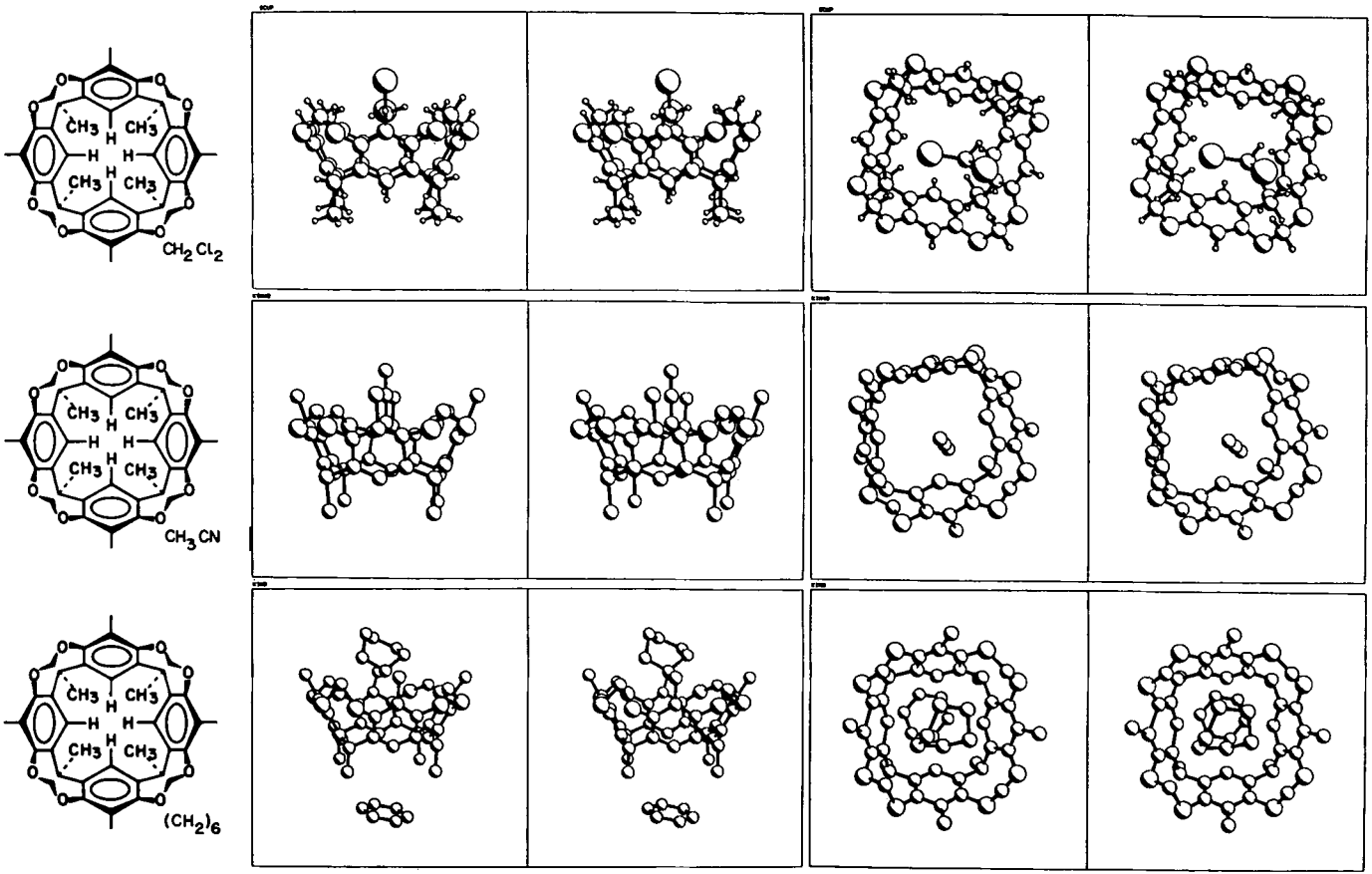


FIGURE 47. Stereoviews of three X-ray crystal structures of cavitands

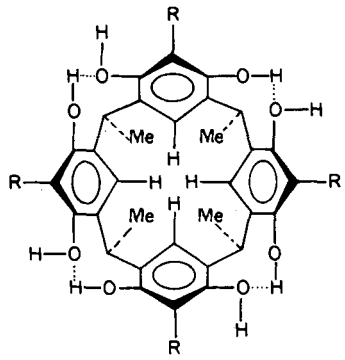
F. Cavitands

1. Introduction

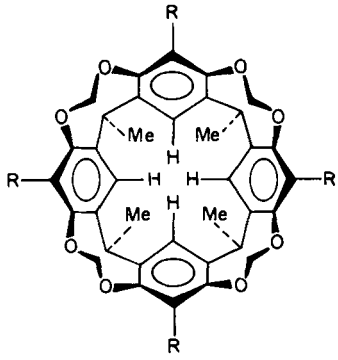
Cavitands have been defined as molecules with enforced cavities of at least the dimensions of smaller ions, atoms or molecules[200]. Such a description covers a great deal of ground. Encompassed within the cavitand fold are many cyclophane and related hosts which have recently been reviewed[30f,201] and will not be considered here. Coverage of cavitands will not be encyclopedic, but rather will highlight interesting systems studied.

2. Representative studies

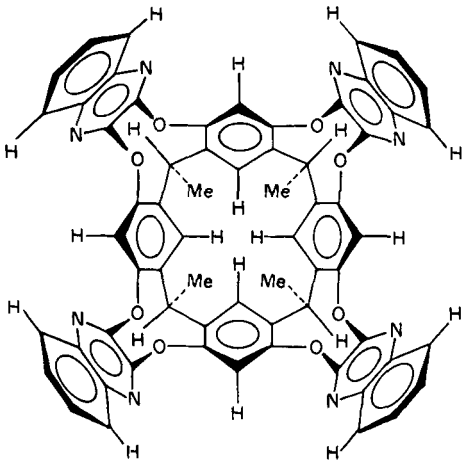
Condensation of resorcinol and acetaldehyde gave cyclophane **269**[202], which was elaborated by Cram and coworkers[203] to yield **270–274**. Of the four cavitands **271–274**, **271** and **274** crystallize only as solvates, and cavitands **272** and **273** crystallize only without



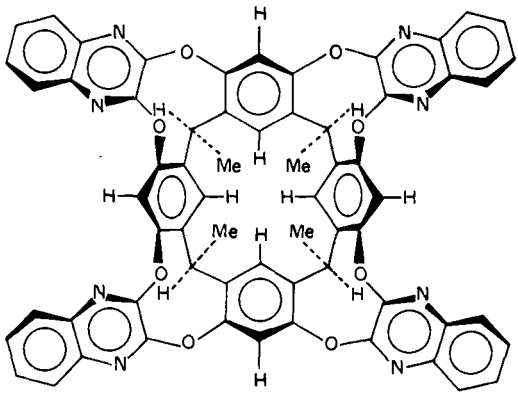
(269) R = H
(270) R = Br



(271) R = H
(272) R = Br
(273) R = CO_2Me

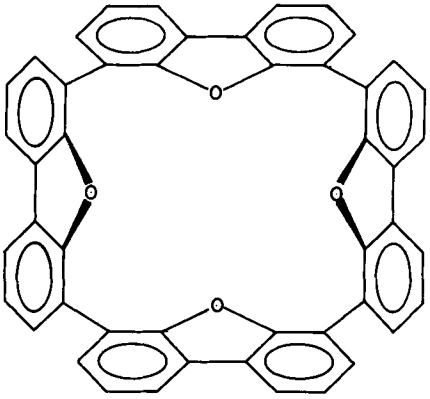


(274a)

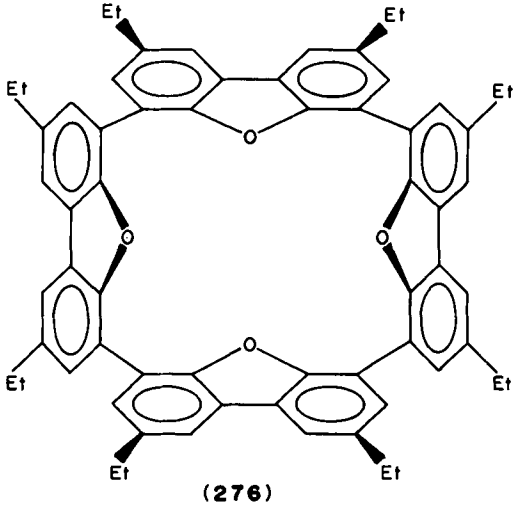


(274b)

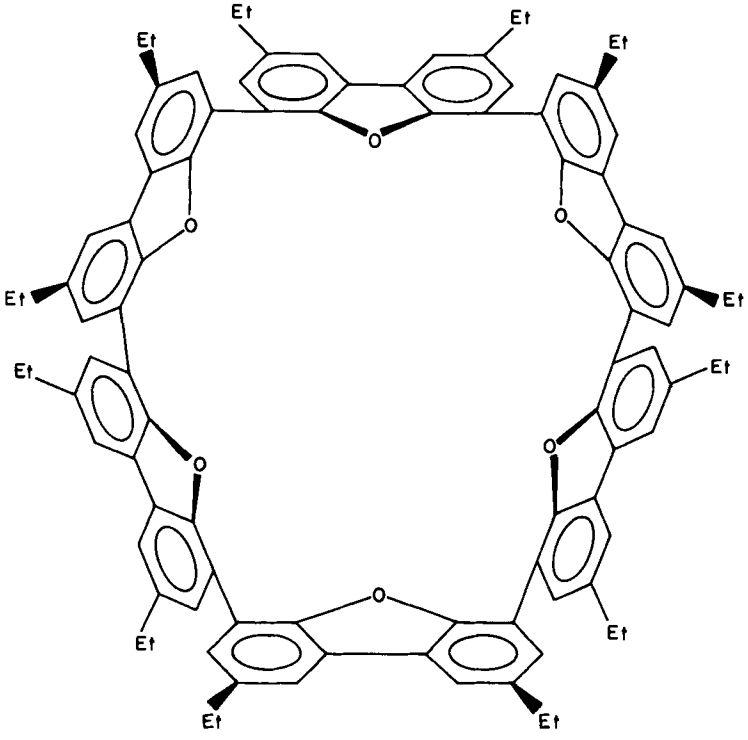
being solvated. Conformer **274a** is the room-temperature conformation of the cavitand, and **274b** is the conformation favored at low temperature. Figure 47 shows stereoviews of three X-ray crystal structures of cavitands derived from **269** and the related tetramethyl derivative[203b].



(275)



(276)

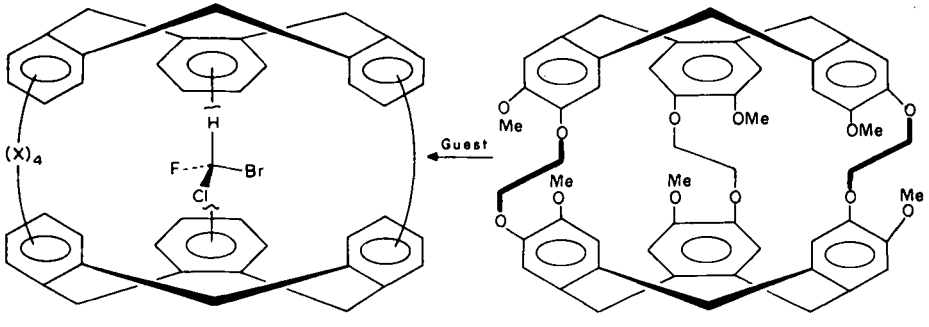


(277)

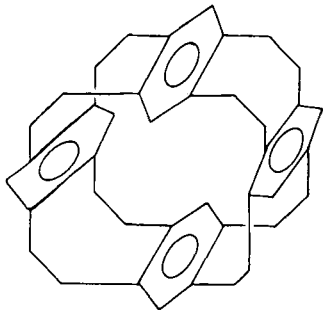
Cavitands formed of dibenzofuran subunits were described by Helgeson *et al.*[204] (**275**–**277**). Cavitand **275** was too insoluble to work with, leading to the synthesis of **276** and **277**.

The study of the properties of the elegant cryptophanes has led to the enantioselective inclusion of bromochlorofluoromethane by host **8**, shown also in a cutaway view complexed with the guest[205].

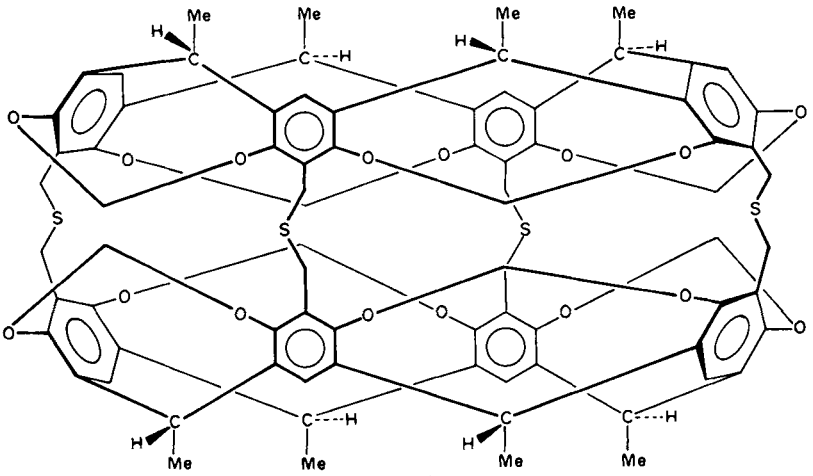
Deltaphane **278** was synthesized and shown to complex with Ag^+TfO^- with the guest inside the host cavity[206].



(8)



(278)



(279)

Shell closure of two cavitands formed from **273** gave the carcerand **279**, which forms with components of the reaction medium permanently enclosed within the cavity[207]. 'Carcer' is from the Latin, meaning prison. Examples of guests which have been incarcerated to date include Cs^+, Ar and $ClCF_2CF_2Cl$.

The very interesting cavitand **7**, formed by a series of Diels–Alder reactions, was recently described by Kohnke *et al.*[208]. Figure 48 shows the crystal structure and corresponding space-filling model of 'molecular belt' **7**.

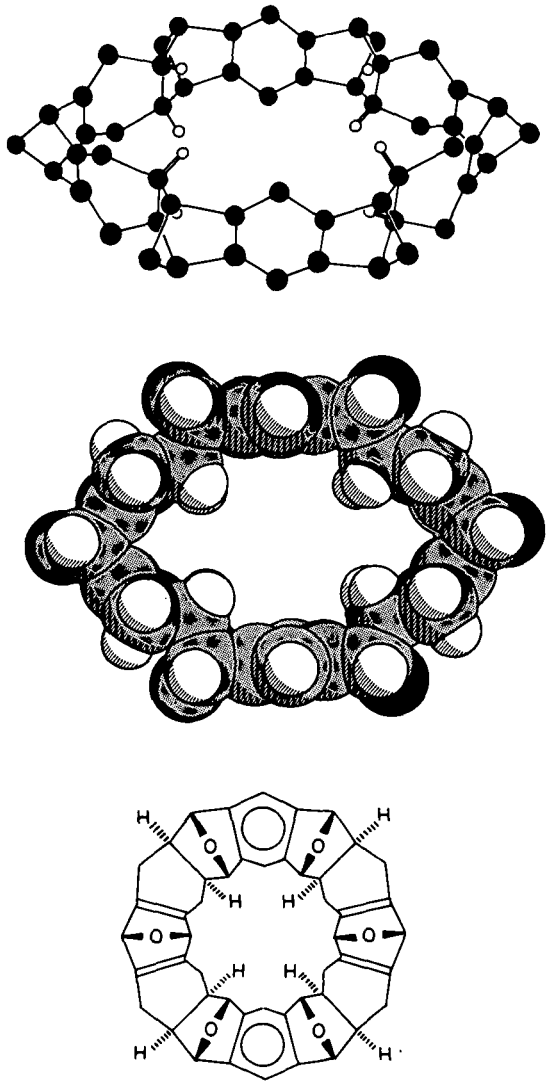
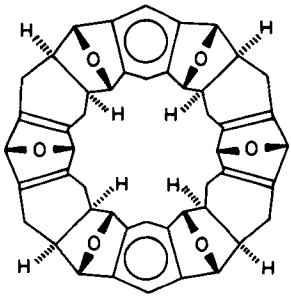
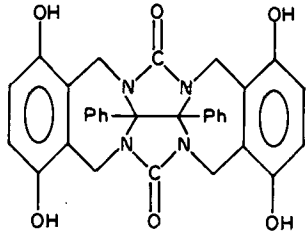


FIGURE 48. X-ray crystal structure and space-filling model of molecular belt **7**

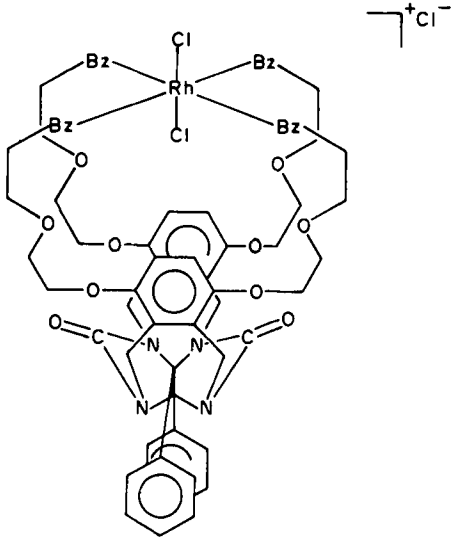
Nolte and coworkers described the synthesis of cavitand **281** from **280**, with the rhodium poised over the cavity of the cavitand[139].



(7)

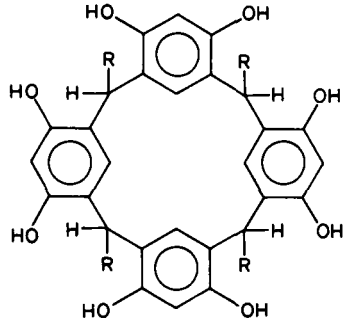


(280)

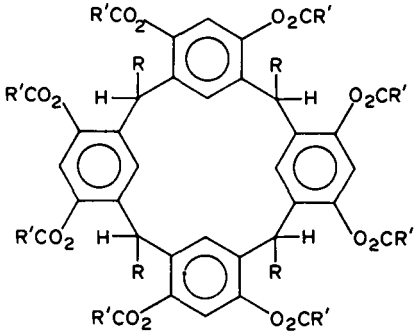


(281)

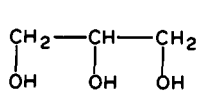
The complexation of uncharged polar hosts by cavitand precursor **282** was demonstrated by Aoyama *et al.*[209]. The host was formed by the acid-catalyzed reaction of resorcinol with dodecanal in EtOH. Host **282** but not the acetylated version, **283**, extracts glycerol (**284**) in concentrated aqueous solutions into CCl_4 or C_6D_6. Similar results were obtained with D-ribose (**286**), whereas D-glucose (**285**) was extracted poorly. Presumably D-ribose was preferentially extracted because it can form three good hydrogen bonds with the host, whereas D-glucose can not. Other guests were also examined.



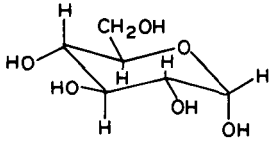
(282) R = $(CH_2)_{10}Me$



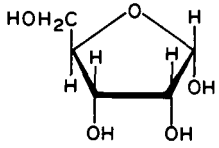
(283) R = $(CH_2)_{10}Me$; R' = Me



(284)

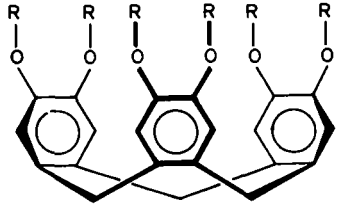


(285) (α-form)

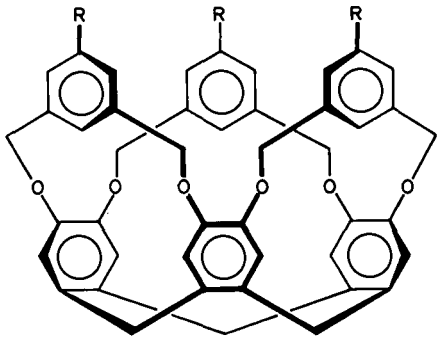


(286) (α-form)

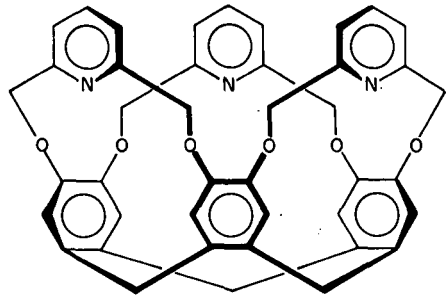
Finally, a new group of cavitands resulted from the chemistry of cyclotriveratrylene (**287**) in work by Cram *et al.*[210]. Demethylation of **287** gave **288**, which was elaborated to give cryptands **289–294**. Plate 12 is a stereoview of the energy-minimized conformer for cavitand **292**. The excellent correspondence between the crystal structure of **289** and the minimized structure using the molecular mechanics program MM2 is shown in Figure 49.



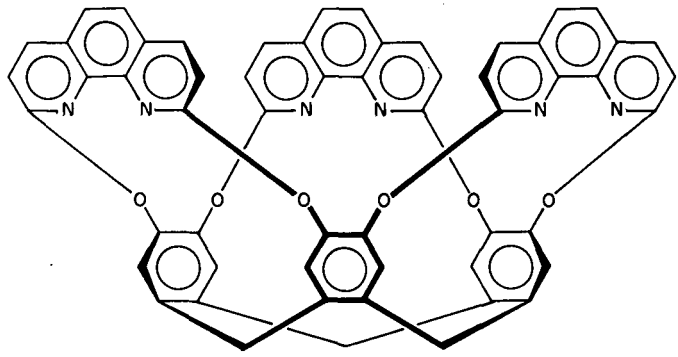
(287) R = Me
(288) R = H



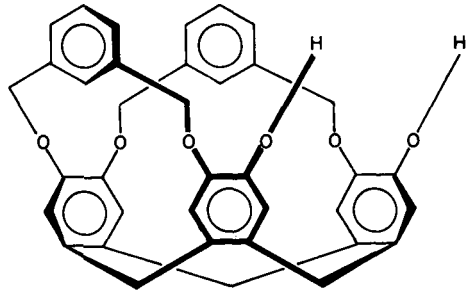
(289) R = H
(290) R = Me_3C
(291) R = Br



(292)



(293)



(294)

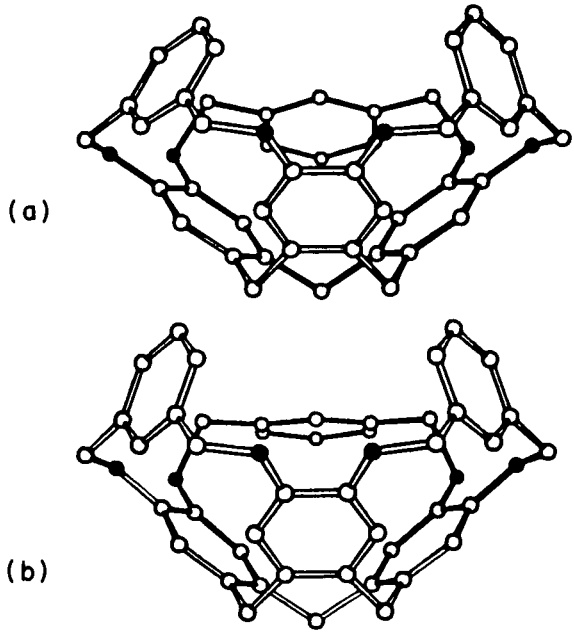
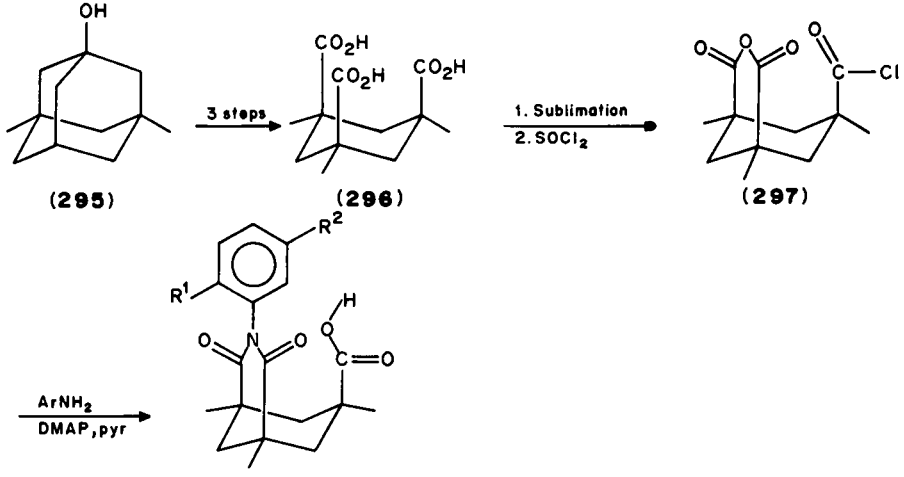


FIGURE 49. Comparison of (a) the MM2 minimized conformation and (b) the X-ray crystal structure of cavitand **289**



(**298**) $R^1 = R^2 = H$
(**299**) $R^1 = Me, R^2 = H$
(**300**) $R^1 = Me, R^2 = CON(i\text{-}Pr)_2$
(**301**) $R^1 = Me, R^2 = CO_2Me$
(**302**) $R^1 = Me, R^2 = Ph$

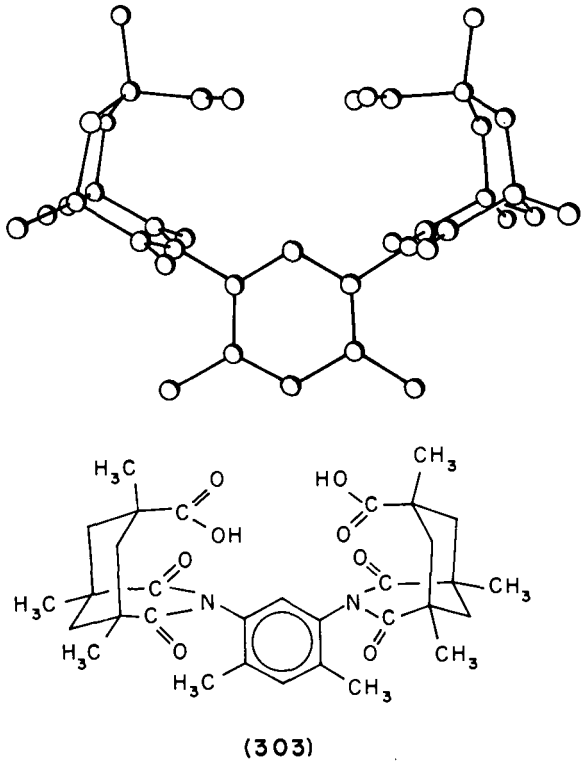
SCHEME 15

G. Molecular Cleft Hosts

1. Design and synthesis

The difficulty in realizing selective peracid olefin epoxidation agents[211] led Rebek and coworkers[212] to pioneer a fascinating new area of host–guest chemistry, the molecular clefts. Oxidative degradation of trimethyladamantanol (**295**) by Kemp and Petrakis[213] gave the interesting tricarboxylic acid **296** (Scheme 15), which has all three carboxylic acid residues in the axial positions, as confirmed by X-ray crystallographic analysis[212e]. At present, tricarboxylic acid **296** is prepared by the alkylation of 1,3,5-cyclohexanetricarboxylic acid. Sublimation of tricarboxylic acid **296** followed by treatment with $SOCl_2$ gave acid chloride anhydride **297**. Compound **297** was then condensed with a number of amines to give **298–302** (Scheme 15). These acids were converted to their acyl chlorides, and the peracids were generated *in situ* with H_2O_2–pyridine. Direct competition experiments between olefin pairs were carried out to determine if *cis*-epoxidation could be enhanced. Modest results were obtained[212a,b].

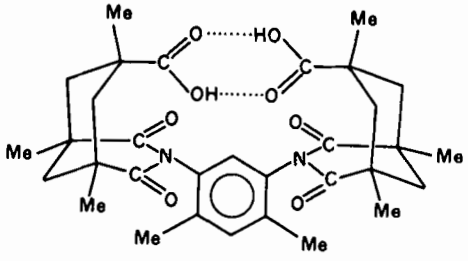
Far more intriguing systems resulted from either condensation of **297** with various aromatic diamines or by heating the neat triacid **296** with the diamines. Structures **6**, **303** and **304** are representative bisimide diacids synthesized. They were chosen, after the structures had been generated using computer graphics, because of the range of distances



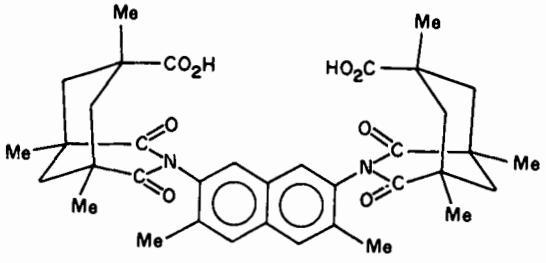
(303)

FIGURE 50. Crystal structure of molecular cleft host **303**

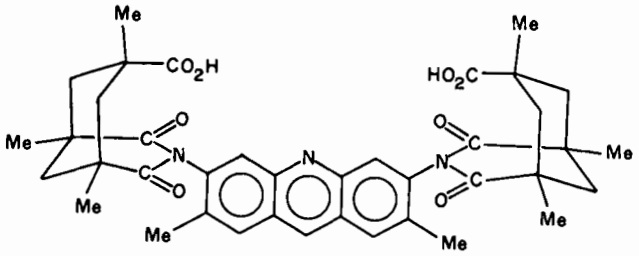
afforded between carboxyls (3–9 Å) and because of synthetic availability[212e]. Figure 50 shows the crystal structure of benzene diamine derivative **303**[212e].



(303)



(304)



(6)

The aromatic methyl groups of hosts **6**, **303** and **304** provide rigidity to the molecules by hindering rotation about the Ar–N bond. Consequently, the carboxyl groups remain focused at each other across the top of the aromatic group. The cleft provided by this arrangement is maintained by restricted Ar–N rotation and by the 'locked' nature of the cyclohexane structure, owing to the cyclohexyl methyl groups. As a consequence of the unique design of the molecular clefts, functionality is focused directly at the 'active site' of the host. Of course, convergence of functional groups at the active site is a common attribute of enzymes, but it has been difficult to achieve with conventional hosts.

2. *Complexation*

Unique structure is paralleled by unique function in the molecular clefts. Host **303** was converted to the monoethyl ester. Then the peracid was generated *in situ* and shown to favor *cis–trans* epoxidation with various olefins by as much as a factor of 8[212b]. MCPBA was essentially non-selective. In addition, owing to the required positioning of the substrate in the molecular cleft, steric effects eventually overcame the normally strong electronic effect in peracid epoxidations of olefins. Stereoelectronic effects at the carboxyl oxygens of cleft molecules have also been studied[214].

Host **303**, as the dicarboxylate, is also capable of lipophilizing Ca^{2+} and transporting it from an aqueous environment through organic liquid membranes (Figure 51)[212f]. Hosts **6** and **304**, with larger clefts than **303**, are unable to form intramolecular carboxylic acid dimers through hydrogen bonding.

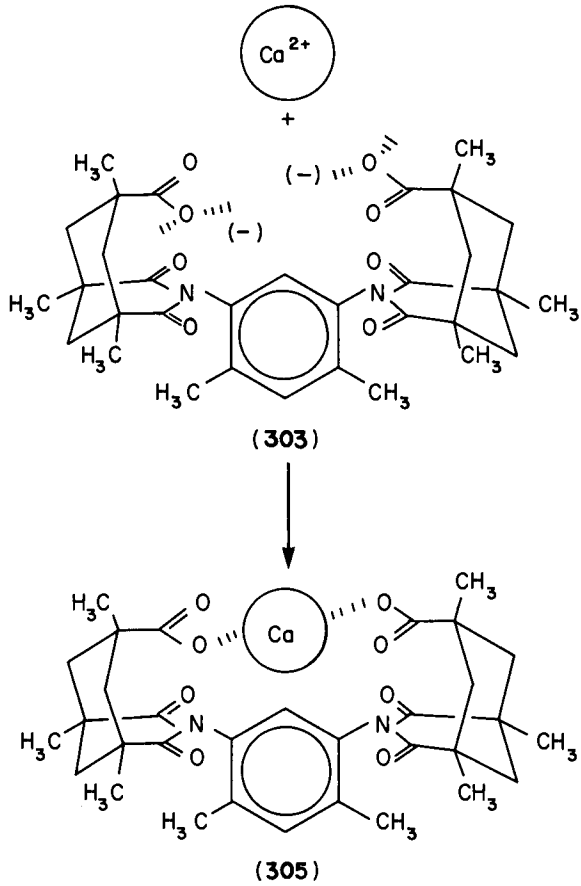


FIGURE 51. Lipophilization of Ca^{2+} by host **303**

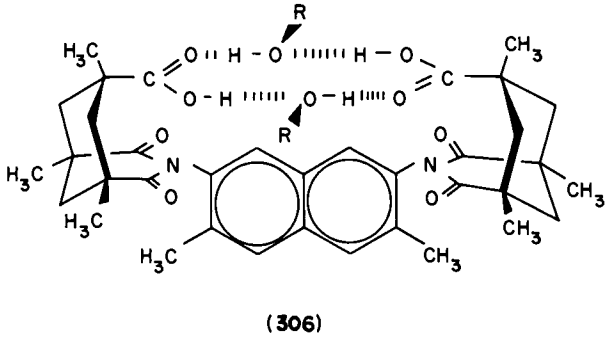
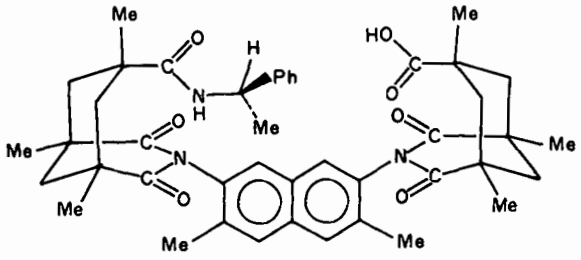


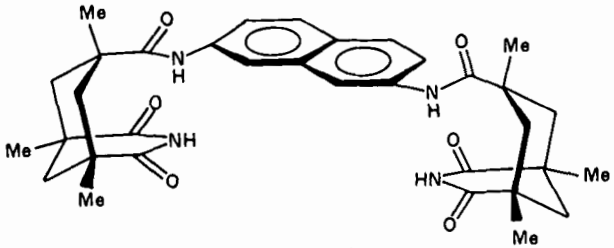
FIGURE 52. Potential structure of the complex between naphthalene cleft host **304** and two alcohol molecules

Naphthalene cleft **304** crystallizes with two molecules of isopropanol. A hypothetical structure for the complex is given in Figure 52[212c]. Monofunctionalization of naphthalene host **304** gave chiral amide **307**. Host **307** acts as a chiral solvating agent in NMR spectroscopy of racemic alcohols, forming rapidly equilibrating diastereomeric complexes with racemic alcohols[212c].

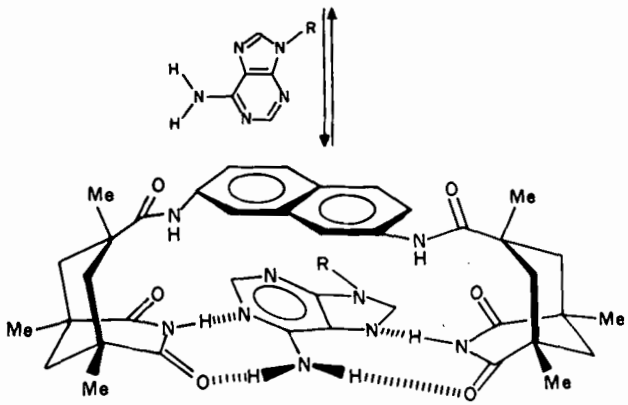


(307)

The more conformationally mobile naphthalene host **308** forms a 1:1 complex with adenine. This fact, together with the high binding constant ($1.1 \times 10^4\,l\,mol^{-1}$), suggested that simultaneous base pairing and stacking with the naphthalene surface occur as shown in Scheme 16[215]. A similar type of host–guest organization has recently been described by

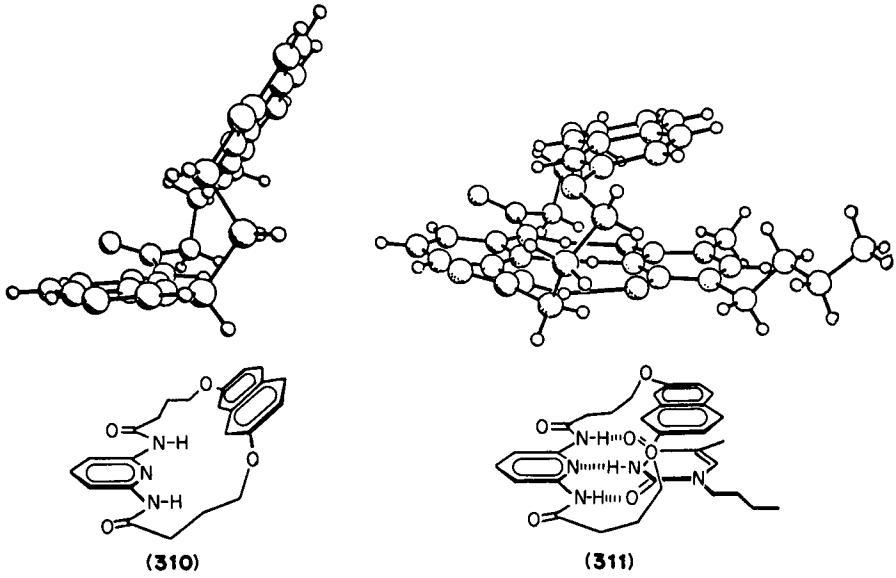


(308)



(309)

SCHEME 16



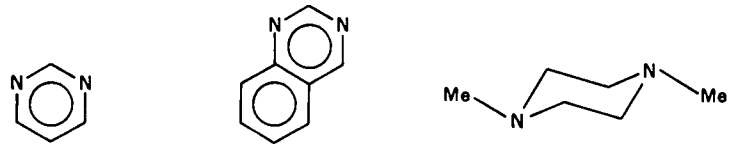
(310) (311)

FIGURE 53. Crystal structures of 'molecular hinge' **310** and its complex with 1-butylthymine (**311**)

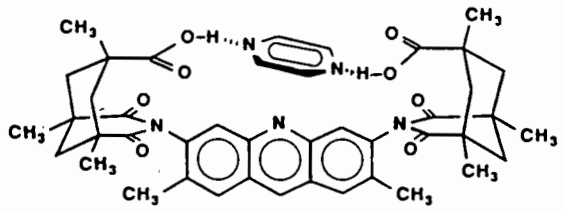
Hamilton and Van Engen[216] with the 'molecular hinge' **310** (Figure 53). Studies on other hosts with designed complementarity for neutral hydrogen-bonding guests are included in Ref. 217.

The complexation chemistry of acridine yellow derivative **6**[212e], with its large cleft of 8–9 Å between carboxyls, has been intensively investigated. Perhaps most obviously, host **6** recognizes and binds diamines[218]. Association constants derived from NMR titration experiments in $CDCl_3$ between host **6** and pyrazine, quinoxaline and DABCO are 1.4×10^3, 2.3×10^4 and $1.6 \times 10^5\,l\,mol^{-1}$, respectively. Suggested structures for the complexes, based on interpretation of NMR data, are shown in Figure 54. Interestingly, complex **312** with pyrazine forms twice as favorably as the analogous complex with pyrimidine (**315**), indicating the importance of optimum spacing between nitrogens of the guest. A space-filling representation of complex **312** is shown in Plate 13[49]. An even greater reduction in binding of quinazoline (**316**) was seen in comparison with the formation of complex **313** with quinoxaline.

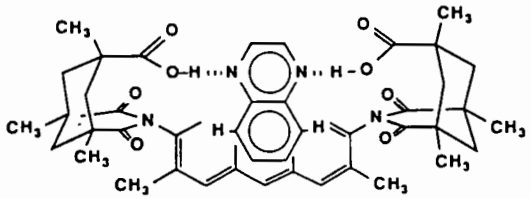
The postulated reason for the increase in binding in going from complex **312** to **313** is the stacking interaction between the benzo group of quinoxaline and the host acridine ring, which is not possible for pyrazine. Upfield shifts on complexation of 0.1 and 0.25 ppm for $H_{5,8}$ and $H_{6,7}$, respectively, of quinoxaline appear to validate this hypothesis. Finally, complexation of host **6** with DABCO was much more efficient than for diamine **317** because the methyl groups of **317** did not fit well in the cleft.



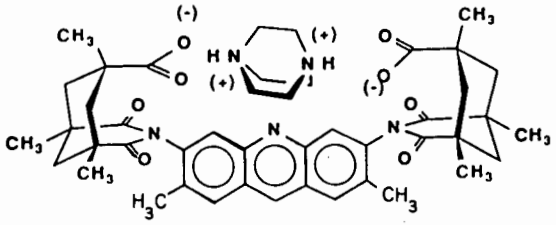
(315) (316) (317)



(312)



(313)



(314)

FIGURE 54. Suggested structures of the complexes of host **6** with pyrazine, quinoxaline and DABCO

In addition to complexing amines, host **6** also effectively binds certain diacids[219], notably solubilizing solid oxalic acid in $CDCl_3$ and forming a 1:1 complex with it. Other diacids bound include malonic acid and derivatives, and maleic and phthalic acid. Fumaric, succinic, and glutaric acid were not bound. The picrate of host **6** also solubilizes oxalic and malonic acids, releasing picric acid (pK_a 0.4) in the process. Oxalic and malonic acids normally have $pK_{a_1} = 1.2$ and 2.9, respectively. The reversal of the normal trend in acidity was attributed to formation of specific complexes between host **6** and the diacids (Figure 55). The postulated structure was also supported by NMR analysis.

Analogous to the complexation of quinoxaline, benzylmalonic acid forms a complex with host **6** which can best be viewed as shown in Figure 56. Homonuclear intermolecular

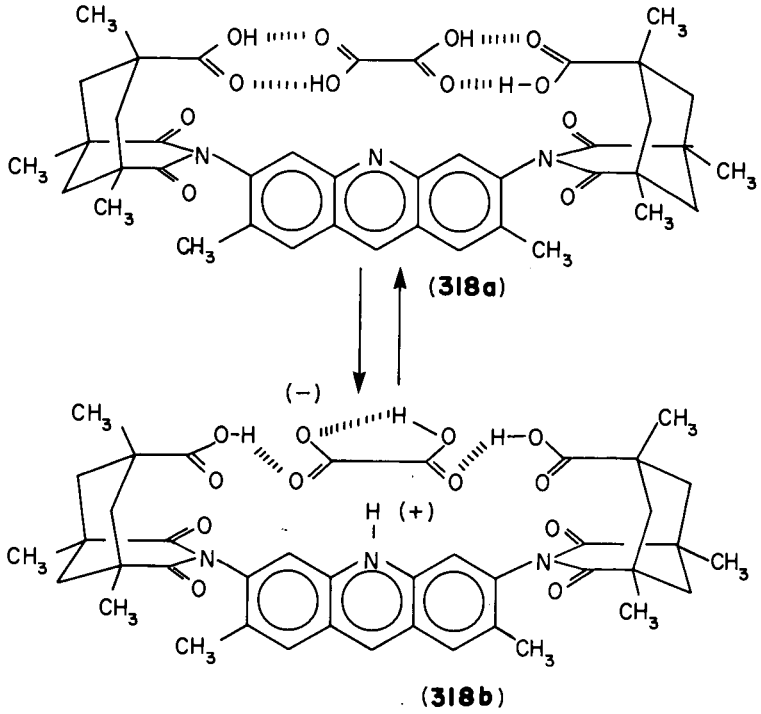


FIGURE 55. Postulated structures of the complex of host **6** and oxalic acid

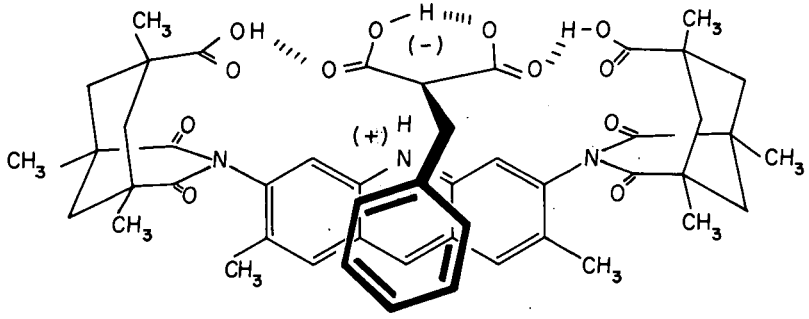
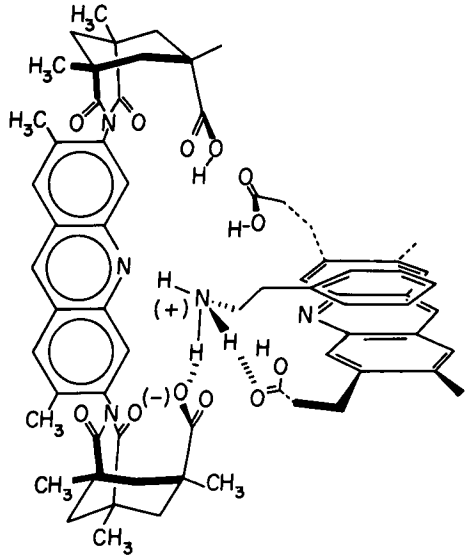


FIGURE 56. Suggested structure of the complex between host **6** and benzylmalonic acid

NOE was observed between the cleft protons of **6** and the *ortho*-protons of benzylmalonic acid. Large upfield shifts of the phenyl protons of complexed benzylmalonic acid suggested the interaction with the acridine ring shown in complex **319**[219].

On the basis of NOE experiments, Rebek *et al.*[220] proposed structure **320** (Figure 57) as a reasonable explanation for the 2:1 (host:guest) binding seen between cleft molecule **6** and β-arylethylamines. The NMR spectrum of host **6** indicates the presence of the zwitterionic form **6a**, which suggested to Rebek and Nemeth[212d] the possibility of complexing



(320)

FIGURE 57. Possible structure of the 2:1 complex between host **6** and β-arylethylamines

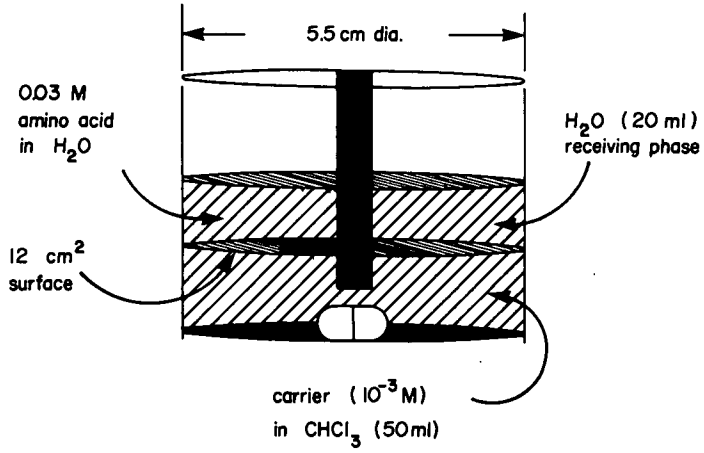
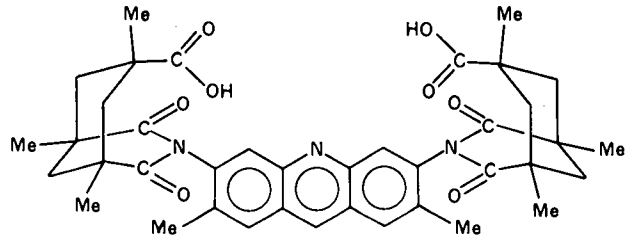
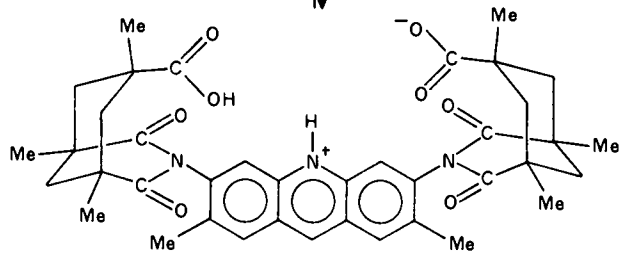


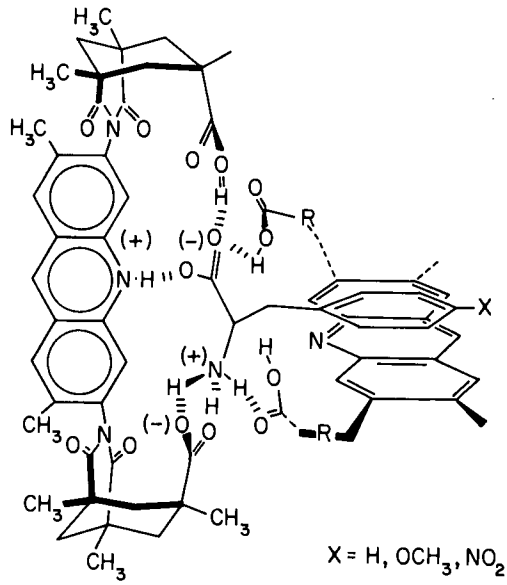
FIGURE 58. Use of the Lehn vessel for transport of aromatic amino acids by host **6**.



(6)



(6a)



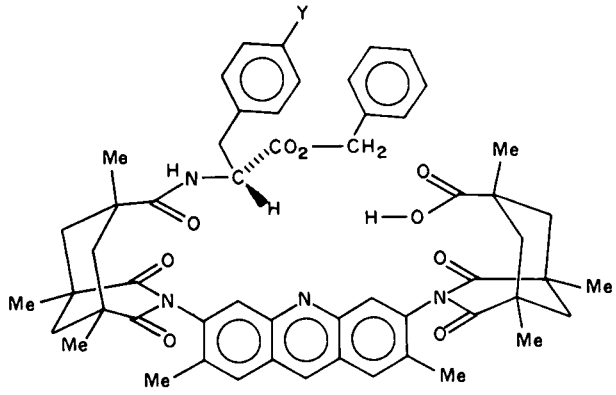
(321)

FIGURE 59. Potential structure of the 2:1 complex of phenylalanine derivatives with molecular cleft host **6**

complemetary amino acids. Complexation of zwitterionic amino acids by synthetic hosts is rare[221]. Using a Lehn transport vessel, it was demonstrated that host **6** complexes and conveys phenylalanine, tryptophan and tyrosine methyl ether from water through $CHCl_3$ (Figure 58). Lipophilic, non-aromatic amino acids such as valine, leucine and isoleucine were not transported by host **6**.

Originally, a 1:1 complex was proposed for the interaction of amino acids with host **6**[212d]. However, the complex was later shown to be 2:1 (host:guest)[222]. Figure 59 shows a postulated structure for the complex between phenylalanine derivatives and two molecules of acridine host **6**. Again, dramatic upfield shifts for the phenyl protons of the guest occur in the NMR spectra of complexes of **6** with aromatic amino acids. At low temperature, two distinct acridine hosts are visible in the NMR spectra of complexes such as **321**[222].

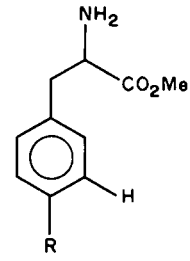
Conversion of host **6** to chiral host **322** was readily accomplished[223]. Host **322** has three distinct domains important in the chiral recognition of amine guests: the carboxylic acid, the acridine surface and the bulky, chiral phenylalanine group. Mixing of host **322b** with (3:1 L:D) *p*-nitrophenylalanine methyl ester (**323b**) produced an upfield shift of 150 Hz for the *meta* proton of the L-isomer of **323b**. Similar results were obtained for L-**323c** and with



(**322**)

(**a**) Y = H

(**b**) Y = NO_2



(**323**)

(**a**) R = H

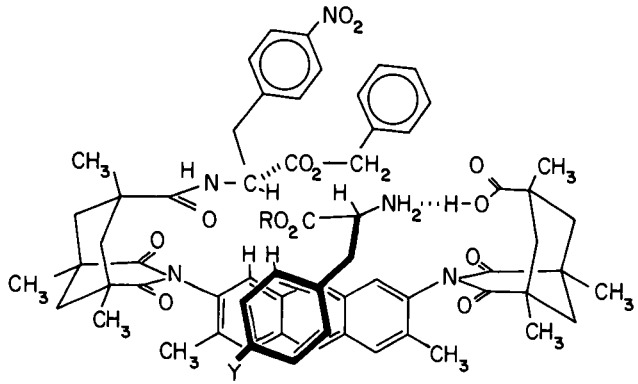
(**b**) R = NO_2

(**c**) R = OH

host **322a**, but guest **323a** was not recognized enantioselectively by either chiral host. A proposed structure for the above complexes is given in Figure 60.

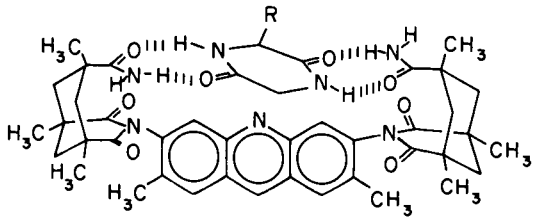
Complexation of neutral guests was studied with the bisamide of host **6** which interacts with diketopiperazines with a binding constant of about $10^4\,l\,mol^{-1}$ in $CHCl_3$ (Figure 61) and with amides such as malonamide[212c]. Molecules of inappropriate shape or hydrogen-bonding capability were not bound. The bisamide host shows finely tuned discrimination, complexing with primidone **326** but not with uracil **327**[212f]. In addition, host **6** has been shown to function as an efficient catalyst for the dissociation of glycoaldehyde dimer to its monomer[224].

Recently, Zimmerman and Van Zyl[225] published the synthesis and some binding properties of 'molecular tweezers' containing an enforced cleft. Dibenzacridine host **328** binds 2,4,7-trinitrofluorenone in $CDCl_3$ with $K_a = 172\,l\,mol^{-1}$ (Figure 62). Host **328** was designed as a preorganized version of natural[226] and synthetic (flexible[227] and rigid[228]) DNA bis intercalators. As such, a key design feature was the capability of the host to force



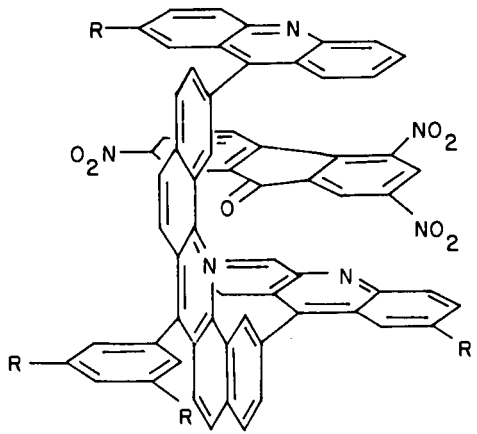
(324)

FIGURE 60. Postulated interaction between chiral molecular cleft host and amino acid ester



(325)

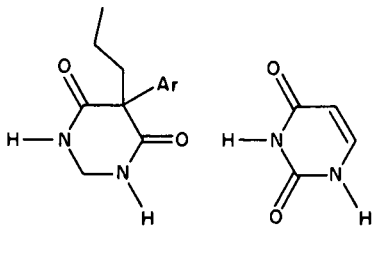
FIGURE 61. Suggested structure of the complex of the diamide of host **6** and a diketopiperazine



(329) R = t-Bu

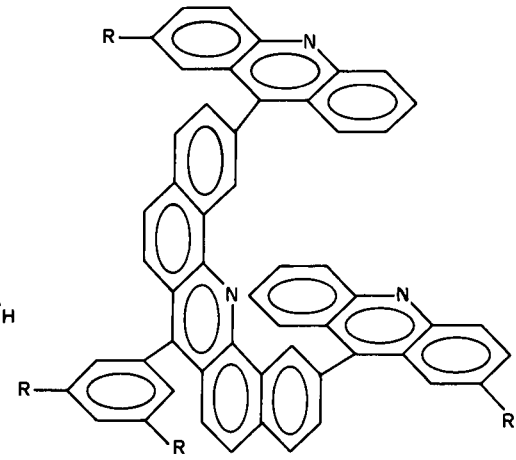
FIGURE 62. Postulated structure of the complex between the preorganized 'molecular tweezers' **328** and trinitrofluorenone

a *syn*-cofacial orientation of the guest, completely different from the Rebek molecular cleft molecules. Helgeson *et al.*[204] have described dibenzofuran-based cavitands **275** and **276**, which have rigidly enforced clefts.



(326)

(327)



(328) R = *t*-Bu

The area of molecular cleft chemistry is still in its infancy. The advances to come concerning chiral recognition, chiral and achiral catalysis, and further properties of these novel hosts should prove very exciting. Most of the complexes shown were propositions based on the assessment of the physical properties (mostly NMR) of these systems. It will be satisfying to be able to examine the subtle features of the host–guest interactions once X-ray crystallographic studies are completed.

V. ACKNOWLEDGEMENTS

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Crown Ethers and Analogs
Edited by Saul Patai and Zvi Rappoport

CHAPTER **4**

Crown ethers–complexes and selectivity

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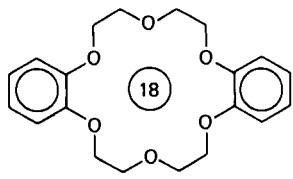
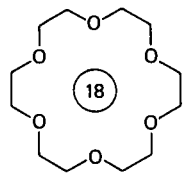
I. INTRODUCTION: CROWN ETHER TYPE NEUTRAL LIGAND SYSTEMS

Since the discovery of *dibenzo[18]crown-6* (1)[1], *[18]crown-6* (2)* and other cyclic polyethers[2] together with the knowledge that these potentially exolipophilic compounds selectively complex alkali and alkaline earth metal cations in their endopolarophilic cavity[3], efforts have continued to modify the widely useful properties[4–6] of such crown ethers by variation of all possible structural parameters in order to make accessible new ligand systems and to study the relationship between structure and cation selectivity as well as their complex chemistry[7].



(1)



(2)

Variable parameters included the number of ether oxygen atoms, ring size, length of the $(CH_2)_n$ bridge, substitution by other heteroatoms (N,S), introduction of aromatic (benzene, biphenyl, naphthalene) and heteroaromatic systems (pyridine, furan, thiophene) in the ring[8,9]. Figure 1 shows some such crown ethers (*coronands*: the corresponding complexes have been called *coronates*)[10].

The possibilities of structural variation are still not exhausted. An important development in the neutral ligand topology is linked with the ability of large-ring bicyclic diamines (*catapinands*, see 17 in Figure 2) to take up protons and anions inside their three-dimensional cavity (*catapinates*)[11]. This has led to the design of *cryptands* – three-sidedly enclosed endopolarophilic/exolipophilic cavities – in

*Crown ether nomenclature: In square brackets the total number of atoms in the polyether ring is given (see encircled numbers in the formulae), followed by the class descriptor 'crown' and the total number of donor atoms in the main ring. Condensed rings are designated by prefixes 'benzo', 'cyclohexano' etc., sulphur or nitrogen donor centres by 'thia' and 'aza'.

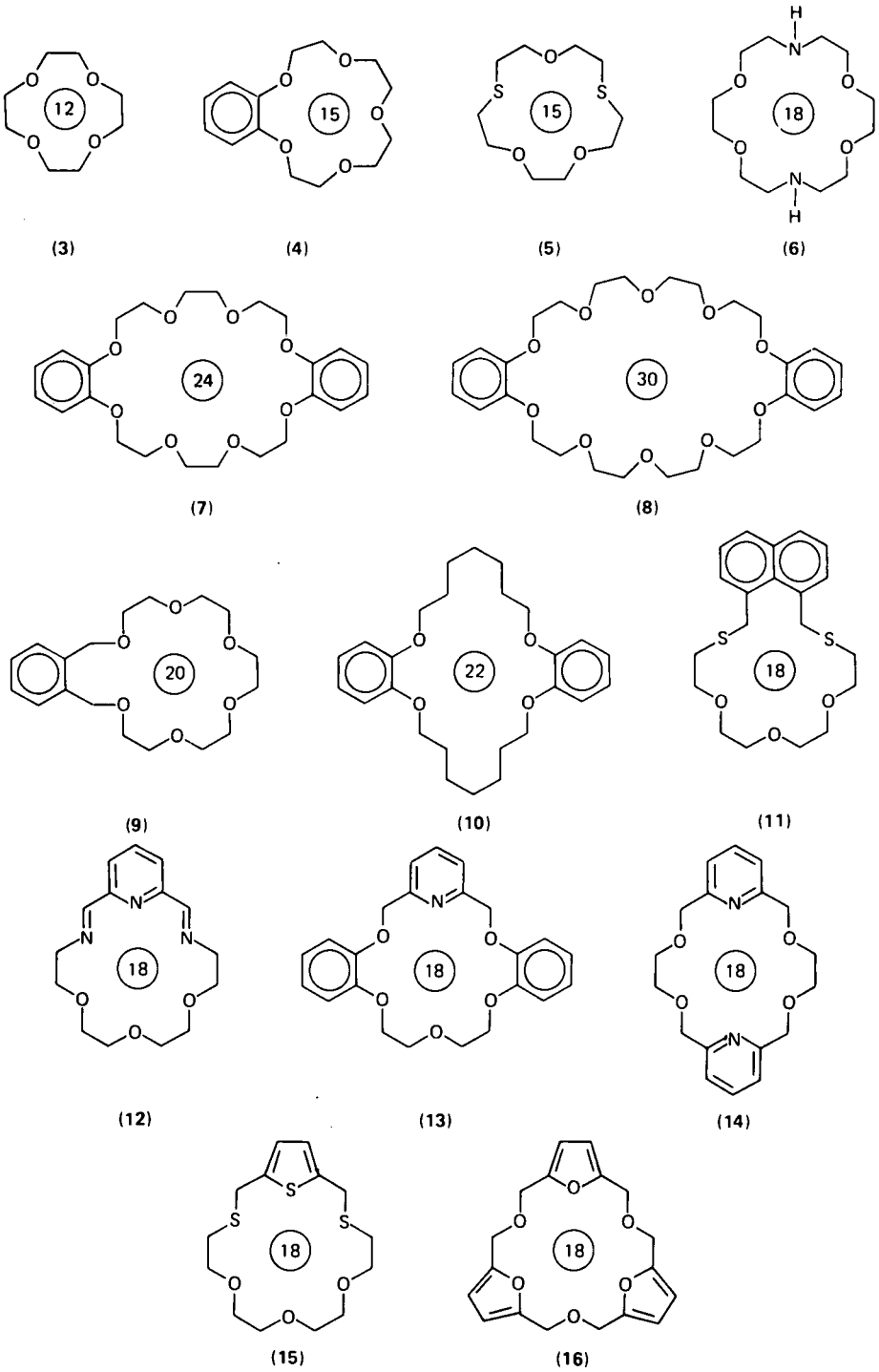


FIGURE 1. Some monocyclic crown ether type neutral ligands (coronands).

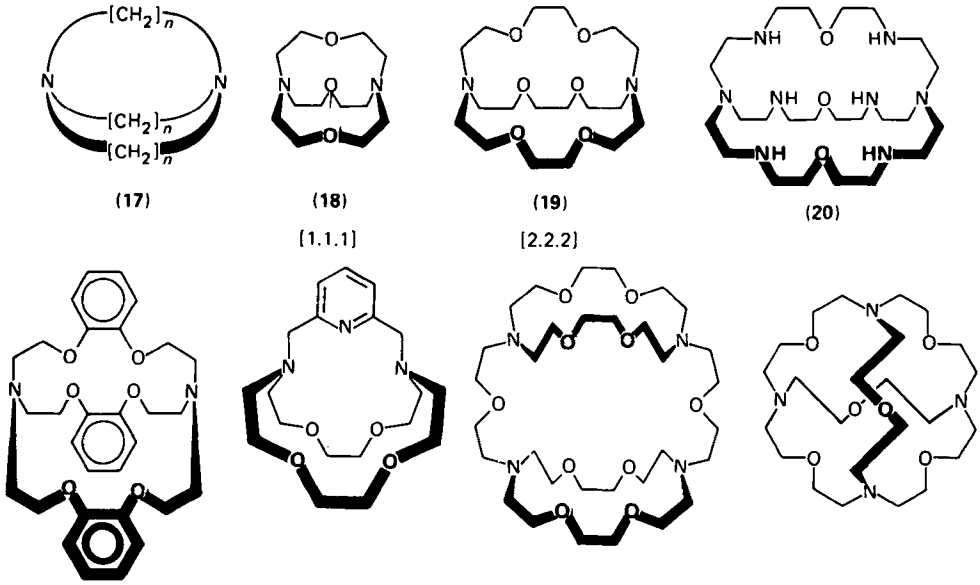


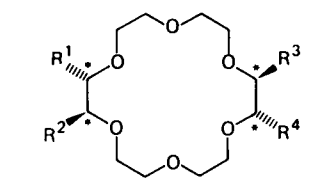
FIGURE 2. A catapinand 17 and some selected cryptand molecules 18–24.

which metal cations can be firmly trapped[12]. The complexes are called *cryptates*[13]*. Numerous structural variations are also possible here,[14,15] as shown in Figure 2†.

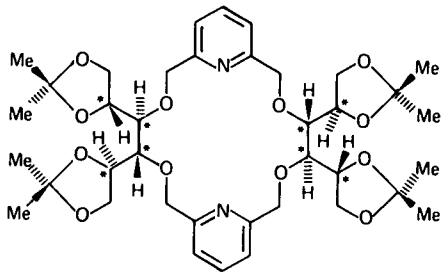
The chemistry of the neutral ligands was essentially enriched by the incorporation of chirality elements into the ring skeleton leading to the formation of *chiral* or optically active crown host compounds[16,17] (Figure 3) capable of differentiating between enantiomeric guest molecules, e.g. amino acids, as shown by some examples (chiroselectivity)[18].

After strong neutral ligands like the cryptands had been more accurately examined, interest grew in the study of *open-chain* ligand topologies[19], which, despite their weaker complexing ability, efficiently discriminate, as has been shown, between different cations[20]. Here the development proceeded with *many-armed* ligand systems (Figure 4) – where profitable use was made of the cooperative effect of piled up donor atoms (*'octopus molecules'*)[21] – ranging from phase-transfer catalytically active analogous triazine compounds[22] and similar *'hexahost'*-type molecules[23] to open-chain skeletons with rigid *terminal donor group systems* (*open-chain crown ethers* and *cryptands*, Figures 5 and 6)[24,25]. Relatively simple donor

*Sometimes '⊂' is used to distinguish a cryptate from a cryptand, e.g. [K⁺ ⊂ 2.2.2].
†Every cipher in square brackets represents one bridge and gives the number of its donor atoms. [2.2.2]cryptand (or only [2.2.2]) is a cryptand with three bridges with two oxygen atoms in every one subscripts, e.g. 2_B, 2_C, 2_D, refers to benzo or cyclohexano condensation and to a decyl residue on the respective bridge.



(25) (a) R^1, R^2 = H; R^3, R^4 = COOEt
(b) R^1, R^2, R^3, R^4 = COOEt
(c) R^1, R^2, R^3, R^4 = $C(=O)NMe_2$



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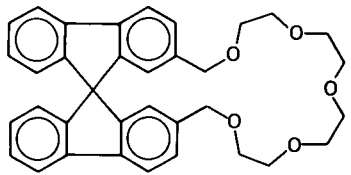
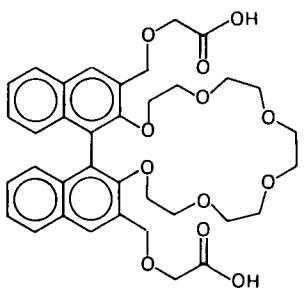


(30)



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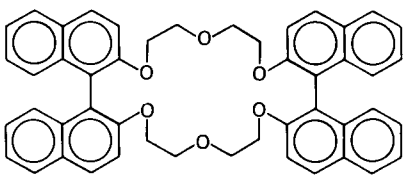

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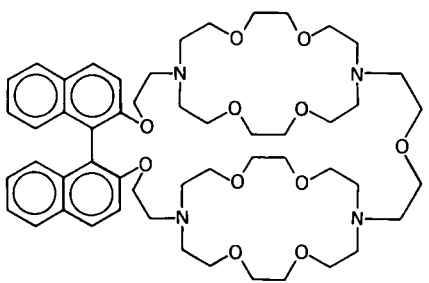
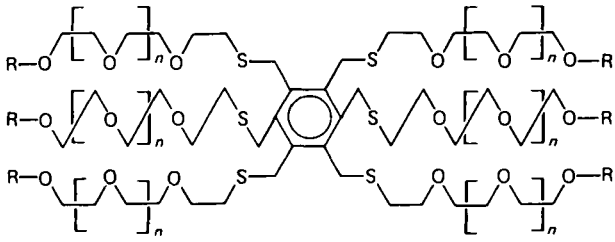


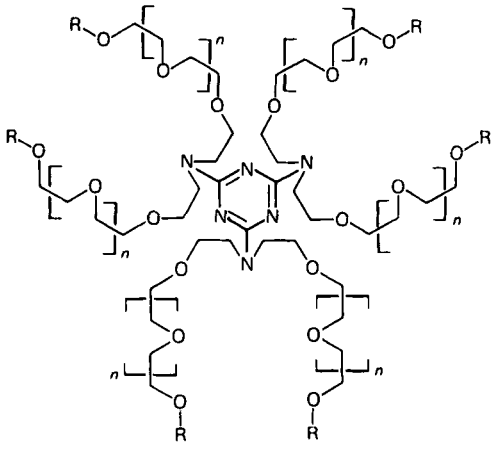
(29)

FIGURE 3. Selected chiral crown ethers.



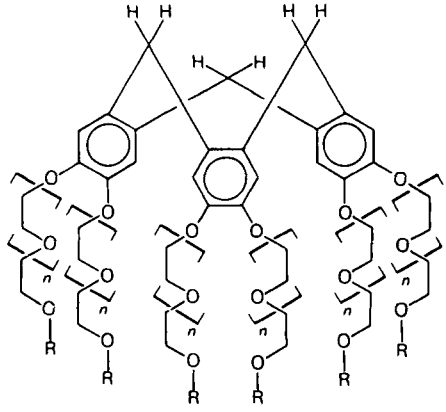
(31)

R = Me, Et, *n*-Bu



(32)

R = *n*-Bu, *n*-Oct



(33)

R = Me, Et, *n*-Bu

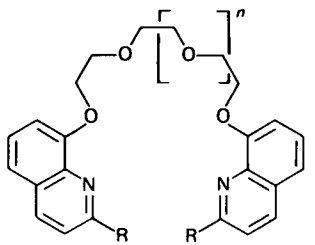
FIGURE 4. Octopus molecules as noncyclic neutral ligand systems.

endgroup-containing *glyme-analogous* compounds easily form crystalline complexes with alkali and alkaline earth metal ions[25,26].

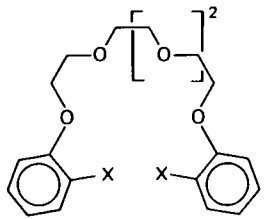
Studies by Simon and coworkers show that on account of their high ion selectivity, weaker open-chain ligands like **42**, and **43** (Figure 7) are of analytical value for microelectrode systems[27].

Interesting are the ligands in the marginal zone between cyclic and open-chain compounds[26b,28], which find their natural counterparts in the nigericin antibiotics[29] and as 'ionophores' are capable of transporting ions across lipophilic media (cell membranes)[30]. Essentially open-chained, they can create a *pseudocyclic* cavity of definite geometry via attractive interaction between their end-groups (see **35c**, Figure 5 and **46**, Figure 7), thereby achieving a higher ion selectivity than common noncyclic ionophores[7b].

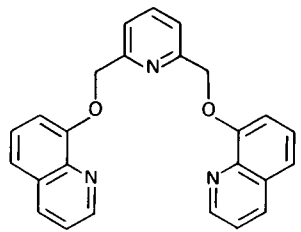
With the isolation of crystalline complexes of glyme-type *short-chain oligoethers* (**47**)[31] possessing only one donor end-group as well as those of longer chain *classical glymes* (**49**) and glyme analogous ligands (**48**)[32] and even those of simple glycols (**50**) such as ethylene glycol ($n = 0$)[33a] (Figure 7) and ethanolamines[33b], the



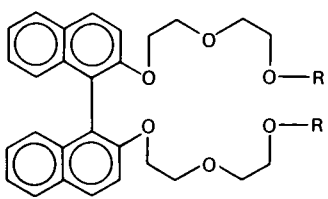
(34) (a) n = 0, R = H
(b) n = 1, R = H
(c) n = 2, R = H
(d) n = 2, R = Me
(e) n = 5, R = H



(35) (a) X = OMe
(b) X = NO_2
(c) X = COOH
(d) X = COOEt
(e) X = NHCMe
(f) X = —CNHCPh
Me

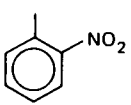


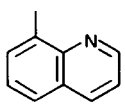
(36)

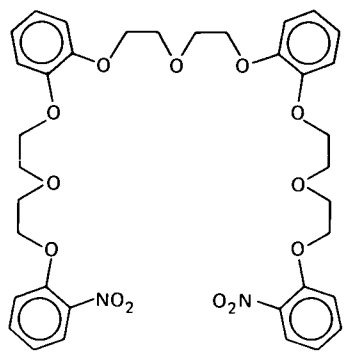


(37)

R =

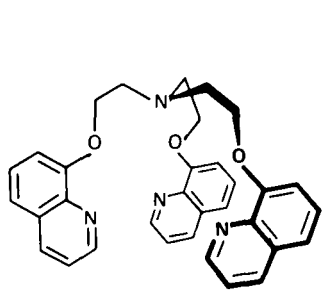




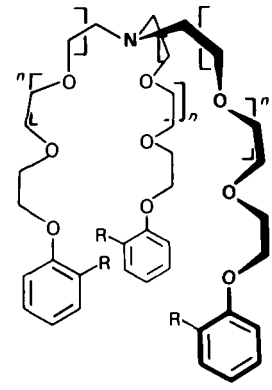


(38)

FIGURE 5. Open-chain crown-type ligands (X = donor centre).

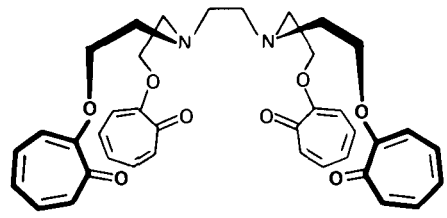


(39)



(40)

R = H, OMe, NO_2



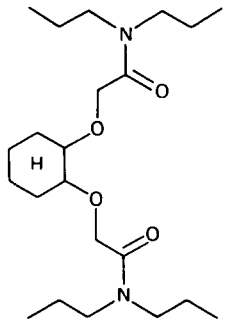
(41)

FIGURE 6. Open-chain-type cryptands (tripodands, tetrapodands).

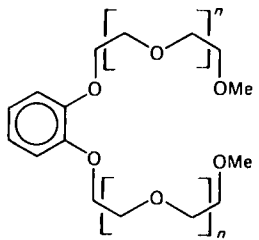
whole range of crown type compounds is covered, extending from the original monocycles via the topologically notable polycyclic analogues to the relatively simple structural open-chain ligand systems with and without donor end-groups.

Investigations on the complexation of glymes and glyme analogues allow the study of the fundamental processes of complexation by neutral ligands with only a few donor centres and binding sites; the latter may be considered to be the most simple model substances for studying complexation processes of biomolecules and biochemical enzyme/substrate or receptor/substrate interactions[34].

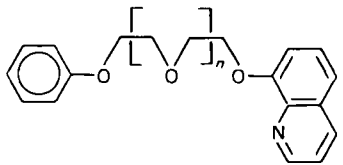
It is remarkable that the historical development could equally well have originated with the open-chain glyme analogues to spread via the more complicated monocyclic crown ethers to the ultimate polycyclic cryptands. Apparently, it was only with the discovery of the very clear complexation behaviour of cyclic systems that interest arose in the alkali/alkaline earth complexation which might be exhibited by open-chain neutral ligands of the glyme type.



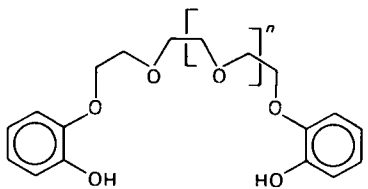
(42)



(44)



(47)



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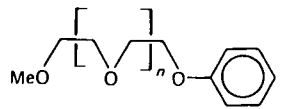

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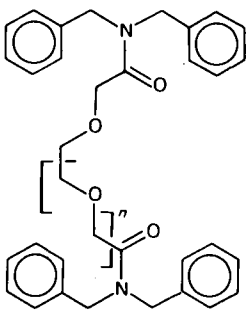

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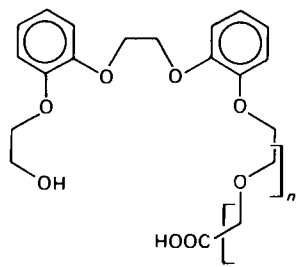

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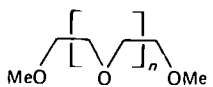

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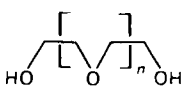


(50)

FIGURE 7. A few weaker complexing neutral ligand systems, glymes and oligoethylene glycols.

II. FUNDAMENTALS OF THE CROWN ETHER COMPLEXATION

A. General Remarks

Stability and *selectivity* of crown ether complexes cannot be properly or significantly understood without first considering the principles of the *kinetics* of complexation (*'dynamic stability'* of complexes).

A different approach to the problem is by determination of *thermodynamic* data pertaining to the system in an equilibrium state (*'static complexation constants'*), omitting consideration of the mechanistic steps of the complexation reaction. Both methods allow the determination of the complex stability constants (K_S values), but significantly differ in points which may be important for the practical use of a particular crown ether. These points will be discussed in detail in Section III, following the general theoretical description of the crown ether complexation.

B. Kinetics and Mechanism of Complexation

1. *Introduction*[7b,d]

Molecular kinetics, i.e. the dynamic behaviour of a system – composed of ligand, cation and solvent – in the sense of a forward (*complexation*) and a reverse (*decomplexation*) reaction (equation 1), give information about the lifetime of a

$$M^+_{solv.} + Ligand_{solv.} \underset{\overleftarrow{k}}{\overset{\vec{k}}{\rightleftharpoons}} [M^+ Ligand]_{solv.} \qquad (1)$$

complex. The ratio of the rate constant of complexation ($\vec{k}$) to that of decomplexation ($\overleftarrow{k}$) is thus directly connected with the stability of (K_S) of the crown ether complex ($K_S = \vec{k}/\overleftarrow{k}$, see Section II.C). Since the rate constants of the forward and reverse reactions depend on the corresponding activation energies (E_A), complex and selectivity constants are in fact results derived from thermodynamic data, composed of an enthalpy ($\Delta H^{\neq}$) and an entropy ($\Delta S^{\neq}$) part. Elucidation of the complexation reaction by consideration – albeit thorough – of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ is not always possible.

2. *Interpretation of the complexation/decomplexation phenomena (desolvation, ligand exchange and diffusion processes)*

Metal complexation in solution is generally a very quick reaction[35]. Nuclear magnetic resonance[36] and relaxation curves[37] have shown, however, that complex formation does not occur instantaneously, and it is not a simple one-step reaction between ligand and cation. Often complexation includes a series of intermediate steps like substitution of one or several solvent molecules from the inner coordination shell of the metal ion and/or internal conformational rearrangements of the ligand, in particular, when the ligand is a multidentate one (crown ether, cryptand, podand)[7b].

The 'complexation reaction' can occur essentially by two border mechanisms[38]:

(1) The solvent molecule leaves the cation, decreasing its coordination number, prior to entry of the ligand: *S_N1-type mechanism*.
(2) The ligand forces its way through the solvent envelope of the cation, increasing the coordination number of the latter and then displaces a solvent molecule: *S_N2-mechanism*.

In the first case, the rate of substitution depends only on the solvated metal ion; in the latter case it is also ligand-dependent.

In aqueous solution, solvent/ligand exchange reactions with many main-group metal ions proceed via the S_N1 mechanism[39], whilst S_N2 mechanisms are mostly associated with metal ions having deformed coordination envelopes[40]. In reality, a *hybrid mechanism* resembling more a 'push–pull' type process must be taken for granted[7b].

In order for a reaction between ligand and metal ion to occur, both partners must collide after diffusing to within critical distance of each other[41]. Thus the following overall system (equation 2) is derived from equation (1):

$$M^+_{solv.} + Ligand_{solv.} \underset{k_{2/1}}{\overset{k_{1/2}}{\rightleftharpoons}} \underset{\text{(within critical distance)}}{[M^+ \ldots Ligand]} \underset{k_{3/2}}{\overset{k_{2/3}}{\rightleftharpoons}} [M^+ Ligand]_{solv.} \qquad (2)$$

where $k_{1/2}$, $k_{2/1}$ are the rate constants of forward and reverse diffusions and $k_{2/3}$, $k_{3/2}$ the rate constants for (stepwise) ligand exchange. The rate constants for the whole complexation ($\vec{k}$) and decomplexation ($\overleftarrow{k}$) reactions can then be expressed by the following quotients (3) and (4):

$$\vec{k} = \frac{k_{1/2} \cdot k_{2/3}}{k_{2/1} + k_{2/3}} \qquad (3)$$

$$\overleftarrow{k} = \frac{k_{2/1} \cdot k_{3/2}}{k_{2/1} + k_{2/3}} \qquad (4)$$

If the reverse diffusion ($k_{2/1}$) is quicker than the ligand exchange reaction, more encounters between the partners are required before a ligand exchange can occur; $\vec{k}$ will then be determined by equation (5). When the reaction step $k_{2/3}$ is rapid

$$\vec{k} = k_{2/3} \cdot \frac{k_{1/2}}{k_{2/1}} \qquad (5)$$

relative to the reverse diffusion, every encounter between the partners leads to the desired product and the whole process can be considered to be *diffusion-controlled* with $k_{1/2}$ as the overall rate constant.

The values for $k_{1/2}$ and $k_{2/1}$ are of the order of 10^9 to 10^{10} (l/mol/s) or (l/s); they depend on the charge and size of the partners as well as on the solvent used[42]. The following sections deal with the comparison and characterization of the various polyether families (natural ionophores, coronands, cryptands, podands) according to their kinetics of complexation.

3. *Kinetics of complexation of a few types of crown ether*

a. Natural ionophores. Open-chain antibiotics like *nigericin* show rate constants k of about 10^{10}/mol/s (Table 1)[7b,43] for recombination (complexation reaction) with alkali metal cations, as is expected for a diffusion-controlled reaction (see above) between two univalent oppositely charged ions[44]. Since the nigericin molecule wraps round the cation, it may be taken for granted that the substitution can be extremely rapid, occurring, however, by a stepwise mechanism. In other words, the solvent molecules are displaced one after the other; in each substitution step, solvation energy is compensated for by ligand binding energy.

The overall rate of complex formation for *valinomycin* depends on the radius of the cation (Table 1)[45,46]: Rb^+ ions complex more rapidly than K^+, Na^+ and Cs^+ ions. The rate of dissociation is, on the other hand, lowest for Rb^+. For this ionophore, exact rate constants of the single reaction step defined by equation (2) are also known (Table 2)[45b].

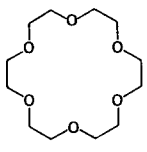
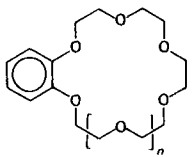
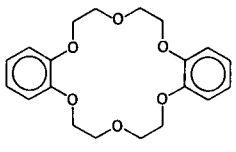
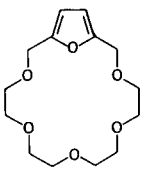
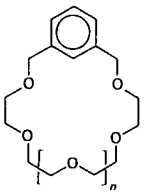
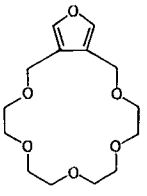
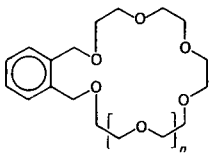
TABLE 1. Kinetic parameters ($\vec{k}$, $\overleftarrow{k}$) for the formation of cation complexes with some natural ionophores

Ligand	Solvent [temp.]	Cation	$\vec{k}$ (1/mol/s)	$\overleftarrow{k}$ (1/s)	Reference
Nigericin	MeOH[25°C]	Na^+	1×10^{10}	1.1×10^5	43
Nonactin	MeOH/$CDCl_3$ [4:1; 21°C]	K^+	1.6×10^5	32	46
Valinomycin	MeOH[25°C]	Na^+	1.3×10^7	1.8×10^6	45a
		K^+	3.5×10^7	1.3×10^3	
		Rb^+	5.5×10^7	7.5×10^2	
		Cs^+	2.0×10^7	2.2×10^3	
		NH_4^+	1.3×10^7	2.5×10^5	

TABLE 2. Rate constants for single steps of the complexation of valinomycin with Na^+ and K^+ (in MeOH, 25°C)[45b]

Cation	$k_{1/2}$ (1/mol/s)	$k_{2/1}$ (1/s)	$K_{1/2} = k_{1/2}/k_{2/1}$ (1/mol)	$k_{2/3}$ (1/s)	$k_{3/2}$ (1/s)	$K_{2/3} = k_{2/3}/k_{3/2}$
Na^+	7×10^7	2×10^7	3.5	4×10^6	2×10^6	2
K^+	4×10^8	1×10^8	4.0	1×10^7	1.3×10^3	7.7×10^3

TABLE 3. Kinetic data and K_s values of t-$BuNH_3^+PF_6^-$ complexes of some crown ethers ($CDCl_3$, 20°C)[3,6]

Crown	 (2)	 (4) $n = 0,1$	 (1)	 (51)	 (52) $n = 1,2$	 (53)	 (9) $n = 0,1$
$\vec{k}$ (1/mol/s)	1.49×10^9	7.75×10^8	1.02×10^9	1.43×10^9	1.19×10^9	7.7×10^8	1.26×10^9
$\overleftarrow{k}$ (1/s)	65	155($n = 1$)	850	1100	5400($n = 1$)	7000	9000($n = 1$)
$\Delta G_i^{\neq}$ (kcal/mol)	14.7	14.2	13.2	13.0	12.1	12.0	11.8
(kJ/mol)	61.53	59.44	55.26	54.42	50.65	50.23	49.49
E_A	19.3	18.0	13.0	15.2	12.2	10.5	9.9
(kJ/mol)	80.79	75.35	54.42	63.63	51.07	43.95	41.44

b. Monocyclic crown ethers. Kinetic investigations of the alkali metal complexation of crown ethers are generally impeded by the following factors[7d]: the complexes are relatively weak and must, therefore, be studied at high metal ion concentrations; the rate constants are very high usually and the experimental difficulties encountered with the higher concentrations required are greater; the complexes often do not display any light absorption in measurable zones, so that spectroscopic determinations of reaction rate constants are usually not possible.

^{1}H-NMR spectroscopic investigations of the complexation kinetics of various *crown ethers* and *t*-butylammonium hexafluorophosphate showed that the rates of complex formation ($\vec{k}$) for all studied ligands are approximately the same, 0.8–1.5 x 10^9/mol/s[36], and are probably, diffusion-controlled[47]. Hence, the differences in complex stabilities must be caused by different rates of decomplexation ($\overleftarrow{k}$), which vary between 10^2 and 10^4/s (see Table 3).

In Table 4 are listed the rate constants ($\vec{k}$, $\overleftarrow{k}$) of *dibenzo[30]crown-10* (8) and various alkali metal ions ($Na^+ \ldots Cs^+$) or NH_4^+[48], measured in methanol according to the temperature jump method[49]. These practically diffusion-controlled $\vec{k}$ values are only possible with appreciable conformational ligand flexibility[50]. A less flexible ligand would require total desolvation of the cation before complexation, leading to an essential decrease of the reaction rate constant. During the complexation of the conformationally very flexible dibenzo[30]crown-10, a solvent molecule is replaced by a crown ether donor location via a low activation energy barrier, i.e. the cation is simultaneously desolvated and complexed.

For *dibenzo[18]crown-6* and Na^+, a rate constant of $\vec{k} = 6 \times 10^7$/mol/s[51] has been found by ^{23}Na-NMR measurements[52] in DMF (Table 4); the value is much greater than that for the complexation of Na^+ ions by a macrobicyclic ligand in water, for example (see Section II.B.3.c).

c. Cryptands. Cryptands with comparably rigid structures should exchange cations more slowly, as has been confirmed experimentally (see Table 5). In the case of these ligands, a slightly modified stepwise mechanism of metal ion complexation is taken for granted, whereby it is again not required that all solvent molecules simultaneously leave the coordinated shell[7b].

The kinetics of complex formation were first measured for the *[2.2.2]cryptand*, **19**; with the help of potentiometry, ^{1}H- and ^{23}Na-NMR spectroscopy, the overall dissociation rates of the complexes have been determined[14c,53,54].

Temperature jump relaxation methods, which allow the determination of rate constants of complex association and dissociation, gave $\vec{k}$ values of 10^5–10^7/mol/s and $\overleftarrow{k}$ values between 10 and 10^3/s for reaction between cryptands [2.1.1] (**54**), [2.2.1] (**55**), [2.2.2] (**19**) (in H_2O, not or singly protonated) and Na^+, K^+[37]. From these results it follows that after the diffusion-controlled formation of the encounter complex, the coordinating atoms of the ligand replace the water molecules of the inner hydrate shell of the metal ion in a stepwise way.

The pronounced selectivity of the cryptands (in MeOH) for alkali metal cations is reflected in the dissociation rates; the formation rates increase only slightly with increasing cation size[55] (Table 5). The specific size-dependent interaction between the metal ions and the cryptands must occur subsequent to the formation of the transition state in the complex formation reaction. For a given metal ion, the formation rates increase with increasing cryptand cavity size; for the [2.2.2] cryptand they are similar to the rates of solvent exchange in the inner sphere of the cations. This suggests that during complex formation, particularly for the larger cryptands, interactions between the cryptand and the incoming cation can compensate effectively for the loss of solvation of the cation[56].

TABLE 4. Overall rate constants for complexation ($\vec{k}$) and dissociation ($\overleftarrow{k}$) of some alkali metal ions with dibenzo[18]crown-6 (1) and dibenzo[30]-crown-10 (8) and values for the complex formation constant K_s

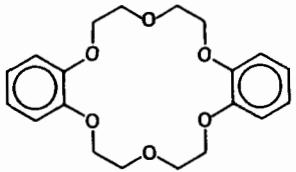
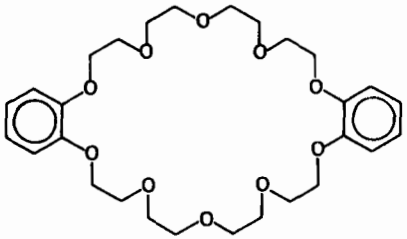
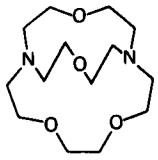
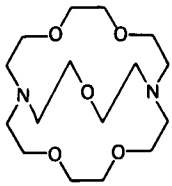
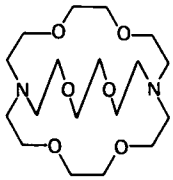
Ligand	Solvent [temp.]	Cation	$\vec{k}$ (1/mol/s)	$\overleftarrow{k}$ (1/s)	K_s	Reference
 (1)	DMF [25°C]	Na^+	6×10^7	1×10^5	600	51
 (8)	MeOH [25°C]	Na^+	1.6×10^7	$>1.3 \times 10^5$	1.3×10^2	48
		K^+	6×10^8	1.6×10^4	3.7×10^4	
		Rb^+	8×10^8	1.8×10^4	4.4×10^4	
		Cs^+	8×10^8	4.7×10^4	1.7×10^4	
		NH_4^+	$>3 \times 10^7$	$>1.1 \times 10^5$	2.7×10^2	

TABLE 5. Overall rates and log K_S values for complex formation between bicyclic cryptands and alkali metal cations (MeOH, 25°C)[55]

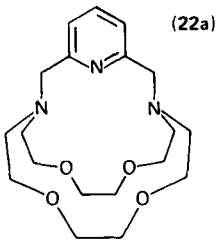
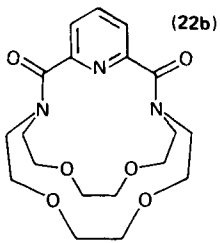
Ligand		Cation	$\vec{k}$ (1/mol/s)	$\overleftarrow{k}$ (1/s)	K_S[7b,14c]
 [2.1.1]	(54)	Li^+	4.8×10^5	4.4×10^{-3}	$>16^6$
		Na^+	3.1×10^6	2.50	1.3×10^6
 [2.2.1]	(55)	Li^+	1.8×10^7	7.5×10	$>10^5$
		Na^+	1.7×10^8	2.35×10^{-2}	$>10^8$
		K^+	3.8×10^8	1.09	$>10^7$
		Rb^+	4.1×10^8	7.5×10	$>10^6$
		Cs^+	$\approx 5 \times 10^8$	$\approx 2.3 \times 10^4$	$\approx 1.0 \times 10^5$
 [2.2.2]	(19)	Na^+	2.7×10^8	2.87	$>10^8$
		K^+	4.7×10^8	1.8×10^{-2}	$>10^7$
		Rb^+	7.6×10^8	8.0×10^{-1}	$>10^6$
		Cs^+	$\approx 9 \times 10^8$	$\approx 4 \times 10^4$	2.5×10^4

Pyridinophane cryptands of type 22 have been particularly well studied[57]. The first step of the complexation mechanism consists in the diffusion-controlled recombination of both reactants and the stepwise substitution of the water molecules of inner hydration sphere by the cryptands. The overall rate of complex formation is determined by structural changes of the ligand occurring at a frequency of approximately 10^4/s subsequent to the encounter and the substitution step. During this slow step, there is either rotation of the ether oxygen atoms into the ligand interior toward the incorporated metal ion or a shift of the *exo/endo* equilibrium at the bridgehead nitrogens of the ligand in favour of the *endo* conformation. Owing to steric restrictions, the latter structural change can be very slow.

At first sight, it may seem surprising that the relatively big potassium cation is more strongly bound by the diamide ligand 22b than by the less rigid diamine 22a (see Table 6), while the affinity of the sodium ion for both ligands remains approximately the same.

This apparent inconsistency has been elucidated by kinetic studies. Comparison of the single rate constants of corresponding reaction steps (Table 6) shows that the difference in the stability of the two complexes is particularly exhibited in the dissociation rate $k_{2/1}$ of the first step with all the other rate constants remaining very similar. This can be attributed to the fact that the diamine does not possess

TABLE 6. Rate constants k and log K_S values for the complexation of pyridinophane cryptands 22 (in H_2O, 25°C)[57]

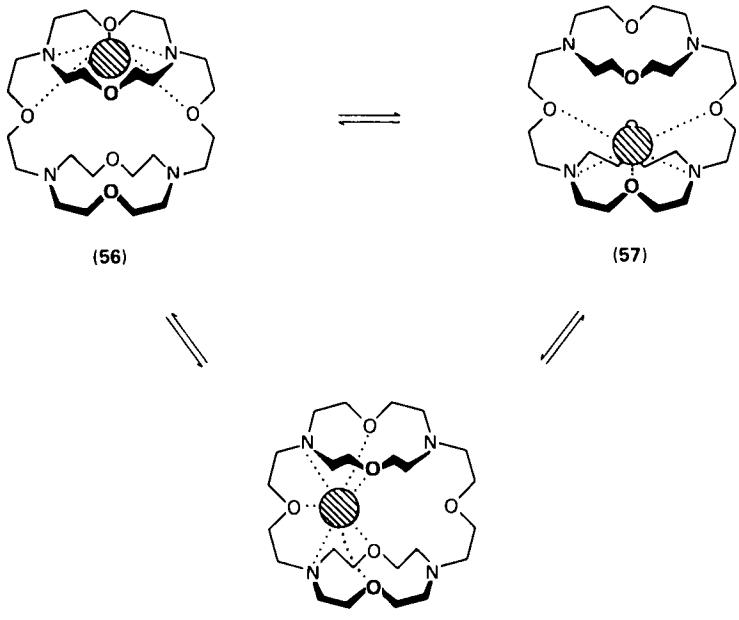
Ligand	Cation	$k_{1/2}$(1/mol/s)	$k_{2/1}$(1/s)	$k_{2/3}$(1/s)	$k_{3/2}$(1/s)	log K_S
 (22a)	Na^+					4.89
	K^+	3×10^8	7×10^3	8×10^3	2.0×10^4	4.78
 (22b)	Na^+	3×10^8	1.5×10^4	1.4×10^4	1.4×10^4	4.58
	K^+	5×10^8	3×10^3	5×10^3	1.8×10^4	5.25

any electronegative carbonyl oxygen atoms on the surface of the molecule. Hence the rate of association $k_{1/2}$ to the intermediate decreases, while the dissociation rate $k_{2/1}$ increases.

The crystalline *Eu(III)* and *Gd(III) cryptates* of [2.2.1] display a remarkable kinetic stability in water and appear to be the first substitutionally inert lanthanide complexes[58]. Neutral solutions show no metal hydroxide precipitate, even after several days of ageing. In strongly basic solution, the complexes are stable for hours. No dissociation of the complex is seen even after several days in aqueous perchloric acid. This inertness renders the $[Gd(2.2.1)]^{3+}$ ion useful as a T_1 (shiftless) relaxation reagent for NMR in polar inorganic solvents or in aqueous solutions.

The kinetics of *protonation and deprotonation* of cryptands have also been studied in detail[59], particularly, with [1.1.1] (**18**), possessing a cavity, into which a proton just fits, and which cannot be totally removed even by boiling for hours with concentrated alkali hydroxide[60]. For the reaction $H_2O + [2.2.2] \rightleftarrows [2.2.2.H]^+ + OH^-$, the following rate constants are found: $\vec{k} = 10^7$/mol/s and $\overleftarrow{k} = 10^3/s$[59a]. The ligand is protonated inside the ligand cavity. The rates of protonation are at least two orders of magnitude smaller than those of proton-transfer reactions of simple tertiary amines.

In */3/cryptates* an *intramolecular* cation exchange process can be observed by means of ^{13}C-NMR spectroscopy; a cation is transferred from one of the two diazacrown ether rings via a process of type **56** → **58** (Figure 8) to the other ring[61]. The activation energy ($\Delta G^{\neq}$) of this exchange reaction decreases with increasing size and decreasing hydration energy of the cation ($\Delta G^{\neq}$:$Ca^{2+} > Sr^{2+}$), i.e. in the



(56) (57) (58)

FIGURE 8. Possible intramolecular cation exchange in [3]cryptates.

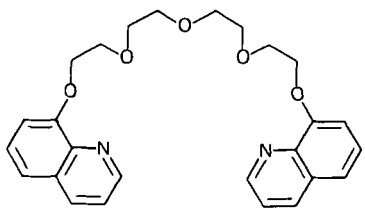
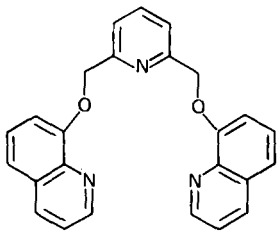
reverse order to that found for the slow *intermolecular* cation exchange in this system.

d. Podands. The results on the *open-chain* ligands agree well with similar studies on other simple chelating agents as NTA and EDTA[62] as well as on various macrotetrolide systems[63]. Both of the open-chain *quinoline polyethers* **34c** and **36** show – as revealed by temperature-dependent UV absorption measurements of the complexation[57] (the stepwise binding of the metal ion induces a bathochromic shift of the absorption maximum of the ligand and a decrease of the absorption coefficient in methanol) – recombinations between ion and ligand (Table 7) that are slower by one order of magnitude than diffusion-controlled processes (10^9 – 10^{10}/mol/s, see Section II.B.2). This points to a stepwise replacement of the solvation sphere of the metal ion by the chelating atoms of the multidentate complexones.

A comparison with the *oligoethylene glycol ethers* of types **35** and **47**, in which donor groups containing aromatic units or simple benzene nuclei replace the quinoline rings, proves to be interesting. The rate constants $\vec{k}$ for recombination between metal ion and ligand are – as determined by temperature jump–relaxation experiments – of the order of 3×10^7 to 4×10^8/mol/s[64]; such values are relatively high, but still lower than those found for diffusion-controlled recombinations in methanol, as e.g. the recombination of the negatively charged, open-chain nigericin antibiotic with Na^+ ions ($\vec{k} = 10^{10}$/mol/s, in methanol, Table 1).

The diminished rates are, as described above, a result of the stepwise replacement of the solvent molecules in the inner coordination sphere of the metal ion by

TABLE 7. Overall rate constants k and log K_S values of alkali metal ion complex formation with some open-chain oligoethers (in MeOH, 25°C)[57]

Ligand	Cation	$\vec{k}$ (1/mol/s)	$\vec{k}$ (1/s)	log K_S
 (34c)	Li^+	3×10^7	4.3×10^4	2.37
	Na^+	1×10^8	3.4×10^4	3.22
	K^+	1.1×10^8	4×10^3	3.51
	Rb^+		$\approx 10^5$	3.06
 (36)	Na^+	4×10^8	2.5×10^4	3.65
	K^+		$\gtrsim 10^5$	2.75

the chelating atoms of the multidentate complexones. In order to account for the high overall rates every single substitution process has to occur with a rate constant of the order of 10^8 to 10^9/s. In general, the rate of solvent substitution decreases with decreasing ionic radius of the metal ion, because the solvent molecules of the inner solvation shell are more strongly bound due to the strong, electrostatic interaction. This is particularly noted in the case of the quinoline polyether **34c** (see Table 7). Furthermore, the stability of the complexes increases with decreasing $\dot{k}$ values, i.e. the most stable K^+ complex of the series dissociates with the lowest frequence. The dependency of the association and dissociation rate constants of ligand **34c** on the metal ion radius is thus in agreement with results found for cyclic complexons like valinomycin [45a] and dibenzo[30]crown-10 (8)[48].

4. Comparison of the different ligand systems

The results obtained for the various ligands described above show that in no case does a one-step reaction between ligand and cation occur.

As a rule, substitution of one or several solvent molecules in the inner coordination shell of the metal ion as well as conformational changes of the ligand take place during complexation at a rate of 10^9 to 10^{10}/mol/s (nigericin 10^{10}) for *open-chain* ligands; these reactions are practically diffusion-controlled (see Tables 1 and 7).

With *monocyclic* crown ethers the rates of alkali metal ion complexation are only slightly smaller (values of about 10^9/mol/s, see Tables 3 and 4), supposing that the ligand is flexible.

For more rigid *cryptand* systems, the results may be summarised as follows (see Tables 5 and 6):

(a) The rates of formation with values between 10^4 and 10^7/mol/s are much slower than the exchange of the hydration shell, but appear to follow the same order.
(b) The transition state lies on the side of the starting materials, i.e. it is accompanied by considerable solvation of the cation.
(c) The dissociation rates of the most stable complexes are slower ($10-10^3$/s) than those of macromonocyclic coronands or antibiotic complexones and decrease with increasing stability constants.
(d) The dissociation can proceed via an acid-catalysed pathway at low pH.
(e) Rapid exchange rates require small cation solvation energies, ligand flexibility and not too high complex stabilities. Conformational change can occur during the process of complexation; the most stable cryptates are *cation receptor complexes*, which release the cation again only very slowly. The less stable ones exchange more rapidly and can, therefore, serve as *cation carriers*.

C. Thermodynamics of Complexation

1. Introduction

Thermodynamics of complexation[65,76] is synonymous with the discussion of the *free enthalpy change* ΔG^0, which accompanies the formation of the complex. The latter is expressed by the Gibbs–Helmholtz equation (equation 6) which

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \qquad (6)$$

consists of an enthalpy and an entropy term, the relative importance of each depending on the type of ligand and cation.

There are altogether four possible combinations of the thermodynamic parameters leading to stable complexes ($\Delta G^0 < 0$):

$$\Delta H^0 < 0 \quad \text{and dominant,} \quad \Delta S^0 > 0 \qquad (a)$$

$$\Delta H^0 < 0 \quad \text{and dominant,} \quad \Delta S^0 < 0 \qquad (b)$$

$$\Delta S^0 > 0 \quad \text{and dominant,} \quad \Delta H^0 < 0 \qquad (c)$$

$$\Delta S^0 > 0 \quad \text{and dominant,} \quad \Delta H^0 > 0 \qquad (d)$$

From (*a*) and (*b*) *enthalpy*-stabilized complexes result, from (*c*) and (*d*) *entropy*-stabilized ones and from (*a*) and (*c*) enthalpy- *as well as* entropy-stabilized complexes. All four types of complexes are found among the coronates, cryptates and podates discussed here.

Combination of a charged ligand with a hard A-type* metal ion to form a complex of *electrostatic* nature is preferentially entropy-driven, while on the other hand, recombination of an uncharged ligand with a soft B-type* metal ion to form a complex of *covalent* nature is preferentially enthalpy-driven[66]. Unfortunately, this empirical rule cannot be used to predict complexation reactions between alkali metal ions and noncyclic crown ether type polyethers, because alkali metal ions belong to group A of the hard, unpolarizable cations while the noncyclic ligands belong to the group of uncharged ligands.

The free enthalpies themselves result from the superposition of several different, partly counteracting increments of ΔG^0:

(*a*) the binding energy of the interaction of the ligand donor atoms with the cations;
(*b*) the energy of conformational change of the ligand during complexation;
(*c*) the energies of metal ion and ligand.

2. *Significance of* ΔH^0, ΔS^0, ΔG^0 *and* ΔC_p^0 *for complexation*

a. Free enthalpy changes. ΔG^0 values are a direct measure of the degree of complexation in solution, and these values are used for comparison of the complex stabilities and cation selectivities of crown ethers. In Tables 8–10 are listed the ΔG^0 values of a few typical ligand/salt combinations. Enthalpy changes of a cation–ligand reaction in solution allow conclusions about the binding energy of cation–donor atom bonds and the hydration energies of reactants and products.

b. Enthalpies. ΔH^0 values of the above ligand/salt combinations are also given in Tables 8–10. The magnitudes of the ΔH^0 values are indicative of the type and number of binding sites (e.g. O,N,S etc.). As a rule, the ΔH^0 values are solvent-dependent. Thus, they often reflect (more accurately than other thermodynamic parameters) the energy changes that accompany bond formation and bond cleavage in cases where the solvent is changed or donor atoms are substituted.

c. Entropies. When ΔG^0 and ΔH^0 values of the complexation reaction are known, the corresponding ΔS^0 values (see Tables 8–10) can be calculated. The

*'A-type' cations have d_0 configuration. In typical 'B-type' cations d-orbitals are fully occupied; for more details see Section III.D.1.a(1) and References 66, 94 and 95.

value of ΔS^0 mostly depends on electrostatic factors such as the relative hydration, and number of product and reactant species. As a rule, one obtains significant ΔS^0 contributions with macrocyclic ligands only when strong conformational changes are present during formation of the complex. So the magnitudes of the ΔS^0 values are indicative of solvent–solute interaction and supply information about the relative degrees of hydration of the metal ion, macrocycle and complex, the loss of degrees of freedom of the macrocycle when complexed with the metal ion and the charge-types involved in the reaction.

d. C_p *changes.* Only a few ΔC_p^0 values for the complexation of crown ether type neutral ligands are known so far[8b,64]. They may give information about the conformational change of the ligand. Such conformational changes play a significant role, for instance during the formation of the K^+ complex of valinomycin and nonactin as well as that of the K^+ complex of [30]crown-10 (8) (see Figure 23, Section IV.B.1.a).

3. *Thermodynamics of a few selected crown ethers*

The thermodynamic parameters of the complexes of the A isomer (*cis–syn–cis* isomer) of *dicyclohexano[18]crown-6* (59a) (see Table 8) have been most thoroughly examined[67]. Favourable ΔS^0 values (positive) are found with cations having a pseudoinert gas configuration, e.g. Ag^+ (ΔS^0 = 11.02 cal/deg/mol) and Hg^{2+} (10.2). Since the ΔH^0 values here are very small (ΔH^0 = 0.07 and −0.71 kcal/mol), complexation with these metal ions is almost/solely entropy-driven. Also in the case of Sr^{2+}, a positive entropy change (ΔS^0 = 2.5 cal/deg/mol), albeit smaller, is measured together with a strongly negative ΔH^0 (−3.68 kcal/mol); hence the complexation of many double-charged cations (alkaline earth ions) is a result of favourable ΔH^0 as well as ΔS^0 values.

The entropy of formation ΔS^0 depends mostly on the change of the number of degrees of freedom of the particles during complex formation, taking participating water into consideration also. The biggest term normally represents the translational entropy of released water molecules, so that highly charged smaller cations, which are more strongly hydrated, should give bigger values of ΔS^0. This is experimentally confirmed, for instance, on going from K^+ to Ba^{2+}: the ΔS^0 value of Ba^{2+} (−0.20 cal/deg/mol) is much more favourable than that of K^+ (−3.80), whilst the enthalpy changes do not differ as much (ΔH^0_{Ba} = −4.92, ΔH^0_K = −3.88 kcal/mol), a fact attributable to stronger cation–ligand interactions and bigger entropy gain during displacement of the solvent shell. From these results, it can be seen that the type of cation as well as its charge plays an important role in the thermodynamics of complexation (for more details see Section III.D).

Of interest in the case of *[18]crown-6* (2), apart from the complexation thermodynamics of the alkali/alkaline earth ions (see Table 8), is that of the rare earth ions La^{3+} to Gd^{3+}, measured in methanol by titration calorimetry[68]. Three features of the results are significant: (*a*) no heat of reaction is found with the *post*-Gd^{3+} lanthanide cations; (*b*) all reaction enthalpies are positive and thus the observed stabilities of entropic origin; (c) with increasing atomic weight, the complex stabilities decrease, contrary to those of the triple-charge lanthanide complexes of most other ligands. The results have been interpreted in such a way as to reflect the balance among ligand–cation binding, solvation and ligand conformation. UO_2^{2+} and Th^{4+} give no measurable heats of reaction with [18]crown-6 in methanol under similar conditions[68]. It seems that complex formation does not

TABLE 8. Thermodynamic data for the interaction of several macrocyclic [18]crown-6-type ligands with various metal ions at 25°C

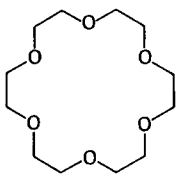
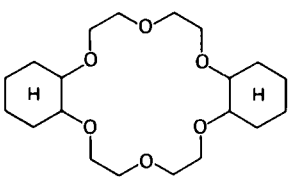
Ligand	Cation	Solvent	ΔH° (kcal/mol) [kJ/mol]	ΔS° (cal/deg/mol) [J/deg/mol]	log K_s	Reference
 (2)	Na^+	H_2O	−2.25 [− 9.42]	− 3.7 [−15.49]	0.80	67b
	K^+	H_2O	−6.21 [−25.98]	−11.4 [−47.52]	2.03	
	Rb^+	H_2O	−3.82 [−15.98]	− 5.8 [−23.86]	1.56	
	Cs^+	H_2O	−3.79 [−15.86]	− 8.1 [−33.91]	0.99	
	Ag^+	H_2O	−2.17 [− 9.08]	− 0.4 [− 1.67]	1.50	
	Ca^{2+}	H_2O			<0.50	
	Sr^{2+}	H_2O	−3.61 [−15.11]	0.3 [1.26]	2.72	
	Ba^{2+}	H_2O	−7.58 [−31.73]	− 7.9 [−33.07]	3.87	
	Pb^{2+}	H_2O	−5.16 [−21.60]	2.2 [9.21]	4.27	
	Hg^{2+}	H_2O	−4.69 [−19.63]	− 4.7 [−19.67]	2.42	

TABLE 8 – continued

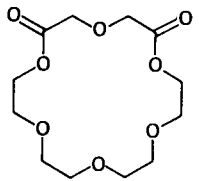


(59)

(a) *cis–syn–cis* isomer

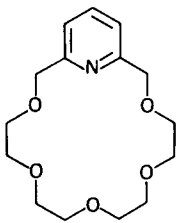
(*b*) *cis–anti–cis* isomer

Li^+	H_2O		–	–	0.60	67b
Na^+	H_2O	(a)	0.16 [0.67]	6.1 [25.53]	1.21	
		(b)	−1.57 [− 6.57]	− 2.1 [− 8.79]	0.69	
K^+	H_2O	(a)	−3.88 [−16.24]	− 3.8 [−15.91]	2.02	
		(b)	−5.07 [−21.22]	− 9.6 [−40.18]	1.63	
Rb^+	H_2O	(a)	−3.32 [−13.90]	− 4.2 [−17.58]	1.52	
		(b)	−3.97 [−16.62]	− 9.3 [−38.92]	0.87	
Cs^+	H_2O	(a)	−2.41 [−10.09]	− 3.7 [−15.49]	0.96	
		(b)	–	–	0.90	
Ag^+	H_2O	(a)	0.07 [0.29]	11.0 [46.05]	2.36	
		(b)	−2.09 [− 8.75]	0.3 [1.26]	1.59	
Tl^+	H_2O	(a)	−3.62 [−15.15]	− 1.0 [− 4.19]	2.44	
		(b)	−4.29 [−17.96]	− 6.0 [−25.12]	1.83	
Hg_2^{2+}	H_2O	(a)	−2.16 [− 9.04]	1.6 [6.70]	1.93	
		(b)	−4.29 [−17.96]	− 7.4 [−30.98]	2.57	
Sr^{2+}	H_2O	(a)	−3.68 [−15.40]	2.5 [10.47]	3.24	
		(b)	−3.16 [−13.13]	1.5 [6.28]	2.64	
Ba^{2+}	H_2O	(a)	−4.92 [−20.60]	− 0.2 [− 0.84]	3.57	
		(b)	−6.20 [−25.95]	− 5.8 [−24.28]	3.27	
Pb^{2+}	H_2O	(a)	−5.58 [−23.36]	3.9 [16.33]	4.95	
		(b)	−4.21 [−17.62]	6.2 [25.95]	4.43	
Hg^{2+}	H_2O	(a)	−0.71 [− 2.97]	10.2 [42.70]	2.75	
		(b)	−2.55 [−10.67]	3.3 [13.81]	2.60	



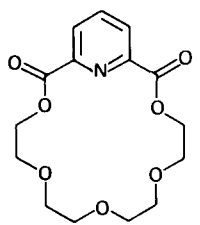
(60)

Na^+	MeOH	−2.27 [− 9.50]	1.1 [4.60]	2.5	70
K^+	MeOH	−5.87 [−24.57]	− 2.06 [− 8.62]	2.79	
Ba^{2+}	MeOH	−0.46 [− 1.93]	3.8 [15.50]		



(61a)

Na^+	MeOH	−5.44 [−22.77]	0.14 [0.59]	4.09	70
K^+	MeOH	−9.11 [−38.09]	− 1.8 [− 7.53]	5.35	
Ba^{2+}	MeOH	−7.72 [−32.32]	0.5 [2.09]	>6	



(61b)

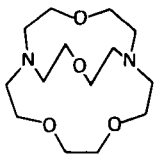
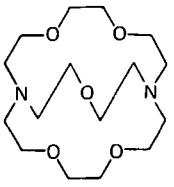
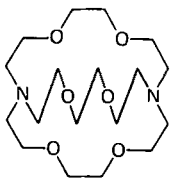
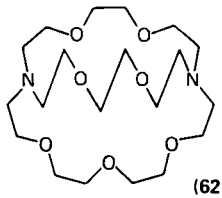
Na^+	MeOH	−6.19 [−25.91]	− 0.34 [− 1.42]	4.29	70
K^+	MeOH	−9.3 [−38.93]	− 2.9 [−12.14]	4.66	
Ba^{2+}	MeOH	−6.03 [−25.24]	− 0.11 [− 0.46]	4.34	

occur under these conditions; this is emphasized by the fact that apart from cocrystallisates (see Section IV.B.1.b), no solid uranyl complexes of [18]crown-6 have been discovered so far.

Thermodynamic data of the complexation of heavy metal ions (Ag^+, Hg^{2+}, Pb^{2+}) have been obtained for crown ethers of various ring size including exchange of oxygen centres by *sulphur*[69].

The thermodynamic origin for differences in complexation between the [18]crown-6-type macrocycles containing *carbonyl oxygen* and those, that do not, seems to vary (see Table 8)[70]. Comparing the two *pyridine-containing* ligands **61a**

TABLE 9. Free energies, enthalpies and entropies of complexation by bicyclic ligands in water at 25°C[75]

Ligand	Cation	ΔG^0 (kcal/mol) [kJ/mol]	ΔH^0 (kcal/mol) [kJ/mol]	ΔS^0 (cal/K/mol) [J/K/mol]
 (54) [2.1.1]	Li^+	− 7.5 [−31.4]	− 5.1 [−21.35]	8 [33.5]
	Na^+	− 4.5 [−18.8]	− 5.4 [−22.60]	− 3 [−12.6]
	Ca^{2+}	− 3.4 [−14.2]	− 0.1 [− 0.42]	11.1 [49.4]
 (55) [2.2.1]	Li^+	− 3.4 [−14.2]		11.4 [47.7]
	Na^+	− 7.2 [−30.1]	− 5.35 [−22.40]	6.2 [25.9]
	K^+	− 5.4 [−22.6]	− 6.8 [−28.47]	− 4.7 [−19.7]
	Rb^+	− 3.45 [−14.4]	− 5.4 [−22.60]	− 6.5 [−27.2]
	Ca^{2+}	− 9.5 [−39.8]	− 2.9 [−12.14]	22 [92.1]
	Sr^{2+}	−10.0 [−41.9]	− 6.1 [−25.95]	13.1 [54.8]
	Ba^{2+}	− 8.6 [−36.0]	− 6.3 [−26.37]	7.7 [32.2]
 (19) [2.2.2]	Na^+	− 5.3 [−22.2]	− 7.4 [−30.98]	− 7 [−29.3]
	K^+	− 7.2 [−30.1]	−11.4 [−47.72]	−14.1 [−59.0]
	Rb^+	− 5.9 [−24.7]	−11.8 [−49.40]	−19.8 [−82.9]
	Ca^{2+}	− 6.10 [−25.1]	− 0.2 [− 0.84]	19.5 [81.6]
	Sr^{2+}	−10.9 [−45.6]	−10.3 [−43.12]	2 [8.4]
	Ba^{2+}	−12.9 [−54.0]	−14.1 [−59.02]	− 4.0 [−16.7]
 (62) [3.2.2]	K^+	− 3.0 [−12.6]	− 3.0 [−12.56]	0 [0]
	Rb^+	− 2.8 [−11.7]	− 4.2 [−17.58]	− 4.7 [−19.7]
	Cs^+	− 2.45 [−10.3]	− 5.4 [−22.60]	− 9.9 [−41.4]
	Ca^{2+}	− 2.7 [−11.3]	0.16 [0.67]	9.6 [40.2]
	Sr^{2+}	− 4.6 [−19.3]	− 3.3 [−13.81]	4.4 [18.4]
	Ba^{2+}	− 8.2 [−34.3]	− 6.2 [−25.95]	6.7 [28.0]

and **61b**, in all cases the stability of complexes of the ligand without carbonyl groups is entropy-favoured. ΔH^0 varies little with no systematic trend. Comparison between **2** and **60** shows that the entropy term favours complexes of the ligand with carbonyl groups, while the enthalpy term for this ligand is comparatively very unfavourable. As Table 8 shows, the increased stability of complexes of **61b** over that of complexes of the parent macrocycle **60** is due almost entirely to the enthalpy term in the case of the monovalent cations. However, a significant drop in entropy stabilization for the Ba^{2+} complex of **61b** from that of **60** results in the reversal of the K^+/Ba^{2+} selectivity sequence between these two ligands.

Cram and coworkers studied the free energies of association between polyethers and *t*-butylammonium salts[71]. For thirteen different eighteen-membered crown ether rings in chloroform (at 24°C) ΔG^0 values lying between −9.0 and −2.9 kcal/mol and depending on the structure of the crown ether were found. Furthermore, *ab initio* molecular orbital calculations of the relative values of the binding energies were drawn up[71,72] and shown to be in qualitative agreement with experimental results.

Regarding the thermodynamics of protonation of the cyclic *oligooxadiaza ligand* **6**[73], the bicyclic **19** and the corresponding open-chain diamine analogue with typical primary, secondary and tertiary amines, the data obtained for the substituent effect[74] cannot be simply correlated. This is understandable, since in the cyclic systems the N atoms can no more be arranged strain-free and the N–N distance is greatly reduced. It can be taken for granted that both H atoms of the diprotonated cyclic ligand are located inside its cavity. This desolvates the protons very strongly, particularly in the case of the bicyclic ligands, thereby causing an increase of ΔS^0 and ΔH^0 compared to normal diamines.

Calorimetric measurements of alkali and alkaline earth metal complexation by *macrobicyclic cryptands* show that here also enthalpy and entropy changes play an

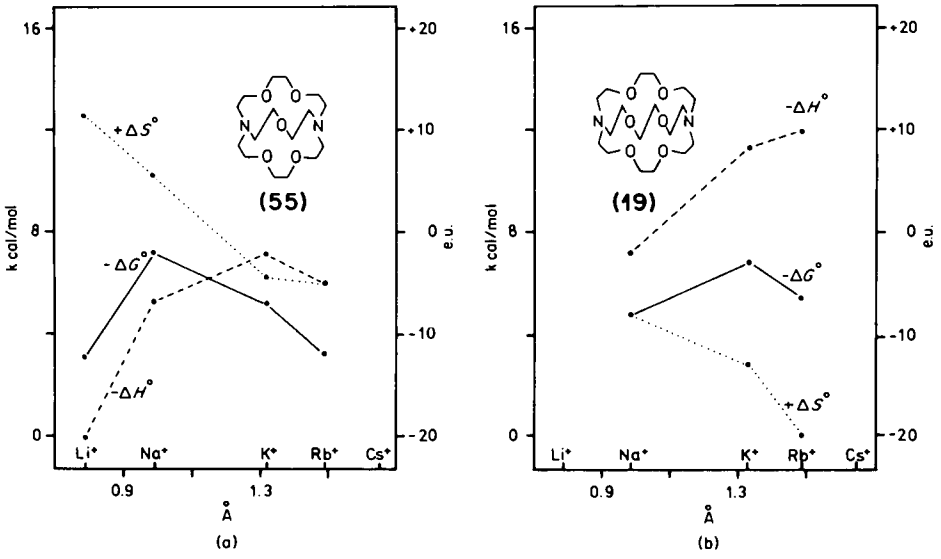
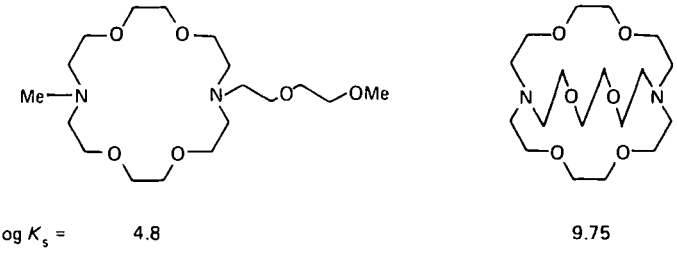


FIGURE 9. Free energies $-\Delta G^0$, enthalpies $-\Delta H^0$ and entropies $+\Delta S^0$ of cryptate formation by several alkali cations with (a) [2.2.1]- and (b) [2.2.2] cryptands in water at 25°C.



$\log K_s$ = 4.8 9.75

$\Delta \log K_s = 4.95$

FIGURE 10. Stability constants ($\log K_S$) of K^+ complexation in MeOH/H_2O (95 : 5)[14d]: *macrobicyclic effect* ([2] cryptate effect).

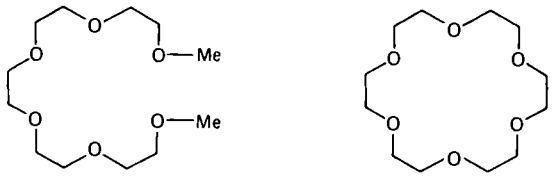
important role[75]. Particularly noteworthy are the high enthalpies and the negative entropies of the complexes with alkali cations such as Na^+, K^+, Rb^+ and Cs^+ (see Table 9). Alkaline earth cryptates (Sr^{2+}, Ba^{2+}) just like the Li[2.1.1] and Na[2.2.1] complexes are marked by dominant enthalpy changes apart from a similarly favourable entropy change. The Ca^{2+} cryptates (and the Li[2.2.1] complex), with a heat of reaction of nearly zero, are completely entropy-stabilized.

The complexation enthalpies show selectivity peaks for various cations in contrast to the entropies (Figure 9)[75]. The entropy term may nevertheless lead to marked differences between enthalpy and free energy selectivities. Thus the selectivity peaks observed in the stability constants of cryptates are intrinsically of enthalpic origin.

The high stability of macrobicyclic complexes compared with analogous monocyclic complexes (Figure 10) is caused by a favourable enthalpy, and is termed the '*macrobicyclic*' or '*cryptate effect*', or more specifically the '*[2]cryptate effect*'[14c,d]. In the case of the topological tricyclic cryptands, one similarly speaks of a *macrotricyclic* or *[3]cryptate effect* etc.

The cryptate effect is enthalpy-influenced[75], which is attributable to the strong interactions of the cation with the poorly solvated polydentate ligand of macrobicyclic topology.

Open-chain podands usually show smaller ΔG^0 or K_S values of complexation than macrocyclic crown ethers[76] (Figure 11, $\Delta \log K_S = 3–4$) or bicyclic cryptands



$\log K_s$ = 2.2 6.1

$\Delta \log K_s = 3.9$

FIGURE 11. Stability constants ($\log K_S$), of K^+ complexation in MeOH[76]: *macrocyclic effect* ([1] cryptate effect).

(Figure 10, $\Delta \log K_s = 7-9$)[14d,65]. With reference to the effective [2]cryptate effect of bicyclic cryptands, a so-called *macrocyclic* (or *[1]cryptate*) effect[14c] for monocyclic crowns has been defined.

More thorough investigations reveal that this is partly caused by a loss of degree of freedom of the open-chain ligand, but more often by a weaker solvation of the complexed cyclic ligand[14d,65,77]. A more accurate elucidation of these results from the point of view of enthalpic and entropic contributions due to solvation and conformation is experimentally difficult[78].

The still effective '*chelate effect*'[14c,79] of open-chain multidentate podands compared with simple monodentate compounds such as ROR and R_3N is often entropy-influenced, though the complexation entropies may differ a great deal according to the type of the podand (see below).

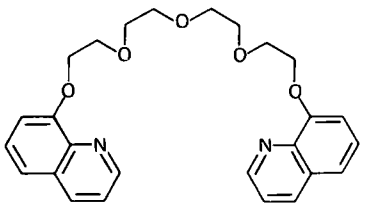
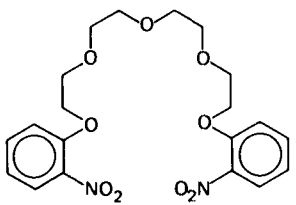
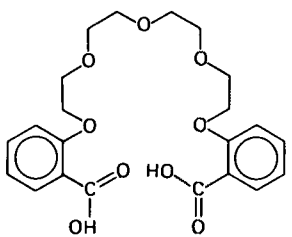
Since the complexation of *podands* has only recently been investigated and detailed results are meanwhile available[64], but still not summarized, it seems proper at this point to give a more thorough description of the subject.

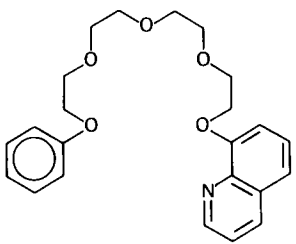
Table 10 shows that the complex stability (ΔG^0) of the noncyclic ligands **34c**, **35b**, **35c**, **39** and **47** is entirely of enthalpic origin accompanied by an unfavourable loss of entropy. The ΔH^0 values of the noncyclic compounds between -20 and -70 kJ/mol are comparable to the values obtained for cyclic complexones in methanol (cf. Table 8); however, for some complexes the decrease of entropy is remarkably high. The largest negative entropies of complexation among the aromatic tetraethylene glycol ethers were found for the lithium complex of **34c**, the sodium complex of **35c** and the potassium complex of **47**. Maximum values of ~ -200 J/K/mol are reached with the rubidium and caesium complexes of the tripodand **39**.

Table 10 also illustrates the influence of the cation size on ΔG^0, ΔH^0 and ΔS^0 of the ligands measured. The dependency of open-chain ligand **34c** regarding the ionic radius is opposite to that of the tripodand **39**, for which values of reaction enthalpy and entropy decrease on going from the lithium complex to the rubidium-complex. For the K^+ and Rb^+ complexes of **34c** the entropy loss is practically zero, while the enthalpic terms reach a negative plateau for the bigger K^+, Rb^+ and Cs^+ cations. In the case of complexones **34c** and **35c** the heat of reaction and the loss of entropy decrease with increasing ionic radius. The reaction enthalpies of the lithium and sodium complexes of **35c** are strongly temperature-dependent, as shown by the large values of the molar heat capacities: ΔC_p^0 (Li^+) = 1 kJ/K/mol and ΔC_p^0 (Na^+) = 4 kJ/K/mol. Ligand **39**, however, behaves like the cyclic complexones; the values of ΔH^0 and ΔS^0 become more negative with increasing ionic radius.

These experimental results have been discussed in the light of different intrinsic contributions to enthalpy and entropy[64]. The *complexation enthalpy* can be split into the contributions from the *cation* and those from the *ligand*. The bonds of the metal ions with the solvent molecules are partly or totally substituted by the bonds to the polar groups of the ligand. Also, the difference between the solvation enthalpies of the solvent molecules outside the complex and outside the first solvation shell of the free metal ion has to be taken into consideration. The changes of the enthalpy of the ligand by complexation are mainly due to the changes of solvation, intramolecular ligand–ligand repulsions, to the stacking of the aromatic residues and the steric deformation of the ligand induced by the bound metal ion. In methanol, the electrostatic interaction between the metal ion and the coordinating sites of the ligand represents one of the important driving forces of the complexation enthalpy, because the counteracting interaction with solvent mole-

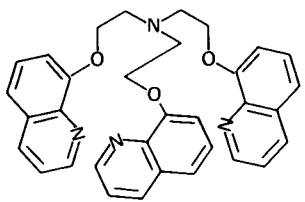
TABLE 10. Thermodynamics of alkali metal ion complex formation with open-chain ligands at 25°C in MeOH[64]

Ligand	Cation	ΔG° (kJ/mol)	ΔH° (kJ/mol)	ΔS° (J/K/mol)	ΔC_p° (J/K/mol)
 (34c)	Li^+	−13.4	−63	−170	4×10^2
	Na^+	−18.4	−36	− 59	1.2×10^2
	K^+	−20.1	−21	− 3	
	Rb^+	−17.6	−20	− 7	
	Cs^+	−15.0	−25	− 33	
 (35b)	K^+	− 9.2	−29	− 67	–
 (35c)	Li^+	−19.7	−41	− 70	1.1×10^3
	Na^+	−19.7	−68	−160	3.8×10^3
	K^+	−20.1	−33	− 22	6.7×10^2
	Rb^+	−18.4	−25	− 23	0.6×10^2
	Cs^+	−11.0	−24	− 40	1.3×10^2



(47)

K^+	−10.5	−59	− 1.6×10^2	−



(39)

Li^+	−13	−29	− 20	−
Na^+	−20.9	−35	− 46	−
K^+	−14.6	−50	−119	−
Rb^+	−11.7	−66	−184	6×10^2
Cs^+	− 8.8	−50	−140	8×10^2

cules is relatively small, as compared to the corresponding interactions in aqueous solution. If the solvent molecules are not too tightly bound, the uptake of the small cations by the ligand should be favoured. The tripodand **39**, however, prefers the large cations as far as the enthalpies are concerned. This may be due to the fact that binding of the small ions leads to an unfavourable conformation of the ligand. In contrast, ligand **34c** prefers the small cations, because the electrostatic attraction is the dominant increment of the negative complexation enthalpy. Because of the high flexibility of the open-chain compounds, sterically unfavourable conformations can be avoided. Furthermore, the stacking energy of the terminal aromatic moieties contributes to the negative ΔH^0 values.

The complex formation for the glyme-analogous **34c**, **35b**, **35c** and **47** and tripodand **39** is enthalpically favoured but entropically disfavoured (see Table 10).

As in the discussion of the enthalpy values a more thorough understanding of the *entropy values* is achieved considering the various intrinsic contributions: for the linear ligands **34c** and **35c** the dependence of the complexation entropy on the ionic radius is opposite to that of the cyclic (Table 8) and bicyclic complexones (Table 9). Here, the release of the solvation shell has to be overcompensated by the other contributions to the complexation entropy. The metal ion may not be completely desolvated. The change of the topology of ligand from a linear conformation in the uncomplexed state to a helical conformation in the complex state leads to a large loss of entropy. This is supported by the experimental finding that the decrease of entropy due to complexation is smallest for the uptake of those cations which do not induce steric deformations of the ligand structure: K^+ and Rb^+ ions fit well into the sterically optimum cavity of ligand **34c**. Thus, the favoured stability of the K^+ complex of ligand **34c** is the consequence of the absence of a destabilizing loss of entropy, and correspondingly the lability of the Li^+ complex is due to the entropy-unfavourable conformational changes of the ligand. Addition and/or variation of the donor groups in the *ortho* position of the terminal aromatic moiety shift the complexation entropy of the K^+ complexes by nearly two orders of magnitude (see Table 10). The podand **39** is much more restricted in its conformational flexibility than the compounds **34c** and **35c**. Thus, the differences of the solvation and of the internal entropies of the ligand between the free and the complexed state are comparably small, and, instead, the difference of the translational entropy due to the release of the solvation shell controls the dependence of the complexation entropy on ionic radius[64].

Recent ^{23}Na-NMR investigations[80] about the thermodynamics of complexation of open-chain podand **35e** with Na cations in pyridine as solvent gave the following results: $\Delta H^0 = -17$ kcal/mol (-71 kJ/mol), $\Delta S^0 = -48$ cal/K/mol (-201 J/K/mol). The very negative ΔS^0 value points to a cyclization or/and polymerization entropy. For a discussion of the X-ray analysis of the K^+ complex of **35e** see Section IV.B.3.b(1). The Na^+ complexation forces the podand to adopt a particularly well-arranged conformation, in which most (or all) of the oxygen donor atoms form van der Waals' bonds to the enclosed sodium ion, thus causing the relatively big enthalpy change. The complexation of **35e** in solution is enthalpy-driven. From ^{23}Na-NMR results, it is to be concluded that the interaction of the open-chain podand **35e** with sodium can best be described by a successive wrap of the sodium cation by the heptadentate ligand.

Thus, with the help of a few concrete examples, it is shown how the various ligand, cation and medium parameters of single thermodynamic data like ΔG^0, ΔH^0, ΔS^0 and ΔC_p^0 are differently influenced, the effects being reflected in the complex stabilities and particularly also in the complexation selectivities.

III. COMPLEX STABILITIES AND SELECTIVITIES

A. General Remarks

The formation of a 'complex' by association of two or more chemical units is one of the most basic molecular processes and of utmost importance in chemistry, physics and biology.

A *host–guest complex*, unlike covalent bonds, arises mostly through weak bond interactions (hydrogen bonding, metal-to-ligand bonding, pole–dipole binding forces, dipole–dipole binding forces, hydrophobic bindings etc.)[81]. Such relatively weak molecular interactions should be a subject of intensified research on the basis of molecular recognition between two chemical units in future, since molecular information is transferred during the process of complexation[14c].

In living creatures, highly specific and complicated molecular aggregates play an important role in *enzyme–substrate interactions*, the *replication of nucleic acids*, the *biosynthesis of proteins*, in *membranes* and in *antigen–antibody reactions*[34]. Their stability, selectivity, structure and reactivity are complicated functions of many variables.

There is a striking similarity between the metal ion selectivity of some antibiotics and certain macrocyclic ligands[7b]. It has proved, therefore, important to synthesize simpler host molecules as model substances and study their analogous interactions with substrates[14e,16g,16m,16n,18b,18c,82]. These investigations have led to a series of results concerning the ligand structure, complex stability and selectivity with diverse guest molecules in various solvents. In this way, it has been possible to separate various variables and achieve an analysis of structural interactions. The different variables can then not only be analysed, but also be controlled[14c,81].

B. Definition of the Complex Stability Constant and of the Selectivity of Complexation

The complexation process between a ligand L and a cation M^{n+} in solvent S may be represented by the general equation (7), where $\vec{k}$, $\overleftarrow{k}$ are defined as the rate

$$(L)_{solv.} + (M^{n+},mS) \underset{\overleftarrow{k}}{\overset{\vec{k}}{\rightleftharpoons}} (L,M^{n+})_{solv.} + mS \qquad (7)$$

constants of formation and dissociation of a complex (see Section II.B.1 and II.B.2). The quotient of $\vec{k}/\overleftarrow{k}$ gives the *stability constant* K_s (kinetic derivation of the stability, cf. Section II.B.1). The *thermodynamic* stability constant K_{th} can be given by equation (8), where f_C, f_L and f_M are the activity coefficients of the three

$$K_{th} = \frac{f_C[L,M^{n+}]}{f_L[L]\,f_M[M^{n+}]} \qquad (8)$$

species present (complex, ligand, cation). Since these coefficients are generally unknown, however, the stability constants K_s (equation 9), based on the concentrations, are usually employed. K_s is an average stability constant for the system in

$$K_s = K_{th}\frac{f_L f_M}{f_C} = \frac{[L,M^{n+}]}{[L]\,[M^{n+}]} \qquad (9)$$

thermodynamic equilibrium on the basis of ligand conformation and complexation[14c].

The relationship between K_s and the free enthalpy of formation ΔG^0 of a complex is given by the following equation (10)[7b]:

$$\Delta G^0 = -RT \ln K_s \tag{10}$$

K_s values are known for many complexes[8b] and a list is given in Tables 4–8, 11, 12, 15. These values also reflect the socalled selectivities of complex formation of the ligands.

'*Selectivity* is concerned with the ability of a given ligand to discriminate among the different cations'[14c]. A measure for the selectivity of a particular ligand with respect to two different metal ions M_1 and M_2 is, per definition (equation 11), the ratio of the stability constants of the complexes LM_1 and LM_2 (L = ligand, M = metal cation). High complex stability, often desirable, does not necessarily

$$\text{Selectivity} = \frac{K_s(LM_1)}{K_s(LM_2)} \tag{11}$$

mean high selectivity. Crown ethers with low complex stability constants may be highly selective; thus this knowledge has proved to be very valuable for the design of carrier molecules for use, e.g. in ion-selective electrodes[27,83].

C. Methods for Determination of Complex and Selectivity Constants

The following methods or devices have been employed for the experimental determination of the complex stability constants K_s : *cation selective electrodes*[76a,84], *pH-metric* methods[33b,85], *conductometry*[51,86], *calorimetry*[67–70,87], *temperature jump* measurements[7b,37,49,57,64], *NMR*[80,88], *ORD*[89], *solvent extraction*[90] and *osmometry*[91]. These methods have been discussed in several reviews[7a,b,d]. It is to be mentioned that cation selective or cation specific organic neutral ligand systems of the crown ether type have proved to be useful in ion-selective electrode systems themselves[6c,6d,27,92].

An advantage and at the same time a drawback associated with the numerous possibilities of measurement is that the complex constants listed in the Tables 4–8, 11, 12, 15 have been obtained according to different methods (often in different solvents) and therefore, cannot be readily compared with one another.

D. Factors Influencing Stability and Selectivity

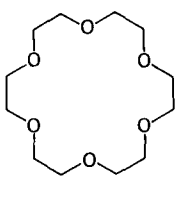
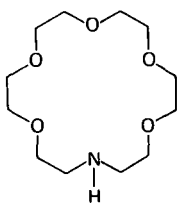
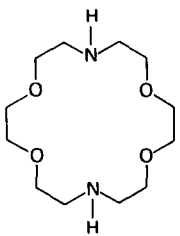
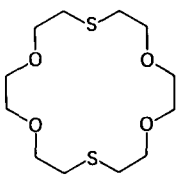
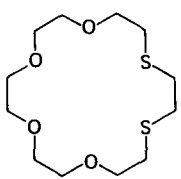
In the following, an attempt is made to discuss the different factors in order to work out their specific influences on the complexation. In reality the several parameters are often strongly connected with each other.

1. Ligand parameters

a. Binding sites. A crown ether may be considered to be a collection of donor heteroatoms (O,N,S,P) distributed strategically. It is clear that the kind of donors employed has a big influence on the complexation behaviour.

(1) *Donor atom type.* In classical crown ethers, *ether oxygens* have been used as donor site[93] As *A-type donors*[66,94], they should most favourably combine with, *A-type metal ions* (alkali/alkaline earth, lanthanide ions) according to the 'hard and soft acid–base' principle[95]. Thus, complexes of purely oxygen crown ethers such as **1**, **2** and **8** with salts of the above cations tend to give high K_s values[8b] (see

TABLE 11. Comparison of log K_S values for the complexation of [18]crown-6 and of some aza and thia analogues with K^+ and Ag^+[69,76a]

Cation	Ligand				
					
	(2)	(63)	(6)	(64)	(65)
K^+ [a]	6.10	3.90	2.04	1.15	–
Ag^+ [b]	1.60	3.30	7.80	4.34	3.0

[a] In CH_3OH.
[b] In H_2O.

Sections II.B.3.b and II.C.3, Table 4). *B-type cations* (Cu^{2+}, Ag^{+}, Co^{2+}, Ni^{2+}, etc.) should less compatibly combine with the 'hard' ether oxygens, thereby resulting in lower stabilities of the complexes, as shown in practice (cf. **2** in Table 11).

On the other hand, such cations interact favourably with 'soft' *B-type donors* like N,S[94]. Investigations on the stepwise substitution of *nitrogen* or *sulphur* atoms in crown ether skeletons and about their stabilizing/destabilizing influences on complexation have already been carried out[76a].

The K_S values of a series of *thia analogues* with [9]crown-3, [12]crown-4, [15]crown-5, [18]crown-6 and [24]crown-8 skeletons have been determined[69,70b] (e.g. **64** and **65**; see Table 11). They are, as expected, very low for alkali/alkaline earth ions, but high for transition metal ions. Substitution of an oxygen in benzocrown ethers by an *NH group* reduces their ability to extract alkali picrates into organic phases[96].

The complex constants of *bicyclic systems* are likewise influenced: The *polyaza ligands* **66**–**68** show lower K_S values for alkali/alkaline earth ions compared to the parent compound, [2.2.2]cryptand (**19**) (Table 12)[85b,97]. The effect is particularly pronounced for the K^{+} complexes of the methylaza cryptands **66**–**68**, the complex stabilities constantly diminishing by a factor of ~10 upon successive substitution of an O by an NCH_3 binding site. Since the dipole moment of the NCH_3 group is smaller than that of O, the substitution of O by NCH_3 leads to a decrease of the electrostatic interaction between cation and ligand. Moreover, the van der Waals' diameter of N is somewhat bigger than that of O (1.5, compared to 1.4 Å), so that the cavity formed by a polyaza cryptand should be a bit smaller [see Section III.D.1.b(1)]. The different hydration of N- compared to O-binding sites should also play a role.

The *selectivities* of complexation are influenced by the substitution of O by N or S donor sites. For instance, the peak selectivity for K^{+} flattens increasingly on going from **19** to **67** or **68**[85b]. While **66** still shows comparable selectivities, **67** hardly shows any.

The experimental results may essentially be summarized as follows[14c,14d,76a] (see Tables 11, 12):

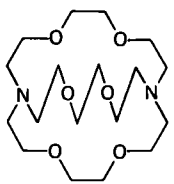
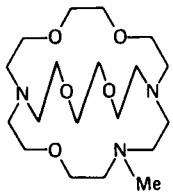
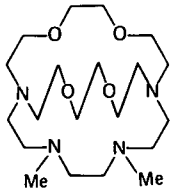
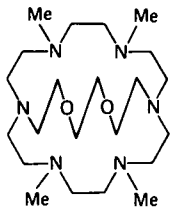
(a) Substitution of ether oxygen atoms by *sulphur* generally reduces the binding ability toward alkali/alkaline earth metal ions, leaving it unchanged or causing it to increase toward Ag^{+}, Pb^{2+}, Hg^{2+} and similar ions.
(b) Incorporation of *nitrogen* atoms has a favourable influence on the complexation of B-type ions; the coordination of alkali metal ions is much less weakened.

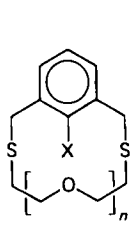
O and N donor atoms, that are integrated in *functional groups*, partly cause other gradations of complex stability and selectivity: Thus *acetal oxygen* atoms, for example, are less effective than $O-CH_2-CH_2-O-$ groups[2,98].

For macrocyclic systems containing one to three β-*diketone* units, constants of complex formation lying $10^{1.8}-10^{6.3}$ times higher than for the corresponding open-chain model substances are found[99].

The influence or coordinating ability of *intraannular functional groups* in cyclic crown ethers **69** was first described by Weber and Vögtle[100]. Cram and coworkers[101] investigated systematically the characteristics (association constants) of the intraannularly substituted macrocyclic polyethers **70** containing *halogen, OH, OMe, CN, COOMe, COOH* as donor groups X.

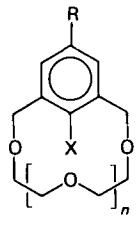
TABLE 12. Stabilities (log K_S) of [2.2.2] and some aza analogues [2.2.2] cryptands with alkali/alkaline earth and heavy metal ions (in H_2O at 25°C)[85b,97]

Cation	 (19)	 (66)	 (67)	 (68)
Li^+	<2	1.5	2.4	–
Na^+	3.9	3.0	2.5	–
K^+	5.4	4.2	2.7	1.7
Rb^+	4.3	3.0	2.3	–
Cs^+	<2	<2	<2.0	–
Mg^{2+}	2	1.9	2.6	–
Ca^{2+}	4.4	4.6	4.3	1.5
Sr^{2+}	8.0	7.4	6.1	1.5
Ba^{2+}	9.5	9.0	6.7	3.7
Ag^+	9.6	10.8	11.5	13.0
Co^{2+}	≤2.5	5.2	4.9	5.3
Ni^{2+}	≤3.5	5.0	5.1	5.7
Cu^{2+}	6.8	9.7	12.7	12.5
Zn^{2+}	≤2.5	6.3	6.0	6.8
Cd^{2+}	7.1	9.6	12.0	10.7
Hg^{2+}	18.5	21.7	24.9	26.1
Pb^{2+}	12.7	14.1	15.3	15.5



(69)

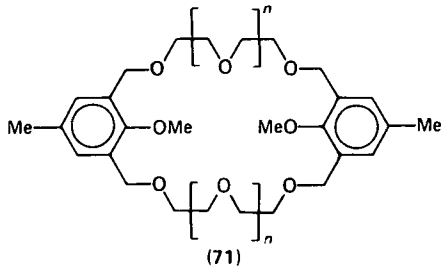
X = H, Cl, Br, OH, SH, NH_2, OMe, CN, COOH, COOMe



(70)

R = H, Me, *t*-Bu, NO_2, CN, COOEt

(n = 1–4,7)



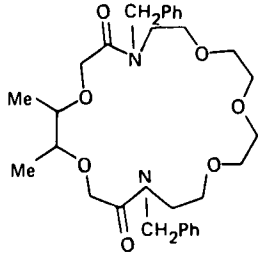
(71)

n = 0,1

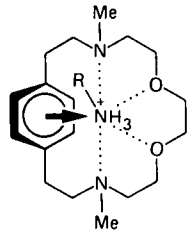
In the case of the eighteen-membered rings **70** (n = 3, R = Me) the K_s values are in the order of $CO_2Me > OMe > H$ for all cations examined, apart from K^+, for which the order of $OMe > CO_2Me > H$ is found[101b]. According to molecular models, the conformation of the complexes should be such that the plane of the benzene ring is rotated approximately 30–60° out of plane of the macro ring (X-ray structure of an analogous *t*-butylammonium salt complex, see Figure 25 in Section IV.B.1.a). Owing to two opposing methoxyphenyl units in **71**, a series of degrees of freedom of the ligand are frozen; thus, formation of cavities for guest molecules is encumbered (see Section III.D.1.c) and the complex constants are comparably low[101b]. In the series of **70** the phenol (X = OH) represents the worst ligand, since the compound forms transannular hydrogen bonds which must be cleaved during cation complexation[102]. Intraannular donor centres may also consist of acidic groups suitable for salt formation. Thus the carboxylic acid **70** (n = 3, X = COOH), in particular, forms a crystalline 1 : 1 salt with *t*-butylamine in cyclohexane/dichloromethane[18c]. These inwards directed substituents act as additional binding sites for cationic guests. The possibility, that they can also act as catalytic sites, is being explored[101a].

Suitably located *pyridine-nitrogen, furane-oxygen, thiophene-sulphur* atoms[8f] (see Figure 1) coordinate as a rule[18a,71,81,103]. They may be useful in achieving particular selectivities, e.g. in increasing the Na^+ selectivity[100,104].

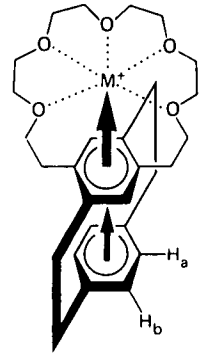
In cyclic and open-chain crown ethers, containing *amide* (**42** and **43**, see Figure 7; **72**) and *ester* functions (**60** and **61b**, see Table 8), the carbonyl groups can cooperatively act as donor centres[105]. Thus ligand **72** is ten times more selective for Ca^{2+} than for Ba^{2+} [106]. Substitution of the coordinating methoxy end-groups of open-chain crown ethers **35a** by primary amide (**35e**, **35f**) or ester groups (**35d**) (Figure 5) reduces the complexing ability of the ligand skeleton[107].



(72)



(73)



(74)

R = Me, *i*-Pr, *t*-Bu, CH_2Ph, CHMePh

Stoichiometric alkaline earth salt complexes of oligoethylene glycols have only lately been systematically synthesized[33]. Thus, it has been shown that even ethylene glycol itself forms a crystalline 1 : 1 complex with $Ba(SCN)_2$[33a]. Similar complexes are formed by 2,6-pyridine dimethanol, diethylene glycol and (several) oligoethylene glycols[33b].

Molecular models of the complexes of primary and secondary alkylammonium salts with *diazaparacyclophane* crown ethers **73** suggest that the *π-electron system* of the aromatic ring should participate in the binding of *p*-alkylammonium cations[108]. Dynamic ^{1}H-NMR spectroscopy is consistent with chiral asymmetric complexes in solution, represented by the stabilizing interaction between the π-electron system of the phenylene ring and the alkylammonium cation, which accounts for the hindered rotation of the phenylene rings in the complex. The aromatic protons H_a and H_b of the outer benzene nucleus **74** show reasonable downfield shifts[109]. This can be explained by a *transannular π-electron release* from the outer benzene ring to the complexed inner benzene nucleus to enhance the π-complexing ability. This effect probably contributes to the high yield of the synthesis.

(2) *Donor atom number.* Since a crown ether in a cation complex is comparable to the inner solvation sphere of a metal ion (see Figure 12), the number of available donor atoms in the crown ether skeleton should, as far as possible, match the *coordination number* of the particular cation[110]. Reference points for the optimum coordination numbers of cations in the complex are provided by their

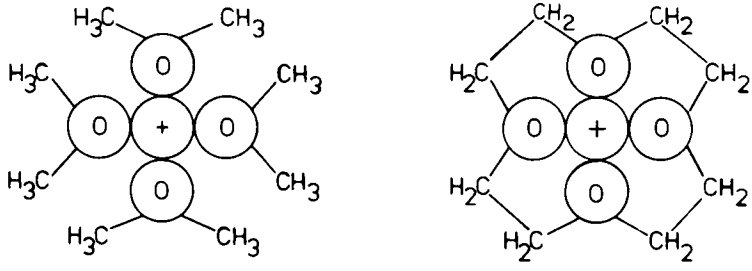
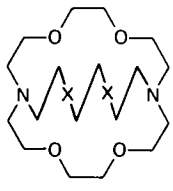


FIGURE 12. Comparison of ion solvation by dimethyl ether to ion solvation by a polyether.

coordination numbers with water molecules[111] : 6 for alkali metal ions, 4 for Be^{2+}, 6 for Mg^{2+}, and 8 for Ca^{2+}, Sr^{2+}, and Ba^{2+} respectively[112].

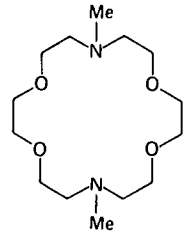
The influence of this factor is clearly revealed by a comparison of [2.2.2] *cryptand* (**19**) and [2.2.C_8] (**75**) with approximately similar size; ligand **75** differs from **19** only in the lack of a pair of O-donor sites in one of the three bridges of the [2.2.2] skeleton[113]. This leads to a reverse of the Ba^{2+}/K^+ selectivity of the order of 10^6. Thus the Ba^{2+}/K^+ ratio is 10^4 for **19**, but $<10^{-2}$ for **75**.

The fact, that *monocyclic* **76** with the same number of donor atoms as bicyclic **75** displays a Ba^{2+}/K^+ selectivity comparable to that of the octadentated cryptand **19**, could be explained by the easier accessibility of the complexed cation in **76** to solvent molecules which can saturate its unoccupied coordination sites[113].



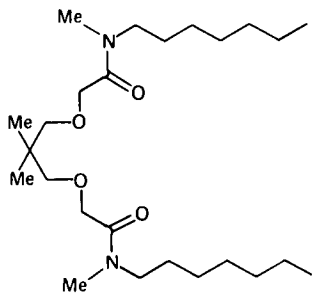
(**19**) X = O

(**75**) X = CH_2

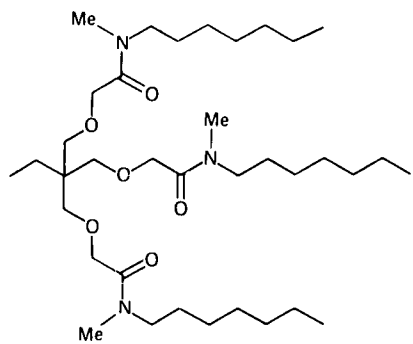


(**76**)

The 1 : 1 association constants of a few *open-chain* oligoethylene glycol ethers with different donor numbers have been determined for various metal ions potentiometrically as well as conductometrically[86b]. The K_S values and the selectivity ratio K^+/Na^+ rise with increasing number of coordination sites. The tetradentate ligand **77**, used as an ionophore in liquid membrane electrodes, shows the selectivity sequence $Li^+ > Na^+ > K^+$. By connecting another complexation arm as in tripodand **78**, the donor atom number can be increased to a total of 6 and the ligand rendered Na^+-selective[27k].



(**77**)



(**78**)

In general, *double-valent cations* should, as molecular models show, selectively be complexed by uncharged ligands with mostly big coordination numbers[112]. However, since the stoichiometry of the complex formation reaction is not known *a priori* consideration of this parameter for the design and choice of ligands remains intrinsically problematic. Other possibilities of influencing the monovalent/divalent selectivity are considered in Section III.D.1.d(1).

(3) *Arrangement of donor atoms.* The symmetrical arrangement of the donor sites in a crown ether skeleton does not seem to play an aesthetic role only[7]. Every deformation of the inner 'charge-shell', which is not in keeping with the geometry of the guest, reduces the binding ability of the ligand and the stability of the complex (host–guest relationship)[18c,81].

For *spherical* metal ions, the optimum charge-shell should also have a spherical form (see 'soccer molecule' **24**, Figure 2); for the *rod-like* azide ion, on the other hand, it should be stretched so as to look like a 'baseball' (see Section III.D.3)[14d]. Crown ethers, in which the oxygen dipole ends are not ideally located in the ring centre (cf. Figure 1), clearly show lower complex stabilities for cations[7,113]. This applies to coronands (Tables 8, 11) as well as cryptands (Tables 9, 12) and less particularly to open-chain podands.

Thus, the K^+ complexation of [18]crown-6 falls to about half on replacing a C_2H_4 by a C_3H_6 unit and again by replacement of another C_2H_4 unit[7a,7d,15d]. A more pronounced *spatial stretch* of individual donor atom pairs, e.g. through insertion of four to seven CH_2 groups (see **10**, Figure 1)[7d] or aromatic units (*o*-, *m*-, *p*-xylylene, naphthalene, biphenylene)[7d,36], leads to more unfavourable complexation (see Table 3). An overall similar effect is noted when individual donor sites are *brought together* within the crown ether skeleton as with acetal ether moieties[7d,98].

Even with a cyclic symmetrical alternating combination of ethano and propano moieties or with only propano units[114], strong stability losses of the complexes result, compared with corresponding ethanocrown ethers[7d], thus revealing the particular role played by *ethyleneoxy groups* in crown ethers[7a]. It is well known that in *five-membered* ring chelates containing a pair of binding sites (X = O,N,S), the intervening $-CH_2-CH_2-$ fragment and the coordinated metal ion are more stable than *six-membered* and *four-membered* ones[85a] (see 'chelate effect', Section II.C.3). Thus $X-CH_2-CH_2-X$ arrangements are preferable to the homologous $X-(CH_2)_{2+n}-X$ and $X-CH_2-X$ ones.

Since every unsymmetry of charge distribution in crown ethers disturbs the complexation of spherical metal ions[15d,113] – apart from donor atom specific interactions – the partial incorporation of other types of donor atoms must also be viewed within this framework. This may be quite particularly useful for gradation of selectivity [see Section III.D.1.a(1)].

b. Shape and topology. (1) *Cavity size and shape.* As was often pointed out earlier, the ratio of cation volume to crown ether/cryptand cavity plays an important role (see also Section IV.B, complex structures). Since spherical cavities, which can enclose cations, can best be formed by *cryptands*, particularly marked effects are observed here[14c].

Figure 13 shows, for instance, the results of measurements of complex constants of cryptands [2.1.1] to [3.3.3] for alkali metal ions ranging from lithium to caesium as well as for the alkaline earth metal ions Mg^{2+} to Ba^{2+}[14d,85a]. Therefore it follows that macrobicycle [2.1.1] **54** with the smallest inner volume possesses the highest K_S value for Li^+, while the cryptands [2.2.1] (**55**) and [2.2.2] (**19**) are best suited to complex Na^+ and K^+ respectively. The very big macrobicycles [3.2.2] (**62**), [3.3.2] (**79**) and [3.3.3] (**80**) combine progressively better with Cs^+ in the order given. For alkaline earth cations cavity size affects the stability constants, as in the case of alkali cations. However, the selectivity peaks (Figure 13) are much less sharp than for the alkali cryptates (see also Section III.D.1.c).

The general point, which can be derived, is that the K_S value is principally

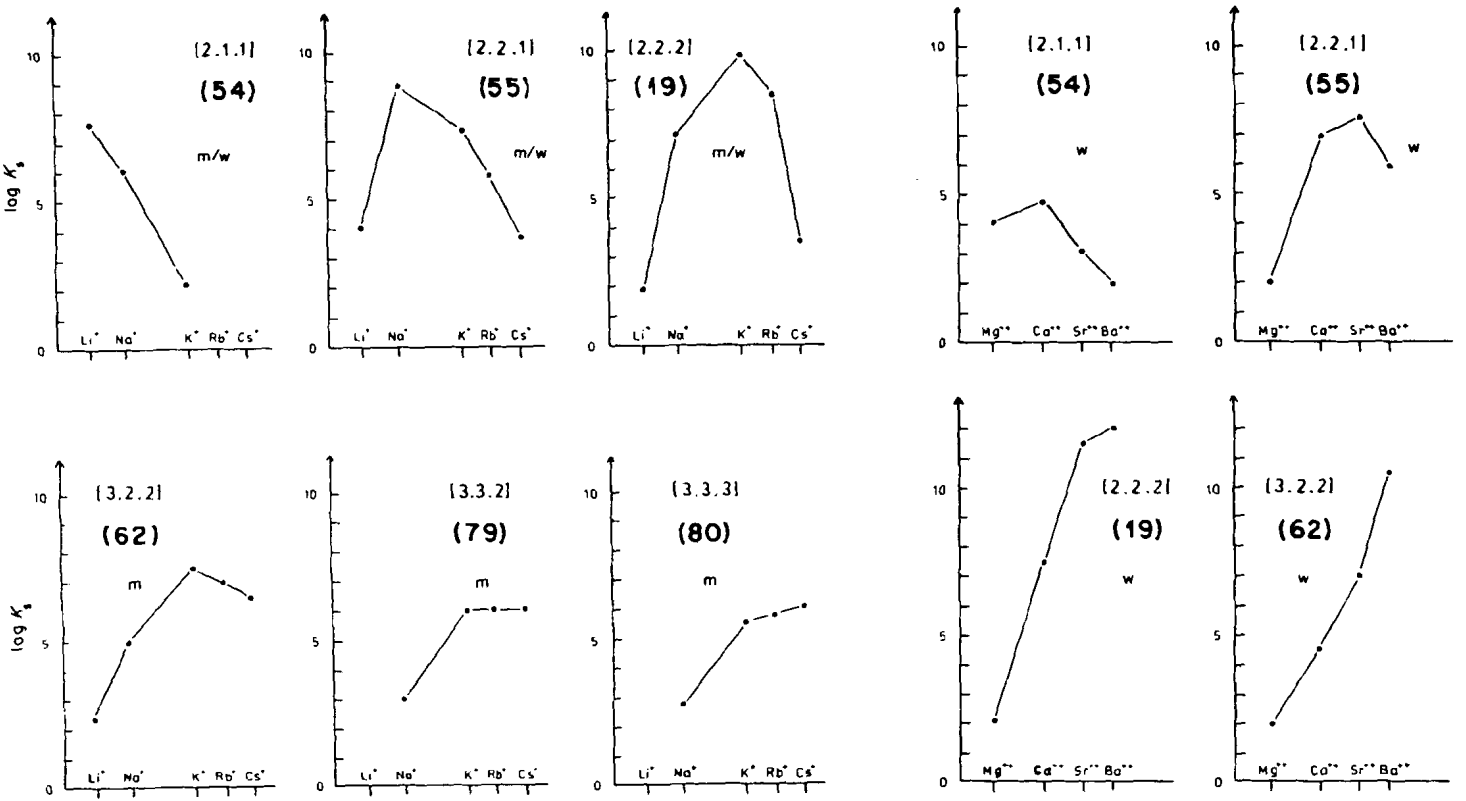


FIGURE 13. Plots of stability constants (log K_S) of various cryptates as a function of the ionic radii of alkali/alkaline earth metal cations at 25°C in 95 : 5 methanol/water (m/w) or pure methanol (m) or in water (w)[b,5a].

highest (Figure 13) and the cation fit particularly good, when the diameter of the *metal cation* roughly matches the hole diameter of the *host*[65] (see Table 13).

Similar rules apply to *coronates*[8b,c,e], as can be seen from Table 4[48], 8[67,69] and Figure 16 (Section III.D.1.c). [12]crown-4 (81) corresponds best with Li^+, [15]crown-5 (82) with Na^+, [18]crown-6 (2) with K^+ etc. (see Table 13).

An example for the influence of slightly differing cavity sizes and shapes on the complexation is given by the four isomers (*trans–anti–trans, trans–syn–trans, cis–anti–cis, cis–syn–cis*) of *dicyclohexano[18]crown-6* ligands (59)[113]. They display different complex constants for alkali metal ions like Na^+, K^+, Rb^+ and Cs^+ (Table 14). Thus the stabilities of the complexes of the *trans–anti–trans* and *trans–syn–trans* isomers with the three metal cations Na^+, K^+ and Cs^+ are lower than those of the corresponding complexes of the *cis–anti–cis* and *cis–syn–cis* isomers (see also Table 8[67b]).

With Na^+, K^+, Rb^+ and Cs^+ ions, the stability constants are higher for the *trans–syn–trans* isomers than for the *trans–anti–trans* isomers. The four isomers of dicyclohexano[18]crown-6 (59) differ most significantly in their complexing ability toward K^+ ions; log K_S values are 3.26, 4.14, 5.38 and 6.01 for the *trans–anti–trans, trans–syn–trans, cis–anti–cis* and *cis–syn–cis* isomers respectively.[115]. The fact that large ΔK_S values are observed for metal ions and also for *t*-$BuNH_3^+$ suggests that the contributions from ion–dipole interactions as well as those from hydrogen bonding, are sensitive to small conformational differences in the host[113] (cf. Section III.D.1.c).

Thus *cavity selectivity* may be used as an operational criterion for predicting selectivity of complexation.

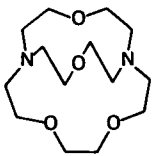
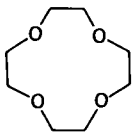
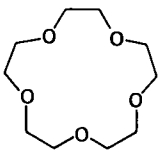
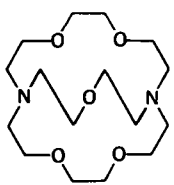
(2) *Ring number and type (ligand constitution).* The overall ligand topology (connectivity, cyclic order, dimensionality)[14c] determines the way in which ligand and cation interact and defines the type of complex formed (*podate, coronate, cryptate*). A selection of possible ligand topologies is given in Figure 14[14c] ranging from a *linear* ligand **A** (mono- or di-podand) to *cylindrical* and *spherical* cryptands **I,K**[116,117], but other systems may be imagined (see 'multi-loop crowns'). Examples are represented in the Figures 1–7.

The ligand should be able to replace as completely as possible the solvation shell of the cation during the complexation steps. Thus the stability of a complex is higher the better the ligand can envelope the cation and replace its coordination shell [see Section III.D.1.a(2), (3)]. On going from *open-chain* oligoethylene glycol ether neutral ligands of the dipod type **A** (Figures 5 and 7) via noncyclic tripod **B**, hexapod ligands (Figures 4 and 6) to *monocyclic* crown ethers **D** (Figure 1) and further to *bi-* and *oligo-cyclic* cryptands **G, I** and **K** (Figure 2), a considerable increase of the complex stability up to 10^9 (see Figures 10, 11) and often of the selectivity also (*toposelectivity*) is observed as a rule[7,8,14,85a].

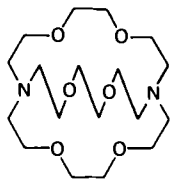
An optimum ligand (receptor, see Section II.B.4) for *cations* should be fairly rigid and held in a conformation defining a spherical cavity such as the 'soccer'-like cryptand **24**[117] (see Figure 2), possessing ten binding sites and a rigid cavity (diameter ~3.6 Å) practically ideal for complexing Cs^+ ions (diameter 3.38–3.68 Å). Thus up until now, this aesthetic ligand of high topology, I, is the best one for complexing selectively Cs^+ metal ions (log K_S = 3.4, in H_2O at 25°C)[117].

An interesting topology is shown by ligands of types **84–86**, combinations of several crown ethers with different ring size and donor atom distribution being connected by *spiro* carbon atoms[118]. Such 'morefold crown ethers' as a rule show the *multiple* selectivity of the combined crown ether rings – 85 being selective for

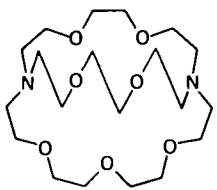
TABLE 13. Correlation of cation and cavity radii (A) of alkali/alkaline earth metal ions and of some crown ethers and cryptands

Cryptand	Cavity radius	Cation	radius	Cavity[a] radius	Coronand
 (54)	0.8	Li^+ Mg^{2+}	0.78	0.72	 (81)
		Na^+	0.98	0.92	 (82)
		Ca^{2+}	1.06		
 (55)	1.15	Sr^{2+}	1.27		

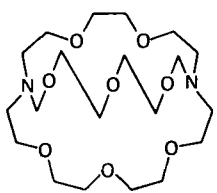
[a] 0.78 + 0.78 = 0.98 + 0.98 = 1.06 + 1.06 = 1.27 + 1.27 = 0.72 + 0.92 = 1.64



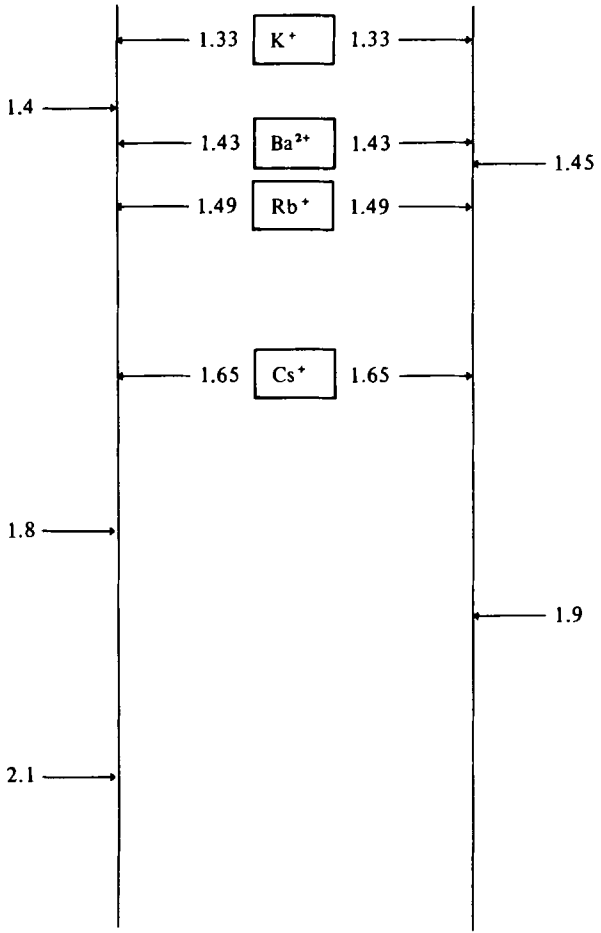
(19)

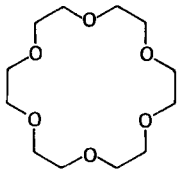


(62)

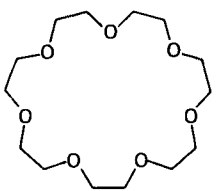


(79)



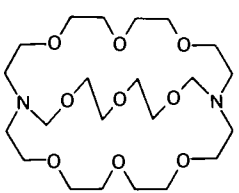


(2)



(83)

TABLE 13 – continued

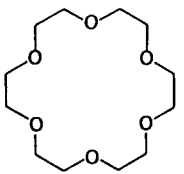
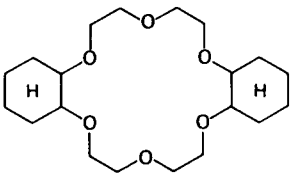


(80)

2.4 ⟶

[a]Average values.

TABLE 14. Complex stabilities (log K_S) of dicyclohexano[18]crown-6 isomers and [18]crown-6 with alkali cations (in MeOH at 25°C)[113]

Cation	Ligand				
					
	(2)	*cis–syn–cis* (59a)	*cis–anti–cis* (59b)	*trans–syn–trans* (59c)	*trans–anti–trans* (59d)
Na^+	4.32	4.08	3.68	2.99	2.52
K^+	6.10	6.01	5.38	4.14	3.26
Rb^+	5.35	–	–	3.42	2.73
Cs^+	4.70	4.61	3.49	3.00	2.27

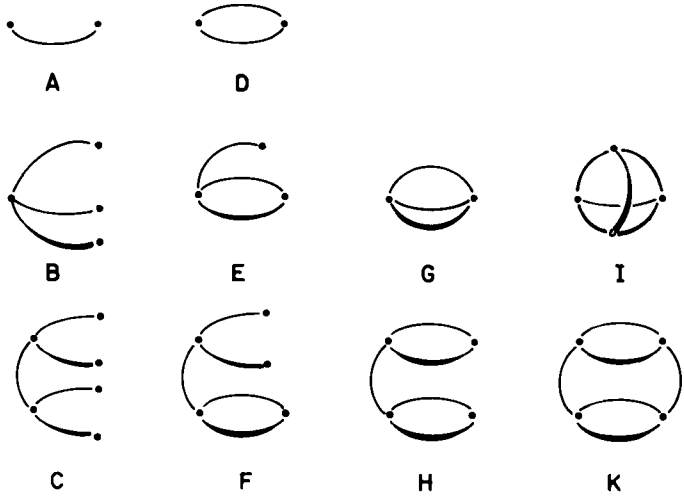
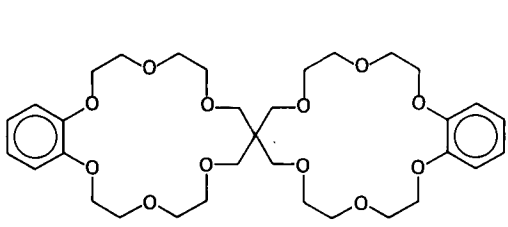
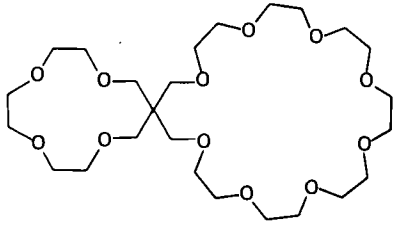


FIGURE 14. Topological representation of various types of organic ligands[14c]. A–C: acyclic (podands); D–F: monocyclic (coronands); G–H: bicyclic (coronands, cryptands); I–K: tricyclic (cryptands).

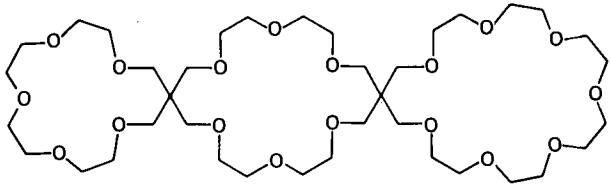
Li^+ and Cs^+, **86** for Na^+, K^+, Rb^+ etc. – but on the other side they may exhibit unexpected selectivities regarding the precipitation of ions from mixtures, that may be explained by the receptor cavities being near enough to each other for interactions between intramolecularly complexed cations.



(84)



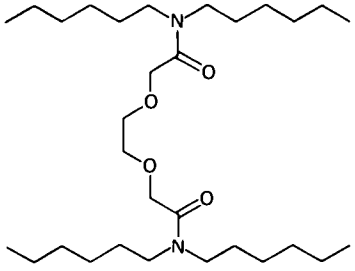
(85)



(86)

For the 3,6-dioxaoctane dicarboxamides **87** and **88** investigations have been carried out concerning the influence of *ring-closure* and *ring-size* on the ion-selectivity of a ligand-impregnated PVC/*o*-nitrophenyl octyl ether membrane and the ability to extract alkali/alkaline earth metal ions, including NH_4^+ and H^+ from an aqueous into an organic phase[119]. The results show that because of ring-closure in

88, the selectivity and extractive ability are more strongly reduced with narrowing ring, in comparison to the open-chain compound 87.



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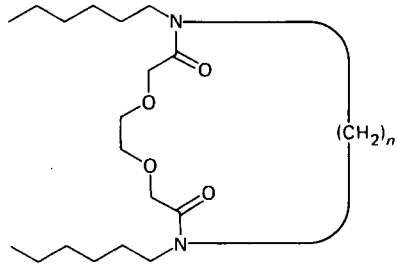


(88)

$n = 2, 6, 10$

A deeper analysis of the origin of such ring formation and (topological) ring number effects ('macrocyclic' and 'cryptate' effect') in terms of enthalpy/entropy contributions was given in Section II.C.3.

(3) *Chiral configuration.* Recognition requires the careful design of a receptor molecule presenting intermolecular complementarity[14c,14d,14e,18,81]. In particular, it involves discerning the proper interactions which will lead to substrate binding and inclusion.

Chiral recognition might be obtained by incorporating a *chiral unit* in the ligand skeleton. To this end, the ligand may contain lateral cavities serving as anchoring sites for polar groups of the substrates and a central cavity large enough for including a molecular ion[14e,81] (cf. Figure 15, 'host'). The complexation of an optically active substrate (e.g. ammonium salt) (+)-S or (−)-S by a chiral ligand (+)-L is represented by the following equations[120]:

$$(+)\text{-L} + (+)\text{-S} \rightleftharpoons [(+)\text{-L}, (+)\text{-S}] \quad (12)$$

$$(+)\text{-L} + (-)\text{-S} \rightleftharpoons [(+)\text{-L}, (-)\text{-S}] \quad (13)$$

The two *diastereomeric* complexes obtained have in principle different association constants. The resulting chiral discrimination may be evaluated by the difference (in percentage) of the two diastereomers formed, i.e. the *enantiomeric excess* (e.e.)[121].

In order to obtain specific ligands for sophisticated chiral guest molecules one is faced up with the task of synthesizing highly structural cavities that will tailor-fit the guests ('moleclar architecture')[18a–c], so that out of two enantiomeric guest molecules only one is able to enjoy the particularly tight, energetically favourable interaction with the host ('host–guest chemistry')[81,122]. Out of this conception arose a series of crown ether and cryptand systems[5b,18] with *chiral centres* (marked with asterisks, Figure 3) in definite arrangement (25 and 26)[16a,e–o,124] or with *chirality axes* in the form of binaphthyl units (27–29)[16b–d,17,122,125] or *spiro* groups (30)[18d].

By means of the *binaphthyl crown ether* 28, Cram and coworkers succeeded in *separating racemates* of amino acids in the enantiomers[122a,126]. The separation of the racemic amino acid cations is possible on account of the different stability of the diastereomeric crown ether complexes[123] (Figure 15): for instance, the crown ether 28a with (*S,S*)-configuration and having two 1,1′-binaphthyl units as chirality barriers preferentially complexes the (*R*)-enantiomer of *methylphenylglycinate*

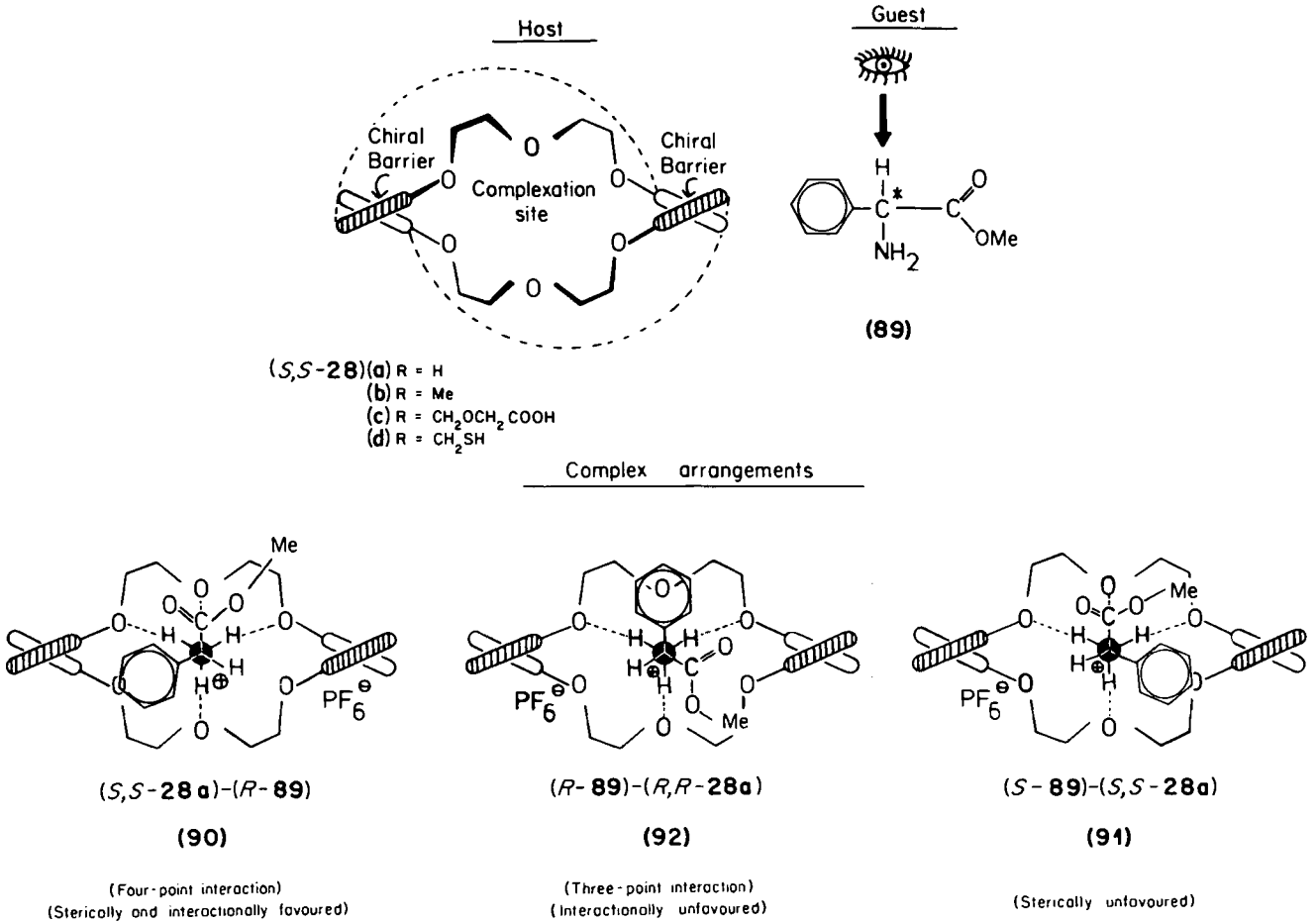


FIGURE 15. Chiral recognition between host 28 and guest 89 in various arrangements. Binaphthyl unit as chiral barrier.

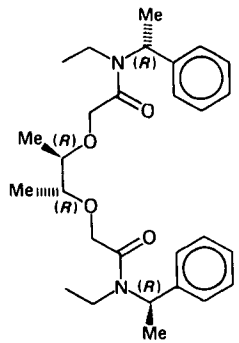
ammonium ion (89)[127]. Thus, when an aqueous solution containing the hydrochloride of *racemic* methylphenylglycinate (89) and $LiPF_6$ is shaken with a solution of (*S,S*)-28a in chloroform, 63.5% (*R*)- and 36.5% (*S*)-amino ester can be isolated from the organic phase and 56% (*S*)- and 44% (*R*)-amino ester from the aqueous phase. The projection 90 illustrates the interaction of (*S,S*)-28a with the preferred enantiomer (*R*)-89 in the complex, in comparision to the unfavourable arrangement of 91 with (*S,S*)-28a–(*S*)-89 geometry[128]. Elusion of the spatial constraint (phenyl nucleus/binaphthyl joint) in 91 through conformational change in the guest molecule reduces the optimum *4-point interaction* in 90 to a less stabilizing *3-point interaction* [see arrangement 92 for the combination of (*R*)-89/(*R,R*)-28a].

Through variation of structural units[122f,g] for specific incorporation of *steric barriers* (alkyl groups as in 28b)[129] or *functional complexing groups* as in 27 and 28c,d[125a,130], the chiral cavity can be more strongly subdivided, the chirality barrier raised and the chiral separation increased further. The optically active crown (*S*)-27 with two additional carboxyl functions as donor centres complexes, for example, (*S*)-valine in preference to the (*R*)-isomer (factor of 1.3)[130a].

Conversely, it has also been possible to carry out the enantiomeric separation of *crown ether racemates* by means of enantiomeric amino acids[130a].

Similar polyethers have been used for the total optical separations of *amines* by chromatographic methods[16i,124b,125b,126a]. The difficulty usually encountered here is the preparation of the free crown ether ligand in optically pure form. Taking advantage of the ready availability of natural compounds, Lehn and coworkers[16f], starting from L-*tartaric acid*, as well as Stoddart and coworkers[124] starting from (D)-*mannitol*, (L)-*threitol*, (D)-*glucose* and (D)-*galactose*, synthesized a few optically pure [18]crown-6 analogous ring skeletons (like 25b,c and 26; see Figure 3) containing several chirality barriers which recently also included binaphthyl[125b] or pyridino units (26)[16i]. Macrocyclic polyethers of this type form complexes with metal ions and primary alkylammonium cations, and show enantiomeric differentiation in the complexation of (±)-(R,S)-*α-phenylethylammoniumhexafluorophosphate*[124b].

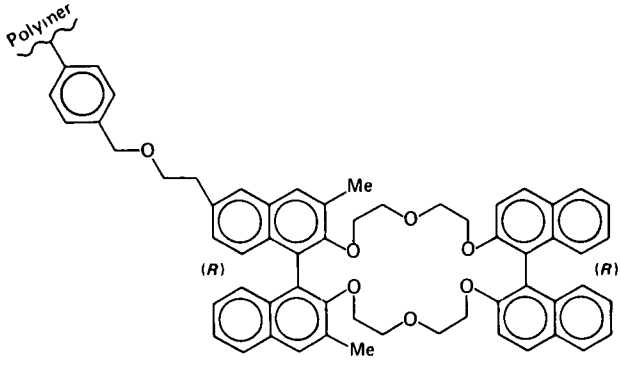
An enantiomeric differentiation has also been observed in transport through liquid *membranes* containing crown 28[131] or podand 93[132]. Thus it is proved that



(93)

the *chiroselective transport* of ions across a membrane can be effected by means of chiral complexation compounds, i.e. out of a racemic mixture it is possible, by using a suitable crown ether as carrier molecule, to transport one particular enantiomer preferentially from one side of a membrane to the other.

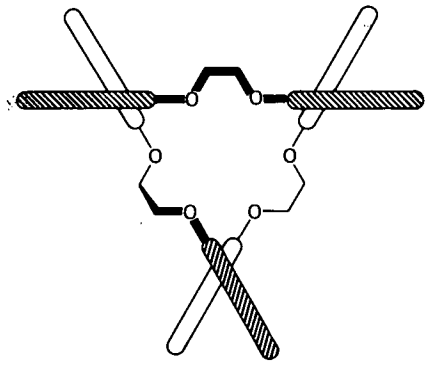
The separation of guest racemates is more economical and at the same time essentially easier, while the optical separation factors are strongly raised, when the chiral crown ethers or cryptands are bound to a *polymeric* supporting material (styrene resin 94, silica gel, etc.) and used as the stationary phase in the form of column fillings[133]. Thus was achieved the total chromatographic enantiomeric resolution of *α-amino acids* and their ester salts via chiral recognition by a host crown ether covalently bound to a polystyrene resin[133b] or on silica gel[122a]. The



(94)

separations were carried out on a preparative as well as on an analytical scale. The values of the separation factors (α) vary between 26 and 1.4 depending on the structure of the guest molecule; the resolution factors R_s have values between 4.5 and 0.21. Here also, a reasonable relationship could be established between the available cavity of the 'isolated' ligand and the size of the substituent in the guest amino acid.

The incorporation of additional chirality barriers in the model system 28 was lately accomplished by the synthesis of 95 with *three* binaphthyl units[16d]. However, no particular results concerning the enantiomer-selective complexation behaviour of these ligands have yet been reported.



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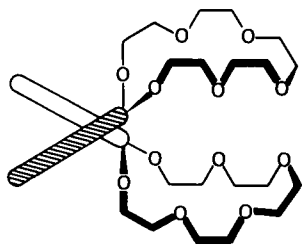


(96)

A new possibility or type of complexation and enantiomer selection is '*cascade binding*'[14e], involving complexation of an alkali cation followed by pairing with an organic molecular anion, e.g. mandelate anion[120]. Compounds of this type may be

considered as metalloreceptor model systems, where binding of an anion substrate is dependent on initial binding of a cation. A weak resolution of chiral racemic substrates has been observed by extraction and transport (through a bulk liquid membrane) experiments[120]. The resolution achieved with the cryptand **29** for the (±)-*mandelate anion* is markedly affected by the nature of the complexed cation.

Semirigid molecular skeletons **96**, in which *two* crown ether units are held together through a binaphthyl joint, represent another topical development on the way to abiotic model systems for biological multifunctional molecular receptors[134]. The fundamental importance here lies in the fact that highly selective molecular complexations between organic molecules must have played a central role in the molecular evolution of biological systems[81]. In other words, the molecular basis for the natural selection of the species depends directly on the selection of partners in molecular complexation based on structural recognition.

c. Conformational flexibility/rigidity. Rigidity, flexibility and conformational changes of a ligand skeleton (*ligand dynamics*) often go hand-in-hand with cavity size in governing cation selectivities[14c,65,85a] [see Section III.D.1.b.(1)]. Ligands with small cavities are generally quite rigid, since a small cavity is delineated by short, relatively nonflexible chains. Larger ligands with cavities above a certain size are generally more flexible and may undergo more pronounced conformational changes. In other words, rigid ligands give definite and only slightly alterable coordination cavities, while flexible, conformationally labile ligands can form cavities of variable dimensions. Hence it follows that rigid skeletons should display higher cation selectivities, i.e. their ability to discriminate between ions, which are either smaller or larger than their cavities, should be better.

This is pictured in Figure 13[85a]. The *cryptands* of the *'rigid' type* [2.1.1] (**54**), [2.2.1] (**55**) and [2.2.2] (**19**) show a stability peak (*peak selectivity*) for the cation of optimum size (cf. Table 13). Ligands of the *'flexible' type* beginning with [3.2.2] (**62**), which contain large, adjustable cavities show *plateau selectivity* for K^+, Rb^+ and Cs^+, whereas K^+/Na^+ selectivity is large (Figure 13). Thus, while rigid ligands can discriminate between cations, that are either smaller or bigger than the one with the optimum size (peak selectivity), flexible ligands discriminate principally between smaller cations (plateau selectivity). That the stability plateau generally starts with K^+ is not too surprising since the largest relative change in cation radius occurs between Na^+ and K^+ (cf. Table 13). An important contribution to this peak–plateau behaviour also results from coordination property facts; the free energies of hydration change much less for K^+, Rb^+ and Cs^+ than for Li^+, Na^+, K^+[14c].

Many macrocyclic *antibiotics* (e.g. enniatin B and valinomycin) show a similar behaviour[7b].

Corresponding rules, though less rigid, apply to *coronands* apart from a few exceptions[65]. The data in Figure 16[76a] show the maximum log K_s value and peak selectivity in the case of K^+ to be reached with [18]crown-6 rings [cyclohexano[18]crown-6 (**97**), dibenzo[18]crown-6 (**1**)]. However, while the log K_s values for K^+-dibenzo[21]crown-7 (**98**) and K^+-dibenzo[24]crown-8 (**7**) interactions decrease as expected, a significant increase is seen in the case of dibenzo[30]crown-10 (**8**). The unexpectedly large stability of the *K^+-dibenzo[30]crown-10 complex*[48] is consistent with the observation based on X-ray crystallographic data (see Figure 23, Section IV.B.1.a), according to which the ligand is held in a conformation where all ten donor sites are 'wrapped' around the K^+ ion[135]. Such unusual ligand conformational change during complexation results from a

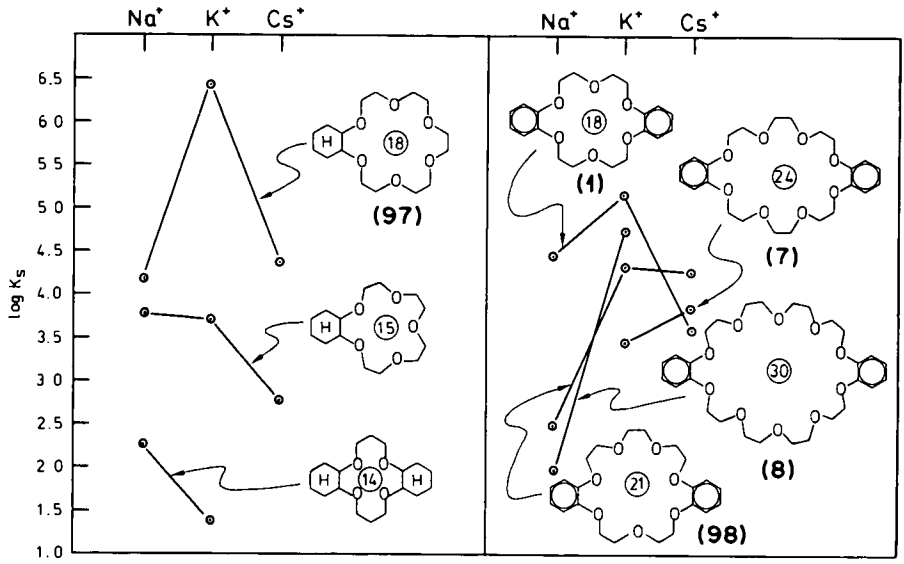


FIGURE 16. Plots of log K_S (in MeOH at 25°C) for complex formation between alkali metal cations and several cyclohexano- and dibenzo-crown ethers[65].

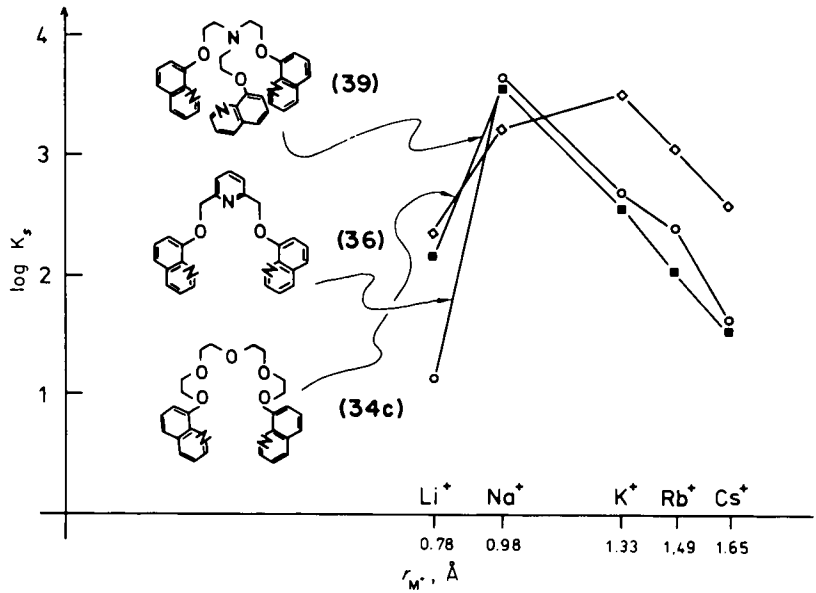
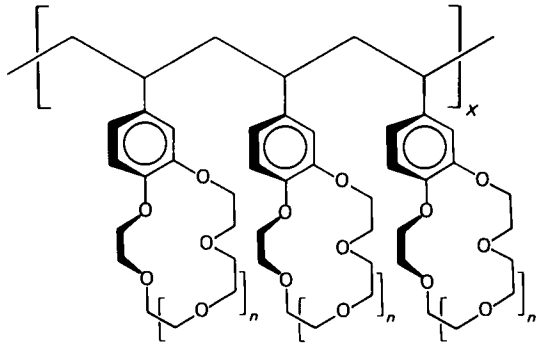


FIGURE 17. Plots of log K_S (in MeOH at 25°C) of complexes of open-chain crown ethers 34c and 36 and open-chain cryptand 39 as a function of the ionic radii of alkali metal cations[64].

stronger interaction of the K^+ ion with the donor atoms than might otherwise be expected. Similar conformational ligand arrangements are also found in the K^+ complex of antibiotics of large ring size (valinomycin, nonactin)[136].

Although *open-chain* ligands belong to crown ether types with the biggest flexibility and ability to adapt to cations of various size, they sometimes show remarkable peak selectivities (Figure 17), particularly when the oligoethylene glycol ether (middle section of **34c**) is partially stiffened by insertion of a pyridino nucleus as in **36**[57,64].

Polyvinyl macrocyclic polyethers **99** are more efficient in complexing cations than their monomeric analogues, especially in those cases where the diameter of the polyether ring is smaller than that of the cation[137] For example, log K_s for



(99)

formation of the K^+–poly(4′-vinyl)benzo[15]crown-5 (**99**, $n = 1$) complex is found to be >5 (obtained by extraction of K^+–fluorenyl), whereas that for the corresponding monomer benzo[15]crown-5(**4**)–K^+ complex is 3.7. This can be explained by cooperative coordination effects, where two neighbouring crown ether rings combine with a single cation.

That macrobicyclic ligands present better *overall selectivities* than all other types of ligands (monocyclic crown ethers, open-chain podands) may be related to their bicyclic topology[85a]. Cryptands have a higher 'connectivity', hence higher rigidity and 'dimensionality' [cf. Section III.D.1.b(2)] than simple monocyclic and open-chain ligands[14c]. The best overall selectivity for all metal ion pairs is displayed by the [2.2.2]cryptand (**19**). In an aqueous solution containing all alkali metal ions, for instance, [2.2.2] would complex K^+ strongly, Na^+ and Rb^+ slightly less, but leave Li^+ and Cs^+ completely uncomplexed[85a].

Pyridino rings lead to stiffening of the skeleton and selectivity shift in cryptand as well as in crown ether and podand systems (e.g. increase of Na^+ selectivity, cf. Figure 17)[57,64,85c].

Instead of the pyridino nucleus, *intraannularly*-substituted benzene rings may also be incorporated in open-chain and cyclic crown ether frameworks [see Section III.D.1.a(1)]. Model inspections show that crown ethers of type **70** adopt a conformation where the plane of the benzene ring is twisted approximately 30° out of the plane of the macro ring[101]. Two opposing methoxyphenyl rings in **71** lead to comparably low constants, since a series of rotational degrees of freedom are frozen, causing difficult formation of cavities for guest molecules[102].

Added *benzene* or *cyclohexane* rings are able to alter the complex constants themselves as well as the selectivities[65]. This can be deduced from Figure 16, where

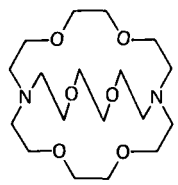
various cyclohexano- and dicyclohexano-crowns are compared with the corresponding dibenzo derivatives[76a]. The decomplexation energy of the Na^+–dibenzo[18]crown-6 complex is the same in various solvents, about 12.6 kcal/mol, and is lowest for the dicyclohexano[18]crown-6-Na^+ complex (8.3 kcal/mol in methanol). The main barrier to removal of Na^+ from the cation complex of dibenzo[18]crown-6 and its derivatives seems actually to be the energy required for a conformational change. The smaller activation energy for the decomplexation of the Na^+-dicyclohexano[18]crown-6 complex is attributed to greater flexibility of the ligand. Addition of rigid benzene nuclei should also diminish the cavity size as is confirmed in several cases [see Section III.D1.b.(1)].

As mentioned above, complexation of conformationally labile ligands is usually accompanied by a stiffening or fixation of the ligand skeleton in the complex. In a few cases, this can be directly derived from the ^{1}H-NMR spectra of ligand and complex[15i,100b]. In the case of crown ethers and cryptands with ester or carbamide structure, complex stability and selectivity are also influenced by hindered rotation about the C–O or C–N bond[138].

d. Substituent effects. (1) *Lipophilicity.* Crown ethers as cation complexing ligands are of the *endopolarophilic/exolipophilic* type with polar binding sites turned inside and a surface formed by lipophilic hydrocarbon groups[4e,8e,18a] (cf. Figure 12). The lipophilic character of a ligand may be controlled by the nature of the hydrocarbon residues forming the ligand framework or attached to it.

Ligands with thick lipophilic shells shield the cation from the medium and decrease the stability of the complex[14c]; therefore very thick ligands cannot usually form stable complexes. Since this effect is four times more strongly felt by doubly charged alkaline earth metal ions than alkali cations, ligand lipophilicity influences in particular the *selectivity* between *mono* and *divalent* cations: the thicker the organic ligand shell (and the lower the dielectric constant of the medium, cf. Section III.D.4), the smaller the selectivity ratio for divalent M^{2+}/monovalent M^+ cations[20,112]. Competition between monovalent/bivalent cations plays a very important role in biological processes[139].

The selectivity between Ba^{2+}/K^+ serves as a test, since these cations have (almost) similar size (cf. Table 13). For instance, the addition of a first *benzene ring* as lipophilicity-enhancing element in the cryptand [2.2.2] (**19**) (see **100**) does not much affect the Ba^{2+}/K selectivity, probably because solvent approach to one side of the bicyclic system remains unhindered[140]. However, when a second



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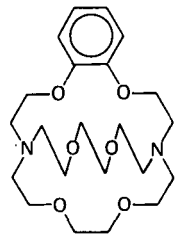

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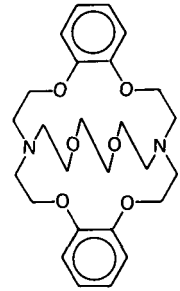


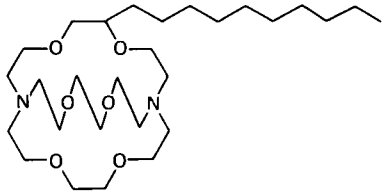
(101)

benzene ring is added as in **101**, the stabilities of the Ba^{2+} and K^+ cryptates become nearly equal and the Ba^{2+}/K^+ selectivity is lost[140]. Analogously, the *NCH_3 group* in

cryptands **66–68** (Table 12) – compared to **19** – thicken the ligand layer and have a destabilizing effect on doubly charged cations[85b,97]. Another influence on complexation selectivity between monovalent and bivalent ions caused by removal of binding sites is discussed in Section III.D.1.a(2).

Lipophilicity enhancement has also been studied in podands of the 3,6-dioxaoctanedioic diamide type **87**[141]: An increase in lipophilicity (lengthening of the N-*alkyl chains*) decreases the ionophoric behaviour of these ligands; at a chain-length of $(CH_2)_{17}-CH_3$, the ability to transport ions across a membrane is practically nil. Nevertheless, a complexation of Ca^{2+} in solution can be detected by ^{13}C-NMR spectroscopy[142]. To account for the surprising electromotoric behaviour, kinetic limitations at the phase boundary have been suggested.

In general, lipophilicity of a ligand and its complex plays a very important role whenever substances should be solubilized in organic media of low polarity[4,143]. This is the case with crown ethers as *anion-activating* agents[4] ('naked anions')[144] and *phase-transfer* catalysts[4,145] and of *cation transport* through lipid membranes[6a,b,7b,30]. In this connection, many crown ethers, cryptands and open-chain ligands fitted with benzene rings (e.g. **21**, **100** and **101**) or with long alkyl side-chains (e.g. **32**, Figure 4 and **102–104**) have been synthesized and used with success[22,146].



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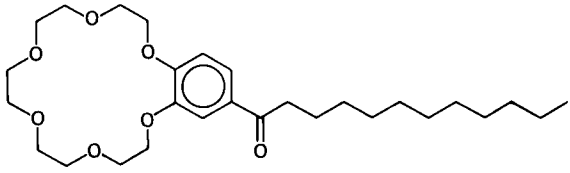

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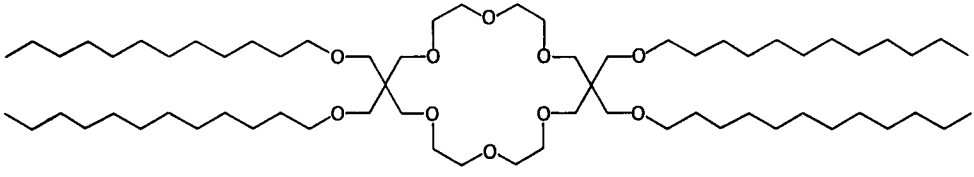
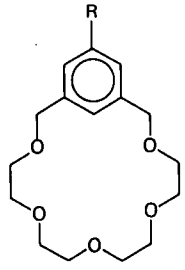


(104)

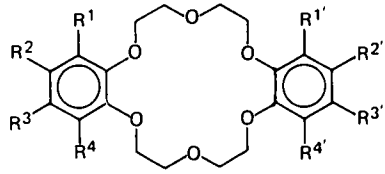
(2) *Electronic influences.* Experiments on the extraction of sodium and potassium salts in the two-phase system water/dichloromethane show a marked substituent effect for substituted *dibenzo[18]crown-6* ethers **105** (*cis*- and *trans*-dinitro, *cis*- and *trans*-diamino, tetrabromo, octachloro) as well as mono- and

bis-(tricarbonylchromonium) derivatives[147]; one observes a reverse of the usual selectivities of dibenzocrown ethers when strong, electron-withdrawing substituents are bound to the aromatic rings[148].

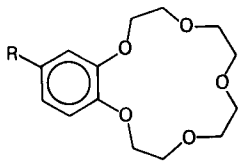
Analogous effects were investigated for *benzo[15]crown-5* systems **106** carrying various electron-donating and -withdrawing substituents in the benzene nucleus[149]. For example, 4′-amino- and 4′-nitro-substituted derivatives differ by a factor of 25 in K_S for complexation with Na^+ ions. Within the whole series of **106** a



(**70**)(a) R = H (−4.8)
(b) R = *t*-Bu (−5.1)
(c) R = CN (−2.7)
(d) R = COOEt (−3.8)



(**105**) R^2, $R^{2'}$ = NO_2, NH_2
R^2, $R^{3'}$ = NO_2, NH_2
R^2, R^3, $R^{2'}$, $R^{3'}$ = Br
R^1, R^2, R^3, R^4, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ = Cl

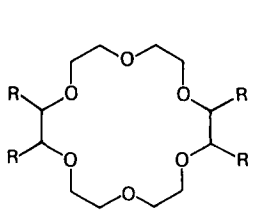


(**106**) R = H, Me, Br, NH_2, NO_2, CHO, COOH, COOMe

good *Hammett correlation* is obtained when log K_S is plotted vs. $(\sigma_p + \sigma_m)$, the ρ value being −0.45. The substituent effect for the system of *benzo[18]crown-6*/Na^+ is much smaller and almost negligible with electron-withdrawing substituents[149]. For the K^+–benzo[18]crown-6 complexes, somewhat bigger effects are found, but no linear Hammett correlation. This could be attributed to the more flexible structure of benzo[18]crown-6. The results show that caution must be applied in extrapolating substituent effects found in one system to other crown–cation combinations.

Complexation of the *m-benzene-bridged* hosts **70** is found to be sensitive to substituents both the 2′- [see Section III.D.1.a(1)] and 5′-positions[18c]. The binding energies of **70**a–d for *t*-$BuNH_3^+SCN^-$ change between 5.1 kcal/mol and 2.7 kcal/mol, which can be explained by the affected electron density of the π-system and correlated by Hammett-type linear free energy relationships[150].

'*Lateral discrimination*' can be obtained by changing sidegroups (R) in the crown ether system **25**[14d]. Within the series **25c–f**, the tetracarboxylate **25d** forms – in accord with the strong electrostatic interaction with K^+ – one of the most stable complexes reported to date for a macrocyclic polyether (K_s = 300,000 in H_2O)[16g]. That the tryptophane derivative **25f** (K_S = 5500) complexes K^+ better than the glycinate **25e** (K_S = 200) might be related to the shielding effect of the lipophilic



(25)

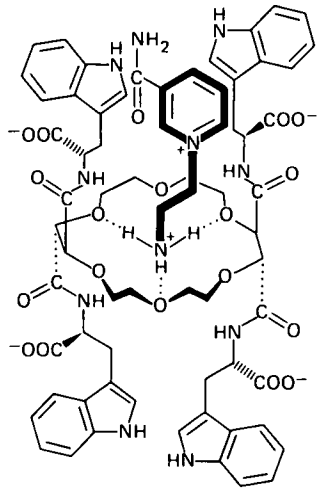
(c) R = $-C(=O)-NMe_2$

(d) R = $-COO^-$

(e) R = $-C(=O)-NHCH_2COO^-$

(f) R = $-C(=O)-NH-CH(COO^-)$-indole

indole groups in the solvation of the carboxylate. Diammonium salts like the nicotinamide derivative in **107** are very strongly bound by the tryptophanate **25f**.



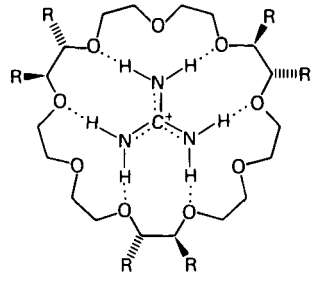
(107)

Thus, the guest is fixed at the NH_3^+ end inside the crown ether ring, and by electrostatic interaction of two carboxylate groups with the pyridinium unit. Moreover, donor–acceptor interaction between the indole and pyridinium groups are effective as shown by a charge-transfer absorption in the electronic spectrum[16g].

2. Guest parameters: type, size and charge of guest ion

An intramolecular complex compound is considered to be composed of a host and a guest component. While hosts are organic molecules or ions, whose binding sites converge, guests have divergent binding sites. In order to complex and to have a good fit, *host and guest* must possess a *complementary* stereoelectronic arrangement of binding sites and steric barriers[81].

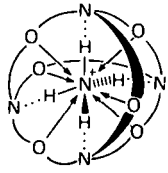
Thus *guanidinium* ion as guest[151] well meets the requirements for coordination inside the circular cavity of the macrocycle **108** (*'circular recognition'*)[14e].



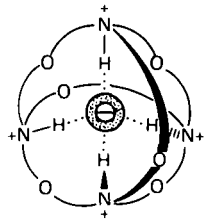
(108)

The spheroidal intramolecular cavity of macrobicyclic ligands is well adapted to the formation of stable and selective complexes with *spherical* cations [cf. Section III.D.1.b(1)]. Spherical macrotricycles of type **24** ('soccer molecule') should be most favourable for the recognition of spherical guest particles (*spherical recognition*)[14d].

Tetrahedral arrangement of nitrogen sites (cf. also **39**, Figure 6) renders ligand **24** also an ideal receptor for the *ammonium* cation in arrangement **109** (*tetrahedral recognition*)[14d,e]. The NH_4^+ ion is fixed in a tetrahedral array by four $\overset{+}{N}$–H . . . N bonds (cf. Figure 30a, Section IV.B.2.b); also six electrostatic O → $\overset{+}{N}$ interactions are effective in addition to twelve hydrogen bondings $\overset{+}{N}$–H . . . O.



(109)

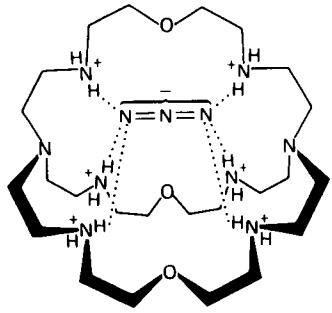


(110)

In its *tetraprotonated* form macrotricycle **24** represents a suitable receptor for spherical anions (*anion recognition*)[117,152]. With *halogenide* anions (chloride, bromide) cryptates (**110**) are formed which show similar cavity selectivities for anions of varying size as in the case of cation cryptates[153]. The selectivity of the anion cryptates **110** is highest for Cl^- as guest ($\log K_s \geqslant 4.0$ in H_2O; Br: < 1.0; cf. catapinates, Reference 11b). Here it seems that the array of hydrogen bonds and the cavity size complement each other ideally.

Linear anionic species such as the triatomic *azide* ion require corresponding ellipsoidal cavities ('*linear triatomic receptor*'). A good example is furnished by the *hexaprotonated* bis-tren* ligand in **111**[154]: Addition of sodium azide to an aqueous solution of free ligand **20** at pH 5 yields a stoichiometric 1 : 1 azide cryptate in which the linear N_3^- ion is held within the molecular cavity by six hydrogen bonds, three on each terminal nitrogen of the guest ion. Thus this hexaprotonated ligand acts as a receptor for triatomic anionic species.

It may be deduced, therefore, that like the coordination chemistry for cations, a *coordination chemistry for anions* appears feasible[14d,e]. Biological systems often make use of charged receptors. An interesting case would be the complexation of the locally triatomic but nonlinear carboxylate group R–COO^- and of CO_2 and NO_2 molecules, whose stereochemistry are close to that of N_3^-.



(111)

The few examples above (related to the guest) make clear once again the importance of a defined interaction between host and guest for achieving a selective complexation between receptor and substrate. The ligand parameters, which have already been discussed thoroughly in Section III.D.1, must also be viewed in this complementary sense, so that further discussion here is superfluous.

Replacement of oxygen by nitrogen or sulphur in crown ethers and cryptands not only causes a rise in the stabilities of *heavy metal* complexes generally [see Section III.D.1.a(1)], but also markedly influences the cation selectivities in certain instances. Thus the Cd^{2+}/Zn^{2+} *selectivities* of the tetraaza **67** and hexaaza ligand **68** lie higher than those of any other known ligand[85b]. The Cd^{2+}/Co^{2+}, Ni^{2+} *and* Cu^{2+}/Zn^{2+}, Co^{2+} *selectivities* of **67** and **68** are similarly pronounced. On the whole, the aza cryptands offer a wide range of complexation selectivities, which are particularly interesting in the field of biological detoxication (decorporation and depollution), since they complex the toxic heavy-metal ions Cd^{2+}, Hg^{2+} and Pb^{2+} very strongly and the biologically important ions Na^+, K^+, Mg^{2+}, Ca^{2+} and Zn^{2+} rather weakly. The development of a 'cryptato therapy' based on the above selectivities has been suggested[14d,85b,155].

That the stability of sodium cryptates is dependent on *isotope effects* may find practical use in nuclear chemistry[14d]. In order to evaluate an isotope effect, the distribution of activity of $^{22}Na^+$ and $^{24}Na^+$ in the heterogeneous equilibrium mixture of a cationic cryptand exchange resin and an aqueous or methanolic solution was measured[156]. The results showed that changes in the isotopic composition occur only in methanolic solutions and not in water. This is surely related to greater solvation of the ions in water, so that mass differences between isotopes are not clearly felt therein. An explanation for the isotopic selective behaviour is that the Li^+-charged resin first takes up $^{22}Na^+$ and $^{24}Na^+$ unspecifically in exchange for Li^+. The enrichment of $^{24}Na^+$ follows in the backward-reaction, where Li^+ displaces $^{22}Na^+$ preferentially from its binding on account of the lower weight and higher thermal lability of the $^{22}Na^{2+}$ in comparison to $^{24}Na^+$. The enrichment of the higher isotope $^{24}Na^+$, thus, can be exploited for practical use. Also, the isotope ^{44}Ca present at a 2% level in naturally occurring calcium could be separated from ^{40}Ca by multiple extraction with dibenzo[18]crown-6 (**1**) or dicyclohexano[18]crown-6 (**59**)[157].

*Tren = tris(2-aminoethyl)amine.

Further, the enrichment of ^{235}U on the crown ether basis, reported recently by a French research group, marks a spectacular achievement of technical interest[158].

3. *Anion interactions, ion-pair effects*

While the foregoing sections have been limited to considerations of the ligand/guest complexation, the following deals with the aspect of guest–counterion (an anion usually) relationship.

Taken as a whole, the *ligand–cation unit* – as seen from its environment (solvent, anion) – is like a cationic species of very large size and of low surface charge density, in other words, like a 'superheavy' alkali or alkaline earth cation (about 10 Å diameter, Cs^+ : 3.3 Å)[159]. Accordingly, the electrostatic anion (and solvent) interactions are here much weaker than even with the largest alkali cation Cs^+. While the complexed cation can still be reached by the corresponding anion from 'top' and 'bottom' of the complex in the case of numerous crown ether and open-chain podand-type complexes (still better in the latter case, cf. Figures in Section IV.B), this is hardly possible in the case of spherical cryptates, depending on the degree of encapsulation. Thus, a more thorough *cation–anion separation* can be achieved by cryptates with a complete 'organic skin', and the latter are also more strongly dissociated in solvents of low polarity[159,160]. In the extreme case, one could speak of a 'gas-phase analogous chemistry in solution'[14d].

The interaction between the anion and the complexed cation may affect the stability of the complex[14d]. In highly solvating media, the charged complex and the counterion are *separately* solvated; no anion effect on complex stability is found. In poorly solvating media, however, *ion pairing* gains weight increasingly in the form of complexed or ligand-separated ion pairs; anion effects, that are controlled by the charge, size, shape and polarizability of the anion, can be observed[4e,161]. For instance, ion-paired complexes of *divalent* alkaline earth metal ions will be much more destabilized by an increase in anion size than those of alkali metal ions.

A dramatic and unusual type of cation–anion interaction is illustrated by the crystalline Na^+–[2.2.2]cryptate (or K^+–[2.2.2]cryptate) containing an *alkali metal anion* (Na^-, K^-) as counterion[162]. With Na^+–[2.2.2] as counterion it has also been possible to isolate polyatomic anions of the heavy post-transition metals (e.g. Sb_7^{3-}, Pb_5^{2-} Sn_9^{4-})[163].

Anion effects may also be responsible for the difference in the *exchange kinetics* of TlCl and $TlNO_3$ cryptates[53].

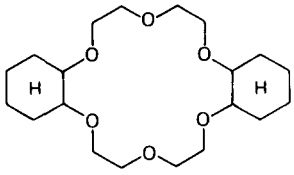
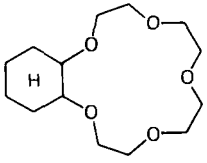
Chiral discrimination of molecular anions by ion pairing with complexed alkali cations via a two-step *cascade complexation* mechanism with chiral cylindrical cryptands (as 29) opens up a new concept of metal receptors where binding of an anionic substrate is dependent on the initial binding of a cation[120] [see Section III.D.1b(3)].

In general, the influence of the *lipophilicity* of the employed anion on the solubility of a complex is of utmost importance. Soft organic and inorganic anions (e.g. phenolate, picrate, tetraphenyl borate, thiocyanate, permanganate) greatly increase the solubility in solvents of low polarity, and this influences cation transport processes, properties and anion activation[4].

4. *Medium (solvent) parameters*

The stability and selectivity of a cation complex are determined by the interaction of the cation both with the solvent and with the ligand[164]. Thus a change in

TABLE 15. Comparison of log K_S values of Na^+ and K^+ complexation in water and methanol solutions at 25°C

Ligand	Na^+		K^+		Cation
	H_2O	MeOH	H_2O	MeOH	Solvent
 (59)	1.21	4.08	2.02	6.01	log K_S
 (112)	<0.3	3.71	0.6	3.58	

media effects *complex stabilities* and simultaneously *selectivities* of complexation, especially where cations are strongly solvated in one solvent but not in another[14c,65].

In *aqueous solution*, most ligands are less selective and the complexes less stable than in *less polar* solvents like MeOH (cf. Tables 4–12, Sections II.B.3, II.C.3 and III.D.1.a). The difference in stability in these solvents is of the order of 10^3-10^5 for cryptates[85a] and 10^3-10^4 for coronates (see Table 15)[65]. For example, the selectivity of benzol[15]crown-5 (4) for K^+ over Na^+ rises continuously as the percentage weight of methanol increases in the solvent system MeOH/H_2O (Figure 18)[165].

The following K_S sequences have been found for [18]crown-6 alkali complexes in the nonaqueous solvents DMSO, DMF and PC (propylene carbonate)[166]:

$$\text{DMSO: } K^+ > Rb^+ > Cs^+ \cong Na^+ \gg Li^+$$
$$\text{DMF: } K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$$
$$\text{PC: } K^+ \gg Na^+ > Rb^+ > Cs^+ > Li^+$$

In many cases the rise in selectivity is approximately proportional to the rise in stability of the complex, and for complexes of comparable stabilities *larger* cations are favoured over *smaller* ones. Furthermore, solvents of low dielectric constants favour complexes of *monovalent* ions over those of *bivalent* ones. This general trend allows new selectivity gradations, particularly for cryptates with a wide spectrum of K_S values[85a].

Thermodynamic measurements[75,165] for gaining information about the origin of the solvent effect show that the higher enthalpies of complexation found in

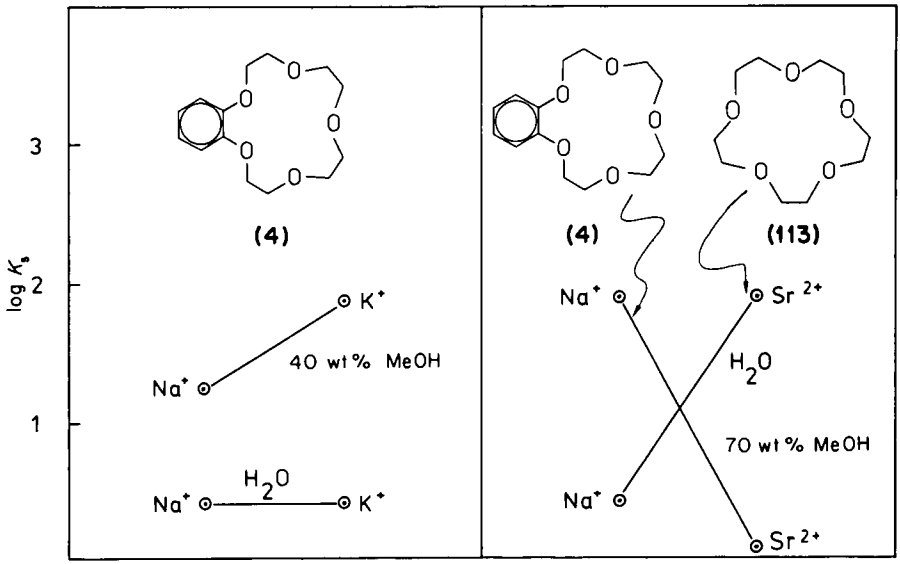


FIGURE 18. Stability constants (log K_S) of complexation for several cation pairs in H_2O and H_2O/MeOH (60 : 40, 30 : 70) as solvents[165].

MeOH/H_2O solutions may be due mostly to an increase of electrostatic interaction of the cation with the ligand and its smaller interaction with the solvent in media of lower dielectric constants. In poorly solvating media the effect becomes very large and complexes, which are soluble in solvents like chloroform or benzene, have extremely high stabilities. This may be important for the preparation of complexes with weakly complexing ligands in water or methanol (cf. Section IV.A).

It is interesting that *podand* 35e is able to compete so well against pyridine as solvent as to allow the determination of the thermodynamics of complexation by the ^{23}Na-NMR method ($K_S = 10^3 - 10$ l/mole in the range of 5–50 °C)[80]. The selectivities of open-chain ligands can be strongly altered, particularly, in such solvents as are used in ion-selective membranes for microelectrodes[27].

These results show that the selectivity of crowns toward alkali and alkaline earth ions is dependent on the physical properties of the solvent and mainly that the relative stability of a complex increases with decreasing solvating power of the medium. The presence of water in solvents may significantly influence the complexation and lead to inaccurate measurements of the complex constants. As Reinhoudt and coworkers showed, concomitant coordination of water molecules in the complex is also possible[167]. During the synthesis of complexes, water is often (inevitably) carried in by the salt employed or in the solvent used for recrystallization (cf. Section IV.A). Numerous crown ethers with water in stoichiometric amounts are known (see below).

IV. CRYSTALLINE COMPLEXES OF CYCLIC AND NONCYCLIC CROWN ETHERS

Having dealt with the more important crown ether skeletons and the stabilities and selectivities of the complexes *in solution*, we will turn now to *crystalline* complex

formation by monocyclic, oligocyclic and noncyclic neutral ligands and discuss their stereochemical peculiarities.

A. Preparation of Crown Ether Complexes

Crystalline crown ether complexes can be prepared by several methods[1a,3c,168]. The choice depends essentially on the solubility behaviour of the complex and its components.

The easiest way is to dissolve the polyether and salt (in excess) in a very small amount of warm solvent (or solvent mixture). On cooling, the complex crystallizes slowly (*method 1*)[1a,168]. Sometimes precipitation of the complex is very slow or does not occur at all. In this case, the solvent is partially or totally removed *in vacuo* and the residue recrystallized (*method 2*)[1a,168]. If there is no appropriate solvent mixture common to both crown ether and salt, a suspension of crown ether and salt solution may be warmed. The free ligand then slowly reacts to form the crystalline complex, even in the absence of a homogeneous phase (*method 3*)[1a,168]. Reaction may also be carried out without a solvent. Both components are thoroughly mixed and heated to melting (*method 4*)[1a]. Under certain circumstances crown ether complexes can directly be formed during the ligand synthesis[169] through a '*template participation*'[151,170,171] of the cation. It is then sometimes even more difficult to obtain the free ligand than its complex[85c]

In all cases, complex formation favours salts with weaker crystal lattice forces[14c]. Thus, alkali metal fluorides, nitrates, and carbonates give complexes with polyethers in alcoholic solution; however, it is often difficult to isolate the complexes since concentration, on account of the high lattice energy, mostly leads to decomposition in the sense that the inorganic salt components assemble back to their stable crystal packing and precipitate uncomplexed out of solution[1a].

However, with *alkali* and *alkaline earth metal thiocyanates*[172], *chlorides*[9i], *bromides*[173], *iodides*[1a,100b,168,169], *polyiodides*[1a,168], *perchlorates*[174], *benzoates*[172a], *nitrophenolates*[172a], *tosylates*[169], *picrates*[172a,175], *tetraphenylborates*[176], *nitrites*[1a,100b]; various *ammonium salts*[1a,18c,26a,168] as well as *heavy metal halogenides*[177], *thiocyanates*[178], *nitrates*[100b,177b,c], *perchlorates*[177c] and *tetrafluoroborates*[177c], numerous well-defined, sharp-melting, crystalline crown ether complexes[179] can be obtained by the above methods 1–4.

Of the *lanthanide salts* coordination compounds with crown ethers and cryptands are also known[26a,180,181]. *Uranyl crown ether complexes*[182] are of interest with respect to isotope enrichment[158] (cf. Section III.D.2).

The stable H_3O^+ *complex* of one diastereomer of dicyclohexano[18]crown-6 represents quite a rare case[183].

Crystalline neutral complexes with *acetonitrile*[184], *malodinitrile*[184] and other *CH-acidic compounds*[184,185] are generally obtained by dissolving or warming the ligand in them. Recently, a stable *[18]crown-6 benzene sulphonamide molecule complex* could also be isolated[186]. With aromatic unit-containing polyethers like **1**, *bromine* forms crystalline complexes that partly have a stoichiometric (1 : 1, 1 : 2) composition[187]. *Thiourea* complexes of [18]crown-6 have already been synthesized by Pedersen[188], while those of open-chain crown ethers have been reported more recently[189].

Noncyclic neutral ligands with different numbers of arms and donor units often give analogous metal/salt and neutral particle complexes as easily as their cyclic counterparts[24].

B. Selectivity of Crystalline Complex Formation and Ligand and Complex Structures

Stoichiometry and crystalline structure of crown ether complexes[130] are not always easy to predict, despite careful use of the rules derived in Section III.D[191-193]. Thus, monocyclic crown ethers may apparently have uneven stoichiometries also (cf. the RbSCN–dibenzo[18]crown-6 complex). Complicated stoichiometric compositions are particularly frequent in the case of open-chain polyoxa ligands[24], while mostly normal stoichiometries are found for cryptates[14a-c].

If the difference in cavity size and cation diameter is not too big, 1 : 1 (ligand : salt) complexes may nevertheless be formed. The cation then is either *shifted* from its ideal position (centred in the ring-plane of the crown ether, *type I*, Figure 19, or in the middle of the cavity of the cryptand) or the ligand is *wrapped* around the cation in a nonplanar way. These circumstances are shown in Figure 19 (*type IIa, type IIIa*) and are discussed in more detail at the appropriate place.

If the cavity is much too large for a cation, then *two* of them may be embedded therein (cf. Figure 19, *type IIb*); on the other hand, if the cation is much to large, a sandwich-type complex may be formed, where the cation is trapped between two ligand units (*type IIIB*). The formation of crystalline 1 : 1 complexes, nevertheless, despite unfavourable spatial requirements of ligand and cation, may be explained, at least in part, by the concomitant coordination of H_2O or other solvent molecules in the crystal lattice of the complexes[190] [see further details and compare also Sections III.D.1.a(2), III.D.3. and III.D.4.].

A general comparison of the structures of the *noncomplexed* ligand molecules with the same molecules in its *complexes* suggests types of conformational changes which may occur during complexation (see Figure 20, cf. also Section III.D.1.c). The number of possible structures of noncomplexed molecules that can be elucidated by X-ray structure analysis is limited, because many of the compounds have

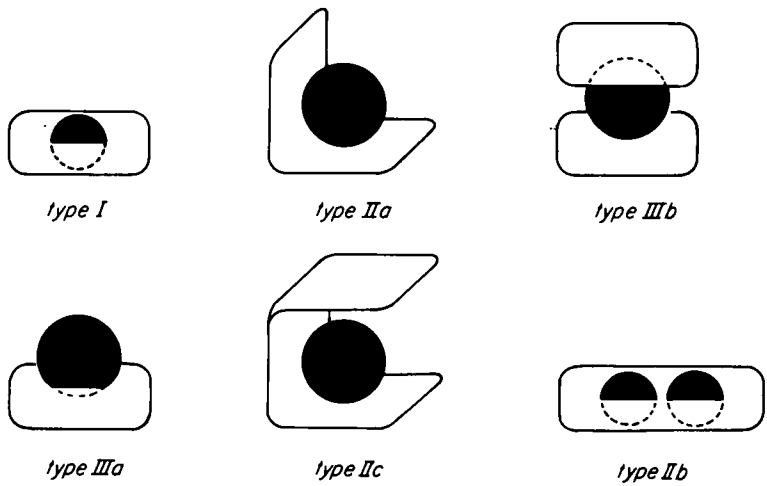


FIGURE 19. Schematic representation of several types of crown ether complexes.

low melting points; a few noncomplexed cyclic polyether molecules have nevertheless been studied[190d]. These include *[18]crown-6* (2)[194], *dibenzo[18]crown-6* (1)[195], *dibenzo[30]crown-10* (8)[135] and some isomers of *dicyclohexano[18]crown-6* (59)[196]. The reported structures[197] have some features in common. None of them have the ordered conformations found in the complexes of groups one and two. Even though the molecules do not have highly ordered structures, there are several cases in which they are located about centres of inversion. This is the case for [18]crown-6, for example (see Figure 20a). In the absence of organizing metal ions, and because energy differences between some conformations may be small, the structures determined for these molecules in the solid state may be effected mainly be packing energies[198].

1. *Monocyclic crown ethers* (see Figure 1)

a. Alkali and alkaline earth metal ion complexes. The architecturally well-examined alkali metal ion complexes of cyclic crown ethers mostly display a 1 : 1 ligand/salt stoichiometry. In addition, there exist polyether/salt combinations of the following compositions: 1 : 2, 2 : 1, 3 : 2 etc.[190].

From the above comparision (Table 13), it follows that Na^+, for example, is too small, Rb^+ and Cs^+ are too big, while K^+ is more likely to be embedded in the cavity of [18]crown-6 (2). All four cations give crystalline, stoichiometric complexes with structures differing significantly, as shown schematically in Figure 19, according to the spatial requirements (*'structure-selectivity'*).

In the *$NaSCN–H_2O$–[18]crown-6 complex* (Figure 20b)[199] the Na^+ ion is coordinated by all six oxygen atoms of the ligand; while five of them lie in a plane

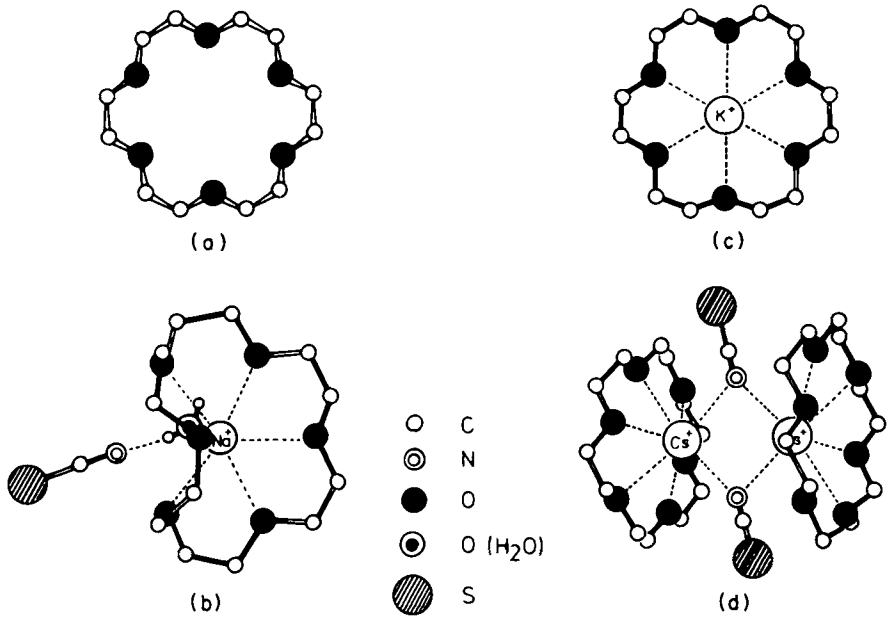


FIGURE 20. Structures of [18]crown-6 and some [18]crown-6 complexes with different alkali metal salts.

containing the cation, the sixth one is folded out of plane and partially envelopes the cation (*type IIA*, diameter ligand > diameter cation; cf. Figure 19). This type of complexation is typical of crown ether rings that are too big for the cation (cf. Table 13). A H_2O molecule additionally participates in the coordination of the Na^+ ion.

In the *KSCN complex of [18]crown-6* (Figure 20c)[200] all six oxygen atoms lie in an almost hexagonal plane coordinating the K^+ ion at the centre of the ring (*type I*, 'ideal' type, diameter ligand ≃ diameter cation). A weak bond to the SCN^- ion was established.

In the *RbSCN–*[201] *or CsSCN–[18]crown–6 complex* (Figure 20d)[202] the cation is situated above the plane of the polyether ring (*type IIIA* diameter ligand < diameter cation). Two cation/ligand units are bridged by two SCN^- ions which also serve to saturate each cation from the 'naked' side of its coordination sphere[203].

From the data given in Figure 13, it can be deduced that regarding the K^+ complex of *benzo[15]crown-5* (4) or *dibenzo[24]crown-8* (7), no ideal spatial conditions are fulfilled for a 1 : 1 stoichiometry of ligand to salt.

As in the combination of [18]crown-6/Rb^+ the cavity of the 15-membered ring 4 is too small for a K^+ ion. However, since the ligand here contains only relatively few donor sites (5 instead of 6), the *KI–benzo[15]crown-5* is formed as a 2 : 1 complex (Figure 21b)[204] with *'sandwich'*-type structure (*type IIIB*, Figure 19). The potassium ion is embedded between two ligand molecules. Both ligand units are arranged approximately centrosymmetrical with respect to each other, all ten oxygen atoms lying at the corners of an irregular pentagonal antiprism.

On the other hand with the fitting Na^+ ion, 4 forms a *sodium iodide complex* (Figure 21a)[205] present as a 1 : 1 monohydrate coordination compound of pentagonal pyramidal configuration, in which the Na^+ ion is coordinated by the five coplanar ligand oxygen atoms lying at an average distance of 2.39 Å and stands 0.75 Å out of the ring-plane. The sixth corner is occupied by a H_2O molecule bound to the Na^+ ion at a distance of 2.29 Å.

Ca^{2+} with a similar ionic radius as Na^+ (cf. Table 13) also gives a 1 : 1 complex with 4[206]; however, differences result in the crown ether structure, reflecting the influence of the cation charge on the ligand arrangement. In the *$Ca(SCN)_2 \cdot H_2O$*[206] or *$Ca(SCN)_2 \cdot MeOH$ complex of benzol[15]crown-5* (Figure 21c) the Ca^{2+} ion is irregularly eightfold coordinated by the crown ether ring on one side and both SCN ions as well as a H_2O and MeOH molecule on the other side. The structures of the H_2O and MeOH complexes differ only slightly by the steric arrangement of one of the two SCN groups. While the Na^+–[15]crown-5 complex displays a very regular crown ether conformation, strong distortions of the bond angles crop up in the calcium complexes. Moreover, the Ca^{2+} ion is displaced farther (1.22 Å) out of the plane of the crown ether.

In the *$Mg(SCN)_2$–[15]crown-5 complex* (Figure 21d)[206b] one notes, just as in the case of the Na^+ complex, the pentagonal bipyramidal structure as well as the high regularity of the crown ether framework. The Mg^{2+} ion is small enough to settle inside the crown ether ring where it is coordinated by the five ether oxygen atoms; two nitrogen atoms of the anion occupy the axial positions of the bipyramid.

Thus with benzo[15]crown-5 magnesium forms only a *1 : 1 complex*, calcium forms both *1 : 1 and 2 : 1 complexes*, and the larger cations (like potassium) form only *2 : 1 crown ether/metal salt complexes*.

Regarding its cavity geometry, the 24-membered cyclic *dibenzo[24]crown-8* (7)

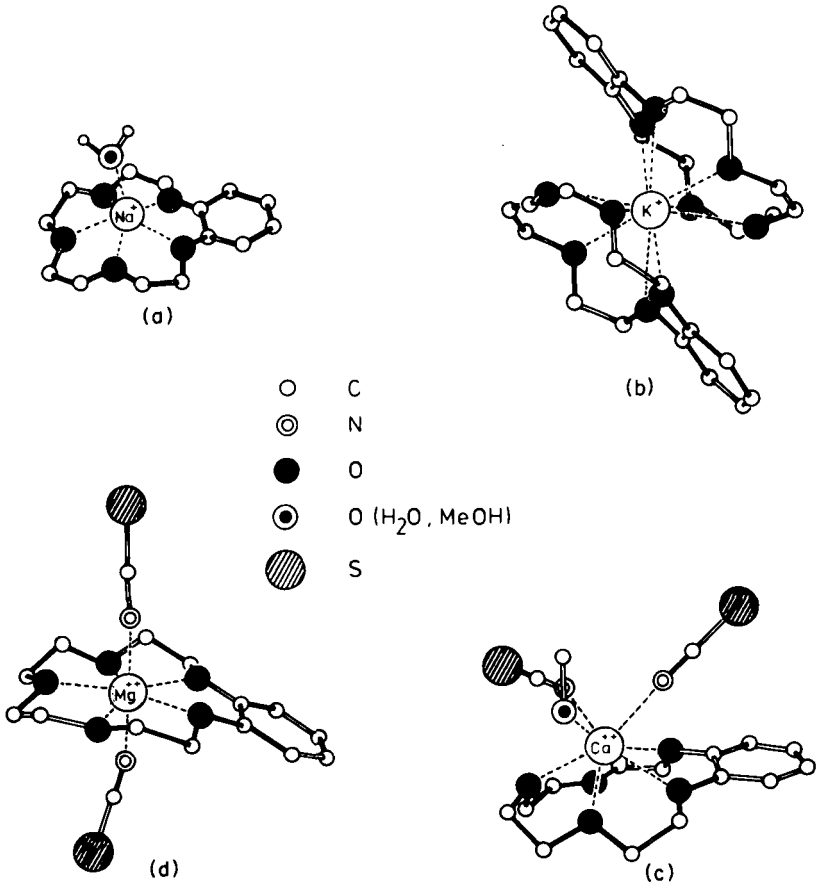


FIGURE 21. Different types of benzo[15]crown-5 alkali/alkaline earth metal ion complexes.

is suited to take up two K^+ ions, thus giving rise to a two nuclei-containing *KSCN complex (type IIB*, Figure 19). The eight oxygen donor sites, which are shared between two potassium ions, cannot completely saturate the coordination sphere of the central ions; thus the corresponding anions participate in the K^+ complexation. The 2 : 1 KSCN complex of dibenzo[24]crown-8 (Figure 22a)[207] shows a symmetry centre with K^+ ions almost coplanarly enclosed by the oxygen atoms. The thiocyanate anions are coordinated to the central ions via the nitrogen atoms; moreover benzene rings of neighbouring molecules seem to participate in the complexation.

The *di(sodium o-nitrophenolate)–dibenzo[24]crown-8 complex* (Figure 22b)[208] differs structurally from the KSCN complex in the sense that two ether oxygen atoms of the octadentate ligand do *not* participate in the coordination. Each Na^+ ion is bound to only three oxygen atoms of the ether. The *o*-nitro-

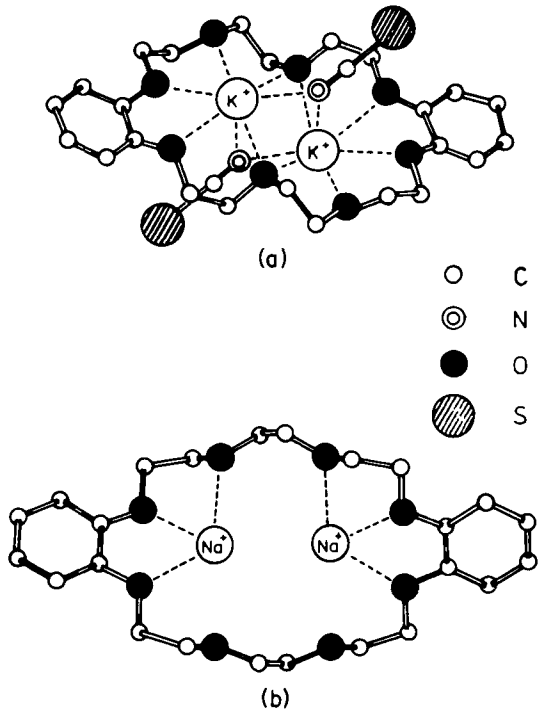


FIGURE 22. Structures of Na^+ and K^+ complexes of dibenzo[24]-crown-8.

phenolate ions serve to bridge both Na^+ ions and complete the coordination at the cation to six.

With the alkaline earth metal ions and dibenzo[24]crown-8, only 1 : 1 complexes have been obtained so far[209,210], although these ions have largely the same radii as the alkali ions. Apparently, the higher charge of double-valent ions prevents their juxtapositional settling within the same cyclic ligand as is possible with single-charged ions. In the *Ba(picrate)$_2$·2H$_2$O-dibenzo[24]crown-8 complex*[209] only *five* of all eight donor sites of the ligand are used for the coordination of the Ba^{2+} ion. The coordination number of ten of the Ba^{2+} ion is attained through a complex arrangement with two H_2O molecules, two phenolate oxygen atoms of the picrate and one oxygen of an *o*-nitro group. It is interesting to note that *one* of the two H_2O molecules is bound to the central Ba^{2+} ion as well as via hydrogen bridges to two unoccupied ether oxygen atoms of the crown ether ring. Up to date this is a unique case of a crowned 'hydrated cation', whereby the cation as well as a water molecule is coordinated by the crown ether.

Large polyether rings with an unfavourable ratio of ligand cavity to cation diameter can also use their numerous oxygen donor atoms to coordinate a single cation. Thus, for instance, the Ba^{2+} ion in the *1 : 1 Ba(ClO$_4$)$_2$–[24]crown-8 complex*[210] is altogether tenfold coordinated by the eight available ether oxygen atoms almost completely encircling the cation and by both perchlorate ions (one of which is possibly bidentated).

Finally the central ion can be completely wrapped up in a spherical ligand as was analogously observed in a few antibiotic complexes[211]. As a prerequisite the ligand must display high, conformational ring flexibility (cf. Section III.D.1.c).

In the *KI complex* of *dibenzo[30]crown-10* (8), the cyclic ligand tightly encloses the central K^+ ion in a 'tennis fissure'-like conformation so that an approximately closed basket structure results (Figure 23b)[135]. The relatively short K–O bond lengths determined by X-ray point to the fact that all ten donor atoms belong to the coordination sphere of the potassium ion.

The *free ligand* 8 (Figure 23a)[135] has a symmetry centre as symmetry element; the K^+ complex on the other hand, has a twofold crystallographic axis passing through the central atom. The coplanar arrangement of several oxygen atoms, which is typical of many crown ethers, is not found in the above complex.

In the *RbSCN complex* of *dibenzo[18]crown-6* (1), however, the six ether oxygen atoms are again coplanarly arranged, though a twisted and complicated structure is to be expected as a result of the uneven stoichiometric ratio of 2 : 3. The sandwich structure that was postulated at first could not be confirmed by X-ray analysis[212]. The unfavourable ligand/salt ratio is rather due to the fact that in the unit cell of the crystal lattice *uncomplexed molecules of* 1 are present besides the coordinating ligand. Thus, though the molecular architecture of crown ether complexes essentially obeys strict topological rules, it may show deviations from

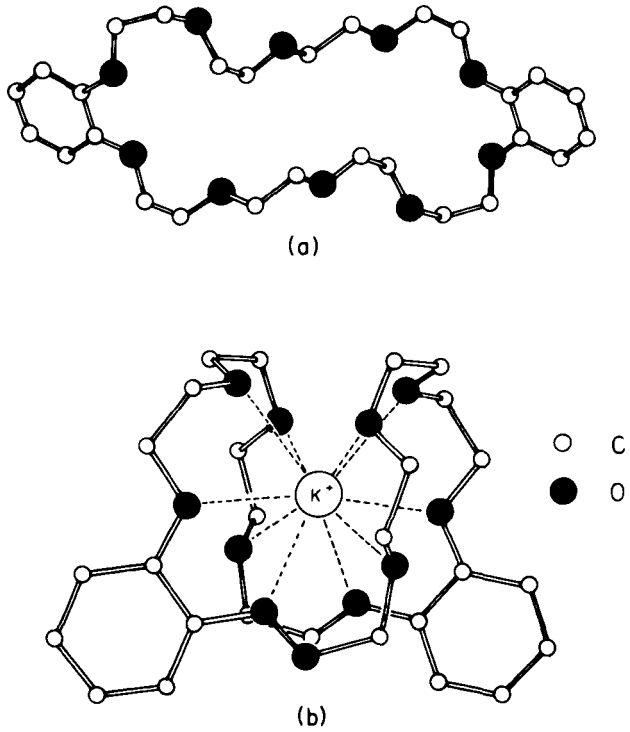


FIGURE 23. Molecular structure of dibenzo[30]crown-10 and of its potassium complex.

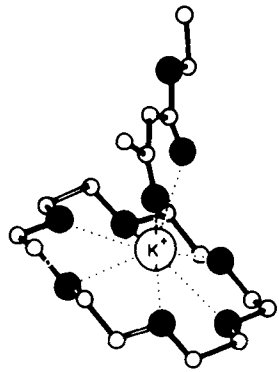


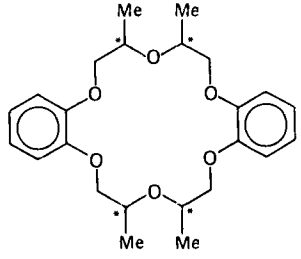
FIGURE 24. Structure of [18]crown-6 potassium ethyl acetoacetate enolate.

time to time[190]. The Rb^+ ion of the coordinately bound cation/ligand unit is expectedly displaced from the centre of the six ligand oxygen atoms; the SCN^- group stands approximately perpendicular to the polyether ring and shares (nitrogen-bonded) the seventh coordination site of the Rb^+ ion in the 'crowned RbSCN ion pair'[213].

A similar geometry is revealed by the *potassium acetoacetate–[18]crown-6 complex* (Figure 24)[214] in which the K^+ ion is coordinated to the six ring oxygen atoms and bound *chelate-wise* to both oxygen atoms of the acetoacetate anion[215].

In the same way that incorporation of benzo nuclei influences the 'crystalline structure selectivity' of cation complexes, alkyl substituents can also play an influential role on the geometry and stoichiometry of the complex.

As an example *tetramethyldibenzo[18]crown-6* (**114**)[16e,197] with four chiral centres shows clearly how slight differences in the stereochemistry of a ligand (same number of donor sites) can influence the formation of a complex. While $Cs(SCN)_2$ and a *racemic* isomer of the five possible isomers of tetramethyldibenzo[18]crown-6 form a 2 : 1 sandwich complex, containing a *twelvefold* coordinated Cs^+ ion, a 1 : 1 complex is obtained with the *meso* configured ligand (**114**)[216]. In the latter complex two Cs^+ ions are joined via a thiocyanate bridge (*N*-coordinated), so that the Cs^+ ion attains only an *eightfold* coordination, if any



(**114**)

interaction with the aryl carbon atoms is neglected. When dibenzo[18]crown-6 is hydrogenated[1b], five isomers of *dicyclohexano[18]crown-6* (**59**) are, in

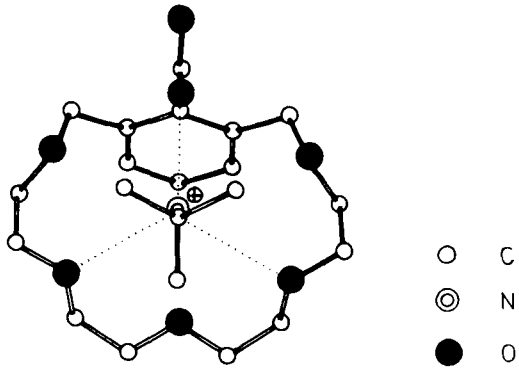


FIGURE 25. Structure of intraannularly substituted *m*-cyclophane crown ether (70)–*t*-$BuNH_3^+$ complex in the perching configuration; NH···O bonds as dotted lines.

principle, possible [217] (cf. Section III.D.1.b, Table 14). The structure of the $Ba(SCN)_2$ complex obtained with **59a** establishes that it is the *cis–syn–cis* isomer[218]. **59b** is shown to be the *cis–anti–cis* isomer in the study of its $NaBr{\cdot}2H_2O$ complex[219]. In the $Ba(SCN)_2$ complex, the Ba^{2+} ion is located on a twofold axis and fits in the cavity of the ligand. In the $NaBr{\cdot}2H_2O$–**59** complex, the sodium ion has a hexagonal bipyramidal coordination with water molecules at the apices, and the structure is held in place by hydrogen bonding.

The structural skeletons of crown ether *ammonium salt complexes* are predominantly marked by *hydrogen bond*[18c,185]. An example of a crystalline complex of host–guest type involving a carboxylate ion and two ether oxygens as hydrogen bonding sites for a *t*-$BuNH_3^+$ ion is given in Figure 25[18c,220]. The X-ray structure indicates a *perching configuration* of the ligand [cf. Section III.D.1.a(1)]. Noteworthy is that the three $NH^+\cdots O$ hydrogen bonds are arranged in a tripod, that the *t*-Bu–N bond is only about 3° from being perpendicular to the least square plane of the binding oxygens, that these oxygens turn inward and somewhat upward toward the NH_3^+, and that the H–N–C–C dihedral angles are about 60°, as predicted by inspection of CPK molecular models[18c].

b. Heavy metal ion complexes. Of the transition metals *lanthanide ions* as class A acceptors[94] show the strongest similarity to the alkali and alkaline earth ions (cf. ionic radii, electropositivities etc.[221]) and should be properly complexed by crown ethers containing five or six oxygen atoms.

The first complex of this group to be examined by X-ray, namely, the *$La(NO_3)_3$ cis–syn–cis isomer of dicyclohexano[18]crown-6* (Figure 26*a*)[222], was also the first example of a tripositive cation–crown compound and the first uncharged molecular *12-coordinated* complex to be described. The La^{3+} ion is bound to six ether oxygen atoms (La–O distances 2.61–2.92 Å) and to six oxygen atoms of the three bidentate nitrate ions (2.63–2.71 Å) (one on the sterically more hindered side of the crown ether ring and two on the more favourable side). The ether oxygen atoms are nearly coplanarly arranged and the cation is situated in the cavity.

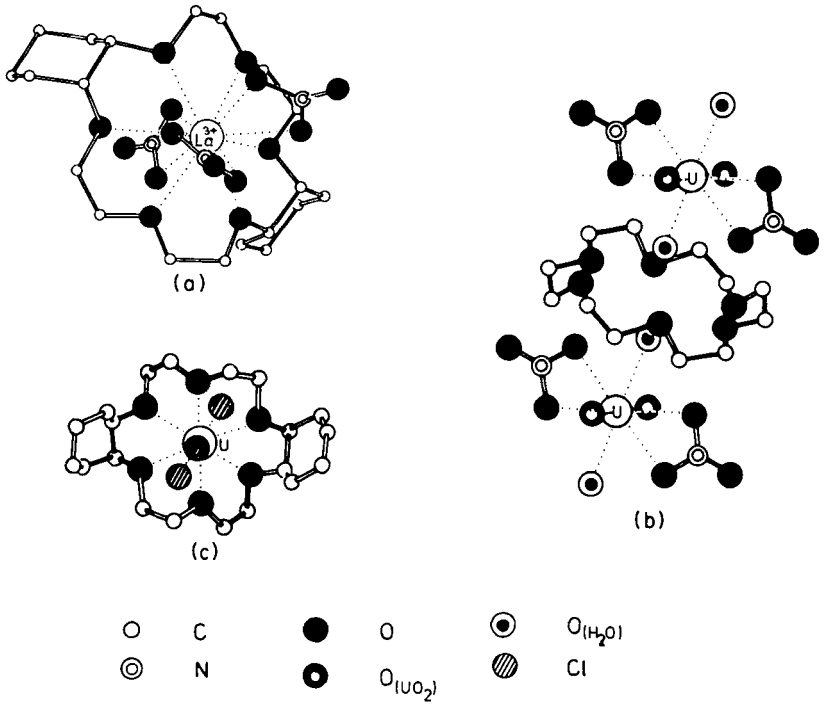


FIGURE 26. Structures of several crown ether complexes of lanthanum and uranium.

The *actinide salts* often consist of complex ions[79], which persist in crown ether aggregates and give rise to structures resembling much less the 'true' crown ether complexes than compounds of the *host–guest type* (cf. Section IV.B.1.c). In the *$UO_2(NO_3)_2 \cdot 2H_2O$–[18]crown-6 complex* (Figure 26b)[223], for example, there is *no* direct bond to the donor atoms of the polyether ligands, but very short H_2O-oxygen/ether oxygen atom distances can be established (2.98 and 3.03 Å). The linear uranyl group is coordinated *only* to the two bidentate nitrate ions and to the water molecules. Therefore the whole structure could be described in terms of polymeric chains with alternation of $UO_2(NO_3)_2 \cdot 2H_2O$ groups and [18] crown-6 molecules connected together through a system of hydrogen bonds. Remarkably the conformation of the ligand in this complex more strongly resembles that found in the KSCN[200] and RbSCN complexes[201] of [18]crown-6 than that of free [18]crown-6 in the crystal[194].

The recently described *UCl_4–dicyclohexano[18]crown-6 complex* (Figure 26c)[224] possesses a structure akin to that of the *true* crown ether complexes. A pair of the three uranium atoms in the unit cell of $UCl_6(UCl_3[18]\text{crown-6})_2$ is directly bound to the crown ether ring, three chlorine atoms acting as neighbours. The third uranium atom is surrounded octahedrally by six chlorine atoms.

Only relatively few of the numerous crown ether complexes with typical heavy metal ions such as those of Fe, Co, Ni, Ag, Zn, Cd, Mg, Pd, Pt, etc.[225] have been structurally examined as yet[226]. In many respects, they resemble the foregoing lanthanide and actinide complexes.

Thus, the *$[MnNO_3(H_2O)_5]^+$–[18]crown-6-$NO_3]^-\cdot H_2O$ complex* (Figure 27a)[226b] displays a structure closely related to that of the $UO_2(NO_3)_2\cdot 2H_2O$–[18]crown-6 complex (cf. Figure 26b) with piled metal/H_2O/anion and crown ether rings connected together through hydrogen bonds.

As for the *$(CoCl)_2$–dicyclohexano[18]crown-6 complex*[226a], sandwich structures are discussed in which the metal ion makes direct contact with three crown ether oxygen atoms.

However, cases are also known, where, as in classical crown ether complexes (*type Ia*, Figure 19) heavy metal ions are located at the centre of the ring.

The [18]crown-6-analogous *triaza ligand* **12** encloses Pb^{2+} in the approximately coplanar arrangement of the ligand donor atoms (Figure 27b)[226e]. Both of the SCN ions serve to fill up the eight coordination sites of the Pb^{2+} ion; they lie above and below the ligand plane, being bound once through nitrogen and once through sulphur to the metal ion. The soft Pb^{2+} ion is *preferentially* coordinated to the softer nitrogen atom (Pb–O distances 3.07 Å, Pb–N 2.60 Å). In this respect, the heavy metal ion complex differs from the corresponding alkaline earth ion complexes of the same ligand, in which *all* donor atoms (N and O) are almost equidistant from the central ion[227].

The differentiation of the heavy metal ion between more (e.g. S, N) and less favourable donors (e.g. O) in substituted crown ethers may be marked to such an extent that whole ligand regions with their donor sites are displaced out of the influence sphere of the cation, thereby remaining uncoordinated (Figure 27c)[228]. Analogous alkali/alkaline earth complexes of *dithiapyridinocrown* (**115**)

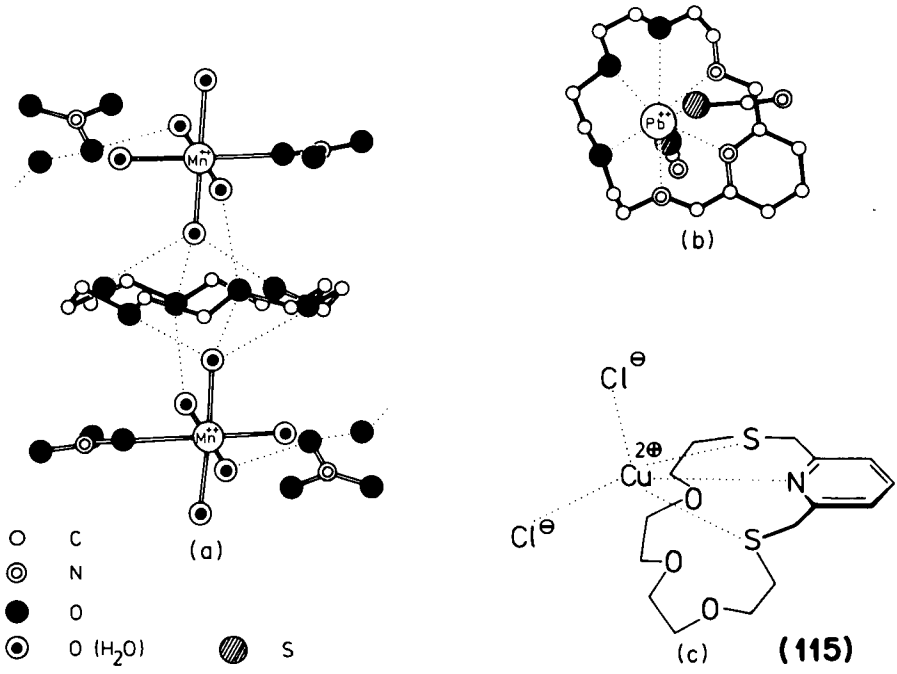


FIGURE 27. Several typical heavy metal ion complexes of [18]crown-6 and nitrogen and sulphur analogues.

show – in contrast to the $CuCl_2$ complex of **115** – nearly ideal proportions relative to all donor atoms[228,229] and this may be termed as a distinct stereochemical answer in the course of the molecular recognition of two ball-shaped cations by the same ligand.

c. Neutral molecule host–guest complexes. The existence of crown ether complexes composed solely of neutral (uncharged) molecules was recognized by Pedersen, who first isolated *thiourea complexes* of some benzocrown ethers[230].

Cram and Goldberg carried out a structural elucidation with the *dimethyl acetylenedicarboxylate [18]crown-6 complex* as example (Figure 28a)[185]. A remarkable feature of the complex is that all six oxygen atoms of each crown ether molecule participate on opposite sides of the crown by means of dipole–dipole interactions between the electronegative oxygen atoms of the crown and the electropositive carbon atoms (methyl groups) of the guest.

In the 1 : 2 host–guest complex of [18]crown-6 with *benzenesulphonamide* (Figure 28c)[186] strong and weak NH . . . O interactions are found, but the crown

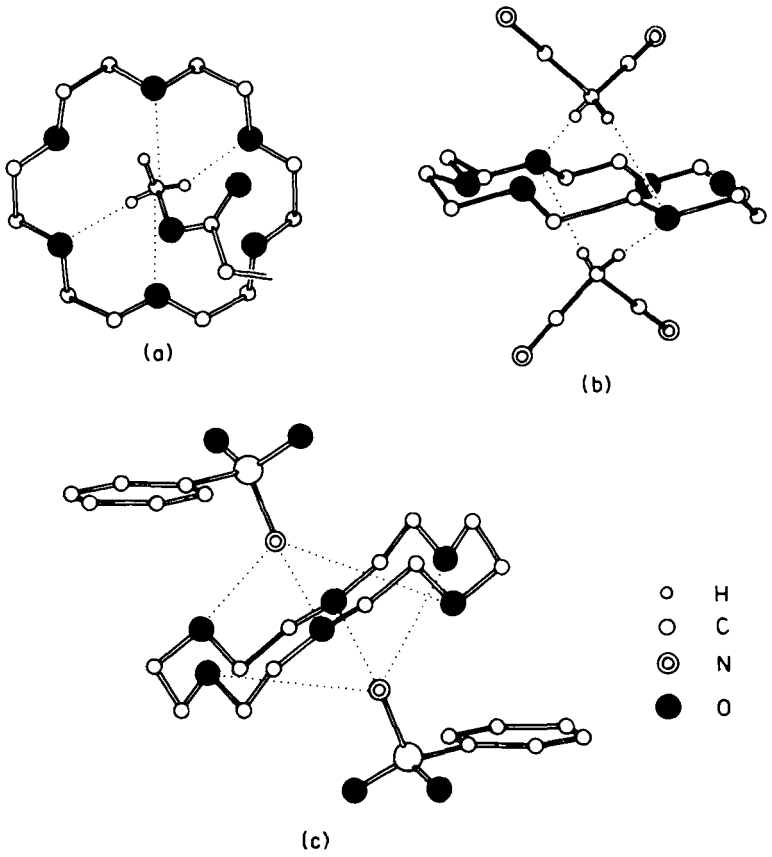


FIGURE 28. Complexes of [18]crown-6 with CH- and NH-acidic neutral guest molecules.

adopts nearly the same conformation as the uncomplexed hexaether (cf. Figure 20a).

Complexes formed by *CH-* (see Figure 28a[185], *malodinitrile–[18]crown-6 complex*, cf. Figure 28b[231]) and *OH-* and *NH-acidic* substrates (Figure 28c), usually show *layered* structures, in which crown ether host and guest molecule are held together through H-bonds and dipole–dipole interactions.

2. *Bi- and poly-cyclic cryptates (see Figure 2)*

a. Bicyclic ligands. X-ray structure analyses of uncomplexed cryptands and their cryptates allow interesting comparative studies of ligand conformation. The free ligands may exist in three forms differing in the configuration of the bridgehead nitrogen: *exo–exo* (out–out), *exo–endo* (out–in) and *endo–endo* (in–in)[11a,12b]. These forms may interconvert rapidly via nitrogen inversion[13c,53]. Crystal structure determinations[232–235] of a number of cryptands and cryptates showed that the alkali, alkaline earth and heavy metal cations were contained in the tridimensional molecular cavity[236] and that in all cases the ligand has the *endo–endo* configuration, even in the uncomplexed state[237].

Figure 29 shows the configuration of the *[2.2.2]cryptand*[237] and of its Rb^+ *complex*[233,234a]. Four ether oxygen atoms and the two nitrogen atoms participate in octahedral coordination of the cation. In both the complex and the free ligand, the two nitrogen atoms are in *endo–endo* configuration. Whereas the ligand is flattened and elongated when free, it has swollen up in the complex.

With increasing ion radius and coordination number of the embedded cation ($Na^+ < K^+ < Rb^+ < Ca^{2+}$) one observes a progressive opening-up of the molecular cavity of the [2.2.2]cryptand with torsion of the ligand around the N/N axis[234b]. Under such circumstances, possibilities of anion or solvent/cation contact are present[234a,234g,235] as, for example, in the *Eu(ClO$_4$)[2.2.2]$^{2+}$ cation*[238], where a pair of the ten coordination sites (eight being shared by the cryptand) of the europium is saturated by a bidentate ClO_4^- ion. The geometry of the coordination polyhedron can be described in terms of a bicapped square antiprism with two nitrogen atoms at the apices.

In the *bivalent* cation complexes anion and/or solvent coordinations are found apart from a few exceptions[234a,234g,235].

Two nuclei-containing complex structures, as are known for voluminous mono-

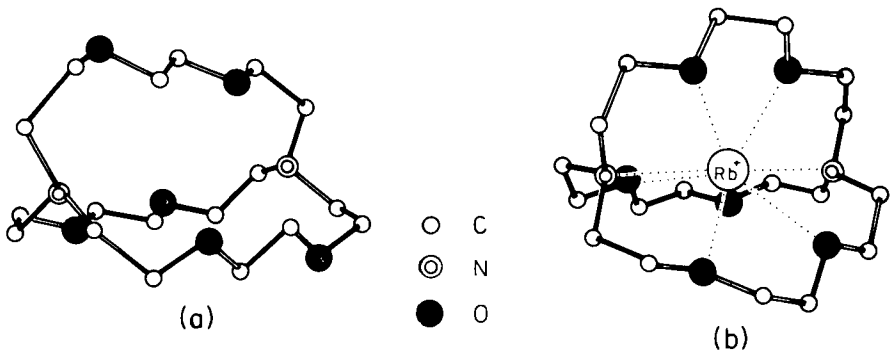


FIGURE 29. Molecular structures of [2.2.2] cryptand (19) and of the rubidium cryptate.

cyclic crown ethers (see Section IV.B.1.a), are nonexistent for bicyclic cryptands. On the whole, the known structures of bicyclic cryptates are not as varied as those of crown ethers.

b. Tricyclic cryptands. Complexes with *two* enclosed cations are, however, known for tricyclic cryptands like **23** (Figure 2). Figure 30a shows the structure of the **23**–*NaI cryptate* in which each Na^+ ion is bound to two nitrogen atoms and five oxygen atoms of the ligand[239]. The lengths of the Na–N and Na–O bonds of both molecular single-cavities are approximately the same as in the [2.2.2]–NaI complex[234e]; the Na^+ ions of both hemispheres lie 6.4 Å apart.

The cation/cation separations of the two corresponding nuclei-containing *heavy metal complexes* of tricyclic ligands are of theoretical interest[240].

Recently two complexes of the spherical macrotricyclic ligand **24** ('soccer molecule', see Figure 2)[117], which contains four bridgehead nitrogens, all in the *in–in* conformations, were reported[241]. One complex (Figure 30b) consists of an *ammonium cation* in the molecular cavity, held in place by hydrogen bonds. In the latter complex (Figure 30c) the *tetraprotonated* ligand **24** forms an unusual *anion inclusion complex* (anion cryptate) with Cl^- (cf. Section III.D.2). The four

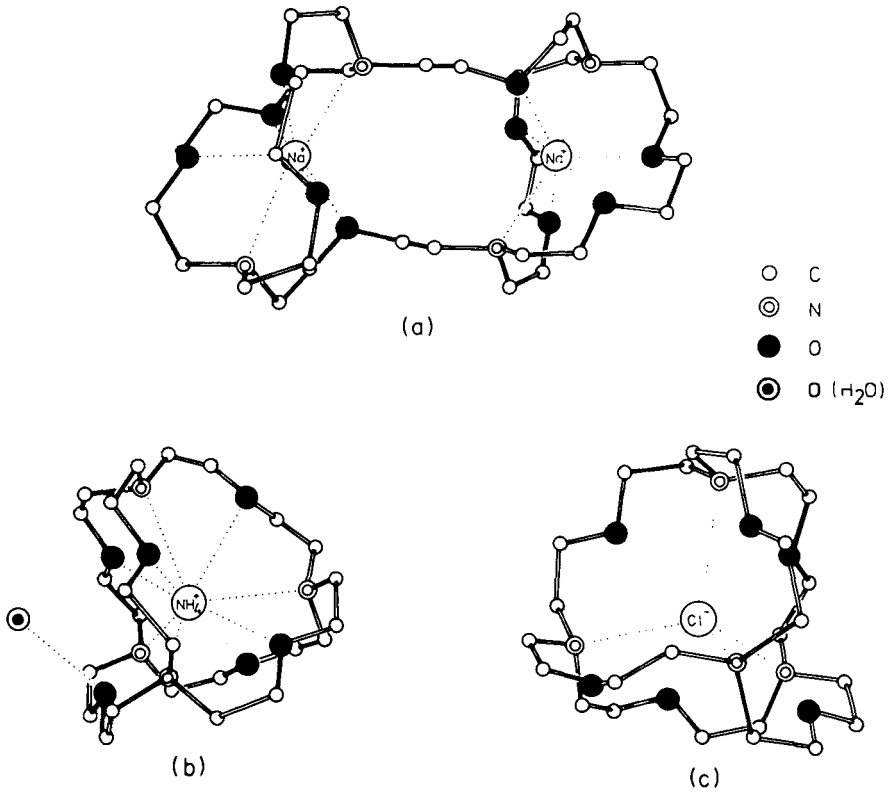


FIGURE 30. (a) Two nuclei-containing Na^+ complex of the tricyclic cryptand **23**; (b) NH_4^+ complex of the soccer molecule **24**; (c) anion cryptate of the tetraprotonated soccer ligand.

hydrogen-bonded nitrogen atoms of the ligand are located at the corner of a tetrahedron, and the six oxygen atoms are at the corner of an octahedron. Noteworthy are the short Cl–N distances of 3.09 Å, which are less than the sum of the van der Waals' radii.

3. Open-chain podates (see Figures 5–7)

a. Glymes, glyme-analogous and simple noncyclic ligands. Until recently little has been known about the synthesis of crystalline alkali complexes of glyme-type poly- and heteropoly-ethers[24]. Subject to better X-ray investigations, however, have been the glyme complexes of *transition metal ions* such as Fe^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} [242], and Hg^{2+} [243] and Cd^{2+} salts[244].

While several ligand units (three as a rule) are required in the case of *dimethoxyethane* (**49**) ($n = 0$) (monoglyme, see Figure 7)[242,245], longer polyether chains (hexaglyme) (**49**) ($n = 5$) sometimes form two nuclei-containing adducts also[243c].

The X-ray structure analysis of the *tetraethylene glycol dimethyl ether (TGM)* (**49**) ($n = 3$)–*$HgCl_2$ complex*[243a] (1 : 1 stoichiometry) shows the following ligand conformation[246] (Figure 31a): All H_2C–O bonds are in antiperiplanar (*ap*) arrangement; the CH_2–CH_2 bonds in each following unit are oriented synclinal (*sc*) and (−) synclinal (−*sc*). In this way, the ligand is fixed in an unclosed circular form with the five oxygen atoms lying almost coplanarly inward and surrounding the Hg^{2+} ion at a short distance of 2.78–2.98 Å.

In the corresponding *tetraethylene glycol diethyl ether (TGE)–$HgCl_2$ complex*[243b] very similar Hg–O distances and bond angles are found. An *sc*-arrangement is present only at one end of the chain, where as such steric hindrance of the ethano groups in an *ap/ap*-conformation is avoided. Armed with seven potential coordination sites, *hexaethylene glycol diethyl ether (HGE)* is able to bind *two* Hg^{2+} ions at a relatively short Hg–O distance (2.66–2.91 Å) (Figure 31b)[243c]. The remarkable feature of the complex structure is the presence of two consecutive *sc/sc*-arrangements at the central oxygen atom, which causes a separation into two coordination cavity halves, each being outlined by four coplanar oxygen atoms and containing one Hg^{2+} ion. The central oxygen atom is coordinated by both Hg^{2+} ions.

The same structural principle is again found in the *tetraethylene glycol dimethyl*

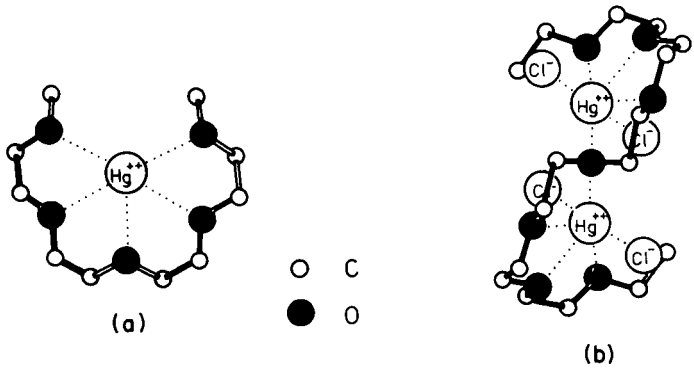


FIGURE 31. Oligoethylene glycol ether complexes of Hg^{2+} ions.

ether (TGM)–$CdCl_2$ complex[244]. Owing to the smaller number of available donor sites, however (five per glyme molecule), coordinating chlorine bridges additionally function to hold together two ligand units via four Cd^{2+} ions.

The synthesis of corresponding *alkali* and *alkaline earth complexes* met with difficulties for quite a long time[26a]. Meanwhile, success has been achieved with *glymes* of various chain-lengths (hexaglymes, heptaglymes)[32], glyme-analogous *oligoethylene glycol mono- and di-phenyl ethers* (47 and 48, see Figure 7)[32] and even with nonalkylated *oligoethylene glycols* (including ethylene glycol itself)[33a]. X-ray structure analyses of these simplest open crown type ether complexes remain to be done.

Crystalline 2 : 1 complexes of the crown ether related *phenacyl cojate* (116) (see Figure 32)[247] with sodium halogenides in methanol were isolated 40 years ago; their structures, however, could be investigated only lately[248].

The geometry of the *NaI complex* (Figure 32a)[248d] resembles that of [18] crown-6 with corresponding sodium salts[249]. Six oxygen donor centres (belonging to two phenacyl cojate units) display a planar arrangement around the sodium ion, while four of them are delivered by a carbonyl group in contrast to the crown ether complex. The crystal structure is held in place by hydrogen bonds between CO and OH groups as well as by H· · · O interactions.

A remarkably stable 2 : 1 complex is formed between O,O′-*catechol diacetic acid* (117) with KCl[250]. It shows a complicated layer structure stabilized by hydrogen bonds with the potassium ions enclosed sandwich-like between ten oxygen atoms (four ether and six carboxyl oxygen atoms) in an irregular pentagonal antiprismatic arrangement (Figure 32b). Corresponding coordination compounds are not obtained with lithium, sodium, caesium and ammonium salts. The observed 'precipitation selectivity' for K^+, which surpasses $NaBPh_4$, is unusual, since all precipitation reagents known so far for K^+ are also applicable to NH_4^+, Cs^+ and Rb^+[251].

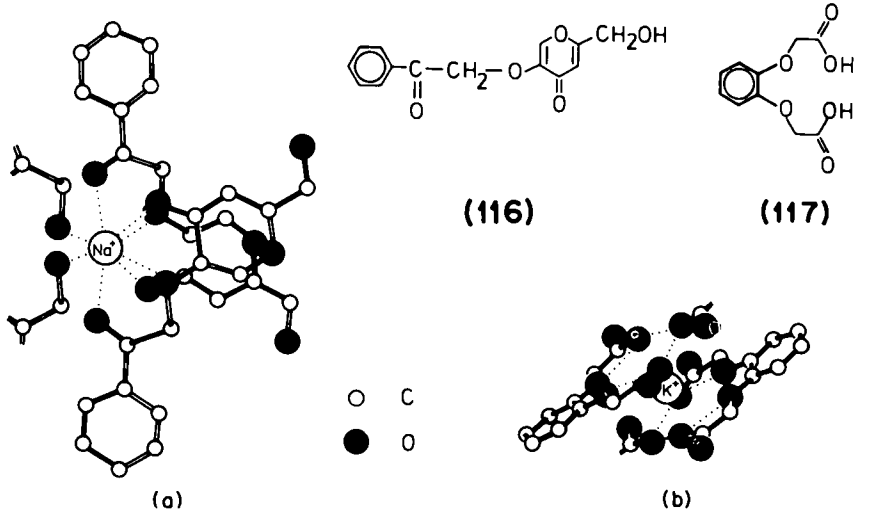


FIGURE 32. (a) Arrangement of Na^+ phenacyl cojate (116) complex; (b) K^+ complex of *O,O′*-catechol diacetic acid 117. Dotted lines in (b) indicate irregular pentagonal antiprismatic arrangement of the oxygen atoms.

b. Noncyclic crown ethers and cryptands. (1) *Alkali and alkaline earth metal ion complexes.* Despite the less strictly defined 'cavity geometry' of noncyclic crown ethers and cryptands to that of cyclic ones, complexes of *definite stoichiometric composition* are formed as a rule (ligand : salt = 1 : 1, 2 : 1, 3 : 2) and also in presence of a large excess of one component of the complex[24–26]. For instance, the open-chain ligand **34c** (see Figure 5) reacts with KSCN to form exclusively the 1 : 1 complex independently of the stoichiometric amounts of ligand : salt (such as 2 : 1 or 1 : 2) used[26a]. Remarkably, water and anion participations in the metal coordination are hardly more frequent for these relatively 'open' ligand structures than for their cyclic counterparts[24].

For the **34c**–*RbI complex*, the X-ray structure analysis (Figure 33a)[252] reveals a participation of all seven heteroatoms (5 O, 2 N) in the complexation and for the

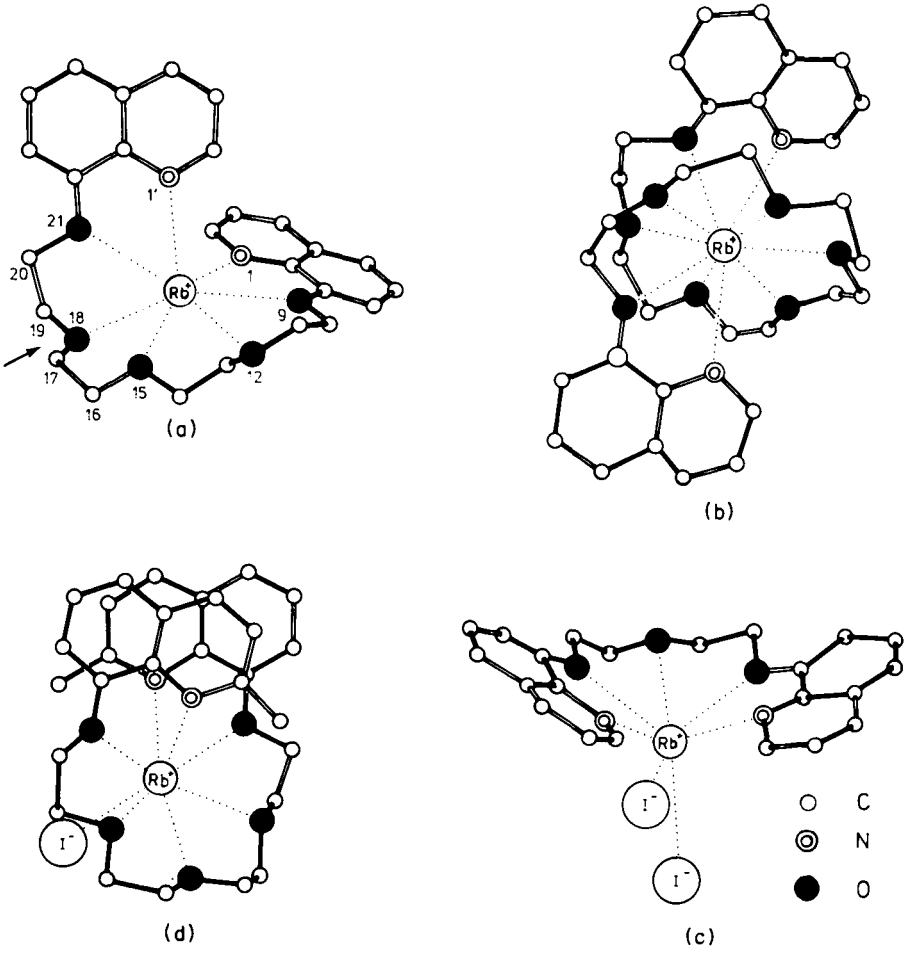


FIGURE 33. Rb^+ complexes of open-chain crown ethers with different numbers of oxygen donor sites.

first time a *helical structure* arrangement of a synthetic open-chain ionophore around an alkali metal ion (racemate of plus and minus helices). The iodide ion is, however, not included in the coordination sphere of the central ion; also it does not come in direct contact with any heteroatom of the quinoline ether. Though the bond lengths and angles between the various heteroatoms (O,N) and the Rb^+ ion differ from one another, they can be considered to be approximately symmetrical about an axis passing through the Rb^+ ion and the $O_{(15)}$ atom (cf. Figure 33a). The most remarkable structural feature is the angle – *sp* instead of *ap* (see arrow mark) – at the atoms $C_{(17)}-O_{(18)}-C_{(19)}-C_{(20)}$, which seems to be necessary for avoiding a collision between both terminal quinoline units. This evokes a fold of heteroatoms $O_{(21)}$ and $N_{(1')}$ together with the attached quinoline skeleton out of the plane of the remaining five donor sites and a 0.748 Å displacement of the Rb^+ ion in the direction of the folded quinoline nucleus, thereby imparting to the complex its particular helical structure.

The *decadentate* ligand **34e**, *lengthened by three* oxaethane units, does not show any upfield shift of the quinoline protons during complexation of alkali metal cations in solution[107], as is observed for the shorter open-chain ligand **34c**[26a]. This may suggest that either the two terminal groups do not participate in the complexation or that during the process of cation complexation, both quinoline moieties are far apart as shown by molecular models. The latter supposition has been confirmed in the RbI complex by X-ray analysis for the crystalline state (Figure 33b)[253]. The eight oxygen atoms are *helically coiled* around the central cation in the equatorial plane, while both of the quinoline moieties coordinate from *above* and *below*. Thus, we have a case of a novel complexation geometry of a decadentate ligand.

The helical skeleton of the **34c**–RbI complex gives way to an approximately planar (butterfly-like folded) arrangement with mirror-image-wise symmetry in the *RbI complex* of ligand **34a**, *shortened by two* oxaethane units (Figure 33c)[228]. In order to fill up the still unsaturated coordination sphere of the Rb^+ ion – five donor locations of the ligand are already involved in the coordination – two iodide ions per ligand unit alternately participate in the complexation.

The X-ray structure analysis of the **34d**–*RbI complex*[228] reveals significant differences in the ligand conformation, compared with the **34c**–RbI complex. While in the first case a discontinuous helix with a folded, but coordinated quinoline end-group is present, the bulky $(quinaldine)_2-ligand$ **34d** is arranged like a *continuous* screw in the complex (Figure 33d).

Also in the **35a**–*NaSCN complex* the ligand forms a continuous helix with one OCH_3 group fixed above/below the other benzene ring[228].

An X-ray structure analysis of the *1 : 2 KSCN complex* of **38** (Figure 34a)[254] shows that the ligand adopts a *S-like coiled* structure with remarkable parallels to the Hg^{2+} HGE complex shown in Figure 31b (see Section IV.B.3.a).

The X-ray structure analysis of the *1 : 1 KSCN complex* of the amide ligand **35e** reveals strikingly that *polymeric* ligand–cation chain structures are present (Figure 34b)[228]. The two carbonyl groups of the ligand do not coordinate the potassium cation enclosed by the five intramolecular ether oxygen atoms, but instead, share their coordination to the central ion of the next pair of ligands. The observation is in keeping with the high entropy of complexation found for the sodium ions, which may point either to a cyclization or/and to a polymerization entropy[80].

Interesting comparisons with structurally related carboxylic antibiotic ionophores (nigericin[7b,7c,29]) are brought about by the complexes of such types of ligands as **35c** and **46**, having potential *intramolecular attractive end-group inter-*

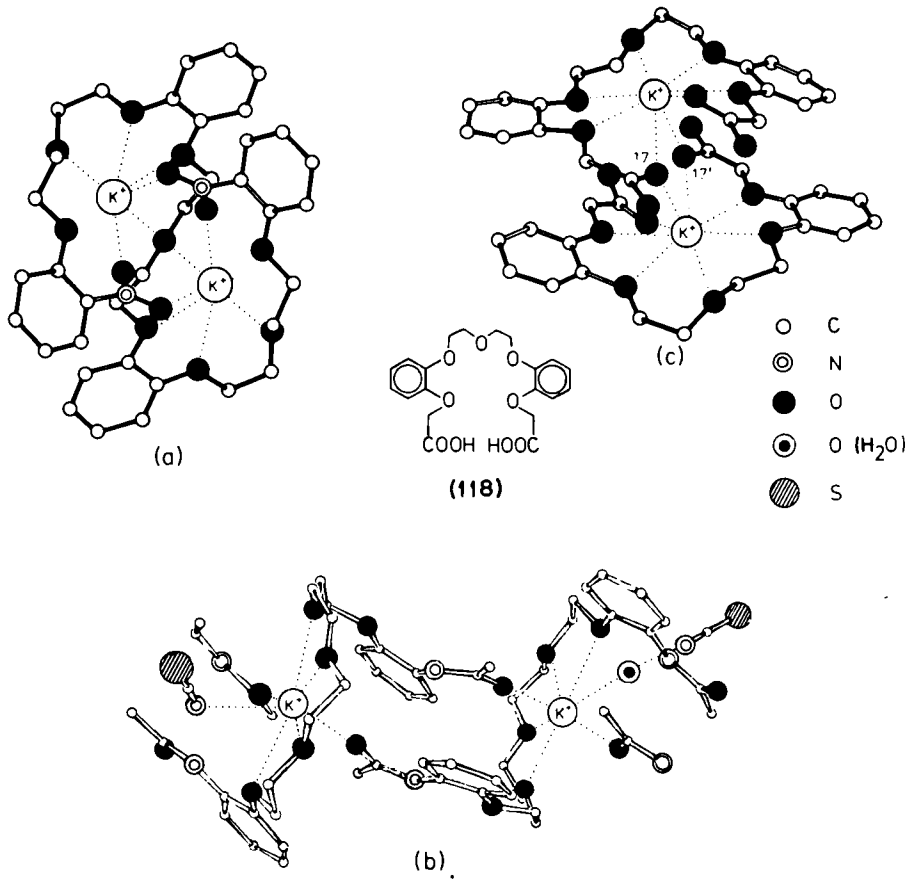


FIGURE 34. (a,c) Two-nuclei K^+ complexes of open-chain polyethers **38** and **118**; (b) section of the polymeric arrangement of the 1 : 1 KSCN complex of amide ligand **35e**.

actions[26b,29]. An X-ray structure analysis of the *potassium picrate complex* of the *polyether dicarboxylic acid* **118** (Figure 34c)[28a,255] is known[256]. Contrary to expectations, no intramolecular 'head-to-tail' hydrogen bonds, that should result in a pseudocyclic 1 : 1 complex unit, are observed. The most significant structural characteristic is rather the *dimeric* complex cation. Every single ligand is conformationally fixed by a potassium ion spiralwise. The end carbonyl oxygens (O_{17}, O_{17}') of the monomer function act as bridging atoms and are each additionally coordinated to a second potassium ion. Thus, each potassium achieves an irregular eightfold coordination. The two K^+ ions are separated by a distance of 4.74 Å.

The *three-armed decadentate* neutral ligand **40** ($n = 0$, R = OMe) reveals as the first example of an alkali metal ion complex of an *open-chain cryptand* (tripodand) a novel complexation geometry in its *KSCN complex* (Figure 35)[228]. All of the ten donor centres and the three OMe terminal groups participate in the coordination of the central cation. In order to achieve this coordination, the three arms wrap

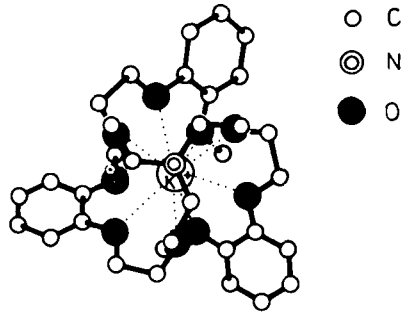


FIGURE 35. K^+ complex of open-chain cryptand 40.

around the cation in a *propeller-like* way. A particularly interesting fact is that coordination by the anion is totally hindered owing to complete envelopment of the cation; thus the anion remains outside the lipophilic periphery of the complex, in analogy to the bicyclic cryptates where the metal cations are also completely enveloped.

(2) *Heavy metal ion complexes.* A series of crystalline heavy metal ion complexes of open-chain crown ethers have been isolated[24-26], but relatively few have been structurally elucidated so far. Often it seems, as in the case of cyclic crown ethers, that water molecules are involved in the construction of a stable crystal lattice. The fact that carbonyl oxygen atoms participate as coordinating ligand locations not only in the undissolved form[257], but also in the crystal of open-chain crown ether complexes[278], has been confirmed by X-ray structure analysis of the *$MnBr_2$ complex* of 42 (Figure 36)[258].

In the above complex, the metal ion is coordinated by four *ether oxygen* atoms and four *carbonyl groups* of a pair of symmetrically equivalent ligands. The oxygen–metal ion distances are longer for the ether oxygens than for the carbonyl

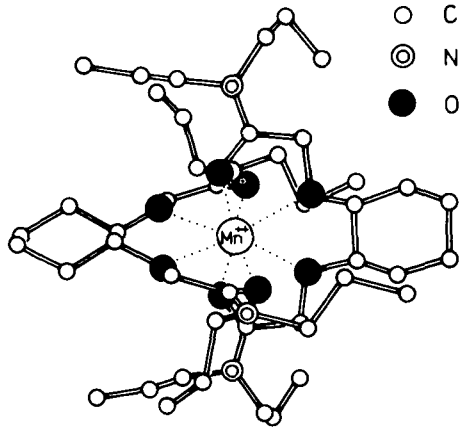


FIGURE 36. $MnBr_2$ complex of open-chain ligand 42.

groups; the latter distances (2.185 Å) are even shorter than the theoretically calculated ion–atom contact distances. (2.20 Å). The crystal lattice of **42**–$MnBr_2$ (1 : 1 stoichiometry) contains *two sorts* of Mn^{2+} ions with different geometrical coordinations; thus one sort is coordinated by a pair of ligand molecules as in the corresponding $CaCl_2$ complex[258], while the other one is surrounded by four bromide ions at the corners of a square.

(3) *Neutral molecules as guests.* Open-chain crown ethers can form stoichiometrical host–guest neutral molecule complexes[189] just as do their cyclic counterparts (cf. Section IV.B.1.c). The X-ray structure of the 1 : 1 adduct of *thiourea* and **35a** (see Figure 5) reveals remarkable characteristics (Figure 37)[259]. The conformation of the polyether host is such that it enables the thiourea guest to utilize all the possible multidentate interactions offered. Thus the thiourea molecule is hydrogen-bonded through NH···O interactions with *all seven* oxygen atoms of the ligand, the central atom $O_{(10)}$ accepting two hydrogen bonds and the other six oxygen atoms accepting one hydrogen interaction each. This geometry gives rise to four *bifurcated hydrogen bonds*, which have previously been demonstrated certainly only in a very few cases[260].

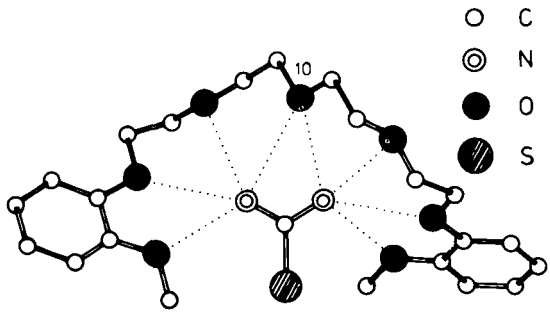


FIGURE 37. Thiourea complex of open-chain crown ether **35a**. Dotted lines indicate NH···O bifurcated hydrogen bonds.

V. OUTLOOK

The selectivity of crown ethers and cryptands toward alkali/alkaline earth and heavy metal cations will surely be exploited for *practical use* in many other cases[4–6]. New possibilites of development are to be expected with *anion receptors*[14d,e]. The intramolecular combination of crown ethers and other important molecular structures such as *dyes*[261], as well as that of *ionophoric* and *pharmaceutical*[262] or *polymeric* structures[137] showed other noteworthy trends of development. The field of organic receptor cavities may certainly be extended to include other very *voluminous, rigid* and *exohydrophilic/endolipophilic* host molecules that have hardly been investigated yet[263], and that can select between *neutral* organic guest molecules, the molecular properties of which are either masked or modified according to the peripheric structural features of the host envelope.

Perhaps, one day there will be concave host molecules with tailor-shaped endopolarophilic as well as endolipophilic cavities for many of the low molecular weight convex organic compounds.

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Crown Ethers and Analogs
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CHAPTER **5**

New developments in crown ether chemistry: Lariat, spherand and second-sphere complexes

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I. INTRODUCTION

The complexation chemistry of uncharged macrocyclic organic ligands (crown compounds) began in 1967[1] and is still a field of great evolution[2]. The original chapter, 'Crown

Ethers—Complexes and Selectivity', was written in 1979 and surveyed the state of knowledge up to that date. In the meantime researchers have made great progress on organic ligand complexation. Since it is necessary to make a selection, we shall discuss here three fascinating topics, viz. lariats, spherands and second-sphere complexes.

II. LARIAT ETHERS: 'ROPE-AND-TIE' COMPLEXATION

A. General

Lariat ethers (lariands)[2c] are compounds which contain a macrocyclic (crown or coronand) ring to which is appended a donor-group-bearing side-arm (podand arm). A generalized structure (**I**) is illustrated in Figure 1a.

It was thought (see Figure 1b) that the macroring would envelop the cation in the fashion normally associated with crown ether binding (**III**) and the donor groups attached to the flexible podand arm would further solvate the bound cation to form a lariat complex (**IV**). The ability of such molecules to 'rope-and-tie' the cation, as a lasso is used to bind an animal, suggested the name 'lariat ethers'[3,4]. In the particular case of **I** we speak of a monobracchial[a] lariat compound. Accordingly, *bi*bracchial *l*ariat *e*thers[5] (BIBLEs, see **II**

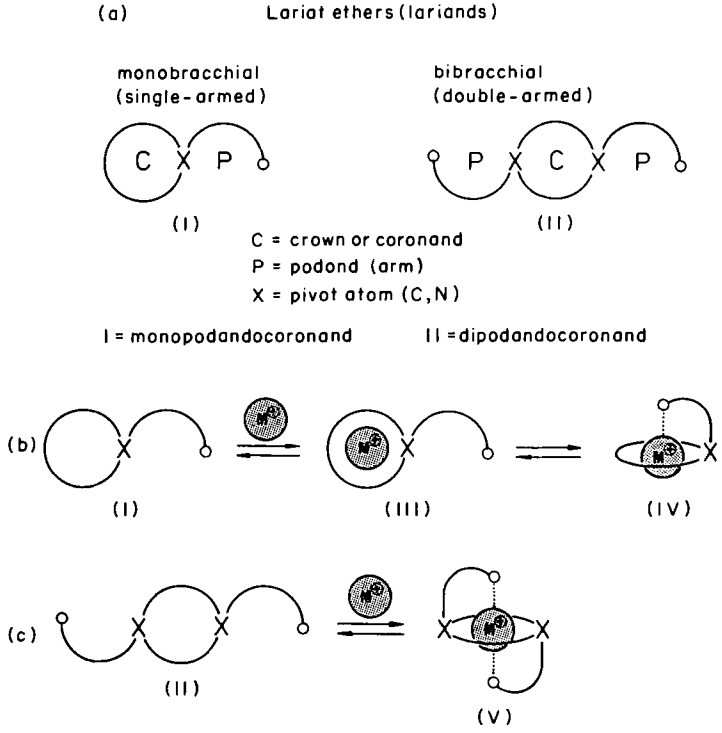


FIGURE 1. (a) Design concept of lariat ethers; (b) and (c) lariat complexation ('rope-and-tie' complexation)

[a]Taken from the Latin *bracchium*, meaning arm.

in Figure 1a) are distinguished by attachment of two flexible podand arms to a crown macroring. Cation complexation is considered to proceed as in **V** in Figure 1c. A further distinction is made in respect to the nature of the pivot atom (X, Figure 1a) which can be a carbon or a nitrogen centre.

Within the more universal terminology of host molecules and host–guest compounds[6], this type of ligand falls into the 'podandocoronand' subclass (see Figure 1a; complexes are called 'podandocoronates', cf. Ref. 37).

In particular, lariat compounds have been designed as cation-complexing agents which exhibit the dynamic properties of simple monocyclic crowns or coronands and the three-dimensional binding character of the less dynamic cryptand molecules (see Sections II.B.3.b and II.C.3 in the original chapter). In other words, they are expected to occupy an intermediate position between these two species: they are better cation binders than simple crowns but poorer than cryptands and they are more dynamic than the cryptands. This has been illustrated for several lariats in solution and in the solid state. Clearly, a precondition for cation-binding enhancement by means of side-arm involvement requires that the lateral donor groups are appropriately situated to form a typical lariat arrangement (cf. **IV** and **V** in Figure 1). Several aspects are discussed below.

B. Carbon-pivot Lariats

The constitutions of carbon-pivot lariats are shown in Figure 2 and Table 1 lists complexation data[3,4,7–11]. From Table 1 it follows that placement of an arm that is

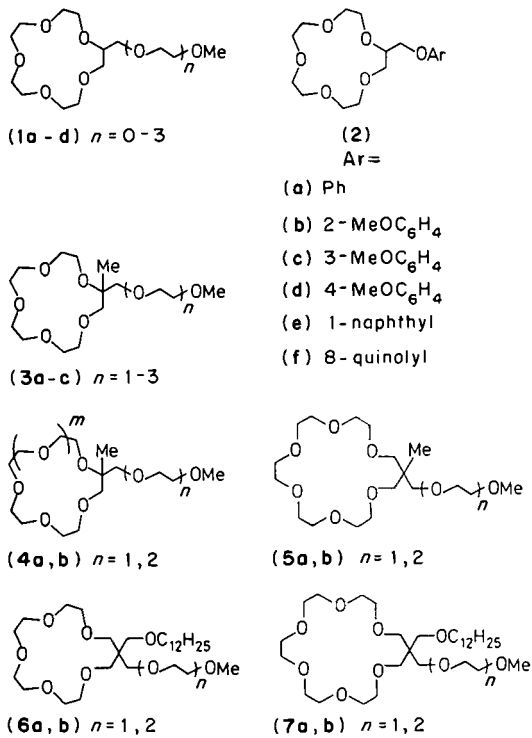


FIGURE 2. Constitutions of C-pivot lariat ethers

TABLE 1. Stability constants (log K_s, potentiometric, 25 °C) for complexes between C-pivot lariat ethers and Na^+ or K^+ chloride in different solvents (15-crown-5 is included for comparison)[9]

		Na^+		K^+	
Ligand	Side-arm	MeOH	M/W[a]	MeOH	M/W[a]
15-Crown-5		3.27	2.97	3.60	3.18
1a	CH_2OMe	3.03	2.81	3.27	2.78
1b	$CH_2OCH_2CH_2OMe$	3.01	2.83	3.20	2.97
1c	$CH_2(OCH_2CH_2)_2OMe$	3.13	2.94	3.50	3.21
1d	$CH_2(OCH_2CH_2)_3OMe$	3.04	2.80	3.45	nd[b]
2a	CH_2OPh	2.51	nd	nd	nd
2b	$CH_2OC_6H_4OMe$-2	3.24	2.97	3.47	3.11
2c	$CH_2OC_6H_4OMe$-3	2.89	2.57	nd	2.86
2d	$CH_2OC_6H_4OMe$-4	nd	2.56	nd	2.73
2e	CH_2O-1-naphthyl	nd	2.74	nd	nd
2f	CH_2O-8-quinolyl	3.72	3.39	nd	3.19
3a	$CH_2OCH_2CH_2OMe$, Me	3.87	nd	3.42	nd
3b	$CH_2(OCH_2CH_2)_2OMe$, Me	3.89	nd	3.98	nd
3c	$CH_2(OCH_2CH_2)_3OMe$, Me	3.87	nd	4.00	nd

[a]90% aqueous MeOH.
[b]Not determined.

sterically incapable of donating to a ring-bound cation generally reduces, rather than enhances, binding[9]. However, when the donor atoms of the side-arm are near the ring and the number of degrees of freedom for the side-arm is minimized, as with **2f**, enhanced cation binding relative to the parent crown (15-crown-5, Table 1) is observed. Figure 2 shows a selection of known constitutions of lariat compounds and BIBLEs (bibracchial lariat ethers).

Another interesting aspect is that the stability constants are greater for K^+ than for Na^+ when more than one potential donor group is available in the side-arm (the first oxygen atom is sterically inaccessible)[7]. A comparison of **1b** with **1c**, which can centre one or two oxygen atoms, respectively, over the ring demonstrates this clearly. It is in keeping with the extended solvation sphere required by K^+ relative to Na^+ and is strongly suggestive of intramolecular participation by the side-arm. This suggests also that considerable stabilization is gained in going from two-dimensional crown to three-dimensional lariat binding. Implicit in this is that K^+ probably perches on the macroring whereas Na^+ nests in it (Figure 3), giving rise to possible repulsions between side-arm and macroring.

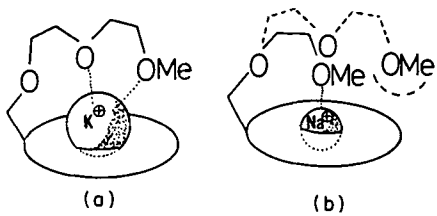


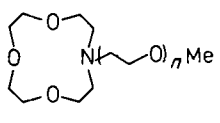
FIGURE 3. Schematic drawings of lariat–cation interactions (crown ether represented by a simple ring)

A number of 15-crown-5-analogous lariat ethers (**3a–c**) having an additional methyl group bonded to the pivot carbon have also been studied[8,10] (Table 1). They invariably show a higher affinity for Na^+ than do the non-methylated parents (**1b–d**). The results are less consistent in the case of K^+. At present it is not completely clear whether the enhanced stability constants observed for Na^+ with the methyl lariats are attributable to reduced side-arm mobility or to conformational changes in either the side-arm or macroring. More flexible ring analogues with an extra methyl group (**4** and **5**) or a larger substituent at the pivot carbon (**6** and **7**) reveal less dramatic effects[11,12].

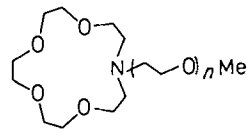
Unfortunately, there is no crystal structure available showing side-arm involvement in a carbon-pivot complex, but cooperativity has been demonstrated by a shift reagent study[13], where the 2-methoxy lariat **2b** is effective but the 4-methoxy lariat **2d** is not.

C. Nitrogen-pivot Lariats

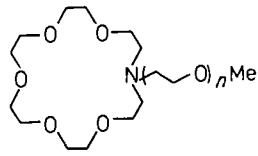
Whereas C-pivot lariat compounds suffer from the inherent disadvantage of 'sidedness' owing to the fixed geometry of the side-arm, N-pivot lariats[14–23] (Figure 4) are more



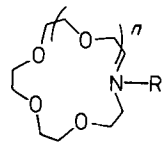
(**8a - d**) n = 1 - 4



(**9a - e, f**) n = 1 - 5, 8



(**10a - e, f**) n = 1 - 5, 8



(**11**) n = 0
(**12**) n = 1
(**13**) n = 2

R =
(**a**) Me
(**b**) allyl
(**c**) Bu
(**d**) benzyl
(**e**) 2-$MeOC_6H_4$
(**f**) 4-$MeOC_6H_4$
(**g**) 2-MeO-benzyl
(**h**) 2-NO_2-benzyl
(**i**) 4-NO_2-benzyl
(**j**) CH_2COOEt

FIGURE 4. Constitutions of N-pivot lariat compounds

flexible because of inversion at the N atom. This reduces the shielding of potential cation access. Hence the number of collisions between a cation and crown which lead to complexation must be scaled up. Correspondingly, binding constants are found to be substantially increased over simple monocyclic systems[14–19]. Some binding data are listed in Table 2. Specific conclusions are as follows.

The expected ring size/cation diameter correlation does not appear to be significant for these compounds and Na^+. Rather, binding constants reflect the total number of oxygens present in both the ring and the side-arm[17,19]. In this respect it is striking that the Na^+

TABLE 2. Stability constants ($\log K_s$, potentiometric, 25 °C) for complexes between N-pivot lariat compounds and Na^+ or NH_4^+ chloride in MeOH[19]

		Log K_s	
Ligand	Side-arm	Na^+	NH_4^+
8a	CH_2CH_2OMe	3.17	nd[a]
8b	$(CH_2CH_2O)_2Me$	3.60	nd
8c	$(CH_2CH_2O)_3Me$	3.97	nd
8d	$(CH_2CH_2O)_4Me$	3.76	nd
9a	CH_2CH_2OMe	3.88	3.14
9b	$(CH_2CH_2O)_2Me$	4.54	3.19
9c	$(CH_2CH_2O)_3Me$	4.32	3.38
9d	$(CH_2CH_2O)_4Me$	4.15	3.48
9e	$(CH_2CH_2O)_5Me$	4.19	3.49
9f	$(CH_2CH_2O)_8Me$	3.52	3.04
10a	CH_2CH_2OMe	4.58	4.21
10b	$(CH_2CH_2O)_2Me$	4.33	4.75
10c	$(CH_2CH_2O)_3Me$	4.28	4.56
10d	$(CH_2CH_2O)_4Me$	4.27	4.40
10e	$(CH_2CH_2O)_5Me$	4.22	4.04
10f	$(CH_2CH_2O)_8Me$	3.44	3.58
11d	Benzyl	2.08	nd
11e	$2\text{-}MeOC_6H_4$	2.75	nd
11f	$4\text{-}MeOC_6H_4$	1.38	nd
11g	2-MeO-benzyl	2.49	nd
11h	$2\text{-}NO_2$-benzyl	1.77	nd
12a	Me	3.39	3.22
12b	Allyl	3.14	nd
12c	Bu	3.02	nd
12d	Benzyl	2.77	nd
12e	$2\text{-}MeOC_6H_4$	3.86	nd
12f	$4\text{-}MeOC_6H_4$	2.12	nd
12g	2-MeO-benzyl	3.54	nd
12h	$2\text{-}NO_2$-benzyl	2.40	nd
12i	$4\text{-}NO_2$-benzyl	2.30	nd
13a	Me	3.93	4.08
13d	Benzyl	3.41	nd
13e	$2\text{-}MeOC_6H_4$	4.57	nd

[a]Not determined.

binding constants for the 15- and 18-membered ring compounds **9** and **10** are superimposable on each other. Binding is generally lower for the 12-membered macrorings **8** but the trend is the same[18]. The similarity for compounds having different ring sizes but an equal number of oxygen atoms even extends to the *N*-methyl derivatives which have no secondary binding sites in the side-arm (compare **9a** with **13a**).

A further trend is the peak for Na^+ binding in the presence of a total of six ring and side-arm oxygen atoms, irrespective of the ring size[17,19] (see **8c**, **9b** and **10a**). This suggests an ability of these lariats to adjust their binding arrays in accord with the requirement of a particular cation and demonstrates intramolecular side-arm participation.

Just as for C-pivot lariats, when no donor is present on the side-arm cation binding is low[18,20] (compare **12c** with **9a**, which differ by nearly a power of 10). This is further evidence for side-arm involvement. In addition, when the donor atoms do not have the appropriate geometry for intramolecular interaction, binding is reduced (compare **12e** with **12f**). If a donor is especially weak, such as a nitro group, binding is low irrespective of geometry (compare **12h** with **12i**).

Ammonium ion binding is more sterically demanding than Na^+ binding and involves hydrogen bonds. A simple analysis of the binding data[16,19] (Table 2) reveals that each N—H···O bond represents about 1.2 log units in binding under these conditions. The binding peak (log K_s) for the 18-membered ring lariats **10** is 4.75; in the 15-membered-ring series **9** it is 3.48. This indicates that four hydrogen bonds are involved in the 18-membered but only three in the 15-membered rings. The prediction is therefore that 12-membered-ring lariats should have binding constants in the range 1–3. The binding constant for **10b** with NH_4^+ is the largest yet reported for an uncharged simple nitrogen macrocycle.

Another phenomenon which is apparent from Table 2 is the decline in binding constants as the number of oxygens in the side-arm increases. Possible explanations for this behaviour are[16,17,19] increased hydrogen bonding by the medium, which reduces the conformational and translational mobility of the side-arm, or coiling of the side-arm, limiting access by the cation. This has been supported by ^{13}C NMR relaxation time measurements[20,21].

Unlike the carbon-pivot compounds, many X-ray crystal structures[a] of nitrogen-lariat complexes are available[22–25]. A few examples together with skeletal drawings of donor atoms and metal ion are given in Figure 5. They strongly confirm the 'rope-and-tie' complexation principle: side-arms are intramolecularly involved in each case.

Figure 5a shows the structure of the KI complex of 18-membered lariat **10a**[22]. In this complex the K^+ is coordinated to all donor atoms of the host, including the side-arm oxygen. There is also a contact between K^+ and I^-, increasing the coordination number of K^+ to eight. The macroring donor atoms are disposed in a chair conformation with K^+ above the plane. The side-arm oxygen is located underneath the plane in an apical position in the coordination sphere (distorted hexagonal bipyramid). Iodide occupies the opposite apical position.

The structure of complex **9b** with KI is illustrated in Figure 5b[25]. All donor sites are involved in coordinating the cation. The five donor atoms of the macroring are arranged in a half-chair conformation (see skeletal drawing), binding the K^+ from one side. The two donor atoms of the side-arm contact form the opposite side with the terminal oxygen being 0.1 Å further from the metal ion than the inner oxygen. The iodide ion also serves as a donor at this side, making the K^+ irregularly octacoordinated.

Figure 5c shows the complex of the 12-membered lariat **8c** with KI[24]. As before, the cation is coordinated to all seven donor atoms present in the host (four in the macroring

[a] Heteroatoms of the host are indicated by dotting (O) and hatching (N) for all crystal structures in this chapter, unless marked with elemental symbols. Metal centres are shaded or hatched and specified by elemental symbols. Full and broken lines represent covalent and coordinative (or hydrogen bridge) bonds, respectively.

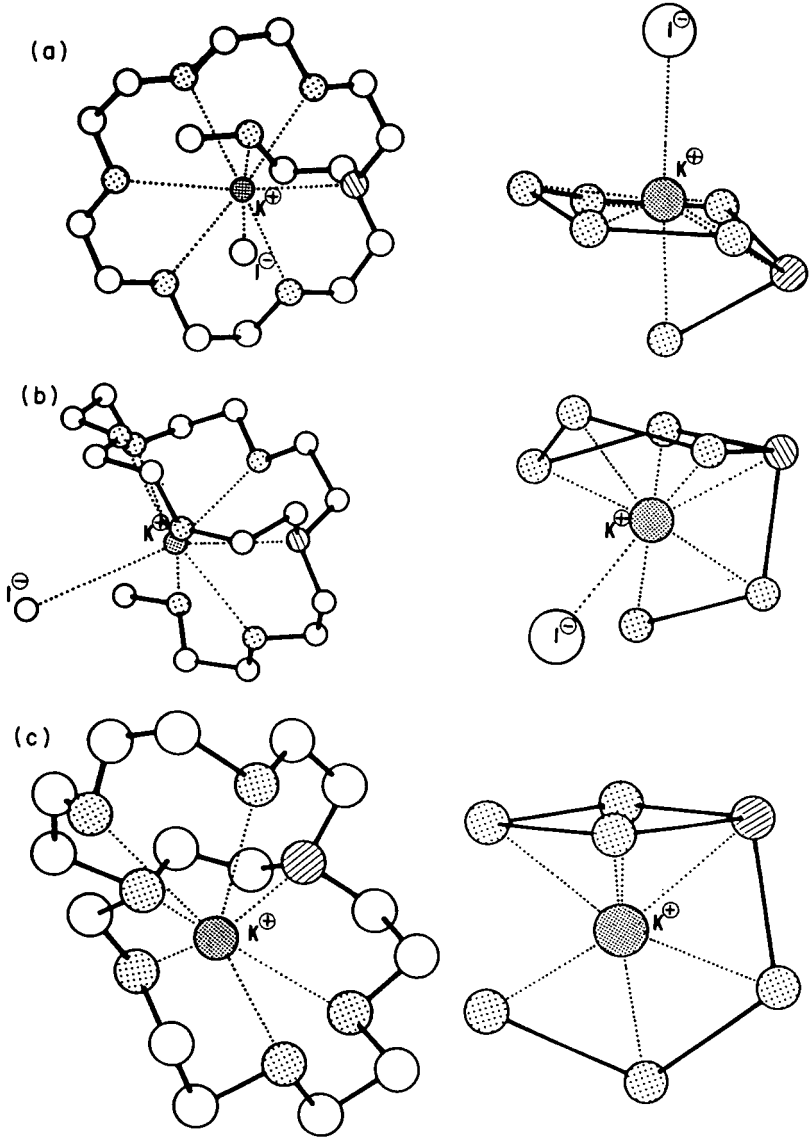


FIGURE 5. Crystal structures and skeletal drawings of donor atoms and metal ion of N-pivot lariat complexes: (a) **10a**·KI; (b) **9b**·KI; (c) **8c**·K^+ (I^- salt). Adapted from Refs. 24 and 25

and three in the side-arm). The oxygens near to the N-pivot are closest to the metal ion; donor atoms of the macroring are in the same plane. The skeletal drawing depicts a basket arrangement of donor sites with the cation completely enveloped; a more figurative designation is 'calabash' complex[24], in which the cation is heptacoordinated. The iodide anion is not within the coordination sphere of K^+ and for this reason the complex is

reminiscent of a cryptate (see Section IV.B.2.a in the original chapter). Actually it has the structure expected for the unknown [3.1.1] cryptate.

In summary, the conclusions are as follows: all lariats in Figure 5 are distinguished by the same total number of donor atoms but with different distributions among the ring and side-arm. Correspondingly, the complexes have very different topographies. Complex **10a**·KI looks approximately like a common crown complex (see Section IV.B.1.a in the original chapter) with one of the extra apical ligands attached to the ring. The cation is not in the cavity between the ring and the side-arm, but rather pushed outside by the lariat arm. Complexes of **9b** and **8c** with K^+ reveal a cavity structure, increasingly closed in this order. It was further shown that with increasing donor capacity of the side-arm the cation is pulled more into the cavity between the ring and side-arm. Accordingly **9b**·KI still has an open edge with respect to the host. It is covered by the anion, whereas **8c** reveals a closed host cavity. Hence rope-and-tie complexation increases from top to bottom in Figure 5. The K^+ complex of lariat **8c** may be appropriately designated a 'pseudocryptate'.

The solution binding data of the N-lariat complexes (see Table 3) are also in line with the solid-state structures. It is suggested that complexation is strong if high encapsulation of the metal ion is possible[25]. In this light, the relatively strong binding of K^+ to **8c** ($\log K_s = 3.84$ in MeOH, 25 °C), despite the presence of a non-fitting 12-membered ring, results from complete K^+ encapsulation (cf. Figure 5c). This points to a second key factor, which is obvious from a comparison of crystal structures and binding constants, viz. the number of donors available at the host or, in other words, the cation's coordination number. It has been demonstrated that an 'effective ionic radius' relationship (cf. Tables 3 and 4) rather than the usual 'cavity size' concept provides an explanation of the binding data[25]. Effective ionic radii (Shannon's radii)[26] increase with increasing number of donors (Table 4).

Hence two ideas proved useful for understanding the structure and binding properties of N-lariats: the effective ionic radii and molecular topography. Recently, investigations were extended to include a wider range of cations and to determine $\Delta H°$ and $\Delta S°$ values for the lariat–cation interactions[27]. Table 5 lists some $\Delta H°$ and $T\Delta S°$ data for lariats **9a**, **10a**, **10b**

TABLE 3. Comparison of host cavity sizes (R) with cation binding constants[25]

	Ligand		
Parameter	**8c**	**9b**	**10a**
R^a (Å)	1.396	1.444	1.541
No. of donors	7	8	8
Log $K_s(Na^+)$	3.97	4.54	4.58
Log $K_s(K^+)$	3.84	4.68	5.77

[a]Complex mean cavity radius (K^+ complex).

TABLE 4. Effective radii (Å) of Na^+ and K^+ as a function of coordination number[26]

	Coordination number				
Ion	4	6	7	8	12
Na^+	0.99	1.02	1.12	1.18	1.39
K^+	1.37	1.38	1.46	1.51	1.64

TABLE 5. Thermodynamic data [$\log K_s$, $\Delta H°$ (kcal mol^{-1}) and $T\Delta S°$ (kcal mol^{-1})] for the 1:1 interaction of N-pivot lariat compounds with metal ions in MeOH at 25 °C (calorimetric titration)[27]

Ligand	Parameter	Na^+	K^+	Cs^+	Ca^{2+}
	$\log K_s$	4.33 ± 0.01	4.20 ± 0.01	2.79 ± 0.2	3.78 ± 0.03
9a	ΔH	-6.39 ± 0.01	-9.08 ± 0.02	-7.87 ± 0.05	-2.58 ± 0.03
	$T\Delta S$	-0.48	-3.35	-4.06	2.58
	$\log K_s$	5.60 ± 0.1	5.35 ± 0.07	4.24 ± 0.01	4.83 ± 0.06
10a	ΔH	-7.44 ± 0.01	-12.38 ± 0.03	-10.72 ± 0.01	-3.17 ± 0.05
	$T\Delta S$	0.2	-5.08	-4.93	3.40
	$\log K_s$	5.7 ± 0.2	$-$[a]	4.34 ± 0.01	4.23 ± 0.04
10b	ΔH	-6.70 ± 0.05	-12.54 ± 0.03	-11.8 ± 0.4	-2.78 ± 0.05
	$T\Delta S$	1.0	$-$[a]	-5.9	2.99
	$\log K_s$	3.22 ± 0.01	2.99 ± 0.01	$-$[a]	2.83 ± 0.03
12c	ΔH	-4.15 ± 0.08	-6.36 ± 0.06	$-$[a]	-3.3 ± 0.2
	$T\Delta S$	0.24	-2.28	$-$[a]	0.6

[a]Not accurately determinable.

and **12c** binding with Na^+, K^+, Cs^+ and Ca^{2+} ions in MeOH at 25 °C. The data were obtained by calorimetric titration. It was found that $\Delta H°$ is dominant in all complexes except for **9a**, **10a** and **10b** with Ca^{2+}. The complexes with Na^+ and Ca^{2+} are both enthalpy- and entropy-stabilized and the complexes with K^+ and Cs^+ are destabilized by entropy. This largely corresponds to the expected behaviour (see Section II.C in the original chapter).

D. Bibracchial Lariats

In order to determine how two arms rather than one would contribute to the overall binding of a cation, the complex formation of several bibracchial diaza compounds (Figure 6) was studied[28–30]. Binding data are specified in Table 6.

In the first instance, it was shown that the presence of donor groups on the side-arms enhances binding for all cations examined[29]. In addition, as the polarity increases, the binding constants mostly increase, being most pronounced for Ca^{2+} (compare **15** with **16**). The explanation is in terms of ion–dipole interactions: Ca^{2+} has the highest charge density of the cations studied, followed by Na^+ and consequently an increase in Ca^{2+} selectivity is involved as the donor groups become more polar [compare **15** (methoxy groups) with **16** (hydroxy groups) or **15** (methoxy groups) with **18f** (ester groups)]. Less polar groups such as ethers favour K^+ if an 18-membered ring is concerned (cf. **15**). Acidic groups, however, cause a drastically reduced binding strength with cations (cf.**18e**), probably owing to interfering intramolecular hydrogen bonding.

When the macrorings are smaller, 15-membered instead of 18-membered, the steric influence of the side-arms is magnified[30]. A consequence is seen in the stability of the complex of **14** with Na^+ in MeOH solution, which exceeds that of any previously studied Na^+ complex involving only ether and amine donor groups.

The results suggest that many of the bibracchial diaza lariats **14–18** interact more strongly with the cation than with the solvent, i.e. intramolecular side-arm participation is demonstrated.

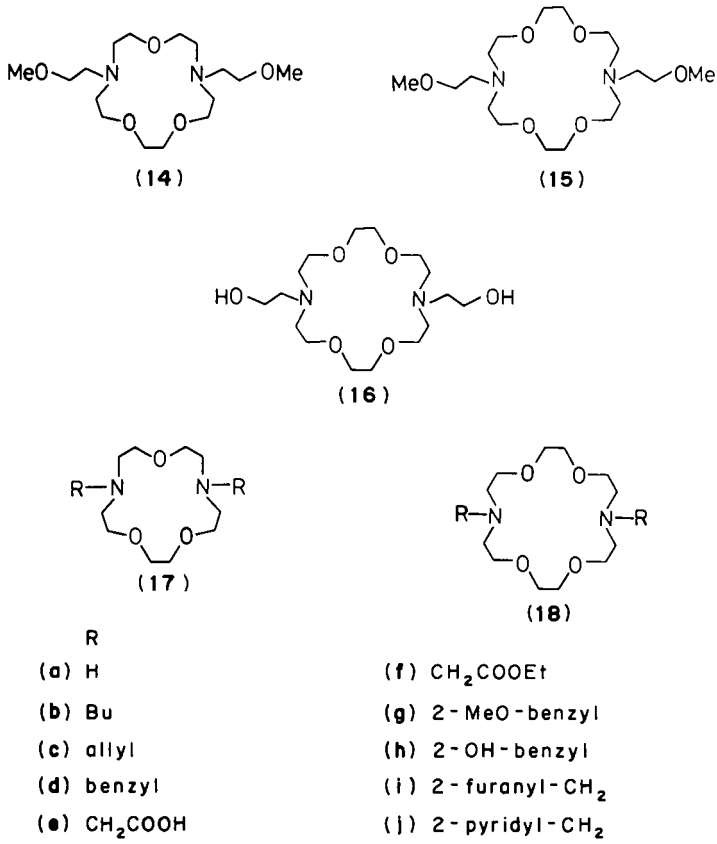


FIGURE 6. Constitutions of bibracchial N-pivot lariats

Intramolecularity of the complexes of bibracchial diaza lariats has also been shown for the solid phase[22,25] (cf. N-pivot lariats). Figure 7 presents the crystal structures together with the skeletal drawings of donor atoms and the metal ion of three representative complexes.

The structure of complex **15** with KI (1:1) is illustrated in Figure 7a[22]. The K^+ is octacoordinated in this complex. Iodide does not contact the metal ion and instead all donor atoms available at the host coordinate. The donor atoms of the macroring adopt a chair conformation (see skeletal drawing). The oxygens of the side-arms are located above and below the mean plane of the macroring. Thus the arrangement of all donor atoms is suggestive of a crown complex (see Section IV.B.I.a in the original chapter) with two quasi-apical ligands attached to the ring.

Figure 7b shows the structure of complex **16** with NaI (1:1)[25]. As before, the metal ion (Na^+) is octacoordinated and I^- does not participate in coordination. The arrangement of all donor atoms, however, is very different in the two complexes. Here both lariat arms coordinate at the same side of the macroring. Actually, the macroring donors are in a twist–boat structure (see skeletal drawing) and the side-arm donors occupy the 'flagpole'

TABLE 6. Stability constants (log K_s, potentiometric, 25 °C) for complexes between bibracchial N-pivot lariat compounds and metal cations in MeOH ([2.2.2]cryptand is included for comparison)[29,30]

Ligand	Ring size	Side-arms	Log K_s		
			Na^+	K^+	Ca^{2+}
14	15	CH_2CH_2OMe	5.09	4.86	nd[a]
15	18	CH_2CH_2OMe	4.75	5.46	4.48
16	18	CH_2CH_2OH	4.87	5.08	6.02
17a	15	H	< 1.5	< 1.5	nd
17d	15	Benzyl	2.59	2.12	nd
17g	15	2-MeO-benzyl	3.59	3.13	nd
17i	15	2-Furanyl-CH_2	3.99	3.87	nd
18a	18	H	1.50	1.80	nd
18b	18	Bu	2.84	3.82	nd
18d	18	Benzyl	2.72	3.38	2.79
18e	18	CH_2COOH	nd	~ 1.8	4.0
18f	18	CH_2COOEt	5.51	5.78	6.78
18g	18	2-MeO-benzyl	3.65	4.94	3.27
18h	18	2-OH-benzyl	2.40	2.59	2.95
18i	18	2-Furanyl-CH_2	3.77	4.98	nd
[2.2.2]			7.98	10.41	nd

[a] Not determined.

position. Correspondingly, the arrangement of all donor atoms is reminiscent of a macrobicyclic cryptate (see Section IV.B.2.a in the original chapter). In a sense, the structure of **16**·NaI is intermediate between those found for the Na^+ cryptates of [2.2.2] and [2.2.1][31].

Figure 7c depicts the complex of **16** with KI (1:1)[25]. The metal ion (K^+) is octacoordinated and I^- is not involved in a K^+ contact. The arrangement of all donor atoms is comparable to that in the Na^+ complex of **16** but, owing to the larger cation, the macroring is less distorted in the K^+ complex. Hence the donor atoms of the ring are arranged in a slightly twisted boat conformation (see skeletal drawing) rather than in a twist--boat structure (cf. Figure 7b). In this complex, the arrangement of all donor atoms is largely suggestive of a [2.2.2] cryptate[31].

The solid-state structures of Figure 7 are in agreement with the data in Table 6 (homogeneous binding constants)[25]. Expected trends are that bibracchial lariat **15** binds K^+ more strongly than **16**, which is attributed to less conformation strain in **15** compared with **16** (cf. Figure 7a and b) and to the better donating ability of ether oxygen than hydroxy. In the same way, binding of **16** with K^+ is more favourable than binding with Na^+ because of the differences in conformational strain (cf. Figure 7b and c). It is also suggested that the simple 'hole-size' concept is inappropriate to the present discussion, whereas the effective ionic radii apply (cf. N-pivot complexes).

Although the structures of bibracchial lariat complexes are reminiscent of cryptates, they do not bind cations as well (see [2.2.2] in Table 6), indicating that the encapsulation is not at the same high level[25]. The energy costs of changing the uncomplexed to the complexed conformation are also higher in the lariat than in the cryptate case.

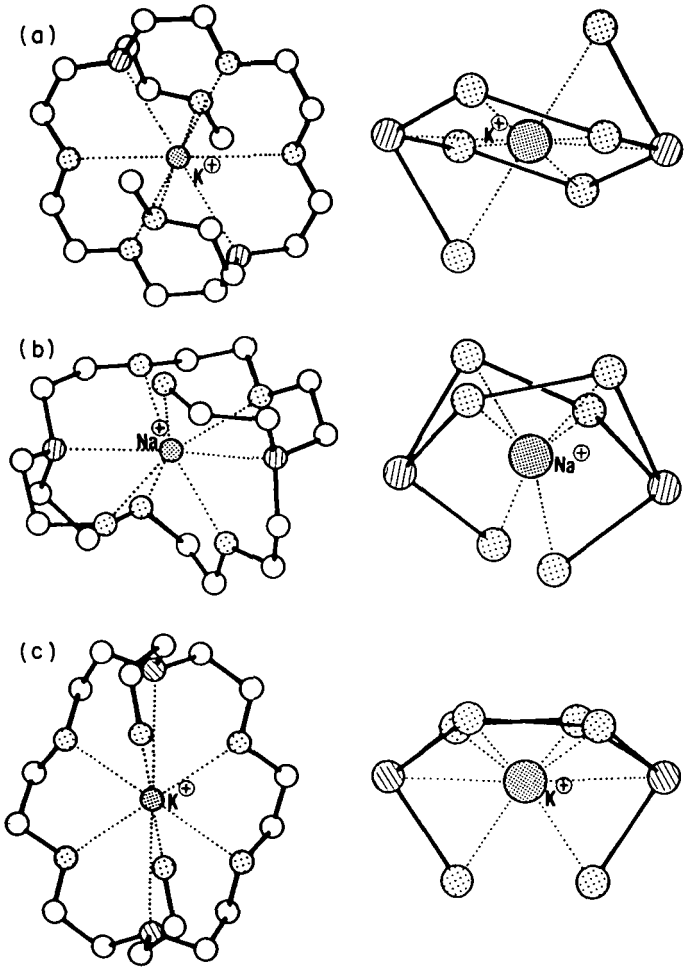


FIGURE 7. Crystal structures and skeletal drawings of donor atoms and the metal ion of bibracchial lariat complexes: (a) **15**·K^+; (b) **16**·Na^+; (c) **16**·K^+ (I^- salts). Adapted from Refs. 22 and 25

A number of C-pivot bibracchial ligands, **19–25** (Figure 8), possessing a variety of side-arms in different positions were synthesized and studied with regard to cation complexation[11,12,32–35]. They include 15-(**19–22**), 16- (**23**) and 19-membered rings (**24**) and also a chiral system (**25**).

Table 7 summarizes the K_s values of homogeneous Na^+ and K^+ binding of ligands **19–22**[32,33]. The most interesting facts emerge from a comparison between the double-armed lariats and corresponding single-armed lariats (e.g. **1** and **3**, Figure 2), and between methyl-containing and methyl-free analogues. For instance, lariat **19** (Table 7), with two separate side-arms, is closely comparable to single-armed **1b** (Table 1) in both Na^+ and K^+ binding, suggesting that one lariat arm of **19** is probably inoperative[33].

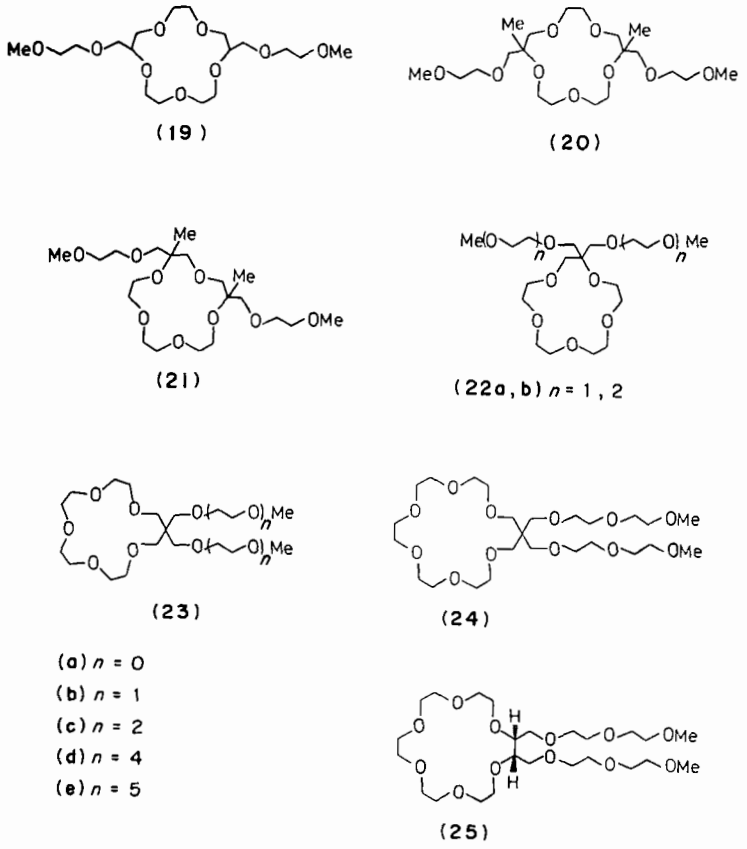


FIGURE 8. Constitutions of bibracchial C-pivot lariats

However, **20** and **21**, having methyl groups at the pivot positions, display over ten times higher stability constants for Na^+ than **19**, which lacks the methyl groups[33]. Also, a higher Na^+/K^+ selectivity is observed in **20** and **21** in accordance with single-armed methyl lariats. This is further proof of conformational fixation caused by pivot methyl groups (cf. Section II.B).

The complexing ability of two-armed lariats **22a** and **22b**, which have geminal oxyethylene chains, is very similar to that of the corresponding methyl analogues **3a** and **3b** (see Table 1)[32]. This finding is reasonable because two geminal oxyethylene chains cannot coordinate a cation at the same time, for reasons of bonding geometry.

The cation-binding ability of geminal double-armed ligands **23** and **24** was evaluated by a solvent extraction technique[12,35]. Extraction data (extractability of picrate salts) are summarized in Table 8.

As for the double-armed 16-crown-5 systems **23a–23e**, it was shown that extractabilities for most cations gradually increase with extension of the oxyethylene side-arms. The trend of the change in extractability with increasing n (number of oxyethylene groups), however, depends substantially on the cation extracted and may be classified into three catagories:

TABLE 7. Stability constants ($\log K_s$, potentiometric, 25 °C) and selectivity factors (Na^+/K^+) for complexes between bibracchial C-pivot lariat ethers and metal cations in MeOH[32,33]

Ligand	Side-arm	$\log K_s$		$K_s(Na^+)$
		Na^+	K^+	$K_s(K^+)$
19	$CH_2OCH_2CH_2OMe$	3.09	3.13	0.9
20	$CH_2OCH_2CH_2OMe$, Me	4.11	3.54	3.7
21	$CH_2OCH_2CH_2OMe$, Me	4.36	3.58	6.0
22a	$CH_2OCH_2CH_2OMe$	3.84	3.44	2.5
22b	$CH_2(OCH_2CH_2O)_2Me$	3.86	3.98	0.8

TABLE 8. Solvent extraction of metal picrates from H_2O into CH_2Cl_2 using bibracchial C-pivot lariat ethers[12]

Ligand	Extractability (%)[a]									
	Na^+	K^+	Rb^+	Cs^+	Ag^+	Tl^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
23a	9.8	2.7	2.5	2.1	24.7	11.1	1.6	1.6	3.1	9.3
23b	19.2	2.6	1.5	0.9	33.7	13.8	0.7	1.0	4.0	19.2
23c	15.0	4.8	2.4	1.2	29.4	15.7	1.2	1.4	3.9	26.2
23d	15.2	5.8	4.3	2.4	30.6	18.5	0.6	1.3	5.6	35.0
23e	15.8	6.4	5.2	3.6	30.2	21.6	0.7	1.6	5.1	32.5
24	7.6	18.4	14.5	5.6	15.9	36.7	0.4	6.2	53.0	68.0

[a]Defined as percentage of picrate extracted into the organic phase.

(1) optimum extractability is obtained at $n = 1$ or **23b**; (2) the extractability increases monotonically with increasing n; and (3) the extractability is not enhanced by the introduction of additional binding sites[12].

Na^+ and Ag^+ fall into category 1, which is probably indicative of the size-fit concept. Obviously **23b**, with two oxygens in the side-arm, allows one of the terminal oxygens to be placed at the most favourable position to access the cation accommodated in the crown cavity (cf. Figure 3b). The extractability drop at $n = 2$ and the subsequent steady extractabilities at $n > 2$ are attributable to steric hindrance of the extra oxyethylene units interacting with the transannular ring oxygen (cf. dashed line in Figure 3b).

Category 2 may involve K^+, Rb^+, Cs^+, Tl^+, Sr^{2+} and Ba^{2+}, which are too large to fit in the cavity of the 16-crown-5 derivatives, and hence lie above the hole of the crown ring (cf. Figure 3a). In this situation, the donor oxygens of the side-arms may support complexation by wrapping the cation, which rationalizes the gradual increase in extractability with increasing n.

Category 3 may involve Mg^{2+} and Ca^{2+}. The extractability is very low for these two cations and no evident improvement is achieved by extending the side-arms. This indicates that lariat ethers of type **23** are unsatisfactory for overcoming the high hydration energy, which is the dominant factor controlling the extractability of these small divalent cations.

The 19-crown-6 lariat **24**[12] reveals a high extractability for K^+, Tl^+, Sr^{2+} and Ba^{2+}.

III. SPHERANDS: PREORGANIZED LIGAND COMPLEXATION

A. Strategy

Spherands are not just a simple constitutional variation of the classical crown concept but represent a much more fundamental idea[36,37].

Cation complexation in solution by an organic ligand involves a sequence of different processes (Scheme 1, equations 1–6): cation desolvation (1), ligand desolvation (2), conformational reorientation of the ligand (3), coordination of the cation (4), solvation of the complex (5). Some of these processes are energy consuming (1–3) whereas others are energy delivering (4 and 5). The total of all energy terms (equation 6) equals the free energy of complexation. Provided that the nature and the number of donor atoms are always the same for different ligands, then the conformational reorientation act (equation 3) becomes dominant.

$$(\text{Cation})_{\text{solv.}} \rightleftharpoons \text{Cation} + \text{Solvent} \quad (1)$$

$$(\text{Ligand})_{\text{solv.}} \rightleftharpoons \text{Ligand} + \text{Solvent} \quad (2)$$

$$(\text{Ligand})_{\text{pre-compl.}} \rightleftharpoons (\text{Ligand})_{\text{compl.}} \quad (3)$$

$$(\text{Ligand})_{\text{compl.}} + \text{Cation} \rightleftharpoons [\text{Ligand}\cdot\text{Cation}] \quad (4)$$

$$[\text{Ligand}\cdot\text{Cation}] + \text{Solvent} \rightleftharpoons [\text{Ligand}\cdot\text{Cation}]_{\text{solv.}} \quad (5)$$

$$(\text{Cation})_{\text{solv.}} + (\text{Ligand})_{\text{solv.}} \rightleftharpoons [\text{Ligand}\cdot\text{Cation}]_{\text{solv.}} \quad (6)$$

SCHEME 1

This leads to the crucial point which can be expressed as follows[36,37]: *the smaller the changes in organization of host and guest required for complexation, the stronger is the binding.* A supplementary guiding principle of complex design is that *in order to complex, hosts must have binding sites that cooperatively contact and attract the binding sites of guests without generating strong non-bonded repulsions.*

Cation solvation, in this approach, is equated with *non-structured* complexation, which competes with *structured* complexation of a ligand. Crowns (coronands)[a], cryptands, podands and also natural ionophores, being examples of ligands[6], owe their cation-binding properties to varying degrees of organization of donor atoms prior to complexation (Figure 9).

Podands (Figure 9a) are acyclic collections of binding sites held together by appropriate spacer units. During the complexing act many degrees of conformational freedom must be frozen out. *Crowns* and *coronands* (Figure 9b) are cyclic collections of binding sites and are less flexible than podands. Nevertheless, they possess a variety of conformations, many of which fill their own potential cavities with their own spacer units (see Figure 9b). *Cryptands* (Figure 9c), which are bridged crown analogues, naturally have a smaller number of non-binding conformations and therefore require less expenditure of reorganization on complex formation than crowns. The so-called *spherands* are at the end of the unfolded progression of ligand structures with regard to the parameter of preorganization[37]:

solvents > podands > coronands (crowns) > cryptands > spherands

Hence they are characterized as completely preorganized ligand systems (prior to complexation, Figure 9d). In other words, in cryptands, crowns (coronands), and even

[a]Recently it was suggested that 'corand' should be used instead[37].

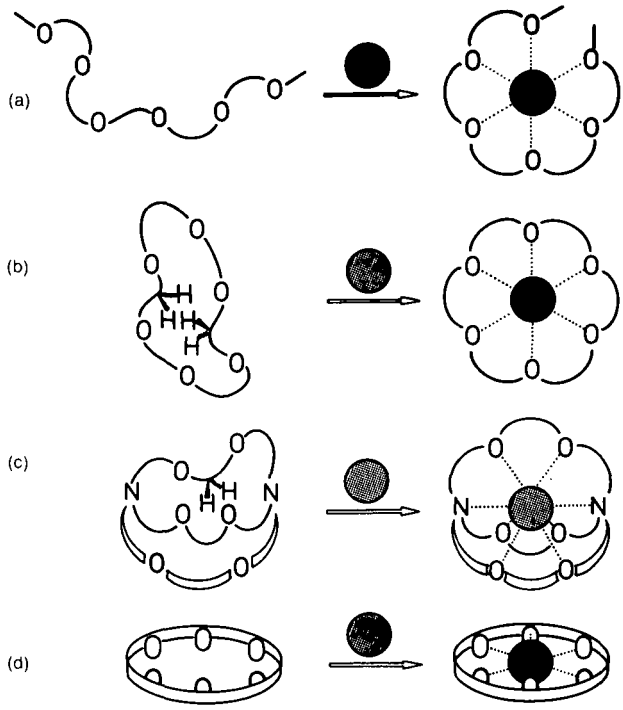


FIGURE 9. Reorganization and preorganization of hosts on complex formation

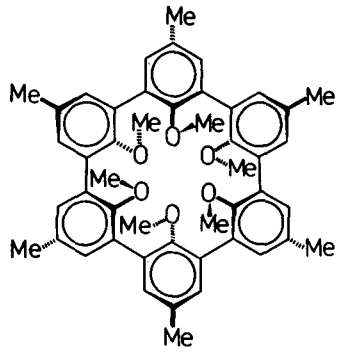
more in podands the unshared electron pairs of their heteroatoms become focused on cations *during complexation* by conformational reorganizations of their supporting chains. In contrast, a spherand must be organized for complexation *during its synthesis* rather than during its complexing act (Figure 9).

Considering equation 1 in Scheme 1, all hosts must desolvate the cation during complexation, the spherands and cryptands most thoroughly. On the other hand, spherands are only poorly solvated, if at all, and therefore give rise to almost no burden of host desolvation (cf. equation 2). Hence the superiority of spherands profits from two factors[37]: low energy for the conformation reorientation act (equation 3) and low energy of host desolvation (equation 2). Generally, we deal with host preorganization to the utmost.

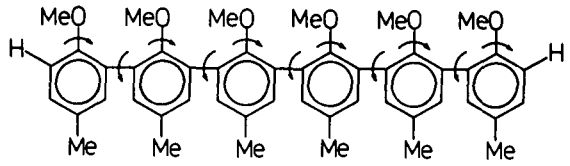
B. Spherands

Hosts endowed with the properties of a spherand[36,37] should provide a roughly spherical cavity lined by appropriate binding sites. The cavity should be enforced by a support framework of covalent bonds. The bonds must be sufficiently rigid for their parts not to be able to rotate to fill their own cavities. Compound **26** (Figure 10) represents an example of a typical spherand constitution[38,39].

A characteristic feature of **26** is the cyclohexametaphenylene skeleton with six convergently positioned methoxy groups. Corey–Pauling–Koltun space-filling molecular models (CPK models) illustrate that an alternating up-and-down arrangement of the six



(26)



(27)

FIGURE 10. Prototypical spherand **26** and open-chain analogue **27**

methoxy groups is essential because of their spatial requirements. Also, the methyl groups are turned away from the centre of the system, three pointing in one direction and three in the opposite direction, otherwise they would cause an inadmissibly high compression. For the same reason the methoxy groups cannot pass through the centre of the macroring. In other words, the anisyl modules are self-organizing[38].

As a result of the particular conformation, the free host possesses an enforced cavity lined with six oxygen atoms (24 unshared electrons), that is, shielded from solvation by six phenyl and six methyl groups. The oxygens are in a perfect octahedral arrangement. The diameter of the central hole varies with the dihedral angle between the six aryl groups, averaging *ca.*1.62 Å, which is between the diameters of Li^+ (1.48 Å) and Na^+ (1.75 Å). Hence the cage is preorganized to be complementary to Li^+ and Na^+ in both an electronic and a steric sense, but not to K^+ and larger cations. Accordingly, the picrate salts of Li^+ and Na^+ in $CDCl_3$ at 25 °C are bound with $-\Delta G°$ values of > 23 and 19.2 kcal mol^{-1}, respectively (Table 9), whereas no binding with other ions is detectable[40].

The favourable effect of the enforced octahedral arrangement of the six oxygens and of the shielding from solvation is further expressed when comparing **26** with the open-chain analogue **27** (Figure 10). This compound binds Li^+ and Na^+ with $-\Delta G° < 6$ kcal mol^{-1} only (Table 9)[40]. The reason is obvious. Unlike **26**, it exists in over 1000 conformations (cf. arrows in formula **27**), among which only two are fully organized for cooperative binding, but most of the conformations expose the donor atoms to solvation rather than to coordination. Hence **27** is not preorganized for binding.

Figure 11 shows a constitutional drawing of spherand complexation with **26** (Figure 11a) together with the crystal structures of **26**, **26**·Li^+ and **26**·Na^+ (Figure 11b, c

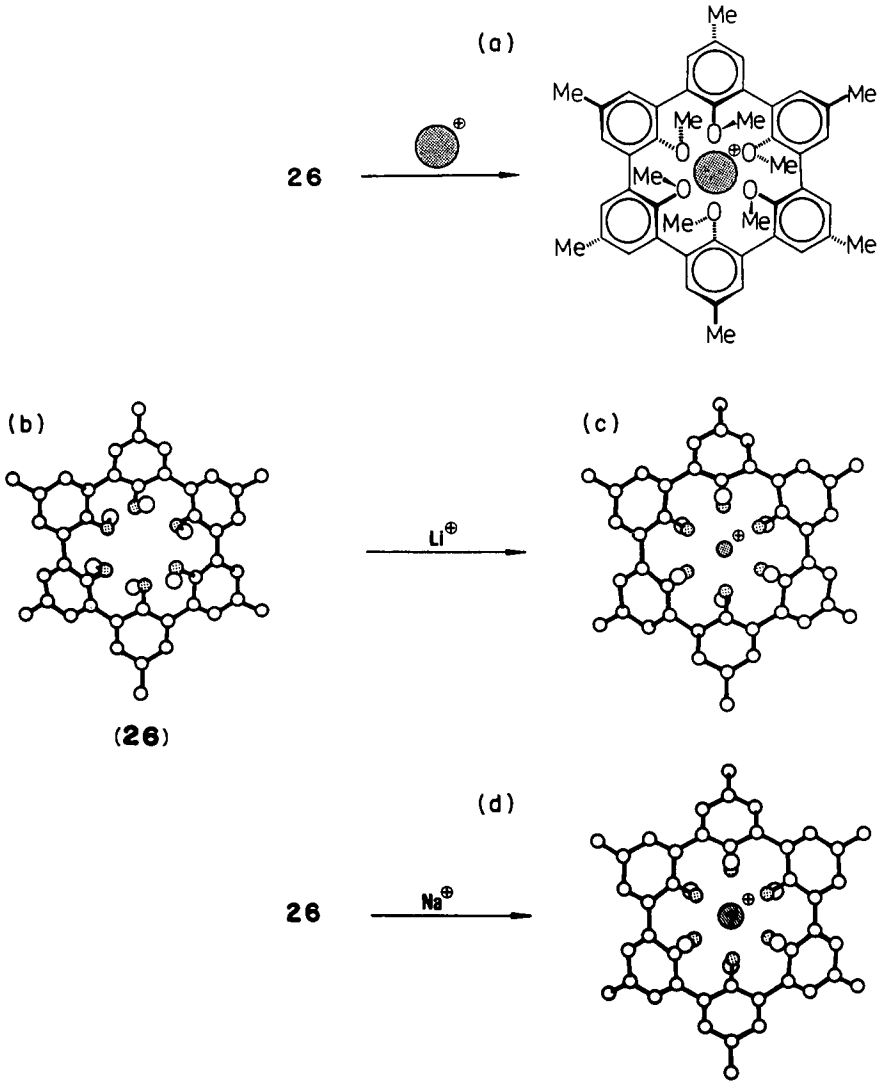


FIGURE 11. Cation complexation of spherand **26**: (a) formula structure of a **26**-cation complex; (b), (c) and (d) crystal structures of free **26** and of the complexes **26**·Li^+ and **26**·Na^+, respectively. Adapted from Ref. 39

and d, respectively)[39]. As expected, these three structures all possess the same conformation and differ mainly in the sense that **26** contains an empty cavity, and this cavity is filled in **26**·Li^+ and **26**·Na^+. Unquestionably, theory and reality are in very good agreement.

Related spherand compounds which were designed and prepared with different motives, e.g. different number of heteroatoms[39,40], different character of binding sites[41–46] or different connectedness[47,48], are listed in Figure 12. The number of heteroatoms in a

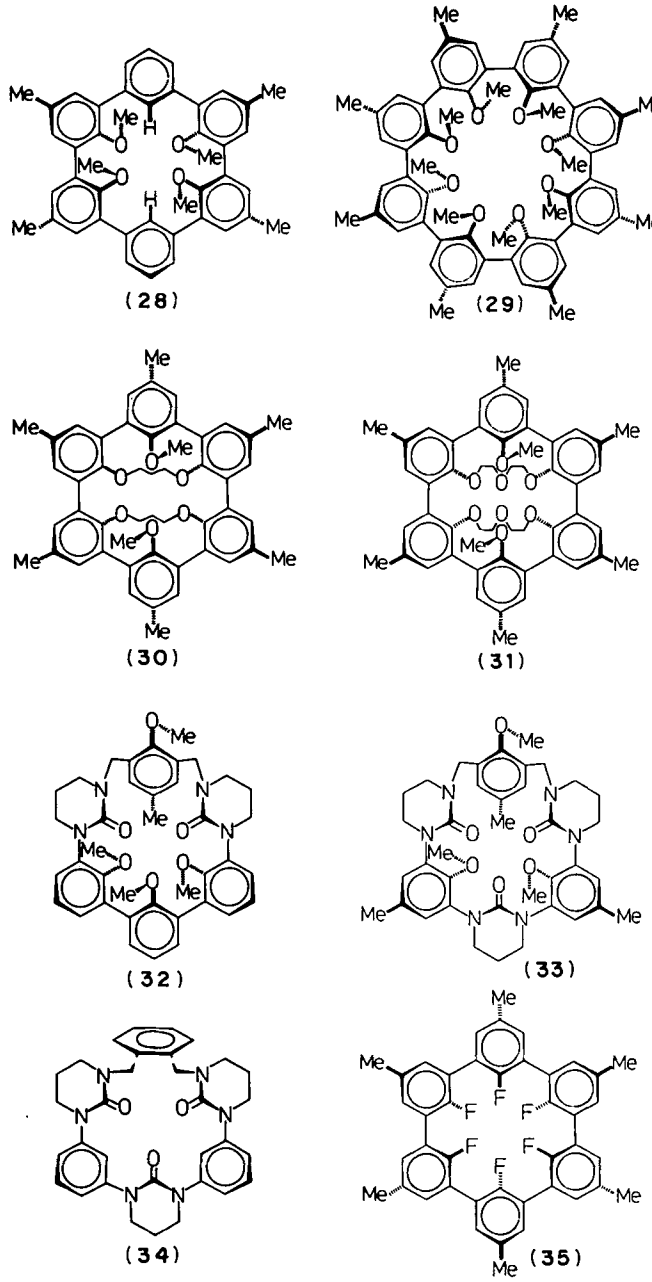


FIGURE 12. Spherands of different design

ligating position range from a maximum of eight for **29** to minimum of three for **34**. Donor site modification ranges between anisole (**28–31**), fluorotoluene (**35**) and cyclic urea molecular modules (**34**) and includes several intermingled combinations (**32** and **33**). The use of urea oxygen[41–45] was suggested since it is less sterically hindered and is intrinsically a much better hydrogen bonding site than an anisyl oxygen.

The basis of complex formation with Li^+ [binding free energies ($-\Delta G°$) at 25 °C, in $CDCl_3$ saturated with D_2O, see Table 9] has been studied. As has been mentioned, **26** with six anisyl binding sites possesses $-\Delta G° > 23$ kcal mol^{-1} for Li^+ complexation[40]. The diminished spherand **34** with only three host ligating sites has $-\Delta G° = 8.5$ kcal mol^{-1} for complex formation with Li^+[43]; **33**, with five ligating sites and **28** with four ligating sites, have $-\Delta G°$ values of 12.1 and < 6 kcal mol^{-1}, respectively[40,43]. Unfortunately the Li^+ binding property of the enlarged spherand **29** with eight donor sites is not available ($-\Delta G°$ for Cs^+ binding is 13.9 kcal mol^{-1})[37], but the eight donor sites of spherand **31** give $-\Delta G° = 15.9$ kcal mol^{-1}[40], which is *ca.* 7 kcal mol^{-1} less than that for **26**.

The effect of an exchange of donor groups, e.g. anisole for the cyclic urea module, or of anisole for fluorotoluene, is obviously shown from a comparison between **26** (> 23 kcal mol^{-1}) and **33** (12.1 kcal mol^{-1})[43] or between **26** and **35** (failed to complex Li^+)[46], respectively.

The problem of donor site connectedness is encountered in the spherands **30** and **31**. Those compounds are bridged analogues of the parent **26**. At first sight the $-\Delta G°$ values of 16.8 and 15.9 kcal mol^{-1}, respectively, for Li^+ complexation are remarkably low compared with **26** (> 23 kcal mol^{-1})[40]. This points to a misshapen cavity for Li^+ or to a distortion of the oxygen atoms from an ideal octahedral arrangement. Both are clearly visible in CPK models.

The facts as given above illustrate some important features of structure–binding correlation. (1) In a series of spherands organized by a particular framework, the binding free energies decrease rapidly with decreasing number of ligating sites (compare **26** with **28**, **33** and **34**). (2) The binding free energy is highly dependent on the electronic character of the donor groups (compare **26** with **33** and **26** with **35**). (3) The extent of complementarity regarding the spherand cavity and the metal ion contributes to the free energy of binding (compare **26** with **29**). (4) Distortion of the ligating atoms from ideal positioning (e.g. an octahedral arrangement) is a decisive factor for the $-\Delta G°$ of binding (compare **26** with **30**).

Some of these factors overlap and in addition it is not always clear which heteroatoms of a given host are used in binding (cf. **32** and **33**). A further problem is that some examples in Figure 12 may not unrestrictedly be designed as a prototypical spherand from reasons of flexibility (e.g. **29** and **33**).

Binding of Li^+ was only an example for the study, and many other metal ions are known to form spherand complexes with various stabilities[41–45]. K_s data are listed in Table 9 together with the $-\Delta G°$ values for the complexation reaction. The binding free energies are dependent on the same parameters (number of donor sites, cavity dimensions, etc.) as given above, e.g. **31** yields a relatively stable complex with Na^+, **33** with K^+ and **29** with Cs^+. Many complexes of spherands with NH_4^+ and primary alkylammonium cations have also been found[41–45]. For some of them $-\Delta G°$ reaches *ca.* 14 kcal mol^{-1}.

Corroborative single-crystal X-ray structures have been reported for many of the complexes[39,40,42,45] and some are shown in Figures 13 and 14 (see also Figure 11). The gross structural features of the complexes in Figure 13 illustrate three different types of host–guest interaction. In **32**·Na^+·H_2O (Figure 13a)[42,45], the Na^+ penetrates deeply into a cavity defined by the coordinating heteroatoms (three anisyl and two carbonyl oxygens). Hence the overall structure corresponds to a nesting complex. The particular host conformation at the bridging anisyl segment causes deshielding of the Na^+ on the top side. As a result, a molecule of water is found to make contact from this side. In both **32**·Cs^+·H_2O (Figure 13b)[42,45] and **33**·*t*-BuNH_3^+ (Figure 13c)[42,45] the guests are too large

TABLE 9. Stability constants (K_s) and binding free energies ($-\Delta G°$) for cation complexation of spherands in $CDCl_3$ saturated with D_2O at 25 °C (open-chain compound **27** is included for comparison)[40,43,45]

Ligand	Cation	K_s ($l\,mol^{-1}$)	$-\Delta G°$ ($kcal\,mol^{-1}$)
26	Li^+	$> 7 \times 10^{16}$	> 23
	Na^+	1.2×10^{14}	19.2
	K^+	—	≪ 6
27	Li^+	—	< 6
	Na^+	—	< 6
	K^+	—	< 6
	Rb^+	—	< 6
	Cs^+	—	< 6
28	Li^+	—	< 6
29	Cs^+	1.5×10^{10}	13.9
30	Li^+	2.0×10^{12}	16.8
	Na^+	5.5×10^{9}	13.8
31	Li^+	4.4×10^{11}	15.9
	Na^+	5.4×10^{13}	18.7
32	Li^+	6.1×10^{8}	12.0
	Na^+	4.2×10^{10}	14.5
	K^+	1.4×10^{11}	15.2
	Rb^+	2.8×10^{9}	12.9
	Cs^+	2.6×10^{8}	11.5
	NH_4^+	5.5×10^{9}	13.3
	$MeNH_3^+$	6.1×10^{8}	12.0
	t-$BuNH_3^+$	1.8×10^{7}	9.9
33	Li^+	7.2×10^{8}	12.1
	Na^+	1.6×10^{11}	15.4
	K^+	2.2×10^{11}	15.6
	Rb^+	1.4×10^{10}	14.2
	Cs^+	3.9×10^{9}	13.1
	NH_4^+	3.5×10^{10}	14.4
	$MeNH_3^+$	3.5×10^{10}	14.4
	t-$BuNH_3^+$	4.5×10^{9}	13.2
34	Li^+	1.7×10^{6}	8.5
	Na^+	5.3×10^{5}	7.8
	K^+	1.6×10^{5}	7.1
	Rb^+	7×10^{4}	6.6
	Cs^+	1.1×10^{5}	6.9
	NH_4^+	1.4×10^{5}	7.0
	$MeNH_3^+$	1.6×10^{5}	7.1
	t-$BuNH_3^+$	2.3×10^{5}	7.3

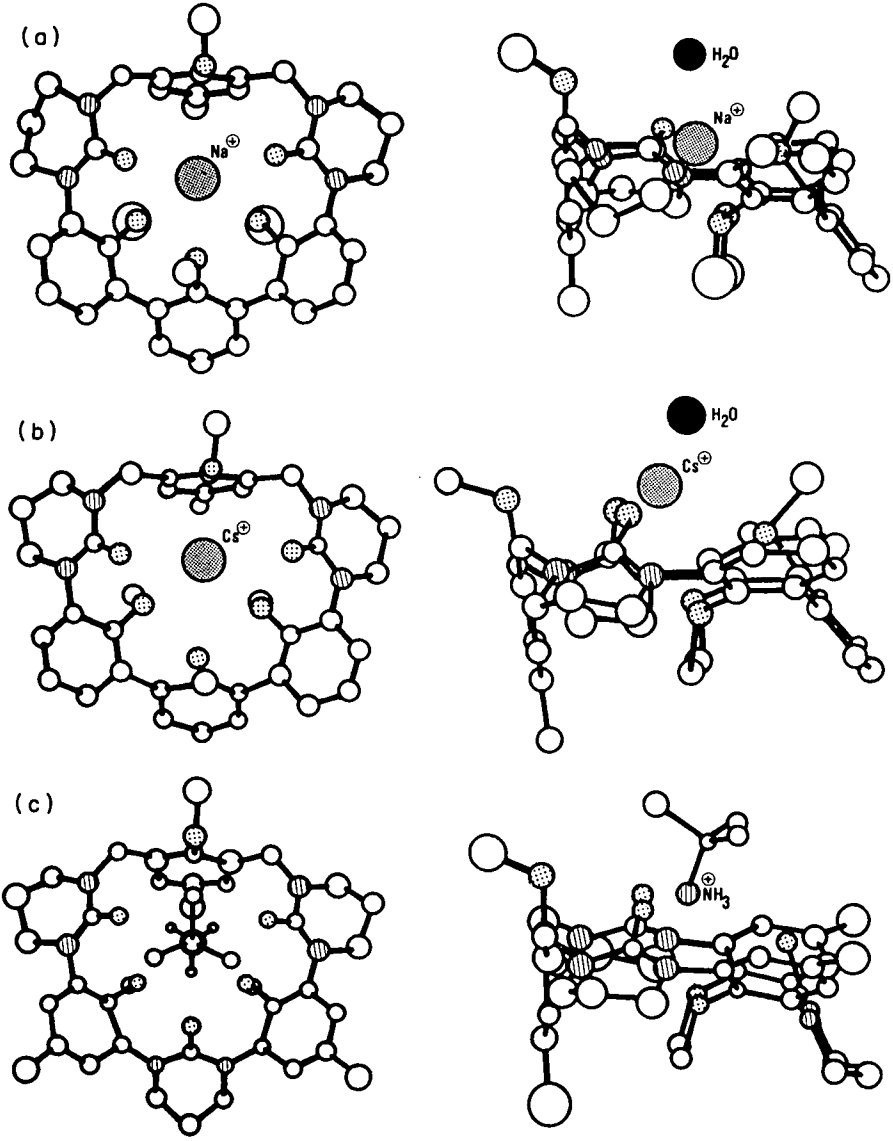


FIGURE 13. Face and side views of urea spherand complexes: (a) **32**·Na^+·H_2O; (b) **32**·Cs^+·H_2O; (c) **33**·*t*-$BuNH_3^+$. Adapted from Ref. 45

to nest in the cavity. Consequently, they are compelled to interact in a perching mode with the donor oxygens. The top face of Cs^+ is occupied by H_2O in the same way as before.

Compared with **26**·Na^+ (Figure 11)[39], the present complexes, at least the Na^+ and Cs^+ complexes of **32**, are not indicative of a fully preorganized host, e.g. because of hydration (see Section III.A). In **26**·Li^+ and **26**·Na^+, the guest is surrounded on all sides by the six *p*-

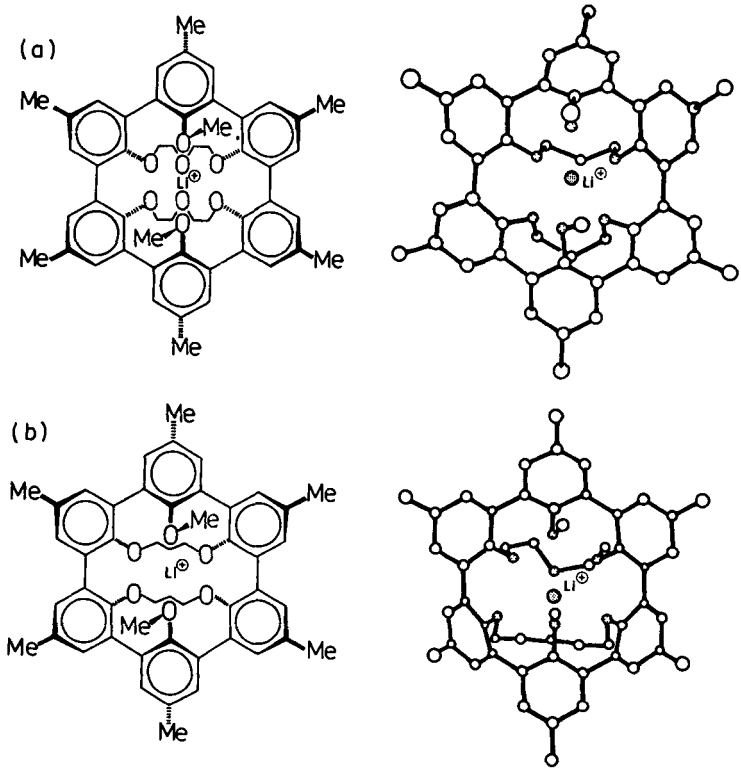


FIGURE 14. Structural formulae and crystal structures of complexes between bridged spherands and Li^+: (a) **30**·Li^+, (b) **31**·Li^+. Adapted from Ref. 40

methylanisyl units (capsular complex) so that no other molecules can approach the guest. Nevertheless, the general conformations of the hosts **32** and **33** in the present complexes are nearly independent of the guest. All oxygen atoms converge on the cavity and the attached methyl groups diverge from the cavity. These results strongly support spherand preorganization.

Figure 14 shows the structures of **30**·Li^+ and **31**·Li^+[39,40]. The hosts are severely strained in these complexes, mainly because of overlapping van der Waals volumes of the bridging oxygens. In **30**·Li^+ (Figure 14a) all six of the pseudo-*ortho* and one of the pseudo-*meta* O—O distances[a] (average 2.64 Å) are less then the normal van der Waals distance of 2.80 Å. In **31**·Li^+ (Figure 14b) steric compression involves the two bridge-terminating pseudo-*ortho* O—O distances, the two shortest of the four MeO—pseudo-*ortho*-$ArOCH_2$ distances and the four near O—O distances in the two bridges (average distance 2.67 Å). Hence **30**·Li^+ has seven and **31**·Li^+ eight O—O distances shorter than usual and the net effect of the bridges in **30** and **31** may be described as squeezing out one of the methoxy oxygens, resulting in a long Li^+—O distance. The remaining five oxygens of **30**·Li^+ and

[a] Pseudo-*ortho* and pseudo-*meta* specify *ortho* and *meta* relationships displaced from the usual homoannular into the transannular context[48a].

seven oxygen of **31**·Li^+ ligate the ions (notice that a sevenfold coordinated Li^+ complex has not been reported previously).

In clear contrast, all of the pseudo-*ortho* O—O distances in **26**·Li^+ or **26**·Na^+ (Figure 11)[39] are close to being normal (2.78 Å). This clearly indicates a partly incomplete preorganization at the bridged spherands. Nevertheless, predictions based on CPK models were shown to fit the observed structures. This is generally true for all complexes presented here, indicating the relatively high degree of conformational rigidity.

C. Hemispherands (Cryptaspherands)

Hemispherands[36,37] are distinguished from true spherands by their lower degree of preorganization. They have a characteristic semi-flexible rather than a completely rigid molecular framework. Hence they occupy a position somewhere above (d) in Figure 9, either between (b) and (d), (c) and (d) or (a) and (d), which means they are *partly* preorganized cryptands, crowns (coronands) or podands. In other words, they combine in the same molecule structural parts of an original cryptand (e.g. bridgehead atoms) together with a spherand (e.g. self-organizing anisyl groups), or a crown (ethyleneoxy segments) and a spherand, or a podand (terminal groups) and a spherand, respectively. Naturally, while preorganization decreases in this order the molecular flexibility increases at the same time. The particular blend of rigidity and flexibility of the hemispherands provides an exceptional basis for studies of structure–binding correlations.

The naming of the different types of hybrid hosts is not completely uniform, unfortunately[37]. The hemi-preorganized cryptands are usually specified as 'cryptaspherands', although they are not at the level of a pure spherand, the partly preorganized crowns are simply designated 'hemispherands', in a non-differentiating way, and the partly preorganized podands are sometimes not classed with spherands at all. In fact they are hemispherands, derived from cryptands or crowns (coronands) or podands by introducing properties of self-organization, and may be properly termed 'cryptahemispherands' (or alternatively 'hemispheracryptands'), 'hemispheracoronands' and 'hemispherapodands', respectively. The prefix usage, e.g. 'hemispheracoronand' or 'hemispherapodand', depends on the extent of preorganization. Generally, the lower the level of preorganization, the more useful is the prefix name (hemisphera).

A selection of structures related to the different subclasses of hemispherands[44,49–55] are shown in Figure 15. Structures **36** and **37** portray prototypical cryptahemispherands[49,50]. As is apparent from CPK molecular models, they have a relatively high level of preorganization. Consequently, strong and specific binding of alkali metal ions by these compounds is to be expected. A list of association constants and free energies of complexation is given in Table 10.

The smallest of the present cryptahemispherands, **36a**, possessing seven potential binding sites, provides a range of $-\Delta G°$ between 20.6 and 10.4 kcal mol^{-1} for the five alkali metal ions[50]. The maximum value occurs with Na^+ and the minimum with Cs^+. The five ions are bound in the decreasing order $Na^+ > Li^+ > K^+ > Rb^+ > Cs^+$. Thus Li^+ appears to be too small and K^+, Rb^+ and Cs^+ too large for inclusion in the cavity of **36a** without causing strain.

The medium-sized cryptahemispherand **36b**, possessing eight potential binding sites, shows the maximum binding free energy with Na^+ or possibly with K^+ ($-\Delta G° = 21.0$ or > 19.9 kcal mol^{-1}); the lowest value of $-\Delta G°$ occurs with Li^+ (13.4 kcal mol^{-1})[50]. Hence Li^+ appears to be much too small (and Cs^+ too large) for the least strained cavity of **36b**.

In the largest cryptahemispherand, **36c**, possessing nine potential binding sites, the maximum $-\Delta G°$ value occurs with Cs^+ (21.7 kcal mol^{-1}) and the minimum with Li^+ (9.9 kcal mol^{-1})[50]. Hence Cs^+ is the most and Li^+ the least complementary ion to the host cavity of **36c**.

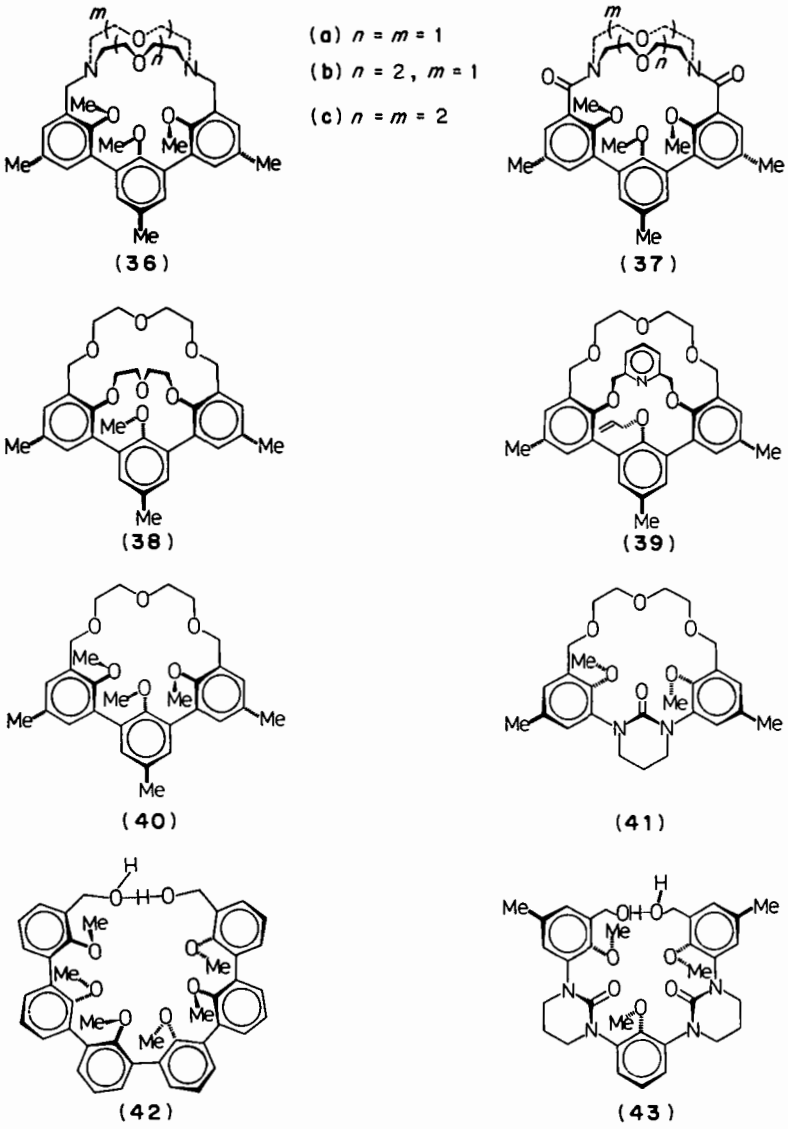


FIGURE 15. Hemispherands at different stages of preorganization

The higher level of preorganization of the cryptahemispherands **36** compared with the pure cryptand analogues (see Table 10) is obvious from the following facts: the highest $-\Delta G^\circ$ values (in $CDCl_3$–H_2O) obtained for the cryptands are for [2.2.2], binding K^+ with 18.0 kcal mol^{-1}, and for [2.2.1], binding Na^+ with 17.7 kcal mol^{-1} (cf. Section II.C.3 in the original chapter)[50]. These values are 3–4 kcal mol^{-1} lower than the peak binding observed for the cryptahemispherands. On the other hand, the lower level of preorganiz-

TABLE 10. Stability constants (K_s) and binding free energies ($-\Delta G°$) for cation complexation of hemispherands in $CDCl_3$ saturated with D_2O at 25 °C (cryptands and naphtho-18-crown-6 are included for comparison)[50,51,53,55]

Ligand	Cation	K_s ($l\,mol^{-1}$)	$-\Delta G°$ ($kcal\,mol^{-1}$)
36a	Li^+	6.13×10^{13}	18.1
	Na^+	1.28×10^{15}	20.6
	K^+	1.00×10^{11}	15.0
	Rb^+	5.67×10^{9}	13.3
	Cs^+	4.24×10^{7}	10.4
36b	Li^+	6.14×10^{9}	13.4
	Na^+	2.59×10^{15}	21.0
	K^+	$> 3.71 \times 10^{14}$	> 19.9
	Rb^+	9.18×10^{14}	20.4
	Cs^+	1.02×10^{12}	16.4
	NH_4^+	4.22×10^{13}	18.6
36c	Li^+	1.82×10^{7}	9.9
	Na^+	7.95×10^{9}	13.5
	K^+	8.59×10^{13}	19.0
	Rb^+	7.72×10^{14}	20.3
	Cs^+	8.21×10^{15}	21.7
	NH_4^+	6.52×10^{14}	20.2
38	Li^+	2.2×10^{5}	7.3
	Na^+	2.1×10^{9}	12.7
	K^+	1.5×10^{10}	13.9
	Rb^+	4.4×10^{8}	11.8
	Cs^+	1.3×10^{7}	9.7
	NH_4^+	1.3×10^{8}	11.1
	$MeNH_3^+$	1.8×10^{7}	9.9
	t-$BuNH_3^+$	3.6×10^{6}	8.9
39	Li^+	5.0×10^{7}	10.5
	Na^+	4.9×10^{10}	14.6
	K^+	4.9×10^{10}	14.6
	Rb^+	2.3×10^{9}	12.8
	Cs^+	1.9×10^{8}	11.3
	NH_4^+	2.0×10^{9}	12.7
	$MeNH_3^+$	5.0×10^{8}	11.9
	t-$BuNH_3^+$	3.7×10^{8}	11.7
40	Li^+	1.3×10^{5}	7.0
	Na^+	9.2×10^{8}	12.3
	K^+	4.6×10^{8}	11.8
	Rb^+	4.6×10^{7}	10.4
	Cs^+	3.7×10^{6}	9.0
	NH_4^+	1.5×10^{7}	9.8
	$MeNH_3^+$	9.9×10^{5}	8.2
	t-$BuNH_3^+$	4.2×10^{5}	7.7

TABLE 10. (*continued*)

Ligand	Cation	K_s(l mol^{-1})	$-\Delta G°$ (kcal mol^{-1})
41	Li^+	8.0×10^4	6.7
	Na^+	6.1×10^8	12.0
	K^+	1.9×10^8	11.3
	Rb^+	1.8×10^7	9.9
	Cs^+	2.3×10^6	8.7
	NH_4^+	6.4×10^6	9.3
	$MeNH_3^+$	4.6×10^6	9.1
	t-$BuNH_3^+$	1.3×10^7	9.7
42	Li^+	$< 2.5 \times 10^4$	< 6
	Na^+	3.5×10^4	6.2
	K^+	4.4×10^5	7.7
	Rb^+	2.0×10^6	8.6
	Cs^+	4.6×10^6	9.1
	NH_4^+	3.1×10^5	7.5
	$MeNH_3^+$	2.1×10^4	5.9
	t-$BuNH_3^+$	4.3×10^2	3.6
43	Li^+		< 6
	Na^+		< 6
	K^+	1.8×10^4	5.8
	Rb^+	2.5×10^4	6.0
	Cs^+	5.9×10^4	6.5
	NH_4^+	2.9×10^4	6.1
	$MeNH_3^+$	3.7×10^4	6.2
	t-$BuNH_3^+$	3.7×10^4	6.2
[2.1.1]	Li^+	1.5×10^{12}	16.6
[2.2.1]	Li^+	2.2×10^7	10.0
	Na^+	9.8×10^{12}	17.7
	K^+	1.7×10^{11}	15.3
	Rb^+	2.1×10^9	12.7
[2.2.2]	Na^+	3.7×10^{10}	14.4
	K^+	1.6×10^{13}	18.0
	Rb^+	2.1×10^{12}	16.8
	Cs^+	3.6×10^7	10.3
N18C6[a]	Li^+	2.2×10^4	5.9
	Na^+	1.2×10^6	8.3
	K^+	8.6×10^7	10.8
	Rb^+	1.1×10^7	9.6
	Cs^+	1.2×10^6	8.3
	NH_4^+	9.8×10^6	9.5
	$MeNH_3^+$	3.3×10^5	7.5
	t-$BuNH_3^+$	1.0×10^5	6.8

[a]Naphtho-18-crown-6.

ation of cryptahemispherands **36a–36c** compared with pure spherands, e.g. **26**, results in a lower $-\Delta G°$ value (by > 2 kcal mol^{-1}) for the cation binding of the former; compare the Li^+ complex of **26** (Table 9) with the Na^+ complex of **36b** (Table 10).

The crystal structures of cryptahemispherand complexes[49] further substantiate the state of conformational preorganization of the host cavity. An illustration is given by Figure 16, which shows complexes of **36c** with different metal cations (Na^+, K^+ and Cs^+). Common to all three crystal structures is the conformational up-down-up arrangement of the spherand-like trianisyl module, which is strongly preorganized for binding. On the other hand, the cryptand-like module offers a site of reorganization to make adaptation to the guest requirements possible.

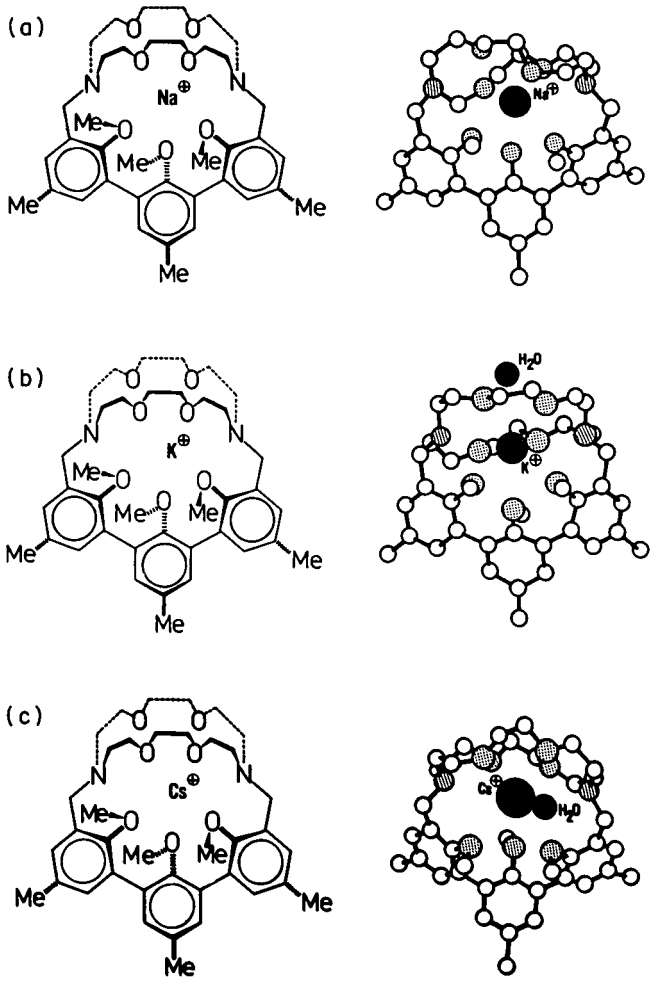


FIGURE 16. Structural formulae and crystal structures of cryptahemispherand–cation complexes: (a) **36c**·Na^+, (b) **36c**·K^+·H_2O; (c) **36c**·Cs^+·H_2O. Adapted from Ref. 49

However, the cavity of **36c** is definitely too large for Na^+ (N—N = 6.68 Å) and is unable to contact in such a way as to allow all eight donor atoms to ligate the Na^+ (Figure 16a)[49]. As a consequence, Na^+ is ligated to five of the oxygens only (close to one of the nitrogens) and the cavity is unfilled except in this region. The apparent Na^+ diameter is 2.56 Å, much greater than normal (see Table 13 in the original chapter).

In case of **36c**·K^+ (Figure 16b)[49], K^+ is large enough to contact all nine ligating sites if there is a preceding small degree of shrinking of the cavity (N—N = 6.36 Å). The apparent K^+ diameter is 2.96, relatively close to normal (see Table 13 in the original chapter). A molecule of water also coordinates the K^+.

Comparison of the metal–donor distances in **36c**·Cs^+ (Figure 16c)[49] ($Cs^+ \cdots O = 3.03$, $Cs^+ \cdots N = 3.40$ Å) with the normal values (3.09 and 3.19 Å, respectively)[35,49] reveals that **36c** is a nearly ideal host for Cs^+, which needs to be neither contracted nor extended (N—N = 6.67 Å; cf. Na^+ complex). Hence all nine donor atoms strongly ligate to Cs^+, whose apparent diameter (3.26 Å) (see Table 13 in the original chapter) is very close to the normal. A molecule of H_2O is also bound to the Cs^+, but in a position different to that in **36c**·Na^+·H_2O.

The conclusions of this study are as follows: **36c** is a case of a prototypical cryptahemispherand[49]; it has a very good fit for Cs^+, moderate for K^+ and poor for Na^+; the relationships are in excellent agreement with the corresponding $-\Delta G°$ data for the complex formation reactions[50] (Table 10) and are also supported by molecular models[49].

The bridged systems **38** and **39** were considered to belong to the next lower level of preorganization. The maximum association constants (K_s) and free energies for complexation ($-\Delta G°$) range between 10^9 and 10^{10} l mol^{-1} and 13 and 14 kcal mol^{-1}, respectively[51] (Table 10). Hence they bind cations with about five powers of ten for K_s and 6–7 kcal mol^{-1} for $-\Delta G°$ weaker than the cryptahemispherands of type **36**[50]. According to the size of the major ring, which is 18-membered, **38** and **39** show peak binding with Na^+ and K^+ but **39**, with an integrated pyridine module, is unusual in the sense that each of the six guests besides Na^+ and K^+ are also strongly bound ($-\Delta G°$ ranges from 10.5 to 14.6 kcal mol^{-1} for **39**)[51]. Molecular models indicate that four of the binding sites of **39** (associated with the trisanisylpyridine ring module) are rigidly preorganized for complexation, whereas the other three (associated with the bisethyleneoxy bridge) have very limited degrees of freedom but can adapt well to the requirements of the different cations.

Hemispherands, being derived from monocyclic coronands[52–54], e.g. **40** and **41**, are on the level of preorganization next lower to cryptahemispherands and bridged hemispherands. Correspondingly, they are weaker binders by several kcal mol^{-1} than the cryptahemispherands or the bridged hemispherands but better binders than the simple (non-preorganized) coronand analogues (e.g. naphtho-18-crown-6, see Table 10)[51,52]. The $-\Delta G°$ values for cation complexation for **40** and **41** are listed in Table 10. Host **40**[53] shows peak binding with Na^+. In fact, molecular models of **40** reveal a cavity diameter in the range 1.8–2.0 Å, thus being complementary to the dimensions of Na^+. The poorest bound metal ion is Li^+. Also hemispherand **41**[53], with one replacing urea building block, binds maximally to Na^+, although K^+ is similar (0.7 kcal mol^{-1} difference in $-\Delta G°$); as for **40**, the poorest bound metal ion is Li^+.

Figure 17 depicts the crystal structures of free hosts **40** (Figure 17a)[51] and **41** (Figure 17b)[53] and that of its complexes with t-$BuNH_3^+$ (Figure 17c and d, respectively)[51,53]. The views (compare Figure 17a with 17c and Figure 17b with 17d) indicate that both the AAA module (A = anisyl) of **40** and the AUA unit (U = urea) of **41** are preorganized for binding during synthesis. They possess essentially the same organization in the free host and in the corresponding complex. However, this is not true for the heteroaliphatic segments in **40** and **41**. In the free hosts (Figure 17a and b), the unshared electron pairs of the three oxygens diverge from the cavity in a non-binding arrangement while most of the central CH_2 groups turn inwards, partly filling the cavity. On

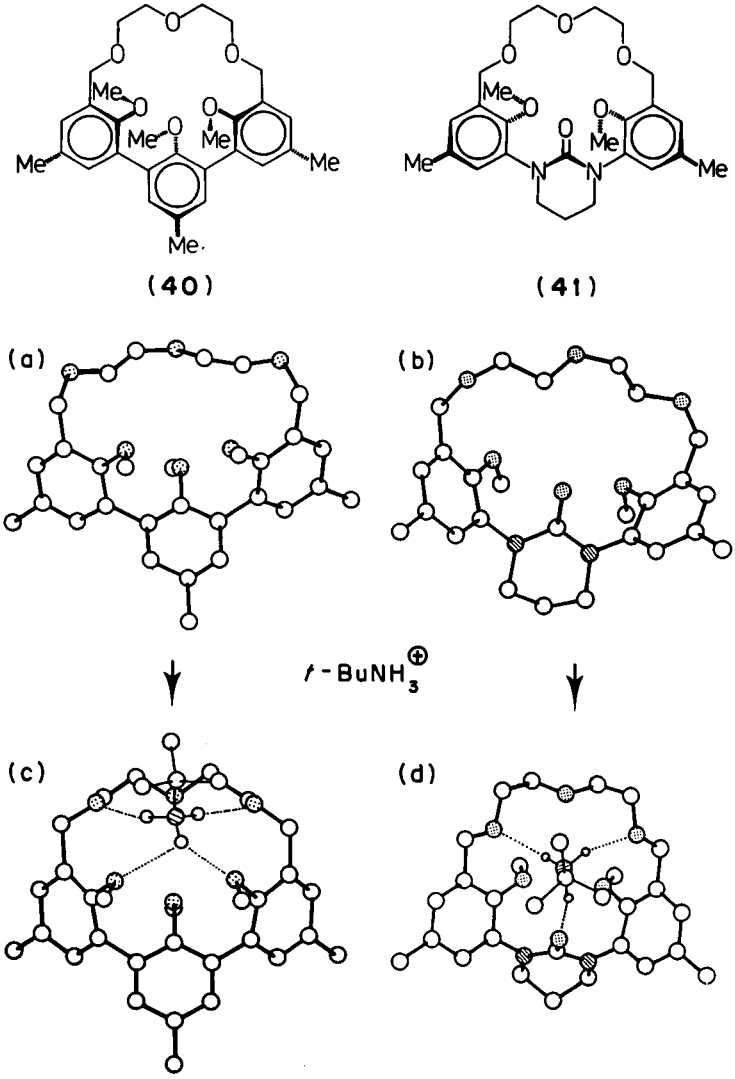


FIGURE 17. Structural formulae and crystal structures of hemispherands (a) **40** and (b) **41**, and (c), (d) of their t-$BuNH_3^+$ complexes. Adapted from Refs. 51 and 53

complexation with t-$BuNH_3^+$, the hydrogens are displaced from the cavity and the oxygen donors are caused to converge (Figure 17c and d). Hence some organization burden rests on the heteroaliphatic segments of **40** and **41** during complexation.

Both complexes involve a tripodal binding of the guest and are in a perching arrangement. In **40**·t-$BuNH_3^+$ (Figure 17c)[51], binding is via two N^+—H···O bonds that involve the benzyl oxygens and a bifurcated N^+—H:::$(OMe)_2$ that involves the two

outer methoxy oxygens. In **41**·*t*-BuNH$_3^+$ (Figure 17d)[53], hydrogen bonds of NH$_3^+$ are to the urea and to the two benzyl oxygens. Accordingly, in both complexes opposite faces of the hosts are occupied. The observed crystal structures are consistent with expectations based on CPK molecular model examinations.

Naturally, analogous open-chain (podand) hemispherands are at the lowest level of preorganization. However, podands having terminal groups which can hydrogen bond with one another might be in a position to preorganize themselves, forming pseudomacrocycles with substantial binding potential[44,45]. The open-chain relatives **42** and **43** in models appear to be capable of completing their ring systems in this way, e.g. by hydrogen bonding between the hydroxymethylene termini.

Compound **42**[55] gives peak binding with Cs^+ as guest, with $-\Delta G° = 9.1\,kcal\,mol^{-1}$, and the values gradually decrease from Rb^+ to Li^+ ($-\Delta G° < 6\,kcal\,mol^{-1}$ with Li^+). With the ammonium guests, the values decrease from $7.5\,kcal\,mol^{-1}$ with NH_4^+ to $3.6\,kcal\,mol^{-1}$ with *t*-BuNH$_3^+$. The differences in metal cation binding, e.g. of K^+ and Na^+ by more than a power of ten, are surprising for a fairly flexible structure. It is therefore suggested that the terminal hydroxymethylene groups play an important role in either preorganizing the system as a pseudocycle or providing additional binding sites, or probably both.

Although the open-chain compound **43**[44] may also be preformed in a pseudocycle, the reorganizational burden for cation complexation seems so heavy in this case that **43** shows remarkably little binding capacity for cations. All measured $-\Delta G°$ values lie between 5.8 and $6.5\,kcal\,mol^{-1}$. Nevertheless, this is an important example relating to the essential point of preorganization, which involves the particular binding arrangement rather than any rigid or semirigid conformation.

D. Kinetics of Spherand and Hemispherand Complexation

A general characteristic of the complex chemistry of crowns and cryptands (see Section II.B in the original chapter) is that conformationally rigid systems show slow kinetic behaviour. Accordingly, kinetic parameters are expected to be slow for the complexes of the rigidly preorganized spherands, whereas the more flexible hemispherands show faster kinetics. Typical kinetic data (rate constants of complexation and decomplexation, $\vec{k}$ and $\overleftarrow{k}$, respectively, of a few compounds are listed in Table 11. They were obtained by ^1H NMR spectroscopy in $CDCl_3$ saturated with D_2O.

The preorganized spherands **26**, **30** and **31** in Figures 11 and 12 at 25 °C complex Li^+ and Na^+ picrate with rate constants $\vec{k}$ that vary between $8 \times 10^4\,l\,mol^{-1}\,s^{-1}$ for **26**·Li^+ to $10^6\,l\,mol^{-1}\,s^{-1}$ for **30**·Na^+; the decomplexation rate constants $\overleftarrow{k}$ range from $< 10^{-12}\,s^{-1}$ for **26**·Li^+ to $2 \times 10^{-4}\,s^{-1}$ for **31**·Na^+[56]. Hence $\overleftarrow{k}$ varies over a much smaller range (a factor of 10) than $\vec{k}$ (a factor of $> 10^8$), showing that the difference of $> 10^7\,l\,mol^{-1}$ in K_s (equilibrium binding constants, Table 9) is largely a consequence of $\overleftarrow{k}$. Correspondingly, $\log K_s$ plotted against $\log \overleftarrow{k}$ gave an essentially linear correlation; a plot of $\log K_s$ against $\vec{k}$ showed no correlation[56].

Cryptands, e.g. [2.1.1] and [2.2.1] (see Section II.B.3.c in the original chapter), which are the most preorganized systems towards Li^+ and Na^+ next to the spherands, logically exhibit similar behaviour, with $\vec{k}$ values (10^4–$10^7\,l\,mol^{-1}\,s^{-1}$)[57] in roughly the same range as for spherands (see Table 11).

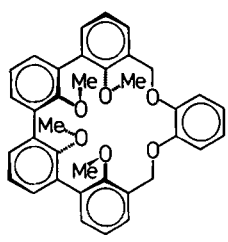
Kinetic data for the hemispherands **40** and **41**, containing three self-organizing units, have not been determined, but for **44** and **45** (Figure 18) with four preorganizing anisyl moieties, $\vec{k}$ and $\overleftarrow{k}$ values for K^+ Pic^- binding are listed in Table 11. The complexation rate constants of **44** and **45** are three to four powers of ten higher than for the spherands; the decomplexation rate constants are about ten powers of ten higher[58]. Moreover, $\vec{k}$ rather than $\overleftarrow{k}$ governs K_s in these cases, in contrast to the spherands and cryptands.

TABLE 11. Complexation ($\vec{k}$) and decomplexation ($\overleftarrow{k}$) rate constants for interaction of spherands and hemispherands with cations[56,59]

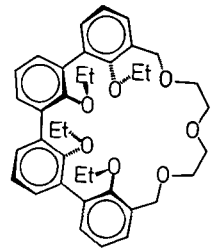
Ligand	Cation	$\vec{k}$ ($l\,mol^{-1}\,s^{-1}$)	$\overleftarrow{k}$ (s^{-1})
26	Li^+	8×10^4	$< 10^{-12}$
	Na^+	4×10^5	3×10^{-9}
30	Li^+	4×10^5	2×10^{-7}
	Na^+	1×10^6	2×10^{-4}
31	Li^+	3×10^5	7×10^{-7}
	Na^+	9×10^4	2×10^{-9}
33	t-$BuNH_3^+$	3×10^{12}	7×10^2
44	K^+	2×10^9	14
45	K^+	2×10^8	4

Rate constants of t-$BuNH_3^+$ binding[59] are given for **33** in Table 11. The host undergoes fast complexation with $\vec{k} \approx 10^{12}$ $l\,mol^{-1}\,s^{-1}$, indicating that the reaction is essentially diffusion controlled. The $\overleftarrow{k}$ value of *ca.* $10^3\,s^{-1}$ is also fast on the present scale.

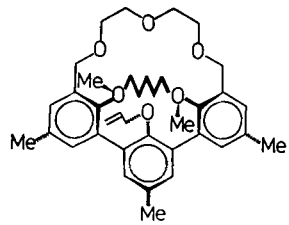
We recognize the following order in the kinetic behaviour: compounds **26**, **30** and **31** (spherands) are slow with respect to both $\vec{k}$ and $\overleftarrow{k}$ for Li^+ and K^+ binding, **44** and **45**



(44)



(45)



(46)

FIGURE 18. Hemispherands containing four self-organizing units (**44**, **45**) or an aliphatic bridge (**46**)

(hemispherands) are fast with respect to $\vec{k}$ and $\overleftarrow{k}$ for K^+ binding and **33** is very fast with respect to $\overleftarrow{k}$ and $\vec{k}$ for binding of t-$BuNH_3^+$. Cryptands [2.1.1] and [2.2.1] are close to the spherands in Li^+ and Na^+ binding, respectively.

This order conforms to a comparison of crystal structures and molecular models[56]. Spherands **26**, **30** and **31**, just as cryptands, show a *capsular* arrangement in the Li^+ and Na^+ complexes (Figures 11 and 14, respectively). Hemispherands **44** and **45** are suggested to have a *nesting* arrangement in the K^+ complexes and **33** undoubtedly shows a *perching* structure in the t-$BuNH_3^+$ complex (Figure 13c). Exchange of the solvation shell, which is a key process of cation complexation, is affected differently in these complexes. The solvation shell of the cation is most disturbed in forming a capsular complex, less disturbed in forming a nesting complex and least disturbed in forming a perching complex.

To complex or decomplex **26** (analogously to **30** and **31**), the cation must pass through a lipophilic sleeve (three MeO groups) with minimum engagement of solvent molecules and counter ions. In fact, the rates of complexation and decomplexation vary slightly with the character of the counter ion and are little affected by the structural differences between the spherands (Table 11).

It is strongly suggested that the transition states of spherand complexation lie very near to the unsolvated host and guest reactants. Therefore, it is hardly surprising that the rates of complexation and decomplexation are so extremely slow for the spherands. The transition states of hemispherand complexes, however, involve simultaneous stabilization by medium and host–guest interactions, leading to higher rates of complexation and decomplexation.

Capsular, nesting and perching complexes correspond to a decreasing order of preorganization. Therefore, the striking generalization[37] that correlates structures with kinetics is that *the more highly preorganized is a host for complexation, the lower are the rates of complexation and decomplexation.*

E. Selectivity of Spherand and Hemispherand Complex Formation

Association constants (K_s, $l\,mol^{-1}$) and free energies of binding ($-\Delta G°$, $kcal\,mol^{-1}$) have been determined at 25 °C in $CDCl_3$ saturated with D_2O for various spherands and hemispherands binding individual alkali metal and ammonium picrates (Tables 9 and 10). In this section we compare the selectivity factors (see Section III.B in the original chapter) as measured by relative values of K_s for various pairs of host–guest partners (Table 12). In particular, the given $K_s^M/K_s^{M'}$ ratios relate to guest ions (M and M') adjacent to one another in the orders of ionic diameters (alkali metal ions) or degrees of substitution (ammonium and alkylammonium ions), thus demonstrating selectivities within the range of analytically and biologically important ions (e.g. Li^+/Na^+, Na^+/Li^+, Na^+/K^+, K^+/Na^+). Examples of distinct selectivities are as follows[37].

The highest Li^+/Na^+ selectivity factors are exhibited by spherands **26** and **30**. The highest Na^+/Li^+ values are those of the cryptahemispherand **36b** and the bridged hemispherand **38**. Large selectivities of Na^+ over K^+ are exhibited by spherands **26**, **30** and **31** and cryptahemispherand **36a**. Cryptaspherand **36c** shows the highest K^+/Na^+, hemispherand **38** the highest K^+/Rb^+, spherand **29** the highest Rb^+/K^+, cryptaspherands **36a** and **36b** the highest Rb^+/Cs^+ and **29** the highest Cs^+/Rb^+ selectivity. Hemispherand **40** provides a relatively high $NH_4^+/MeNH_3^+$ selectivity but the highest value is exhibited by the **39**-analogous hemispherand **46** (Figure 18), which has a pentane-1, 5-diyl instead of a pyridinebismethylene bridge. This host also shows a relatively high $MeNH_3^+/t$-$BuNH_3^+$ selectivity.

A few observations are important. The highest selectivities shown in Table 12 ($> 10^{10}$ and 10^9 for **26** and **31**, respectively) binding Na^+ over K^+ belong to spherands. Of all the hosts, substantial selectivity of Li^+ over Na^+ is observed with spherands (cf. **26** and **30**).

TABLE 12. Cation selectivity of spherand-type hosts for complex formation in $CDCl_3$ saturated with D_2O at 25 °C (cryptands are included for comparison)[37]

Specification	Data (selectivity factors)[a]
Li^+/Na^+	**26** (> 600), **30** (360), [2.1.1] (4800)
Na^+/Li^+	**31** (125), **36b** (420 000), **36c** (440), **38** (9500), **40** (7100), **41** (7600), [2.2.1] (440 000)
Na^+/K^+	**26** (> 10^{10}), **30** (> 10^5), **31** (> 10^9), **36a** (13 000)
K^+/Na^+	**36c** (11 000)
K^+/Rb^+	**38** (34), **41** (11)
Rb^+/K^+	**29** (14), **42** (5)
Rb^+/Cs^+	**36a** (134), **36b** (900), **38** (34)
Cs^+/Rb^+	**29** (370), **36c** (11)
$NH_4^+/MeNH_3^+$	**38** (7), **40** (15), **46** (31)
$MeNH_3^+/t\text{-}BuNH_3^+$	**38** (5), **42** (49), **46** (40)

[a] Defined as the ratio of K_s^M to $K_s^{M'}$ (cf. Table 7).

Hence the spherands **26**, **30** and **31** appear to be unique with their high specificity for binding Li^+ over Na^+ and for binding Na^+ and Li^+ better than any other ions. Only the small cryptands [2.2.1] or [2.1.1] (see Table 12) and a few cryptahemispherands (**36a** and **36b**) show comparably high specificities for Li^+ and Na^+. These compounds belong to host classes at the immediately lower levels of preorganization[37], showing that the principle of preorganization applies not only to binding power but also to ion selectivity.

IV. SECOND-SPHERE COORDINATION

A. Background and Definitions

The phenomenon that ligands in the primary coordination sphere of a central atom, e.g. of a transition metal complex, can interact in an ordered manner with neutral molecules or charged species to give a 'second-sphere' or 'outer-sphere' complex is defined as 'second-sphere coordination'[60] (Figure 19a). It was Alfred Werner who initially pointed to this principle over 75 years ago[61], but in the past, second-sphere coordination has usually been regarded simply as an aspect of solvation[62] and only when crown ethers were established to form hydrogen-bonded complexes with primary alkylammonium ions[2a,2h] (cf. Figure 19b) or even with less acidic uncharged organic molecules (see Section IV.B.c. in the original chapter) was second-sphere coordination rediscovered[63]. Actually it was the recognition of a simple geometric and electronic analogy between a primary alkylammonium ion (see Figure 19b) and a transition metal ammine complex (see Figure 19c) which led to the idea that crown ethers may act as second-sphere ligands. The supramolecular structures arising from second-sphere coordination between complexes and crowns are designated 'adducts'[6b]. Constitutions of crown compounds efficient in second-sphere coordination are shown in Figure 20.

B. Involving 18-Crown-6 (18C6) and Derivatives

1. Borane complexes

Complexes of BX_3 (X = H or Hal) with NH_3 are amongst the simplest ammine complexes for which crystalline second-sphere adducts are known[64–66]. X-ray crystallographic

studies confirm close structural relationships between the adducts and the corresponding primary ammonium complexes (cf. Figure 19). Figure 21a shows the X-ray crystal structure[a] of the $[BF_3NH_3]\cdot 18C6$ adduct as its CH_2Cl_2 solvate[64].

In this adduct, the 18C6 ring adopts the same all-*gauche* conformation with pseudo D_{3d} symmetry as commonly found in RNH_3^+ complexes of 18C6[67]. Moreover, the geometry of the three strong N—H···O bonds [N···O ≤ 2.95 Å] which link the NH_3 centre to three alternate oxygen atoms of the 18C6 ring corresponds to the so-called perching mode of binding in $18C6\cdot RNH_3^+$ complexes[67] (cf. Figure 19).

Despite this similarity, differences between BX_3NH_3 and RNH_3^+ complexation to crowns also exist, since BF_3NH_3, but not RNH_3^+ renders the formation of 2:1 (complex: crown) adducts possible. This is the case when the 18C6 ring carries shielding substituents. Thus, both the octamethyl-18C6 derivative **48**[65] and the (*R*, *R*, *S*, *S*)-tetraphenyl derivative of 18C6 **49**[66] form crystalline 2:1 adducts. Their X-ray crystal structures[65,66] demonstrate that, in each case, the two BH_3NH_3 species are hydrogen-bonded to the opposite faces of the macrocycles which adopt a characteristic all-*gauche* conformation. Figure 21b illustrates the $BH_3NH_3\cdot$**49** (2:1) adduct[66].

In this respect there is close analogy with the 1:2 complexes of crown ethers with N-containing uncharged organic guests (e.g. 18C6 with benzenesulphonamide; see Figure 28 in Section IV.B.c in the orignal chapter). A reasonable explanation is weaker coulombic repulsion for BH_3NH_3 compared with ammonium ions. Hence the guest behaviour of BH_3NH_3 for crowns lies mid-way between ammonium cations and uncharged organic

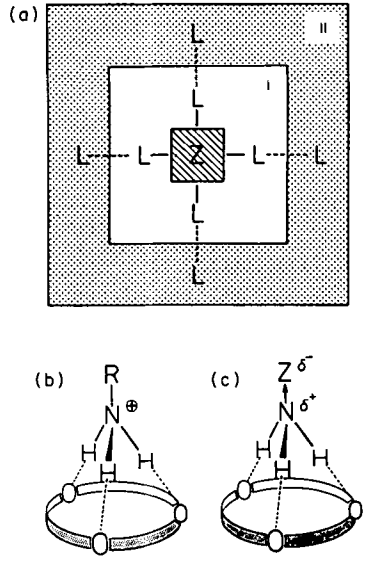
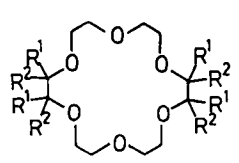
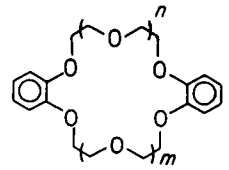


FIGURE 19. Second-sphere coordination: (a) definition (I, first coordination sphere; II, second coordination sphere); (b) and (c) strategy

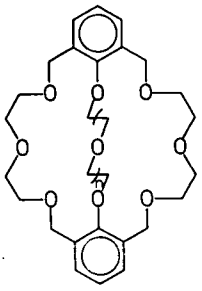
[a]In all second-sphere adducts, covalent bonds and bonds in the first coordination sphere of the metal centres are indicated by full, bold and light lines, respectively; second-sphere interaction is specified by broken lines.



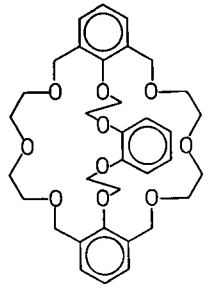
(47) $R^1 = R^2 = H$ [18C6]
(48) $R^1 = R^2 = CH_3$
(49) $R^1 = Ph$, $R^2 = H$
(2*R*,3*R*,11*S*,12*S*)



(50) $n = m = 1$ [DB18C6]
(51) $n = 2$, $m = 1$ [DB21C7]
(52) $n = m = 2$ [DB24C8]
(53) $n = m = 3$ [DB30C10]
(54) $n = m = 4$ [DB36C12]



(55) $n = 1$
(56) $n = 2$



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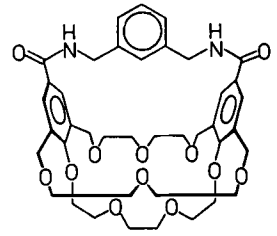

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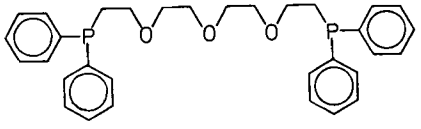

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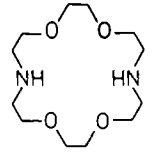


(60)

FIGURE 20. Constitutions of crown compounds efficient in second-sphere coordination

molecules. That packing effects also play a role is shown by the lack of 2:1 stoichiometry (in favour of 1:1) when using stereoisomers of tetrasubstituted 18C6 derivatives different to **49**[63b]. A high crystallinity is typical of all the adducts involving BH_3NH_3 and crown ethers[68].

2. *Transition metal–ammine complexes*

Unlike the ammine–boranes, ammine complexes of transition metals, mainly of platinum(II), have a high tendency to form 2:1 (complex:crown) adducts with 18C6 (**47**) in which both faces of the macrocycle are involved[69,70].

In these adducts, as shown, e.g. by the structure of [*trans*-$Pt(PMe_3)Cl_2(NH_3)]_2 \cdot$18C6 (Figure 22a)[70], the 18C6 ring still retains the familiar all-*gauche* conformation characteristic of BX_3NH_3 interaction with 18C6 (cf. Figure 21a). A difference, however, is that all

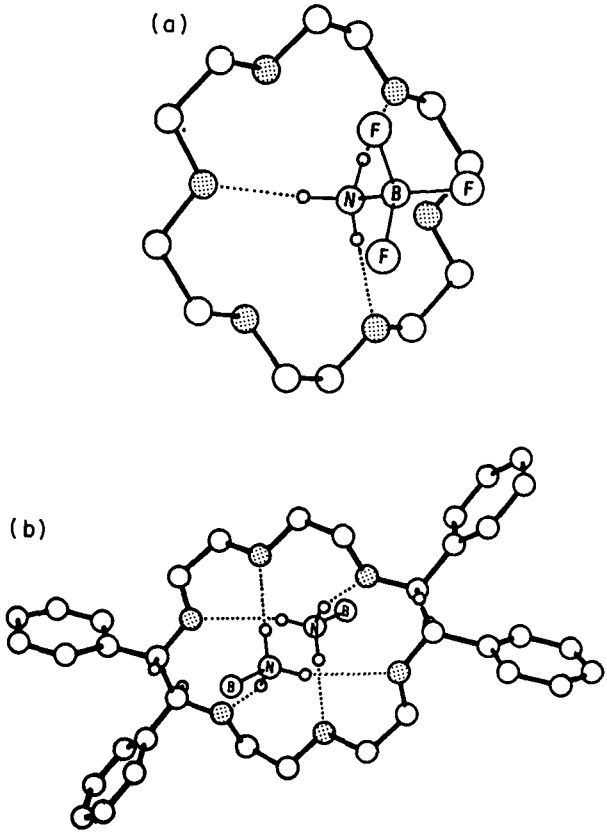


FIGURE 21. Crystal structures of crown adducts with boron–ammine complexes: (a) $[BF_3NH_3]\cdot 18C6$; (b) $[BH_3NH_3]_2\cdot$**49**. Adapted from Refs. 64 and 66

six oxygen atoms in 18C6 are included in hydrogen bonding to the two perching NH_3 ligands of the platinum complex. Another distinction between the second-sphere adducts of metal–ammine complexes and ammine–boranes is in the hydrogen bond lengths. Generally, they are significantly longer (by up to 0.4 Å) in the metal complexes[63b].

The bireceptor nature of 18C6 is also manifest in the series of platinum–diammine complexes: [*trans*-$Pt(NH_3)_2Cl_2$] forms a highly insoluble 1:1 adduct which (probably) has a polymeric hydrogen-bonded super-structure as indicated schematically in Figure 22b[70]; [*cis*-$Pt(NH_3)_2Cl_2$], the antitumour drug Cisplatin, because of the orientation of the ammine ligands gives rise to a soluble non-polymeric 2:1 adduct[71] whose structure (dimethylacetamide solvate) is shown in Figure 22c.

In the latter adduct both ammine ligands of the platinum complex are hydrogen bonded to the same face of the macroring. One NH_3 is bound in the normal trigonal manner and the other forms a single hydrogen bond to an occupied donor oxygen and (not specified in Figure 22c) is further involved in intermolecular hydrogen bonds to the chlorine ligands of adjacent Cisplatin and solvating dimethylacetamide (dma) molecules. This mode of inter-

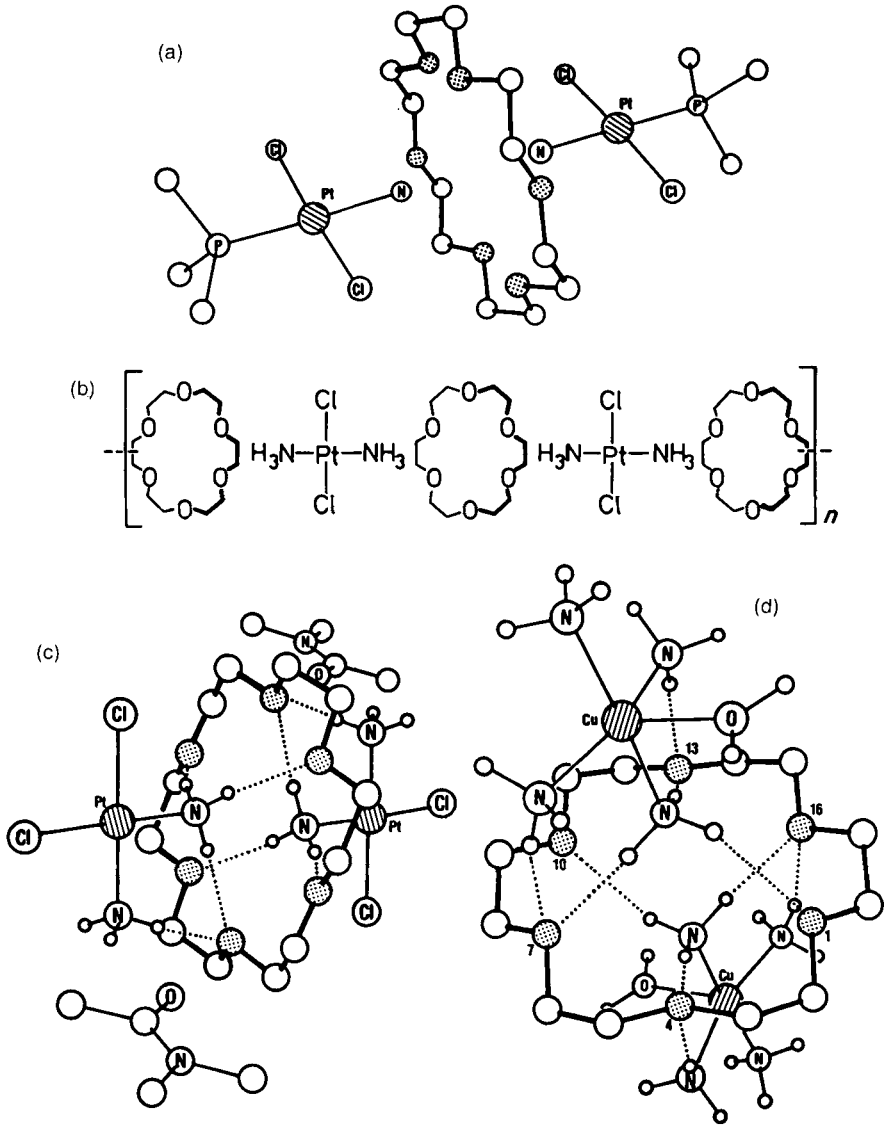


FIGURE 22. Crystal structures of 18C6 adducts with heavy metal–ammine complexes: (a) [*trans*-$Pt(PMe_3)Cl_2(NH_3)]\cdot 18C6\cdot dma$; (b) [*trans*-$Pt(NH_3)_2Cl_2]\cdot 18C6$; (c) [*cis*-$Pt(NH_3)_2Cl_2\cdot 18C6\cdot dma$ (d) $[Cu(NH_3)_4(H_2O)]^{2+}\cdot 18C6$ (PF_6^- salt). Adapted from Refs. 70–72

action causes that Pt—N vectors of the triply bonded ammine ligands to be no longer orthogonal to the mean plane of 18C6.

Interaction of 18C6 with the dicationic copper(II) complex $[Cu(NH_3)_4(H_2O)]^{2+}$ $[PF_6]_2^-$ shows a further increase in structural complexity (Figure 22d)[70,72]. In the polymeric 1:1 adduct formed, each macrocycle is involved in no fewer than ten hydrogen

bonds, including oxygens with trigonal [$O_{(1)}$, $O_{(10)}$] and tetragonal approach geometry [$O_{(4)}$, $O_{(7)}$, $O_{(13)}$, $O_{(16)}$] and six of the eight ammine ligands. Hence hydrogen bonding of this complex may be regarded as an extension of that described for the *cis*-diammine platinum species. Significantly, the aqua ligand in $[Cu(NH_3)_4(H_2O)]^{2+}$ does not interact with 18C6. However, this is not synonymous with a general inefficiency of aqua ligands in 18C6 coordination—quite the contrary (see below).

3. *Metal–aqua complexes*

Crown metal complexes, characterized by an intact hydration sphere around the metal ion, have been known for a long time and in great numbers[73] (see Section IV.B.1.b in the original chapter). X-ray crystal structures of many of these complexes have been determined (for details, see Ref. 63b). They clearly demonstrate that second-sphere coordination, e.g. of 18C6 (**47**), is also popular with metal–aqua complexes.

As before (cf. Figures 21 and 22), the 18C6 rings normally adopt the usual D_{3d}-type conformation; *trans*-aqua ligands are hydrogen-bonded to the ring faces of 18C6 to afford linear polymeric structures of alternating metal complex and 18C6 (see Figures 26b and 27a in the original chapter). A more recent example is illustrated in Figure 23a[74] (cf. Figure 22b). Figure 23b shows that H_2O molecules of the metal-aqua complex $[SnCl_4(H_2O)_2]$ which support the hydrogen-bonded polymeric structure may also be *cis* to each other[75] (cf. Figure 22c).

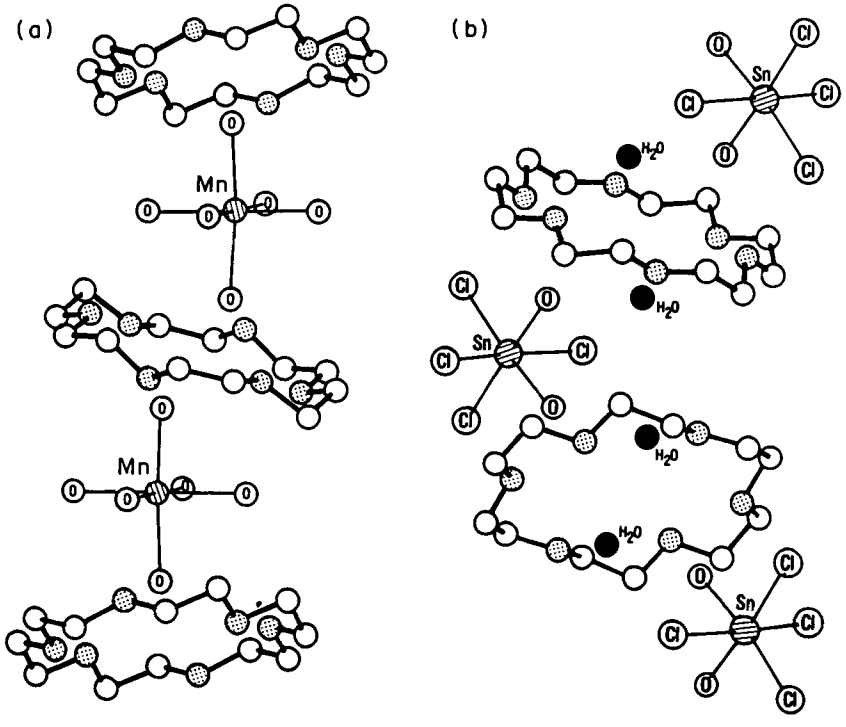


FIGURE 23. Crystal structures of 18C6 adducts with metal–aqua complexes: (a) $[Mn(H_2O)_6]^{+}\cdot$18C6 (ClO_4^- salt); (b) $[SnCl_4(H_2O)_2]\cdot$18C6. Adapted from Refs. 74 and 75

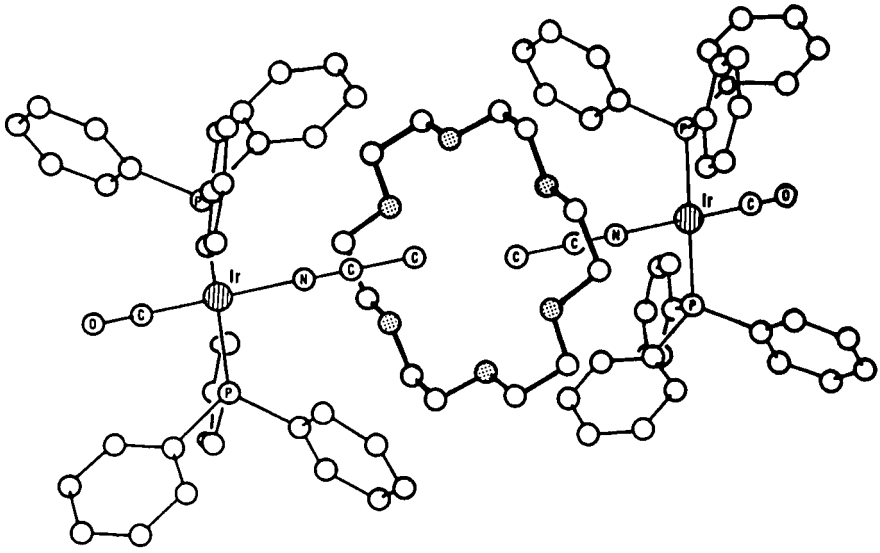


FIGURE 24. Crystal structure of the adduct [*trans*-Ir(CO)(MeCN)$(PPh_3)_2]_2^+ \cdot$18C6 (PF_6^- salt). Adapted from Ref. 77

4. Complexes with CH-acidic and other ligands

Since weak CH-acidic organic molecules, such as acetonitrile and dimethyl sulphate, readily form hydrogen-bonded complexes with 18C6 (**47**)[76] (see Section IV.B.1.c in the original chapter), analogous second-sphere interaction which involves a prepared metal complex is obvious. Accordingly, [*trans*-Ir(CO)(MeCN)$(PPh_3)_2$] [PF_6] gave a crystalline 2:1 (complex-crown) adduct with 18C6[77]. This adduct reveals the expected second-sphere structure including C—H···O hydrogen bonds between ligated MeCN and the macroring (Figure 24); 18C6 is in the familiar conformation. The structural analogy between the second-sphere adduct and known MeCN–crown complexes[78] is very close. Probably an extensive range of first-sphere ligands involving, e.g. PH_3, $CS(NH_2)_2$, $(H_2NCS)_2$, MeN^+C^- and Me, is able to be effective in second-sphere binding also.

C. Involving Dibenzo-18-crown-6 (DB18C6) and Larger Ring Analogues

A subdivision between aromatic and non-aromatic crown compounds is reasonable in view of the following factors: (1) aromatic crown compounds such as DB18C6 (**50**) (Figure 20) are no longer symmetrical compared with the D_{3d} conformation of 18C6 (**47**); (2) they are conformationally less flexible than their aliphatic analogues; (3) oxygen donors are not of the same kind and the phenolic ether group is less basic, and (4) the aromatic rings may cause a favourable or unfavourable steric shielding effect with regard to possible guest inclusion. In addition, the benzo units could be a sensitive means of probing stereochemical aspects of second-sphere coordination in solution if aromatic ring current shifts in the NMR spectrum are present.

A first consequence of the above factors is evident from the stoichiometric ratios. Whereas 18C6 (**47**) forms a 1:2 (host–guest) second-sphere adduct with [*trans*-$Pt(PMe_3)Cl_2NH_3$] (cf. Figure 22a), the analogous adduct of DB18C6 (**50**) has 1:1

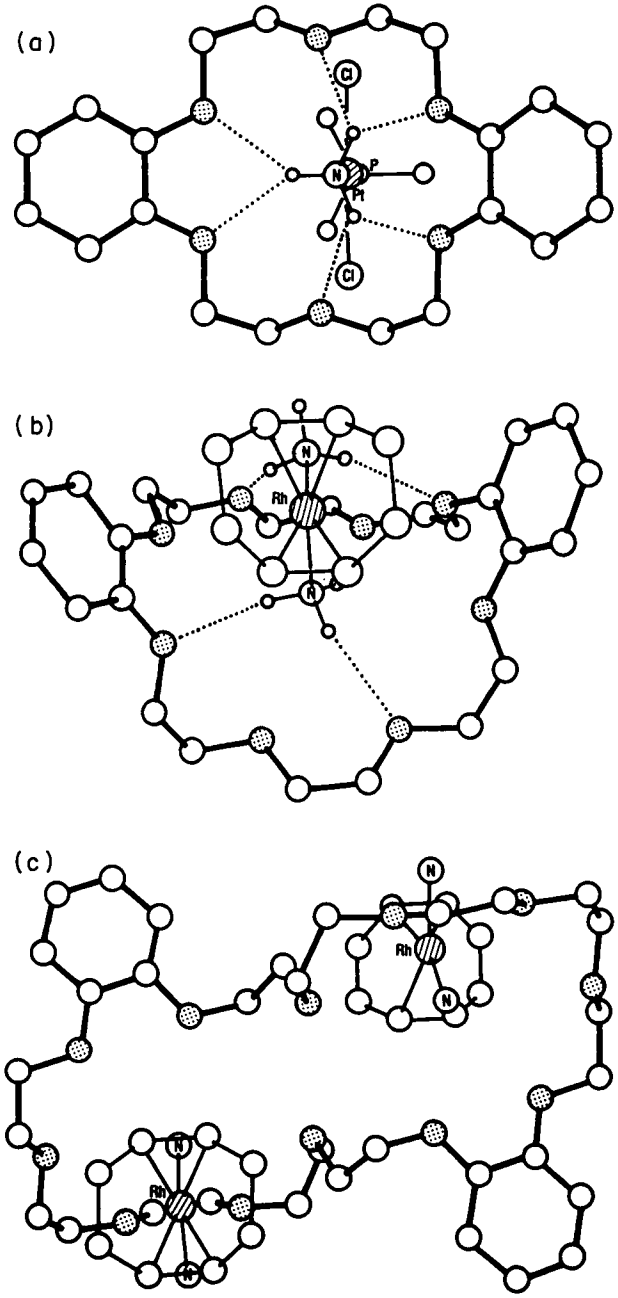


FIGURE 25. Crystal structures of adducts between benzo-condensed crowns and transition metal–ammine complexes: (a) $[Pt(PMe_3)Cl_2(NH_3)]$·DB18C6 (**50**); (b) $[Rh(cod)(NH_3)_2]^+$·DB24C8 (**52**) (PF_6^- salt). Adapted from Refs. 70 and 81

stoichiometry[70]. The same ratio is also found in the adduct of DB18C6 with $[W(CO)_5NH_3]$[70]. An illustration is given by the platinum derivative, which has been characterized crystallographically (Figure 25a)[70].

It is easily seen that the macroring has a conformation with the benzene rings folded away from the Pt—N vector. Hence, the macroring has only one approachable face, which is the convex side of the molecule. The ammine ligand contacts all six donor atoms, forming a system of three bifurcated hydrogen bonds. Variable-temperature ^1H NMR spectroscopy in CD_2Cl_2 solution indicates a dissociation free energy of 7.9 kcal mol^{-1} for this adduct[70]. A corresponding non-neutral adduct of DB18C6 with $[Fe(\eta^5Cp(CO)_2(NH_3)]^+ BPh_4^-$ (Cp = cyclopentadienyl) gave 10.7 kcal mol^{-1} for the same dissociation process[70].

Larger ring analogues of DB18C6, **51–54** (Figure 20), are attractive because they are potential sites for the simultaneous binding of more than one protic first-sphere ligand, e.g. a pair of ammine groups being *cis*-positioned at a metal centre. The cationic rhodium complexes $[Rh(cod)(NH_3)_2]^+$ (cod = cycloocta-1, 5-diene) and $[Rh(nbd)(NH_3)_2]^+$ (nbd = norbornadiene), which provide such a pair of *cis*-ammine ligands on the one hand, and DB21C7 (**51**), DB24C8 (**52**) or DB30C10 (**53**) on the other, were determined to be suitable test compounds[79–81]. Specific ring-current shifts in the ^1H NMR spectra (in CD_2Cl_2) indicate adduct formation in solution for all four complex–crown combinations and suggest a superstructure in which the rhodium complexes have approached 'face on' between the two aromatic rings in the respective crown ether[81]. Evidence for this superstructure was also provided by the observation of intermolecular nuclear Overhauser effects[80].

X-ray structure determinations of the isolated adducts demonstrate that the same building principle as mentioned above also applies in the crystalline state[81]. Figure 25b shows one representative example, $[Rh(cod)(NH_3)_2 \cdot \mathbf{52}]^+$[81]. In the first instance, all four adducts are of 1:1 stoichiometry. Moreover, (see Figure 25b) they have many features in

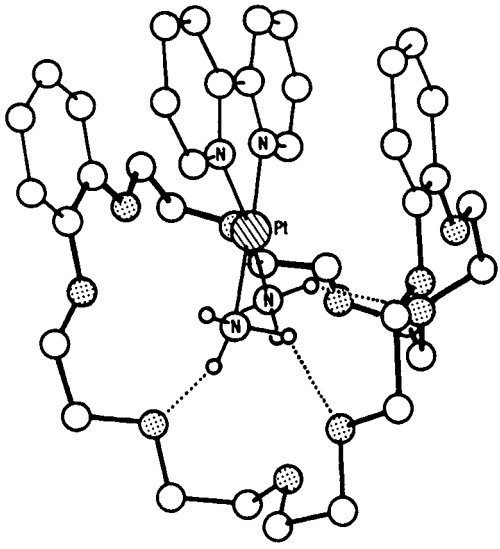


FIGURE 26. Crystal structure of the adduct $[Pt(bpy)(NH_3)_2]^{2+} \cdot$DB30C10 (**53**) ($PF_6^-$ salt). Adapted from Ref. 85

common, including: (a) the characteristic V-shaped conformation of the macroring; (b) binding of rhodium complex on the concave side of the crown (cf. Figure 25a); (c) straddling of the two *cis*-ammine ligands at one chain of the macroring which in fact results in only one ammine ligand being hydrogen bonded within the cavity, the other binding from outside; (d) a sandwich arrangement of the diene ligand between the two aromatic rings of the crown ether, suggesting possible CH ··· arene interaction; and (e) a large number of Rh ··· O and Rh ··· C contacts at about van der Waals distances, which are also likely to contribute to stabilization of the superstructure. A further important observation is that the hosts undergo considerable conformational changes from relatively flat in the free state[82] to V-shaped in the adducts[81] (cf. Figure 25b).

In contrast to the 21- to 30-membered ring analogues as before, DB36C12 (**54**) has its own way of forming a second-sphere adduct with $[Rh(cod)(NH_3)_2]^+$ (Figure 25c)[81]. The greatest differences are the 2:1 (complex: crown) stoichiometry and the relatively flat conformation of the crown which is retained in the bound state. The two $[Rh(cod)(NH_3)_2]^+$ ions are hydrogen-bonded centrosymmetrically to opposite faces of the macroring. There is only one common feature between the adducts of DB24C8 (**52**) or DB30C10 (**53**) and DB36C12 (**54**), namely the straddling relationship of the *cis*-ammine ligands with respect to the polyether chains (cf. Figure 25b and c).

The above considerations show that hydrogen bonding and charge transfer are the important factors for stabilization of the adducts. Hence incorporation of a π-acceptor co-ligand such as 2,2′-bipyridine into the primary coordination sphere of a metal–ammine complex should have useful consequences for adduct stabilization, since both charge transfer[83] and ligand acidity[84] are improved. Solution (^{1}H NMR shifts and charge-transfer absorption) and solid-state (X-ray crystallographic) studies on the adducts of $[Pt(bpy)(NH_3)_2]^+$ (bpy = 2,2′-bipyridine) with DB24C8 (**52**) or DB30C10 (**53**) clearly indicate that this is true[85,86]. Direct evidence of strong charge-transfer interactions in the present adducts is given by Figure 26[85], showing the structure of $[Pt(bpy)(NH_3)_2]\cdot$**53**.

The factor that is so strongly suggestive of charge-transfer interaction in Figure 26 is the parallel arrangement and close contact between the relatively π-electron-deficient bpy ligand and both of the π-electron-rich catechol units of the macroring. Features of the structure with which we are more familiar are the U-shaped conformation of the crown, the position of the ammine ligands within the host cavity, the straddling of the *cis*-ammine ligands with respect to one of the polyether chains and the mode of hydrogen bonding. Some stabilization due to charge–dipole interaction between the dicationic complex and some oxygens atoms of the macrocycle is also likely.

As indicated by charge-transfer absorption studies[85,86] (concentration dependence), DB30C10 (**53**) forms the most stable second-sphere adduct with $[Pt(bpy)(NH_3)_2]^{2+}$ in solution ($-\Delta G^\circ = 7.2$ kcal mol^{-1}) compared with crowns with other ring sizes. Presumably this reflects an optimum combination of hydrogen bonding and charge transfer in the same adduct, which may only be exceeded in the corresponding $[Pt(bpy)(NH_3)_2]^{2+}$ adduct of a dinaphtho analogue of **53**[63b].

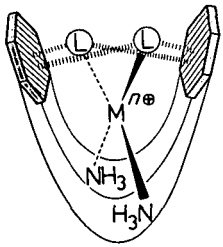


FIGURE 27. Construction principle of macrobicyclic hosts for binding of *cis*-diammine complexes. Adapted from Ref. 63b

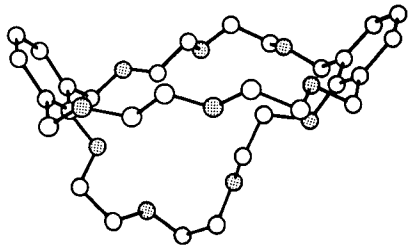


FIGURE 28. Crystal structure of free host **56**. Adapted from Ref. 63b

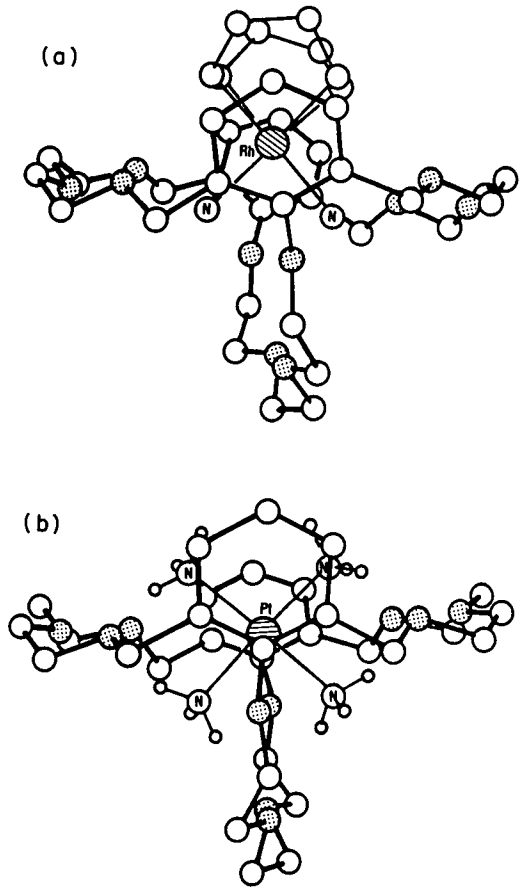


FIGURE 29. Crystal structures of adducts between transition metal–ammine complexes and **56**: (a) $[Rh(cod)(NH_3)_4]^+ \cdot$**56** ($PF_6^-$ salt); (b) $[Pt(NH_3)_4]^{2+}$ **56** (PF_6^- salt). Adapted from Refs. 63b and 87

D. Involving Macrobi- and Macropoly-cyclic Crown Compounds

Macrobi- and macropoly-cyclic crown compounds were considered to stabilize a preformed host cavity, i.e. preorganization of binding sites for adduct formation (cf. Section III). A suitable receptor conformation for binding of *cis*-diammine complexes with transition metals would involve a macrobicyclic polyether containing at least two aromatic units and two side-by-side crown ether rings. This is shown diagrammatically in Figure 27[63b]; the respective host constitutions are given by formulae **55–58**. The suitability of the concept is evident from Figure 28, showing the crystal structure of uncomplexed **56**[87]. The macrocycle offers a more preorganized cavity than do all the other monocyclic crowns discussed previously.

Figure 29a[87] shows the crystal structure of a typical inclusion adduct of **56** with a *cis*-diammine complex, $[Rh(cod)(NH_3)_2]^+$. There are eight N···O contacts within the hydrogen bond distance. The N atoms of the ammine ligands are clearly inserted in the host cavity and bind to different subcycles. However, penetration of the whole complex into the receptor cavity is not deep enough to allow all oxygen atoms in the central polyether chain of **56** (the two middle ones) which line the bottom of the cavity to be involved in binding, so they remain uncomplexed. A more surprising fact is that **55**, with a shorter central chain, does not undergo crystalline adduct formation with $[Rh(cod)(NH_3)_2]^+$ [63b].

Compared with $[Rh(cod)(NH_3)_2]^+$, containing the bulky cod ligand, $[Pt(NH_3)_4]^{2+}$ is less sterically demanding and makes further penetration into the cavity of **56** possible (Figure 29b)[63b]. Consequently, the middle two oxygen atoms in the central polyether chain now participate in coordination. Moreover, all four ammine ligands are involved in hydrogen bonding to the polyether chains.

The tricyclic diamide host **58**[63b] is another interesting molecule in this context. It forms an unexpected 2:1 (crown:complex) adduct with $[Pt(NH_3)_4]^{2+}$ (solvated with acetone). X-ray crystallography (Figure 30)[63b] shows that, as before, the four ammine ligands are involved in hydrogen bonding, including contacts to the amide oxygen atoms. However,

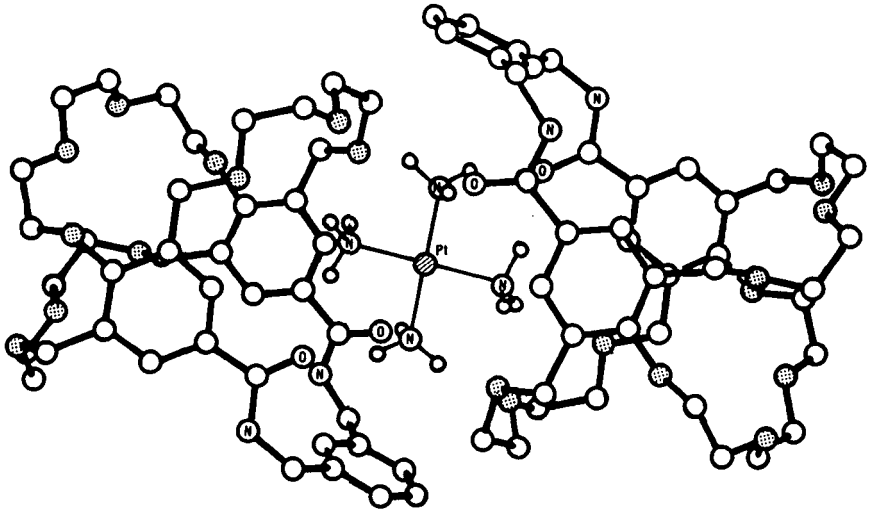


FIGURE 30. Crystal structure of the adduct $[Pt(NH_3)_4]^{2+}\cdot$**58** (PF_6^- salt). Adapted from Ref. 63b

the preformed cleft in the receptor molecule is scarcely exploited. This is the first example of a second-sphere adduct in which two host molecules coordinate simultaneously to a transition metal complex.

E. Further Varieties of Second-sphere Coordination

Depending on their nature there are possibilities of crown ligands occupying sites in both the first *and* the second coordination spheres of a transition metal. Two of the rare systems having this feature are the complexes $[Rh(CO)H_2O \cdot \mathbf{59}]^{+}$ [88] and $[Rh(cod)(NH_3)_2 \cdot \mathbf{60}]^{+}$ [89], the crystal structures of which are shown in Figure 31.

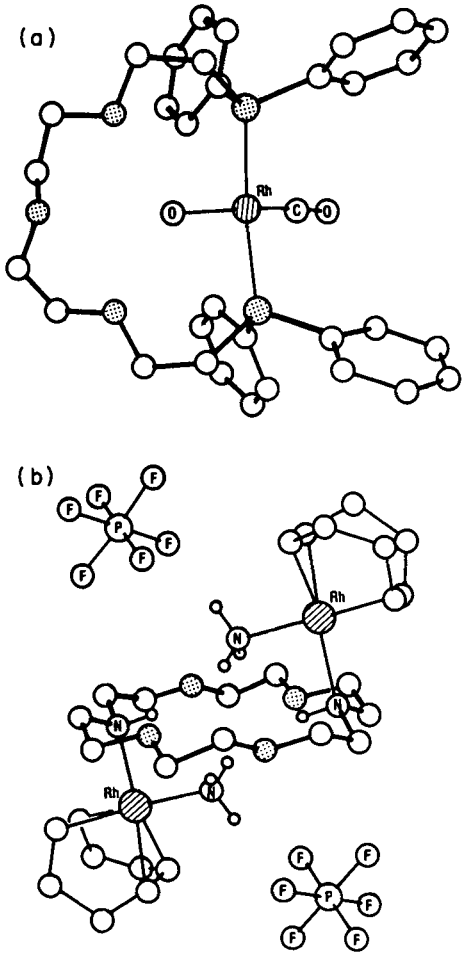
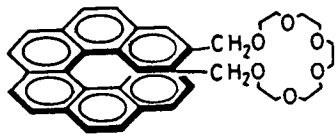
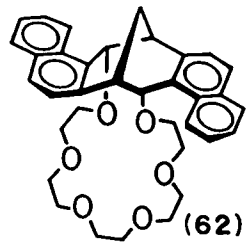


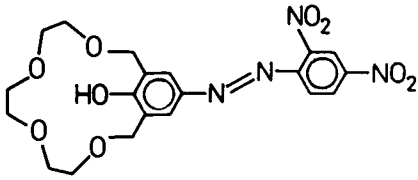
FIGURE 31. Crystal structures of adducts (a) $[Rh(CO)(H_2O]^{+} \cdot \mathbf{59}$ (PF_6^- salt) and (b) $[Rh(cod)(NH_3)_2]^{+} \cdot \mathbf{60}$ (PF_6^- salt). Adapted from Refs. 88 and 89



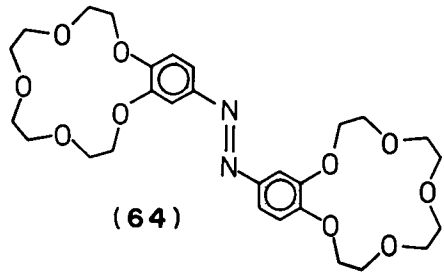
(61)



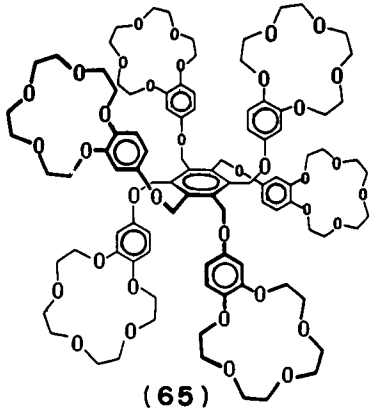
(62)



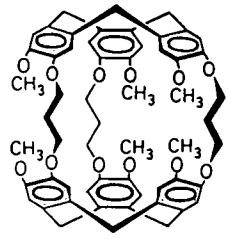
(63)



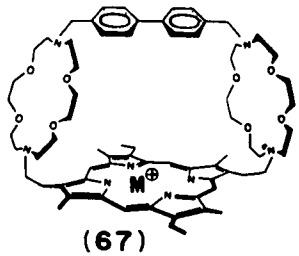
(64)



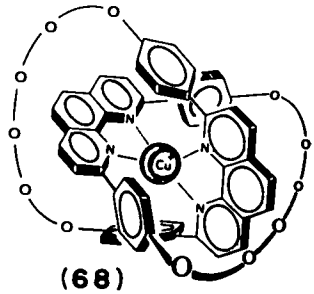
(65)



(66)



(67)



(68)

FIGURE 32. Examples of new host designs[105-108]

The *trans*-phosphino-coordinated aqua complex in Figure 31a[88] reveals strong linear hydrogen bonds between water in the first and two of the ether oxygens in the second coordination sphere of Rh. Cooperativity of first- and second-sphere coordination causes such strong binding of the water that it is hardly possible to remove it using dissolution and evacuation procedures.

Also in the adduct in Figure 31b[89] the macrocycle coordinates Rh simultaneously in the first and second spheres. Binding in the first sphere is through a ring nitrogen—Rh contact and in the second sphere through N—H···O (ring oxygen–amino ligand) contact. Admittedly the N···O distances are relatively long in this adduct but the orientation of the ammine ligands over the faces of the macroring are clearly indicative of second-sphere interaction.

Finally, it should be mentioned that second-sphere coordination of ammine–transition metal complexes by natural ionophores[90] and cyclodextrins[91] is also common.

V. FINAL REMARKS

Clearly, lariats, spherands and second-sphere complexes are recent milestones in organic complex chemistry. They have presented us with principles important for future ligand design and in understanding complexation phenomena more thoroughly—in short, a complementary relationship between preorganization and second-sphere involvements has been developed.

The ideal ligand would have a high binding affinity and guest selectivity and also fast on–off rates. The lariats and spherands approach this ideal. Spherands with functional groups in the outer sphere[92] and even a pyridino-analogous constitution (cyclosexipyridine)[93] have recently been synthesized, and their particular complexation behaviour will be studied. Hosts relating to a spherand structure are also promising in enzyme mimicry[94]. Lariats have been modified in different directions, with phosphine[95], anthracene[96], nicotine[97], pharmacophoric[98] and electrochemically reducible groups[99] in the side-arm, the number of side-arms has been increased[100] and side-arms have been used for intramolecular complexation[101]. In addition, oxygen atoms in the macroring have been replaced with sulphur[102] or nitrogen[103]. Potential applications of the second-sphere coordination principle also exist, e.g. in separation[70] and protection chemistry[104] of transition metal complexes and in the development of drug delivery systems[63b]. A main objective in the latter respect is to encapsulate the antitumour agent Cisplatin.

Many research groups have applied new methods in order to improve ligand properties, involving the design and use of novel building blocks[105], binding sites[106] and topologies[107]. Others are characteristic of a so-called responsible module[108]. Complexation is controlled by an on–off switch of donor sites in this case. A very limited selection of examples is shown in Figure 32. Also, the field of nonionic molecule complexes of crown compounds has forged ahead[109] and inclusion chemistry using water-soluble ligands[110] is of increasing interest. Most of the above topics have recently been reviewed[111–115].

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Crown Ethers and Analogs
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CHAPTER **6**

Geometry of the ether, sulphide and hydroxyl groups and structural chemistry of macrocyclic and non-cyclic polyether compounds

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I. INTRODUCTION

Various diffraction and spectroscopic methods have proved particularly useful in the analysis of characteristic molecular dimensions and conformations of the compounds under discussion in this chapter. Most of the experimental techniques have been significantly improved in recent years and their application extended to numerous molecular structures of varying complexity. The mutually complementary tools of electron diffraction (ED) and microwave spectroscopy (MW) are suitable for the examination of simple and highly symmetric molecules which exist only in the vapour phase or can be vaporized easily. This applies for example, to the simplest of the title compounds such as dimethyl ether, dimethyl sulphide and

methanol. Of special merit in the ED and MW methods is the fact that they directly yield detailed structural information about the shape of the molecules in the gaseous state where the intramolecular forces are exclusively responsible for the conformational choice. A major limiting factor of the ED technique itself lies in an inadequate treatment of the effects of thermal motion, and in order to determine a structure precisely one often has to calculate vibrational amplitudes from spectroscopic data. However, in favourable cases combination of ED with spectroscopy can readily lead to a reliable determination of exact atomic positions, including those of the light hydrogen atoms.

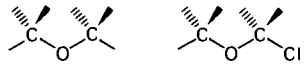
X-ray diffraction (XD) crystallography is at present the most convenient method for the study of moderately complex molecules that produce single crystals. The development of computer-controlled diffractometers for rapid acquisition of accurate X-ray intensity data and the enhanced efficiency of algorithms for the solution of the phase problem in diffraction have caused a sharp increase in the number of crystallographic determinations in organic and inorganic chemistry. It should be kept in mind, however, that the amplitudes of atomic thermal vibrations, and particularly the positions of hydrogen atoms, can be determined with a considerably greater accuracy by neutron diffraction than by XD crystallography. The neutron diffraction technique has therefore an important function in the study of hydrogen bonds and electron density distributions; it also is experimentally more difficult and its applicability requires the immediate neighbourhood of an atomic reactor.

The structural data are being presented in this article mainly in terms of geometrical factors such as bond lengths, bond angles and torsional angles (when available, the estimated standard deviations are expressed in parentheses in units of the last decimal place). It is important to emphasize here that the MW, ED and XD molecular dimensions are derived from observed quantities which are affected in different ways by molecular vibrations. The conventional results of XD (as well as neutron diffraction) experiments correspond to distances between average atomic positions in a molecular coordinate system, those obtained in the reduction of ED data usually refer to an average over the molecular vibrations, while the distance parameters in a MW study are calculated from ground-state rotational contants. Hence, a detailed comparison of the corresponding r value should be carried out with much care. These anticipated differences are generally small, and seem to be not significant with respect to the following discussion. Therefore, the literature values of bond parameters are quoted in this article without modification. Presently available structural information about ethers, crown ethers, hydroxyl groups and their sulphur analogues suffices to fill at least one separate volume on this matter. Hence, an attempt to cover the whole field adequately and to present a comprehensive survey of all structural properties within the scope of a single chapter would (obviously) be unsuccessful. In fact, a few relevant specific subjects, such as those dealing with stereochemistry of dioxanes and hydrogen bonding by hydroxyl groups, have already been reviewed in detail. In the present article we have chosen to confine the discussion to (*a*) the reference structural parameters of the title functions, and (*b*) the structural chemistry of crown ether compounds which has been developing significantly in the recent years. The subjects (*a*) and (*b*) are dealt with below, in Sections II and III respectively.

II. STRUCTURAL PARAMETERS OBTAINED FROM ELECTRON DIFFRACTION AND MICROWAVE STUDIES

A. The C—O—C Group

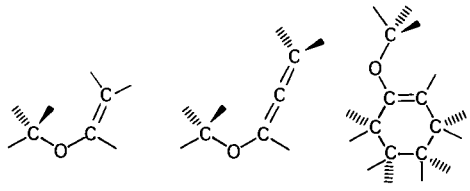
The geometry and conformation of a number of small organic species that contain the ether group were investigated by ED and MW methods. Two accurate and independent structure determinations of dimethyl ether (1), by Kimura and Kubo[1] from ED patterns and by Kasai and Myers[2,3] from MW spectra, provided reference structural parameters for the $C(sp^3)—O—C(sp^3)$ moiety. The respective results of these two studies are very similar: 1.416(3) and 1.410(3) Å for the C—O bond distance, 111.5(15) and 111.4(3)° for the C—O—C bond angle. The experimental evidence showed conclusively that the dimethyl ether molecule has in the gas phase C_{2v} symmetry, the methyl groups being staggered with respect to the opposite C—O bonds. In the MW work the molecular dipole moment of $(CH_3)_2O$ was determined to be 1.31(1) D. The structure of monochlorodimethyl ether (2) was



(1) (2)

also examined by means of ED of the vapour[4], yielding an averaged C—O bond of 1.38 Å and a C—O—C angle of 113.2°. A careful analysis of the experimental radial distribution function for this molecule led, however, to the conclusion that the two C—O bonds are not equal; the best fit between the structural model and data was obtained with $CH_2Cl—O$ and $CH_3—O$ bond distances of 1.368 and 1.414 Å, respectively. It has been difficult to rationalize the significant difference between the two C—O bond distances without invoking interaction between the oxygen atom and the lone-pair electrons of the chlorine atom (see below).

In unsaturated olefinic systems the C—O bond is also shortened considerably through influence of the double bond. This feature was observed in the structures of gaseous methyl vinyl ether (3), methyl allenyl ether (4) and 1-methoxycyclohexene (5). In the gas phase, methyl vinyl ether was found as a mixture of 64% of a

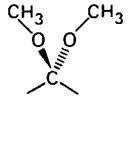


(3) (4) (5)

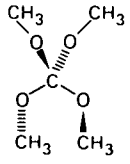
cis form having a planar skeleton in which the methyl group is staggered with respect to the CH—O bond and 36% of a second conformer which has its $CH_3—O$ bond approximately at right angles to the plane of the vinyl group[5]. The following parameters for the ether group structure were obtained: $C(sp^3)—O$ = 1.424 Å, $C(sp^2)—O$ = 1.358 Å and C—O—C = 120.7°. The molecule of methyl allenyl ether adapts an equilibrium planar *cis* conformation with C_s symmetry[6]. From inspection of the ED data it was concluded that at room temperature there is a large torsional motion of the OCH_3 group around the other ether linkage which

could be characterized by a displacement angle from planarity of about 23°. The reported results include the bond distances C(sp^3)—O = 1.427(8) and C(sp^2)—O = 1.375(7) Å and the bond angle C—O—C = 115.0(12)°. 1-Methoxycyclohexene is a substituted vinyl ether having a methoxyl group bonded to one of the double-bonded carbon atoms in the cyclohexene ring. In the gas phase, the molecule was also found to exist predominantly in the *cis* conformation[7]. The structural parameters associated with the methoxy group are C—O = 1.364(6) Å for the distance from the sp^2 carbon to the oxygen atom, C—O = 1.421(6) Å for the distance from the oxygen atom to the methyl carbon atom and C—O—C = 119.7(25)°. Evidently, the above data on the three alkenes are quite consistent with respect to the bond lengths; there is, however, a fairly severe disagreement between the refined magnitudes of the C—O—C angle.

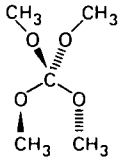
Further information on the molecular geometry of simple acyclic ethers was obtained in the investigations (by ED) of dimethoxymethane[8] (6) and tetramethoxymethane compounds[9] (7). The diether molecule (6) has a C_2 symmetry.



(6)



(7a)



(7b)

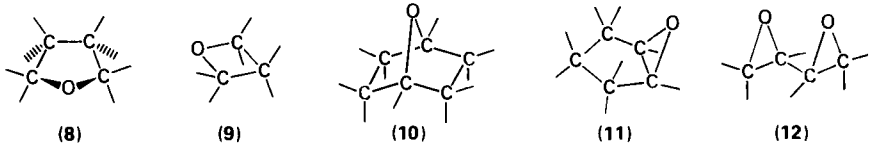
The *gauche* arrangement about the two C—O bonds apparently minimizes the repulsive interaction of lone-pair electrons on the oxygen atoms. In this conformation the molecular dipole moment was calculated to be 1.08 D. Two possible forms of tetramethoxymethane, with staggered methyl groups each belonging to a face of the oxygen tetrahedron, were considered as best models for this species. The diffraction study showed that the molecule has S_4 symmetry (7a); the D_{2d} model (7b) was estimated to be roughly 6 kcal/mol less stable than the S_4 rotamer. The conformation of the C—O—C—O—C sequence in the molecule is either *gauche–gauche* or *gauche–trans*, in good agreement with the observed geometry of dimethoxymethane. Relevant structural parameters of $CH_2(OCH_3)_2$ and $C(OCH_3)_4$ are compared in Table 1. The experimental findings clearly indicate that the central CH_2—O bonds are consistently shorter by 0.03–0.05 Å than the terminal

TABLE 1. Structural parameters of di- and tetra-methoxymethane

	$CH_2(OCH_3)_2$	$C(OCH_3)_4$
Bond lengths (Å)		
(C—O) av.	1.405	1.409
CH_3—O	1.432	1.422
CH_2—O	1.382	1.395
Bond angles (deg.)		
C—O—C	114.6	113.9
O—C—O	114.3	114.6
Methoxy torsional angle (deg.)		
C—O—C—O	63	63

ones. Similar shortening of the C—O bond was also observed in a number of other α-X substituted compounds containing the C—O—C—X moiety, where X is an atom bearing lone-pair electrons (X = OR, halogen, etc.)[10,11]; the monochlorodimethyl ether (2) provides a perfect example. This well-known aspect of the molecular structure has been explained in the literature by various considerations based on the anomeric effect[10,11], its most attractive interpretations involving dipole–dipole electrostatic interactions and n-electron delocalization into the adjacent antibonding orbital.

Tetrahydrofuran (8) is an example of a cyclic monoether compound. Its gas-phase molecular structure was investigated simultaneously and independently by two research groups[12,13]. The structural parameters resulting from both ED studies are identical within the experimental error. It was indicated that gaseous tetrahydrofuran undergoes essentially free pseudorotation between two conformational states, the 'half-chair' form with C_2 symmetry and the 'envelope' form with C_s symmetry. The average single C—O and C—C bond distances 1.428(3) and 1.537(3) Å, respectively, were assumed to be independent of the pseudorotation. The bond angles in the molecule were defined in three different ranges: C—C—C 101–104°, C—C—O 104–107° and C—O—C 106–110°. A MW study of tetrahydrofuran[14] confirmed that the C_2 and C_s conformers are almost equally stable at room temperature with an estimated barrier hindering pseudorotation of 20 cal/mol. The dipole moment of the molecule was determined from the Stark effect in the pure rotational spectrum, and was found to vary from 1.52 to 1.76 D depending upon the pseudorotational state.

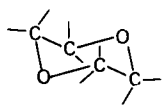


(8) (9) (10) (11) (12)

The effect of intramolecular strain on the geometry of the ether moiety is clearly demonstrated in the structures of trimethylene oxide (9), 7-oxanorbornane (10) and compounds containing a three-membered epoxide ring. The structure of **10** was investigated by making joint use of the experimental ED intensities and rotation constants determined from MW spectra[15]. The thermal-average parameters reported for the ether group are C—O = 1.442(10) Å and C—O—C = 94.5(22)°. From MW spectra of four isotopic species of trimethylene oxide it was deduced that the molecular framework is essentially planar but that the ring-puckering vibration is of a fairly large amplitude, of the order of 0.06 Å[16]. The preferred bonding parameters of this molecule include: C—O = 1.449(2) Å and C—O—C = 92.0(1)°. It is evident, therefore, that in the conformationally strained structures **9** and **10**, the C—O bond is about 0.02–0.03 Å longer and the C—O—C angle is about 17–18° smaller than the corresponding parameters in dimethyl ether and tetrahydrofuran. Long C—O bonds were also observed in the studies of gaseous cyclopentene oxide (**11**) (by a simultaneous least-squares analysis of ED and MW data)[17] and 1,2,3,4-diepoxybutane (**12**) (from ED patterns)[18]. The respectively reported values for the C—O bond distance, 1.443(3) and 1.439(4) Å, and for the ring C—C bond distance, 1.482(4) and 1.463(5) Å, are in good agreement with the corresponding early data obtained by Cunningham and coworkers for ethylene oxide, 1.436 and 1.472 Å[19].

1,4-Dioxane, 1,3-dioxane and 1,3,5-trioxane are six-membered heterocycles that

contain more than one ether group in the molecular ring. The molecular dimensions of 1,4-dioxane (13) obtained by Davis and Hassel[20] by ED differ only slightly from those of tetrahydrofuran. The observed structural parameters are C—C = 1.523(5), C—O = 1.423(3) Å, O—C—C = 109.2(5)° and C—O—C = 112.4(5)°. The latter value is larger than 'tetrahedral' (109.5°), and there is a certain flattening of the 'ideal-chair' structure. This could have been expected, since in 1,4-dioxane four oxygen lone electron pairs are present instead of C—H bonds as in cyclohexane. A chair conformation was also found in the structure of 1,3-dioxane (14) with ring angles close to the tetrahedral angle, the O—C—O angle of 115.0° being the only exception[21]. The C—O bonds separated by this angle are 1.393(25) Å long, substantially shorter than the other C—O bonds which are 1.439 (39) Å long. Perhaps, this comparison demonstrates again that where two oxygen atoms are attached to the same carbon atom, the C—O bond is shorter. The torsional angles for 1,3-dioxane range from 56 to 59°, and the C—C distance was found to be 1.528(13) Å.



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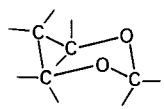

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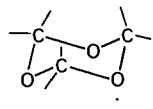


(15)

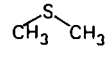
1,3,5-Trioxane (15), a cyclic trimer of formaldehyde, and its 2,4,6-trimethyl derivative have been extensively studied by several spectroscopic and diffraction (including X-ray) techniques. Even in the vapour state the trioxane species were found to exist in a stable chair configuration (15) characterized by a C_{3v} symmetry, the axial carbon-hydrogen bonds being nearly parallel to the threefold symmetry axis. The molecular dipole moment of 2.07(4) D was determined from a microwave spectrum[22]. The most recent investigations of the molecular structure of trioxanes by ED are those of Clark and Hewitt[23] (trioxane at 75°C) and Astrup[24] (trimethyltrioxane). In the substituted compound, the three methyl groups occupy equatorial sites with almost no distortion of the chair configuration of the molecule except for a slight flattening of the ring; the OCOC torsional angle is 55(1)°. The structural parameters obtained in several investigations of trioxanes are compared in Table 2, which shows that there is a considerable agreement between the various sets of results. The potential energy calculations from vibrational spectra by Pickett and Strauss[25] are of particular interest in this context. They indicate that in saturated oxanes the C—O—C angle is expected to be larger than the O—C—C angle, an argument rationalized by taking into account the repulsions between protons across the C—O—C angle that are absent for the O—C—C angle. Recent results of accurate XD studies on polyether compounds are in accord with this expectation (see below).

TABLE 2. Molecular dimensions of 1,3,5-trioxanes

Method	C—O (A)	O—C—O (deg.)	C—O—C (deg.)	Reference
ED	1.410(4)	110.7(7)	112.3(8)	24
ED	1.411(2)	111.0(7)	109.2(10)	23
MW	1.411(10)	111.2(10)	108.2(10)	22
XD (at −170°C)	1.421(6)	109.6(3)	110.4(3)	55

B. The C—S—C Group

A considerable amount of work has also been performed on sulphides, the sulphur analogues of ethers. An early MW study of the molecular structure of dimethyl sulphide (**16**) in the gas phase yielded the following reference parameters for the sulphide moiety: $C(sp^3)$—S = 1.802(2) Å and C—S—C = 98.9(2)°[26]. The above values are very similar to the results obtained by Tsuchiya and Kimura[27] in a more recent ED work: C—S = 1.805(3) Å and C—S—C = 99.0(3)°. In the equilibrium conformation of gaseous $(CH_3)_2S$ both methyl groups are staggered with respect to the adjacent C—S bond axes. The estimated barrier of internal rotation of a methyl group in dimethyl sulphide (2.1 kcal/mol) is about 0.6 kcal/mol lower than the rotational barrier in dimethyl ether (2.7 kcal/mol)[28]. It was also observed that the symmetry axes of the two methyl groups form an angle of 104.4°, thus not coinciding with the C—S bond axes. The molecular dipole moment of dimethyl sulphide was found to be 1.50 D, 0.2 D greater than that of dimethyl ether. Reliable structural parameters of dimethyl disulphide (17) were determined by Beagley and



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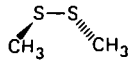
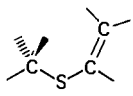


(17)

McAloon from ED patterns[29]. The two methyl groups were established to be nearly staggered with respect to the S—S bond, the torsion angle about this bond being 83.9°. The C—S length in dimethyl disulphide, 1.806(2) Å, is very close to the ED value in $(CH_3)_2S$. The C—S—C angle and the S—S bond distance are 104.1(3)° and 2.022(3) Å, respectively.

The geometry of unsaturated organic sulphides is probably affected to a certain extent by the involvement of sulphur d-orbitals in the π-system of the molecule. In methyl vinyl sulphide (**18**) the observed CH_3—S length of 1.806(6) Å is normal for



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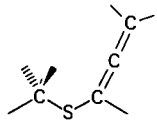


(19)

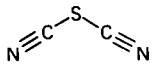
a $C(sp^3)$—S single bond but, as expected, the =CH—S bond is 0.06 Å shorter, 1.748(6) Å. The observed angular values are C—S—C = 104.5(7)° and C=C—S = 125.9(5)°. This ED work showed that the molecule exists as a mixture of at least two conformations. Molecular structures of methyl vinyl sulphide and methyl allenyl sulphide (**19**) were also investigated recently by Derissen and Bijen by means

TABLE 3. Molecular dimensions of methyl vinyl sulphide and methyl allenyl sulphide

	Methyl vinyl sulphide		Methyl allenyl sulphide
	Reference 30	Reference 31	Reference 31
$C(sp^3)$—S(Å)	1.806(6)	1.794(12)	1.800(10)
$C(sp^2)$—S(Å)	1.748(6)	1.752(10)	1.745(10)
C—S—C (deg.)	104.5(7)	102.5(2)	98.1(8)
C=C—S (deg.)	125.9(5)	127.0(15)	125.4(6)

of ED[31]. The structural parameters obtained from their study at 40°C are summarized in Table 3. In contradiction with the previous suggestion of Reference 30, Derissen and Bijen concluded that the two compounds exist predominantly in the planar *syn* conformation, the nonplanar *gauche* conformers being less important. It is interesting to note that the barrier to free rotation of the methyl group in the *syn* form of methyl vinyl sulphide was found to be unusually large (about 3.2 kcal/mol)[32], probably in large part due to nonbonding interactions between the hydrogen atoms.

The structural effect of the interaction between bivalent sulphur and a carbon–carbon or carbon–nitrogen triple bond was investigated by means of the MW spectra of sulphur dicyanide (20), methyl thiocyanate (21) and methyl thioethyne (22). The following bond lengths and angles were observed for the sulphide moiety:



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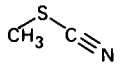

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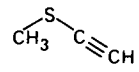
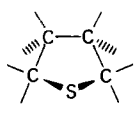


(22)

C(sp)—S = 1.701(2) Å and C—S—C = 98.4(2)° in $S(CN)_2$[33]; C(sp)—S = 1.684 Å, $C(sp^3)$—S = 1.820 Å and C—S—C = 99.9° in CH_3SCN[34]; C(sp)—S = 1.685(5) Å, $C(sp^3)$—S = 1.813(2) Å and C—S—C = 99.9(2)° in CH_3SCCH[35]. The results reported for molecule **21** are somewhat inferior in precision, and do not include estimated standard deviations of the parameters. It appears that the C(sp)—S bond distance is 0.10–0.12 and 0.05–0.06 Å shorter than the $C(sp^3)$—S and $C(sp^2)$—S bonds, respectively. The above range of the observed C—S values may thus correspond well to the differences in hybridization of carbon bonding orbitals in the respective molecules. Nevertheless, Pierce and coworkers indicated in their work on sulphur dicyanide that the ground electronic state of the molecule is probably also affected to a considerable extent by back-bonding by sulphur[33]. Accordingly, the structure of the —SCN fragment was described by resonance formulae $-S-C\equiv N \leftrightarrow -{}^{+}S=C=N^{-}$.

Turning to cyclic sulphides, the investigation of a gas-phase ED pattern obtained from tetrahydrothiophene (23) enabled a fairly reliable determination of its molecular structure[36]. While gaseous tetrahydrofuran was found to exhibit a free pseudorotation between two conformations with respective C_2 and C_s symmetries, the study of Reference 36 indicated strongly that tetrahydrothiophene exists preferentially in the C_2 conformation. In fact, by theoretical energy calculations, this conformation was found to be between 2 to 3 kcal/mol more stable than the C_s form. Strain in the five-membered ring is reflected in some of the bonding parameters. The C–S bond distance in 23 is 1.839(2) Å, 0.03 Å longer than the $C(sp^3)$—S distance found in dimethyl sulphide. Furthermore, the ring angles C—S—C = 93.4(5), S—C—C = 106.1(4) and C—C—C = 105.0(5)° are several degrees smaller than the corresponding bond angles in unstrained molecules. The observed C—C bond distance of 1.536(2) Å is essentially identical to that in tetrahydrofuran.

The strain effect is even more pronounced in the molecular structures of



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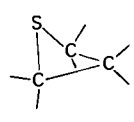

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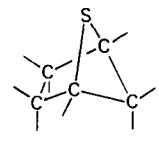

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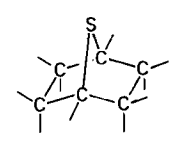


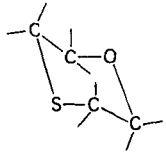
(26)

TABLE 4. Bond lengths and angles for 1,4-dioxane, 1,4-thioxane and 1,4-dithiane

	1,4-Dioxane (Reference 20)	1,4-Thioxane (Reference 39)	1,4-Dithiane (Reference 40)
C—C (Å)	1.523	1.521(6)	1.54
C—O (Å)	1.423	1.418(4)	
C—S (Å)		1.826(4)	1.81
C—C—O (deg.)	109.2	113.2(17)	
C—C—S (deg.)		111.4(10)	111
C—O—C (deg.)	112.5	115.1(22)	
C—S—C (deg.)		97.1(20)	100

trimethylene sulphide (24), 5-thiabicyclo[2,1,1]hexane (25) and 7-thiabicyclo [2,2,1]heptane (26). All of these structures were determined by an analysis of ED intensities[37,38]. The mean vibrational amplitudes of compounds 25 and 26 were estimated from the amplitudes found in norbornane; those of molecule 24 were derived from rotational spectra. Some skeletal parameters of the three molecules are listed below, the values identified with each parameter being referred to compounds 24, 25 and 26 respectively: C—S = 1.847(2), 1.856(4) and 1.837(6) Å, C—C_{av} = 1.549(3), 1.553(3) and 1.549(3) Å, C—S—C = 76.8(3), 69.7(5) and 80.1(8)°. It is of particular interest to note that the C—S bond is longer and the C—S—C angle is smaller in the strained rings than in other environments. Analogous trends have been observed in related ethers and hydrocarbons.

1,4-Thioxane (27) is composed of one C—S—C and one C—O—C unit, thus exhibiting the structural features of both the ether and sulphide functional groups. The molecular structure, as determined by means of an ED study[39], shows a chair conformation with an average puckering angle of 58.3°. The parameters obtained for the 1,4-thioxane ring geometry are summarized in Table 4. Comparison of the results for 1,4-thioxane with those of vapour-phase studies of 1,4-dioxane[20] and 1,4-dithiane[40] reveals no major differences. However, while the C—O—C angle in 27 is 3.6° larger than that in dimethyl ether, the C—S—C angle is somewhat smaller than that in dimethyl sulphide; the opposite trends are probably effected by the structural asymmetry of the 6-membered ring.



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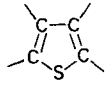

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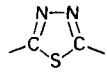


(29)

The final example refers to two pseudoaromatic compounds that contain a formally bivalent sulphur atom: thiophene (28) and diazathiophene (29). In the gas phase both molecules resemble each other by virtue of their planarity and geometry of the C—S—C fragment. The relevant parameters are C—S = 1.717(4) Å and C—S—C =91.9(3)° in 28[41], and C—S = 1.723(3) Å and C—S—C = 86.4(4)° in 29[42]. The above C—S lengths lie between those of the C(sp^2)—S (1.75 Å) and C(sp)—S (1.69 Å) single bond distances. This probably reflects a limited contribution of the sulphur heteroatom to the π-system of the thiophene-type species which is much less aromatic than is the benzene ring.

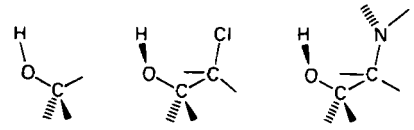
TABLE 5. Molecular dimensions of gaseous methanol

	Reference		
	43	1	44
C—O (Å)	1.427(7)	1.428(3)	1.425(2)
O—H (Å)	0.956(15)	0.960(15)	0.945(3)
C—H (Å)	1.096(10)	1.095(10)	1.094(3)
C—O—H (deg.)	109(2)	109(3)	108.5(5)

C. The C—O—H Group

Table 5 presents the molecular dimensions of gaseous methanol (**30**) as they were obtained from MW[43] and ED[1,44] data. The results of Reference 44 rely solely on experimental data, and no structural assumptions other than that of symmetry of the methyl group about its axis were made. The agreement between the three sets of parameters given in Table 5 is remarkable. Hence, the accurate structure of the —COH moiety can be reliably described by C—O = 1.426 ± 0.002 Å, O—H = 0.95 ± 0.01 Å and C—O—H = 108.5 ± 0.5°. Apparently, the C—O—H angle is larger by about 4° than the angle of the water molecule and smaller by about 3° than the C—O—C angle in dimethyl ether (see above). The experimental values for the total dipole moment of methanol and its projection along an axis parallel to the O—H bond were found to be 1.69 and 1.44 D, respectively[45]. The molecular structure of ethyl alcohol was investigated by Imanov and Kadzhar from MW spectra[46]. The Russian workers reported a rather low value for the C—O—H angle (104.8°), but their results for the C—O (1.428 Å) and O—H (0.956 Å): bond lengths are essentially identical to those in methanol.

The above reference geometry of the —COH functional group was found to be altered significantly in the presence of highly electronegative substituents in close proximity to the hydroxyl site, as well as by the hydroxyl group involvement in hydrogen bonds. The MW studies of the molecular structures of 2-chloroethanol (**31**)[47] and 2-aminoethanol (**32**)[48] provided relevant information. Reportedly, the



(30) (31) (32)

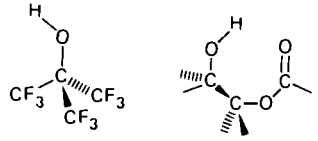
most stable conformation of **31** and **32** is *gauche*, the O—C—C—X (X = Cl or N) torsion angles about the ethylenic bond being 63.2 and 55.4°, respectively. The molecular conformation was assumed to be stabilized by a dipole–dipole interaction between the nearly parallel O—H and C—Cl dipoles in 2-chloroethanol and by a stronger O—H···N hydrogen-bonding interaction in 2-aminoethanol. These interactions are also reflected in the respective H···Cl (2.61 Å) and H···N (2.14 Å) nonbonding distances that appear to be shorter by about 0.5 Å than the corresponding sums of van der Waals' radii. Furthermore, the main structural results summarized in Table 6 show that the alcohol part of both species has a structure significantly different (with consistently longer O—H bond, shorter C—O bond and

TABLE 6. Molecular geometry of substituted ethanols

	2-Chloroethanol[47]	2-Aminoethanol[48]
C—C (Å)	1.520(1)	1.526(16)
C—O (Å)	1.411(1)	1.396(10)
O—H (Å)	1.010(10)	1.139(10)
C—O—H (deg.)	105.8(4)	103.7(2)
C—C—O (deg.)	112.8(1)	112.1(1)

smaller C—O—H angle) from that of methanol. A relatively short C—O bond length of 1.414 Å was also found by Yokozeki and Bauer[49] in a recent least-squares analysis of intensities for perfluoro-*t*-butyl alcohol (**33**).

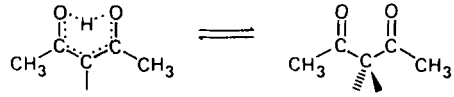
Another example of the structural effect of possible intramolecular interactions in alcohols has been provided by the structural analysis of glycol monoformate (**34**)



(33) (34)

in the gas phase[50]. The molecule was found to be stable in two *gauche* conformations with respect to the central C—O bond, both with internal hydrogen bonds but involving different acceptor sites (the carbonyl oxygen atom in one rotamer and the ether oxygen atom in the second rotamer). The resulting geometry was defined by the following parameters: C—C = 1.525(4), C—O = 1.412(7), O—H = 1.18 Å and C—C—O = 109.4(7)°, which are in good agreement with those of 2-aminoethanol. Because of certain assumptions concerning the molecular geometry, the initially assumed value of 107° for the C—O—H angle was not refined in that work.

Finally, there is another group of interesting compounds, exemplified by acetylacetone (**35**), which exhibit distinct features of the molecular structure. Separate ED studies by Karle and collaborators (at 110°C)[51] and Andreassen and Bauer (at



enol (35) keto

room temperature)[52] showed that the molecule of acetylacetone exists in two tautomeric forms in dynamical equilibrium. In the gas phase, the enol species, which is characterized by a nearly linear intramolecular hydrogen bond, appears to be a predominant form. At 110°C the equilibrium mixture is composed of 65% of the enol form and 35% of the keto form, while at room temperature the relative amount of the enol tautomer is increased to about 97%. The two structure determinations led to essentially similar descriptions of the molecular geometry. The hydrogen bond in the enol is part of a planar ring in which the C—C bond distances (1.416[51] and 1.405 Å[52]) are close to aromatic values. Furthermore, the observed C—O bond lengths of 1.315[51] and 1.287 Å[52] are intermediate between

TABLE 7. The characteristic geometry of the ether, sulphide, hydroxyl and thiol groups

(a) The C—O—C group		*(b) The C—S—C group*	
1. $C(sp^3)$—O	1.42 Å	1. $C(sp^3)$—S	1.80 Å
2. Shortened in presence of electronegative substituent	≤1.40 Å	2. Stretched in sterically strained molecules	≥1.84 Å
3. Stretched in sterically strained molecules	≥1.44 Å	3. $C(sp^2)$—S	1.75 Å
4. $C(sp^2)$—O	1.36 Å	4. C(sp)—S	1.69 Å
5. $C(sp^3)$—O—$C(sp^3)$	112°	5. $C(sp^3)$—S—$C(sp^3)$	99°
(c) The C—O—H group		*(d) The C—S—H group*	
1. $C(sp^3)$—O	1.43 Å	1. $C(sp^3)$—S	1.82 Å
2. Shortened in presence of electronegative substituent or hydrogen bond	≤1.41 Å	2. Shortened in presence of electronegative substituent or hydrogen bond	<1.81 Å
3. O—H	0.95 Å	3. S—H	1.33 Å
4. Stretched in hydrogen bonded moieties	≥1.00 Å	4. $C(sp^3)$—S—H	96°
5. $C(sp^3)$—O—H	109°		

(e) Molecular dipole moments

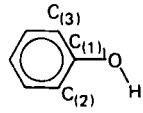
Dimethyl ether	1.31 D
Methanol	1.69 D
Dimethyl sulphide	1.50 D
Methanethiol	1.52 D

the double bond value in acetone (1.21 Å) and the single bond distances in methanol and dimethyl ether (1.42 Å; see above).

D. Comparison of Averaged Results

The characteristic average bonding parameters of the title species are summarized in Table 7. The structural chemistry of the thiol group, the sulphur analogue of hydroxyl, has recently been reviewed by Paul[53] in an earlier volume of this series; for the sake of completeness some of the relevant data including those on methanethiol (CH_3SH)[54] are also given in the Table. The following structural features emerge: The $C(sp^3)$—O single bond is consistently shorter in ethers than in alcohols. The C—O—C angle is about 3° greater than the C—O—H angle. This trend also appears to occur in the sulphide and thiol groups. As a result of the difference in hybridization of carbon and sulphur bonding orbitals the bond angles around sulphur are about 13° smaller than the corresponding bond angles around oxygen Apparently, due to the latter feature the conformational strain in sulphides is generally larger than in the corresponding oxygen analogues.

The above data should be supplemented by structural information on phenols (36) where the hydroxyl function is attached to an aromatic carbon atom. A large



(36)

amount of relevant data is available from X-ray crystal structure determinations of a variety of phenol derivatives. Recently, a systematic review of phenol structures has been published by a French group[56], and some observations of general validity are summarized below. An obvious remark should be made. Although the hydroxyl hydrogen atom can often be located in a particular structure by means of difference electron density calculations, the determination of its position by conventional XD methods is in general inaccurate. An inspection of the molecular geometries of about 20 crystallographically independent phenol moieties points to the following features. The observed values (not corrected for the effects of thermal motion) of the C—O bond length range between 1.37 and 1.40 Å with an average near 1.38 Å. The benzene ring is planar in most of the compounds studied, but the three bond angles at $C_{(1)}$ are strikingly different. The average value of the internal $C_{(2)}—C_{(1)}—C_{(3)}$ bond angle is slightly larger than trigonal (121.4°); most probably, this is associated with the electron-withdrawing nature of the hydroxyl group. Moreover, the $O—C_{(1)}—C_{(2)}$ bond angle on the side of the H atom is usually larger by several degrees than the $O—C_{(1)}—C_{(3)}$ angle; the reported angular values which are scattered over a relatively wide range appear to cluster around 121.3 and 117.3° respectively. This difference could be interpreted in terms of steric repulsions between H and $C_{(1)}$ and $C_{(2)}$ that are absent for $C_{(3)}$ on the other side of the ring. Intermolecular hydrogen bonds involving the OH group are important in the various crystal structures of phenols, but their comprehensive discussion should be postponed at least until reliable positions of the H atoms have been determined by neutron diffraction. The $C(sp^2)—O$ parameters in phenols are consistent with the data shown in Table 7.

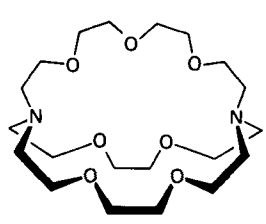
As mentioned above, a structural anomaly occurs in compounds such as dimethyl ether and dimethyl sulphide; the axes of symmetry of the methyl groups were found to be inclined with respect to the $O—CH_3$ and $S—CH_3$ bonds. This effect was attributed by Hirshfeld[57] to the steric repulsion between the two methyl groups that cause the C—O and C—S bonds in $(CH_3)_2O$ and $(CH_3)_2S$ to be bent.

III. STRUCTURAL CHEMISTRY OF POLYETHER COMPOUNDS

Recent developments of macrocyclic polyethers (termed 'crown' ethers because of the appearance of their molecular models) pioneered by Pedersen[58] in 1967 have aroused considerable interest in several unique properties of these compounds. Their most outstanding feature is that they are capable of combining stoichiometrically with a variety of organic and inorganic species to form inclusion complexes which are stable both in the crystalline state and in a wide range of solvents[58,59]. Selected crown ethers, acting as host molecules, show in solution varying degrees of stereoselectivity in complexation of guest molecules and ions of appropriate size, and also appear to catalyse certain chemical reactions. Hence, they have been referred to as models for interacting biological systems[60,61]. Most recently, the multidentate polyethers have been the subject of an extensive, systematic research in which a series of *chiral* crown ether macrocycles are being

designed and synthesized to exhibit properties of chiral recognition toward natural guest moieties[62]. X-ray structure analyses of the crown ethers and their host–guest-type complexes have been carried out in several laboratories to investigate the stereochemical relationships in these compounds, and in particular, the geometry of inclusion in relation to the stereospecificity of crown ether-catalysed reactions as well as crown ether–substrate interactions.

Numerous chemical studies have been reported in the literature on diaza macrobicyclic (37) and tricyclic (38) polyether ligands which also exhibit remarkable complexation properties toward alkaline earth, transition metal and toxic heavy metal cations[63]. These bicyclic and tricyclic cation inclusion complexes (called [2]-cryptates and [3]-cryptates respectively) have cylindrical or spherical topology, either one or two guest ions being enclosed within the central cavity of the ligand. The structures of several cryptates have been established by X-ray crystallography[64]. The cryptates and the macrocyclic crown complexes have in general different spatial geometries. However it seems that, apart from effects due to the bridging nitrogen atoms in the former compounds, the conformational behaviour and ligand–cation interaction modes in both systems are, at least in principle, controlled by similar factors which hold for all molecular structures of polyether compounds. A recent structural analysis of the tricyclic heterocrown **39** provided experimental evidence in support of this assumption[65]. Since a detailed description of both cryptates and crown ethers would exceed the scope of this article, the present discussion is limited to the sterically simpler class of macrocyclic crown compounds.



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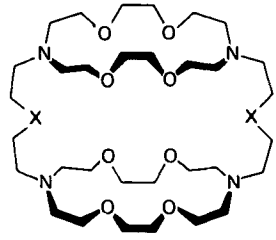

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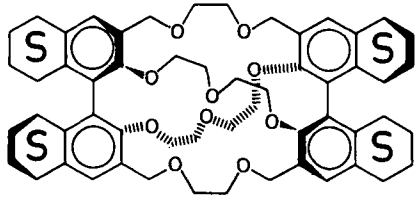
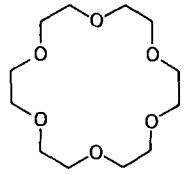


(39)

The next two sections deal with structural properties of cyclic polyethers. The third refers to several examples of noncyclic polyethers displaying similar cation-binding characteristics.

A. The Macrocyclic 18-Crown-6 System, and some General Considerations

The structural features of polyether macrocycles can be exemplified by systems containing the unsubstituted 1,4,7,10,13,16-hexaoxacyclooctadecane (**40**; 18-



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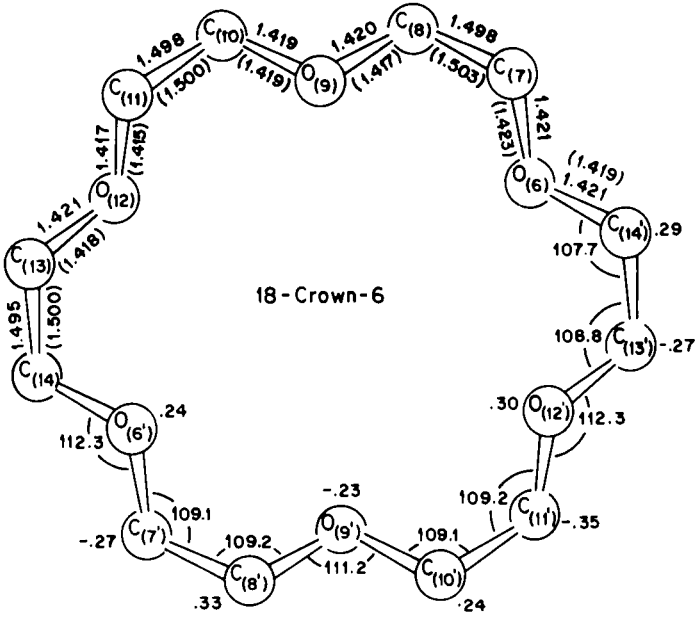
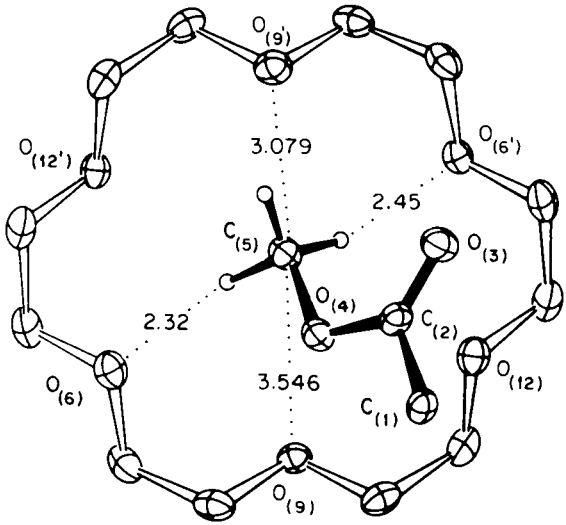
crown-6) ligand, an almost ideal molecular model of a crown ether. Crystal structure analyses of the uncomplexed hexaether and its complexes with NaNCS, KNCS, RbNCS, CsNCS[66], $UO_2(NO_3)_2 \cdot 4H_2O$[67], $NH_4Br \cdot 2H_2O$[68], $CH_2(CN)_2$ (malononitrile)[69], $C_6H_5SO_2NH_2$ (benzenesulphonamide)[70] and $CH_3OOCC{\equiv}CCOOCH_3$ (dimethyl acetylenedicarboxylate)[71] have recently been reported in detail. The latter structure was studied at low temperature (ca. $-160°C$), thus yielding more precise geometrical parameters (Figure 1a).

Figure 2 illustrates some characteristics of the molecular geometry of 18-crown-6 resulting from the ten independent structure determinations. In general, the distribution of bond lengths and angles in the 18-crown-6 ligand is very close to that found in previous studies of other moieties (see above). All observed C—O bond lengths are in the range 1.39–1.45 Å with a mean value near 1.42 Å. Most of the O—C—C angles are close to tetrahedral, while the C—O—C angles are about 3° larger averaging 112.6° (in agreement with the theoretical results of Pickett and Strauss[25]). The C—C single bond distances range from 1.46 to 1.52 Å, with an average of 1.495 Å, showing the characteristic shortening observed in all crystal structure analyses of the crown ethers so far published; the usually quoted reference value for a single aliphatic C—C bond is $\geqslant$1.53 Å[72]. The apparent shortening of C—C bonds in crown ether moieties has been a controversial issue[66,73]. It was recently considered by Dunitz and coworkers as a spurious effect arising from inadequate treatment of molecular motion in crystallographic analysis[66]. However, in view of the continuously increasing evidence from low-temperature studies, it seems now that the short bonds indeed reflect a genuine feature of the molecular structure; the origin of this effect has not been clarified as yet. The structural investigations referred to above indicate that there are no *systematic* changes in bond lengths between the 18-crown-6 molecules given in different conformations. On the other hand, the dimensions of valency angles are clearly dependent on the local conformation within the macroring (see below).

The detailed conformation of 18-crown-6 found in the various crystal structures is best described in terms of the torsion angles about the ring bonds (Table 8). In seven of the complexes the hexaether molecule has a remarkably similar and nearly ideal 'crown' conformation with approximate D_{3d} symmetry. All torsion angles about C—C bonds are *syn*-clinal and those about C—O bonds are antiplanar (Table 8, columns 1–7). The C and O atoms lie alternately about 0.2–0.3 Å above and below the mean plane of the ring. The six ligating oxygens are turned toward the centre of the macrocycle, forming a hexagonal cavity of side approximately 2.8 Å (Figure 1). Assumedly, the energetically favourable symmetric crown conformation of the ether ring is stabilized by effective pole–dipole and dipole–dipole interactions with the corresponding guest species. Except for the potassium ion the other guests are too large to fit in the cavity of 18-crown-6. Thus, within the KNCS complex K^+ occupies exactly the centre of the hexagon of the ether oxygen atoms (Figure 1c), but in the remaining structures the interacting guests are displaced


18-Crown-6
C(10)
C(8)
C(11)
C(7)
O(9)
O(12)
O(6)
C(13)
C(14)
C(14')
C(13')
O(6')
O(12')
C(7')
C(8')
O(9')
C(11')
C(10')
1.498
1.419
1.420
1.498
1.500
1.419
1.417
1.503
1.423
1.421
1.419
1.421
1.417
1.418
1.495
1.500
107.7
.29
108.8
-.27
.30
112.3
.24
112.3
109.2
-.35
109.1
-.27
109.2
-.23
109.1
111.2
.33
.24

(a)


O(9')
3.079
O(12')
O(6')
2.45
C(5)
O(3)
O(4)
C(2)
2.32
O(12)
O(6)
3.546
C(1)
O(9)

(b)

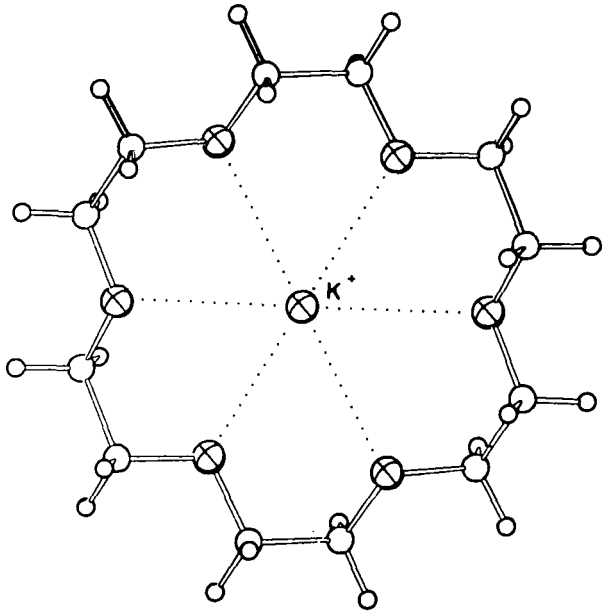


FIGURE 1. The 18-crown-6 ligand in a regular conformation with approximate D_{3d} symmetry. (a) Molecular dimensions[71]; (b) interaction of 18-crown-6 with dimethyl acetylenedicarboxylate[71] (only one half of the guest molecule is shown); (c) interaction of 18-crown-6 with K^+ guest ions[66].

from the mean oxygen plane by 1.00 Å ($-NH_3^+$), 1.19 Å (Rb^+), 1.44 Å (Cs^+), 1.50 Å ($\geq CH_2$) and 1.89 Å ($-CH_3$), in direct correspondence with their relative size. In the crystalline complex of 18-crown-6 with uranyl nitrate, the crown molecules are not bound directly to the uranyl group.

The 18-crown-6 framework when complexed with NaNCS or with benzenesulphonamide deviates markedly from the above described structure. The Na^+ and $R-NH_2$ substrates appear to be too small to 'fill' the annular space within the ligand cavity given in an unstrained conformation. In order to optimize the host–guest interactions the 18-crown-6 molecule is distorted, the deformation strain being preferentially accommodated in torsion angles about the C—O bonds without affecting the *gauche* arrangement of the OCH_2CH_2O units. At this point it is relevant to illustrate the effect of local conformation on bond angles. In the complex of benzenesulphonamide the torsion angle about the $O_{(7)}-C_{(8)}$ bond is *syn*-clinal (72.5°) rather than antiplanar[70]. Such deformation of the ring system introduces 1–4 steric repulsions between the $CH_2(6)$ and $CH_2(9)$ methylene groups, causing the bond angle at $C_{(8)}$ to assume value much greater than tetrahedral (113.3°). Similarly, the small torsion angles about the $C_{(9)}-O_{(10)}$ (70.5°), $O_{(13)}-C_{(14)}$ (76.8°) and $O_{(16)}-C_{(17)}$ (73.7°) bonds in the Na^+ complex cause short contacts between the $CH_2(8)$ and $CH_2(11)$, $CH_2(12)$ and $CH_2(15)$, and $CH_2(15)$ and $CH_2(18)$ methylene groups. This is reflected in a significant widening

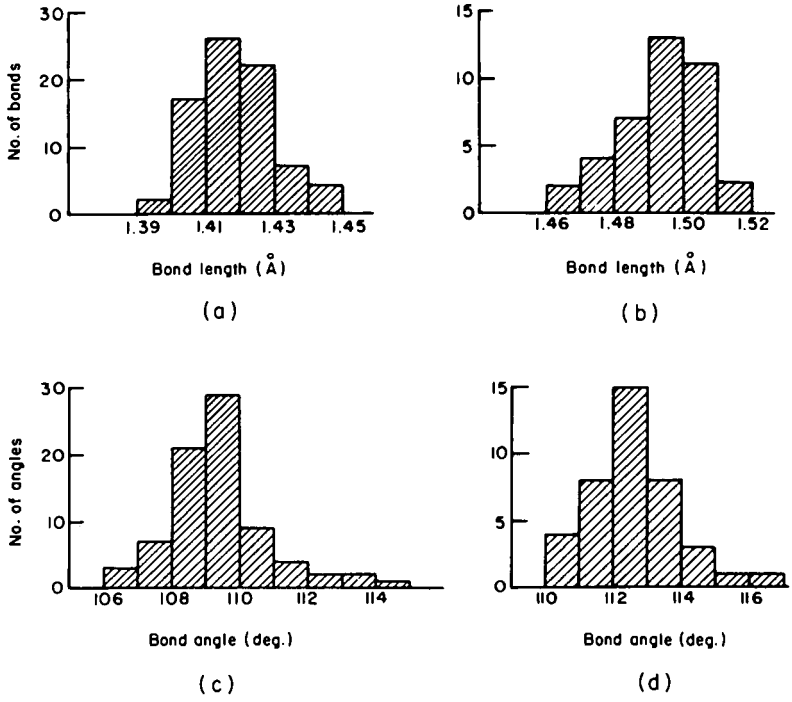


FIGURE 2. A distribution of the bonding parameters observed for 18-crown-6 in ten different structure determinations (References 66–71); (a) C—O bond length, (b) C—C bond length, (c) C—C—O bond angle and (d) C—O—C bond angle.

of bond angles at $C_{(9)}$, $C_{(14)}$, $O_{(16)}$ and $C_{(17)}$ to 112.4, 113.6, 116.5 and 112.1°, respectively[66].

The uncomplexed 18-crown-6 ligand adopts a different type of conformation in the solid. Figure 3 shows that the molecular framework has an elliptical shape because the arrangement about two of the ethylenic bonds becomes antiplanar rather than *gauche*. It appears that the empty space inside the molecule is filled by two H atoms that form transannular H···O contacts; a possible indication that intramolecular van der Waals' and C—H···O dipolar attractions play a major role in determining the overall shape of the uncomplexed macrocycle. This conclusion is consistent with recently published energy calculations of Truter[74]. Her results show that when only nonbonded intramolecular interactions are taken into account, the 18-crown-6 ring has a more favourable energy in the asymmetrical form corresponding to the uncomplexed molecule than in the one with approximately D_{3d} symmetry. An elliptical arrangement of the heteroatoms has also been observed in uncomplexed molecules of the 18-membered crown when two of the oxygen atoms were replaced by sulphur atoms. The interesting feature of the 1,10-dithio-18-crown-6 structure is, however, that the sulphur atoms are directed out of the cavity, while the four oxygen atoms remain turned inward[75]

The conformation of oxyethylene oligomers (chains and rings) has been investigated by various experimental and theoretical methods. References 76 and 77

TABLE 8. Torsion angles (deg.) in 18-crown-6 and its complexes

Guest species	Regular conformation							Irregular conformation		
	$C_6H_6O_4$	$CH_2(CN)_2$	NH_4Br	KNCS	RbNCS	CsNCS	$UO_2(NO_3)_2$	NaNCS	$C_6H_5SO_2NH_2$	none
	Ref. 71	Ref. 69	Ref. 68	Ref. 66	Ref. 66	Ref. 66	Ref. 67	Ref. 66	Ref. 70	Ref. 66
$C-O_{(1)}-C_{(2)}-C$	180	179	180	−171	−179	−178	180	173	177	−80
$O-C_{(2)}-C_{(3)}-O$	72	64	−67	−65	67	68	−63	61	−66	75
$C-C_{(3)}-O_{(4)}-C$	176	179	−174	179	−178	−177	175	−171	158	−155
$C-O_{(4)}-C_{(5)}-C$	179	−177	−175	178	179	179	179	−177	180	166
$O-C_{(5)}-C_{(6)}-O$	−76	−60	65	70	−61	−63	64	−59	−67	−68
$C-C_{(6)}-O_{(7)}-C$	177	179	−176	−176	−173	−173	−175	−173	180	176
$C-O_{(7)}-C_{(8)}-C$	−169	175	178	−177	176	177	−173	−174	−73	175
$O-C_{(8)}-C_{(9)}-O$	70	65	−71	−65	60	61	−72	52	−68	175
$C-C_{(9)}-O_{(10)}-C$	179	178	−171	−178	167	172	−178	71	173	170
$C-O_{(10)}-C_{(11)}-C$					175	174		−172		
$O-C_{(11)}-C_{(12)}-O$					−64	−66		63		
$C-C_{(12)}-O_{(13)}-C$					−176	−176		−176		
$C-O_{(13)}-C_{(14)}-C$	*a*	*a*	*a*	*a*	−172	−172	*a*	77	*a*	*a*
$O-C_{(14)}-C_{(15)}-O$					64	65		47		
$C-C_{(15)}-O_{(16)}-C$					172	173		115		
$C-O_{(16)}-C_{(17)}-C$					−178	−179		−74		
$O-C_{(17)}-C_{(18)}-O$					−64	−65		−59		
$C-C_{(18)}-O_{(1)}-C$					−179	180		167		

[a]In these structures 18-crown-6 is located on inversion centres or mirror planes.

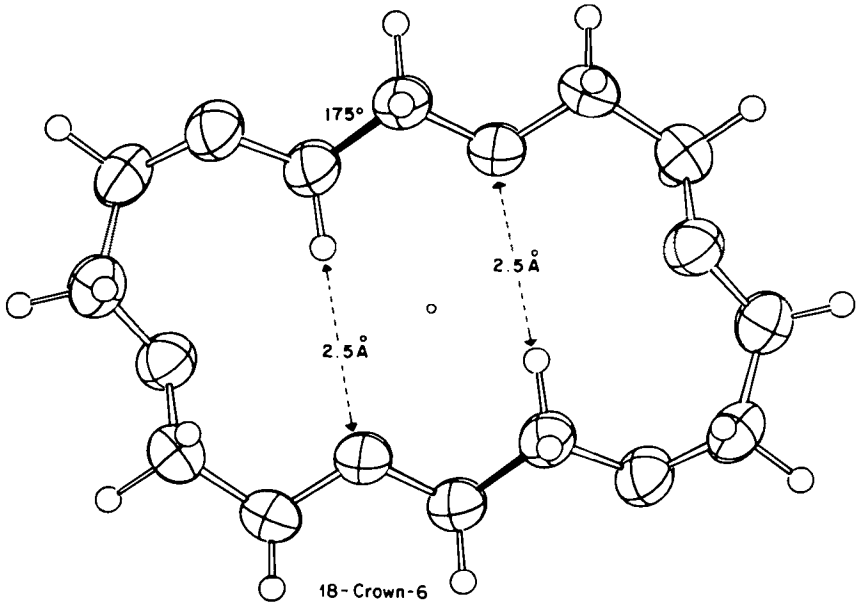


FIGURE 3. View of the conformation adopted by the uncomplexed 18-crown-6 hexaether[66].

report conformational analyses of ethers consisting of CH_2CH_2O units by spectroscopy; a *gauche* conformation was found to be 0.3–0.5 kcal/mol more stable than a *trans* form for a CH_2—CH_2 bond[76], whereas the *trans* form is 1.1 kcal/mol more stable than a *gauche* form for a CH_2—O bond[77]. The latter trend was interpreted in terms of a stabilizing interaction between the oxygen lone-pair orbitals and the nearest hydrogen atom of a methylene group. Indeed, the chemical shifts and vicinal coupling constants observed in n.m.r. spectrum of several cyclic ethers and their cation complexes indicated that the OCH_2CH_2O fragments have the same *gauche* structure in a number of solvents; in a solution there is a rapid interconversion between the *anti-* and *syn-gauche* rotamers[78]. The most recent Raman and infrared spectral observations, combined with the normal coordinate calculation, suggested that the stable form of 2,5-dioxahexane is that with a *trans* arrangement about the CO—CC axis and a *gauche* arrangement about the OC—CO axis[79]. Finally, potential functions for bending of some six-membered oxane rings were determined from vibrational spectra by Pickett and Strauss[25]. On the assumption that the methylene groups are constrained to move as units with constant geometry, the calculated torsional barriers for the OCCO and COCC fragments were 3.45 and 2.02 kcal/mol respectively. The general conclusion that the monomeric unit —O—CH_2—CH_2—O— has the preferred *trans–gauche–trans* conformation is consistent with XD measurements.

The structures of 18-crown-6 discussed above provide an excellent example of the most common features of conformation occurring in macrocyclic polyether species[80] (see below). Regular, energetically optimal, geometries corresponding closely to *syn*-clinal torsion angles about the C—C bonds and

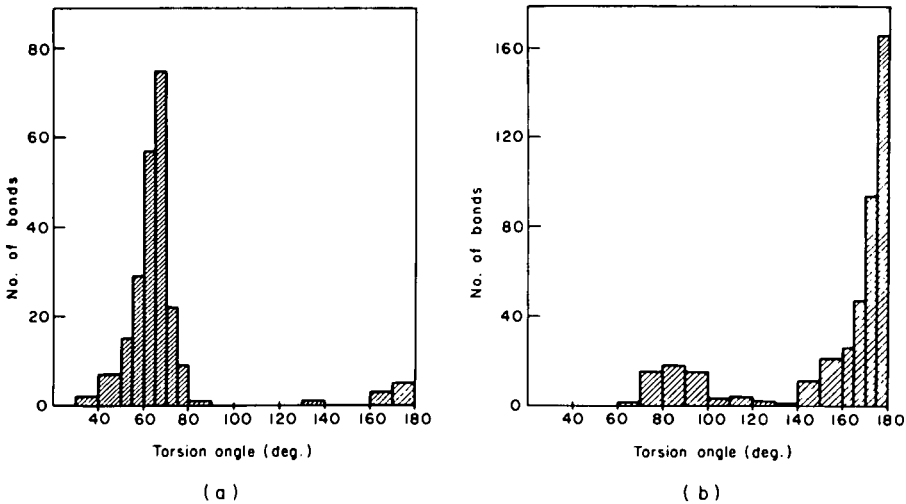


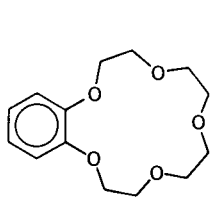
FIGURE 4. Histograms showing the characteristic distribution of (a) O—C—C—O and (b) C—O—C—C torsion angles in macrocyclic polyethers; they are based on data found in about 40 independent structure determinations[8,9].

antiplanar torsion angles about the C—O bonds are attained for most of the conformational parameters in these macrorings. Irregular geometries containing an antiplanar arrangement of the $O—CH_2—CH_2—O$ group, associated with the formation of transannular C—H···O contacts, have been found in several crystal structures of 'empty' ligands. In the various complexes, and particularly in those involving substrates too small to fit into the ligand cavity, conformational changes about the C—O bonds from antiplanar to *syn*-clinal arrangements occur more frequently; their apparent function is to optimize the specific interactions bonding the host to the guest species. Finally, crown ether macrocycles lacking a sufficiently extended pattern of stabilizing interactions of specific nature tend to be partially disordered in the crystal phase even at low temperatures. In such case the average conformation of the disordered fragment of the molecule is often characterized by torsion angles having magnitudes intermediate between *gauche* and *trans* geometries. It is of interest to note in this context that a survey of the structural details available from the work so far published on crown ethers suggests that the crystal forces acting on the ligands or on their complexes in the various structures usually have a minor effect on the molecular geometry. The above described stereochemical aspects of polyether macrocycles are illustrated by histograms in Figure 4 which were compiled from structural data of about 40 different polyether moities. A few of them will be described in more detail in the following section. The observed properties of the conformation support the view that the complexing capability of the crown ethers can in part be attributed to tendency of the $+CH_2—CH_2—O+$ units to assume an unstrained *gauche–trans* structure, and to the fact that only a limited number of degrees of freedom is usually involved in the conformational changes associated with the complex formation. Furthermore, host–guest complexes are expected to have a more stable conformation the more thoroughly filled are the macrocyclic cavities.

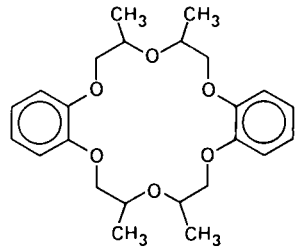
B. Structural Examples of Host–Guest Complexes with Crown Ethers

Representative examples of two different types of host–guest compounds are being discussed in this section. The first concerns complex formation between macrocyclic polyethers and metal cations, which is stabilized mainly by ion–dipole interactions; hitherto, no indications for *enantiomer* selectivity of chiral crown compounds with alkali and alkaline earth salts have been reported. The second involves crown ether complexes with organic guest moieties where hydrogen bonding is the main contributor to the intermolecular attraction. Chiral recognition properties of polyether macrocycles, containing steric barriers in the form of bulky rigid substituents, towards primary amine salts have been extensively investigated in the recent years[81].

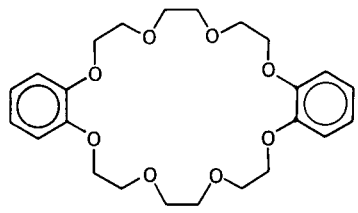
Benzo-15-crown-5 (**41**) was found to form crystalline complexes with hydrated sodium iodide[82], potassium iodide[83], solvated calcium thiocyanate[84] and calcium 3,5-dinitrobenzoate trihydrate[85]. Apparently, the structural relationships between Na^+ and the 15-crown-5 derivative are more favourable than those in the 18-crown-6 complex. The 15-membered ring roughly preserves its crown conformation, the guest cation lying 0.75 Å above the mean plane of the pentagonal cavity of oxygen atoms. The Na···O(ring) distances, which range from 2.35 to 2.43 Å, are significantly shorter than the corresponding contacts in the sodium thiocyanate complex of 18-crown-6 (2.45–2.62 Å). In both structures the Na^+ is also coordinated to a water molecule at about 2.3 Å; as a result it is surrounded either by a pentagonal pyramid or a pentagonal bipyramid of ligating sites. Potassium iodide forms a 1 : 2 adduct with the cyclic polyether. The potassium ion is located between two centrosymmetrically related host molecules, and consequently coordinated to the ten ether oxygens (Figure 5). It deviates 1.67 Å from each mean plane of the two enclosing ligand cavities as compared with 0.75 Å for Na^+ in the sodium iodide complex of **41**. This is consistent with the fact that the ionic radius of K^+ (1.33 Å) is considerably larger than that of Na^+ (0.95 Å). All K···O(ring) distances are within the range of 2.78–2.95 Å, and the iodide anions do not seem to affect the



(41)



(42)



(43)

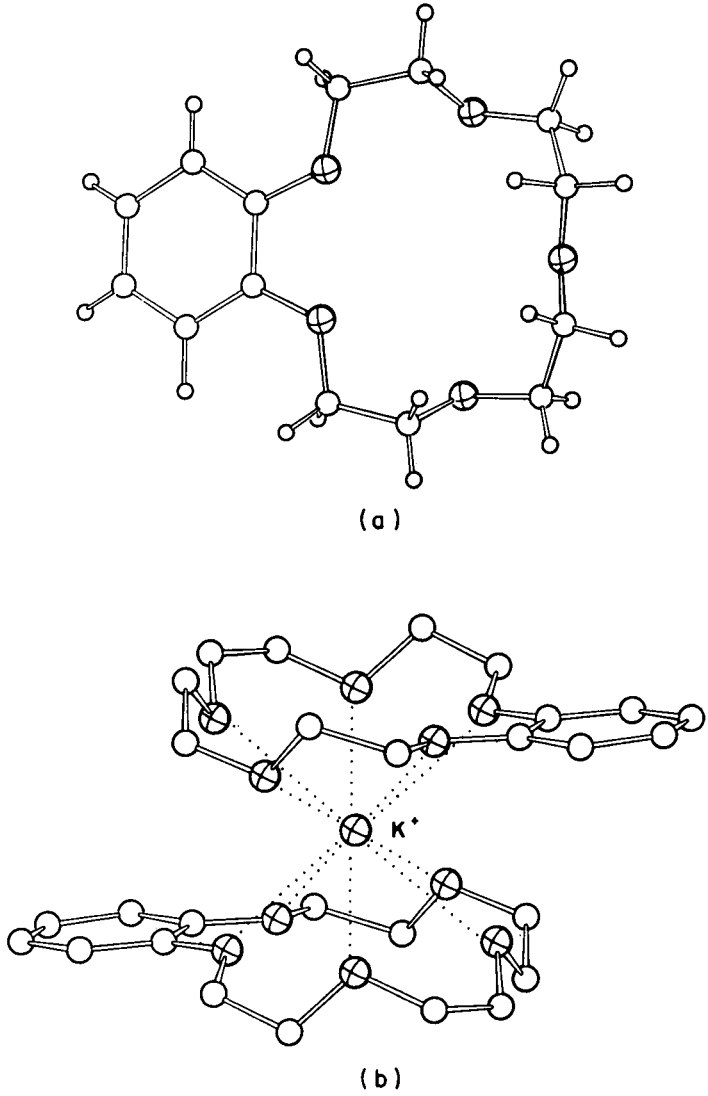


FIGURE 5. The structures of (a) benzo-15-crown-5[86] and (b) its complex with potassium cation[83].

configuration of the complexed entities. In the complex of benzo-15-crown-5 with $Ca(NCS)_2 \cdot CH_3OH$ and $Ca(NCS)_2 \cdot H_2O$ the metal cation interacts with the five ether oxygen atoms on one side and two isothiocyanate nitrogen atoms and an oxygen from the solvent on the other side[84]. In the crystalline complex of **41** with calcium dinitrobenzoate the guest ion is coordinated to the pentaether ring and four benzoate oxygen atoms[85]. The deviation of Ca^{2+} from the cross-section of the macroring cavity (1.23–1.38 Å), and its separation from the interacting oxygen

sites ($\geqslant$2.52 Å) are intermediate between those observed in the sodium and potassium adducts. Cradwick and Poonia[85] rationalized the presence of direct cation–anion interactions in the complexes of calcium by the small size combined with relatively high charge density of the Ca^{2+} ion. However, similar associations have also been observed in a few structures with larger monovalent cations. Since, obviously, the mode of interaction between metal salts and crown hosts in the crystal phase depends on many factors, it seems difficult to predict for a particular structure whether the guest species will be completely enclosed within crown ether cavities or if it will directly coordinate with counterions as well.

The molecular structure of uncomplexed **41** was most recently investigated by Hanson at -150°C with the aid of photographically collected data[86]. The conformation of the free ligand was found to be somewhat different from any of the complexed structures. In the absence of an interacting substrate the pentagon defined by the oxygen atoms is contracted along the principal molecular axis (via deformation of two torsion angles about C—O bonds which assumed values of 81 and 85°) in order to reduce the empty space within the macroring (Figure 5). Moreover, even at the low temperature several atoms in the peripheral part of the ring have relatively large mean-square amplitudes of vibration and are possibly disordered.

Considerable changes in molecular conformation of the tetramethyldibenzo-18-crown-6 host (**42**) were observed to occur on complex formation with alkali metal salts. In the crystal of uncomplexed **42** the hexagon defined by the ether oxygen atoms is expanded along two diagonals and contracted along the third giving rise to an elliptical arrangement of the heteroatoms[87]. Since two of the methyl substituents are turned toward the centre of the molecule, it seems likely that the observed conformation is stabilized by transannular van der Waals interactions (Figure 6). Two out of the five configurational isomers of **42** were found to form two different crystalline complexes with caesium thiocyanate in which the ligand conformation is more regular, all C—O bonds being nearly *trans* and the C—C bonds *gauche*[88]. The isomer which has methyl groups configuration *cis, anti, cis* forms a 1 : 1 complex with CsNCS. The Cs ion lies 1.71 Å out of the mean oxygen plane, and is coordinated to the thiocyanate anions as 3.19 and 3.25 Å in addition to the six ether oxygens at 3.07–3.34 Å. The crystal structure is composed of centrosymmetrically related dimeric units of the complex (Figure 6). The ligand molecules with *trans, anti, trans* configuration of the methyl groups form 2 : 1 complex with CsNCS. As in the potassium iodide complex of **41**, the Cs^{+} guest ion is completely surrounded by two hosts. All twelve Cs···O contacts again vary from 3.12 to 3.36 Å, this range being similar to that in the CsNCS complex with 18-crown-6.

Another interesting crown system is that of dibenzo-24-crown-8 (**43**)[89]. This macrocycle is large enough to complex simultaneously two small guest ions, as in its complexes with two molecules of sodium nitrophenolate[90] or potassium isothiocyanate[91]. Coordination modes of Na^{+} and K^{+} in the two crystal structures (Figure 7) are characterized by the following features. In the complex of KNCS the ligating ether oxygen atoms are almost coplanar. Each K^{+} ion interacts with only five oxygens (at 2.73–2.98 Å), two of the bonding sites being shared between the two interacting cations. The potassium atoms lie 0.66 Å from each side of the cavity, and are in contact with the thiocyanate moieties. Somewhat different steric relationships were observed in the structure with sodium-nitrophenolate. The ligand molecule is folded around the two smaller Na^{+} ions, each of them coordinating three ether oxygens (at 2.47–2.62 Å). The nitro group and the phenolate oxygen

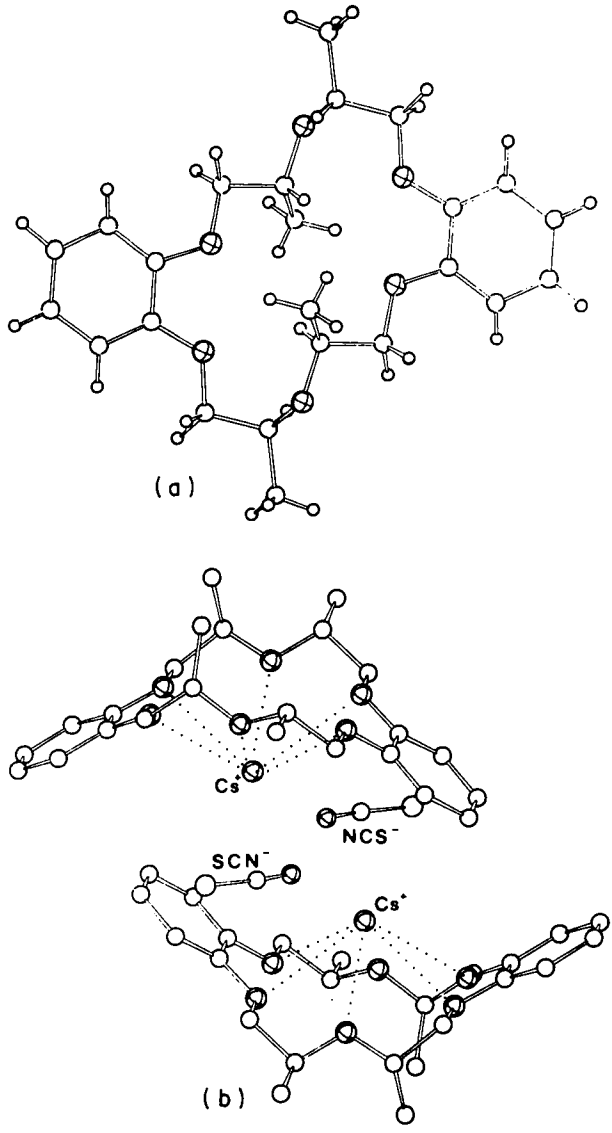


FIGURE 6. The structures of (a) one isomeric form of tetramethyldibenzo-18-crown-6[87] and (b) its complex with caesium thiocyanate salt[88]. Two centrosymmetrically related entities of the complex are shown.

atoms of chelating anions are included in the sphere of interaction around each cation. A small section of the macroring is not involved in direct coordination of the guest species, and has a partially disordered conformation. Host **43** also forms stable complexes of 1 : 1 stoichiometry with alkaline earth metal salts; reported

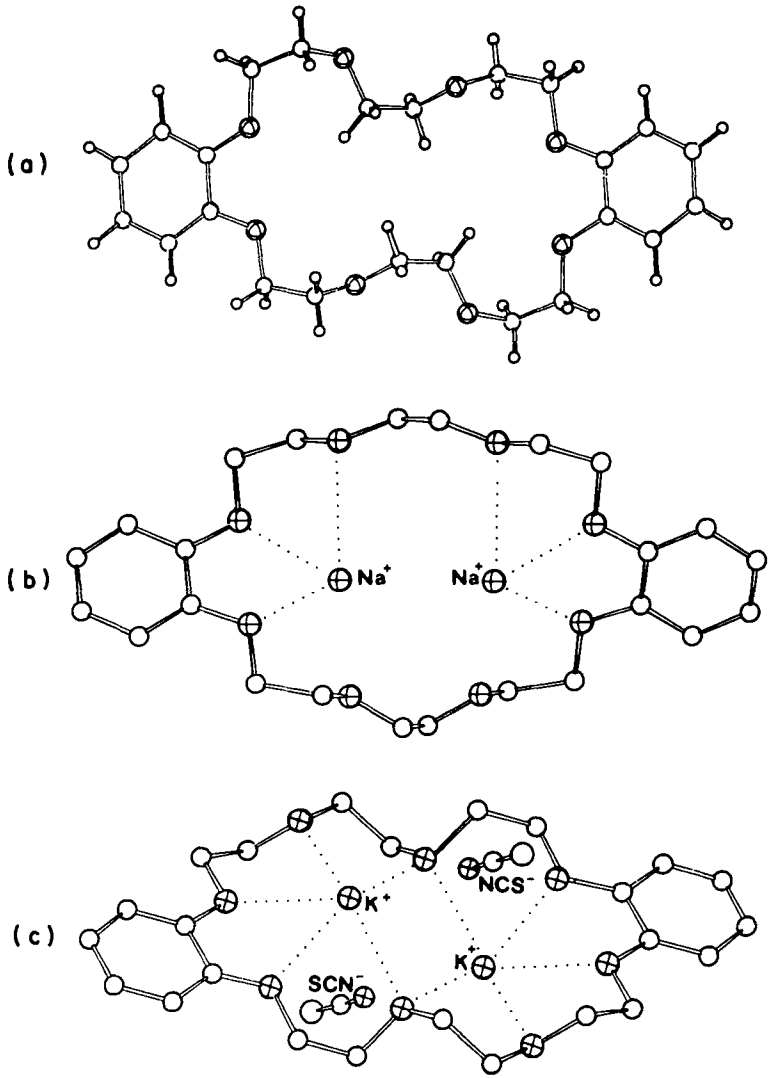
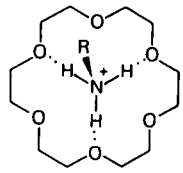


FIGURE 7. (a) Molecular conformation of dibenzo-24-crown-8[89]; (b) interaction of two Na^+ ions with this ligand[90]; (c) view of the complex with two molecules of potassium isothiocyanate[91].

examples involve adducts with barium perchlorate[92] and barium picrate[93]. As in other 1 : 1 compounds involving metal guest species, the Ba^{++} cation interacts both with the macrocyclic ligand and the counterions and solvent molecules. Characteristic distances between barium and ligating oxygen atoms range from 2.7 to 3.1 Å. Some details of the molecular conformation of **43** in the five structures referred to above are considerably different.

Many effective syntheses of hydrogen-bonded complexes of alkylammonium ions and cyclic polyethers have been developed in recent years, with the host and guest species being subjected to a wide range of structural modifications[62,94]. An idealized scheme of the intermolecular association involving crown hexaethers suggests NH···O hydrogen bonding between the three acidic hydrogens of the NH_3^+ group and three alternate oxygens of the macroring, and direct polar N···O interactions in between the hydrogen bonds with the remaining ring-oxygen atoms (**44**). In sterically undistorted structures, as that of 18-crown-6 with NH_4Br[68], the ammonium ion is usually centred and tightly fitted within the hydrophilic macrocyclic cavity. The characteristic geometrical parameters of this interaction include N^+···O distances ranging from 2.9 to 3.1 Å, H···O distances from 1.9 to 2.1 Å and nearly linear NH···O bonds. Theoretical calculations on simple model systems (e.g. NH_4^+ with $(OCH_3)_2$) indicated that the energy of the hydrogen-bonding interaction is about three times that of the direct electrostatic interaction[95].



(**44**)

The first crystal structure of an alkylammonium crown ether adduct described in the literature is that of 2,6-dimethylylbenzoic acid-18-crown-5 with *t*-butylamine[96]. The 1 : 1 salt was analysed at 120 K, and its geometry is depicted in Figure 8. The host molecule contains a polar functional substituent which is directed towards the polyether cavity, and (after proton transfer) acts also as an internal counterion for the ionic guest. The complex is held together by hydrogen-bonding and ion-pairing interactions. Although the 18-membered ring contains only five oxygen atoms that are available for binding the guest ion, the ligand adopted a conformation in which a symmetric hexagonal cavity is formed with one of the carboxylate oxygen atoms. The carboxylate and ammonium moieties that ion-pair are on the same side of the macroring. The resulting coordination around the $-NH_3^+$ group in this structure includes, therefore, one very short (1.70 Å) NH^+···O^- and two longer (2.21 Å) NH^+···O(ring) hydrogen bonds in a tripod arrangement, the *t*-Bu—N bond being nearly perpendicular to the mean plane of the six ligating oxygens. (The second carboxylate oxygen atom takes part in lateral CH···O^- interactions that connect adjacent adduct entities related by a glide plane symmetry.) The observed geometry of the host–guest complex is characterized by a very high organization, and it has a higher degree of symmetry (the molecular units are situated on crystallographic mirror planes) than the constituents in their stable form. Correspondingly, the molecular structure of the uncomplexed ligand (Figure 9)[97] is different from that found in the complex with *t*-butylamine. The skeleton of 2,6-dimethylylbenzoic acid-18-crown-5 exhibits only approximate C_2 symmetry with the carboxyl group rigidly located in the centre of the ether ring. The overall conformation is uniquely stabilized by internal transannular hydrogen bonding and attractive dipole–dipole O(ring)···C=O interactions. In the complexed as well as uncomplexed ligand structures all ether oxygen atoms turn inward, the methylene atoms turn outward, and the OCH_2CH_2O fragments have *gauche* conformations.

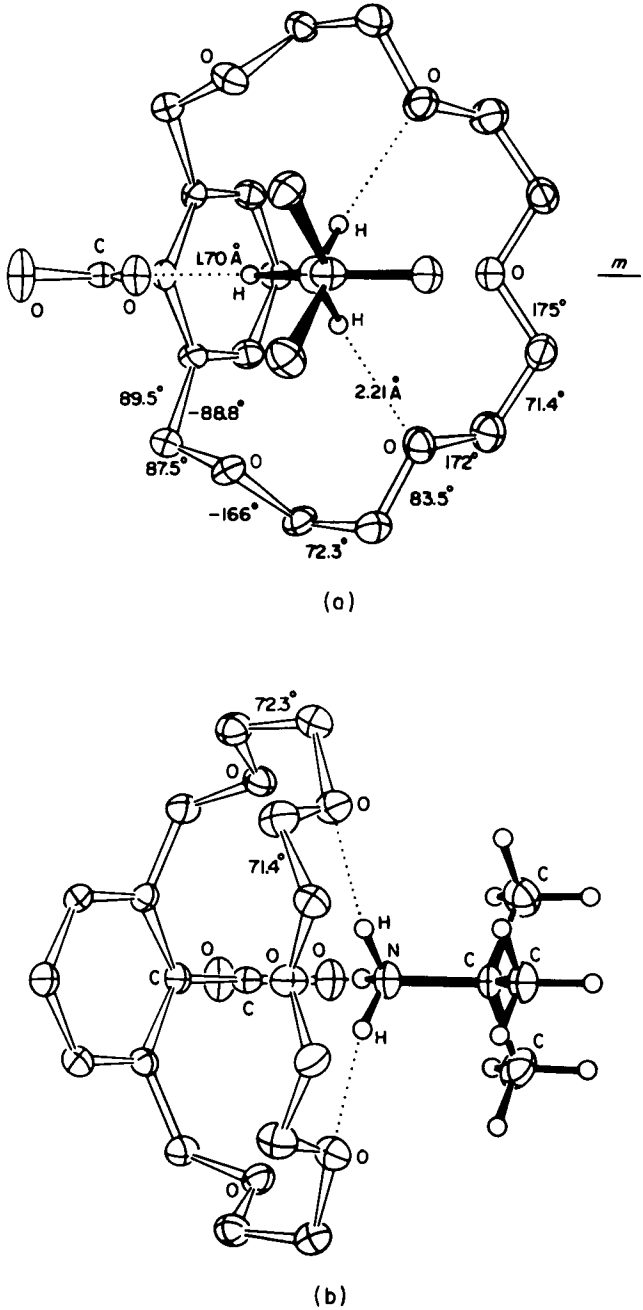


FIGURE 8. Two views of the molecular complex of 2,6-dimethylylbenzoic acid-18-crown-5 with *t*-butylamine[96].

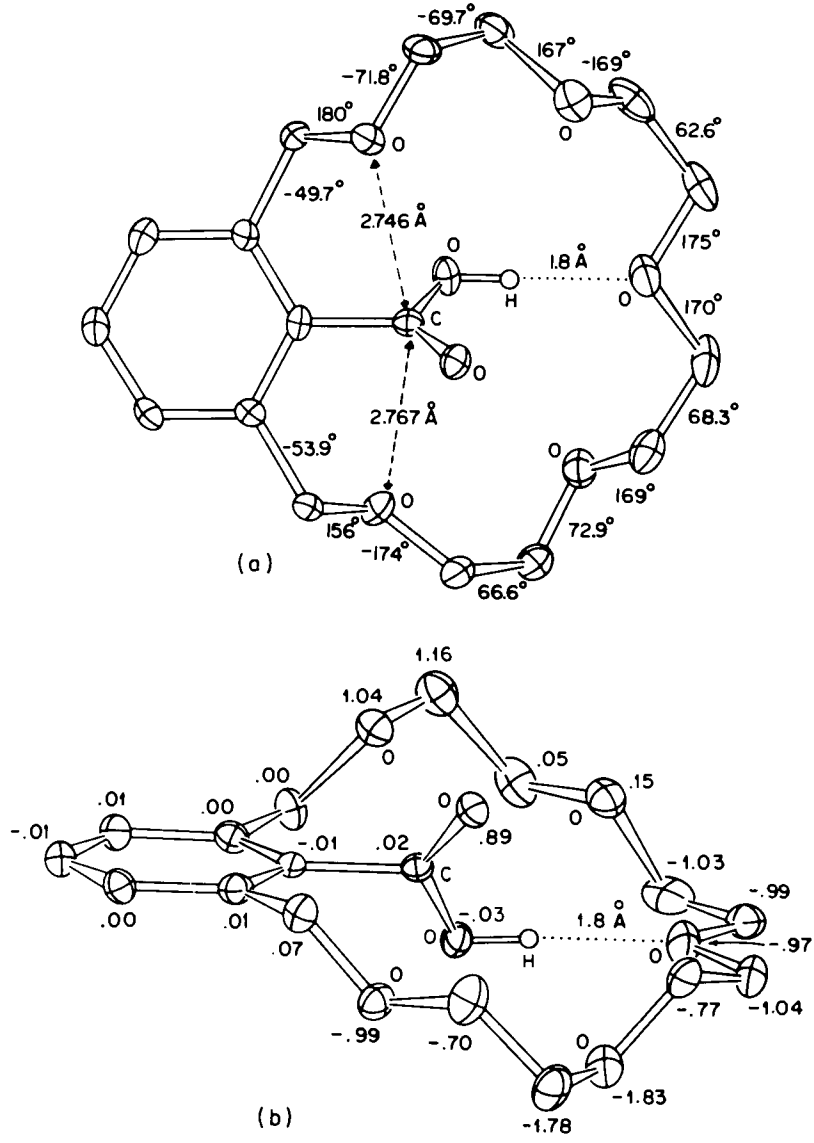
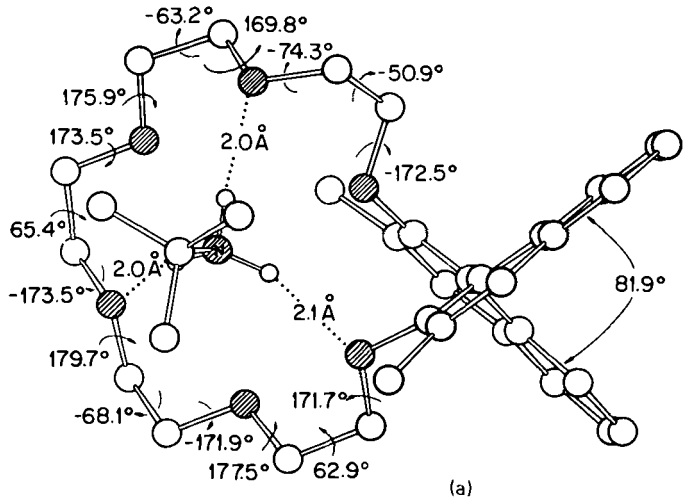


FIGURE 9. Two views of the molecular structure of uncomplexed 2,6-dimethylylbenzoic acid-18-crown-5[97].

In the course of the author's investigation into the structural chemistry of crown compounds a hexaether system containing a 2,2′-substituted 3,3′-dimethyl-1,1′-dinaphthyl unit and its 1 : 1 inclusion complex with *t*-butylammonium perchlorate have recently been characterized by low-temperature X-ray analysis (Figure 10)[98]. Conformational properties of the macrocycle and the geometry of its binding to t-$BuNH_3^+$ are generally similar to those already described earlier in this article. The

observed host–guest association is mainly due to complexation through a tripod arrangement of $NH^+\cdots O$ hydrogen bonds on one face of the macrocyclic cavity. The $C-NH_3^+$ bond is perpendicular to the complexation site of the crown, the ammonium hydrogen atoms being donated to three alternate ether oxygens in a favourable geometry. Furthermore, the structural data suggest that three donor oxygen atoms are involved in direct pole–dipole interactions with the substrate, one of their lone-pair orbitals pointing almost directly at the electrophilic N^+. Apparently, the spatial relationship between the host and the guest is free from severe steric constraints, which allows an undistorted complementary arrangement of the binding sites. The overall conformations of the complexed and uncomplexed ligand molecules are very similar, the macroring forming an angle of about 40° with the 1,1′-dinaphthyl bond. Consequently, one of the methyl substituents covers and directly interacts with one face of the cavity. This may lead to an interesting conclusion, that even in solution the two sides of the macrocycle are not necessarily equivalent with respect to complexation of guest species. The complexed host exists in an ordered and regular conformation with all oxygens turned inward, and with characteristic *syn*-clinal and antiplanar (with a single exception) torsion angles about the C–C and C–O bonds respectively. The conformation of one part of the uncomplexed molecule is disordered, and therefore exhibits (on the average) an irregular pattern of torsion angles. The remaining fragment of the ring is stabilized by an intramolecular $CH\cdots O$ attraction and has one OCH_2CH_2O group in an antiplanar arrangement.

Synthetic compounds containing more than a single macroring assembly of binding sites are of particular interest since they can act as potential hosts for a variety of bifunctional guest moieties such as dihydroxyphenylalanine, lysine, etc. A model system of this type consists of a chiral ligand, containing two 18-crown-6 rings connected by a 2,3- and 2′,3′-substituted 1,1′-dinaphthyl unit, that interacts with the bis(hexafluorophosphate) salt of tetramethylene diamine[99]. Evidently, the organic host complexed simultaneously the hydrogen-bonding parts of the guest, the two crown rings being thus held in a convergent relationship (Figure 11). The



(a)

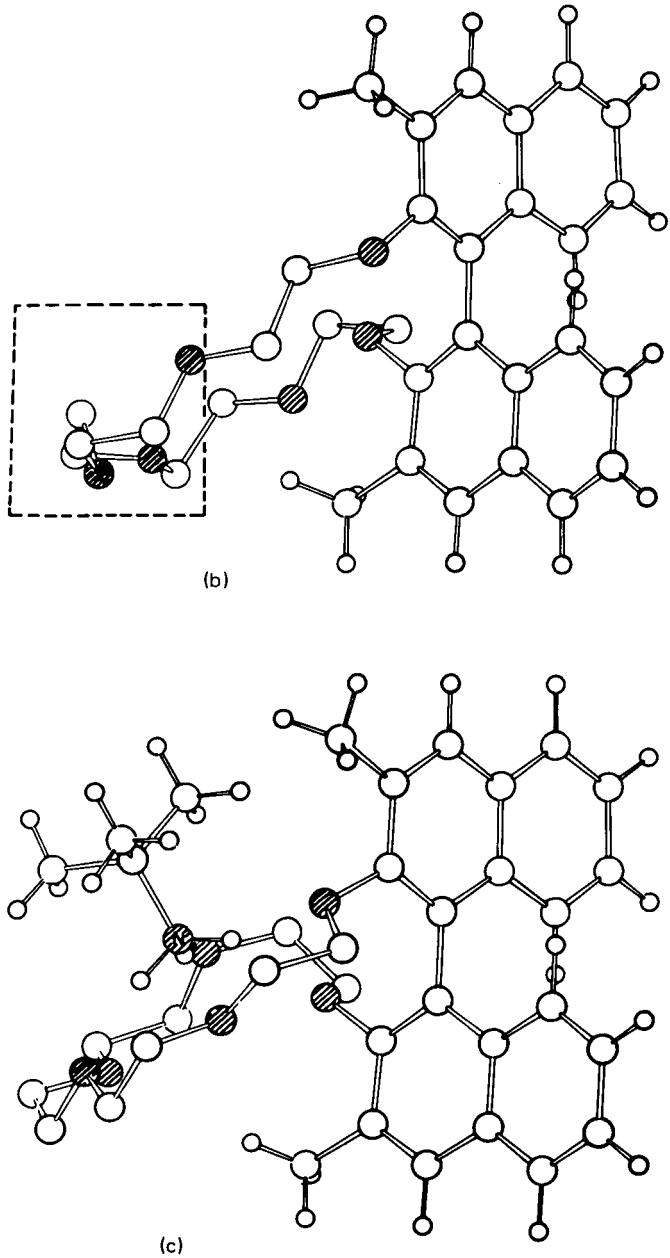


FIGURE 10. A host–guest complex between a 1,1′-dinaphthyl-20-crown-6 ligand and a *t*-butylammonium ion (a). The overall conformations of the uncomplexed and complexed ligand are shown in (b) and (c) respectively[98]. The marked frame encloses the conformationally disordered part of the uncomplexed molecule.

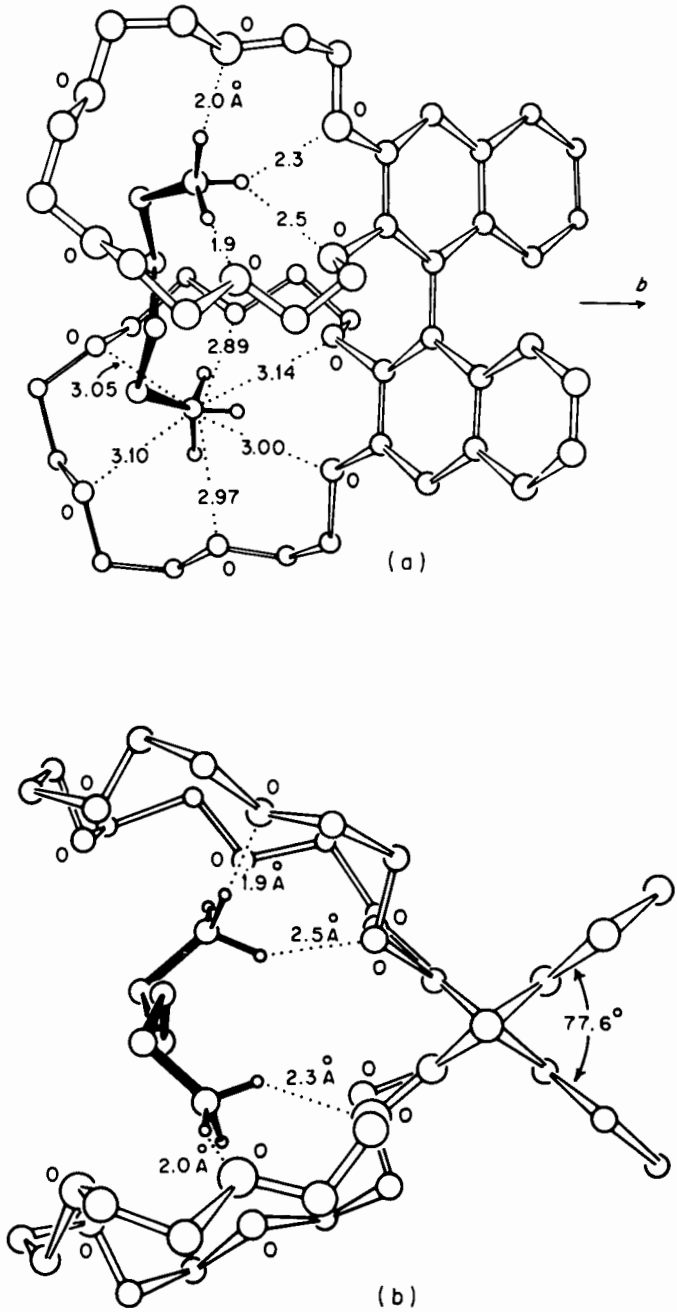
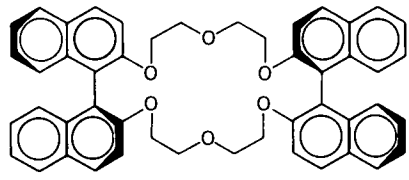


FIGURE 11. An illustration of a host–guest organic crown complex containing two assemblies of binding sites[99].

ammonium groups centre into the hydrophilic cavities, and the tetramethylene chain is strung between the two macrorings. The overall shape of this structure and the geometry of host-to-guest interaction are influenced by the relatively short dimension of the $(CH_2)_4$ bridge. Thus, in the observed conformation the dihedral angle between the planes of the naphthalene rings attached to one another is 77.6°; in the uncomplexed and isolated molecule of the host the dihedral angle can vary between extremes of about 60 to 120°. Moreover, the peripheral region of the 18-crown-6 unit is not directly involved in the hydrogen bonding, and its framework deviates significantly from the D_{3d} conformation. Nevertheless, the molecular dimensions of the crown ring preserve the characteristic features usually observed in structures of poly(ethylene oxide) compounds. It should be pointed out that the PF_6 counterions which fill the intercomplex cavities in the crystal structure seem to have little effect on the geometry of interaction between the host and the guest. Since the space group of these crystals is centrosymmetric, the two enantiomers of the complex were not resolved upon crystallization.

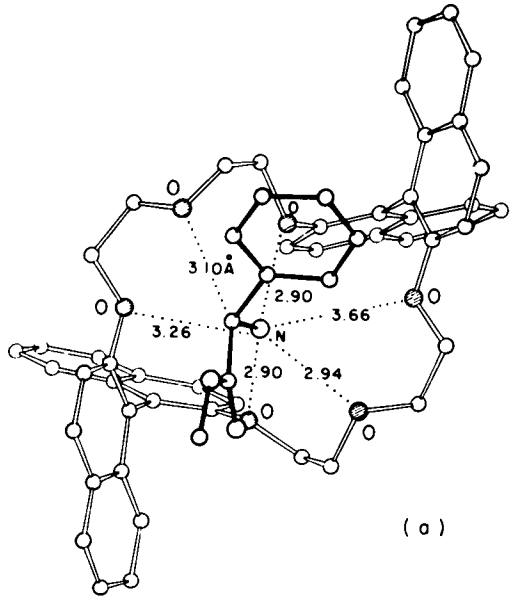
Chiral recognition in molecular complexation between multiheteromacrocycles containing 1,1′-dinaphthyl units as steric and chiral barriers and primary amine salts has been reported by Cram and coworkers[81], and to a lesser extent by other research groups. Suitably designed diastereomeric complexes were found to differ in their free energy of formation in solution by as much as 2 kcal/mol; consequently, a complete optical resolution of racemates of primary amine salts could be achieved[100,101]. From the structural point of view, the complexation stability of a given ligand–substrate system is closely related to the nature and geometrical details of the binding interactions, while stereoselectivity in the complex formation is associated with the degree of complementary structural relationships between the intervening species. The chemistry of ligands containing two chiral 1,1′-dinaphthyl units separated by a central macrocyclic binding site and bound to ether oxygen in their 2,2′-positions is particularly well known[81]. These compounds contain six hexagonally arranged and inward-turning oxygens positioned to hydrogen-bond the ammonium group of a potential guest. Unfortunately, to date it has been possible to crystallize very few diastereomeric complexes of this kind, and to our knowledge accurate structural results are available only for a single optically pure model compound[102]. A similar study was carried out on optical resolution of asymmetric amines by preferential crystallization of their complexes with the *naturally* occurring lasalocid antibiotic[103].

Figure 12 describes the structure of a complex between chiral (*S*,*S*)-host-45 and the hexafluorophosphate salt of (*R*)-phenylglycine methyl ester as determined by XD at −160°C[102]. From the two diastereomeric complexes resolved in solution,

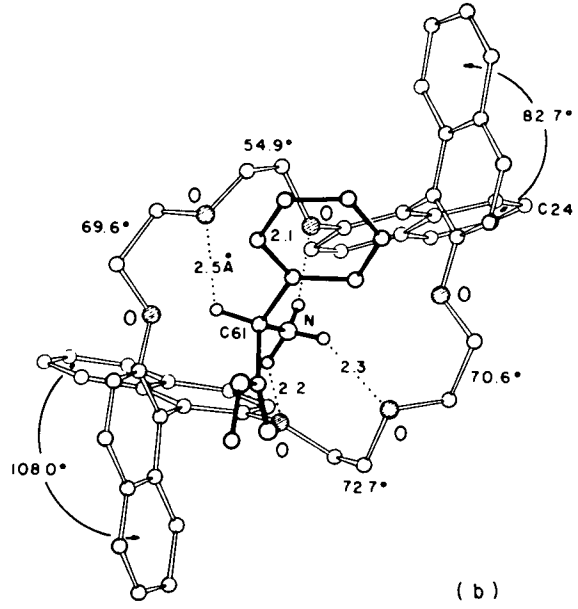


(45)

this structure corresponds to the less stable isomer. The observed attraction of an organic host to an organic guest via specific interaction of the NH_3^+ ion with the polyether cavity is similar, in general terms, to that described for other inclusion compounds. On an idealized molecular model of the ligand the rigid naphthyl


3.10Å
2.90
3.66
3.26
N
2.90
2.94
O
O
O
O
O
O
O
O

(a)


82.7°
54.9°
C24
69.6°
2.1
2.5Å
O
O
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O
C61
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2.3
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70.6°
108.0°
72.7°

(b)

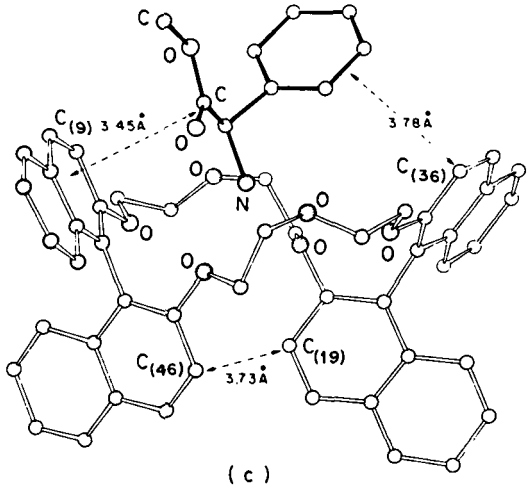

FIGURE 12. An illustration of the main attractive and repulsive interactions within the inclusion compound of phenylglycine methyl ester with a chiral ligand[102].

groups divide the space around the macroring into four equivalent cavities, two below and two above the ring. In actual structure, the host–guest interaction is confined to one face of the ligand. The three substituents attached to the asymmetric centre of the guest phenylglycine derivative are arranged in such a way that the large phenyl group and the small hydrogen atom are located in one cavity, while the medium ester group resides in the other site (Figure 12). In the more stable (*S*,*S*)–(*S*) diastereomer, these substituents are expected to be arranged more favourably with respect to the steric barriers of the ligand. It appears that the accommodation of the α-amino ester within the host requires some conformational adjustments and a partial reorganization of the ligand binding sites. This is reflected, for example, in the following structural features. The NH···O hydrogen bonds are far from linear, the nitrogen atom is in close contact with only three of the six ether oxygen atoms, and the naphthalene substituents on the interacting side of the ring are pushed away from each other. However, as in the former example, the PF_6 counterions appear to play no role in structuring the host–guest adduct. The complex crystallizes with 1 mol of chloroform solvent, and the charge separation in this structure is stabilized by delocalization of the negative charge in the relatively large anions as well as by their hydrogen bonding to chloroform. In spite of the fact that reliable structural data on the more stable diastereomer of this compound were not available, correlation of the crystallographic results with solution studies on chiral recognition led to some interesting interpretations. One striking example refers to a higher chiral recognition towards phenylglycine methyl ester observed when the bisdinaphthyl hexaether ligand was modified by introduction of two methyl groups in the 3-positions of one dinaphthyl unit (in Figure 12 this corresponds to $-CH_3$ substitutions on atoms $C_{(9)}$ and $C_{(46)}$ or $C_{(19)}$ and $C_{(36)}$)[100]. On the assumption that the overall structure of the corresponding compound is similar to that shown in Figure 12, the methyl substituents apparently increase the steric

hindrance between the host and the guest as well as between the naphthalene rings on the noninteracting side of the cavity. The stronger repulsive interactions thus contribute to further destabilization of the less stable diastereomer of the modified system. Opposite reasoning could be applied to account (in part) for the decrease of stereoselectivity in complexation of smaller amino esters by the bisdinaphthyl polyether hosts.

C. Inclusion Compounds of Noncyclic Polyethers

A synthesis of noncyclic crown-type polyethers containing quinoline functions attached to terminal oxygens has recently been reported by Vögtle and his coworkers[104,105]. The open-chain polyether compounds were found to exhibit strong complexing properties as the crown ethers, forming stoichiometric crystalline adducts with a variety of alkali, alkaline earth and ammonium salts. Figure 13 illustrates the structure of a 1 : 1 complex between the heptadentate 1,11-bis(8-quinolyloxy)-3,6,9-trioxaundecane species and RbI[106]. The crystallographic analysis showed that the Rb^+ ion strongly interacts with all seven donor heteroatoms at characteristic distances between 2.9 and 3.1 Å. The host species is wrapped around the cation in a conformation resembling one turn of a helix, the conformational details being quite similar with those observed in the macrocyclic ethers; i.e. *gauche* torsion angles about all C—C bonds that vary from 59° to 69° and *trans* torsion angles about all but one C—O bonds. The iodine ions are located in spaces between molecules of the complex. Observations from u.v. spectra indicate that the molecular conformation of the ligand itself changes considerably upon inclusion complex formation with a magnesium salt[104]. Reportedly, further work is now in progress to investigate the conformational properties of complexes with longer-chain hosts; such compounds may form helices with more than one turn.

In correlation, a few earlier studies of ethylene oxide oligomers showed that a polyethylene oxide chain adopts a helical structure in the crystalline state[107]. Approximately the same conformation was found to represent the lowest energy form of the polymer in solution where the compound is probably an equilibrium mixture of conformers. Moreover, oligomers of oxyethylene seem to have a specific property of interaction with some alkali and heavy metal salts and ions. A detailed XD structural study of molecular complexes of tetraethylene glycol di-

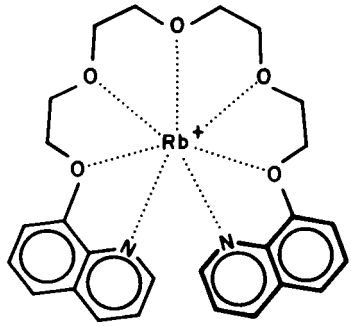

FIGURE 13. The complex of 1,11-bis(8-quinolyloxy)-3,6,9-trioxaundecane with RbI[106].

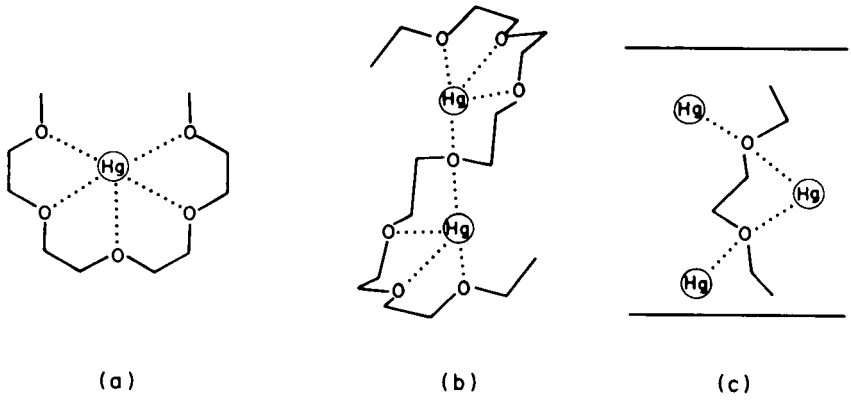

FIGURE 14. Modes of the interaction between the oxygen and mercury atoms in complexes of tetraethylene glycol dimethyl ether (a), hexaethylene glycol diethyl ether (b) and polyethylene oxide (c) with $HgCl_2$[108].

methyl and diethyl ethers and hexaethylene glycol diethyl ether with $HgCl_2$ and $CdCl_2$ have recently been carried out by Iwamoto and coworkers; less precise structural data are available for adducts between $HgCl_2$ and a polymer of oxyethylene[108,109]. In the complexes of tetraethylene glycol ethers with mercuric chloride the chain molecule exhibits a nearly circular conformation. The five ether oxygen atoms are nearly coplanar and turned inward to coordinate efficiently the mercury atom at distances between 2.8 and 3.0 Å. The larger ligand, hexaethylene glycol diethyl ether, was found to interact with two moles of $HgCl_2$. Three oxygens of either half of the molecule are coordinated with one mercury atom, the central oxygen being coordinated simultaneously to the two guest atoms. Interatomic distances between mercury and ligating oxygen are within 2.7–2.9 Å. Interestingly, the resulting molecular structure resembles a helix with two turns. The observed coordination modes between the oxygen and mercury atoms in the inclusion complexes are shown schematically in Figure 14[108]. The overall shape of the complex of tetraethylene glycol dimethyl ether and ionic $CdCl_2$ is different from that of covalent $HgCl_2$. The ligand is coordinated to two cadmium atoms and has an extended rather than a convergent conformation; the difference between the molecular conformations is probably due to the different coordination radii of Cd and Hg atoms. Relevant interaction distances are 2.4–2.5 Å for the Cd···O and 2.4–2.7 Å for the Cd···Cl contacts. The crystal structure consists of paired adduct entities that are linked to each other through Cl bridges[109].

In summary, the observed features of molecular conformation in the noncyclic oligomers are very consistent with the general characteristics of cyclic $(-CH_2CH_2O-)_n$ species reviewed in this article.

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Note Added in Proof

An interesting structural study on the 1 : 1 complex of monopyrido-18-crown-6 with *t*-butylammonium perchlorate has recently been published[110]. The host–guest association in this compound was found to be stabilized mainly by a tripod arrangement of hydrogen bonds between the alkylammonium ion and two oxygen atoms and the pyridine nitrogen atom in the crown ether ring. Interaction of the other three ether oxygen atoms with the ammonium nitrogen is less important. The results of the crystallographic study of cation complexes formed by long noncyclic polyethers have now appeared[111]. In the complex between 1,20-bis(8-quinolyloxy)-3,6,9,12,15,18-hexaoxaeicosane and RbI, the cation is spherically wrapped in the decadentate ligand with more than one turn. The 1 : 2 complex of 1,5-bis{2-[5-(2-nitrophenoxy)-3-oxapentyloxy]phenoxy}-3-oxapentane with KSCN has S-shaped arrangements, with one cation included in each S-loop of the polyether.

Crown Ethers and Analogs
Edited by Saul Patai and Zvi Rappoport

CHAPTER **7**

Structural chemistry of crown ethers

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I. INTRODUCTION

The first publication of the chapter on geometry and structural chemistry in 1980 (Chapter 6) provided only a preliminary survey of these aspects of crown chemistry. Since then the exciting field of host–guest chemistry continued to grow and flourish, syntheses of novel molecular receptors have become more complex, sophisticated and challenging and tens or even hundreds of original papers reporting new determinations have appeared. The impact made by these developments on natural sciences is enormous; it has formally been recognized by the award of the 1987 Nobel Prize in Chemistry jointly to C. J. Pedersen for his pioneering work on crown ethers in the late 1960s and to J.-M. Lehn and D. J. Cram for their fascinating contributions to host–guest chemistry in the last 15 years. A more extensive compilation of the published structural data has therefore become essential for a better characterization and understanding of the observed structure types and of the binding forces by which various host and guest constituents are held together in a structured way. This Appendix refers to selected groups of crown ether systems that have been published since 1980 (through 1987). The following discussion is based on results obtained from crystallographic investigations, at present still the most convenient source of detailed structural information on moderately complexed compounds. Several reviews concerning the structures of crown ethers have already appeared in the past[1–6].

II. CHARACTERISTIC MODES OF HOST–GUEST INTERACTION IN THE SOLID STATE

A. Guest binding with the 18-crown-6 ligand

The unsubstituted 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) ligand is undoubtedly the most extensively studied crown ether species. It readily forms complexes with a wide variety of substrates, and over 200 crystal structures containing 18-crown-6 have been reported so far. The conformation of this crown can best be described by a sequence of torsion angles within the successive $-OCH_2CH_2O-$ units of the ring, the symbols *a* and *g* being used for *anti* and *gauche* conformations about the respective bonds. Genuine corners and pseudocorners in the macroring are defined by the occurrence of $g^{\pm}g^{\pm}a$ and $g^{\pm}g^{\mp}a$ torsions, respectively; conformations most frequently encountered in crown ether macrocycles contain chiefly $ag^{\pm}a$ units[7].

The most accurate determination of the molecular structure of the free ligand was conducted at 100 K by Maverick *et al.*[8]. The overall conformation, characterized by the torsion sequence $aaa\,g^{+}g^{-}a\,ag^{+}a\,aaa\,g^{-}\,g^{+}a\,ag^{-}a$, was found to be essentially the same as that observed in a previous investigation at room temperature. Moreover, the mean C—O and C—C distances obtained from the accurate low-temperature study are 1.42 and 1.51 Å, respectively, both short compared with standard values, confirming the correctness of earlier observations (see Chapter 6) with regard to these unusual features of the molecular structure. Molecular mechanics studies of 18-crown-6 showed that in a low-dielectric environment the lowest energy conformation is of the same centrosymmetric symmetry type (C_i') as that found in the crystal structure of the uncomplexed ligand. This structure is characterized by a low internal electrostatic energy, mainly owing to weak repulsions between the unshared electron pairs of the oxygen atoms. In a more polar environment the centrosymmetric D_{3d} and the acentric C_1 structure types were shown to have similarly low energies[9]. The former is the most commonly observed form in crystals containing complexes of 18-crown-6 with both charged (e.g. metal and ammonium ions) and uncharged guest moieties. This structural mode of the crown consists of six equivalent conformational units with all torsion angles about the C—O bonds close to 180° and about the C—C bonds close to 70°; $ag^{+}a\,ag^{-}a\,ag^{+}a\,ag^{-}a\,ag^{+}a\,ag^{-}a$. The asymmetric C_1

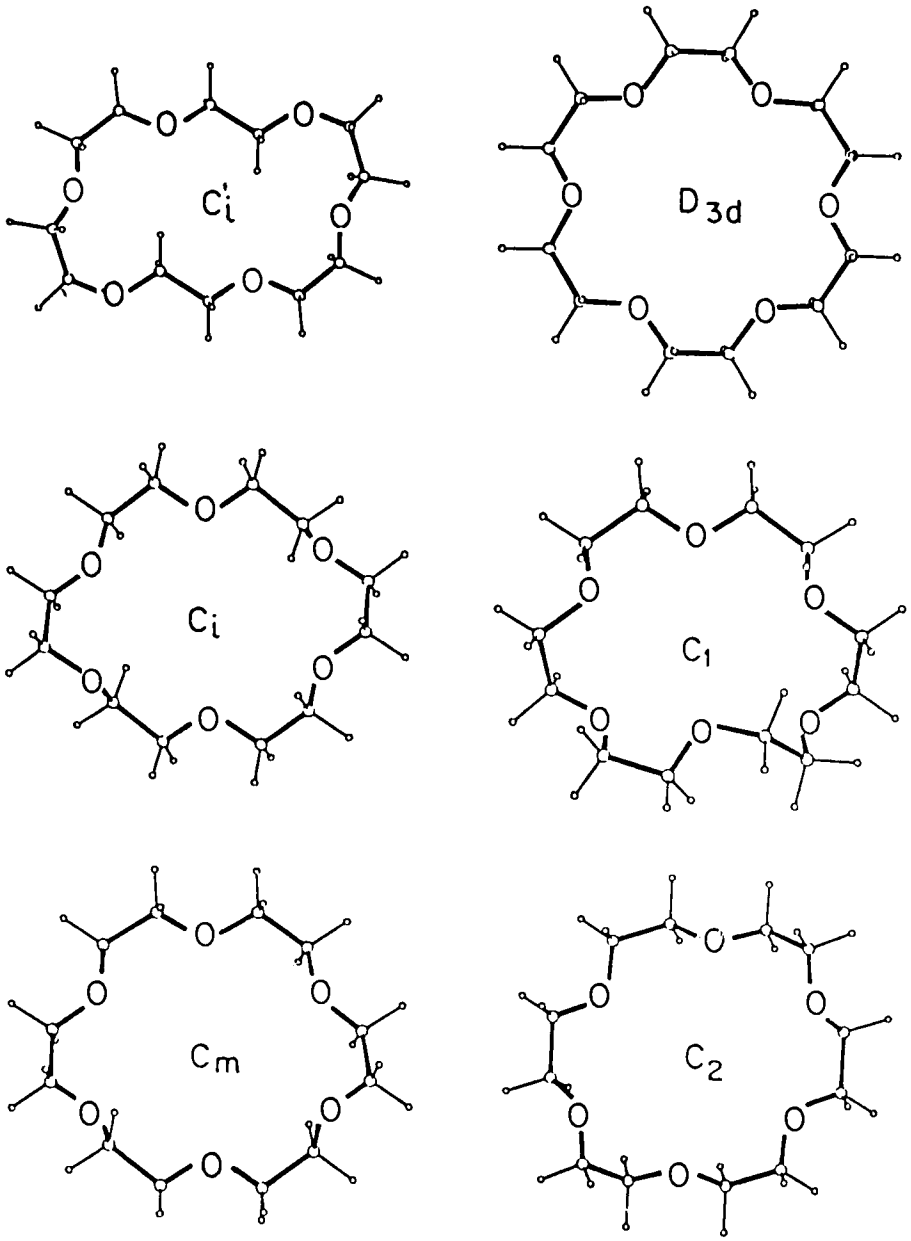


FIGURE 1. Illustration of the most common conformational modes adopted by the 18-crown-6 ligand in solid structures

structure is that observed in the 18-crown-6 complex with Na^+, where the torsion sequence can approximately be described by $ag^+a\ g^+g^+a\ ag^-a\ ag^+a\ ag^-g^-\ g^+g^+g^+$. Although internally more strained than the D_{3d} conformer, it allows more favourable $Na^+\cdots$crown interaction with the metal cation. Similarly strained but slightly less stable is another centrosymmetric conformation, C_i, found in a few crystal structures of various complexes[9]. This conformation consists of $ag^-a\ ag^-a\ g^-g^-a\ ag^+a\ ag^+a\ g^+g^+a$ units with two genuine corners positioned transannularly within the ring, and is termed 'biangular'. A few other conformational modes of the 18-crown-6 host were encountered in complexes with charged guests (see below); a detailed analysis of the conformational possibilities for crown ethers has been reported[10]. The most common conformations are illustrated in Figure 1.

1. Interaction with uncharged guest molecules

18-Crown-6 forms crystalline complexes with a variety of neutral guest molecules containing proton-donating sites such as acidic CH, NH or OH. These compounds are stabilized by dipole–dipole or hydrogen-bonding interactions of the guests with the ether oxygens of the crown, which compensate for the intramolecular electrostatic repulsions between lone-pair electrons of the oxygen. Almost invariably the stoichiometry of the host–guest interaction in these compounds involves one molecule of the hexaether and two coordinating units of the guest species. The latter lie in a perching position (above and below) with respect to the macroring, usually approaching the equivalent opposite sides of the crown in a symmetric manner. In general the overall stoichiometry of the complexes is 1:2 (host:guest) when the guest molecule contains only one donor group, the interacting constituents occupying general positions in the unit cell. A 1:1 composition becomes more favourable when the guest contains two well spaced (> 5 Å) donor functions which can bind simultaneously to two different crown units. The 1:1 complexes usually form polymeric chains in the crystal lattice, most systems possessing D_{3d} or C_i symmetry with a centre of inversion in the plane of the crown ether. Crystalline complexes with other host to guest ratios have also been characterized. However, with regard to the additional guest species the packing arrangement represents clathrate type structures rather than normal host–guest complexes. Table 1 lists the relevant crystal structures that have been reported in the literature.

The different modes of the complex formation are illustrated by the following examples, considering first guests which contain methyl and methylene coordinating entities. The dimethyl sulphone complex consists of isolated host–guest assemblies with a 1:2 stoichiometry[13]. The methyl carbons are 1.63 Å distant from the mean plane of the hexaether cavity, linking from both sides via C—H$\cdots$O interactions with alternate oxygen atoms of the crown. The 1:2 18-crown-6 complex with nitromethane is very similar, the N—CH_3 bonds being almost normally directed at the crown ether plane[11]. On the other hand, in the 1:1 dimethyl sulphate complex every guest is linked by its terminal methyl groups to two different molecules of 18-crown-6, thus forming in the crystal infinite chains of coordinated species[12]. In this structure only two hydrogens of each methyl group are involved in the C—H$\cdots$O bonds, the third hydrogen pointing away from the crown. Adiponitrile is also bifunctional. The crystal lattice of its 1:1 complex with 18-crown-6 is thus composed of polymeric chains of alternating crown ether and adiponitrile moieties[14]. The methylene groups, which are bound to and activated by the electron-withdrawing nitrile functions, have their positive poles oriented toward the ring oxygens, forming relatively short contacts (2.4–2.6 Å) with them. In the above examples the crown host adopts the open D_{3d} conformation with all its nucleophiles converging on the centred guest (Figure 2).

A similar association has been observed in the solid with guests containing amine-

TABLE 1. Molecular complexes of 18-crown-6 with neutral guests

Guest compound	Ref.	Host:guest ratio	Guest coordinating function	Host symmetry
Nitromethane	11	1:2	CH	D_{3d}
Dimethyl sulphate	12	1:1	CH	D_{3d}
Dimethyl sulphone	13	1:2	CH	D_{3d}
Adiponitrile	14	1:1	CH	D_{3d}
2,4-Dinitroaniline	15	1:2	NH	C_i
4-Nitro-1,2-diaminobenzene	16	1:2	NH	C_i
Phenyl carbamate	17	1:2	NH	D_{3d}
m-Nitroaniline	18	1:1	NH	D_{3d}
Formamide	19	1:2	NH	D_{3d}
Dithiooxamide	19	1:2	NH	C_i
N,*N*′-Diformhydrazide	20	1:2	NH	D_{3d}
2-(2-Benzimidazolyl)guanidine	21	1:2	NH	D_{3d}
2,4-Dinitrophenylhydrazine	22	1:2	NH	D_{3d}
p-Nitroaniline	23	1:2	NH	D_{3d}
Urea	24	1:5	NH	C_i
Thiourea	25	1:4	NH	C_i
Thiourea	26	1:2	NH	D_{3d}
Chlorophenylurea	27	1:2	NH	C_i
Methyl 4-aminobenzoate	14	1:4	NH	D_{3d}
Cyanamide	14	1:2	NH	D_{3d}
1-Chloroethylsulphonamide	14	1:2	NH	D_{3d}
N,*N*′-Dimethylthiourea	28	1:2	NH, CH	D_{3d}
N-Methylthiourea	19	1:1	NH, CH	D_{3d}, C_i
4,4′-Biphenyldiol·$2H_2O$	29	1:1	OH	D_{3d}
2,4-Dinitrophenol·H_2O	30	1:2	OH	D_{3d}
3-Nitrophenol·H_2O	19	1:2	OH	D_{3d}
p-Nitrobenzaldehyde oxime·H_2O	19	1:2	OH	D_{3d}
Cyanoacetic acid·H_2O	14	1:1	OH, CH	D_{3d}

coordinating entities. Suitable examples include complexes with guests such as cyanamide[14], 1-chloroethylsulphonamide[14], phenyl carbamate[17], formamide[19], 2,4-dinitrophenylhydrazine[22] and *p*-nitroaniline[23]. The corresponding crystal structures consist of isolated units of a 1:2 complex in which the two guest molecules approach from both sides of the ether moiety, each NH_2 group forming N—H···O hydrogen bonds with two or more nucleophilic sites of the ring. Although in several structures the host and guest components are held together by four hydrogen bonds (with H···O distances usually ranging from 2.0 to 2.4 Å), the remaining ring oxygens are also attracted to the polar guests by dipole–dipole interactions, thus preserving the D_{3d} symmetry of the crown. Association of all six ether oxygens acting as acceptors *via* bifurcated hydrogen bonds has also been observed[22]. In the complex of 18-crown-6 with *N*,*N*′-diformhydrazide, however, only one N—H···O binds the host to the guest[20]. In this structure host–guest and guest–guest bindings have comparable strength, leading to the formation of an infinite network of hydrogen-bonded molecules with only minor distortion of the D_{3d} conformation of the crown. Representative structures are shown in Figure 3.

The 'irregular' biangular conformation (C_i) of the 18-crown-6 framework observed previously in its 1:2 complex with benzenesulphonamide has recently also been found in other adducts with guests containing N—H proton donors. Suitable examples include the 1:2 complexes with 2,4-dinitroaniline[15] and 4-nitro-1,2-diaminobenzene[16]. The inter-

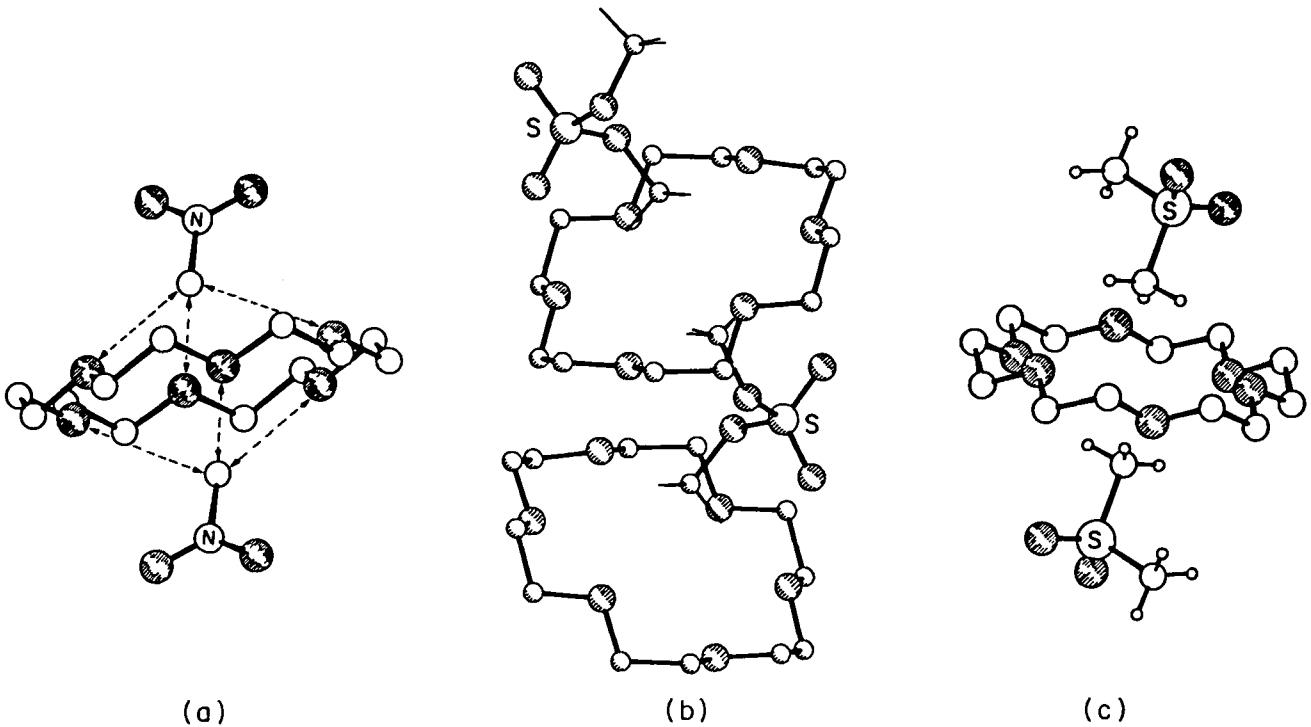


FIGURE 2. Complexes of 18-crown-6 with (a) nitromethane (1:2)[11], (b) dimethyl sulphate (1:1)[12] and (c) dimethyl sulphone (1:2)[13]

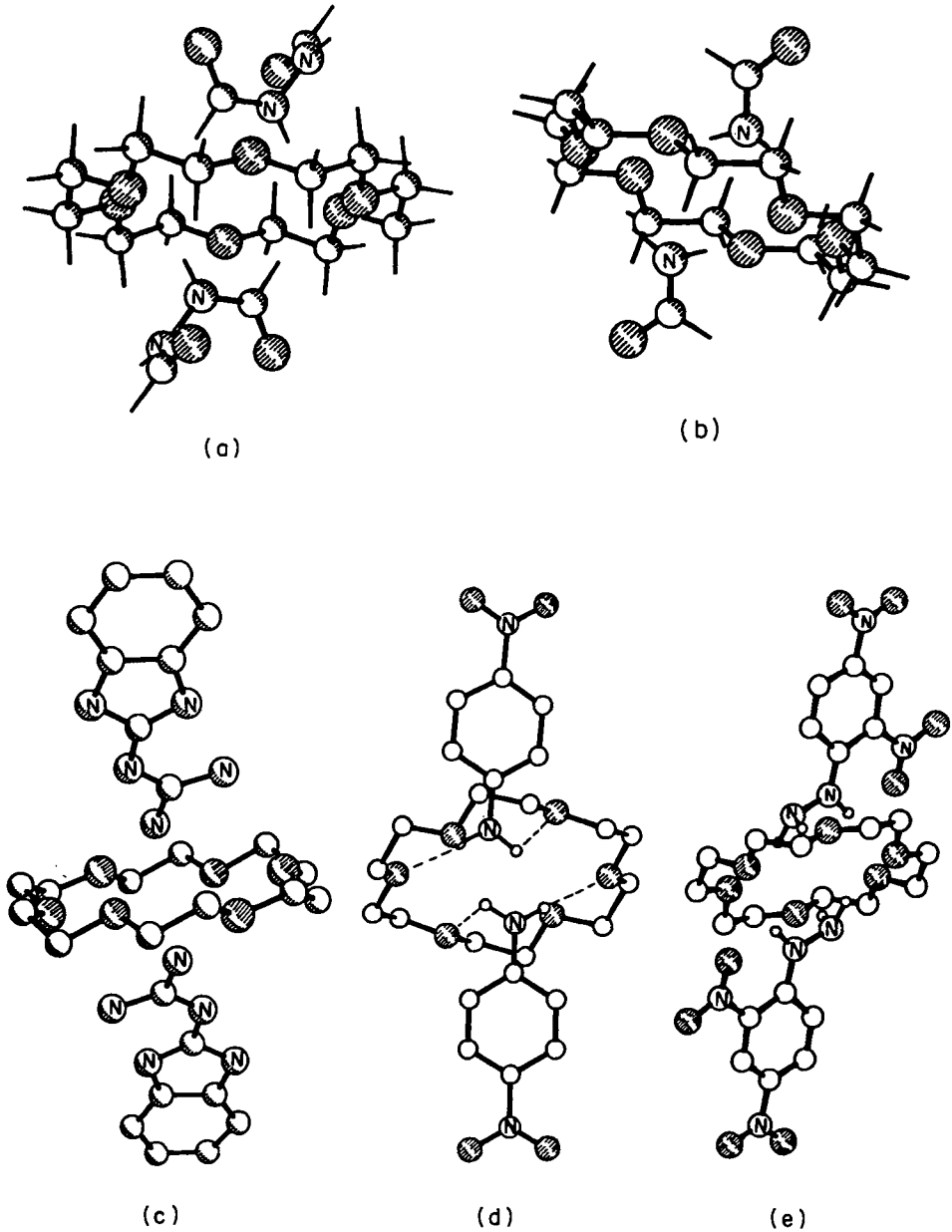
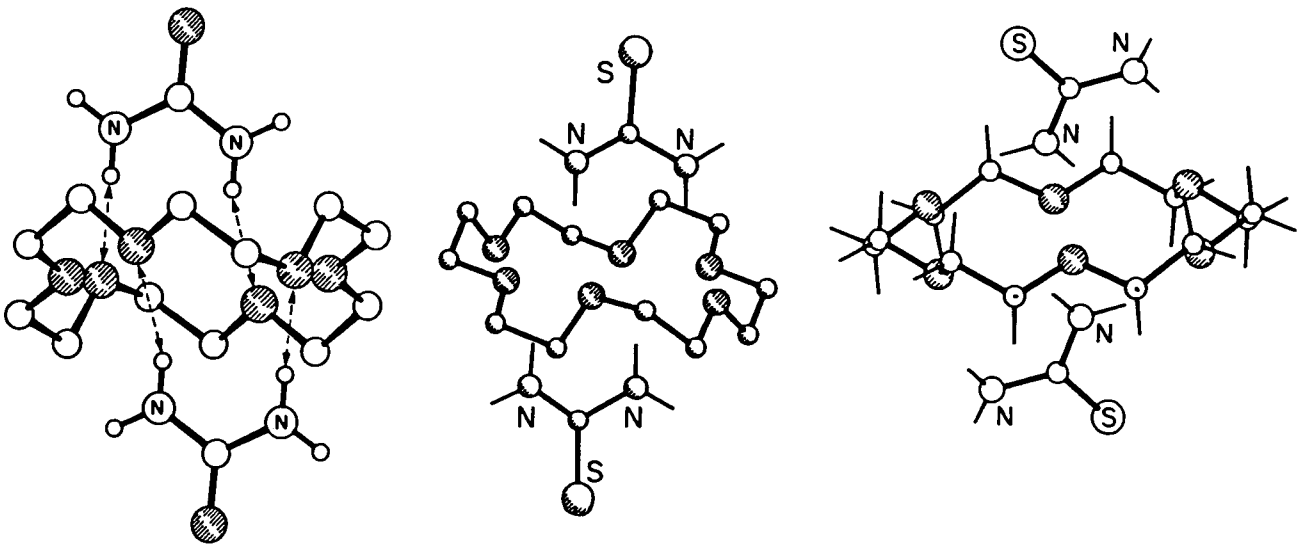


FIGURE 3. 1:2 Complexes of 18-crown-6 with (a) *N,N'*-diformhydrazide[20], (b) formamide[19], (c) 2-(2-benzimidazolyl)guanidine[21], (d) *p*-nitroaniline[23] and (e) 2,4-dinitrophenylhydrazine[22]

molecular hydrogen-bonding pattern in the former also contains apparently bifurcated N—H···O bridges. Similar elongated conformations of the crown occur in complexes with urea[24] and thiourea[25], which are characterized by a slightly different interaction scheme. These crystal structures consist of alternating layers of guest-18-crown-6 adducts and uncomplexed urea or thiourea molecules. While the overall stoichiometry is one molecule of the polyether and five molecules of urea[24] or four molecules of thiourea[25], the stoichiometry of the direct host-to-guest interaction remains 1:2 as in the previous examples. Each crown ether ring is linked *via* four N—H···O bonds to two urea/thiourea molecules which interact from opposite sides of the macrocycle, as shown in Figure 4. The crystal structures of these ternary complexes are stabilized by additional guest-to-guest hydrogen bonds which involve the remaining potential proton donors and proton acceptors. Interestingly, an 18-crown-6-thiourea complex of 1:2 stoichiometry has also been crystallized[26]. In this structure two thioureas are hydrogen bonded on either side of the 18-crown-6 molecule *via* three N—H···O interactions. The adducts are interconnected *via* N—H···S bonds to form a polymeric chain along one of the crystal axes. An approximate D_{3d} symmetry characterizes the polyether ring in this compound. Similar conformers of the crown have been observed in its complex with *N*, *N'*-dimethylthiourea where the two centrosymmetrically related guest molecules are linked to the host only through a single N—H···O hydrogen bond (H···O = 2.08 Å)[28]. The open conformation of the crown appears to be stabilized by additional C—H···O interactions which involve the methyl substituents. As in the previous complex with monosubstituted thiourea, the guest molecules of adjacent complexes are connected *via* N—H···S interactions (at H···S = 2.54 Å).

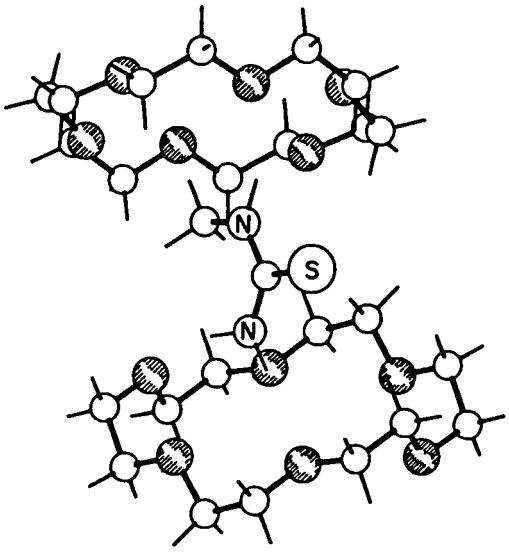
The above studies have indicated that there are several, energetically almost equal, ways to form intermolecular hydrogen bonds between the thiourea molecules. A similar argument may apply to the urea complexes, anticipating that it should also be possible to crystallize a 1:2 18-crown-6–urea complex. It is not surprising that guests with an extensive hydrogen-bonding capability will tend to form ternary complexes to maximize the number of hydrogen bonds in the structure. In fact, solution studies have shown that different stoichiometries in some of the host–guest complexes may occur, e.g. 1:1 and 1:2 for *p*-nitroaniline and 1:2 and 1:4 for methyl 4-aminobenzoate[14]. The actual composition of the compound which crystallizes is determined by several factors, including the reaction time, the temperature and the composition of the solution mixture.

In addition to the ternary complexes with urea and thiourea, several other complexes with different guest species also reveal unique conformational and binding patterns (Figure 5). The *N*-methylthiourea–18-crown-6 complex is characterized by a 1:1 stoichiometry, and forms a polymeric arrangement in the solid[19]. The amino group fits into the cavity of one ligand which adopts the C_i conformation, whereas the methyl group and the adjacent NH function perch on the cavity of second 18-crown-6 molecule, exhibiting a D_{3d} conformation. Each ligand is centrosymmetrically hydrogen bonded either to two NH_2 or to two pairs of CH_3 (only one hydrogen of the three interacts with the crown ring at CH···O = 2.6 Å) and NH (at NH···O = 2.1 Å) coordinating entities related by inversion. An unusual binding scheme is present in the 1:1:1 complex between 18-crown-6, cyanoacetic acid and water. In spite of the acidic hydrogen, the carboxyl group does not interact directly with the crown ether but rather binds to one face of the crown through an intermediate water molecule. The binding distances are OH(acid)···OH_2 = 1.80 Å and OH_2···O(ether) = 1.95 and 2.30 Å. A second molecule of cyanoacetic acid links to the other side of the crown ring *via* its CH_2 groups; the shortest CH···O = 2.5 Å. The presence of such a polyfunctional bonding pattern leads to a polymeric structure composed of a repeating sequence crown–water–cyanoacetic acid. The crown ether possesses approximate D_{3d} symmetry in spite of the asymmetric coordination from both sides. In fact, this structure provides a unique example in which the 18-crown-6 ligand coordinates two

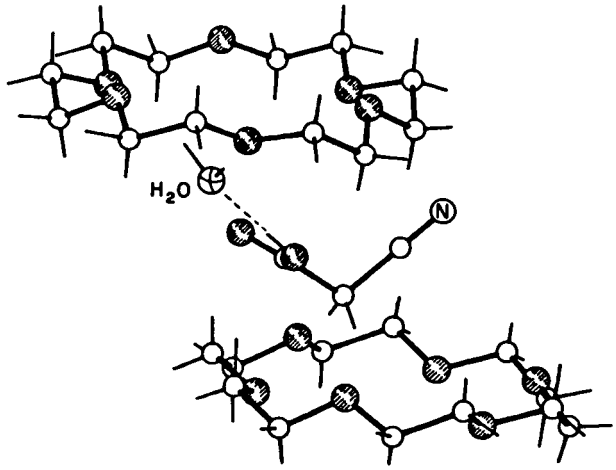


(a) (b) (c)

FIGURE 4. Host–guest interactions in 18-crown-6 complexes with (a) urea (1:5)[24], (b) thiourea (1:4)[25] and (c) thiourea (1:2)[26]. Guest species not bound directly to 18-crown-6 in the ternary complexes are omitted



(a)



(b)

FIGURE 5. Asymmetric binding of guests to 18-crown-6 in the 1:1 complexes with (a) *N*-methylthiourea[19] and (b) cyanoacetic acid hydrate[14]

different guest entities. Most of the other systems referred to above exhibit a symmetry of inversion in the plane of the crown ether.

The 1:2 18-crown-6–dithiooxamide complex also shows unique structural features[19]. In this structure the ligand, which occupies a centre of inversion in the crystal and adopts the strained biangular conformation, is bound to four different substrate molecules. All six ether oxygen atoms take part in the hydrogen bonding, four to one pair and two to another pair of centrosymmetrically related guest molecules. From the two NH_2 groups of the guest molecule only one acts as a bifunctional donor, the other being involved in only one hydrogen bond due to steric constraints. The overall hydrogen-bonding scheme in the crystal lattice is complicated as the four substrate molecules attached to one ligand serve also as bridges to four additional 18-crown-6 hosts.

Another structure of an unusual stoichiometry is that of the 1:4 18-crown-6–methyl 4-aminobenzoate complex[14]. Here, two ester molecules approach the centrosymmetric crown ligand from above and below and coordinate to it through $NH_2 \cdots O$ hydrogen bonds. The remaining two molecules of the ester are hydrogen bonded *via* one $N—H \cdots O{=}C$ bond to the crown-bound ones, resembling a ternary-type complex (see above). An unusual structural accommodation exists also in the 18-crown-6 complex with *m*-nitroaniline[18]. Although the overall stoichiometry of this compound is 1:1, the complexed host and guest species are in a 1:2 ratio. The guest molecules are disordered in the solid in such a manner that the NH_2 coordinating groups associate 38% of the time with one ether (while a second ether species remains uncomplexed) and 62% of the time with a second host (while the first one remains uncomplexed), always in 2:1 guest-NH_2–crown fashion. In spite of this peculiar arrangement all crown ether molecules adopt a D_{3d} conformation.

Guests containing monodentate acidic OH groups such as substituted phenols, dihydroxybenzenes and oximes do not associate directly with 18-crown-6. On the other hand, these hydrophilic molecules easily associate with water. The hydrated species have an increased proton-donating capability for binding to the crown ligands. The bonds formed by the water bridges are strong enough to affect the orientation of the bound substrate, but weak enough to be broken readily through changes of conformation or solvation. Several crystalline complexes with guest species having OH_2 as coordinating element have been analysed, showing the characteristic 1:2 host-to-guest coordination (Figure 6). For example, in the complex of 18-crown-6 with 4,4′-biphenyldiol dihydrate the two water molecules are each hydrogen bonded to two oxygen atoms of the crown ring located on a crystallographic centre of symmetry. The bifunctional planar guest molecules also occupy centres of symmetry, being hydrogen bonded to the water molecules. Correspondingly, every guest bridges between two crown ethers *via* hydrogen bonds to water molecules[29]. Similar guest–water–host interaction schemes were observed in the 1:2 complexes of 18-crown-6 with the hydrates of the monodentate guests 2,4-dinitrophenol[30], 3-nitrophenol[19] and *p*-nitrobenzaldehyde oxime[19]. The $OH(guest) \cdots OH_2$ interactions are usually at about 1.7 Å and those of $OH_2 \cdots O(ether)$ at about 1.9–2.0 Å. In all these examples the 18-crown-6 host has an approximate D_{3d} symmetry, with two water molecules (one from above and one from below) acting as hydrogen-bond donors to crown ether oxygen atoms. There are discrete units of the ternary complex in the crystal lattice.

A very small number of structures that exhibit an exclusive inclusion of neutral water molecules within a crown ether macrocycle are known (Figure 7). The first example involves a 1:1 water adduct of the 3,3′-(1,1′-bi-2-naphthol)-21-crown-5. In this complex the water molecule is too small to fit into the ligand cavity, and occupies only a part of it[31]. The guest moiety is slightly displaced from the mean plane of the oxygen ligating atoms. Two relatively weak hydrogen bonds with the water hydrogens donated to two ether oxygens ($O \cdots O = 2.95$ Å) and a stronger hydrogen bond from one of the acidic phenolic

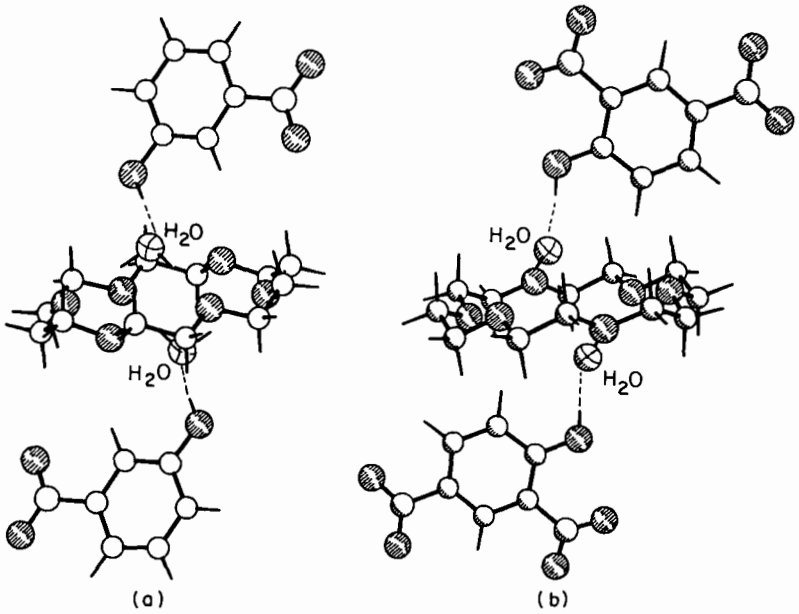


FIGURE 6. 1:2 Complexes of 18-crown-6 with (a) 3-nitrophenol hydrate[19] and (b) 2,4-dinitrophenol hydrate[30]

groups to the water oxygen (O···O = 2.69 Å) provide the main interactions. Other, structurally analysed, complexes with water involve a polyethereal bis-lactone 18-membered macrocycle[32], a larger tetraethylene glycol (bis-2-pyridyl) ketone ligand[33] and a smaller *sym*-hydroxydibenzo-14-crown-4 host[34]. In the two larger ligands, water molecules interact weakly with the surrounding oxygen nucleophiles; stronger host–guest interactions characterize the smaller 14-crown-4 ligand owing to the presence of the hydroxy substituents.

2. *Coordination of metal–ligand assemblies*

Several crystalline adducts between 18-crown-6 and neutral ligands coordinated to transition metals or cations have been reported. A detailed discussion and illustration of such systems, usually referred to as 'second-sphere' complexes, is given by Prof. E. Weber in Chapter 5. However, it is important to emphasize here that the second-sphere association of the crown with the metal–ligand assemblies is determined by patterns of interaction essentially identical with those previously characterized in complexes with smaller organic substrates. Selected adducts of this type, listed in Table 2, are illustrated in Figure 8.

In the crystal structure of the 1:2 complex between 18-crown-6 and [*trans*-$Ir(CO)(CH_3CN)(PPh_3)_2](PF_6)_2$, the interaction of the two iridium-bound acetonitrile moieties with the crown ring is through the acidic methyl group C—H bonds[35]. The methyls approach the crown ring from both sides (at 3.24–3.38 Å), being interrelated by inversion at the centre of the ring. The distance between the two perching methyl carbons across the cavity is 3.93 Å. The 1:2 complex with *trans*-$PtCl_2(P(CH_3)_3)NH_3$ contains an ammine ligand as the coordinating entity[36]. One molecule of the platinum ammine is

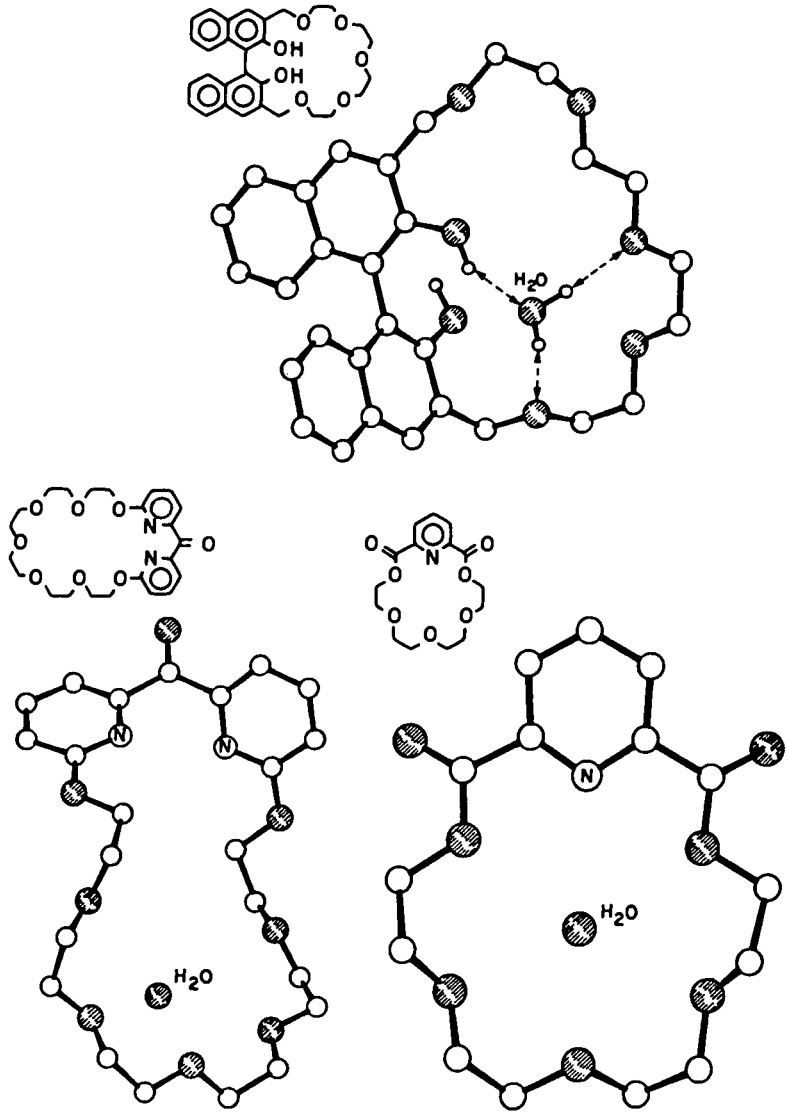


FIGURE 7. Water inclusion by various crown ether macrocycles[31-33]

bound to each face of the open crown ether (D_{3d}), all six ether oxygen atoms being involved in hydrogen bonds with the two NH_3 ligands (at N···O distances from 3.04 to 3.31 Å). A similar 1:2 interaction has been observed between the 18-crown-6 and a close derivative of the platinum complex, *cis*-$PtCl_2(NH_3)_2$[37]. As before, the platinum–ammine ligands approach opposite sides of the macrocycle, and are bound *via* N—H···O bonds (at N···O distances within the range 3.06–3.17 Å) to the ring oxygens. The axially oriented ammines

TABLE 2. Complexes of 18-crown-6 with metal–ligand assemblies

Guest compound	Ref.	Host:guest ratio	Guest coordinating function
trans-$Ir(CO)(CH_3CN)(PPh_3)_2 \cdot (PF_6)_2$	35	1:2	CH
trans-$PtCl_2(P(CH_3)_3)NH_3$	36	1:2	NH
cis-$PtCl_2(NH_3)_2$	37	1:2	NH
$Cu(NH_3)_4H_2O \cdot (PF_6)_2$	38	1:1	NH
$Pt(NH_2CH_2CH_2NH_2)_2 \cdot (PF_6)_2$	39	1:1	NH
$Co(CoCl_4) \cdot 6H_2O$	40	1:1	OH
$Mn(ClO_4)_2 \cdot 6H_2O$	41	1:1	OH
$Mn(NO_3)_2 \cdot 6H_2O$	42	1:1	OH
$Gd(NO_3)_3 \cdot 3H_2O$	43	1:1	OH
$SnCl_4 \cdot 3H_2O$	44	1:1	OH
$SnCl_2(CH_3)_2 \cdot 2H_2O$	45	1:2	OH
$Sn(NSC)_2(CH_3)_2 \cdot 2H_2O$	46	1:1	OH
$MoO(O_2)_2 \cdot 3H_2O$	47	1:1	OH
$Ni_2Cl_4 \cdot 8H_2O$	48	1:1	OH
$UO_2(NO_3)_2 \cdot 2H_2O$	49	1:1	OH
$UO_2(NO_3)_2 \cdot 4H_2O$	50	1:1	OH

form a three-point perching arrangement, and there are additional hydrogen bonds between the equatorially located ammines and the macrocycle. This structure contains dimethylacetamide as solvent of crystallization, which is also involved in the overall hydrogen bonding pattern stabilizing the crystal lattice.

The coordination complex $[Cu(NH_3)_4H_2O](PF_6)_2$ forms a 1:1 adduct with 18-crown-6[38]. The crown is located on a centre of inversion and interacts simultaneously *via* hydrogen bonding with two alternate $[Cu(NH_3)_4H_2O]^{2+}$ ions related by this symmetry. Each cation is in turn located between two adjacent crown moieties, thus forming a nearly linear hydrogen-bonded polymeric chain. Of the four ammine ligands, two lie close to and interact directly with the adjacent crowns, effecting two tripods of hydrogen bonds. The other ammine functions donate one proton to each one of the rings. The H_2O ligand is not involved in hydrogen bonds in this structure. The through-ring N···N distance between the interacting axially oriented ammines is 3.37 Å, compared with 3.22 Å in the Cisplatin adduct and 3.48 Å in the second platinum derivative. A 1:1 polymeric adduct has also been observed between 18-crown-6 and the $Pt(en)_2(PF_6)_2$ salt[39]. The dication and the crown rings alternate within the chains, each amine group donating one proton to hydrogen bond an ether oxygen atom and the other proton to hydrogen bond the PF_6^- counter ion. As in the preceding examples, the crown ligand adopts an approximate D_{3d} symmetry in spite of its involvement in a relatively poor hydrogen-bonding scheme; the molecular conformation is probably affected by weaker secondary interactions with the enamine ligands.

Analogous to water-containing complexes of hydroxybenzene derivatives with 18-crown-6, coordination of the crown moiety to *aquo* complexes of metals and metal cations has also been observed. In these structures the metal species are not directly associated with or located within the crown ring. Instead, the corresponding crystals could best be described as consisting of separate 18-crown-6 and metal-complex entities connected by hydrogen bonds through the ligands. The latter were usually neutral water molecules with enhanced dipoles and acidity; the coordination of water molecules to the metal makes their hydrogen atoms sufficiently acidic to facilitate hydrogen bonding to the

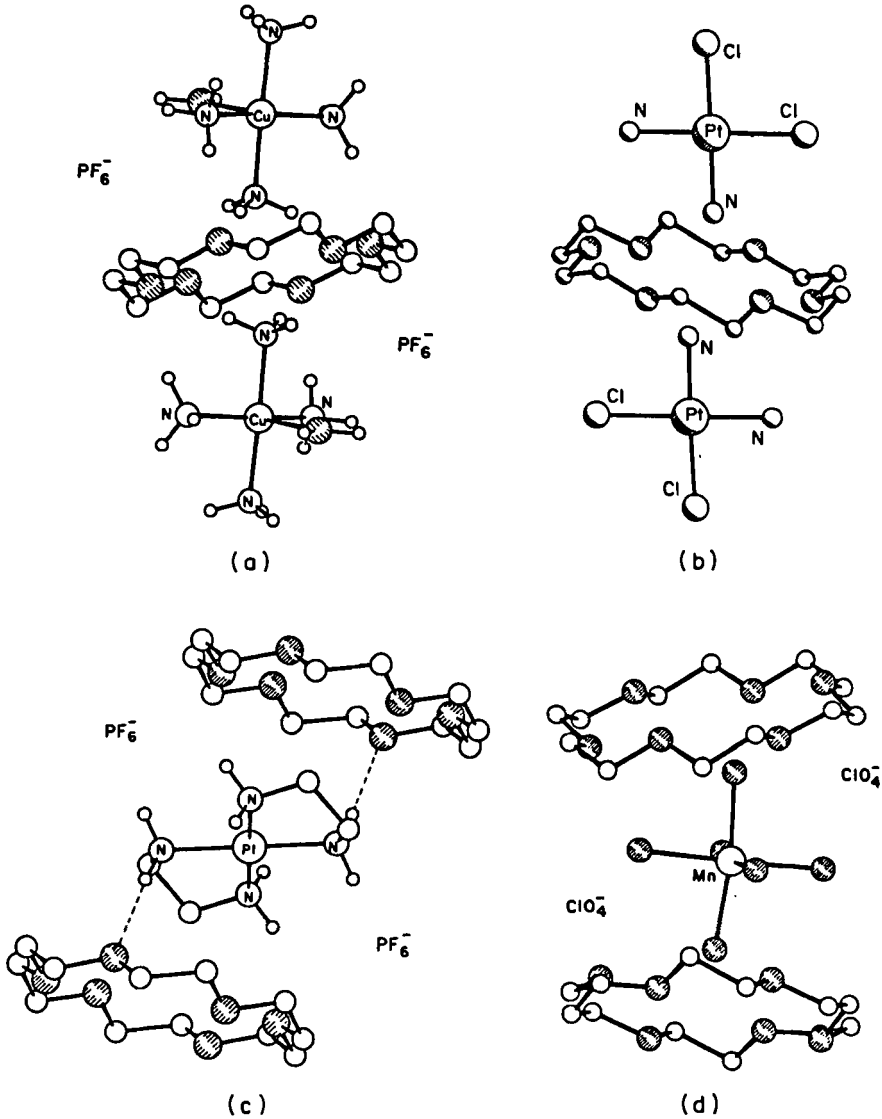


FIGURE 8. Complexes of 18-crown-6 with (a) $Cu(NH_3)_4H_2O\cdot(PF_6)_2$ (1:1)[38], (b) *cis*-$PtCl_2(NH_3)_2$ (1:2)[37], (c) $Pt(en)_2\cdot(PF_6)_2$ (1:1)[39] and (d) $Mn(H_2O)_6\cdot(ClO_4)_2$ (1:1)[41]

crown. Selected examples include coordination of 18-crown-6 (from both sides of the ring) to complexes of transition and other metals such as Co^{II}, Ni^{II}, Mn^{II}, Gd^{III}, Sn^{IV}, Mo^{VI} and U^{VI} (Table 2). With one exception, the stoichiometric ratios are 1:1, the corresponding compounds exhibiting polymeric arrangements in the solid. Considering only the close surrounding of the polyether macrocycle, the above examples provide additional structural evidence for a direct association between the 18-crown-6 host and water guest

(no stable binary complexes of the two species have been isolated). In a few cases, however, the presence of the heavy atoms prevented the presentation of highly precise geometric parameters relating to the intermolecular interaction (and also to the host conformation). In other (e.g. Refs 45 and 47) the crown–water interaction could be well characterized to reveal an effective bonding.

3. *Adducts with charged guests*

Interaction with guests containing charged (or partially charged) coordinating entities adds significant electrostatic factor to the structure. Generally, crown ethers form more stable complexes with cations than with neutral moieties, owing to the electronegative potential in the cavity of the macrocycle[14]. On the other hand, a simultaneous approach of two cations (large with respect to the size of the cavity) from opposite sides of the 18-crown-6 would involve strong electrostatic repulsions unfavourable to the structure. Nevertheless, the 1:2 stoichiometric relationship at the interaction site was found in several crystalline compounds in which the coordinating group of the substrate is only partially charged owing to charge delocalization over the entire host species (Table 3, Figures 9 and 10).

For example, methyltriphenylphosphonium hexafluorophosphate forms a characteristic 2:1 complex with 18-crown-6 which has a very high crystallographic symmetry[51]. The two $[Ph_3PMe]^+$ ions approach the open crown ether (D_{3d}) from opposite sides along a common threefold axis coincident with the P—Me···(crown)···Me′—P′ directions. The two methyl groups, the acidity of their protons being enhanced by the positive charges, perch on the cavity. All methyl hydrogen atoms are involved in discrete hydrogen bonds

TABLE 3. Molecular complexes of 18-crown-6 with charged guests

Guest compound	Ref.	Host:guest ratio	Guest coordinating function	Host symmetry
$Ph_3PCH_3 \cdot PF_6$	51	1:2	CH	D_{3d}
$PhCOCHPhS(CH_3)_2 \cdot PF_6$	52	1:2	CH	D_{3d}
$PhCOCH_2S(CH_3)_2 \cdot PF_6$	52	1:1	CH	D_{3d}
Guanidinium nitrate	53	1:2	NH	C_i
Uronium *p*-toluenesulphonate	54	1:2	NH	D_{3d}
S-*t*-Butylthiouronium·ClO_4	55	1:2	NH	D_{3d}
Uronium nitrate	56	1:1	NH	C_2
Uronium picrate	57	1:1	NH	C_2
Amminetrifluoroboron	58	1:1	NH	D_{3d}
Amminetrihydroboron	58	1:1	NH	D_{3d}
Benzylammonium thiocyanate	61	1:1	NH	D_{3d}
Methylammonium perchlorate	62	1:1	NH	D_{3d}
Phenylacylammonium·PF_6	63	1:1	NH	D_{3d}
Hydroxylammonium perchlorate	62	1:1	NH	D_{3d}
Hydrazinium perchlorate	62	1:1	NH	D_{3d}
Toluenediazonium·BF_4	64	1:1	N≡N	D_{3d}
Phenyldiazonium·PF_6	64	1:1	N≡N	D_{3d}
Hydronium perchlorate	67	1:1	OH	—[a]
Hydronium chloride	68	1:1	OH	—[b]

[a]Complex with dicyclohexano-18-crown-6.
[b]Complex with 18-crown-6-tetracarboxylic acid.

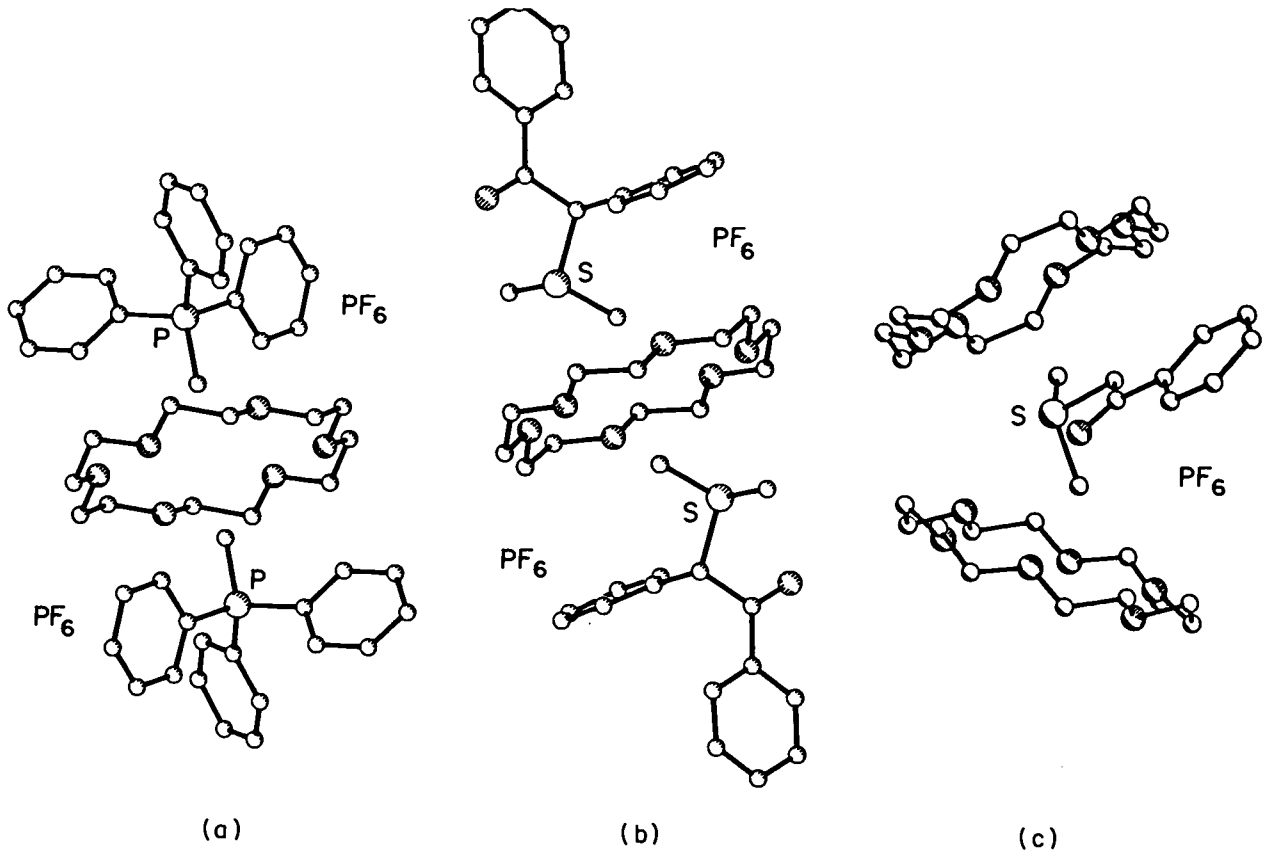


FIGURE 9. Complexes of 18-crown-6 with hexafluorophosphate salts of (a) triphenylphosphonium (1:2)[51], (b) (α-benzoyl)benzyldimethylsulphonium (1:2) and (c) benzyldimethylsulphonium (1:1)[52]

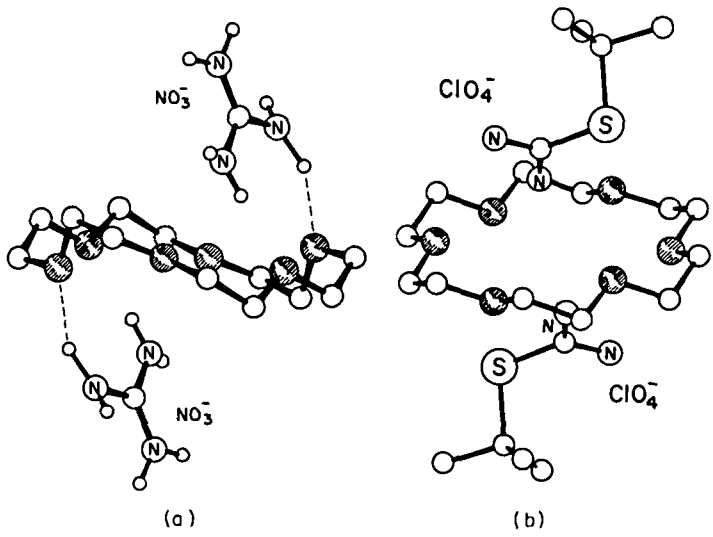


FIGURE 10. 1:2 Complexes of 18-crown-6 with (a) guanidinium nitrate[53] and (b) *S*-*t*-butylthiouronium perchlorate[55]

to single ether oxygens. It appears that owing to the electrostatic repulsion between the two interacting methyls, the C—H···O distances are exceptionally long (C···O = 3.60, H···O = 2.7 Å). The α-CH groups in alkylsulphonium cations, like those in alkylphosphonium cations, are sufficiently acidic to form strong complexes with 18-crown-6. Correspondingly, crown ether complexes with the hexafluorophosphate salts of benzyldimethylsulphonium and α-benzoylbenzyldimethylsulphonium cations have been characterized[52]. The former exists as a polymeric 1:1 structure in which every cation is sandwiched between two 18-crown-6 rings. The host molecules are located on crystallographic centres of inversion and provide a direct facial relationship to the cations. The latter forms a discrete 2:1 complex with the crown, very similar to that found with the phosphonium salt. In this structure all four methyls are directed toward the centrosymmetric ring. Two axially oriented methyls approach toward the ring centre, the other two methyls binding to the side of the crown. The methyl···O(ether) contacts are relatively long (the H···O distances are within the range 2.5–2.7 Å), as in the preceding example.

A 1:2 complex was obtained also between 18-crown-6 and guanidinium nitrate[53]. The guanidinium ion has three equivalent canonical forms, and its positive charge is thus equally distributed between the three NH_2 groups. It is noteworthy that solution experiments indicated only a 1:1 interaction ratio between host and guest. The complexation of 18-crown-6 with uronium *p*-toluenesulphonate led also to the formation of a 1:2 crystalline adduct[54]. Only one NH_2 group per uronium ion is hydrogen bonded to the crown (the relevant N···O distances are within the range 2.9–3.0 Å). The other amino groups are bound to the counter ions, an interaction that plays an important role in reducing electrostatic repulsions between the two cations attached to opposite faces of a single crown ring. The 1:2 complex of 18-crown-6 with *S*-*t*-butylthiouronium perchlorate shows the same characteristics of the complexation[55]. In both structures the macroring adopts the open D_{3d} conformation.

Other uronium and thiouronium salts were found to complex only one side of the crown host. For example, in the 1:1 complex between 18-crown-6 and uronium nitrate there is a perching structural relationship between host and guest, the planar uronium ion lying almost perpendicular to the mean plane of the crown ether[56]. Three amine hydrogens are hydrogen bonded to two neighbouring oxygen atoms on the upper side of the ring and to one oxygen on the lower side of it. In order to optimize the bonding interactions, the conformation adopted by the crown is unusual, consisting of two sets of $ag^+ a\,ag^- a\,ag^+ g^+$ units (C_2 symmetry). Consequently, the two faces of the macroring seem to have different complexing properties, which prevents an effective association with another guest species. A very similar structural pattern characterizes the 1:1 adduct with uronium picrate[57]. Two additional 1:1 crystalline complexes of 18-crown-6 with *O*-*n*-butyluronium picrate and *S*-*t*-butylthiouronium perchlorate have been reported (complexes of the latter with both 1:1 and 1:2 host:guest ratios were obtained from solution mixtures with different concentrations of the components)[57]. However, these structures turned out to be disordered, and neither the host–guest interaction pattern nor the conformational features could be defined precisely.

In neutral complexes of ammonia with electron-deficient compounds such as trifluoroboron and trihydroboron a formal positive charge is associated with the nitrogen atoms. The BH_3NH_3 substrate is isoelectronic with the ionic methylammonium ion, $CH_3NH_3^+$,

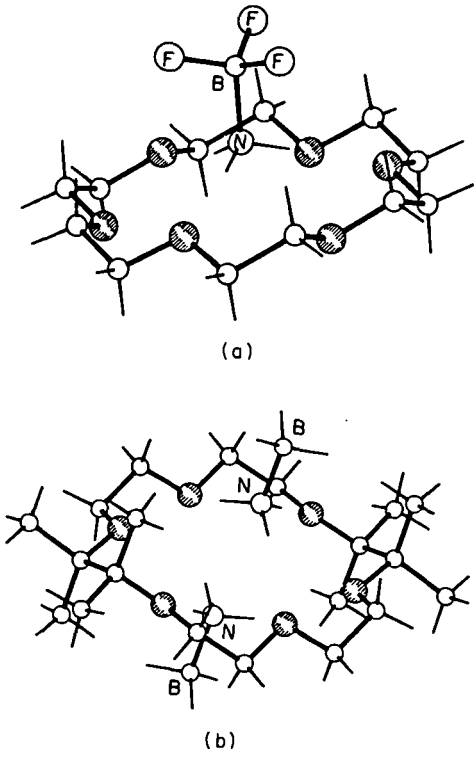


FIGURE 11. (a) 1:1 Complex of 18-crown-6 with BF_3NH_3[58] and (b) 1:2 complex of octamethyl-18-crown-6 with BH_3NH_3[60]

which forms a 1:1 complex with 18-crown-6 (see below). However, in the neutral molecule only a partial charge is localized on the ammine function. Nevertheless, the corresponding borane–ammines were found to form also 1:1 complexes with 18-crown-6 (Figure 11)[58]. Although in the two structures the crown exhibits the common D_{3d} symmetric conformation, the intermolecular N—H···O hydrogen bonding interaction between the host and the guest moieties occurs only on one face of the macrocyclic polyether, involving the ammine centre and the upper triangle of the ether oxygen atoms. The empty spaces in the corresponding crystal lattices are occupied by dichloromethane and methanol solvents, respectively. Presumably, cation repulsion prevents the arrangement of two BX_3NH_3 molecules on opposite faces of the crown. As in the uronium guest, where the entity coordinating to the crown is only partially charged owing to electron delocalization, the boron–ammine guests represent a borderline case. While crystallizing as a 1:1 adduct with 18-crown-6, its complexes with the octamethyl and tetraphenyl derivatives of this ligand are characterized by a 2:1 stoichiometry. In agreement with previous observations, in the latter compounds the two guest molecules are hydrogen bonded in a centrosymmetric manner to the opposite faces of the macrocycle which adopts a typical D_{3d} conformation[59,60].

In all other observed structures involving ammonium guests and the crown host (the positive charge is localized mostly on the NH_3 group anchored to the crown), the stoichiometric ratio of association is 1:1, the ammonium nitrogen is displaced between 0.11 and 1.00 Å (in the complex with ammonium bromide referred to in Chapter 6) from the mean plane of the D_{3d} conformer of the macrocycle (Figure 12).

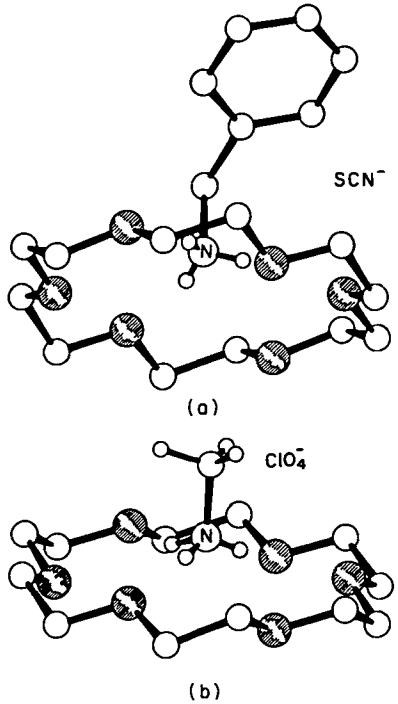


FIGURE 12. 1:1 Complexes of 18-crown-6 with (a) benzylammonium thiocyanate[61] and (b) methylammonium perchlorate[62]

Suitable examples include the structure of the 1:1 complex of 18-crown-6 with benzylammonium thiocyanate, which is stabilized by three linear hydrogen bonds from the ammonium cation to the upper triangle of the ether oxygens (N···O = 2.8–2.9 Å)[61]. The other three oxygen nucleophiles are within a close range of 2.9–3.0 Å from the ammonium nitrogen, indicating a strong dipolar attraction. The nitrogen atom in this structure is displaced only 0.86 Å from the median plane of the crown ring. Replacement of the benzyl moiety by a methyl group has a negligible effect on the structure, and the 1:1 18-crown-6 complex with methylammonium ions reveals nearly identical structural parameters relevant to the host–guest interaction[62]. Another example of an almost identical interaction scheme involves the complex with phenylacylammonium hexafluorophosphate[63]. This crystal structure shows again a face-to-face type adduct, the carbonyl oxygen atom of the guest having no effect on the intermolecular hydrogen bonding pattern. These observations confirm previous findings that the ammonium guest is generally bound to the crown ligand by two different types of interaction: hydrogen bonding to a triangle of alternate oxygen atoms located on one face of the crown, and dipole–dipole attractions involving oxygens positioned on the opposite side of the ring (Figure 13).

The perching type of binding can be modified by the introduction of small proton donating functions α to the ammonium cation. This is clearly exhibited by the 1:1 complexes of 18-crown-6 with hydrazinium perchlorate and hydroxylammonium perchlorate[62]. In the latter the ammonium nitrogen lies only 0.68 Å from the mean plane of the ligand oxygens, and the previously observed tripod arrangement of the hydrogen

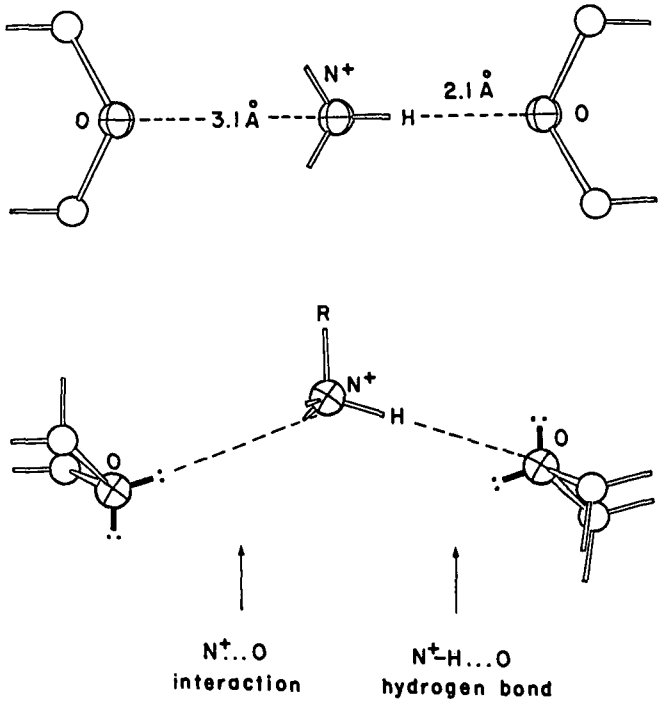


FIGURE 13. Schematic illustration of the geometry of interaction between 18-crown-6 and a perching ammonium ion

bonds is significantly distorted (the crown is slightly disordered and the NH_3^+ group is involved in bifurcated interactions). Additional water molecules are present in the crystal lattice of this compound, hydrogen bonding simultaneously to the hydroxyl groups and the counter ions. The hydrazinium cation can donate five protons to the crown ligand. In order to form the maximum number of hydrogen bonds, the ammonium nitrogen atom penetrates more deeply into the centre of the crown, lying only 0.11 Å from the median plane of the six ether oxygens. The ammonium moiety binds effectively to the lower triangle of the oxygen atoms (N···O = 2.8–2.9 Å), while the NH_2 group forms hydrogen bonds with two oxygens in the upper part of the crown (N···O = 3.05 Å). Undoubtedly, the driving force for the increased depth of penetration of the ammonium into the 18-crown-6 cavity (forming an essentially nesting arrangement) is provided by the additional hydrogen bonding interactions between the host and guest species (see Figure 14, and additional examples below).

Crystalline complexes of 18-crown-6 with diazonium salts have also been reported. Structural investigation of the 1:1 complexes with phenyldiazonium hexafluorophosphate and toluenediazonium tetrafluoroborate showed that the $-N\equiv N^+$ entity, its cylindrical diameter estimated to about 2.4 Å, is fully inserted into the host cavity[64]. This complexation is very sensitive to both electronic factors and to steric effects due to aromatic substitution[65]. For example, the replacement of a benzenediazonium ion by one methyl group in the *ortho* position prevents any effective complexation with the crown ligand. Moreover, the stability of the potential host–guest complex is severely reduced when the positive charge is delocalized into the aromatic ring away from the diazonium group. A very similar inserted-type structure has been reported for the 1:1 complex between 21-crown-7 and *p*-methoxybenzenediazonium tetrafluoroborate (Figure 15)[66].

Although several reports indicated that 18-crown-6 readily complexes hydronium (H_3O^+) ions in acidic aqueous solutions, no crystalline complex has yet been isolated.

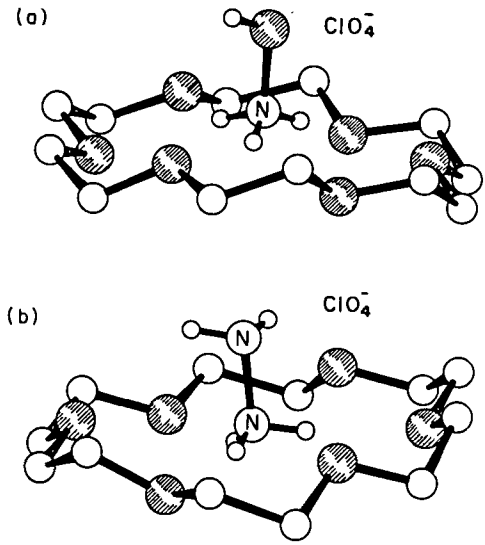


FIGURE 14. 1:1 Complexes of 18-crown-6 with the perchlorate salts of (a) hydroxylammonium and (b) hydrazinium[62]

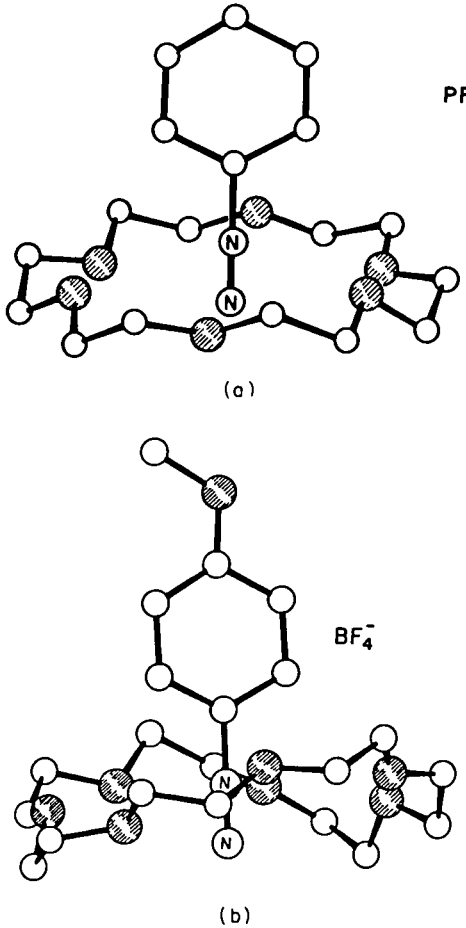
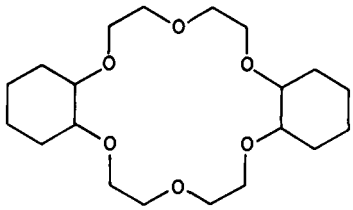
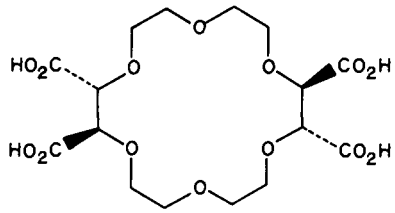


FIGURE 15. 1:1 Complexes of (a) 18-crown-6 with phenyldiazonium·PF_6[64] and (b) 21-crown-7 with *p*-methoxybenzenediazonium·BF_4[66]

However, the characterization of the hydronium–crown ether interactions has become feasible in closely related compounds. Thus, in the 1:1 complex between hydronium perchlorate and dicyclohexano-18-crown-6 (**1**) the hydronium cation is centred above the polyether cavity in a pseudo-perching position, forming a tripod arrangement of the hydrogen bonds to three of the ether oxygens (the corresponding H···O distances cluster around 1.7 Å)[67]. The guest ion is characterized by a pyramidal geometry. The cyclohexyl rings extend a lipophilic envelope around the complexed hydronium cation, preventing direct contact between the positive and the negative ions in the crystal. The second example relates to the inclusion compound formed by 18-crown-6-tetracarboxylic acid (**2**) with hydronium chloride[68]. When the four carboxylic groups are attached to a single 18-crown-6 ring, the affinity of the ligand for cationic guests is increased by several orders of magnitude. Because of the apparently smaller size of the hydronium ion, it was found



(1)



(2)

to penetrate deeper into the centre of the crown ring than the ammonium ion in related compounds (e.g. ammonium bromide). The mean distance of the guest oxygen from the plane of the ligating oxygens is 0.61 Å. The structure is stabilized by three O—H···O bonds to the 'lower' oxygens at about 2.7 Å, and three ion–dipole interactions to the 'upper' oxygens at ca 2.8 Å, from the central pyramidal guest to the ligand. In this respect there is a significant resemblance between this interaction pattern and that found in the 18-crown-6 complex with a hydrazinium cation (see above). The four neutral carboxylic substituents extend above and below the pseudo-planar macroring. Neither these groups nor the chloride counter ions interact directly with the central guest moiety; the latter is fully lipophilized by the ether-oxygen nucleophiles (Figure 16).

The reactive tetracarboxy-macrocyclic receptor was used also to form a 1:1 complex with diethylamine. The complexation is associated with a transfer of two protons from the acid residues to the diamine guest. In the resulting structure the dication extends roughly perpendicular to the crown ring and parallel to the pseudoaxial substituents, with one ammonium group fitting tightly into the centre of one face of the crown[69]. Owing to the strong electrostatic interactions with the side-chains in this structure, the guest penetrates into the macrocyclic cavity more than in most of the ammonium guests referred to above; the ammonium nitrogen lies only 0.56 Å above the mean plane of the ether oxygen atoms. The complexed entities are stacked in the crystal one on top of the other, and the ammonium ion which projects from one complex is in contact with the two carboxy residues at the bottom of the adjacent one. As in the previous examples, insertion of the nearly spherical NH_3^+ guest within the 18-crown-6 cavity effects an all-*gauche* conformational pattern of all the ethyleneoxy fragments along the ring (Figure 17a).

Replacement of the carboxy groups by other functional residues (e.g. CONHPh) could provide secondary interaction sites for the polyfunctional ammonium guests. In fact, the structural effects in binding of organic and biogenic ammonium ions by polyfunctional macrocyclic polyethers bearing amino acid and other side-chains have recently been discussed[70]. It has been concluded that the complexation selectivity of organic ammonium cations in such systems is determined both by the strength of binding of the ammonium entity within the crown cavity and by secondary interactions between the substrate and the side-chains borne by the macrocycle. As already indicated in Chapter 6, an efficient binding of a bifunctional substrate such as $^+NH_3(CH_2)_nNH_3^+$ can be achieved by using two crown ether rings bound to the same molecular framework. Structural studies of such complexes in which the diammonium cation is contained in the central molecular cavity of the receptor and anchored simultaneously by its two NH_3^+ groups to the lateral macrocycles (appropriately spaced within the host) have been reported[71]. The above discussed features are illustrated in Figure 17b and c.

Most earlier work on direct complexation of metal cations by crown ethers was devoted to alkali and alkaline earth metal ions. Most of the complexes formed had 1:1 and 1:2 ligand-to-cation stoichiometry, depending on the ratio of the radii of the cation and the cavity of the crown. Over the years the ability of the crown species to lipophilize metal cations have been extensively applied in a variety of chemical reactions. Many of the

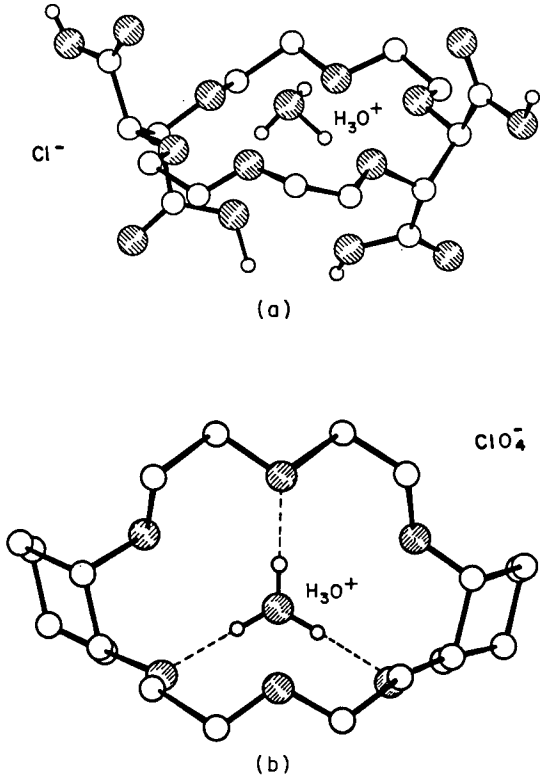


FIGURE 16. Complexes of hydronium ions with (a) 18-crown-6-tetracarboxylic acid[68] and (b) *cis-syn-cis*-dicyclohexano-18-crown-6[67]

recently determined structures resemble, in fact, the structural patterns observed in the well known series of metal–crown complexes described by Dunitz, Truter and coworkers more than 10 years ago (see Refs 66 and 74 Chapter 6). For example, in the 1:1 complex between 18-crown-6 and potassium perchlorotriphenylmethide, a normal K^+ centring within the ligand has been observed[72]. In the bis(dibutylphosphato)aquabarium complex with 18-crown-6 the Ba^{2+} ions are also located inside the macrocyclic cavity[73]. An open D_{3d} conformation of the ligand is found in the former example, whereas a distorted conformation occurs in the complex with the smaller Ba^{2+}. Indeed, in the known structures of the 18-crown-6 complexes with metal cations of different radii a wide variation in the shape of the ligand, from the symmetrical one in the KSCN complex (D_{3d}) to the distorted one in the NaSCN complex (C_1), has been observed. Complexes with the Li^+ cation will be referred to separately in more detail in Section IV.D.

There are several non-standard structural forms of alkali metal complexes with the 18-crown-6 host which deviate from the usual trend. The 1:2 adduct between dipotassium phthalocyanine (K_2Pc) with 18-crown-6 crystallizes as a trimacrocyclic sandwich complex 18-crown-6. K^+PcK^+. 18-crown-6[74]. This crown ether complex is atypical in that potassium is external to the 18-crown-6 cavity. The K^+ ions are located 1.6 Å from the

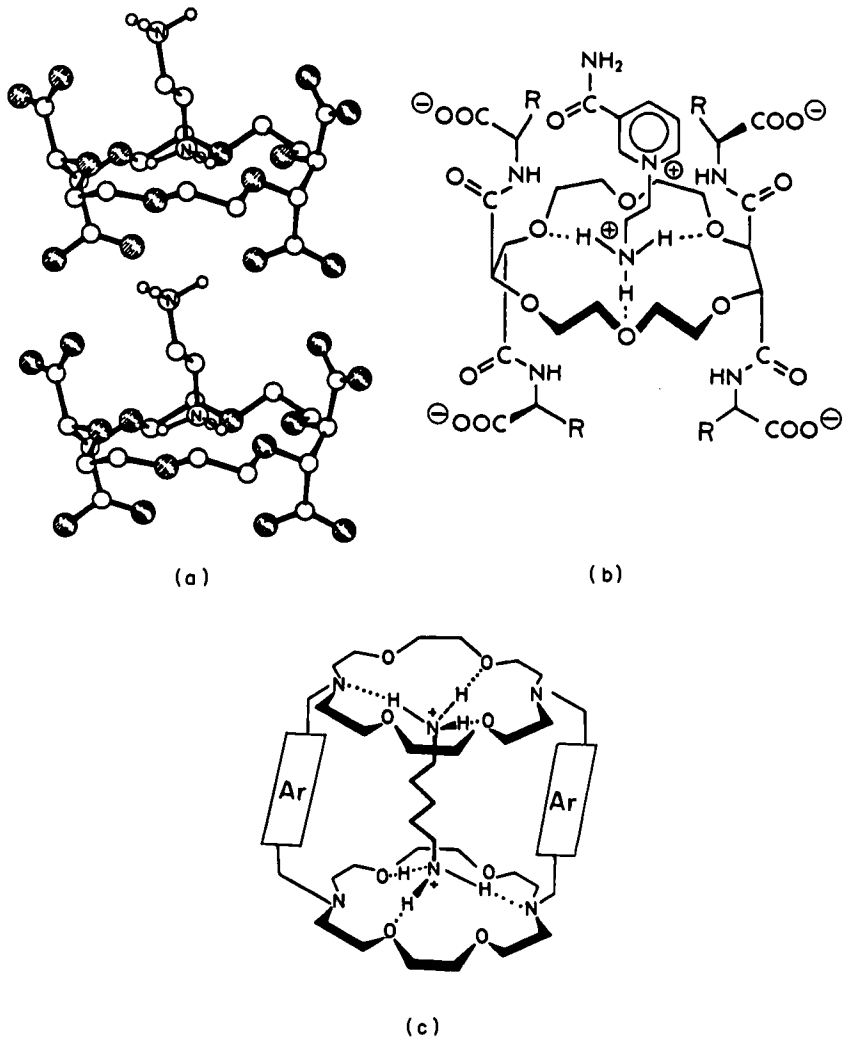
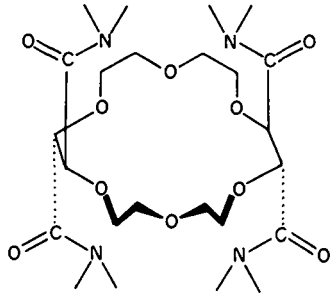


FIGURE 17. Association of alkylammonium ions with functionalized macrocycles: (a) 18-crown-6 bearing carboxylate anions[69]; (b) 18-crown-6 with amide side-chains providing secondary interaction sites[70]; and (c) bifunctional molecular receptor consisting of two crown rings bridged by rigid aryl (Ar) groups[71]

mean plane of the ether oxygens, which clearly indicates a competitive coordination between the crown and phthalocyanine ligands. Similarly, in the complex of 18-crown-6 with potassium trihydrotris(triphenylphosphine)ruthenate the K^+ occupies a site 0.75 Å away from the crown plane and points toward the ruthenium[75]. This deviation appears to be effected by the coulombic interaction between the potassium cation and the ruthenium anion (at $K \cdots Ru = 3.61$ Å) approaching from one side of the crown. Another 'irregular'

K^+-binding scheme has been observed in the crystal structure of the complex between potassium cation and a tetracarboxamide derivative (**3**) of 18-crown-6[76]. This structure



(**3**)

contains 1 mol of the substituted crown ether, 1.5 mol of KBr and 3.5 mol of water. The macrocyclic units in it are organized in a polymolecular stack and the K^+ ions are located alternatively inside (0.25 Å from the mean plane of the six ether oxygen atoms; $K\cdots O = 2.8$ Å) and on top of (at 1.13 Å from the mean oxygen plane) successive macrocycles. The coordination around the second K^+ is supplemented by the amide carbonyl side-groups and by water molecules. Additional metal cations, water molecules and the Br^- counter ions are located is separate zones of the structure. The observed packing arrangement has been considered as a solid-state model of a molecular channel with a 'frozen state' of potassium ion propagation through the stacked crowns from one binding site to the next (Figure 18).

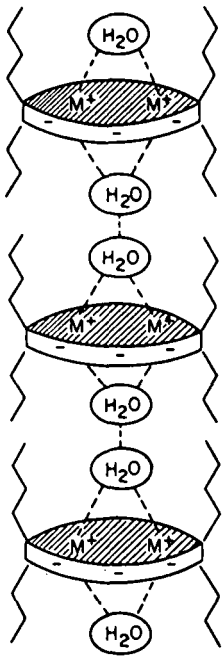


FIGURE 18. Schematic illustration of the stacking arrangement in the solid complex between a tetracarboxamide host **3**, KBr and water; the Br^- ions are located outside the stacks[76]

Several interesting structural species involving Cs^+ ions have also been characterized. In addition to the 1:1 adduct of 18-crown-6 and Cs^+ known from previous studies, a 2:1 sandwich-type complex $[Cs(18\text{-crown-}6)_2]^+$ and 3:2 club sandwich complex $[Cs_2(18\text{-crown-}6)_3]^+$ have been found[77]. A 1:2 crown-to-caesium structural form has also been obtained in a recently studied reaction between aluminium alkyls and alkali metal salts. The compound $[Cs_2\cdot(18\text{-crown-}6)][Al_3Me_9SO_4]$ was found to crystallize in infinite chains: (sulphate/aluminium)–caesium–(18-crown-6)–caesium–(sulphate/aluminium)[78]. The two caesium cations are located on opposite sides of a single crown moiety, being asymmetrically disposed with respect to the mean plane of the coordinating ether oxygens. The corresponding distances are 1.79 and 2.37 Å, both markedly larger that the 1.44 Å distance observed in the 1:1 complex with CsSCN, owing to the electrostatic cation–cation repulsion across the ring. Each caesium is coordinated to the six crown oxygens, two sulphate oxygens and the other Cs^+. The cation–cation distance across the crown ring of 3.92 Å exceeds only slightly the sum of the ionic radii of caesium (3.56 Å).

The number of crystal structures in which a transition metal has been found to interact directly with 18-crown-6 is small. An early example involves the inclusion of the UCl_3^+ cation within the centre of 18-crown-6, which is accompanied by a distortion of the crown conformation from the D_{3d} symmetry[79]. Subsequently, the complexation of trivalent lanthanide ions within crown ethers deserved considerable attention[43,80]. These ions are nearly spherical without large directional effects in their binding properties. The stabilities of the complexes formed in methanolic solution were found to decrease with decreasing atomic number from La to Gd, a trend related to the relative sizes of cation and ligand cavity[81]. The 18-crown-6 forms several types of compounds with M^{3+} lanthanide ions: $MCl_3\cdot$(18-crown-6), $M(NO_3)_3\cdot$(18-crown-6), $[M(NO_3)_3]_4\cdot$(18-crown-6)$_3$ and $M(NO_3)_3(H_2O)_3\cdot$(18-crown-6). In the first three derivatives the metal ion is inserted into the macrocycle. In the fourth derivative the crown ether is bound only to the coordinated water molecules *via* hydrogen bonds (see Section II.A.2)

In the two isostructural 1:1 complexes of 18-crown-6 with $Nd(NO_3)_3$[82] and with $La(NO_3)_3$[39], the metal cation lies in the centre of the crown ring, being 12-coordinated to the six ether oxygen atoms and the three bidentate nitrato groups approaching from both sides of 18-crown-6 (Figure19a). In these structures the macrocycle adopts an unusual boat conformation with one nitrate ion approaching the more sterically hindered side and the two remaining nitrates approaching the opposite side. The shape of the distorted ligand cavity is adjusted by small changes in the conformation to the slightly different ionic radii of Nd^{3+} and La^{3+}. The 4:3 complex of $Nd(NO_3)_3$ with the crown consists of three crystallographically independent moieties in the ratio 1:1:2:$[Nd(NO_3)_6]^{3-}$, $[Nd(NO_3)_2\cdot(18\text{-crown-}6)]^+$ with D_{2h} symmetry and $[Nd(NO_3)_2\cdot(18\text{-crown-}6)]^+$ with C_s symmetry and with a distorted polyether oscillating between two positions[83]. In the ordered D_{2h} structural species the metal ion is enclosed in the centre of the polyether and is held in the cavity by one bidentate nitrate group on each side (10 coordination). The crown ether is considerably flattened with respect to its usual D_{3d} conformation, indicating a strained arrangement. It has been concluded from the structural data that the 4:3 complex preferentially forms when the ratio of the ionic diameter of the cation to the diameter of the cavity is smaller than 1. In the 1:1 complex between 18-crown-6 and the $GdCl_2^+$ moiety the cations are similarly inserted in the macrocycle[84]. The coordination shell around Gd^{III} is supplemented by one molecule of ethanol, and the conformation of the crown ring is distorted as that in the UCl_3–18-crown-6 cationic moiety. The third Cl^- is located outside the complexed entity. Crystalline complexes of various lanthanides with other crown ethers and counter ions, and the factors influencing their stoichiometry and structure, have also been discussed[80].

Additional structural features relate to the 1:1 complexes of 18-crown-6 with mercury(II) and cadmium(II) halides. Three structures of high molecular symmetry with $HgCl_2$,

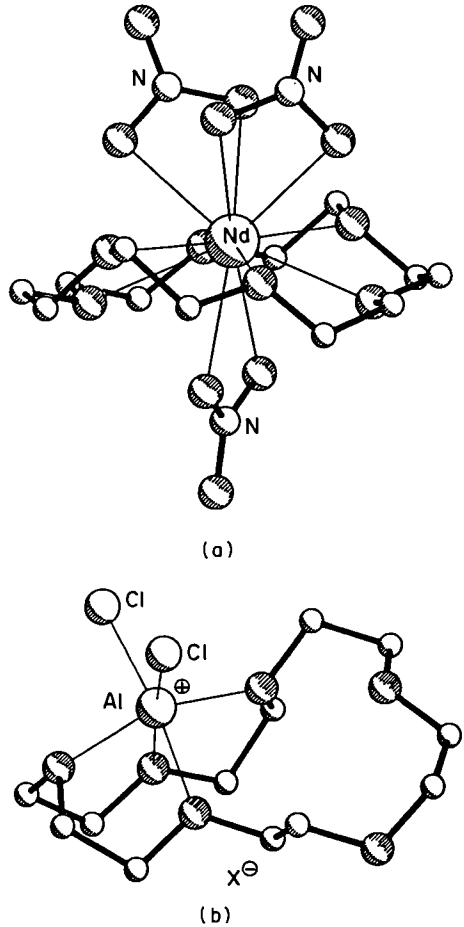


FIGURE 19. 1:1 Complexes of 18-crown-6 with (a) $Nd(NO_3)_3$[82] and (b) $[AlCl_2]^+ \cdot [AlCl_3Et]^-$[87]

$CdCl_2$ and HgI_2 have been reported[85,86], composed of linear MX_2 entities inserted normal to the mean plane of the macrocycle with the spherical metal atoms positioned at its centre. The metal coordination is considered to be hexagonal bipyramidal with Hg···O and Cd···O distances of 2.83–2.86 and 2.75 Å, respectively. Only a few structures in which an Al^{III} cation is encapsulated by a crown ether host are known. One of them is a 1:1 complex between $AlCl_2^+$ and 18-crown-6, in which the aluminium cation is located in an octahedral environment made up of four of the crown oxygens and the two chlorines (Figure 19b)[87]. Since two of the ring oxygens are not involved in the interaction, the host assumes a very distorted conformation. The Al···Cl and Al···O bonds are within the ranges 2.15–2.21 Å and 1.95–2.06 Å, respectively.

Izatt *et al.*[88] have summarized detailed thermodynamic and kinetic data for cation–macrocycle interaction.

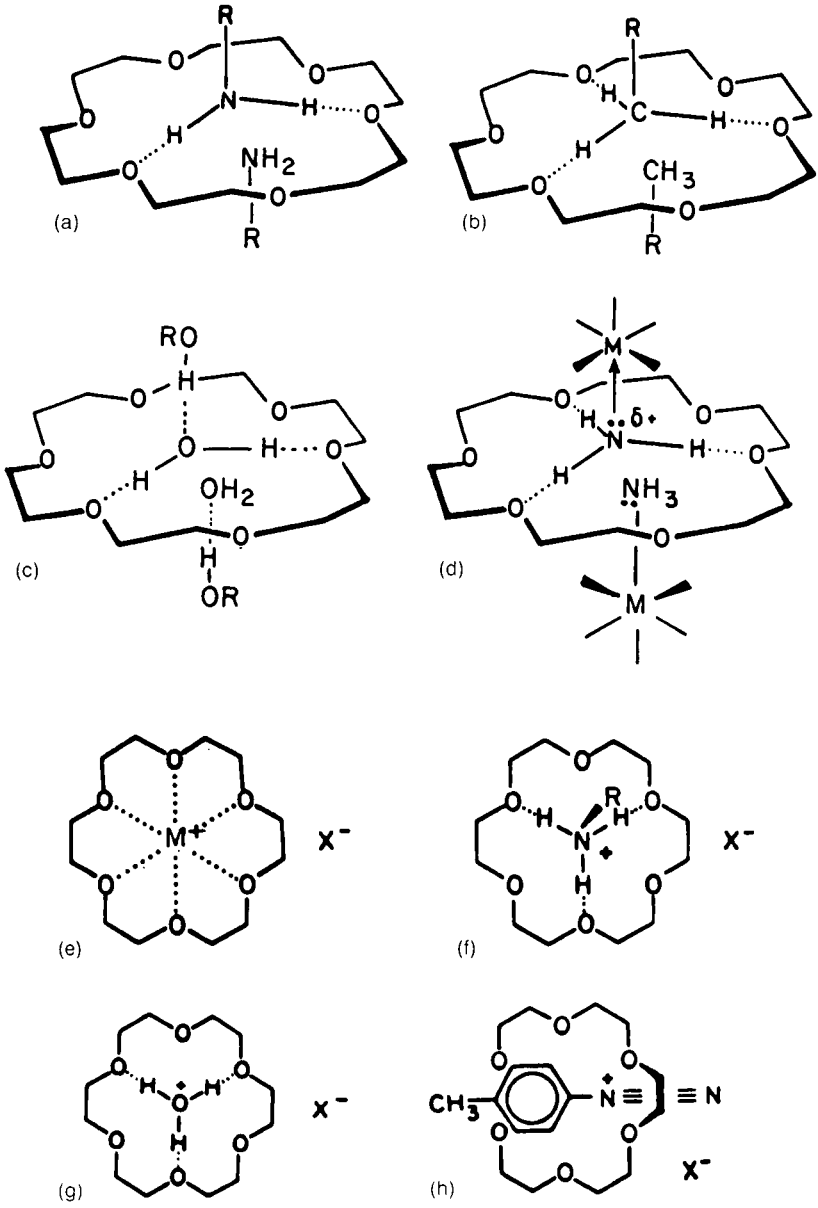


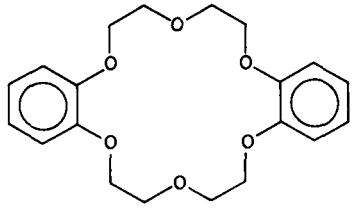
FIGURE 20. Schematic representation of binding modes between 18-crown-6 and various substrates discussed in Section II.A.: (a) alkylamine; (b) guest with an 'activated' methyl group; (c) hydrated phenol; (d) metal–ammonia assembly; (e) metal cation; (f) alkylammonium ion; (g) hydronium ion, and (h) aryldiazonium ion

Figure 20 summarizes schematically some of the above-described modes of interaction between 18-crown-6 and a neutral or a charged guest moiety.

B. Structural Analogues of the 18-Crown-6 Framework as Hosts

1. Crown ethers containing benzo, cyclohexano and 1,3-xylyl ring constituents and additional side-arm nucleophiles

A wide variety of structural analogues of the 18-crown-6 framework can be synthesized by replacing some of the ether oxygens with other nucleophiles, by introducing different structural elements into the ring or by adding substituents to the methylene or the heteroatom sites (three such analogues, **1**–**3**, have already been referred to in the previous section). The most common hexaether derivatives of 18-crown-6 are the dicyclohexano-18-crown-6 (**1**) and the dibenzo-18-crown-6 (**4**) species. The substituents in **1** and **4** make the crown ether framework more rigid; the endocyclic ether torsion angle at the C—C bridge participating in an aromatic ring is restricted to 0°, while the C—C bond participating in a saturated hydrocarbon ring preferentially assumes a *gauche* conformation. In dibenzo-18-crown-6 the two aromatic substituents usually lie on the same side of the macroring (the molecule has a basket-like shape), providing an extended lipophilic envelope for the complexed guest species. Two isomers of the dicyclohexano-18-crown-6 host encountered in the crystallographic literature are characterized by a *cis* substitution on the ring junctions, and either a *syn* or *anti* relative arrangement of the cyclohexyl rings with respect to the hexaether cavity. Generally, the above ligands exhibit binding features similar to those described for the unsubstituted 18-crown-6, with minor conformational modifications affected by the presence of the side substituents. Several unique examples emerge from the recently published structures.



(**4**)

The dibenzo-18-crown-6 and both isomers of the dicyclohexano-18-crown-6 macrocycles are involved in the first recorded dimethylthallium compounds having six ligating oxygen atoms (Figure 21)[89,90]. The complexes formed by the three ligands with dimethylthallium picrate salt consist of $[Me_2Tl{\cdot}crown]^+$ cations and picrate anions. The linear Me_2Tl entities are centred within the respective macrorings, lying normal to the plane of the six ether oxygens. The Tl···O distances range from 2.68 to 2.98 Å. In a similar manner, the linear $HgCl_2$ molecule was found to be held perpendicularly in a quasi-planar ring of the six oxygens of dibenzo-18-crown-6, as previously observed for the 18-crown-6 ligand[91]. The least square planes of the two phenyl substituents incline at 40 and 44° to the plane defined by the ligating atoms. In the resulting conformation all oxygen atoms direct one of their lone pairs to the centred mercury atom (mean Hg···O = 2.79 Å).

The dibenzo crown ligand has also been involved in second-sphere type interactions with various metal–ligand assemblies. Such an interaction between an 'activated' methyl group and the crown is found in the structure containing $(CuICH_3CN)_4$ clusters[92]. The copper displays tetrahedral geometry by its coordination to three iodine atoms and a

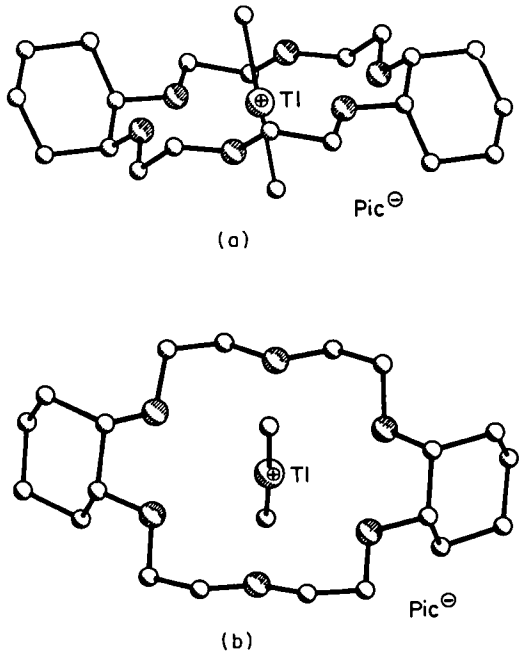


FIGURE 21. 1:1 Complexes of dimethylthallium picrate with (a) the *cis-anti-cis* and (b) the *cis-syn-cis* isomers of dicyclohexano-18-crown-6[90]

nitrogen-bound acetonitrile molecule; the methyl end of the acetonitrile perch on the hexaether cavity at C···O distances between 3.22 and 3.41 Å. *trans*-Ammine-dichlorotrimethylphosphineplatinum also binds dibenzo-18-crown-6 in the second sphere[36]. This association takes place *via* the NH_3 group which is involved in three bifurcated hydrogen bonds to the six oxygens of the crown (N···O distances are within the range 3.3–3.4 Å). Owing to the large size of the platinum complex it binds to the convex side of the crown, the aryl groups thus being oriented away from the attracted NH_3. The stoichiometry of the crown–ammine interaction in this structure is 1:1, and not 1:2 as with the 18-crown-6, the coordinated-metal substrate being too large to approach the concave face of the crown cavity.

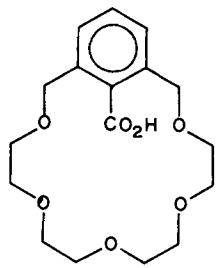
A characteristic association of ammonium ions with the dibenzo-18-crown-6 ligand occurs in the 1:1 complex of the crown with ammonium tetraisothiocyanatocobaltate[93] and the 1:1:1 ternary complex including *t*-butylammonium perchlorate and 2, 3-dichloro-5, 6-dicyano-*p*-benzoquinone (DDQ)[94]. In the former the NH_4^+ cation interacts directly with the crown ring. It is located 1.02 Å above the mean plane of the six ether oxygen atoms, which are coplanar within ± 0.11 Å. The benzene rings are turned toward the complexed face of the cavity. The ammonium hydrogens have not been located. All six N···O distances range from 2.87 to 2.96 Å, indicating either bifurcated or disordered hydrogen-bonding interactions. The structure of the ternary complex can be best described as packing of two columns with opposite charges. The first type contains DDQ molecules with perchlorate anions. In the second type the *t*-butylammonium cations are

bound to the crown ether by N—H···O hydrogen bonds and electrostatic $N^+ \cdots O$ interactions in the usual manner.

The *cis-syn-cis* conformer of dicyclohexano-18-crown-6 appears to be a good complexer of hydronium ions. One such structure containing $H_3O^+ \cdot ClO_4^-$ has already been referred to in Section II.A.3[67]. Another example is provided by the crystal structure consisting of $[H_3O, H_2O,$ dicyclohexano-18-crown-6$]^+$ cations and $[Ce(NO_3)_6]^{2-}$ anions[95]. As before, the H_2O and H_3O^+ species (being statistically disordered between the ligands) centre above the macroring in a perching arrangement. They are linked to the crown by strong hydrogen bonds with the ether oxygens at O···O distances ranging from 2.54 to 2.68 Å.

A large number of complexes between the dibenzo and dicyclohexano derivatives of 18-crown-6 and sodium or potassium cations centred within the crown cavity have been reported. Among these are several interesting structures of a new type in which trimethylaluminium moieties are attached to the ether oxygens of the crown[96,97]. In some other cases the use of the alkali metal complexes led to the preparation of previously unknown species, e.g. the reaction of CuI with dicyclohexano-18-crown-6 in the presence of KI produced a linear CuI_2^- which is not complexed by the crown[98]. Structures of complexes with alkaline earth metals are less frequent. More recent references included complexes of host **1** with hydrated barium isothiocyanate[99] and with a CCl_4 solvate of dinitratostrontium[100].

The introduction of the 1,3-xylyl fragment into the 18-membered crown ring has already been referred to in Chapter 6 by showing the structures of the 2′-carboxy-1′, 3′-xylyl-18-crown-5 (**5**) ligand and its complex with *t*-butylamine. The free ligand forms an intramolecular 'complex'; the carboxyl group is centred within the macrocycle and takes part in a short and almost linear hydrogen bond with the transannularly located ether oxygen. The structure of a larger bis(2-carboxy-1,3-xylyl)-24-crown-6 ligand also represents an intramolecular complex with two carboxyl groups converging on each other to provide an ideal hydrogen bonding arrangement (Figure 22)[101]. The potential cavity within this host is effectively filled by the two coplanar carboxyl functions which form an intramolecular cyclic pair of equivalent O—H···O bonds. This structure is characterized by a very high organization in the crystal due to the well defined pattern of intramolecular interactions and the partly constrained configuration inherent to the 2-carboxy-1,3-xylyl residues.



(**5**)

As shown before, when such ligands are treated with a suitable alkylamine or alkylammonium substrate, stable intermolecular host–guest type complexes can be formed; the multiple $NH_3^+ \cdots O$ interactions between ligand and substrate will then compensate for the loss of the intramolecular hydrogen bonds. More recently, structural studies of the 2′-hydroxy-1′,3′-xylyl-18-crown-5 and 2′-hydroxy-5′-nitro-1′,3′-xylyl-18-crown-5 (**6**) hosts and a 1:1 complex of the latter with ammonia have been reported[102]. In

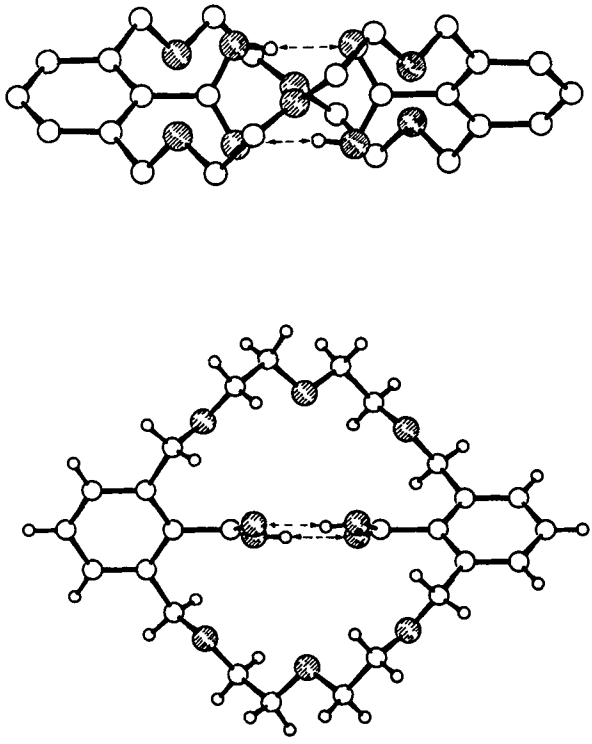
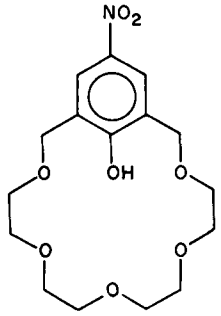


FIGURE 22. Two views of the molecular structure of bis(2-carboxy-1,3-xylyl)-24-crown-6, showing intramolecular hydrogen bonding between the carboxyl substituents[101]

the two free ligands the phenolic group is oriented toward the centre of the cavity and forms intramolecular hydrogen bonds (at OH···O distances of 2.71 and 2.86 Å) to the ring oxygens. In the complex there is a proton transfer from the OH group to the ammonia. The NH_4^+ cation thus formed is held in a perching position close to the ring by three N—H···O bonds at 2.88 Å to the ether oxygens and 2.69 Å to the phenolate oxygen. There is



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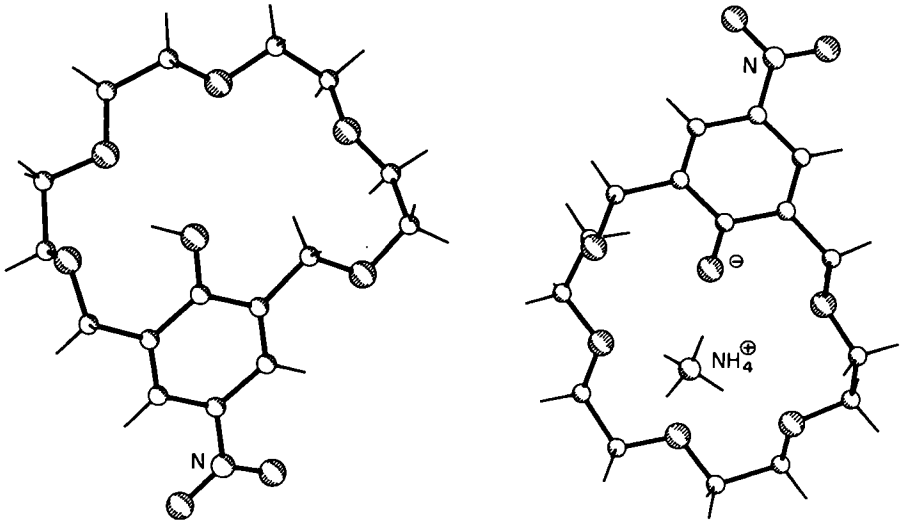
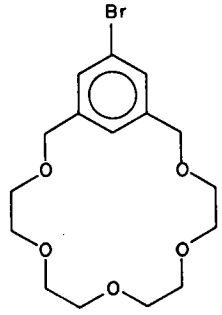


FIGURE 23. Molecular structures of (a) host **6** and (b) its 1:1 complex with ammonia[102]

also a fourth hydrogen bond of the axial proton to phenolate oxygen of a neighbouring molecule, yielding centrosymmetric hydrogen-bonded dimers. As in the carboxy compound, the phenyl ring is located opposite to the binding site (Figure 23).

The 5′-bromo-1′, 3′-xylyl-18-crown-5 (**7**) ligand containing only five oxygen ligating sites can also interact with ammonium ions[103]. In fact, its complex with t-$BuNH_3^+ \cdot PF_6^-$ shows a characteristic tripod of hydrogen-bonding interactions between the ammonium ion and the ether oxygens, and an approximate all-*gauche* conformation of the macroring. Owing to the absence of the polar substituent at the 2-position of the 1, 3-xylyl subunit the interacting cation and the aryl group are located on the same face of the macroring. The structure of the complex between 1, 3-xylyl-18-crown-5 and t-butylammonium perchlorate reveals similar features (Figure 24)[104]. The NH_3^+ group is hydrogen bonded to three next-nearest-neighbour oxygen atoms of the macrocycle which has an approximate D_{3d} symmetry. The unsubstituted aryl group of the crown and the cation lie on the same side of



(**7**)

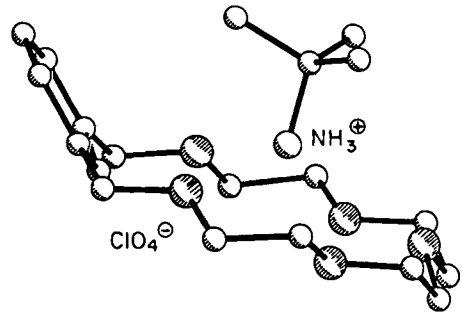
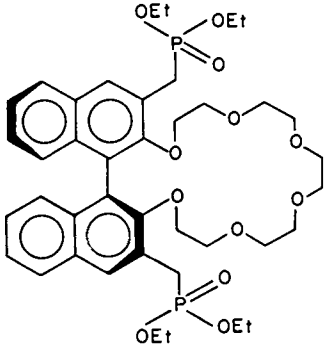


FIGURE 24. 1:1 Complex of 1,3-xylyl-18-crown-5 with t-$BuNH_3^+ \cdot ClO_4^-$ [104]

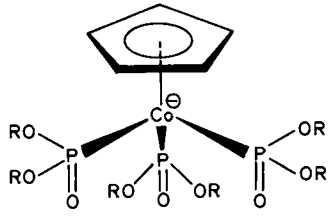
the macroring. The distance of the nitrogen atom from the mean plane of the ether oxygens is 1.1 Å. A molecule of CH_2Cl_2 solvent is located on the opposite face of the macroring, the shortest $Cl \cdots N^+$ distance through the cavity being 3.55 Å. A slightly different binding scheme was observed, however, in the structure of the 1:1 complex of the same ligand with *S*-*t*-butylthiouronium perchlorate, which contains coordinating entities of lower symmetry[105]. Only one of the two NH_2 groups of the guest cation is hydrogen bonded to the crown ether molecule (the relevant $N \cdots O$ distances are 2.82 and 2.93 Å); the other NH_2 group interacts with the anion. In this structure the butylthiouronium cation, the anion and the aromatic ring are positioned on the same side of the crown ether.

An interesting structure is found for the complex between 2′-methoxy-1′,3′-xylyl-18-crown-5 and samarium(III) nitrate[106]. The complex consists of neutral $[Sm(NO_3)_3 \cdot crown \cdot H_2O]$ species in which the metal atom is 10-coordinated. It is directly bound to three ligand oxygen atoms, three bidentate nitrato groups and one molecule of water; the $Sm \cdots O$ distances range from 2.38 to 2.87 Å. The samarium atom is not enclosed within the crown cavity. As in the previously discussed compounds substituted at the 2-position of the 1,3-xylyl subunit, the methoxy group is directed above the plane of the macroring, coordinates to the guest moiety and prevents a close approach between the metal and the crown cavity.

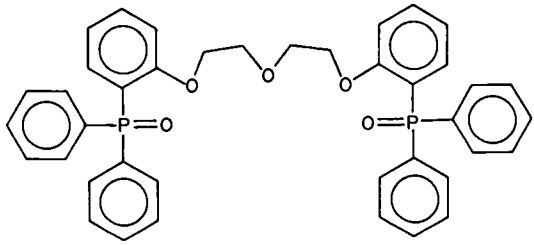
The introduction of additional binding sites in a crown host can strongly influence its binding power and affect its selectivity for the guest. For example, a 20-crown-6 macrocyclic ligand system containing two phosphonate groups at the binding site (**8**) is a



(**8**)



(**9**) (R=C_2H_5)

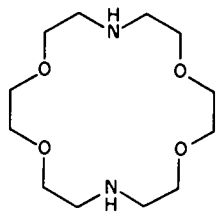


(10)

very powerful binder for Na^+ and K^+, with a slight preference for the former. In the 1:1 complex of this ligand with KSCN the K^+ ion is coordinated in a chiral hexagonal-bipyramidal arrangement to the six oxygen atoms of the hexaether macrocycle (at $K^+ \cdots O = 2.72$–2.82 Å) and to one oxygen atom of each of the two diethylphosphonate groups (at $K^+ \cdots O = 2.70$ Å)[107]. No crystalline complexes of Na^+ with diphosphonate crown hosts have been reported. The diethylphosphonate sites were also found to be very effective in binding alkali metal cations to other systems. A recent example is provided by an organometallic ionophore incorporating these sites (**9**) which binds alkali metal cations with a strong preference for Li^+ over other ions[108]. On the other hand, a different open-chain ligand containing three ether oxygens and two terminal triphenylphosphine oxide groups (**10**) was found to exhibit a remarkable degree of selectivity towards ammonium compounds in extraction experiments[109].

2. *Ligands containing nitrogen binding sites*

All previous examples involved polyether rings with only oxygen and carbon ring atoms. In aza-crown ethers one or more of the ether oxygen atoms are replaced by the > NH structural element. The amine group is more basic than an ether oxygen, and it can be protonated by strong acids. The diaza-18-crown-6 moiety **11**, in which the nitrogens are located transannularly in the ring, has been involved in many structural investigations. Interestingly, this ligand can adopt an open D_{3d} conformation even in the uncomplexed state. Such a structure is stabilized by the two inward-turning amine hydrogen atoms which fill the cavity between the four centrally located lone pairs of the ring oxygens. On complexation with metal cations the relative orientation of the hydrogen atom on N is inverted; the hydrogen atoms now point outward while the nitrogen lone pairs are directed toward the centred cation, preserving the D_{3d} conformation of the ring.



(11)

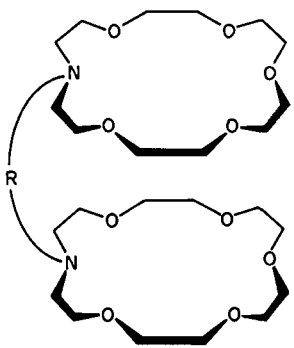
Recent studies have shown that the intramolecular N—H···O interactions can be distorted even upon formation of weak complexes with neutral substrates. Thus, a very typical 1:2 complex is formed between diaza-18-crown-6 and 2-guanidinobenzimida-

zole[19]. The guest molecules approach from both sides of the plane of the crown ring (D_{3d}) and bind to it by multiple N—H···N and N—H···O bonds at 2.9–3.0 Å. Since the positions of hydrogen atoms could not be located in this structure, it has not been established whether the two nitrogen sites in the ligand are proton donors or acceptors. The structure of a 1:4 adduct between diaza-18-crown-6 and thiourea has also been reported[110]. It is centrosymmetric with the normal 1:2 stoichiometry of direct coordination between host and guest. The additional molecules of thiourea are peripheral to the complexed entities. In fact, as in the 18-crown-6 complexes with urea (1:5) and thiourea (1:4) described above, this structure resembles a ternary complex which contains layers of thiourea held together by a network of hydrogen bridges. All N···O and N···N bonding distances range from 2.9 to 3.0 Å, the diaza-crown adopting the biangular C_i conformation.

In the protonated form the aza crowns can form complexes not only with neutral molecules but also with anions. For example, in the complex formed between diaza-18-crown-6 and HNO_3 the crown ether is protonated at both nitrogen atoms, forming a 1:2 complex with the nitrate ions[57]. Again, the macroring adopts the biangular conformation in which all four ammonium hydrogens are equally directed to both sides of the macroring, thus allowing efficient hydrogen bonding to two nitrate anions. Earlier, a 1:1:1 complex of monoaza-18-crown-6·H_2O·HCl, in which the macrocycle is also protonated at the nitrogen atom, was investigated[111]. One of the $>NH_2^+$ hydrogens was found to form a hydrogen bond to the water molecule centred within the macrocycle, which in addition donates its two protons to the ether oxygens.

The additional bonding valency of nitrogen (in comparison with oxygen) allows many interesting structural variations. For example, it is possible to connect two monocyclic ligands into one bifunctional paracyclophane-like host by a suitable bridge (see Ref. 71; Figure 17c). The number of bridging strands can vary according to the number of nitrogen atoms in each macrocyclic ring. Correspondingly, bis(monoaza)-crown ethers with one connecting bridge (**12**), doubly bridged diaza-18-crown-6 ligands (**13**) and triply bridged triaza-18-crown-6 rings (**14**) have been synthesized[112]. It has been shown that some of these hosts exhibit high selectivity in complexation towards $^+NH_3(CH_2)_nNH_3^+$ dications characterized by different chain lengths. Further discussion of the macropolycyclic systems is, however, beyond the scope of this survey.

Another family of N-containing macrocycles is that of pyrido-crown ethers. The conformation of the uncomplexed 2,6-pyrido-18-crown-6 (**15**), $ag^+g^+\ ag^+g^-\ ag^-a\ ag^-a\ ag^+g^-\ aaa$, resembles that of the unsubstituted 18-crown-6 in the solid state[113]. Two of the methylene groups turn inward and fill the space within the elongated cavity. During



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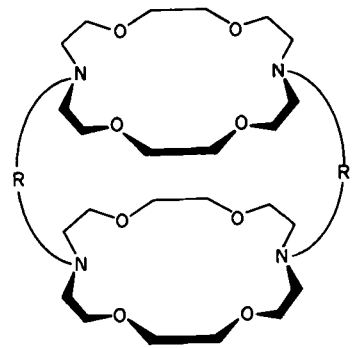

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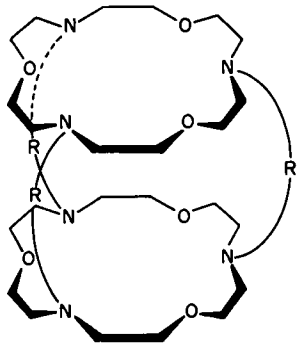

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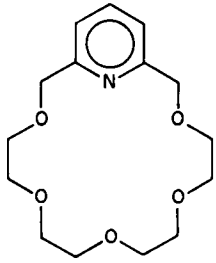


(15)

complex formation a conformational reorganization takes place to allow interaction with the guest moiety. A 1:1 complex of this host with *t*-butylammonium perchlorate was referred to briefly at the end of Chapter 6. The NH_3^+ is located above the cavity and bound in a characteristic tripod arrangement to next-nearest heteroatoms of the crown ring (including the N-site). The observed hydrogen-bonding pattern demonstrates that the pyrido nitrogen is preferred over the ether oxygen as proton acceptor (Figure 25).

The pyridine nitrogen can be protonated easily in a strongly acidic environment, leading to the formation of complexes in which the positive charge is mainly located on the ligand rather than on the guest. This is indeed the case in the complexes of 2, 6-pyrido-18-crown-6 with water in perchlorate and picric acid environments (Figure 26)[113]. In both structures one molecule of water is bound to the 18-membered macrocycle. It is located above the mean plane of the ring atoms (0.64 and 0.93 Å), forming a pyramidal arrangement of the hydrogen bonds (O···N = 2.70–2.74 Å; O···O = 2.84–2.95 Å). The conformation assumed by the ligand is D_{3d} in the picric acid complex and a more strained one ($ag^+a\,ag^-a\,ag^+a\,ag^-a\,ag^-a\,ag^+a$) in the perchlorate complex. When a larger 2, 6-pyrido-21-crown-7 ligand (**16**) is used for complexation with $H_2O{\cdot}HClO_4$ the water molecule is encapsulated almost at the centre of the cavity, the three hydrogen bonds being nearly coplanar. Owing to its larger size, the macroring adopts an asymmetric conformation to optimize the host–

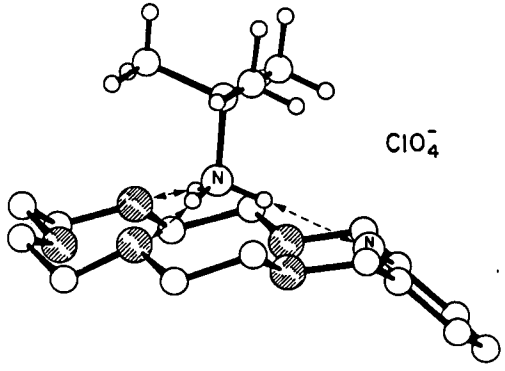


FIGURE 25. 1:1 Complex of 2,6-pyrido-18-crown-6 with t-$BuNH_3^+{\cdot}ClO_4^-$ (Ref. 110 in the Chapter 6)

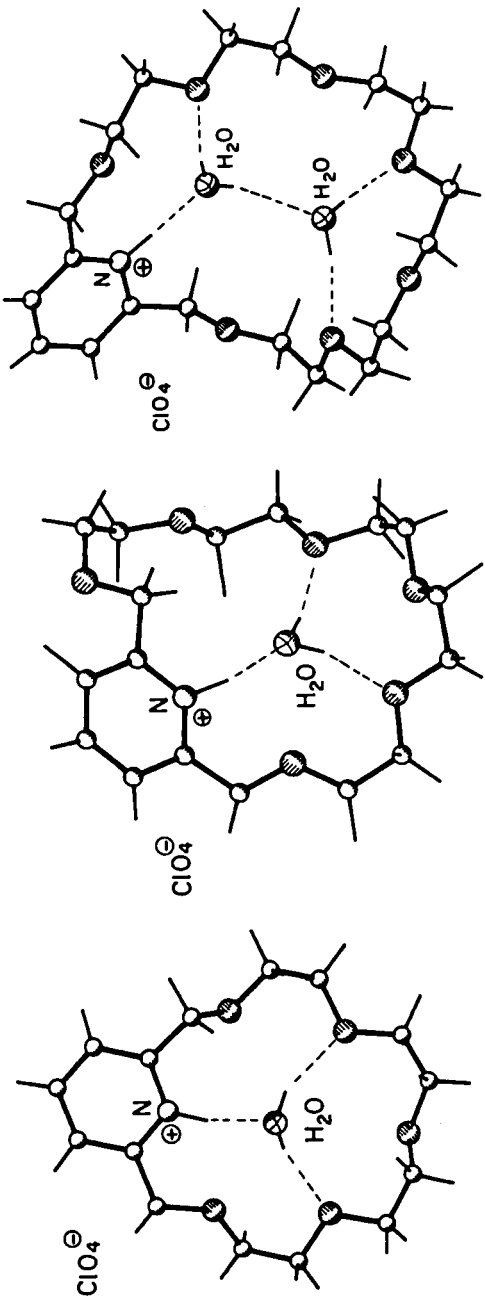
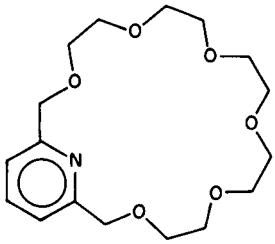
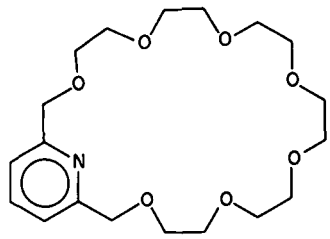


FIGURE 26. Inclusion of water molecules within (a) 2, 6-pyridinium-18-crown-6, (b) 2, 6-pyridinium-21-crown-7 and (c) 2, 6-pyridinium-24-crown-8[113] ligands

guest interactions. The extended 2,6-pyrido-24-crown-8 (**17**) ligand is too large to accommodate only one molecule of water. It thus associates with a hydrogen-bonded pair of water molecules (O···O = 2.90 Å). In the resulting structure, each water is surrounded by an 18-membered-like environment, consisting of six heteroatoms in an almost planar arrangement (Figure 26)[113].



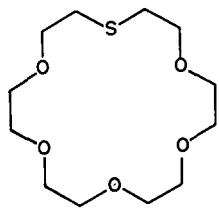
(**16**)



(**17**)

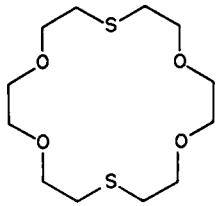
2. Sulphur analogues of 18-crown-6

The sulphur analogues of 18-crown-6 are also of interest. Uncomplexed thia-18-crown-6 (**18**), with one S heteroatom instead of O, adopts the same conformation as its hexaoxa analogue. The sulphur atom occupies the position corresponding to one of the outward-directed oxygens in the free 18-crown-6 ligand[114]. In the complexes of this ligand with NaSCN, KSCN, RbSCN and $AgNO_3$, the small Na^+, K^+ and Ag^+ cations (with ionic radii of 0.95, 1.33 and 1.26 Å, respectively) are accommodated within the centre of the cavity, while the larger Rb^+ ion (ionic radius 1.48 Å) is located about 1 Å above the mean plane of the ligating atoms[115]. The various cations coordinate to all five ether oxygens of the ligand. Their interaction with sulphur depends, however, on the cation. Thus, the sulphur atom is involved in relatively strong and even partially covalent interaction with the 'soft' Ag^+, it interacts only weakly with K^+ and Rb^+ and there is no coordination at all with the 'hard' Na^+. Correspondingly, the sulphur atom is turned towards the centre of the ligand, more in the Ag^+ complex than in the K^+ or Rb^+ complexes. On the other hand, in the Na^+ complex the sulphur heteroatom is directed away from the cavity. As in the previous series of metal ion complexes with 18-crown-6, the crown-bound alkali metal cations are also coordinated in the crystal to the counter ions.



(**18**)

Of the four adducts of the thia-18-crown-6 ligand, the Ag^+ complex appears to be the most stable, probably because of the strong interaction of the soft Ag^+ cation with the soft sulphur atom. Similar reasoning can be applied to explain the high stability constant found for the Pb^{2+} complex with 1,10-dithia-18-crown-6 (**19**)[116].



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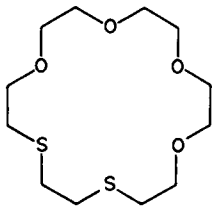

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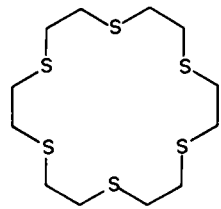


(21)

Structures of uncomplexed 1,10-dithia-18-crown-6, 1,4-dithia-18-crown-6 (**20**)[117] and hexathia-18-crown-6 (**21**)[118] have also been reported. The latter assumes a $g^+g^+g^-\ g^+ag^-\ g^+ag^-\ g^+g^+g^-\ g^+ag^+\ g^+ag^-$ conformation, having both endo- and exodentate sulphur atoms and also several inward-turning methylene groups. All torsions about C—S bonds in this structure are *gauche*. The pronounced preference of C—S bonds to adopt the *gauche* conformation (in relation to the preferred *anti* conformation about C—O bonds) can be rationalized by the convenient van der Waals separation between the adjacent methylene groups. In a *gauche* arrangement the 1,4-methylenes are separated by 3.4 Å in a thiacrown moiety compared with 2.8 Å in the oxycrown species.

A very compact conformation is adopted by the hexathia-18-crown-6 ligand in its 1:1 complex with Ni^{II} (picrate)$_2$[119]. The polythiaether wraps itself around the cation in an almost spherical conformation, forming an encapsulated complex in which the six sulphur atoms build a nearly perfect octahedral coordination sphere around the Ni^{2+} (Figure 27). The ligand has D_{3d} symmetry but with a very peculiar sequence of torsion angles consisting of three ($g^+g^+g^+\ g^-g^-g^-$) equivalent fragments. A similar complex was formed with Co^{II} (picrate)$_2$[120]. The Co^{II} ion is coordinated solely by thioether groups to yield a rare example of low-spin (tetragonally distorted) octahedral complex; Co—S_{eq} = 2.25 and 2.29 Å, Co—S_{ax} = 2.48 Å.

The Cu^I and Cu^{II} complexes of hexathia-18-crown-6 have also been studied. In the complex with Cu^IBF_4 there is a distorted four-coordinate geometry around the Cu^I ion, which can be considered to be derived from a linear two-coordinated complex by addition of two thioether groups (Cu—S = 2.25–2.36 Å)[121]. The hexathia-18-crown-6 host can bind also simultaneously two Cu^I ions to yield a binuclear complex as in 1:2 adduct with $Cu(NCCH_3)ClO_4$[122]. In the observed centrosymmetric structure each Cu^I ion is bound (from a different side of the ring) in a distorted tetrahedron to three sulphur donor atoms of the hexadentate macrocycle and to one acetonitrile molecule (Figure 28). The sulphur atoms of the macrocycle adopt a chair-like conformation, each copper atom lying 1.08 Å above the plane of its coordinated nucleophiles. There is no apparent interaction between the two copper atoms, the metal–metal separation being 4.25 Å. On the other hand, in common with the related Co^{II} and Ni^{II} complexes, the Cu^{II} (picrate)$_2$ crystallized as the

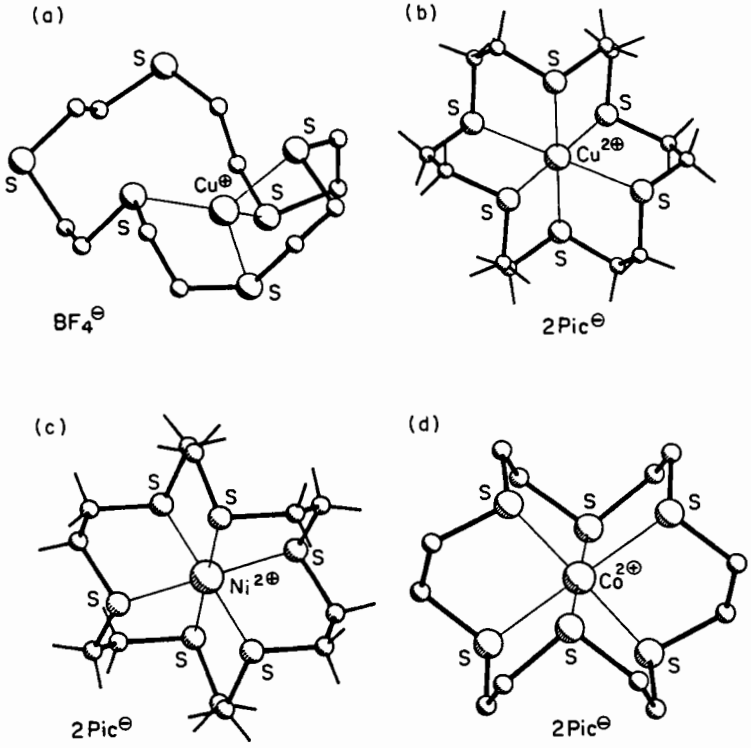


FIGURE 27. Complexes of hexathia-18-crown-6 with (a) $Cu(BF_4)$[121] and the picrate salts of (b) Cu^{2+} [123], (c) Ni^{2+} [119] and (d) Co^{2+} ions[120]

centrosymmetric *meso* isomer with an axially elongated octahedral symmetry around the metal (Cu—S_{eq} = 2.32 and 2.40 Å, Cu—S_{ax} = 2.62 Å)[123]. This arrangement maximizes the number of *gauche* torsions at the C—S bonds, a marked tendency of macrocyclic thioethers.

C. General Comments

Although mostly 18-membered crown ethers have been discussed so far, the main structural features encountered are also valid for crown ethers with other ring sizes. In general, if the guest species fits into the crown cavity (nesting arrangement), usually a high-symmetry conformation is found. When it is too large, the symmetrical conformation is usually preserved, with the guest entity positioned above the crown plane (perching arrangement); here either a 1:1 or a sandwich-type 1:2 complex can be formed. If the guest is too small to fill the open cavity of the host, the crown ether will 'wrap' itself around the guest moiety if it is flexible enough, or it may even include two guests within the macroring. Uncomplexed crown ethers often adopt a more elongated conformation with methylene groups pointing into and filling the cavity. Similarly, an elongated conformation often occurs in ligands complexed with asymmetrically shaped coordinating entities.

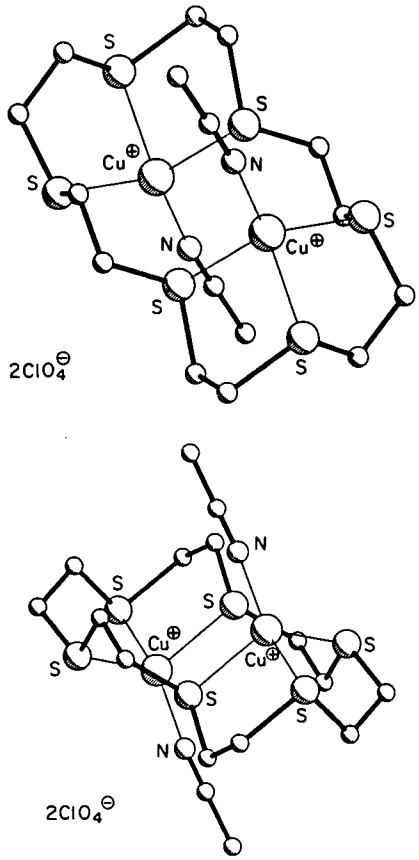


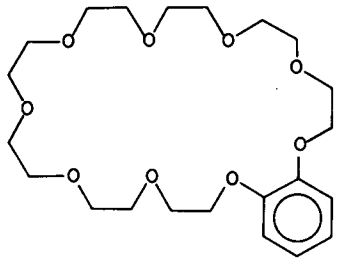
FIGURE 28. Two views of the binuclear complex of hexathia-18-crown-6 and $Cu(NCCH_3)ClO_4$[122]

III. INCLUSION COMPOUNDS WITH LARGE MONOCYCLIC HOSTS

A. Encapsulation of Uronium and Guanidinium Guests

In the complexes of 18-crown-6 with urea, uronium nitrate and guanidinium nitrate (or perchlorate) the cavity of the host is too small to encapsulate the guest species, and therefore perching-type structures occur. Consequently, the guests associate *via* hydrogen bonds not only with the 18-crown-6 host but also with other surrounding moieties. Molecular models showed, however, that the urea-like species may fit well in and be complexed selectively by the cavity of larger 27-crown-9 and 30-crown-10 frameworks. This has also been confirmed by extraction experiments which showed that the larger crowns are capable of transferring uronium and guanidinium salts from an aqueous to a chloroform medium[124]. Various hosts were used for the structural investigations, including benzo-27-crown-9 (**22**), 1,3-xylyl-27-crown-8 (**23**), *asym*-dibenzo-27-crown-9

(**24**), 2,6-pyrido-27-crown-9 (**25**), *asym*-dibenzo-30-crown-10 (**26**) and 2,6-pyrido-30-crown-10 (**27**).



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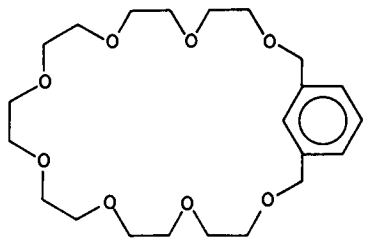

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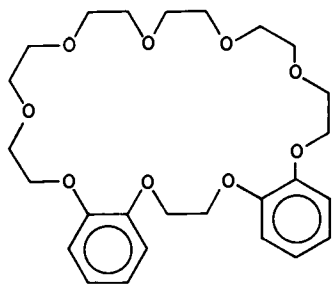

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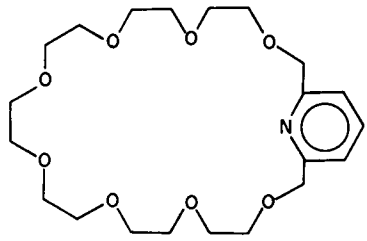

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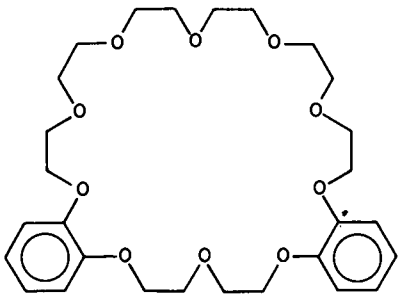

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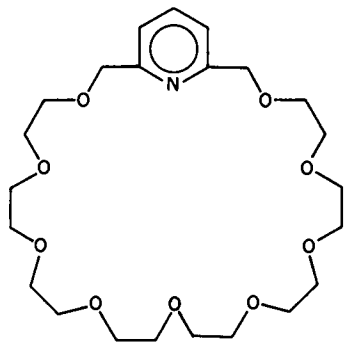


(**27**)

In the 1:1 complex between uronium perchlorate and benzo-27-crown-9 the cation is completely encapsulated within the macrocycle with its molecular framework almost coinciding with the best plane defined by the crown ether oxygen atoms[125]. All oxygen sites of the macroring are directed at the guest moiety, involving all five uronium hydrogen atoms in relatively short hydrogen bonds. The O—H···O bond (2.54 Å) is much shorter

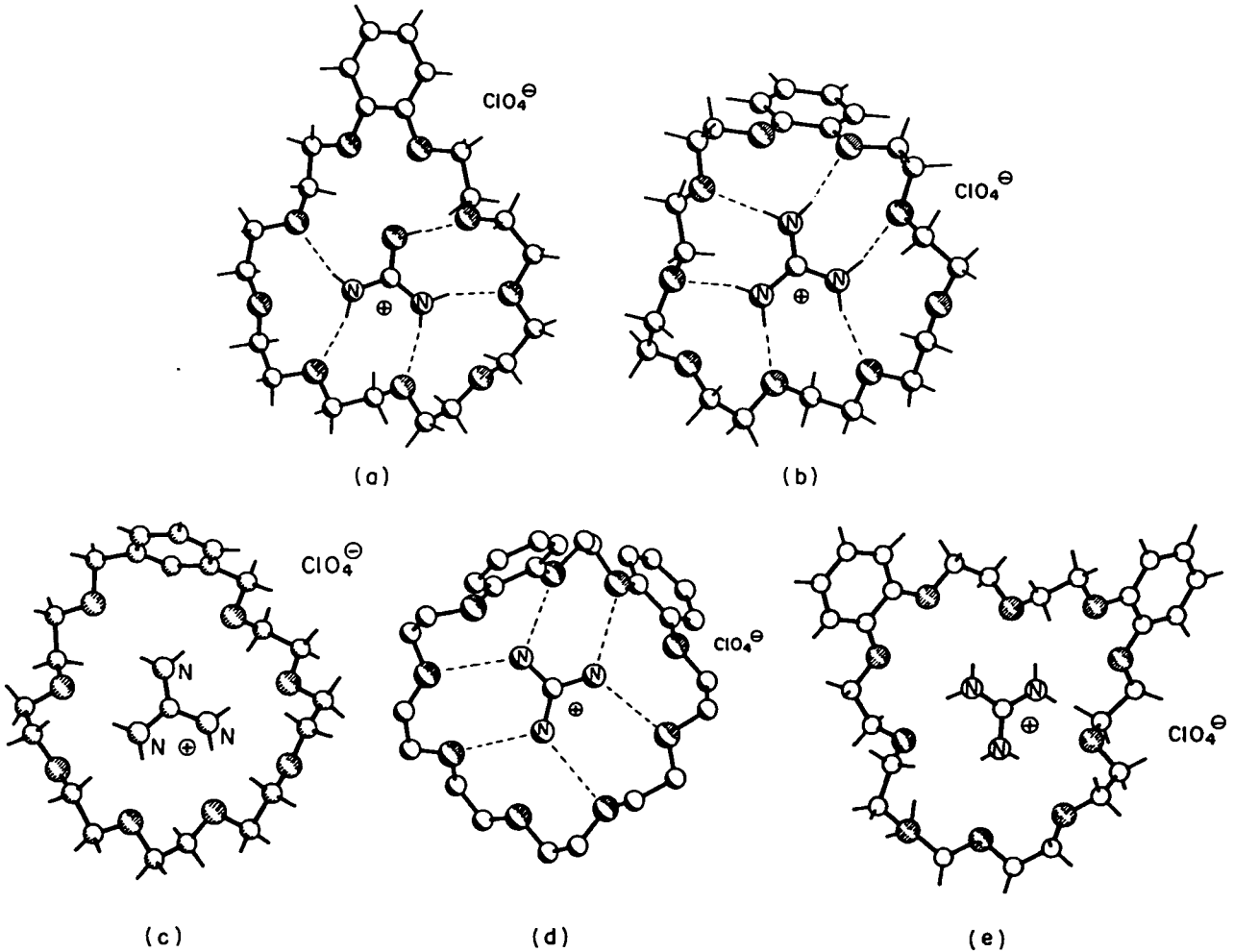


FIGURE 29. Encapsulation of (a) an uronium ion by host **22** and a guanidinium ion by (b) host **22**, (c) host **23**, (d) host **24** and (e) host **26**[124–126]

than the N—H···O bonds (2.84–2.93 Å), indicating that the positive charge is mostly localized on the urea oxygen. The two catecholic oxygen atoms contribute only weakly to the interaction. The macroring has a flat conformation, the aromatic ring being directed away from the cavity. The anion is not involved in hydrogen bonds.

Similarly, in the 1:1 complexes of guanidinium perchlorate with 27-membered crown ethers (benzo-, dibenzo- and 1,3-xylyl-27-crown-9) the guanidinium ions are totally encapsulated within the macrocycle[124,126]. Each NH_2 group of the guest forms two hydrogen bonds to next-nearest neighbour oxygen atoms of the host, the N···O hydrogen-bonding distances varying between 2.84 and 3.12 Å. The other oxygens which are not involved directly in hydrogen bonding turn towards and interact dipolarly with the centred guest as well. The aromatic rings in the three ligands are oriented almost perpendicular to the flattened macroring, avoiding steric hindrance with the guanidinium cation. In all three complexes there are no short contacts between either the crown or the guanidinium cation and the perchlorate counter ion.

The hydrogen-bonding scheme in a complex of guanidinium perchlorate with a larger dibenzo-30-crown-10 is different[126]. This polyether lacks the threefold symmetry in the arrangement of the ether oxygens. Therefore, in order to accommodate the guanidinium in a complementary manner the large crown is wrapped around the cation in a fairly irregular way. In the resulting structure only five of the six guest hydrogens are bound to four out of ten crown ether oxygens (N···O = 2.81–3.12 Å), one of the oxygens acting as an acceptor of two hydrogen bonds. Moreover, each NH_2 group is bonded in this structure to second-nearest neighbour oxygens, rather than to next-nearest oxygen atoms as in the previous examples.

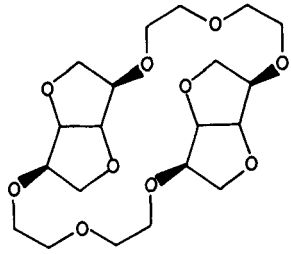
The 2,6-pyrido-substituted 27-crown-9 and 30-crown-10 polyethers encapsulate the guanidinium guest ion in a similar way[57,126]. As expected from previous observations, in both complexes the pyridyl nitrogen acts as an acceptor of hydrogen bonds. In the larger structure all six guanidinium hydrogens are used in relatively strong hydrogen bonds, the macroring adopting a saddle-like conformation. The smaller crown is roughly planar in the other structure. In neither case did proton transfer from guest to host occur. Selected complexes are shown in Figure 29.

Apart from the different conformational details, the structural features of the guest inclusion are similar in all the above compounds (Figure 29). These results indicate that the 27-membered macrocycles are well suited to form stable nesting-type complexes with uronium and guanidinium guests. In the respective structures the appropriately sized crown hosts can assume a relaxed nearly planar conformation, the arrangement of the oxygen binding sites being complementary to that of the NH_2 interacting entities. Formation of similar complexes with the larger 30-crown-10 macrocycles requires a considerable conformational reorganization in the host. The pyridine nitrogen was found to be the most effective acceptor of hydrogen bonds, while the aryl oxygens are the least effective ones.

The pyrido nitrogen in 2,6-pyrido-27-crown-9 can also be protonated in the presence of a strong acid, as shown in the 1:1 complex of this host with picric acid[126]. In the corresponding crystal structure, however, the ligand reveals a collapsed conformation with the pyridyl nitrogen turning toward the centre of and filling the macrocyclic cavity. The protonated nitrogen is directed outward and interacts strongly with the phenolic oxygen atom of picrate anion (N···O = 2.62 Å) located outside the cavity.

B. Other Complexes Involving 21-, 24-, 27- and 30-Membered Macrocycles

The large polyether ligands with suitably constrained geometries are also able to form stable complexes with boronammine and alkylammonium ions. Such an association both in the solid and in the solution was observed with the bisdianhydro-D-mannitolo-30-



(28)

crown-10 derivative **28**[127,128]. Structures of both the free and complexed molecules were analysed, providing another illustration of conformational changes that occur in polyether ligands during reactions of complexation (Figure 30). Thus, the uncomplexed host does not contain an open hydrophilic cavity. Rather, it exhibits a compressed conformation with several lipophilic C—H bonds turning towards the centre of the ring. On complexation with α-methylbenzylammonium perchlorate the ligand conformationally reorganizes in order to create the essential hydrophilic cavity and bind simultaneously the ammonium cation and a water molecule from the solvent. Seven of the ten oxygen atoms of the host are involved in hydrogen bonding. Two ammonium and one water hydrogens form bifurcated hydrogen bonds to three pairs of the oxygens, and the second hydrogen atom of water binds to another oxygen. The third hydrogen of the ammonium group provides a hydrogen-bonding bridge to the oxygen atom of the H_2O molecule.

Bisdianhydro-D-mannitolo-30-crown-10, on the other hand, forms a 1:2 complex with the boronammine (BH_3NH_3) substrate[129]. In fact, the latter was found to be an excellent guest species for forming crystalline supramolecular structures with a wide range of chiral crown ether hosts containing carbohydrate residues. This includes 1:1 complexes with D-mannitolo-20-crown-6 (**29**), αα-DD-bismannosido-18-crown-6 (**30**) and α-D-galactosido-18-

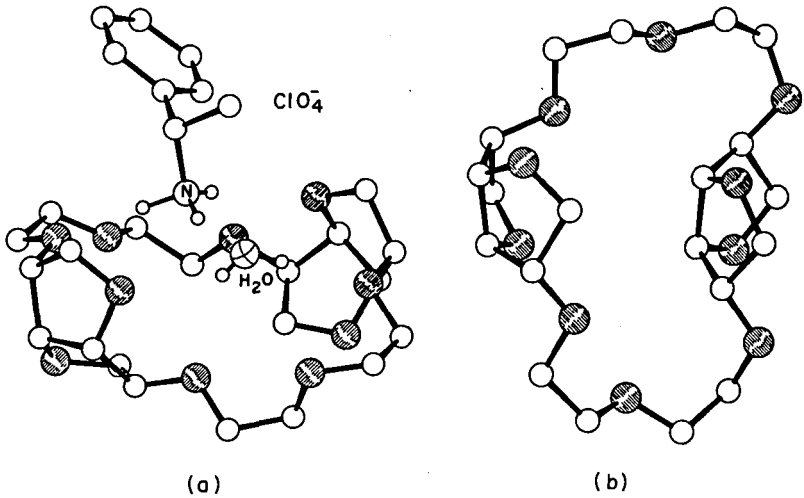
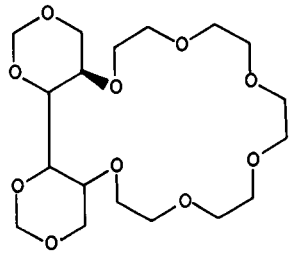


FIGURE 30. Comparison of the molecular conformation of host **28** in (a) its complex with α-methylbenzylammonium perchlorate and (b) the free ligand[127,128]



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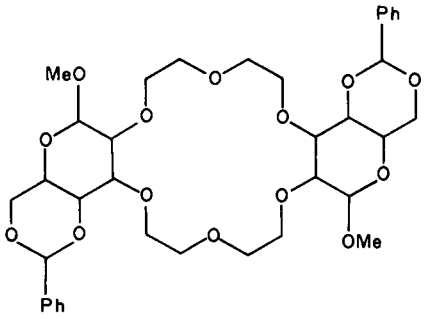

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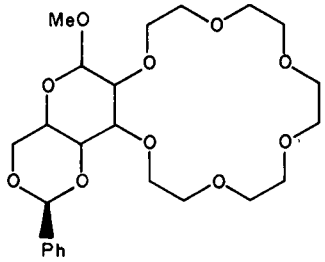
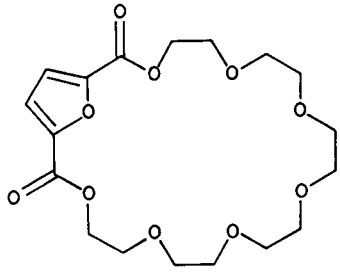


(31)

crown-6 (**31**). The α-D-mannosido-18-crown-6 is involved in a 1:2 complex, the neutral boronammine guests (with a formal positive charge on the nitrogen) occupying the two diastereotopic faces of the crown ring[129].

A unique association occurs between benzylammonium perchlorate and a 24-crown-8 ligand containing a 2, 5-diacylfuran unit as part of the polyether ring (**32**)[130]. The overall geometry of this compound is shown in Figure 31. Although all the torsion angles about C—C bonds are close to *gauche* and those about C—O bonds are nearly *anti* as in complexed 18-crown-6 moieties, the large ring is not pseudo-planar but rather resembles a cradle. The guest ion penetrates into the ring from its concave side in such a manner that the phenyl moiety is perpendicular and the C—NH_3^+ bond is roughly parallel to the mean plane of the ligating oxygens, in obvious contrast with previous observations. As a result,



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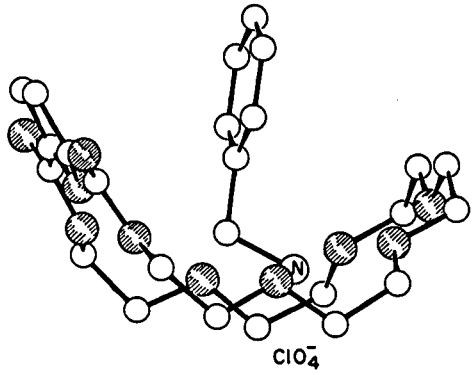
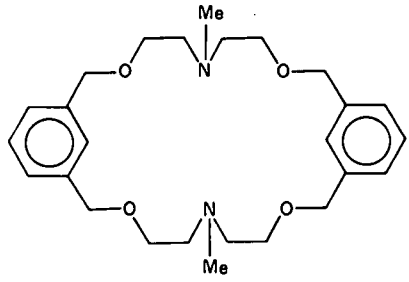


FIGURE 31. Complex of host **32** with benzylammonium perchlorate[130]

both the methylene and the ammonium groups interact directly with the polyether macrocycle. The former occupies one part of the cavity with two weak C—H···O interactions. The ammonium ion strongly hydrogen bonds to two ether oxygens in another part of the ring. The third ammonium hydrogen penetrates deeply into the cavity and hydrogen bonds to the perchlorate counter ion located on the opposite face of the macrocycle.

The above examples indicate that the 30-membered and even the 24-membered polyether rings are too large to form a monomolecular inclusion complex with a single ammonium entity. Instead, such ligands tend to interact with two (or more) guest species. Another evidence is provided by the structure of a 2:1 complex between the benzylammonium guest and a monocyclic diaza-24-crown-6 containing two transannularly located NMe groups (**33**). In order to avoid electrostatic ion–ion repulsion, the ammonium ions do not penetrate into the centre of the cavity from opposite sides. Rather, the guest species lie roughly parallel to the average plane of the diaza-24-crown-6 ligand (Figure 32)[131]. Each benzylammonium cation interacts only weakly with the host macrocycle *via* a single hydrogen bond, being attached at the same time to two neighbouring thiocyanate anions. Again, the nitrogen rather than oxygen heteroatoms are preferred in hydrogen-bonding interactions with the guest cations.



(**33**)

It has recently been shown that the dibenzo-24-crown-8 and its larger 30-crown-10 analogue can enter into second-sphere coordination with suitable transition metal

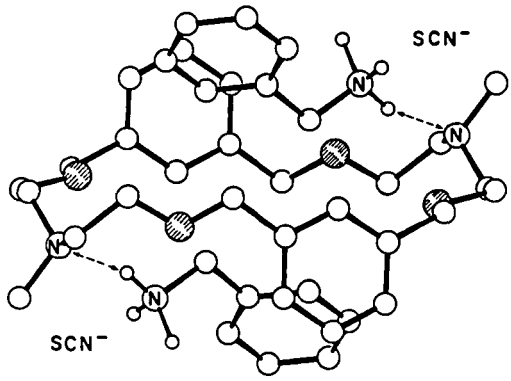
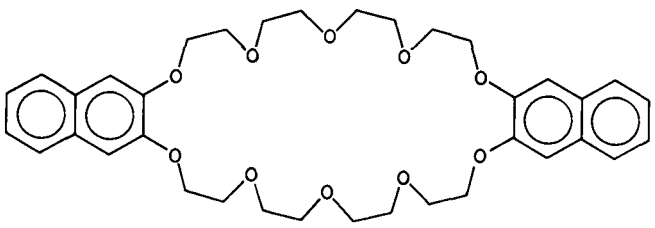


FIGURE 32. 1:2 Complex of host **33** with benzylammonium thiocyanate[131]

complexes by utilizing charge-transfer and van der Waals stabilization in addition to Coulombic and hydrogen-bonding interactions. In complexes of these two hosts with a cationic platinum(II) complex having a square-planar environment of one 2,2′-bipyridyl and two monodentate NH_3 ligands, the latter are involved in N—H···O hydrogen bonds to several oxygens of the respective crown ether. In addition, however, the macrocyclic ether envelops the transition metal complex to allow an effective charge-transfer interaction between the two benzene substituents (π-donors) of the crown host and one of the pyridine rings (π-acceptor) in the guest ligand[132]. The presence of charge-transfer interactions has been confirmed by ^{1}H NMR and UV–visible spectroscopy. The dinaphtho-30-crown-10 receptor **34**, which has a significantly more extented π-system, forms a similar complex with the coordinated platinum guest species. The ligand adopts a V-shape conformation as its dibenzo analogue and the guest entities are inserted deeply into the clefts thus provided[133]. There is a considerable overlap between the aromatic rings of host and guest constituents. X-ray structural investigations of the 1:1 crystalline complexes formed between a hexafluorophosphate salt of 6,7-dihydrodipyridopyrazidinium (diquat, **35**) and disubstituted dibenzo-30-crown-10 derivatives (**36**) reveal identical features[134]. In both cases charge-transfer in addition to electrostatic binding and weak C—H···O interactions combine to give the complexes their remarkable stabilities. The ability to add functional substituents to the benzo rings of the host paved the way to a design of a more rigid macrobicyclic host (**37**) by reacting the bishydroxymethyl derivative of dibenzo-30-crown-10 with 1,2-bisbromomethylbenzene[135]. Apparently, the additional bridge confers both increased



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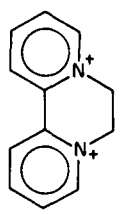

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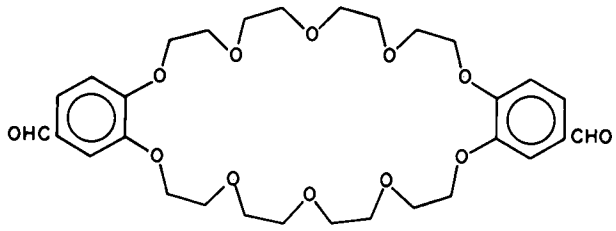

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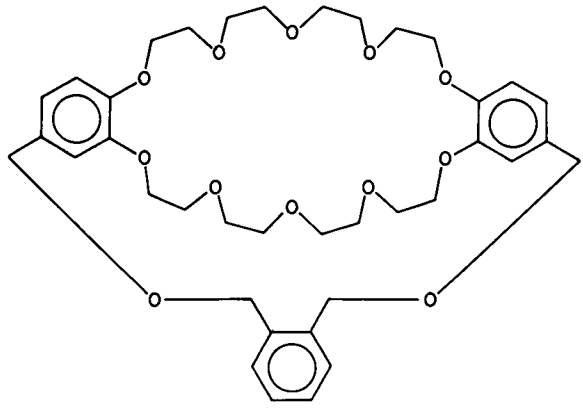
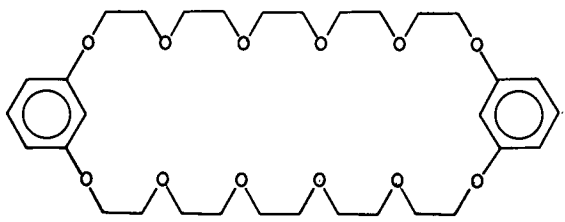


(37)

conformational stability and enhanced guest binding capability upon the host. The 1:1 complex formed with the diquat dication, however, showed structural features very similar to those observed in the unbridged structure.

Similar structural relationships are found in the complexes of the two dibenzo hosts and the $[Rh(1,5\text{-cyclooctadiene})(NH_3)_2]^+$ and $[Rh(norbornadiene)(NH_3)_3]^+$ guest cations (present as hexafluorophosphate salts)[136]. Here, in addition to hydrogen bonding between the NH_3 ligands and ether oxygens, the stability of the adducts is enhanced by attractive van der Waals interactions between the cyclooctadiene and norbornadiene ligands and the lipophilic benzene rings. These second-sphere type coordination complexes are reviewed (and their structures are illustrated) in more detail in Chapter 5.

The stabilizing combination of intermolecular CT interactions, ion–dipole forces and hydrogen bonding is also apparent in the 1:2 complex between dibenzo-36-crown-12 (**38**)



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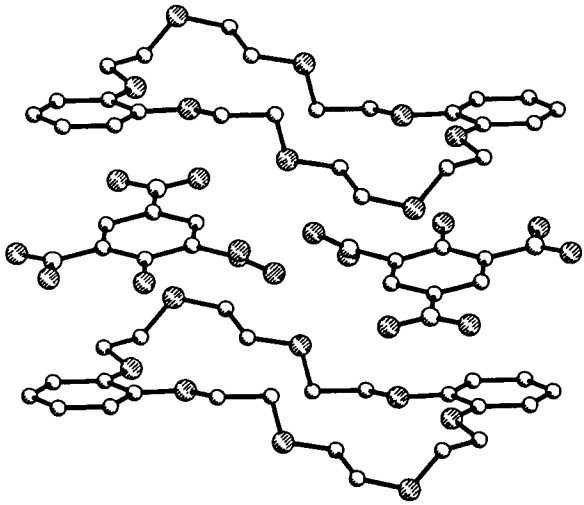


FIGURE 33. Structure of the 1:2 complex between dibenzo-24-crown-8 and picric acid, showing a stacked arrangement of the aromatic fragments[138]

and hydrated lithium picrate[137]. In this structure the two Li^+ ions approach different parts of the crown. Each of the cations is 5-coordinated within a distorted bipyramidal geometry to one water molecule, to crown ether oxygens and the phenoxide and nitro group oxygen atoms of the picrate counter ion. The picrate rings are nearly parallel to the benzo rings in the host with a minimum separation between them of 3.37 Å. The charge-transfer interactions were found to provide the main stabilizing contribution in the unusual structure of a 1:2 complex of dibenzo-24-crown-8 with picric acid[138]. This compound can be best described as a layered structure (Figure 33). It consists of alternating layers of picric acid and crown molecules with stacking of the π-electron-deficient aromatic rings in the acid molecules and the π-electron-rich aromatic rings in the ligand. Two molecules of picric acid are positioned between any pair of the crown species, which assume extended conformations, but there is no apparent hydrogen bonding between the constituent moieties. The interplanar distance between the overlapping catechol rings and picric acid rings is about 3.4 Å. The presence of charge-transfer interactions is well reflected in the pronounced red colour of the crystals.

Complexation of the [diquat]·$(PF_6)_2$ salt with dibenzo-30-crown-10 leads to a structure very similar to that exhibited by [Pt(bipyridyl)$(NH_3)_2$]$(PF_6)_2$ (Figure 34)[139]. The diquat dication (**35**) is located within the V-shaped host. The two benzo rings of the crown and the dipyridinium ring of the diquat guest cation are aligned in a parallel manner. The average distance of 3.4 Å between these planes is ideal for a charge transfer between the π-electron-rich catechol units in the host and the π-electron-deficient bipyridinium rings in the guest. Favourable electrostatic interactions between the aryl oxygen atoms in the host and the positively charged atoms in the guest rings contribute further to the stability of the host–guest complex, replacing the ammine–crown hydrogen bonding interactions present in the platinum complex. A very similar interaction scheme can be used to describe the 1:1 complex between dinaphtho-30-crown-10 and the diquat cation reported recently[133]. Again, NMR studies strongly indicate that the binding geometries observed for these compounds in the solid are also retained in solution.

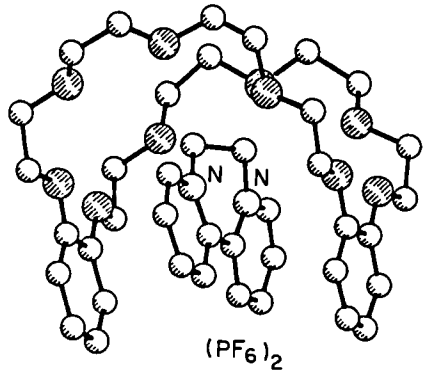
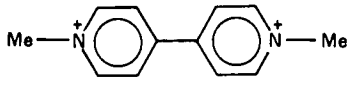


FIGURE 34. 1:1 Complex of dibenzo-30-crown-10 with [diquat]·$(PF_6)_2$[139]

Only a small number of other structures involving the 21-crown-7, 24-crown-8, 27-crown-9 and 30-crown-10 frameworks have been reported in recent years. They include complexes of potassium cation with benzo-21-crown-7[140], dibenzo-24-crown-8[141] and dibenzo-30-crown-10[142].

C. Molecular Inclusion of Diquat and Paraquat Dications

As a natural development of the preceding observations, major efforts have been devoted to the design of encapsulation-type host–guest complexes involving larger polyether receptor and substrate constituents, by incorporating sites available for cooperative charge-transfer, pole–dipole and hydrogen-bonding interactions into the system. The bipyridinium herbicides diquat (**35**) and paraquat (**39**) dications were chosen as potential guests entities. Their successful complexation in solution was achieved using bismetaphenylene-32-crown-10 (**40**) and a series of bisparaphenylene-(3*n* + 4)-crown-*n* (*n* = 7–12) hosts[143–146]. Normally, large uncomplexed macrocyclic rings such as dibenzo-30-crown-10 and its analogues exhibit a tendency to collapse on themselves, by turning inward fragments of the macroring. However, the uncomplexed bismetaphenylene-32-crown-10 reveals an unusually open conformation with a rectangularly shaped cavity of dimensions 4.9 × 7.8 Å[143]. The free bisparaphenylene-34-crown-10 (**41**) also shows a perfectly preformed cavity. The approximate dimensions of the cavity in one of the observed conformations are 4.7 × 10.6 Å[144]. Consequently, minimal conformational changes are required of these molecular receptors to encapsulate effectively the nearly rigid diquat and paraquat substrates.



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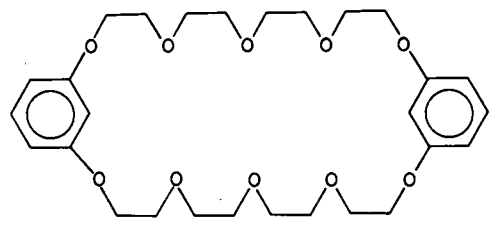

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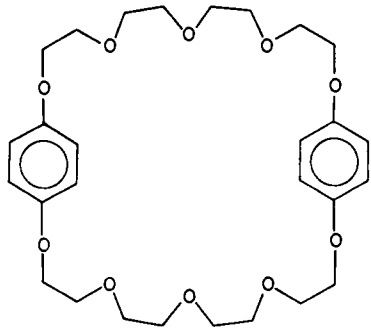

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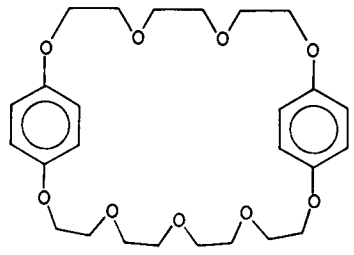
Indeed, the bismetaphenylene-32-crown-10 derivative forms 1:1 complexes with diquat and paraquat dications, in which the bipyridinium unit of the substrate becomes sandwiched between the two resorcinol rings of the ligand (Figure 35a)[143]. A crystallographic study of the diquat complex confirmed that the guest dication is inserted between approximately parallel resorcinol subunits in the receptor. The observed structural features are also consistent with the presence of the three different types of interaction in the structure. Evaluation of a bisparaphenylene-34-crown-10 derivative as a potential complexer for diquat and paraquat dications has also led to successful results. This receptor forms a 1:1:1 complex with diquat and 1 mol of water, both encapsulated simultaneously within its oval-shaped cavity[144]. The diquat dication is found to overlap significantly the two hydroquinolinol rings of the host, yet it appears to be too small to occupy the entire cavity. The paraquat dication is much better suited to complex with the 34-crown-10 receptor, and 1:1 molecular inclusion complexes could be identified both in acetone solution and in the solid state (Figure 35c)[145]. The solid structure reveals that the conformation of the receptor in the 1:1 complex (in which the main axis of the paraquat guest species nearly coincides with the long axis of the cavity) is virtually unchanged on complexation from that observed for the free macrocycle.

UV and NMR spectroscopic studies have also indicated that the 34-crown-10 derivative is the best receptor for the paraquat dication. However, to match optimally the size of the diquat cation a smaller macrocycle is required. In fact, for this guest cation bisparaphenylene-31-crown-9 (**42**) turns out to be the most effective receptor. A nearly perfect match between the size of the cavity and that of the cation is also reflected in the



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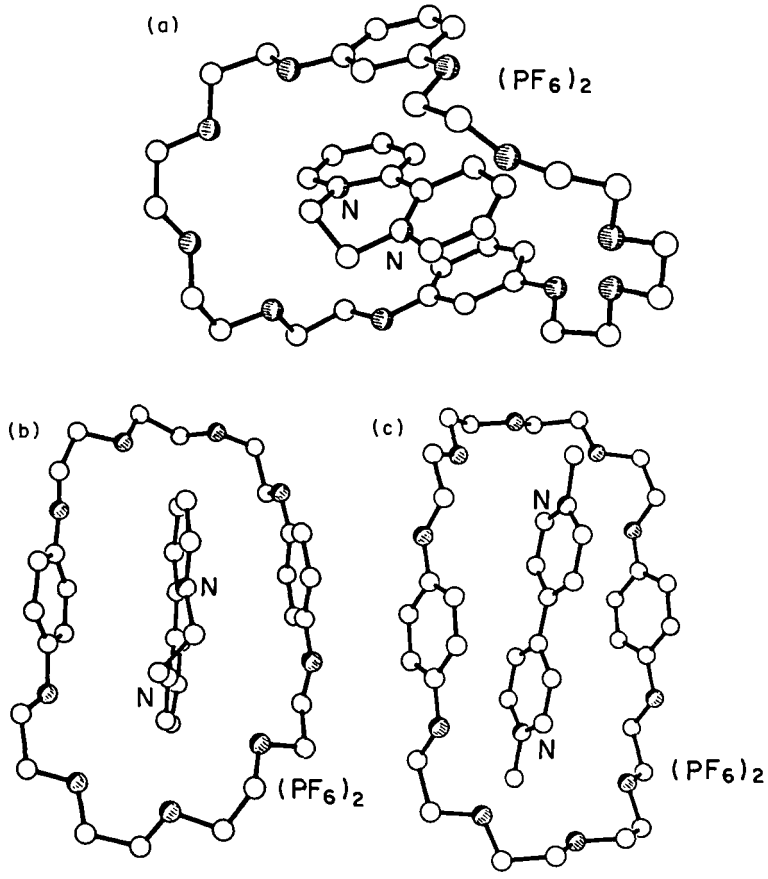
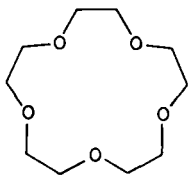


FIGURE 35. Encapsulation of diquat dication within (a) host **40**[143] and (b) host **42**[146] and (c) paraquat dication within host **41**[145]

crystal structure of this complex, which does not require additional complexation of water (Figure 35b)[146]. The solids of all the above-described complexes are characterized by a deep colour. The analyses of the corresponding structural details clearly indicate that the geometry of guest binding is determined by the balance between charge-transfer, electrostatic, and hydrogen-bonding interactions. In this context it is interesting to compare the conformational features of the various bisparaphenylene crown receptors as a function of size. Crystallographic studies show that the conformation of the 34-crown-10 derivative supports a large open molecular cavity (perfectly suited for the paraquat dication) even in the uncomplexed state, the two hydroquinone rings lying parallel to each other. However, when the macrocyclic ring size increases as in the 37-crown-11 and 40-crown-12 derivatives the receptor cavity collapses progressively; a sizeable void is still present in the former, whereas the cavity is completely filled in the latter host[147]. Further, on moving to the smaller 25-crown-7 and 28-crown-8 bisparaphenylene homologues, the potential cavity also contracts. These results are in agreement with previous observations that conformationally preorganized receptors are best suited for stable complexations.

IV. HOST–GUEST COMPOUNDS WITH SMALL CROWN ETHERS

Crown rings smaller than the 18-crown-6 moiety are used mostly to complex metal cations. The conformational modes adopted by free and complexed 15-crown-5 (**43**), 14-crown-4 (**44**) and 12-crown-4 (**45**) macrocycles have been reviewed[7,10].



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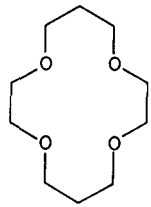

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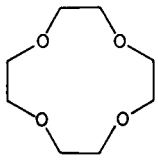

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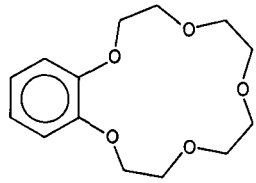

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A. Benzo-15-crown-5

The complexing properties of benzo-15-crown-5 (**46**) host have been studied most extensively. This host was found to form crystalline complexes with salts of alkali and alkaline earth metals with a crown-to-metal ratio of 1:1 for small cations (Mg^{2+}) and 2:1 for larger cations (K^+, Cs^+, Sr^{2+}, Ba^{2+})[148]. Na^+ and Ca^{2+} have similar ionic radii, and are exceptional in that they can form either 1:1 or 2:1 complexes depending on the crystallization conditions and type of anion. For example, when tetraphenylborate is used as the counter ion 2:1 complexes are formed with both cations. Ca^{2+} forms 1:1 complexes with anions that can act as a coordinating ligand such as isothiocyanate and 3,5-dinitrobenzoate. Moreover, in dilute solutions sodium perchlorate associates with one molecule of the crown host, whereas in very concentrated media it binds to two hosts.

The structural aspects of complexes involving benzo-15-crown-5 as host and Group IA and IIA cations as guests have been further reviewed more recently by Poonia *et al.*[149]. They emphasized the effect of charge density in the cation on the geometry and stoichiometry of interaction with other species[150]. They concluded also that 'the interaction stoichiometry of an alkali metal cation with a cyclic multidentate ligand is not only a function of the ion and cavity size alone, but also of its Lewis acid strength as modified by the charge of the counter ion'[151].

Potassium and rubidium cations are characterized by a fairly low charge density and form charge separated sandwich complexes M^+(benzo-15-crown-5)$_2$ (M = K, Rb) in which the M^+ ion is 10-coordinated to all the oxygens of the two crown molecules[152–154]. The corresponding contact distances are $K^+ \cdots O = 2.76$–3.11 Å and $Rb^+ \cdots O = 2.92$–3.07 Å. In the 1:1 complexes of the same host with sodium, the cation is coordinated by the five ether oxygen atoms and also by the anion (e.g. picrate), forming a pentagonal pyramid-type structure[150]. The Na^+ lies above the crown cavity and is in contact from its opposite

side with the counter ion. Similar 1:1 anion paired complexes were found in the structures of benzo-15-crown-5 with sodium thiocyanate hemihydrate[155] and caesium picrate[151] and of 2,3-dimethoxybenzo-15-crown-5 with sodium bromide[156].

Cations with a higher charge density such as Ca^{2+} and Li^{+} bind with the anion and the solvent (water), the macrocyclic ligand being hydrogen bonded to the water molecules in the coordination sphere of the cation[157]. The 1:1 complex of barium 3,5-dinitrobenzoate with benzo-15-crown-5 crystallizes as a dimer in which the two Ba^{2+} ions are 9-coordinated by the oxygen sites of the macrocycle in addition to the carboxylate moieties[158].

There are two interesting examples of complexes with other metals which are situated in the central cavity of the crown (nesting), involving $CuCl_2$ and $AlCl_2^+$ guest moieties (Figure 36). The former shows a unique structure of a 7-coordinated Cu^{II}; the complex has a pentagonal-bipyramidal geometry with the two Cl^- anions coordinated axially (at Cu···Cl = 2.24–2.25 Å) and the five ether oxygen atoms equatorially (at Cu···O = 2.24–2.34 Å)[159]. An almost identical coordination polyhedron was observed for the 7-coordinated aluminium; the interaction distances are at Al···Cl = 2.20 Å, Al···O(aryl) = 2.28–2.30 Å and Al···O(non-aryl) = 2.03–2.08 Å, indicating a lower ligating capability of the aryl oxygens[160].

Only a few examples of a direct interaction between a small crown species and an uncharged organic guest molecules are known. Most recently, two complexes of the benzo-15-crown-5 host with dithiooxamide and thioacetamide have been reported, revealing host–guest interaction details very similar to those described previously for 18-crown-6[161]. Thus, crystals of the 1:1 complex with the bifunctional thiooxamide consist of

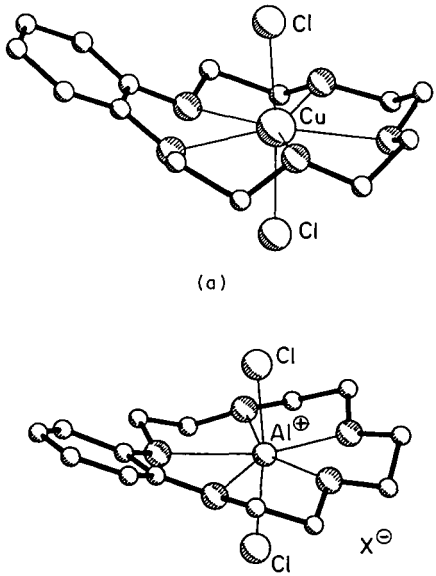


FIGURE 36. 1:1 Complexes of benzo-15-crown-5 with (a) $CuCl_2$[159] and (b) $[AlCl_2]^+\cdot[AlCl_3Et]^-$[160] (X represents the anion)

infinite chains of alternating constituent molecules. In the 1:2 complex of thioacetamide the host forms a distinct molecular entity with two molecules of the guest. In both structures the crown host is approached from both sides by two coordinating species, its oxygens being involved in one bifurcated and one normal hydrogen-bonding interaction on each face. The oxygen atoms of the host form an approximate pentagon with the amide nitrogen atoms lying 2.2 Å above the mean oxygen plane. The conformation of the ligand, characterized by *gauche* torsions within the ethyleneoxy units, is the same in both structures.

B. 15-Crown-5

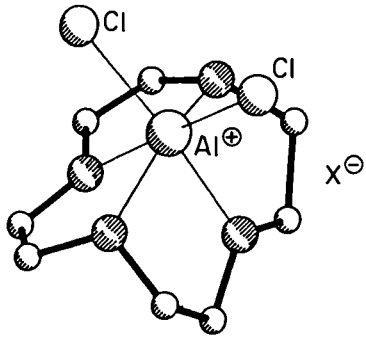
The unsubstituted 15-crown-5 host is also an effective ligand for metal cations. In its 1:1 complexes with Na^+ and K^+ ions, the latter are complexed by the crown as contact ion pairs, being displaced out of the mean plane of the crown ring. The observed displacements are 1.05 and 1.10 Å for sodium[162,163] and 0.9 Å for potassium[162], the alkali metals showing strong interactions with the anionic entities. On the other hand, crystalline complexation with barium leads to a sandwich-type $Ba(15\text{-crown-}5)_2^{2+}$ structures in which the cation is entirely surrounded by two crown rings. The BaO_{10} core has D_{5d} symmetry[164].

As with the other ligands, one finds in the literature two main types of complexes between transition elements and 15-crown-5, those with direct metal–crown interaction and those with the crown ether oxygens bonded to a metal *via* a bridging water. In the $[Y(H_2O)_8]Cl_3$-15-crown-5 complex the yttrium ion is 8-coordinated to the oxygen atoms of the eight water molecules[165]. Three of the latter are further hydrogen bonded to the crown ether molecule (second-sphere coordination). In a different structure, the samarium(III) ions was found to be coordinated directly to five oxygens of 15-crown-5 (at an average Sm···O distance of 2.51 Å) and also to four water molecules (at an average distance of 2.43 Å)[166]. Similarly, in crystals of $[Co(H_2O)_2$-15-crown-5$](NO_3)_2$ the oxygen atoms of the crown ether ring are directly coordinated to Co^{II}. The 7-coordination of the metal cation is supplemented by additional interactions with two molecules of water[167]. In most cases the 15-crown-5 host adopts an open conformation, with the five oxygens of the ligand being nearly coplanar.

C. 12-Crown-4

The even smaller 12-crown-4 ligand also exhibits binding properties toward metal entities. It was found to form 1:1 crystalline complexes with $Co(NO_3)_2$[167] and $Y(NO_3)_3$[168], in which the metal cation is surrounded by and directly interacts with both the crown ether rings and the anions. As in the previous example, the Co^{II} is 7-coordinated. The coordination around the yttrium ion involves ten ligating sites at average distances of Y···O(ether) = 2.46 Å and Y···O(nitrate) = 2.44 Å. Anhydrous 2:1 sandwich complexes of 12-crown-4 with $NaClO_4$ and $AgAsF_6$ have also been observed. The 8-coordination about the sodium ion may be described as slightly distorted rectangular antiprismatic, with the heteroatoms being planar to within ± 0.01°[169]. The other crystal structure contains an 8-coordinated Ag^I cation sandwiched between two 12-crown-4 rings, with an average Ag···O bond length of 2.57 Å[170]. Figure 37 illustrates the perching-type interaction of 12-crown-4 with $Eu(NO_3)_3$[80] and $(AlCl_2)\cdot(AlCl_3Et)$[87] species.

Very interesting features have been revealed by a tetraaza-12-crown-4 ligand with 2-hydroxyethyl side-arms substituted on the four nitrogens (**47**). On complexation with alkali metal cations this host uses a varying number of side-arm OH ligating sites for optimized guest coordination[171]. In the 1:1 complex of this ligand with KSCN all four side-arms are used to make the K^+ cation 8-coordinated. In the complex with NaSCN the



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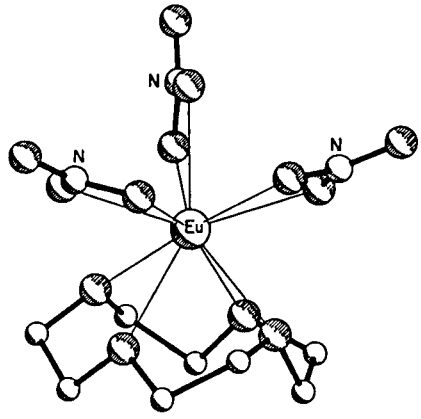
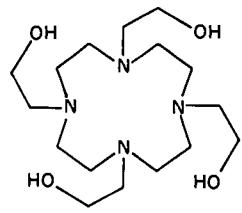


(b)

FIGURE 37. 1:1 Complexes of 12-crown-4 with (a) $[AlCl_2]^+ \cdot [AlCl_3Et]^-$[87] (X represents the anion) and (b) $Eu(NO_3)_3$[80]

Na^+ cation is 7-coordinated, making use of only three side-arms. The third observed structure contains a 5-coordinated Li^+ guest, involving the four nitrogen sites of the ligand and one side-arm bent in. Finally, in the 1:1 complex with a molecule of water the latter is

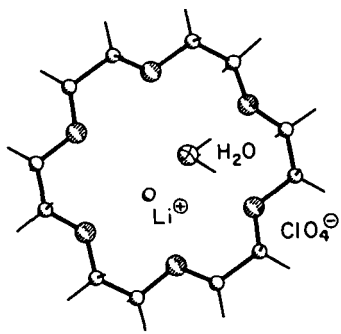


(47)

completely encapsulated within the ligand, donating two hydrogen bonds to two transannular N-sites and receiving two hydrogen bonds from side-arms attached to the other two ring nitrogens. In none of these structures is any direct anion–cation interaction apparent. The conformation of the 12-membered ring remains roughly the same in all structures, consisting of ag^+g^+ torsions within the four N—C—C—N subunits.

D. Inclusion of Lithium Cations

We conclude the discussion on the structural features of complexes between small crown ethers and metal cations by examining the complexes formed by Li^+ with a series of different host species. These compounds have been extensively studied in recent years in order to improve the selectivity of the crown ethers for Li^+ over other ions (a possible application involves the regulation of Li^+ concentration in the brain). Coordination



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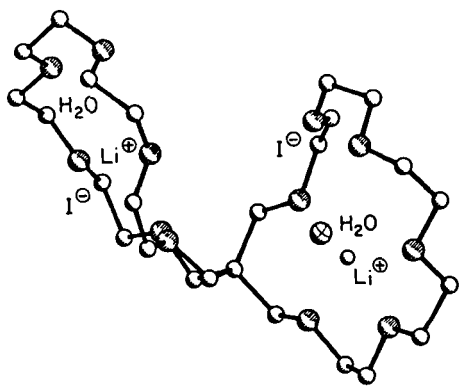


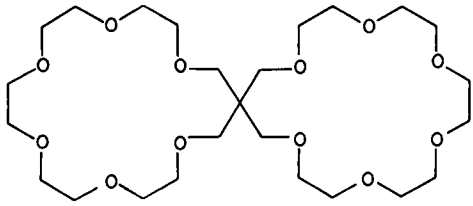
(b)

FIGURE 38. (a) 1:1 Complex of 18-crown-6 with $LiClO_4$ hydrate[172] and (b) 1:2 complex of host **48** with LiI dihydrate[173]. Only the crown-bound molecules of water are shown

numbers varying from 2 to 8 are now known for the lithium cation. This allows the formation of a large variety of structures with different modes of crown–metal interaction.

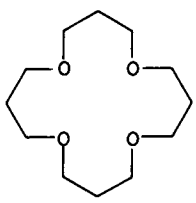
With the 18-crown-6 ligand two types of adducts have been observed: a 1:1 complex with $LiClO_4$ and a 1:2 complex with LiSCN, both including two additional moles of water (Figure 38a)[172]. The 18-crown-6 ring skeleton is too large for the small Li^+. It is effectively narrowed by encapsulating a water molecule within the cavity. The water has a double role, acting as a coordinating agent toward Li^+ and donating its protons to the ether oxygens. In the perchlorate complex the crown adopts a D_{3d} conformation and the Li^+ is coordinated to the ring oxygens and to two molecules of water. In the thiocyanate complex the crown adopts the biangular C_i conformation. The lithium ions have a fourfold coordination: one is coordinated to two ether oxygens and two waters and the other to one ether oxygen, one water and two SCN^- ions.

A very similar arrangement was found in the crystal structure of the 1:2 complex of 18,18′-spirobi(19-crown-6) (**48**) with lithium iodide dihydrate (Figure 38b)[173]. Both macrorings of this ligand bind a Li^+ ion and one of the water molecules in the same cavity. The metal ion in this structure is five-coordinated to three ether oxygen atoms of the crown, to the bound water and to the free H_2O of solvation, forming a distorted trigonal bipyramid.



(48)

In a large series of ligands, all containing four ether oxygen binding sites, the association of Li^+ is characterized by pentacoordination with a square-pyramidal geometry (Figure 39). For example, in the 1:1 complex between 16-crown-4 (**49**) and LiSCN the metal ion is coordinated to four ether oxygens at 2.07–2.09 Å and to the nitrogen of the anion at 2.04 Å, being displaced 0.55 Å out of the oxygen plane toward the coordinating SCN^- [174]. Similarly, in the 1:1 complexes of $LiNO_3$ with benzo-14-crown-4 (**50**) and dimethyl-14-crown-4 (**51**) the Li^+ ligates to the four ether oxygens and the bidentate NO_3^- counter ion, being displaced 0.85 Å from the plane of the former towards the adjacent nitrate[175]. Pentacoordinated Li^+ was found also in the 1:1 crystalline complexes of LiSCN with dibenzo-14-crown-4 (**52**) and benzo-13-crown-4 (**53**)[176]. Both ligands are bent with all four oxygens directed toward the convex side of the molecule, allowing simultaneous



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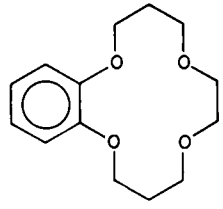

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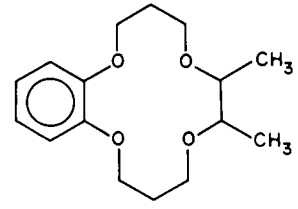

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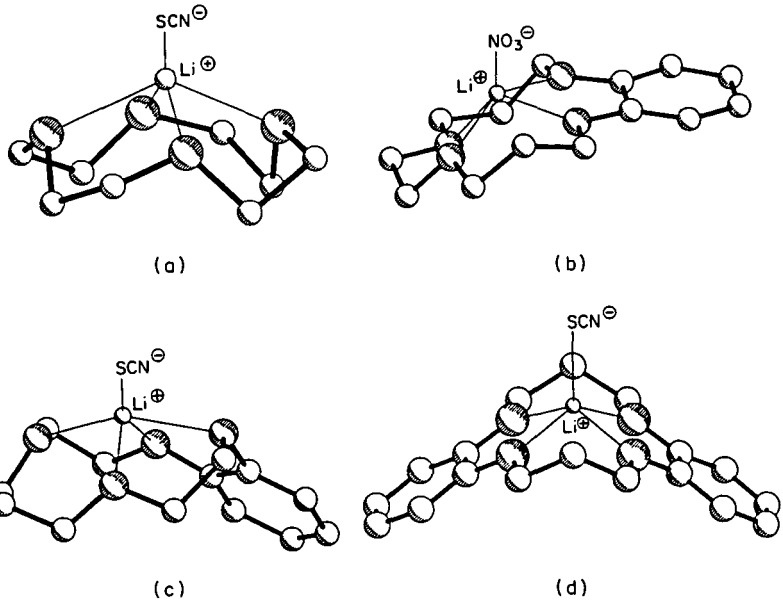
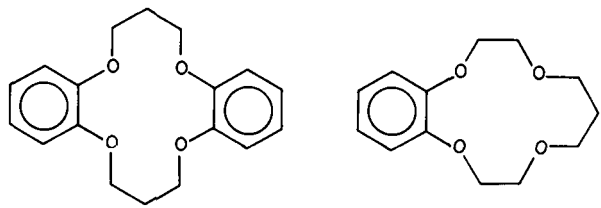


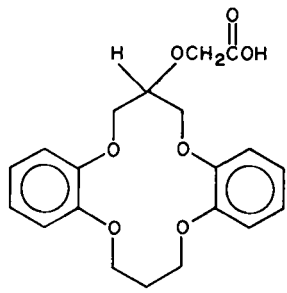
FIGURE 39. Complexes of Li^+ salts with (a) 12-crown-4[178], (b) benzo-14-crown-4[175], (c) benzo-13-crown-4 and (d) dibenzo-14-crown-4[176]



(52) (53)

coordination to the lithium cation. The metal lies about 0.8 Å out of the plane of the oxygens, its fifth coordination being occupied by SCN^-. In the two complexes the crown cavity is thus open only to one side, which is approached in the crystal by the S-end of an adjacent entity of the complex. Despite the small size of the macrocyclic rings and a limited flexibility of the molecule due to the rigid catechol groups, most of the aliphatic O—C—C—O and C—C—O—C torsion angles are close to 60 and 180°, respectively.

The non-specific anionic ligand can be easily exchanged for another, or it can be eliminated entirely from the coordination sphere of Li^+. In a search for possible enhancement of the lithium selectivity the dibenzo-14-crown-4 has been modified by adding a side-arm which bears a carboxylic acid end-group[177]. This provides a potential intramolecular counter ion to occupy the apical coordination site of the Li^+. However, crystallographic studies of the hydrated complex between *sym*-dibenzo-14-crown-4-oxyacetate (**54**) and Li^+ revealed that the carboxylate is much too distant from the anticipated apical coordination position of the lithium cation. Instead, this site is occupied



(54)

by a molecule of water which forms a bridge between the Li^+ and the negatively charged carboxylate group (Figure 40). In addition, this structure contains an extensively ordered hydrogen-bonded water network; attempts to isolate water-free crystals have failed so far. The conformational features of the host are very similar to those observed for the unsubstituted dibenzo-14-crown-4 ligand. A successful encapsulation of Li^+, using side-arm binding sites, has been referred to in Section IV.C.

Interestingly, in some cases the association of Li^+ with even smaller 12-crown-4 is characterized also by a square-pyramidal pentacoordination. Suitable examples include 1:1 complexes of this ligand with LiSCN[178] and with $LiN(SiMe_3)_2$[179]. In these two structures the coordination sphere around Li^+ consists of four basal oxygen atoms and an apical N-site of the thiocyanate or the bis(trimethylsilyl)amide ions. In other complexes of this host the lithium ions exhibit a coordination number of 8 (previously unknown). This includes 2:1 complexes between 12-crown-4 and the lithium cation with diphenylarsenide, diphenylphosphide[180], dimethylcopper and diphenylcopper as counter ions[181]. Here the Li^+ is surrounded by two separate crown ether entities to form a puckered sandwich arrangement $[Li(12\text{-crown-}4)_2]^+$, being coordinated only by the crown ether oxygens

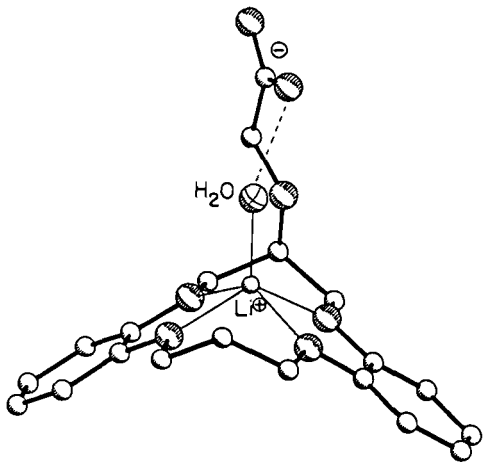


FIGURE 40. 1:1 Complex between host **54** and hydrated Li^+ [177]

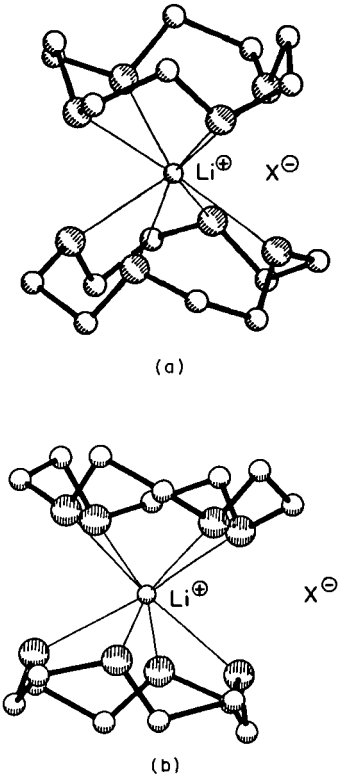


FIGURE 41. 2:1 Complexes of 12-crown-4 with (a) diphenyl phosphide and (b) dimethylcopper(I) lithium salts, showing 8-coordination of the cation[180,181] (X represents the corresponding counter ions)

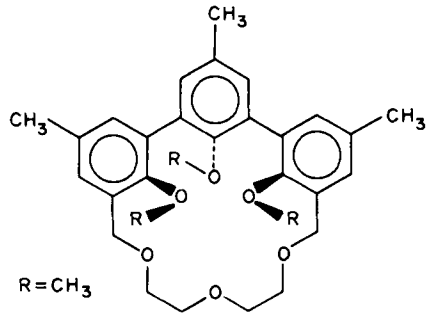
(Figure 41). Incidentally, these structure types demonstrate the use of a crown ether in effecting metal cation and organometalloid anion separation.

As expected, in the octagonal coordination the Li···O interaction distances are unusually long, ranging from 2.21 to 2.56 Å with an average of 2.36 Å. Characteristic averages of Li···O distances observed for other coordination geometries of Li^+ are 1.97, 2.06 and 2.16 Å for tetra-, penta- and hexa-coordination, respectively. While the effective cavity size in the 18-crown-6 ligand is too large for the Li^+ cation (see above), that in the various tetraoxa hosts appears too small to accommodate Li^+ within the plane of the four macrocyclic ether oxygens. For example, the van der Waals diameter of the cavity in dibenzo-14-crown-4 was estimated from the diagonal distances between the opposite oxygen atoms across the macrocyclic ring (after subtracting their size) to be only 0.97 Å[176]. It can thus be anticipated that a host of an intermediate size will be an optimal choice for the encapsulation of single non-hydrated Li^+ ions; this remains to be confirmed by suitable structural investigations.

V. HEMISPHERANDS, SPHERANDS AND CAVITANDS—MACROCYCLIC HOSTS WITH ENFORCED CAVITIES

A. Ligands with Ether Oxygen Binding Sites

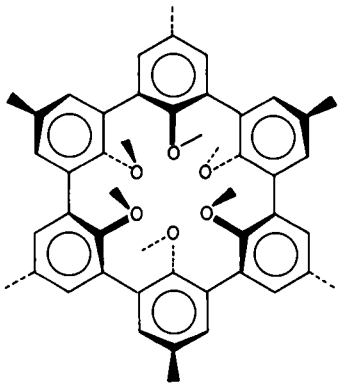
In the formation of molecular inclusion complexes the free energy of complexation is higher as the number of host ligating sites, organized for maximum binding during synthesis rather than during complexation, is larger[1]. Hemispherands and spherands, containing a different organization of binding sites than in the crown macrocycles, are unique examples of synthetic polyethers which possess either partially or fully enforced cavities. The first ligands of this type were prepared from anisyl or 4-methylanisyl moieties joined in the 2- and 6-positions. For example, hemispherand **55** contains one rigid *m*-teranisyl unit as part of the macroring. The oxygen ligating sites of anisole units are held in sterically enforced conformations; however, this ligand remains conformationally flexible to some extent, mainly in the diethylene glycol bridge. In the crystal structure, the cavity within the empty ligand is filled with two inward-turning methylene groups of the aliphatic fragment, while the unshared electron pairs of the non-aryl oxygens point outward[182]. On complexation with *t*-butylammonium perchlorate the host conformation reorganizes (mainly by a change of the OCH_2CH_2O torsions within the bridge) to accommodate the interacting guest[1].



(**55**)

The cyclohexametaarylene prototype spherand **56** is fully organized during synthesis, and its overall conformation remains unchanged on complexation with guest species[183]. In this ligand the intramolecular cavity is defined by the six aryl oxygens, which are octahedrally arranged around the molecular center. The entire molecule has approximate D_{3d} symmetry and is covered by a lipophilic skin of C—H bonds which shields the unshared electrons on oxygen from interaction with the solvent. Additional examples of rigid and highly strained spherands (due to electron–electron repulsions between the inward-turning oxygen lone pairs) are provided by compounds **57** and **58**, in which two pairs of the aryl oxygens are bridged[184]. These and similar spherands were found to complex efficiently alkali metal and ammonium cations in both nesting and perching arrangements. Moreover, having preorganized rigid cavities, they exhibit enhanced selectivities toward those metal ions which can be fully encapsulated within the host (on insertion of a cation between the host oxygens the electrostatic strain is reduced)[185].

More recently, spherands and hemispherands containing cyclic urea groups and other moieties in addition to anisyl groups have also been used for the complexations. The cyclic urea unit exhibits a dominant contribution to the binding ability of these hosts toward



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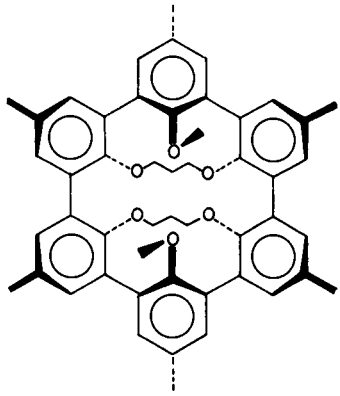

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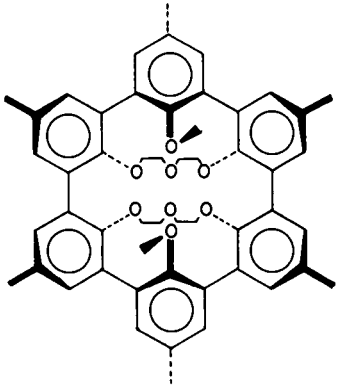

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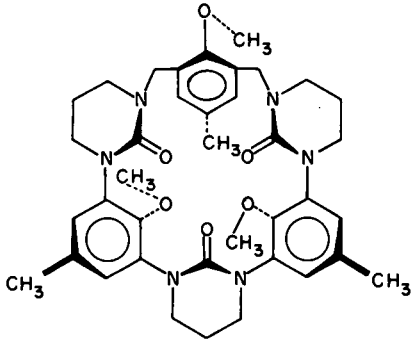


(59)

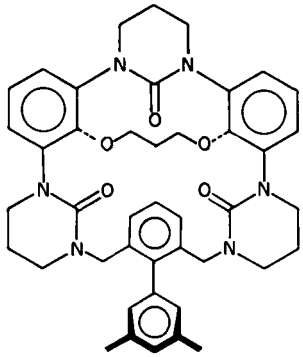
metal and ammonium ions[186,187]. In a typical spherand-type structure (**59**), three cyclic ureas are bound to one another in a triangular arrangement through phenylene spacer units. The carbonyl groups are held in convergent positions with their unshared electron pairs directed towards the centred guest moiety. The complexes formed are thus stabilized mainly either by pole–dipole interactions with the metal cations or by tripod hydrogen bonding with alkylammonium ions.

A detailed review of the spherand and hemispherand structures is given by Weber in Chapter 5. The various properties of these highly structured systems have recently been summarized by Cram, who designed them and studied their behaviour[188].

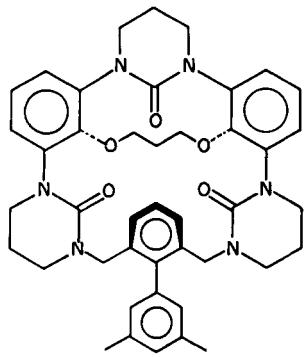
B. Ligands Containing >C=O Binding Sites

In this section some additional features of the synthetic macrocyclic hosts are discussed. Recent complexation studies with a series of hosts containing only cyclic urea binding sites (**60–63**) have shown that host–guest type complexes with uncharged guests can also be formed in spite of the fact that much weaker forces determine their structures[189]. The two

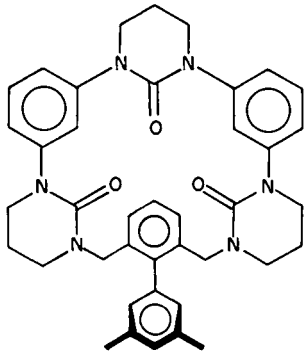
bridged isomeric macrocycles (**60**, **61**) have preorganized configurations, in contrast to their unbridged analogue (**62**). The terminal rings in the non-cyclic ligand **63** provide additional sites for hydrogen bonding.



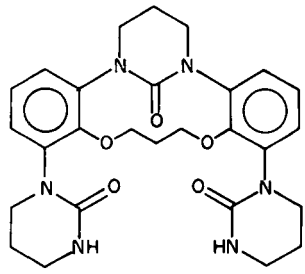
(**60**)



(**61**)



(**62**)



(**63**)

These host species were found to be particularly suitable to interact with proton donating H_2O and CH_2Cl_2 guest moieties. The bridged ligands contain concave cavities with carbonyl groups lined on the surface and held in convergent positions by the molecular framework. Such an arrangement seems perfect for the association with either one or two molecules of water, each H_2O hydrogen bonding in a 'dipode' fashion to two adjacent appropriately spaced carbonyls of the host (Figure 42). The coordination sphere of the bound water is supplemented in the crystal by another molecule of H_2O or CH_2Cl_2, which approaches the bound species from the opposite side. The significance of configurational preorganization of the host structure to an efficient guest binding is emphasized by an observation that no stable complexes of a similar but unbridged macrocyclic ligand (**62**) could be crystallized. In the structure of **62** the central cyclic urea and the two flanking carbonyls are tilted towards opposite surfaces of the molecular framework. One face of the molecule has a convex form, being also covered by lipophilic CH groups. The other face with the flanking carbonyls on it constitutes a concave and polar surface. The distance

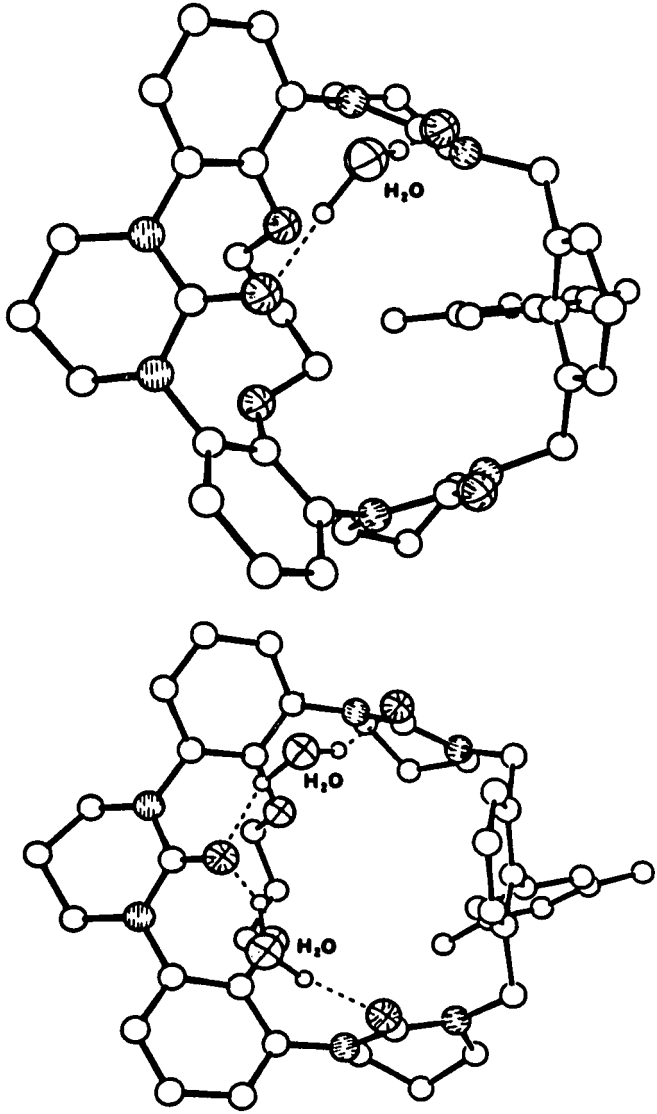


FIGURE 42. Complexes of host **61** with either one or two molecules of water[189]

between the two oxygens, 6.08 Å, appears to be too large for an effective complexation of either CH_2Cl_2 or H_2O.

The bridged non-cyclic ligand **63** takes part in a more complexed molecular inclusion-type structure. In this host the additional proton-donating sites on the terminal urea functions are used for a hydrogen-bonded dimerization of the ligand rather than for association with potential guest species. The dimeric entity contains a polar cavity at each

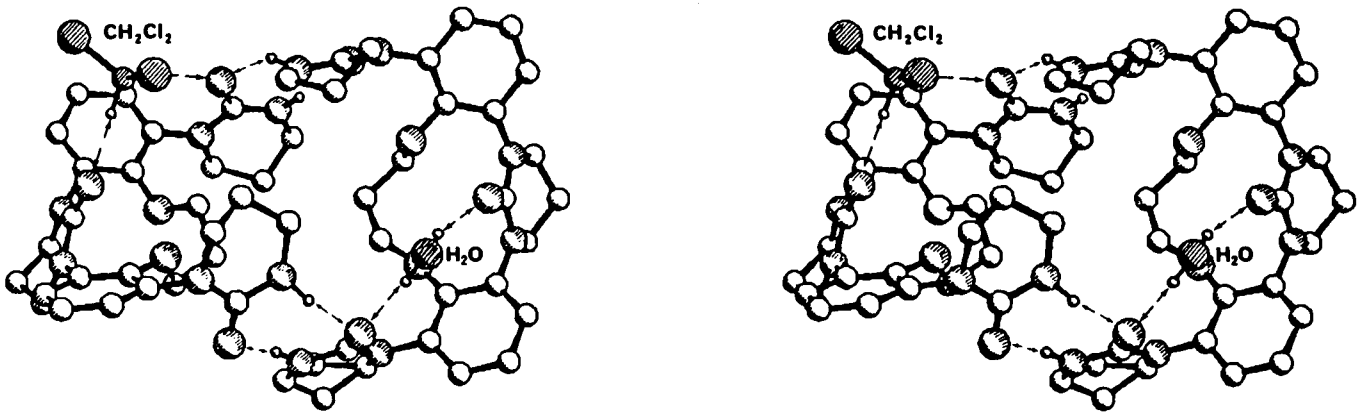


FIGURE 43. Stereoview of the complex formed between a hydrogen-bonded dimer of **63** and molecules of H_2O and CH_2Cl_2[189]

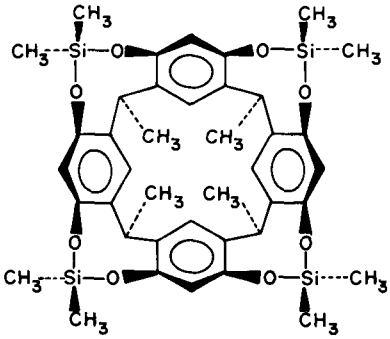
end, the two sites being separated from each other by a lipophilic barrier of methylene groups. In the observed structure two different guests interact directly with the two cavities: CH_2Cl_2 occupies one site whereas an H_2O molecule is located in the second cavity (Figure 43). As before, the crystal structure contains two additional solvent species which lie outside the complex within hydrogen-bonding distance from the bound water.

The above host–guest complexes are stabilized by multiple O—H···O and C—H···O interactions in a similar manner to that observed in complexes of the crown ethers with uncharged species. Polyether macrorings such as 18-crown-6 have a roughly planar shape and are usually coordinated from opposite sides by two proton-donating units of the neutral guest (see above). The cyclic urea hosts contain binding sites with more concave shapes, which leads to a better spatial complementarity between the host and guest constituents.

C. Hydrophobic Cage Design

As a natural development of the molecular inclusion concept, increasing interest has been shown in the study of the separation and storage of uncharged molecules with hydrophobic surfaces within similarly neutral and apolar host species. It appears that such complexes, although stabilized only by weak non-specific binding forces, can be achieved in both the crystal and solution states. Only a relatively small number of structures of synthetic inclusion complexes between apolar hosts and guests have been published, most of them involving calixarene, cyclophane, oligolactone and oligolactam derivatives as hosts and a small number of molecular guests[190–192].

A fascinating design of the cavitands, macrocyclic ligands containing enforced cavities (as in the spherands, the free energy for the cavity formation has already been supplied during the host synthesis), provided a rich source of suitable hosts which can be useful for the complexation and transport of apolar guests[193]. This important phenomenon of molecular host–guest complexation, which lies beyond the scope of a survey on crown ethers (as stated at the outset), is illustrated below by only a single example. In cavitands based on framework **64** the host cavity is in the form of a cylindrical well of limited diameter and can accommodate only slim linear guests such as CS_2, $CH_3C{\equiv}CH$ and O_2. Complexations with the non-polar partners have originally been observed in deuterated chloroform and benzene solutions[194]. The crystallographic analysis of the 1:2 compound formed between host **64** and CS_2 revealed a 1:1 molecular inclusion complex with CS_2, the guest species being almost entirely encapsulated within the cavity of the host (Figure 44)[194]. The host cavity has the form of a rectangular well, its walls being lined with



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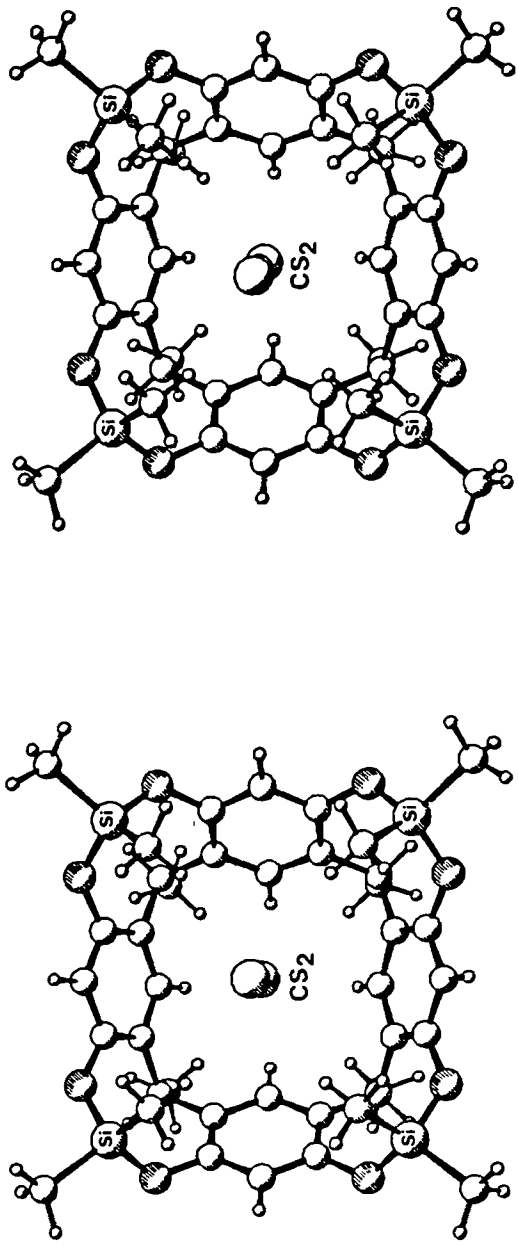

FIGURE 44. Stereoview of the complex between host **64** and CS_2, showing encapsulation of the latter within the hydrophobic cavity[194]

four phenyl rings. The molecular axis of the accommodated guest is nearly perpendicular to the cross-section of the cavity, forming an angle of about 50° with the planes of the four phenyls. The second CS_2 molecule is located in the crystal lattice between molecules of the complex and is slightly disordered.

The above structure is a perfect example of a purely van der Waals molecular inclusion complex between apolar guest and host species. The stability of the complex both in solution and in the crystal should be mainly attributed to two factors: the fact that the host framework was specially designed to contain a rigid cavity that would not collapse in solution and the steric complementarity between the interacting components.

VI. CONCLUDING REMARKS

The list of references included in this Appendix, representing recent structural investigations of macrocyclic crown ethers, is by no means complete. Several new developments in crown ether structural chemistry (lariat, spherand and second-sphere complexes) have already been referred to in more detail in Chapter 5, and only a few representative references have been quoted here. A discussion of other interesting topics, such as complexation with cryptates and other macropolycyclic hosts, the binding of anions (rather than cations) by macrocyclic polyammonium crown-like ligands and the complexing features of open-chain ligands, has also been omitted because of the limited space available; the reader is referred to other review articles (e.g. Refs 3, 5 and 196). No further reference has been made to the topic of chiroselective complex formation by crown ether derivatives as, surprisingly, very little progress has been reported on this subject in recent years. On the other hand, new topics related to the structural chemistry of crown ethers are on the increase. For example, the complexes of 18-crown-6 and 15-crown-5 with alkali metal cations have been used to synthesize a new kind of crystalline matter which exhibits unusual electronic and optical properties. In the crystals of these complexes, termed electrides, the anions are completely replaced by electrons, which are trapped in voids formed between the tightly packed crown–metal cation assemblies[197].

The possibilities of structural variations in potential receptor molecules are enormous, and almost every new issue of the relevant journals contains novel structural characterizations. However, the host–guest chemistry of even the most complexed systems is determined by localized complementary interactions between the constituent species. In this survey we have therefore chosen to emphasize the most fundamental features of binding in adducts of the crown ethers and related macrocycles. The need to understand better the processes of structured molecular complexation and molecular recognition stimulates continuous efforts in this fascinating field of research.

VII. ACKNOWLEDGEMENTS

The author is grateful to Mrs Z. Stein for her invaluable assistance. He also thanks Mrs R. Magen for her help with the diagrams. Figures 2a, c, 3d, e, 4a, 7, 8a, c, d, 10a, b, 12a, b, 13, 14a, b, 15a, b, 17a, 23a, b, 25, 30 and 32 are reproduced from I. Goldberg, in *Inclusion Compounds* (Eds J. L. Atwood, J. E. D. Davies and D. D. MacNicol), Academic Press, London, 1984, Volume 2, by permission of Academic Press. Illustrations of other structures were produced with the aid of data retrieved from the Cambridge Crystallographic Data Base.

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Crown Ethers and Analogs
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CHAPTER **8**

Complexation of aryldiazonium ions by polyethers

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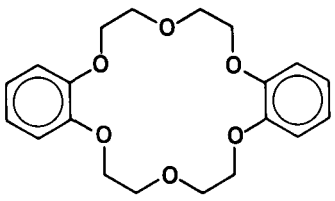
I. INTRODUCTION

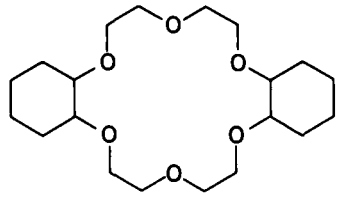
Since their discovery in 1858[1], aryldiazonium salts and their chemistry have been intensively investigated[2–6]. Today arenediazonium salts are well-known and versatile intermediates for the synthetic chemistry which is practised in both academic and industrial settings. Mechanisms of aryldiazonium salt reactions continue to receive attention for both practical and theoretical reasons.

An exciting, recent development in this field is the discovery that arenediazonium ions can be complexed by polyethers. This complexation alters the spectral properties of the aryldiazonium ion and markedly modifies its reactivity. Polyethers are also employed as phase-transfer catalysts which allow reactions of aryldiazonium salts to be carried out in nonhydroxylic media. It is the purpose of this chapter to summarize the presently available information concerning the complexation of aryldiazonium salts by polyethers and the synthetic applications of this phenomenon.

In many studies of aryldiazonium ion complexation, macrocyclic polyethers (crown ethers) are utilized. Therefore, a brief review of crown ether nomenclature is in order. The trivial naming system for crown ethers[7] involves listing, in order: (1) Substituents on the polyether ring, (2) the number of atoms in the polyether ring, (3) the class name crown and (4) the number of oxygen atoms in the polyether ring. Thus, the crown ethers (**1**), (**2**), and (**3**) are dibenzo-18-crown-6, dicyclohexano-18-crown-6 and 18-crown-6, respectively.



(**1**)



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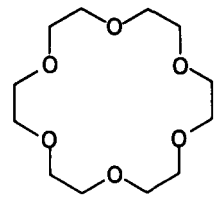
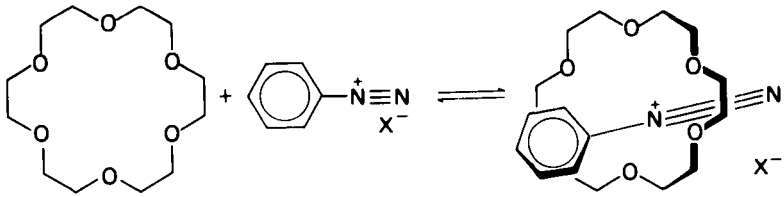


(**3**)

II. DISCOVERY OF THE PHENOMENON

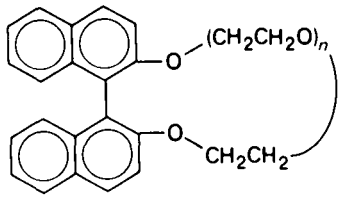
Due to their ionic nature, aryldiazonium salts are usually insoluble in nonhydroxylic organic solvents of low polarity, such as chlorocarbons and hydrocarbons. Using Corey–Pauling–Koltun (CPK) molecular models, Gokel and Cram[8] deduced that crown ethers might complex with aryldiazonium ions by insertion of the positively charged, rod-like diazonium group into the polar cavity of the macrocycle, as illustrated in equation (1). These authors reasoned that the complexation would increase

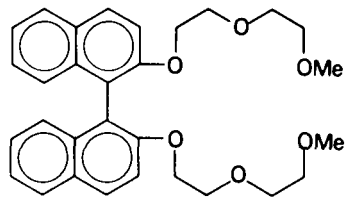


(1)

the lipophilicity of the aryldiazonium cation and thereby facilitate the dissolution of aryldiazonium salts in nonpolar organic solvents.

In 1973, Gokel and Cram[8] reported that substituted benzenediazonium tetrafluoroborates can indeed be solubilized in deuteriochloroform by the use of certain crown ethers. Integration of the proton magnetic resonance (PMR) spectrum of a solution which results from contacting a $CDCl_3$ solution of binaphtho-20-crown-6 (**5**) with solid *p*-toluenediazonium tetrafluoroborate reveals that 0.9 mol of the diazonium salt is dissolved per mole of the crown ether. Under the same conditions, the open chain analogue **8** does not solubilize any *p*-toluenediazonium tetrafluoroborate. This suggests the possible requirement of a preformed polyether cavity in order for complexation to occur.





(4) $n = 3$ **(6)** $n = 5$ **(8)**

(5) $n = 4$ **(7)** $n = 6$

The influence of crown ether cavity size upon the complexation phenomenon has been investigated using *p*-toluenediazonium tetrafluoroborate and the binaphtho crown ether series of **4–7**. For this series of macrocyclic compounds, the crown ether cavity diameters are estimated to be 2.2, 2.7, 3.7 and 5.6 Å, respectively. The observed ratios of moles of diazonium salt solubilized per mole of binaphtho crown ether are 0, 0.9, 0.6 and 0.1 for **4–7**, respectively. As estimated from the X-ray contour map of benzenediazonium chloride[9], the cylindrical diameter of the diazonium group is approximately 2.4 Å. Therefore, the solubilization results indicate that a ratio of cation diameter to crown ether cavity of ~0.8–0.9 produces the greatest complexation. Similar ratios have been noted for the complexation of alkali and alkaline earth cations by crown ethers[10].

Further evidence for the insertion of the diazonium group 'neck' of the benzenediazonium cation into the 'collar' of the crown ether[11] is provided by the observation

that binaphtho-20-crown-6 (**5**) solubilizes one mole of 3,4-dimethylbenzenediazonium tetrafluoroborate per mole of crown ether, but the corresponding 2,6-dimethylbenzenediazonium salt is not measurably solubilized. For the latter diazonium ion, CPK models reveal that insertion of the diazonium group into the crown ether cavity would cause serious steric repulsions between the *ortho* methyl groups and the crown ether ring.

Thus, the research of Gokel and Cram[8,11] provides the first evidence for the complexation of aryldiazonium ions by crown ethers as well as an initial assessment of the structural requirements for the two complexing species.

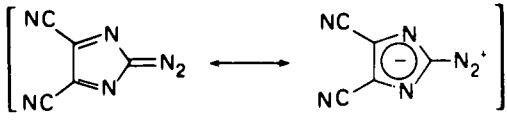
III. SOLID-STATE COMPLEXES OF ARYLDIAZONIUM SALTS AND CROWN ETHERS

A. Isolation

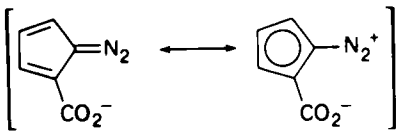
Less than two years after Gokel and Cram[8] had demonstrated the complexation of aryldiazonium tetrafluoroborates by crown ethers in solution, Haymore, Ibers and Meek[12] reported the isolation of the first diazonium-salt–crown-ether complex. When acetone solutions of benzenediazonium hexafluorophosphate and the *cis–anti–cis* isomer of dicyclohexano-18-crown-6 (**2**) are combined and allowed to stand, large, well-formed prisms of the complex are deposited. Alternatively, the complex can be precipitated by a gradual addition of diethyl ether to the acetone solution of the two components. Correct elemental analysis for a one-to-one complex is obtained.

Several complexes of benzenediazonium tetrafluoroborates with 18-crown-6 (**3**) have now been reported[13,14]. Although decomposition points of benzenediazonium salts are notoriously unreproducible, reasonable melting-point behaviour is observed for the complexes of *p*-bromo, *p-t*-butyl-, and *p*-chloro-benzenediazonium tetrafluoroborates with **3**.

Diazodicyanoimidazole (**9**) apparently forms a one-to-one complex with 18-crown-6 by complexation through the zwitterionic form[15]. On the other hand, the complex of the potassium salt of diazocyclopentadiene-2-carboxylate (**10**) with dicyclohexano-18-crown-6 appears to involve complexation of the potassium ion rather than the diazonium group[16].



(**9**)



(**10**)

B. X-Ray Diffraction Structure

Very recently, Haymore[17] has determined the structures of benzenediazonium tetrafluoroborate and of the 18-crown-6 complex of benzenediazonium hexafluoro-

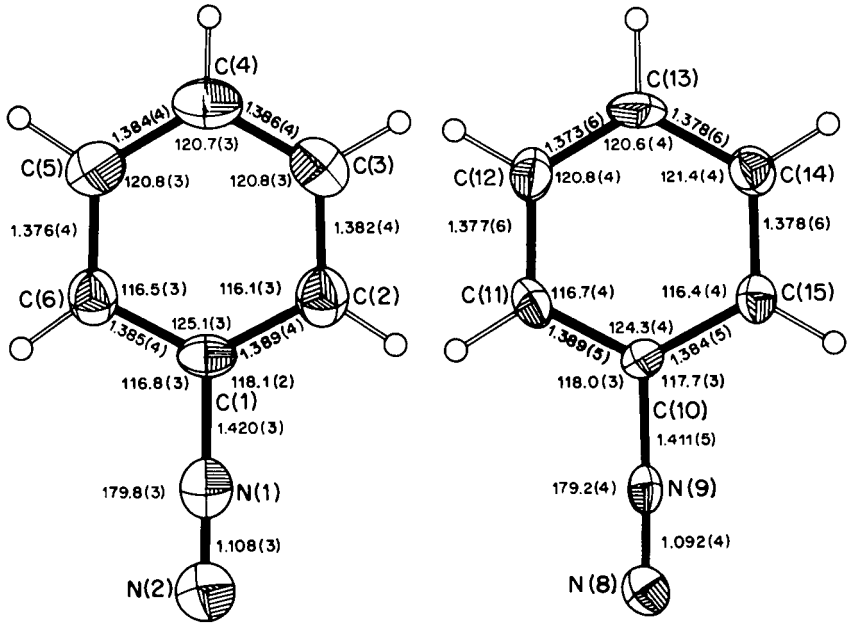


FIGURE 1. ORTEP drawings with measured bond angles and lengths for uncomplexed (left) and 18-crown-6 complexed (right) benzenediazonium ion. Reproduced by courtesy of B. L. Haymore.

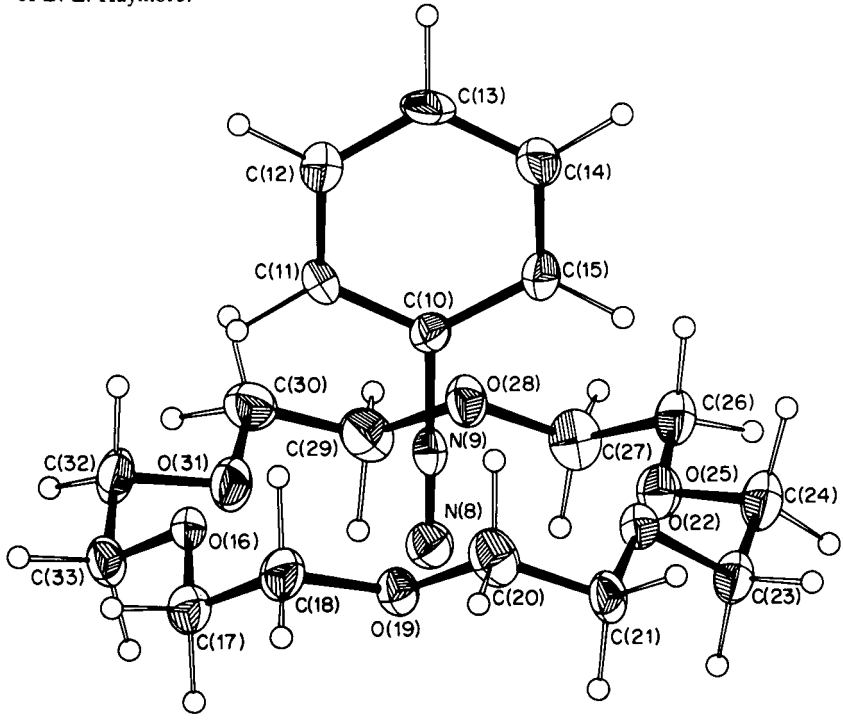


FIGURE 2. ORTEP drawing for the complex of benzenediazonium hexafluorophosphate with 18-crown-6. Reproduced by courtesy of B. L. Haymore.

phosphate by low-temperature X-ray diffraction. The measured bond angles and lengths for the uncomplexed and complexed benzenediazonium ions are recorded on the ORTEP (Oak Ridge Temperature Elipsoid Plotting Program) drawings (Figure 1). The structure of the 18-crown-6 complex of benzenediazonium ion is presented in Figure 2.

Thus, the X-ray diffraction structure verifies the earlier conclusion (Section II) that complexation involves insertion of the diazonium group into the crown ether cavity. The approximate plane formed by the crown ether oxygens roughly bisects the N_α—N_β bond. Further insertion is prevented by steric repulsions between the *ortho* hydrogens of the benzenediazonium ion and methylene hydrogens of the crown ether ring.

Comparison of the structural parameters for the complexed and uncomplexed benzenediazonium cation (Figure 1) reveals a linearity of the C(1)—N_α—N_β bond in both cases. However, both the N_α–N_β and C(1)–N_α bonds are significantly shorter in the complexed diazonium ion.

C. Molecular Orbital Calculations

The interaction of aryldiazonium ions with crown ethers has been probed by Bartsch and Čársky[18] using CNDO/2 calculations. For the uncomplexed diazonium ion, the bond lengths and angles are taken to be those reported for the X-ray crystal structure of benzenediazonium chloride[9]. A complexing crown ether molecule is simulated by three dimethyl ether molecules which are symmetrically arranged about N_α of the benzenediazonium cation and oriented so they match the overall structure of 18-crown-6 in its complexed state[19].

The results of the molecular orbital calculations suggest that complexation of an aryldiazonium ion by an appropriate crown ether involves electrostatic rather than charge-transfer interactions. Comparison of the calculated Wiberg bond indices and atomic charges[20] for the uncomplexed and complexed benzenediazonium ions indicates that upon complexation the multiplicities of both the C(1)—N_α and N_α—N_β bonds increase. This prediction is consistent with the shortening of these bonds upon complexation which is noted in the X-ray diffraction studies (Section III.B). The calculations also predict that complexation increases the positive charges on N_α and C(1), but reduces the amount of positive charge on N_β.

D. Infrared Spectra

When a complex of a crown ether and an aryldiazonium salt is formed as a solid and then mulled with Nujol, a single N≡N stretching absorption band is observed at a

TABLE 1. Infrared spectra of uncomplexed and crown-ether-complexed benzenediazonium salts in the solid state[a]

	$\nu_{N\equiv N}$ (cm^{-1})		
Complex	Complex	Uncomplexed diazonium salt	Reference
$PhN_2^+ PF_6^-$·2	2317	2285	12
p-*t*-$BuC_6H_4N_2^+ BF_4^-$·3	2306	2277	13
p-$ClC_6H_4N_2^+ BF_4^-$·3	2322	2297	14
p-$BrC_6H_4N_2^+ BF_4^-$·3	2321	2295	14

[a]Taken as Nujol mulls.

frequency which is different from that for the same vibration in the uncomplexed diazonium salt[12-14] (Table 1). The occurrence of a single, new, absorption band reveals that the complex does not revert to the uncomplexed diazonium salt and crown ether when it is suspended in Nujol. The observed increases in $\nu_{N\equiv N}$ for a benzenediazonium ion upon complexation by a crown ether are unique[12]. Complexation of aryldiazonium cations with other types of ligands produces diminished $\nu_{N\equiv N}$ values[12].

The increase in $\nu_{N\equiv N}$ which results from complexation is consistent with the enhanced $N_\alpha—N_\beta$ bond order predicted by molecular orbital calculations (Section III.C) and the observed $N_\alpha—N_\beta$ bond-shortening noted in the X-ray diffraction structural studies (Section III.B).

E. ESCA Spectra

Bohman and coworkers[21] have measured the ESCA spectra of *p-t*-butylbenzenediazonium tetrafluoroborate and its complex with dibenzo-18-crown-6 (1).

In contrast to the previously examined complexation of alkali metal cations by dibenzo-18-crown-6[22], the O1s line (the two types of oxygen exhibit only a single ESCA line) shifts upon complexation with *p-t*-butylbenzenediazonium tetrafluoroborate. This indicates the operation of different relaxation effects for complexed aryldiazonium and alkali metal cations.

Two nonequivalent nitrogen peaks are observed in the N1s spectra of both the uncomplexed and complexed diazonium salts. Simple resonance theory considerations of an uncomplexed benzenediazonium cation predicts that the carbon-bonded nitrogen, N_α, will be more positive than N_β. It should be noted that a recent *ab initio* calculation[23] for the ground state of a free benzenediazonium cation places the main positive charge on N_β. However, such calculations often show large deviations for complex systems. Therefore, unless the positions of the two N1s ESCA peaks are altered by relaxation effects, one expects N_α to have the higher binding energy.

The binding energy difference between the nonequivalent nitrogens decreases from 1.6 eV to 1.2 eV upon complexation[21]. The N1s line at 403.3 eV (interpreted as coming from N_β) shifts by 0.5 eV towards higher binding energy, while the N1s line at 404.9 eV (thought to arise from N_α) remains almost constant.

These results are anomalous since both simple resonance theory and the CNDO/2 calculations of Bartsch and Čársky[18] (Section III.C) predict that the amount of positive charge on N_α should increase upon complexation. One explanation could be that due to unusual relaxation effects N_α has a lower binding energy than N_β in the uncomplexed benzenediazonium ion. If this were the case, the observed binding energy shifts upon complexation would be consistent with the predicted changes in charge density.

The ESCA spectra of *p-t*-butylbenzenediazonium tetrafluoroborate and its complex with dibenzo-18-crown-6 are time-dependent[21]. After extended irradiation, the spectrum for the uncomplexed diazonium ion exhibits another N1s line in addition to the two original N1s lines. The new line appears at the expense of the two original nitrogen lines and is attributed to molecular nitrogen or some kind of symmetrical complex. In contrast, extended irradiation of the dibenzo-18-crown-6-complexed diazonium salt produces only a gradual disappearance of the two original N1s lines.

Comparison of the spectra obtained from the uncomplexed and complexed diazonium salts after 15 hours of irradiation shows that the complex decomposes more rapidly than does the uncomplexed diazonium salt. This result contrasts sharply with the stability enhancements which usually accompany the complexation of aryldiazonium salts by crown ethers (Section V).

IV. SPECTRAL STUDIES OF COMPLEXES OF ARYLDIAZONIUM SALTS AND CROWN ETHERS IN SOLUTION

A. Infrared Spectra

Gokel, Petcavich and their coworkers[14,24] have investigated the effects of crown ether addition upon $\nu_{N\equiv N}$ for benzenediazonium tetrafluoroborates in chlorocarbon solvents. Selected data are presented in Table 2.

TABLE 2. Effect of 18-crown-6 upon the $\nu_{N\equiv N}$ absorption of benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$) in chlorocarbon solvents[14,24]

		$\nu_{N\equiv N}$ (cm^{-1})		
X	Solvent	No 18-crown-6	1 equiv. 18-crown-6	5 equiv. 18-crown-6
t-Bu	$CHCl_3$	2272	2271(1)[a], 2308(1.4)	2308
	CH_2Cl_2	2270	2272(1), 2309(1.3)	2309
Et	$CHCl_3$	2270	2271(1), 2307(1.2)	2306
	CH_2Cl_2	2275	2270(1), 2309(1.5)	2310
n-BuO	$CHCl_3$	2245	2245(1), 2294(2.4)	2245[b], 2294
Cl	$CHCl_3$	—[c]	2280(1), 2314(2.4)	2314

[a]Relative intensities of the two bands are given in parentheses.
[b]The 2245 cm^{-1} absorption appears as a weak shoulder.
[c]In the absence of 18-crown-6 the diazonium salt is insoluble in chloroform.

Addition of one equivalent of 18-crown-6 (**3**) to solutions of p-t-butyl-, p-n-butoxy-, and p-ethyl-benzenediazonium tetrafluoroborates in chloroform or dichloromethane gives rise to two $\nu_{N\equiv N}$ absorptions. One occurs at or near the position of the $\nu_{N\equiv N}$ absorption which is observed in the absence of crown ether and a new peak appears in the range of 2300–2325 cm^{-1}. Similarly, two $\nu_{N\equiv N}$ bands are noted for chloroform-insoluble p-chlorobenzenediazonium tetrafluoroborate in the presence of one equivalent of 18-crown-6. For a solution of p-t-butylbenzenediazonium tetrafluoroborate in dichloromethane, addition of one equivalent of 12-crown-4 (whose cavity is too small to accommodate the diazonium group) neither alters the position of the free diazonium ion band nor produces any new band in the 2300–2325 cm^{-1} region. Thus, these results demonstrate that the presence of one equivalent of an appropriately sized crown ether yields a mixture of the complexed and uncomplexed aryldiazonium ion species. In agreement with the observations made for the Nujol mull spectra of the solid-state complexes (Section III.D), $\nu_{N\equiv N}$ is shifted to higher wave number values when a benzenediazonium salt becomes complexed by 18-crown-6 in a chlorocarbon solvent.

Addition of five equivalents of 18-crown-6 converts p-t-butyl-, p-ethyl, and p-chloro-benzenediazonium tetrafluoroborates totally into the complexed form in chloroform and even in the more polar solvent dichloromethane. However, a small amount of uncomplexed p-n-butoxybenzenediazonium ion remains discernible in chloroform even in the presence of seven equivalents of 18-crown-6.

Haymore[17] has probed the influence of the solvent upon the $\nu_{N\equiv N}$ values of p-ethoxybenzenediazonium salts in the uncomplexed and 18-crown-6 complexed states (Table 3). Interestingly, the $\nu_{N\equiv N}$ values for the crown-ether-complexed diazonium ion are found to be independent of the solvent identity even though $\nu_{N\equiv N}$ for the uncomplexed diazonium ion varies considerably as the solvent is changed.

TABLE 3. Infrared spectra for *p*-ethoxybenzenediazonium salts and their complexes with 18-crown-6 in solution[17]

Anion	Solvent	$\nu_{N\equiv N}$ (cm^{-1})	
		Free ion	Complexed ion
BF_4^-	H_2O	2246	2296
PF_6^-	Me_2SO	2257	2297
PF_6^-	MeOH	2249	2297
PF_6^-	Me_2CO	2252	2297
PF_6^-	CH_2Cl_2	2234	2297

Haymore[17] has also determined the $\nu_{N\equiv N}$ values for two benzenediazonium hexafluorophosphates and their complexes with 18-crown-6, 21-crown-7 and 24-crown-8 in acetone (Table 4). Increases in the $\nu_{N\equiv N}$ values upon crown ether complexation are noted to diminish in the order 18-crown-6 > 21-crown-7 > 24-crown-8. As will be shown later (Section VI.A), the complexation of aryldiazonium tetrafluoroborates by 21-crown-7 in chlorocarbon solvents is considerably greater than is that by 18-crown-6 or 24-crown-8. Therefore, there appears to be no correlation between the complexation constants for different crown ethers and the changes in $\nu_{N\equiv N}$ which result when an aryldiazonium salt is complexed.

TABLE 4. Infrared spectra of benzenediazonium hexafluorophosphates (p-$XC_6H_4N_2PF_6$) and their crown ether complexes in acetone[17]

X	$\nu_{N\equiv N}$ (cm^{-1})			
	Free ion	18-Crown-6 complex	21-Crown-7 complex	24-Crown-8 complex
H	2292	2317	2301	2294
EtO	2252	2297	2268	2254

B. Ultraviolet and Visible Spectra

Bartsch and coworkers[13] first reported the shifting of the ultraviolet absorption maximum for benzenediazonium tetrafluoroborates to shorter wavelengths in the presence of an appropriate crown ether. Thus, the absorption maximum of *p*-*t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane decreases from 285 nm in the absence of crown ether to 276 nm in the presence of one equivalent of 18-crown-6. Addition of a large excess of 18-crown-6 results in a further decrease to 268 nm. These results indicate that crown ether complexation of a benzenediazonium ion causes a localization of the π electron system.

In more recent work[25,26], similar decreases of 15–20 nm in the ultraviolet absorption maxima are noted for complexation of a variety of benzenediazonium tetrafluoroborates by 18-crown-6 in 1,2-dichloroethane.

Hashida and Matsui[26] have measured the ultraviolet spectra of *p*-methoxybenzenediazonium tetrafluoroborate in the free ion and the 18-crown-6-complexed forms in seven different solvents. Although complexation always produces a shift of the absorption maximum to shorter wavelengths, no correlation of the magnitude of the shift (4–33 nm) with solvent properties (e.g. dielectric constant, E_T values) is evident.

Complexation of benzenediazonium tetrafluoroborates with binaphtho-20-crown-6(**5**) in chloroform produces yellow to red colours[8,11] which suggests the presence of π–π complexation between the arenediazonium ions (π acids) and a naphthalene ring of the crown ether (π base). The failure to observe such colours in the complexation of *p-t*-butylbenzenediazonium tetrafluoroborate with a variety of other crown ethers which also contain aromatic groups[27] suggests that the π–π complexation observed with binaphtho-20-crown-6 is rather unique.

C. Nuclear Magnetic Resonance Spectra

1. *The crown ether*

For simple crown ethers, the proton magnetic resonance (PMR) spectra of the polyethers exhibit only minor changes in the presence of aryldiazonium salts. Thus, complexation of *p*-toluenediazonium tetrafluoroborate by 18-crown-6 in $CDCl_3$ shifts the methylene singlet from 3.62 to 3.58 ppm[8].

However, larger changes are observed for certain more complicated crown ethers[8]. For example, the four $ArOCH_2$ proton absorption of binaphtho-20-crown-6 (**5**), which appears as an eleven-line multiplet centred at 4.06 ppm, becomes two multiplets (one of six lines centred at 3.89 ppm and one of seven lines centred at 4.21 ppm) when the crown ether complexes *p*-toluenediazonium tetrafluoroborate in $CDCl_3$.

2. *The aryldiazonium salt*

Considerable insight into the changes which result when benzenediazonium salts are complexed by 18-crown-6 can be obtained from nuclear magnetic resonance spectral studies. The effect upon the aromatic ring is probed using a combination of proton, fluorine and carbon nuclear magnetic resonance spectra. Changes in the diazonium group caused by crown ether complexation are investigated using nitrogen nuclear magnetic resonance spectra. Finally, fluorine nuclear magnetic resonance spectral variations are employed to study the interactions of free and complexed benzenediazonium cations with tetrafluoroborate and hexafluorophosphate counterions.

a. Aromatic ring substituents. Juri and Bartsch[28] have detected a small, but real, upfield PMR shift of benzenediazonium cation *ortho* hydrogens upon crown ether complexation. Thus, the *ortho* hydrogen absorptions (of the A_2B_2 pattern) of *p-t*-butylbenzenediazonium tetrafluoroborate and hexafluorophosphate in deuterated dimethyl sulphoxide shift upfield by 0.07 and 0.08 ppm, respectively, in the presence of one equivalent of 18-crown-6. Neither the chemical shifts for the *meta* hydrogens (of the A_2B_2 pattern) nor those for the hydrogens of the *t*-butyl group are affected by crown ether complexation.

Changes in the ^{19}F-NMR chemical shifts of *p*-, *m*-, and *o*-fluorobenzenediazonium salts caused by the addition of 18-crown-6 have been investigated by Gokel and coworkers[24]. For the ring-bound fluorine of *p*-fluorobenzenediazonium tetrafluoroborate dissolved in acetonitrile, acetone and methanol, upfield shifts of the fluorine resonance by approximately 4 ppm are observed when one equivalent of 18-crown-6 is added. In contrast, for *m*-fluorobenzenediazonium tetrafluoroborate in the same three solvents there is very little influence of 18-crown-6 upon the ^{19}F-NMR absorption position. For neither *p*- nor *m*-fluorobenzenediazonium tetrafluoroborate is any effect of crown ether discernible in water, a solvent in which only weak complexation is expected (Section VI.D).

When $CDCl_3$-soluble *p*-, *m*- and *o*-fluorobenzenediazonium chlorides are prepared

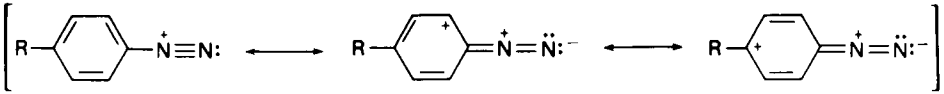
by counterion interchange from the corresponding tetrafluoroborates[29], the addition of one equivalent of 18-crown-6 causes upfield ^{19}F-NMR absorption shifts of 2.3, 0.2 and 3.2 ppm, respectively[24].

When taken together the PMR and ^{19}F-NMR studies indicate that complexation by an appropriate crown ether significantly influences the environments of *ortho* and *para*, but not *meta*, substituents.

b. Aromatic ring carbon atoms. Changes in the ^{13}C-NMR spectra of *p-t*-butylbenzenediazonium tetrafluoroborate in dichloromethane[14] and of 4-*n*-butyl- and 4-*n*-butoxy-benzenediazonium tetrafluoroborates in $CDCl_3$[24] caused by adding one equivalent of 18-crown-6 are recorded in Table 5. Additional amounts of 18-crown-6 produce further shifts in the same direction but of lesser magnitudes.

For all three benzenediazonium salts, the addition of 18-crown-6 produces an approximately 3 ppm downfield shift in the C(1) absorption and upfield shifts of 2–3 ppm for the *ortho* and *para* carbons. Chemical shift changes for the *meta* carbons are considerably smaller.

The ^{13}C-NMR spectral changes may be rationalized by the following resonance theory argument[31]. Consider that the resonance hybrid for the benzenediazonium cation is comprised of contributions from the diazonium and diazo resonance forms **11–13**. In the presence of crown ether the contribution of the diazonium resonance



(11) **(12)** **(13)**

form **11** to the hybrid should be enhanced by interactions of the crown ether with the localized positive charge.Therefore, crown ether complexation should increase the amount of positive charge on the diazonium group and reduce the positive charges on the *ortho* and *para* carbons because of the decrease in charge dispersal by resonance. According to this rationalization, there should be an upfield shift for the *ortho* and *para* carbons and C(1) should be deshielded due to the increased positive charge on the diazonium group and shift downfield. These predictions are in agreement with the observed spectral shifts. The downfield chemical shift for C(1) caused by crown ether complexation is also consistent with the results of CNDO/2 molecular orbital calculations (Section III.C) which indicate that the amount of positive charge on C(1) will increase in the crown-ether-complexed form[18].

Chemical shift values for C(1) in five 18-crown-6-complexed, *para*-substituted benzenediazonium salts have now been determined[14,24,30] (Table 5). The C(1) chemical shifts for benzenediazonium ions with *p*-hydroxy and *p-n*-butoxy substituents are 9–11 ppm upfield from those with *p*-methyl, *p-t*-butyl, and *p-n*-butyl groups. If contributions from both diazonium and diazo resonance forms are again considered, the relative contribution of diazo forms to the hybrid should be greater for the substituent Y due to the supplemental resonance interactions illustrated by **14** and **15**. Therefore

(14) **(15)**

TABLE 5. Effect of 18-crown-6 upon the ^{13}C-NMR chemical shifts of benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$)[14,24,30]

			^{13}C-NMR chemical shift (ppm)[a]							
							X group			
X	Solvent	No. equiv. 18-crown-6	C(1)	*Ortho*	*Meta*	*Para*	C_α	C_β	C_γ	C_δ
t-Bu	CH_2Cl_2	0	110.19	132.43	128.87	167.33	36.66	30.08	—	—
t-Bu	CH_2Cl_2	1	113.58	130.29	128.43	164.54	36.19	30.14	—	—
n-Bu	$CDCl_3$	0	110.39	132.47	131.25	159.10	36.42	32.23	22.14	13.56
n-Bu	$CDCl_3$	1	113.19	130.63	129.87	156.23	35.62	31.78	22.65	13.14
n-BuO	$CDCl_3$	0	101.26	135.64	117.50	168.87	70.13	30.43	18.77	13.48
n-BuO	$CDCl_3$	1	104.49	133.40	116.80	167.05	[b]	30.00	18.30	13.05
HO	$CHCl_3$	1.2–1.8	102.1	—	—	—	—	—	—	—
Me	$CHCl_3$	1.2–1.8	113.3	—	—	—	—	—	—	—

[a] Downfield from TMS.
[b] Obscured by a large peak due to 18-crown-6.

TABLE 6. Effect of 18-crown-6 upon the ^{15}N-NMR chemical shifts of benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$)[30,32]

X	Solvent	No. equiv. 18-crown-6	^{15}N-NMR chemical shift (ppm)[a]	
			N_α	N_β
t-Bu	CH_2Cl_2	0	143.8	58.3
t-Bu	CH_2Cl_2	1	148.9	56.8
t-Bu	CH_2Cl_2	5	149.9	56.4
NO_2	$CDCl_3$	1.2–1.8	152.2	57.1
H	$CDCl_3$	1.2–1.8	150.2	57.2
Me	$CDCl_3$	1.2–1.8	149.4	56.9
MeO	$CDCl_3$	1.2–1.8	148.5	53.2
HO	$CDCl_3$	1.2–1.8	146.8	50.8

[a] Upfield from external 1 M $H^{15}NO_3$.

the diazonium group is less deshielding when the *para* substituent possesses an unshared electron pair and the C(1) resonance moves upfield[30].

c. The diazonium group. ^{15}N-NMR chemical shifts for the two nitrogen atoms of five benzenediazonium tetrafluoroborates which were solubilized in $CDCl_3$ by 18-crown-6 have been reported by Duthaler, Förster and Roberts[30]. Very recently, Casewit and Roberts[32] have measured these chemical shifts for chlorocarbon-soluble p-t-butylbenzenediazonium tetrafluoroborate in dichloromethane in the absence and presence of 18-crown-6. These data are collected in Table 6.

For p-t-butylbenzenediazonium tetrafluoroborate, complexation by 18-crown-6 produces an upfield chemical shift for N_α, and a smaller downfield shift for N_β. This finding is completely consistent with the results of CNDO/2 molecular orbital calculations (Section III.C) which predict that complexation will enhance the positive charge density on N_α, but decrease the amount of positive charge on N_β.

For the five benzenediazonium tetrafluoroborates which were solubilized in $CDCl_3$ by adding 1.2–1.8 equivalents of 18-crown-6, a general downfield shift for both N_α and N_β is noted as the electron-releasing character of the *para* substituent is enhanced. Electron release by a *para* substituent should lead to larger contributions of structures such as **13** and **15** to the resonance hybrid[30]. The resulting increase in the diazo character of the resonance hybrid should produce downfield shifts for both nitrogens, as is observed. The only anomalous feature of these data is the absence of an anticipated change in the N_β chemical shift in going from the p-nitrobenzenediazonium ion to the benzenediazonium ion[30].

d. The anion. Juri and Bartsch[28] have determined the ^{19}F-NMR chemical shifts for p-t-butylbenzenediazonium tetrafluoroborate and hexafluorophosphate dissolved in 1,2-dichloroethane in the absence and presence of 18-crown-6. The addition of one equivalent of 18-crown-6 causes an upfield shift of 2.5 ppm for the tetrafluoroborate and 1.4 ppm for the hexafluorophosphate anions. A control experiment has demonstrated that the ^{19}F-NMR chemical shift of tetra-n-butylammonium tetrafluoroborate is unaffected by the presence of 18-crown-6.

These results provide evidence for ion-pairing interactions of benzenediazonium ions with even such charge-dispersed anions as tetrafluoroborate and hexafluorophosphate in solvents of low polarity. The somewhat greater change in chemical shift which is observed when 18-crown-6 is added to the diazonium tetrafluoroborate is ascribed to tighter ion pairing in the uncomplexed diazonium tetrafluoroborate than in the hexafluorophosphate.

V. MODIFIED REACTIVITY OF CROWN-ETHER-COMPLEXED ARYLDIAZONIUM SALTS

Complexation with a crown ether modifies the reactivity of an aryldiazonium salt. As discussed earlier (Section III.E), the complex of *p*-*t*-butylbenzenediazonium tetrafluoroborate and dibenzo-18-crown-6 is decomposed by X-ray irradiation more rapidly than is the uncomplexed diazonium salt. However, this behaviour is atypical, since in a variety of other situations the crown-ether-complexed diazonium salt is more stable. In this section, the reduced reactivity of crown-ether complexed diazonium salts will be surveyed.

A. Thermal Stabilization in Solution

Bartsch and coworkers[13] reported the first evidence for diminished arenediazonium ion reactivity upon complexation by crown ethers. To examine the influence of crown ethers upon the thermal decomposition of aryldiazonium ions, these authors employed a special modification of the Schiemann reaction. The thermal decomposition of an aryldiazonium salt in an organic solvent of low polarity may be studied under homogeneous conditions using chlorocarbon-soluble *p*-*t*-butylbenzenediazonium tetrafluoroborate[33] (equation 2). Kinetics are followed by measuring the rate of disappearance of the diazonium ion ultraviolet absorption.

$$p\text{-}t\text{-BuC}_6\text{H}_4\text{N}_2^+\text{BF}_4^- \xrightarrow[\text{ClCH}_2\text{CH}_2\text{Cl}]{50^\circ\text{C}} \underset{39\%}{p\text{-}t\text{-BuC}_6\text{H}_4\text{F}} + \underset{61\%}{p\text{-}t\text{-BuC}_6\text{H}_4\text{Cl}} \qquad (2)$$

Although the presence of 18-crown-6 has no effect upon the thermolysis products, the rate of decomposition of the diazonium salt is markedly decreased. The observed retardations are rationalized in terms of specific diazonium salt complexation by the crown ether, as depicted in equation (3) where ○ represents the crown ether. For this

$$\begin{array}{ccc} \text{ArN}_2^+\,\text{BF}_4^- + \bigcirc & \overset{K}{\rightleftharpoons} & \text{Ar}\overset{\bigcirc}{(}\text{N}_2^+\,\text{BF}_4^- \\ \downarrow k_1 & & \downarrow k_2 \\ \text{products} & & \text{products} \end{array} \qquad (3)$$

scheme, appropriate kinetic derivation[13] reveals that a plot of $1/(k_1 - k_{obs})$ vs. 1/[18-crown-6] should be linear with a slope of $1/(k_1 - k_2)K$ and an intercept at 1/[18-crown-6] = 0 of $1/(k_1 - k_2)$ under the condition that [18-crown-6] $\gg$ [ArN_2^+ BF_4^-]. In the absence of crown ether, the value of k_1 at 50°C is 2.51×10^{-4} s^{-1} [28]. A plot of the rate data obtained with different crown ether concentrations is strictly linear with an intercept of $1/(2.49 \times 10^{-4})$ s^{-1}. Therefore, k_1 must be at least one hundred times greater than k_2.

This kinetic analysis establishes that the crown-ether-complexed *p*-*t*-butylbenzenediazonium ion is thermally stable under conditions which converts the uncomplexed diazonium salt into products. Thus, complexation with crown ethers represents a new method of stabilizing arenediazonium ions.

From the slope of the linear plot, a complexation constant of 1.71×10^4 M^{-1} is calculated for the association of 18-crown-6 with *p*-*t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane at 50°C.

More recently, Kuokkanen and Virtanen[25] have applied a similar kinetic analysis to the thermal decomposition of seven benzenediazonium tetrafluoroborates in 1,2-dichloroethane at 50°C. For *p*-acetyl-, *m*-acetyl-, *p*-methyl, and *m*-methylbenzenediazonium ions as well as benzenediazonium ion itself, values of $k_1 - k_2$ are close to the value of k_1, so $k_1 \gg k_2$. For *p*-chlorobenzenediazonium ion, k_2 is approximately 15% of k_1. However, for the *o*-methylbenzenediazonium ion, which should complex with 18-crown-6 only weakly due to steric factors, the crown-ether-complexed diazonium ion is almost as reactive as the uncomplexed species.

Thus, with the exception of *ortho*-substituted compounds it appears that the thermolysis of benzenediazonium ions in 1,2-dichloroethane in the presence of 18-crown-6 proceeds almost exclusively via the uncomplexed diazonium ion form. Extension of these studies to include a wider range of substituents as well as solvents in which the complexation of diazonium ions by crown ethers is weaker (Section VI.D) would be most useful.

B. Thermal Stabilization in the Solid State

A quantitative investigation of the influence of 18-crown-6 upon the thermal stability of benzenediazonium tetrafluoroborate has been conducted by Bartsch and Shiu[34]. Small samples of the diazonium salt and its one-to-one complex with 18-crown-6 are sealed in glass ampoules and placed in a 50°C constant-temperature bath. At appropriate time intervals, ampoules are removed and the remaining diazonium ion is converted into an azo dye whose concentration is determined spectrophotometrically.

The uncomplexed diazonium salt exhibits thermal stability for approximately two hours. A rapid decomposition then commences and after five hours the diazonium salt is completely decomposed. The complex of the diazonium salt and 18-crown-6 can be heated for 20 hours before the onset of decomposition. Also, the decomposition itself proceeds more slowly than does that of the uncomplexed salt. After 30 and 45 hours, 90% and 50%, respectively, of the diazonium activity remains.

C. Photochemical Stabilization in the Solid State

Somewhat less familiar than the thermal Schiemann reaction is the preparation of fluoroarenes by the photolysis of arenediazonium tetrafluoroborates and hexafluorophosphates[35]. In several instances, considerably higher yields of aromatic and heteroaromatic fluorides are realized from the photochemical Schiemann reaction than from analogous thermal processes[35–39].

Using the technique developed by Petterson and coworkers[35], Bartsch, Haddock and McCann[40] have demonstrated that complexation of benzenediazonium tetrafluoroborate with 18-crown-6 produces dramatic photochemical stabilization when compared with the uncomplexed diazonium salt.

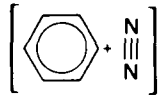
Irradiation (3500 Å lamps) of thin films of solid benzenediazonium tetrafluoroborate deposited on the walls of borosilicate glass tubes produces 73–80% yields of fluorobenzene and 1.9–2.0 equivalents of gas (N_2 + BF_3). Evaporation of an equimolar acetone solution of the diazonium salt and 18-crown-6 also deposits a thin, solid, film on the walls of a borosilicate glass tube. Irradiation of this solid film for the same period of time as before produces only a 4% yield of fluorobenzene and slight gas evolution. Since mostly undecomposed aryldiazonium salt remains after the irradiation, the function of the crown ether is photochemical stabilization rather than the diversion of a photointermediate to form other products.

D. Reduced Shock Sensitivity in the Solid State

Shephard and coworkers[15] have demonstrated a reduced shock sensitivity of diazonium compounds when complexed with crown ethers. As a dry solid, diazodicyanoimidazole (**9**) is shock-sensitive and detonates on impact. In contrast, the crystalline, one-to-one complex of **9** and 18-crown-6 can be handled with ease and does not detonate under the conditions of several standard impact tests.

E. Diminished N_α, N_β, Interchange During Solvolysis

That N_α, N_β interchange may accompany the reactions of aryldiazonium ions was first established by Lewis and Insole[41]. More recent studies by Lewis[42,43], Swain[42,43], and especially by Zollinger[44,45] have revealed that the interchange involves a phenyl-cation–nitrogen-molecule ion pair **16** which either recombines or dissociates to form the free phenyl cation.



(16)

As part of a mechanistic study of the N_α, N_β interchange reaction which occurs when (β-^{15}N) benzenediazonium tetrafluoroborate is solvolysed in 2,2,2-trifluoroethanol, Tröndlin, Medina and Rüchardt[46] have determined the influence of dibenzo-18-crown-6 upon the solvolysis rate and extent of N_α, N_β interchange in the reactant recovered from incomplete reaction. The presence of 4.4 equivalents of dibenzo-18-crown-6 reduces the solvolysis rate to 22% of its value in the absence of crown ether. Such rate reductions are anticipated if the crown ether partially converts the diazonium salt into a less reactive complex (Section V.A).

Interruption of the solvolysis reaction after 70% completion and recovery of the unreacted diazonium salt shows 6.9 ± 0.1% of ^{15}N inversion in the absence of crown ether, but only 5.7 ± 0.1% inversion when the crown ether is present. Although the reason for the 17% decrease in the N_α, N_β interchange is currently unknown, it is clear that the presence of crown ether does influence the exchange reaction.

F. Deactivation of Azo Coupling

The presence of crown ethers retards the azo coupling of aryldiazonium ions with electron-rich aromatic compounds in both homogeneous and two-phase reaction systems.

Butler and Shepherd[47] have studied the effect of varying concentrations of dicyclohexano-18-crown-6 upon the reaction rate of *p*-methoxybenzenediazonium tetrafluoroborate with pyrrole in 1,2-dichloroethane. In the presence of 1–5 equivalents of the crown ether, an approximately linear decrease in the azo coupling rate is noted as the crown ether concentration is increased. This suggests that both uncomplexed and crown-ether-complexed diazonium ions are present, but only the former are reactive.

Juri and Bartsch[48] have reported that the coupling of *p*-*t*-butylbenzenediazonium tetrafluoroborate with *N,N*-dimethylaniline in 1,2-dichloroethane is diminished by the presence of one equivalent of 18-crown-6 to a rate which is approximately 10% of that found under comparable conditions but in the absence of crown ether.

The azo coupling rate of *p*-nitrobenzenediazonium chloride with *N*-ethylcarbazole in the two-phase solvent system of dichloromethane–water decreases by 78% in the presence of 0.05 equivalents of 18-crown-6[49].

Further evidence for the unreactivity of crown-ether-complexed aryldiazonium ion is provided by the observance of only normal azo coupling products in the three studies referenced above as well as that by Gokel and Cram[8]. Formation of azoarene–crown-ether rotaxanes (axle-in-wheel type of compounds[50]) from crown-ether-complexed aryldiazonium ions may be prohibited by steric factors or by a reduced electrophilicity of the complexed diazonium ion.

G. Diminished Nucleophilic Attack *Para* to the Diazonium Group

The diazonium group is strongly activating for nucleophilic aromatic substitution because of its positive charge. Gokel, Korzeniowski and Blum[51] have probed the influence of crown ether complexation upon nucleophilic aromatic substitution reactions of the *p*-bromobenzenediazonium ion.

Reaction of *p*-bromobenzenediazonium tetrafluoroborate with benzyltrimethylammonium chloride in chloroform produces a 55% yield of the nucleophilic halogen displacement (Cl for Br) product. Under the same conditions but in the presence of one equivalent of 18-crown-6, the reaction is incomplete and only a 30% yield of the halogen displacement product is obtained. Thus, the activating effect of the diazonium group is diminished by crown ether complexation.

VI. FACTORS WHICH AFFECT THE COMPLEXATION OF ARYLDIAZONIUM SALTS BY POLYETHERS

Thus far in the discussion, the qualitative solubilization studies (Section II) provide the only information regarding the effect of crown ether structure upon the complexing efficiency for aryldiazonium ions. In this section the available information concerning the influence of the crown ether structure, the aryldiazonium ion substituent, the anion and the solvent is summarized. In addition, the complexing abilities of crown ethers and acyclic polyethers for aryldiazonium ions are compared.

A. The Crown Ether

Limited information regarding the relationship between the cavity size of a crown ether and its ability to complex an arenediazonium ion is provided by the solubilization studies of Gokel and Cram[8] which utilize the binaphtho crown ethers **4**–**7**. The results (Section II) suggest that a crown ether cavity size of approximately 2.7 Å should be optimal.

To more completely probe the effects of structural variation within the crown ether upon the capacity for aryldiazonium ion complexation, Bartsch and Juri[27] have undertaken a screening study the results of which allow the relative complexing abilities of approximately 40 macrocyclic multidentate compounds to be compared.

The relative complexing abilities are determined by measuring the rates of decomposition of *p-t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane in the presence of one equivalent of the macrocyclic compounds. As described in Section V.A, it has been established that for 18-crown-6 the entire thermolysis reaction proceeds via the uncomplexed diazonium ions species (equation 4). Based upon the assumption that other crown ethers similarly convert the diazonium salt into a thermally stabilized complex, the reduced decomposition rate caused by one equivalent of a crown ether provides a qualitative measure of the complexing ability. A larger complexation constant K is manifested by a greater rate retardation. Rate data for selected crown ether compounds are presented in Table 7.

TABLE 7. Observed first-order rate constants for the thermolysis of *p-t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane at 50°C in the presence of one equivalent of crown ether[27]

Entry	Crown ether	$k_{obs} \times 10^4$ (s^{-1})
1	None	2.51
2	12-Crown-4	2.48
3	15-Crown-5	2.22
4	18-Crown-6	1.35
5	21-Crown-7	0.13
6	Dicyclohexano-18-crown-6	1.34
7	Dicyclohexano-21-crown-7	0.76
8	Dicyclohexano-24-crown-8	1.33
9	Dibenzo-18-crown-6	1.94
10	Dibenzo-21-crown-7	0.54
11	Dibenzo-24-crown-8	0.86
12	Benzo-18-crown-6	1.68
13	3-Methylbenzo-18-crown-6	1.56
14	3-Formylbenzo-18-crown-6	1.99

$$ArN_2^+ BF_4^- + \text{complexing agent} \overset{K}{\rightleftharpoons} \text{complex} \quad (4)$$

$$\downarrow k_1$$

products

The presence of 12-crown-4 does not change the thermolysis rate from that observed in the absence of crown ether. This is consistent with a crown ether cavity[52] (Table 8) which is too small to accommodate a diazonium group with an estimated[8] cylindrical diameter of ~2.4 Å. The slight rate retardation noted with 15-crown-5 indicates only weak complexation. For 18-crown-6 there should be a good match between the crown ether cavity diameter and the diazonium group and the thermolysis rate is reduced by approximately 50%.

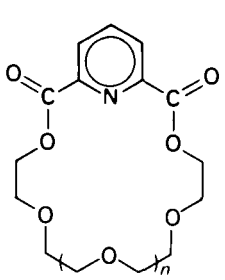
Considering only the relative diameters of the crown ethers and the diazonium group, it would be anticipated that 21-crown-7 should be a poorer complexing agent that 18-crown-6. Since the rate data reveals that 21-crown-7 complexes the diazonium ion more strongly, some additional factor must be important. Bartsch and Juri[27] suggest that this factor is a greater flexibility of the larger ring which relieves steric interactions between the *ortho* hydrogens of the benzenediazonium cation and the crown ether framework. Of the approximately 40 macrocyclic compounds examined, 21-crown-7 is the strongest complexing agent for the aryldiazonium ion. The series

TABLE 8. Estimated cavity diameters for crown ethers[52]

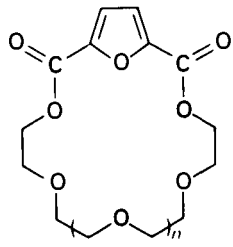
Crown ether	Cavity diameter (Å)
12-Crown-4	1.2–1.5
15-Crown-5	1.7–2.5
18-Crown-6	2.6–3.2
21-Crown-7	3.4–4.3

could not be extended to include 24-crown-6 because of difficulties in obtaining the crown ether in a pure state.

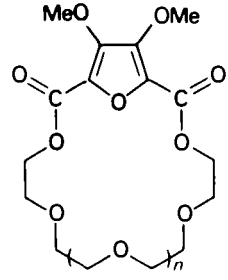
For both the dicyclohexano and dibenzo crown ether series (Table 7, entries 6–8 and 9–11, respectively) the 21-membered macrocycle provides stronger complexation than either of the corresponding 16- or 24-membered ring compounds. Strongest complexation with the 21-membered ring macrocycle is also observed for three series of pyridyl, furanyl and dimethoxyfuranyl crown ether esters, **17**, **18** and **19**, respectively.



(17)



(18)



(19)

n = 1, 2, 3

The rate data for benzo-18-crown-6 compounds (Table 7, entries 12-14) demonstrates that electron-donating substituents on the crown ether enhance complexation, but electron-withdrawing groups diminish it.

Krane and Skjetne[53] have reported the use of low-temperature NMR techniques to assess the ring-size effect in the complexation of *p*-toluenediazonium tetrafluoroborate by 18-crown-6, 21-crown-7 and 24-crown-8 in $CHCl_2F$. Of these three crown ethers, 21-crown-7 provides the strongest complexation of the aryldiazonium salt.

Complexation constants for the association of *p*-ethoxybenzenediazonium hexafluorophosphate with six crown ethers in acetone have been determined by Haymore[17] using infrared spectroscopy. Results are recorded in Table 9. Preferred complexation with 21-crown-7 is again observed. The weaker complexation noted in going from 18-crown-6 to *cis*-cyclohexano-18-crown-6 to *cis–syn–cis*-dicyclohexano-18-crown-6 to *cis–anti–cis*-dicyclohexano-18-crown-6 probably results from increasing levels of steric interactions of the crown ether with the *ortho* hydrogens of the benzenediazonium ion.

TABLE 9. Association constants for *p*-ethoxybenzenediazonium hexafluorophosphate with crown ethers in acetone[17]

Crown ether	log K (M^{-1})
12-Crown-4	—[a]
15-Crown-5	—[a]
18-Crown-6	2.0
21-Crown-7	3.1
24-Crown-8	1.9
cis-Cyclohexano-18-crown-6	1.8
cis–syn–cis-Dicyclohexano-18-crown-6	1.5
cis–anti–cis-Dicyclohexano-18-crown-6	1.2

[a]No measurable complexation.

B. Ring Substituents of the Aryldiazonium Ion

The influence of aromatic ring substituents upon the complexation of benzenediazonium salts by 18-crown-6 has been investigated in three solvents by four research groups using four different experimental methods.

By titration calorimetry Izatt and coworkers[54,55] have determined log K, ΔH and $T\Delta S$ values for the association of eight benzenediazonium tetrafluoroborates with 18-crown-6 in methanol. A good linear correlation between log K and $\sigma\rho^+$ with $\rho^+ = 0.65$ is observed. From association constant determinations using ultraviolet spectroscopy, Hashida and Matsui[26] have reported $\rho = 0.98$ for the correlation of σ constants vs. log K values for interactions of eight *meta*- and *para*-substituted benzenediazonium tetrafluoroborates with 18-crown-6 in methanol. Examination of the data reveals that the difference in the magnitudes of the ρ values in these two studies results entirely from the choice of σ substituent constants.

It is clear that electron-withdrawing aromatic ring substituents enhance the complexation of the benzenediazonium ion by a crown ether and electron-donating substituents disfavour the association. This is entirely consistent with the electrostatic interactions between the diazonium ion and the crown ether predicted by the CNDO/2 calculations (Section III.C). However, when compared with diazo systems which involve cation–anion association, such as arenediazocyanides[56] ($\rho = 3.53$), arenediazosulphones[57] ($\rho = 3.76$) arenediazosulphonate[58] ($\rho = 5.5$) and arenediazotate formation[56] ($\rho = 6.58$), the ρ value for the complexation of benzenediazonium ions by the neutral crown ether is quite low.

Using infrared spectroscopy and a limited number of compounds, Haymore[17] has observed that log K values for the association of benzenediazonium hexafluorophosphates with 18-crown-6 are identical to those reported[54,55] for the complexation of the corresponding tetrafluoroborate salts in methanol. Thus, the change from methanol to acetone does not measurably affect the ρ value.

Compared with these results, a small increase in ρ was noted ($\rho = 1.19$) when Kuokkanen and Virtanen[25] determined the association constants for seven benzenediazonium tetrafluoroborates with 18-crown-6 in 1,2-dichloroethane using a kinetic technique. An enhancement of the sensitivity of complexation to substituent effects with diminishing solvent polarity was indicated.

A quantitative assessment of the effects of *ortho* substituents upon the complexation of benzenediazonium tetrafluoroborates by 18-crown-6 has been made by two groups. When compared with *p*-methylbenzenediazonium ion, movement of the methyl group to an *ortho* position decreased the association constant by approximately a factor of ten[26]. Introduction of a second methyl group causes an additional diminution by a factor of 100. For benzenediazonium ions with acetyl groups[25], a change of the substituent position from *para* to *ortho* produces a 10^5 decrease in K. Such behaviour undoubtedly results from steric interactions of the *ortho* substituents with the crown ether framework.

Compared with anilinium ions, aryldiazonium ions are much more sensitive to the steric effects of *ortho* substituents because of the markedly different geometries of the complexes[53].

C. The Anion of the Aryldiazonium Salt

In solvents of low polarity, the association of aryldiazonium salts with crown ethers is disfavoured by anions which exhibit ion pairing with the uncomplexed anion. Thus, from several lines of evidence, Juri and Bartsch[28] conclude that complex formation for *p-t*-butylbenzenediazonium hexafluorophosphate with 18-crown-6 in 1,2-dichloroethane is greater than for the corresponding tetrafluoroborate salt.

TABLE 10. Anion and concentration effects upon log K for the complexation of p-ethoxybenzenediazonium salts by 18-crown-6 in dichloromethane at 35°C[17]

Diazonium salt concentration (mmol)	Apparent log K (M^{-1})	
	Tetrafluoroborate	Hexafluorophosphate
1000	1.94	2.31
100	2.86	3.17
10	3.43	3.61
1	3.58	3.69

Very recently, Haymore[17] has obtained more quantitative data concerning anion and concentration effects for the complexation of p-ethoxybenzenediazonium tetrafluoroborate and hexafluorophosphate in dichloromethane using an infrared spectroscopic method. Results are recorded in Table 10.

Increases in log K with diminishing diazonium ion concentrations result from reduced ion pairing of the uncomplexed diazonium salt with the anion. However, at all concentrations a greater complexation of the hexafluorophosphate salt is evident.

D. The Solvent

The effect of solvent upon the association constants for 18-crown-6 with p-methoxybenzenediazonium tetrafluoroborate[26] and p-ethoxybenzenediazonium hexafluorophosphate[17] is shown in Table 11. The data obtained for the latter suggest a possible inverse correlation between solvent polarity and the magnitude of the association constant. However, the data for the former which include a larger number of low polarity solvents reveal that there is no simple relationship between log K and the dielectric constant or E_T value of the solvent[26].

TABLE 11. Log K values for the association of benzenediazonium salts with 18-crown-6 in different solvents[17,26]

Solvent	ε	E_t	log K (M^{-1})	
			p-$MeOC_6H_4N_2BF_4$[a]	p-$EtOC_6H_4N_2PF_6$[b]
H_2O	78	—	—	−0.5[c]
Me_2SO	47	—	—	0.5
MeOH	33	—	2.09	1.7
Acetone	21	42.2	2.56	2.0
$ClCH_2CH_2Cl$	10	41.9	4.67	—
CH_2Cl_2	9	41.1	3.23	3.7
THF	8	37.4	2.27	—
$CHCl_3$	5	39.1	3.45	—
Dioxane	2	36.0	1.87	—

[a]At 15°C.
[b]At 35°C.
[c]The anion was tetrafluoroborate.

E. Acyclic Polyethers

Interactions of arenediazonium ions with acyclic polyethers have been probed by Bartsch and coworkers for individual glymes from diglyme to decaglyme[59] and for

TABLE 12. Log K values for the complexation of *p-t*-butylbenzenediazonium tetrafluoroborate by acyclic polyethers in 1,2-dichloroethane at 50°C[59]

Polyether	log K (M^{-1})
Diglyme	2.26
Triglyme	2.19
Tetraglyme	2.35
Pentaglyme	2.73
Hexaglyme	2.90
Heptaglyme	3.00
Octaglyme	2.65
Nonaglyme	2.77
Decaglyme	3.14

oligoethylene glycols, $HO(CH_2CH_2O)_nH$, and their monomethyl and dimethyl ethers[60]. The retarding influence of the acyclic polyethers upon the thermal decomposition rate of *p-t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane is measured. The rate retardations are considered to result from the conversion of the diazonium ion into an unreactive form upon complexation (equation 5) as has earlier been established for the crown ether 18-crown-6[13].

$$ArN_2^+ BF_4^- + \text{acyclic polyether} \underset{}{\overset{K}{\rightleftharpoons}} \text{complex} \qquad (5)$$

$$\downarrow k_1$$

products

Using this assumption and an excess of the acyclic polyether, complexation constants may be calculated directly from the observed first-order rate constants for the diazonium ions thermolysis in the presence and absence of the potential complexing agent. Log K values for the individual glymes are recorded in Table 12.

The log K values are essentially the same for diglyme, triglyme and tetraglyme and then increase monotonically for pentaglyme, hexaglyme and heptaglyme as the ability of the polyether to form a pseudo-cyclic cavity is enhanced. For octaglyme and nonaglyme, the pseudo-cyclic cavity can contain only a portion of the ether oxygens because of repulsions of the polyether chain-ends. Therefore, weaker complexation is observed. CPK models indicate that, for decaglyme, seven or eight oxygens may form a pseudo-cavity with the remaining oxygens in an arm which passes over the face of the cavity. Thus when complexed with the benzenediazonium ion, decaglyme appears to assume a conformation which is not only crown-ether-like, but also cryptand-like.

To determine the increase in complexation efficiency that is derived by preforming the cyclic cavity of the polyether ('the macrocyclic effect'), complexation constants for acyclic and cyclic polyethers with the same number of oxygen atoms have been compared. From comparison of K values for the association of pentaglyme and of 18-crown-6 with *p-t*-butylbenzenediazonium ion in 1,2-dichloroethane at 50°C, a macrocyclic effect of approximately 30 has been calculated[59].

Based upon the same two polyethers, a macrocyclic effect of 18,700 has been reported for the complexation of *t*-butylammonium thiocyanate in chloroform[61]. Thus, the magnitude of the macrocyclic effect is shown to be highly dependent upon the nature of the cationic species which is being complexed.

In further research, the complexing ability of commercially available oligoethylene glycols and oligoethylene glycol monomethyl ethers as well as synthesized oligoethylene glycol dimethyl ethers for *p*-*t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane has been assessed[60]. Oligoethylene glycols with methylated end-groups offer no significant advantage over the corresponding unmethylated compounds. Polyethylene glycols 1000 and 1500 complex arenediazonium salts about 10% as efficiently as 18-crown-6. These findings raise the possibility of substituting inexpensive, commercially available polyethylene glycols for crown ethers as solubilizing and stabilizing agents for aryldiazonium salts.

VII. POLYETHERS AS PHASE-TRANSFER CATALYSTS FOR ARYLDIAZONIUM SALT REACTIONS IN SOLVENTS OF LOW POLARITY

Gokel and Cram[8] reported the first use of crown ethers as phase-transfer catalysts for aryldiazonium salt reactions in nonpolar organic solvents in 1973. Descriptions of several phase-transfer-catalysed reactions of a variety of aryldiazonium salts by cyclic and acyclic polyethers have now appeared and are summarized in this section.

These reactions are categorized according to the systematic nomenclature for substitution reactions proposed by Bunnett[62]. The name of the group (or atom) which is introduced is given first. This is followed by de- and the name of the leaving group. For example, an arenediazonium salt reaction in which N_2 is replaced by H is a protodediazoniation.

A. Proto- and Deuterio-dediazoniation

Using 10 mole % of dicyclohexano-18-crown-6 as a phase-transfer catalyst, Hartman and Biffar[63] have reported that benzenediazonium tetrafluoroborates with electron-withdrawing groups are readily reduced by powdered copper in dichloromethane. No reaction occurs in the presence of 15-crown-5 or in the absence of crown ether. From benzene- and *p*-toluene-diazonium tetrafluoroborates mixtures of proto- and fluorodediazoniation products are obtained.

Korzeniowski and Gokel[29] have noted a quantitative protodediazoniation of *p*-bromobenzenediazonium tetrafluoroborate when the diazonium salt is stirred with two equivalents of potassium acetate and 5 mole % of 18-crown-6 in chloroform for one hour at room temperature. Use of deuteriochloroform as the solvent gives 4-deuteriobromobenzene in quantitative yield. A mechanism in which aryl radicals (equation 6) abstract hydrogen atoms is proposed.

$$\begin{aligned} ArN_2^+\ BF_4^- + AcO^- &\longrightarrow Ar{-}N{=}N{-}OAc \\ Ar{-}N{=}N{-}OAc + AcO^- &\longrightarrow Ar{-}N{=}N{-}O^- + Ac_2O \\ Ar{-}N{=}N{-}O^- + ArN_2^+ &\longrightarrow (ArN{=}N)_2O \\ (ArN{=}N)_2O &\longrightarrow Ar{-}N{=}N{-}O\cdot + N_2 + Ar\cdot \end{aligned} \qquad (6)$$

B. Halodediazoniation

An alternative to the Sandmeyer reaction for the preparation of aryl bromides and iodides from aryldiazonium salts has been developed by Korzeniowski and Gokel[64]. The halodediazoniations are conducted by stirring a benzenediazonium salt with potassium acetate and a moderate excess of a halogen atom source (bromotrichloromethane, iodomethane or molecular iodine) in chloroform at room temperature in the

presence of a catalytic amount of 18-crown-6. Yields of aryl bromides and iodides are good-to-excellent from benzenediazonium tetrafluoroborates which possess either electron-donating or electron-withdrawing substituents in *meta* and *para* positions. When *ortho* substituents are present, lower aryl halide yields are obtained.

The bromodediazoniation reactions also produce significant amounts of hexachloroethane. Presumably this product arises by the coupling of trichloromethyl radicals which result when aryl radicals (equation 6) abstract bromine atoms from bromotrichloromethane.

Bartsch and Yang[65] have demonstrated that the substitution of polyethylene glycol 1000 for 18-crown-6 as the phase-transfer agent provides yields of halodediazoniation products which equal or surpass those obtained using the crown ether. Although a considerably higher concentration of polyethylene glycol 1000 must be employed, the very low cost of this acyclic polyether is an important compensating factor.

C. Aryldediazoniation

Good-to-excellent yields of a wide variety of mixed biaryls may be prepared by a phase-transfer catalytic Gomberg–Bachman reaction. Korzeniowski, Blum and Gokel[66] have employed 18-crown-6 as a phase-transfer catalyst for the reactions of *ortho*-, *meta*- and *para*-substituted benzenediazonium tetrafluoroborates with potas-

$$ArN_2^+\,BF_4^- + KOAc + 18\text{-crown-6} \xrightarrow[\text{r t } 1.5\text{ h}]{C_6H_6} \underset{60-85\%}{ArPh} \qquad (7)$$

sium acetate in benzene (equation 7). Intermediate aryl radicals (equation 6) attack the solvent to form the unsymmetrical biaryls. Extended reaction periods are required to obtain appreciable biaryl yields in the absence of crown ethers. With polyethylene glycol 1000 as the phase-transfer catalyst[65], somewhat lower biaryl yields are realized than with 18-crown-6.

Other aromatic or heteroaromatic compounds may be used in place of benzene[66]. Thus mixed biaryls are also obtained using mesitylene and thiophene as solvents.

D. Azocyanide Formation

Ahern and Gokel[67] have reported the facile synthesis of *trans*-arenediazocyanides by the phase-transfer-catalysed reactions of *meta*- and *para*-substituted benzenediazonium tetrafluoroborates with potassium cyanide in dichloromethane in the presence of 18-crown-6 (equation 8). The azocyanides serve as dieneophiles for the synthesis of novel heterocyclic compounds by Diels–Alder reactions.

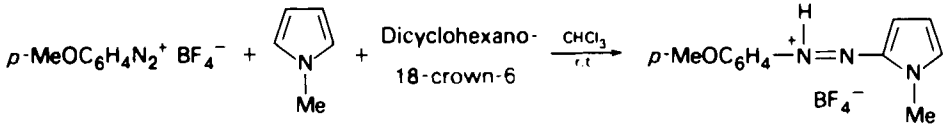
$$ArN_2^+\,BF_4^- + KCN + 18\text{-crown-6} \xrightarrow[\text{r t } 6\text{ h}]{CH_2Cl_2} \underset{80-95\%}{Ar{-}N{=}N{-}CN} \qquad (8)$$

Recent results by Bartsch and Yang[68] have demonstrated that polyethylene glycol 1000 may also be used as the phase-transfer catalyst for this reaction. The acyclic polyether appears to offer the special advantage that *ortho*-substituted benzenediazonium ions may also be converted into the corresponding *trans*-arenediazocyanides.

E. Azo Coupling

Phase-transfer catalysis of the azo coupling reaction of aryldiazonium salts by a crown ether was first reported by Gokel and Cram[8]. A quantitative yield of the azo coupling product is obtained from the reaction of *p*-chlorobenzenediazonium tetrafluoroborate with *N,N*-dimethylaniline in dichloromethane at −78°C in the presence of 18-crown-6. Attempts to form azoarene–crown ether rotaxanes by treating binaphtho-20-crown-6(**5**)-solubilized *p*-toluenediazonium tetrafluoroborate with several organometallic reagents have yielded only nonencircled, conventional azo coupling products.

Crown-ether-catalysed reactions of aryldiazonium salts with pyrroles in chloroform have been described by Shepherd[47]. Treating a chloroform solution of 1-methylpyrrole with solid *p*-methoxybenzenediazonium tetrafluoroborate at room temperature gives no apparent reaction due to the insolubility of the diazonium salt. However, after the addition of dicyclohexano-18-crown-6, complete reaction occurs within 15 minutes. The precipitated reaction product is not the anticipated azopyrrole, but the analytically pure tetrafluoroborate salt of the protonated azopyrrole (equation 9). The free azopyrrole is liberated by treatment of the tetrafluoroborate salt with



(9)

aqueous ammonia. Similar results are obtained when benzenediazonium tetrafluoroborate is the electrophile.

If the 2- and 5-positions of the pyrrole are blocked, electrophilic attack of the aryldiazonium ion occurs at the 3-position.

F. Nucleophilic Substitution *Para* to the Diazonium Group

Gokel, Korzeniowski and Blum[51] have reported stirring *p*-bromobenzenediazonium tetrafluoroborate with potassium chloride in chloroform in the presence of one equivalent of 18-crown-6 for 24 hours at 30°C. Following reduction of the diazonium group prior to analysis, a 55% yield of chlorobenzene is obtained. This result demonstrates a rather facile nucleophilic substitution on the activated aryl bromide.

VIII. CONCLUSIONS

The complexation of aryldiazonium salts by polyethers adds a new dimension to the chemistry of this important chemical species. As has been illustrated, substantial spectral and reactivity changes result when the diazonium group 'neck' of the aryldiazonium ion is inserted into the 'collar' of an appropriately sized crown ether. Several reactions which utilize polyethers as phase-transfer catalysts for aryldiazonium salt reactions in nonhydroxylic solvents of low polarity have also been described. Due to an uncommonly small 'macrocyclic effect' in the complexation of aryldiazonium ions by polyethers, inexpensive, environmentally safe, polyethylene glycols may often be substituted for crown ethers in these reactions.

For the future, it is anticipated that additional phase-transfer-catalysed reactions of aryldiazonium salts which utilize polyethers will be developed. Also, the stability enhancements observed for crown-ether-complexed aryldiazonium ions may find application in improving diagnostic reagents for clinical chemistry and for advances in

photoreproduction and polymerization processes. It also seems reasonable that stability enhancements similar to those noted for crown ether complexation of aryldiazonium ions may also be realized for less stable diazonium ion species, such as heteroaromatic, vinylic and perhaps even alkyldiazonium ions.

Hopefully, the summary provided in this chapter will serve as a catalyst for further developments in the chemistry of diazonium ions complexed by polyethers.

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Crown Ethers and Analogs
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CHAPTER **9**

Appendix to complexation of aryldiazonium ions by polyethers

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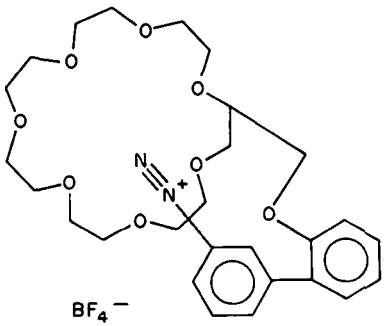
In this Appendix, additional information on the complexation of aryldiazonium ions by polyethers which has appeared since the original chapter was submitted is summarized. To provide continuity, the advances are collected under the same major headings which were used in the original chapter.

I. SOLID-STATE COMPLEXES OF ARYLDIAZONIUM SALTS AND CROWN ETHERS

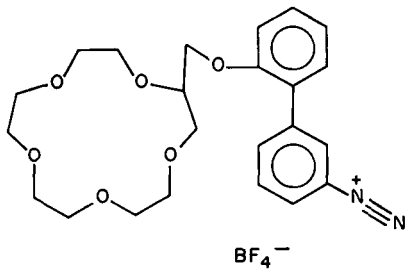
A. Isolable Complexes

Several additional complexes of benzenediazonium tetrafluoroborates with polyethers have been isolated. Crystalline complexes of *p*-methylbenzenediazonium[1] and benzenediazonium tetrafluoroborates[2] with 18-crown-6 and of *p*-chlorobenzenediazonium and benzenediazonium tetrafluoroborates[2] with 21-crown-7 augment those listed in the original chapter. Kuokkanen[3] reported the preparation of crystalline complexes of arenediazonium tetrafluoroborates and the acyclic polyether polyethylene glycol 1000 by precipitation from 1,2-dichloroethane solutions with diethyl ether. Solid complexes of PEG 1000 with *p*-methyl- and *p*-chlorobenzenediazonium tetrafluoroborates and also benzenediazonium tetrafluoroborate itself were synthesized.

The intramolecular arenediazonium cation–crown ether complex **1** was described by Gokel and coworkers[4,5]. Infrared and proton magnetic resonance spectra (see below) of the glassy solid are consistent with insertion of the diazonium ion into the 21-crown-7 cavity. However, for the corresponding 15-crown-5 derivative **2**, in which the polyether cavity is too small to accommodate the diazonio group, the spectra are those of an uncomplexed benzenediazonium ion. Complex **1** is deemed an 'ostrich complex' owing to the popular belief that this bird hides its head in a hole when endangered[4,5].

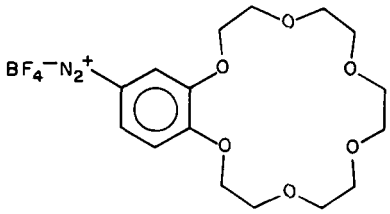


(1)

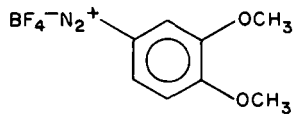


(2)

Molecule **3**, which also possesses both a benzenediazonium ion portion and a crown ether ring, was prepared by Israel[6] and compared with the model compound **4**.



(3)



(4)

TABLE 1. Infrared spectra of uncomplexed and crown ether-complexed benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$) in the solid state[a]

X	$\nu_{N\equiv N}$ (cm^{-1})			Ref.
	Uncomplexed	Complexed with 18-crown-6	Complexed with 21-crown-7	
H	2300	2320	2300	2
p-t-Bu	2277	2306	2282	6
p-Me	2286	2315	2283	1,6
p-Cl	2297	2319	2302	2
p-MeO	2247	—[b]	2261	6
p-BuO	—[b]	—[b]	2262	6

[a]Taken as Nujol mulls.
[b]Not reported

B. Infrared Spectra

As described in the original chapter, when mulled in Nujol solid complexes of 18-crown-6 and a benzenediazonium salt exhibit a single N≡N stretching absorption band which is at a significantly higher frequency than that of the uncomplexed diazonium salt. Additional examples of the phenomenon are presented in Table 1. Thus for complexes of four different benzenediazonium tetrafluoroborates with 18-crown-6 increases of 20–29 cm^{-1} in $\nu_{N\equiv N}$ are noted[1,2,7]. In contrast, the observed $\nu_{N\equiv N}$ values for solid complexes of four benzenediazonium tetrafluoroborates with 21-crown-7 are found to be within $\pm 5\,cm^{-1}$ of the uncomplexed salts[2,7]. Only for the 21-crown-7 complex of p-methoxybenezendiazonium tetrafluoroborate does $\nu_{N\equiv N}$ show a significant increase of $14\,cm^{-1}$. The smaller shifts noted for complexes with 21-crown-7 are surprising since the equilibrium constants for complex formation between benzenediazonium tetrafluoroborates with 21-crown-7 in solution are larger than those for 18-crown-6[2,8,9]. This apparent anomaly is discussed further in the next section.

II. SPECTRAL STUDIES OF COMPLEXES OF ARYLDIAZONIUM SALTS WITH CROWN ETHERS IN SOLUTION

A. Infrared Spectra

Gokel and coworkers expanded their earlier investigation of the effects of 18-crown-6 addition on $\nu_{N\equiv N}$ for benzenediazonium tetrafluoroborates in chlorocarbon solvents[10] to include the larger ring crown ethers 21-crown-7 and 24-crown-8[7]. Selected data are presented in Table 2.

As noted in the original chapter, the addition of one equivalent of 18-crown-6 to a solution of p-*tert*-butylbenzenediazonium tetrafluoroborate in chloroform gives rise to two $\nu_{N\equiv N}$ absorptions. One band is at the frequency of the diazonium salt in the absence of crown ether and the other is at higher frequency and is ascribed to the crown ether-complexed diazonium salt. In the presence of five equivalents of 18-crown-6 only the higher frequency band is present, which demonstrates complete conversion into the complexed form. When one equivalent of 21-crown-7 is added to a solution of p-*tert*-butylbenzenediazonium tetrafluoroborate in chloroform, only a single higher frequency band for the complexed form is noted, which remains unchanged if the amount of 21-crown-7 is increased to five equivalents. Since only one equivalent of 21-crown-7 is required to convert the arenediazonium salt totally into the complexed form, 21-crown-7

TABLE 2. Effect of crown ethers on the $\nu_{N\equiv N}$ absorption of benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$) in chlorocarbon solvents[7,10]

X	Solvent	Crown ether	$\nu_{N\equiv N}$ (cm^{-1}) No crown ether	1 equiv. of crown ether	5 equiv. of crown ether
t-Bu	$CHCl_3$	18-Crown-6	2272	2271, 2308[a]	2308
		21-Crown-7		2286	2287
		24-Crown-8		—[b]	2278
Me	$CHCl_3$	21-Crown-7	—[c]	2286	2287
		24-Crown-8		—[b]	2275
BuO	$CHCl_3$	18-Crown-6	2245	2245, 2294[d]	2250, 2295[e]
		21-Crown-7		2262	—[b]
	CH_2Cl_2	21-Crown-7		2260	—[b]

[a]The peak intensities were approximately (1) (2271):(1.36) (2308).
[b]Not reported.
[c]In the absence of crown ether the diazonium salt is insoluble.
[d]The peak intensities were approximately (1) (2245):(1.0) (2294).
[e]The peak intensities were approximately (1) (2250):(2.33) (2295).

must be a better complexing agent than 18-crown-6 for the diazonium salt. The same conclusion was reached earlier in kinetic studies[2,8] and dynamic nuclear magnetic resonance measurements[9]. For p-butoxybenzenediazonium tetrafluoroborate, which could not be converted solely into the complexed form even with five equivalents of 18-crown-6, one equivalent of 21-crown-7 suffices in chloroform and even in the more polar solvent dichloromethane.

Since 21-crown-7 clearly interacts stronger with benzenediazonium ions than 18-crown-6, it is surprising that $\nu_{N\equiv N}$ values for complexes with the former ligand are lower than for the latter. Indeed, the absorption frequency decreases in the order 18-crown-6 complex > 21-crown-7 complex > 24-crown-8 complex, whereas the complexation constants for interactions of the crown ethers with benzenediazonium ions decrease in the order 21-crown-7 > 18-crown-6 > 24-crown-8[9]. To rationalize this anomaly, Beadle *et al.*[7] proposed that 21-crown-7 employs most of its oxygens nearly to encircle the diazonio group with a 'crown collar' but uses the remaining donor atom(s) either to solvate the terminal nitrogen atom or to interact as a base with the π-acidic aromatic ring, providing additional stability. Such secondary interactions would be reflected in a reduced $\nu_{N\equiv N}$ value in the complex.

Nakazumi *et al.*[2] reported results from a more limited infrared study. For benzenediazonium and p-chlorobenzenediazonium tetrafluoroborates in acetone, a $\nu_{N\equiv N}$ of 2300 cm^{-1} was noted. When the solid 1:1 complexes of the former diazonium salt with 18-crown-6 and with 21-crown-7 were dissolved in acetone, $\nu_{N\equiv N}$ values of 2320 and 2310 cm^{-1}, respectively, were observed. For the corresponding complexes of the latter diazonium salt dissolved in acetone, $\nu_{N\equiv N}$ values of 2325 and 2315 cm^{-1} were recorded. These results corroborate those obtained by Beadle *et al.* in chlorocarbon solvents in that the shift in $\nu_{N\equiv N}$ caused by complexation of the diazonium salts with 18-crown-6 is greater than that produced by 21-crown-7.

For the intramolecular 'ostrich molecule' complex **1**, $\nu_{N\equiv N}$ in chloroform was observed at 2290 cm^{-1} and did not shift when 18-crown-6 was added. On the other hand, for **2**, $\nu_{N\equiv N}$ was found at 2272 cm^{-1} and increased to 2302 cm^{-1} in the presence of 18-crown-6. These findings strongly indicate that **1** exists as the intramolecular complex whereas **2** does not[4,5].

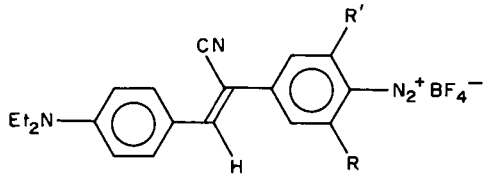
B. Ultraviolet and Visible Spectra

As recorded in the original chapter, ultraviolet absorption maxima for benzenediazonium tetrafluoroborates in 1,2-dichloroethane shift to shorter wavelengths in the presence of 18-crown-6. Subsequent studies by two groups showed that the magnitude of the shifts are dependent on the crown ether ring size. For a variety of benzenediazonium tetrafluoroborates in 1,2-dichloroethane, Nakazumi *et al.*[2] reported that the wavelength shift decreases in the order 18-crown-6 > 21-crown-7 > dicyclohexano-24-crown-8. Beadle *et al.*[7] observed the largest wavelength shift with 18-crown-6, a smaller shift with 21-crown-7, and λ_{max} values equal to or greater than those found in the absence of crown ether with 24-crown-8 for four benzenediazonium tetrafluoroborates in chloroform. These results further indicate that the type of complexation achieved by 18-crown-6 is modified for the larger crown ethers.[7]

Becker *et al.*[1] observed broad charge-transfer absorptions up to 550 nm for complexes of *p*-methylbenzenediazonium tetrafluoroborate with benzo-18-crown-6, dibenzo-18-crown-6 and 2,3-naphtho-18-crown-6 in acetonitrile–dichloromethane (1:9).

Ultraviolet absorption bands of benzenediazonium tetrafluoroborates in 1,2-dichloroethane shift to shorter wavelengths by 11–15 nm in the presence of polyethylene glycols[3]. PEG 300, PEG 600, PEG 1000 and PEG 2000 all produce shifts of the same magnitude.

Electronic spectra of high colored diazonium salts **5** (R = R′ = H; R = R′ = Me; R = H, R′ = Me) are influenced by the presence of crown ethers. The influence of crown ether ring size and substituent variation have been assessed[11,12].



(**5**)

C. Nuclear Magnetic Resonance Spectra

The influence of the crown ether ring size on the ^{13}C NMR chemical shifts for the ring carbon atoms of four *para*-substituted benzenediazonium tetrafluoroborates in $CDCl_3$ was assessed by Beadle *et al.*[7] (Table 3). Spectra for 4-methyl-, 4-*tert*-butyl-, 4-methoxy- and 4-butoxybenzenediazonium tetrafluoroborates in the presence of 18-crown-6 (5 equivalents), 21-crown-7 (1 equivalent) and 24-crown-8 (5 equivalents) are listed. Owing to weaker complexation of arenediazonium tetrafluoroborates by 18-crown-6 and 24-crown-8 than by 21-crown-7, larger amounts of these two crown ethers are needed to produce the fully complexed diazonium ion species. Both 4-*tert*-butyl- and 4-butoxybenzenediazonium tetrafluoroborates possess sufficient solubility in $CDCl_3$ for spectra to be measured in the absence of crown ether, whereas this is not possible for 4-methyl- and 4-methoxybenzenediazonium tetrafluoroborates.

As noted in the original chapter, complexation by 18-crown-6 produces a 2.5–3.5 ppm downfield shift in the *ipso*-carbon absorption [previously identified as $C_{(1)}$] and upfield shifts of 3–4 ppm for the *ortho*- and *para*-carbons with considerably smaller chemical shift changes for the *meta*-carbons. Overall, the chemical shift changes produced by crown ether complexation decreases in the order 18-crown-6 > 21-crown-7 > 24-crown-8.

With respect to the diazonio group, ^{15}N NMR chemical shifts of N_α and N_β

TABLE 3. Effects of crown ethers on the ^{13}C NMR chemical shifts of benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$) in $CDCl_3$[7]

X	Crown ether (equiv.)[b]	^{13}C NMR chemical shift (ppm)[a]			
		ipso	*ortho*	*meta*	*para*
Me	18-Crown-6 (5)	113.31	131.38	129.60	151.58
	21-Crown-7 (1)	112.20	131.99	130.33	152.60
	24-Crown-8 (5)	110.33	131.90	130.07	152.71
t-Bu	None	110.46	132.61	128.79	166.93
	18-Crown-6 (5)	112.76	129.25	127.50	163.05
	21-Crown-7 (1)	112.85	132.76	127.50	165.15
	24-Crown-8 (5)	110.46	132.14	126.51	164.43
MeO	18-Crown-6 (5)	105.44	132.51	116.19	166.77
	21-Crown-7 (1)	104.37	135.55	115.67	169.98
	24-Crown-8 (5)	102.38	135.75	115.67	168.06
BuO	None	101.26	135.64	117.50	168.87
	18-Crown-6 (5)	104.68	132.14	116.05	165.76
	21-Crown-7 (1)	104.31	135.91	116.44	167.95
	24-Crown-8 (5)	102.65	136.54	116.78	168.47

[a]Downfield from TMS.
[b]Equivalents of crown ether per equivalent of benzenediazonium tetrafluoroborate.

benezenediazonium tetrafluoroborates in the absence and presence of one equivalent of crown ether were reported in two studies[1,13]. The results are presented in Table 4.

Complexation of a benzenediazonium ion by a crown ether produces an upfield chemical shift for N_α and a smaller downfield shift for N_β. As noted in the original chapter, these results are in accord with the results of CNDO/2 molecular orbital calculations, which predict that complexation will increase the positive charge density on N_α but decrease the amount of positive charge on N_β.

Izatt *et al.*[14] determined that electron-withdrawing *para*-substituents enhance the complexation of benzenediazonium cations by 18-crown-6 in MeOH. Therefore, the smaller influence of one equivalent of 18-crown-6 in DMF on the N_α and N_β resonances for

TABLE 4. Effect of crown ethers on ^{15}N NMR chemical shifts of benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$)

X	Solvent	Crown ether	$\Delta\delta N_\alpha$[a,b]	$\Delta\delta N_\beta$[a,b]	Ref.
MeO	DMF	18-Crown-6	−4.5	1.5	12
Bu	DMF	18-Crown-6	−4.5	2.3	12
H	DMF	18-Crown-6	−5.7	3.2	12
Br	CD_3CN–$CHCl_3$ (1:1)	18-Crown-6	−5.8	1.4	1
Cl	CD_3CN–$CHCl_3$ (1:1)	18-Crown-6	—[c]	1.2[d]	1
		Benzo-18-crown-6	—[c]	1.5[d]	1
		Dibenzo-18-crown-6	—[c]	1.6[d]	1

[a]A positive number indicates a downfield shift in the presence of crown ether.
[b]In ppm.
[c]Not measured.
[d]Chemical shift measured in CD_3CN in the absence of crown ether.

benzenediazonium ions bearing electron-donating *para*-substituents may arise from a smaller proportion of the arenendiazonium salt being converted into the crown ether-complexed form[13].

Although the magnitude of the differences is small, it appears that the downfield shift at N_α for *p*-chlorobenzenediazonium tetrafluoroborate decreases in the order dibenzo-18-crown-6 > benzo-18-crown-6 > 18-crown-6. This is surprising since 18-crown-6 is a better complexing agent for *p-tert*-butylbenzenediazonium tetrafluoroborate than is dibenzo-18-crown-6[15]. However, these ^{15}N NMR results may be complicated owing to the strong interactions of MeCN with 18-crown-6[16].

III. MODIFIED REACTIVITY OF CROWN ETHER-COMPLEXED ARYLDIAZONIUM SALTS

A. Thermal Stabilization in Solution

Zollinger and coworkers[2,17] evaluated the de-diazoniation kinetics of various *meta*- and *para*-substituted benzenediazonium tetrafluoroborates in 1,2-dichloroethane in the absence and presence of 18-crown-6, 21-crown-7 and dicyclohexano-24-crown-8. The kinetic results were analysed according to the equation which was introduced by Bartsch *et al.*[8] and subsequently utilized by Kuokkanen and Virtanen[18]. Of particular interest are the relative magnitudes of k_2, the rate constant for thermolysis of the diazonium ion–crown ether complex, and k_1, the decomposition rate of the uncomplexed diazonium salt, as a function of the crown ether ring size and benzenediazonium ion substituents. The results are presented in Table 5.

$$\begin{array}{ccc} ArN_2^+BF_4^- + \text{Crown} & \overset{K}{\rightleftharpoons} & ArN_2^+ \cdot \text{Crown} + BF_4^- \\ \downarrow -N_2,\ k_1 & & \downarrow -N_2,\ k_2 \\ \text{Products} & & \text{Products} \end{array} \qquad (1)$$

With the exception of two strongly electronegative diazonium salts (*m*-Cl and *m*-CN), the k_2 values are generally 1–2% of k_1 for complexation with 18-crown-6, 0.1–0.5% with 21-crown-7 and 2-10% with dicyclohexano-24-crown-8. Since the equilibrium constants for complex formation (K) decrease in the order 21-crown-7 > 18-crown-6 > dicyclohexano-24-crown-8[2,17], it is evident that the k_2/k_1 ratio is lower for a more stable complex.

TABLE 5. De-diazoniations of uncomplexed and crown ether-complexed benzenediazonium tetrafluoroborates ($XC_6H_4N_2BF_4$) in 1,2-dichloroethane at 50 °C[2,17]

	100 k_2/k_1 (%)		
Substituent	18-Crown-6	21-Crown-7	Dicyclohexano-24-crown-8
p-Me	1.5	0.22	9.7
m-Me	1.1	0.53	4.8
H	1.4	0.12	4.8
m-MeO	1.2	0.08	2.3
p-Cl	9.8	1.7	17
m-COMe	0.70		
m-CN	34		

When logarithms of the rate constants for reactions within the complex ($\log k_2$) were plotted against those for reactions of the free diazonium ions ($\log k_1$), a linear dependence was observed for each of the crown ethers studied, with slopes of 0.92, 0.95 and 0.66 for reactions in the presence of 18-crown-6, 21-crown-7 and dicyclohexano-24-crown-8, respectively[2]. Therefore, the thermal de-diazoniation of the complexed diazonium ions must proceed by basically the same mechanism as that of the free diazonium ions.

Two of the diazonium salts studied (*p*-Cl and *m*-CN) give extraordinarily high k_2/k_1 ratios and exhibit marked divergences in the $\log k_2$ versus $\log k_1$ plot. In these cases, the de-diazoniation rates of the complexed diazonium ions are much faster than expected, which indicates that addition of crown ethers causes a change in mechanism. Product studies verified the change from a predominantly heterolytic mechanism in the absence of crown ethers to a homolytic mechanism for the crown ether-complexed diazonium ions[2]. This is the first example of a complete change in reaction mechanism and de-diazoniation products due to the addition of crown ethers.

By product studies, Court and coworkers[19,20] investigated the thermal decomposition mechanisms of two crown ether-complexed benzenediazonium tetrafluoroborates which bear electron-withdrawing groups in anisole and in *p*-iodoanisole solvents. The thermal de-diazoniation of *p*-nitrobenzenediazonium tetrafluoroborate complexed with 18-crown-6 proceeds exclusively by a radical pathway. For *p*-chlorobenzenediazonium tetrafluoroborate complexed with 18-crown-6, the mechanism is predominantly heterolytic, but a substantial proportion of homolysis (about 30%) is also detected.

Becker *et al.*[1] observed products of both heterolysis and homolysis in the decomposition of *p*-methylbenzenediazonium tetrafluoroborate complexed with 18-crown-6 or dibenzo-18-crown-6 in acetonitrile–dichloromethane (1:9) at 40 °C.

Results for the thermal decomposition of benzenediazonium tetrafluoroborates in the presence of pentaglyme and polyethylene glycols (PEG 300–PEG 2000) in 1,2-dichloroethane at 50 °C were presented by Kuokkanen[3,21]. Except for benzenediazonium tetrafluoroborates with strongly electron-withdrawing substituents (e.g. *p*-CN), for which a change to a homolytic decomposition mechanism is evident, the presence of acyclic polyethers retards the thermal de-diazoniation of the benzenediazonium salts. Analysis of the kinetic data according to equation 1 established that decomposition of the complexed and free diazonium salt species occurs concurrently with calculated k_2/k_1 values of 15–22% for pentaglyme[21] and the PEG[3] systems. Corresponding values in the presence of 18-crown-6 are 1–2% (Table 5)[2,17]. This difference between the acyclic and cyclic polyethers may be attributed to a macrocyclic effect[3].

Decomposition rates of the complex (k_2) are independent of the PEGs studied. A plot of $\log k_2$ for decomposition of benzenediazonium tetrafluoroborate–PEG 1000 complexes versus $\log k_1$ for the uncomplexed salts gives a linear correlation with a slope of 0.98, which establishes that the de-diazoniation mechanisms of the complexed and uncomplexed arenediazonium ions are very similar.

Israel[6] reported different effects of solvent variation on the thermal decomposition of the crown ether diazonium salt **3** and the model compound **4**. Although the unimolecular thermolysis rate for **4** remains invariant when the solvent polarity is decreased on going from MeCN to MeCN–CH_2Cl_2 (1:9), the decomposition rate decreases by 80% for the same solvent change with **3**. It is rationalized that two molecules of **3** associate to form a thermally stabilized complex. Dissociation of the complex should be favored by a more polar solvent which produces the higher thermolysis rates in MeCN.

B. Photochemical Stabilization in Solution

Israel[6] also investigated the influence of solvent polarity on photochemical de-diazoniations of the crown ether diazonium salt **3** and the model compound **4**. The quantum yield for irradiation of **4** with a high-pressure mercury lamp is unaffected by a

change of solvent from MeCN to MeCN–CH_2Cl_2 (1:9). However, the quantum yield for irradiation of **3** decreases by 15% with this solvent change. Hence the decrease in solvent polarity is found to retard both the thermolysis and photolysis of **3**, presumably by favoring complexation of the diazonium group of **3** with the crown ether ring of another molecule.

Becker *et al.*[22] investigated the influence of 18-crown-6, benzo-18-crown-6, dibenzo-18-crown-6 and polyethylene glycols (PEG 400 and PEG 1500) on the photochemical decomposition (with a medium-pressure mercury lamp) of *p*-methyl-, *p*-methoxy- and *p*-chlorobenzenediazonium tetrafluoroborates. In the presence of 18-crown-6 in MeCN–CH_2Cl_2 (1:9), the photolysis of *p*-methylbenzenediazonium tetrafluoroborate yields primarily the products of heterolytic de-diazoniation. In contrast, when the photolysis is conducted in the presence of dibenzo-18-crown-6 mainly the products of homolytic dediazoniation result as a consequence of electron transfer from the crown ether to the complexed diazonium ion[22].

Quantum yields for the photolysis of *p*-methoxybenzenediazonium tetrafluoroborate in aqueous solution are unaffected by the addition of 18-crown-6. However, in CH_2Cl_2 the quantum yields falls from 0.66 for the free diazonium ion to 0.08 when complexed by 18-crown-6. For the diazonium salt complexes with PEG 400 and PEG 1500 in CH_2Cl_2 the quantum yields are 0.24 in both cases. Hence complexation by either 18-crown-6 or a polyethylene glycol provides substantial stabilization of the benzenediazonium salt in solution, a greater effect being produced by the cyclic polyether.

On the other hand, quantum yields for the photolysis of *p*-methybenzenediazonium tetrafluoroborate complexed with dibenzo-18-crown-6 are found to increase with decreasing wavelength of the exciting light from 0.09 (436 nm) to 0.32 (366 nm). This wavelength dependence arises from the formation of a correlated radical pair after excitation. In agreement with this rationalization, a photo-CIDNP effect is observed in the ^{15}N NMR spectrum of isotopically labeled ($^{15}N_\beta$) *p*-chlorobenzenediazonium tetrafluoroborate complexed with dibenzo-18-crown-6 or benzo-18-crown-6, but not 18-crown-6, in MeCN–$CHCl_3$ (1:9).

C. N_α–N_β Interchange during Solvolysis

The extent of N_α–N_β interchange which accompanies the thermal de-diazoniation of $^{15}N_\beta$-labeled *p*-methylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane was assessed by Nakazumi *et al.*[2] for both the free and crown ether-complexed diazonium ions. In the absence of crown ether, 4.0% rearrangement occurs when the de-diazoniation is interrupted after 70% completion. Under conditions which produce 99% of the diazonium salt in the crown ether-complexed form, 18-crown-6, 21-crown-7 and dicyclohexano-24-crown-8 give 3.4, 4.2 and 3.9% rearrangement, respectively. Hence, within the experimental error of $\pm$ 1%, complexation of the diazonium salt by a crown ether has no discernible influence on the N_α–N_β rearrangement process in 1,2-dichloroethane. In addition, no exchange with external nitrogen is detectable[2].

As noted in the original chapter, the presence of dibenzo-18-crown-6 has been shown to reduce the extent of N_α–N_β rearrangement which accompanies thermal dediazoniation of $^{15}N_\beta$-labeled benzenediazonium tetrafluoroborate in the more polar solvent 2,2,2-trifluoroethanol.

IV. FACTORS WHICH AFFECT THE COMPLEXATION OF ARYLDIAZONIUM SALTS BY POLYETHERS

A. The Crown Ether

Zollinger and coworkers[2,17] used a kinetic method to determine the association constants for seven benzenediazonium tetrafluoroborates with 18-crown-6, 21-crown-7

TABLE 6. Association constants for benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$) with polyethylene glycols in 1,2-dichloroethane at 50 °C[3]

	$K \times 10^3$ ($l\,mol^{-1}$)			
Substituent	PEG 300	PEG 600	PEG 1000	PEG 2000
t-Bu	0.884	2.59	4.32	9.92
Cl	2.94	11.1	20.3	38.3

and dicyclohexano-24-crown-8 in 1,2-dichloroethane at 50 °C. In all cases, the association constants decreased with variation of the crown ether in the order 21-crown-7 > 18-crown-6 > dicyclohexano-24-crown-8. Since the complexation rates are approximately the same for all three crown ethers, the magnitude of the association constant ($K = k_{comp}/k_{decomp}$) is determined primarily by the rate of decomplexation[2].

In another study[1], association constants for the complexation of p-methylbenzenediazonium tetrafluoroborate by three crown ethers in $MeCN–CH_2Cl_2$ (1:9) at 20 °C were determined spectroscopically. The association constants decrease with variation of aromatic group substituent for a common 18-crown-6 ring in the order benzo-18-crown-6 > dibenzo-18-crown-6 > 2,3-naptho-18-crown-6.

B. Ring Substituents of the Aryldiazonium Ion

Further confirmation that electron-withdrawing aromatic ring substituents enhance the complexation of benzenediazonium ions by a crown ether and electron-donating substituents disfavor the association has appeared[1,2].

When association constants for the complexation of benzenediazonium tetrafluoroborates with crown ethers in 1,2-dichloroethane at 50 °C are plotted against the Hammett substituent constants, good linear correlations with ρ values of 1.38, 1.26 and 1.18 were obtained for 18-crown-6, 21-crown-7 and dicyclohexano-24-crown-8, respectively[2]. For the acyclic polyether PEG 1000 in 1,2-dichloroethane, Kuokkanen[3] found an excellent correlation also with $\rho = 1.12$. When the solvent was changed to $MeCN–CH_2Cl_2$ (1:9), the Hammett ρ value for complexation by 18-crown-6 decreased to 0.8[1].

C. Acyclic Polyethers

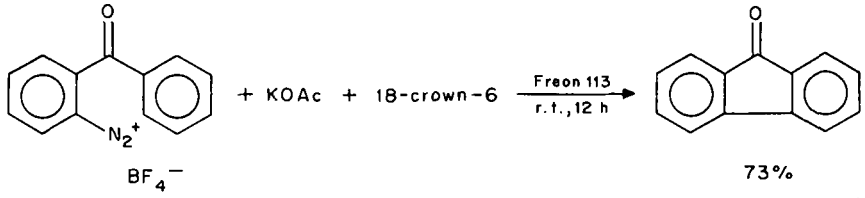
Association constants for complex formation between two benzenediazonium tetrafluoroborates and a series of polyethylene glycols (PEG 300, PEG 600, PEG 1000, PEG 2000) as determined by kinetic measurements in 1,2-dichloroethane at 50 °C are presented in Table 6. Increasing the number of ethyleneoxy units in the polyethylene glycol chain enhances the association constant.

V. POLYETHERS AS PHASE TRANSFER CATALYSTS FOR ARYLDIAZONIUM SALT REACTIONS IN SOLVENTS OF LOW POLARITY

A short review of phase-transfer-catalysed arenediazonium salt reactions with representative procedures has appeared[23]. Full papers were published by Gokel and coworkers which provide additional details of phase-transfer-catalysed arylation by arenediazonium salts[24] (Gomberg–Bachman reactions) and reactions with potassium cyanide to form azocyanides[25]. In both cases, crown ethers function as phase-transfer catalysts by solubilizing one or more ionic reactant in organic solvents of low polarity.

A. Pschorr Cyclization

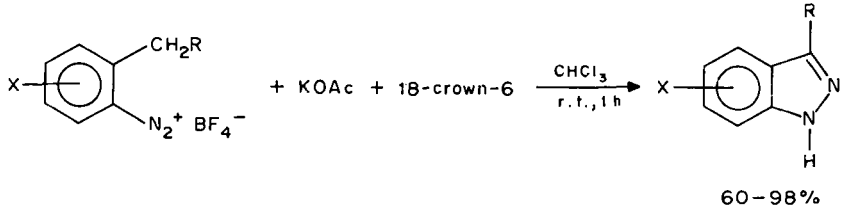
Phase-transfer-catalysed, Pschorr-type cyclizations were reported by Beadle *et al.*[24]. Reaction of an appropriate arenendiazonium tetrafluoroborate with potassium acetate and a catalytic amount of 18-crown-6 in the inert solvent $F_2ClCCFCl_2$ (Freon 113) may provide an intramolecular cyclization product in good yield (equation 2).



(2)

B. Indazole Formation

Bartsch and Yang[26] found that reactions of *o*-methyl- and *o*-ethylbenzenediazonium tetrafluoroborates with potassium acetate and 18-crown-6 as the catalyst in ethanol-free chloroform produces indazoles in good to excellent yields (equation 3).



(3)

VI. INTERACTIONS OF ARENEDIAZONIUM SALT GUESTS WITH OTHER HOST MOLECULES

In the original chapter and in this Appendix, interactions of arenediazonium ions as guests with cyclic and acyclic polyether host molecules have been summarized. Within the past 5 years, some information has become available concerning host–guest[27] interactions of arenediazonium ion guests with other types of host molecules.

A. Cyclodextrins

Cyclodextrins form host–guest complexes with many molecular and ionic species and exert an influence on the rate and/or regioselectivity of several reactions[28]. Fukunishi and coworkers[29,30] found that β-cyclodextrin accelerates the thermal decomposition of substituted benzenediazonium tetrafluoroborates in aqueous solution. De-diazoniation proceeds by a homolytic mechanism.

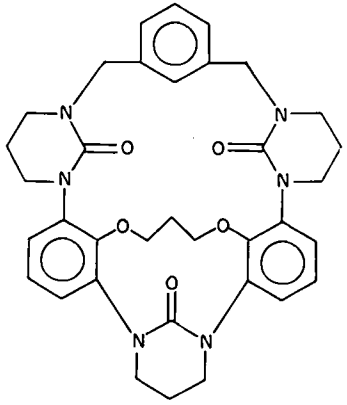
B. Micelles

Although micelles are not formally considered as hosts, they do represent an organized assembly. Moss *et al.*[31] reported rate and product studies for de-diazoniation reactions of

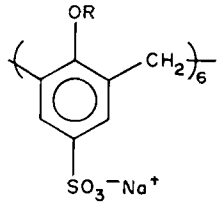
non-micellar (*p*-diazoniobenzyl)trimethylammonium dibromide and micellar (*p*-diazoniobenzyl)dimethylhexadecylammonium dibromide in aqueous solutions in the presence of various concentrations of bromide ion. Although a heterolytic de-diazoniation mechanism is evident for both diazonium salts, the product identity is controlled by the reaction environment. In the concentration range $0.005 \leqslant [Br^-] \leqslant 0.050$ M, micellar de-diazoniation gives only the corresponding aryl bromide, whereas non-micellar de-diazoniation produces only the corresponding phenol.

C. Spherands

Recently, Cram and Doxsee[32] reported the complexation of *p-tert*-butylbenzenediazonium tetrafluorate by spherand **6**. Quantitative infrared studies yielded a binding free energy of -5.9 kcal mol^{-1} for complexation in 1,2-dichloroethane at 25 °C, which is appreciably higher than the -3.6 kcal mol^{-1} determined for complexation by 18-crown-6 under identical conditions. When a colorless solution of the *p-tert*-butylbenzenediazonium tetrafluoroborate–spherand complex and *N*,*N*-dimethylaniline in CH_2Cl_2 is treated with an aqueous solution of sodium carbonate, the aryldiazonium ion is immediately released and couples to form the azo dye. Thus sodium ion, which binds to **6** more strongly than does the diazonium ion, acts as a trigger for dye formation.



(6)



(7)

D. Calixarenes

Recently, Shinkai *et al.*[33] have reported the suppression of thermal de-diazoniation of benzenediazonium ions in water in the presence of the sulfonated calixarenes **7** with R = hexyl or dodecyl. Under the same conditions, the presence of neither 18-crown-6 nor anionic micelles had any influence on the de-diazoniation reaction.

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Crown Ethers and Analogs
Edited by Saul Patai and Zvi Rappoport

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