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PREPARATION OF DERIVATIVES AND ANALOGS OF THE MACROCYCLIC OLIGOMERS OF ETHYLENE OXIDE (CROWN COMPOUNDS)

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1. INTRODUCTION

The importance of macrocyclic ligands has been recognized for some time. The important biological molecules chlorophyl and hemin are both macrocyclic pyrroles which bind magnesium and iron respectively. More recently, large numbers of macrocyclic antibiotics (e.g. depsepetides, macrolides, ferroximes, etc.) have been isolated and their roles as ligands in complexing various alkali and transition metals has been identified.

   Early exploration into the synthesis of macrocyclic multidentated ligands centered on the polyaza compounds and their relationship to porphorins in the complexation of transition metals. Although oligomers of ethylene oxide[1] and even its cyclic oligomers[2] have been know for some time it was not until the pioneering work of Pedersen in 1967 that the tendency of these cyclic oligomers (referred to as "crown ethers" by Pedersen) to strongly bind alkali and alkaline earth metals was recognized.[3]

   The exploitation of the tendency of crown ethers and their derivatives and analogs to strongly bind certain cations has followed two paths. Both are based generally on the fact that the small and hydrated alkali or alkaline earth cations become large and lipophilic as crown complexes. This allows the metal ions to be readily extracted into organic solvents. Crown complexes have therefore been used extensively as phase transfer catalysts.[4,5]

The second major area of utilization is additionally dependent on the cation selectivity of this class of ligands. Because the macrocycles contain hydrophilic cavities of specific sizes, different macrocycles exhibit selectivity for certain cations. This has resulted in a number of potential applications in ion transport and separation schemes.

The number and areas of crown ether applications are rapidly growing. In the five-year period 1972–76 there were only 166 references to the basic crown compounds (18-crown-6, 15-crown-5, dibenzo-18-crown-6, dicyclohexano-18-crown-6). In 1977 there were 93 such references and in 1978 there were 140. Of the 1978 publications more than 22% are patents, primarily in the areas of medicinal, polymer, photo, and separations chemistry. Specific applications of the crown ethers have recently been reviewed.[4-7]

2. PURPOSE AND SCOPE

As the availability and utility of crown compounds has become more generally known, many workers have sought to modify, by a variety of devices, the physical and chemical properties of these ligands. There now exists a considerable body of information concerning the functionalization and modification of crown ethers and related compounds. To date, this work has not been categorized and reviewed. As a result, some current work continues to be duplicative. It is the purpose of this review to provide such a summary and, wherever possible, to discuss the purpose for and the results of such modifications. Since the syntheses of basic crown systems has already been reviewed extensively,[6-9] only a brief discussion is presented in order to provide a background for the reader. In some cases, segments of this work have been recently reviewed. In such instance only a cursory discussion is provided in deference to the existing review. In most cases only ligands containing oligomers of ethylene oxide will be discussed. For example, the well known macrocyclic polyaza ligands (porphorins and cyclams, etc.) are not discussed.

3. SIMPLE CYCLIC OLIGOMERS OF ETHYLENE OXIDE (CROWN COMPOUNDS)

(A) Basic systems and variations

In his initial report, Pedersen reported the synthesis of the cyclic hexamer (18-crown-6) via a Williamson ether synthesis, which proceeded in a low yield (eqn 1).[3] Cram, Liotta et al. later improved

$$HO(CH_2CH_2O)_5CH_2CH_2Cl \longrightarrow \qquad (1)$$
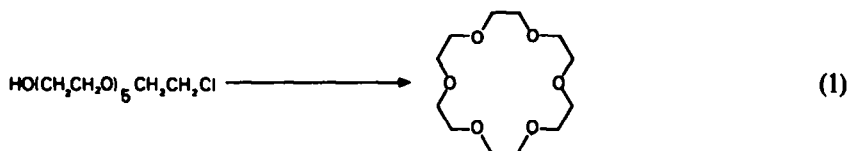
the yield of 18-crown-6 to 25% by using triethylene glycol and triethylene glycol dichloride and a novel purification procedure based on the formation of an acetonitrile complex.[10,11] Similar procedures for the synthesis of 12-crown-4 and 15-crown-5 have been introduced.[12] Reese and coworkers found that the use of a slight deficiency of base and a large excess of the chloro compound gave improved yields of 18-crown-6 and nearly tripled the yield of 15-crown-5 (to about 30%).[13] The dichloride has been replaced as a reactant by the oligoethylene glycol ditosylate in some procedures.[14] A novel modification of the ditosylate procedure has recently appeared (eqn 2).[15] Significantly, the use of hexaethylene glycol in this procedure gave a 75% isolated yield of 18-crown-6.[15]

$$HO(CH_2CH_2O)_nCH_2CH_2OH \longrightarrow \qquad (2)$$
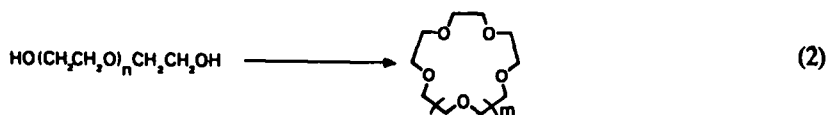
All of these procedures are variations of the Williamson either synthesis. Dale has developed an alternate method based on direct acid catalyzed oligomerization of ethylene oxide using a cationic template.[16,17] Varying the cation allows adjustment of the product ratios (eqn 3). Yields are generally

$$x\left[\begin{array}{c}O\\H_2C\!-\!CH_2\end{array}\right] \longrightarrow \qquad (3)$$

only about 10% based on ethylene oxide. The trimer, heptamer, and octamer can be made by similar processes.[18] Both the Cram–Liotta method and the Dale method are currently utilized in small scale commercial production of 12-crown-4, 15-crown-5 and 18-crown-6.

(B) *Functionalized derivatives* (Table 1)

Several approaches have been utilized to prepare cyclic ethylene oxide oligomers which are substituted on one or more carbon atoms. Nearly all of these involve cyclization of the macrocycle in the final step.

1. *Carbonyls in the macrocycle.* Diacids or their derivatives may be reacted with glycols or their
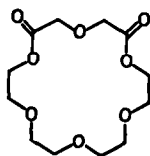
derivatives to produce macrocycles such as the dioxo compound shown above. Inclusion of the ester functions causes increased rigidity in the macrocycle and results in lower cation binding constants. In addition, the ester linkage is labile. This class of compounds has recently been thoroughly reviewed.[19]

2. *Macrocycles with alkyl side chains.* Italian chemists, Cinquini and Tundo, recognized the importance of favorable water/organic solvent partition coefficients for efficient phase transfer catalysis. They prepared a series of alkylated 18-crown-6 compounds via a rather tedious route, in order to successfully shift the partition in favor of the organic phase (eqn 4).[20] A more convenient route to such compounds was later reported by Okahara et al. (eqn 5).[21]


(4)

(5)
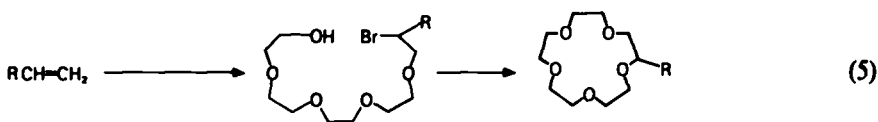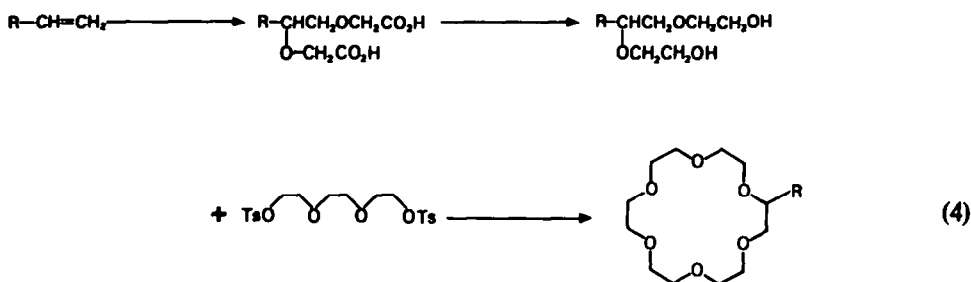
Montanari et al. later prepared ω-aminoalkyl substituted crowns from undec-10-enenitriles by a method similiar to eqn (4).[22] The inclusion of such reactive functional groups of the side chain allows for the attachment of the macrocycle to polymer supports or may provide additional binding sites. Reactive functionality also results from the photo chemical reaction of the crown with aryl ketones.[23] In order to obtain reasonable yields, the ketone must include some functional group that can be complexed by the macrocycle (e.g. potassium carboxylate, nitrile, etc.) (eqn 6).


(6)
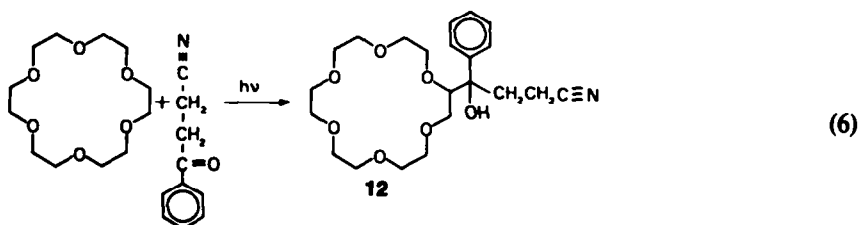
Several alkylidenyl derivatives of 16-crown-5 and 19-crown-6 have been prepared from 3-chloro-2-chloromethyl propene (eqn 7).[24] The alkenes can readily be converted to a large number of functional

groups. Even though inclusion of a three carbon bridge often results in lower cation binding, these workers report that the ligands were efficient phase transfer catalysts.

$$(7)$$
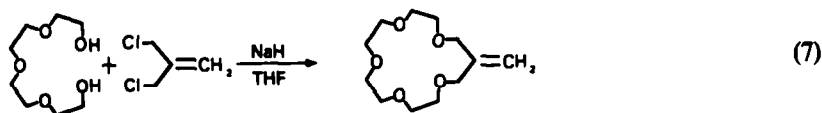
Other crown compounds containing substituents attached to a three carbon bridge were prepared by the potentially useful reaction between cyclic formals and alkenes (eqn 8).[25]

$$(8)$$

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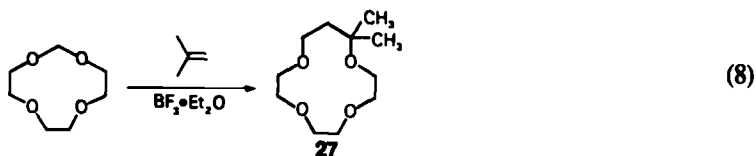
3. *Macrocycles derived from pentaerythritol.* In the early 1970s, workers at DuPont prepared a series of crown ethers derived from 3,3-bis-(chloromethyl)oxetane (a pentaerythritol derivative). The resulting products are spiro linked to one or two oxetane moeities. Such functional groups can readily be polymerized.[26,27]

Stoddart and Coxon subsequently prepared additional compounds of this type, as well as others derived from 5,5-bis(hydroxymethyl) dioxolane.[28,29] Reduction of the oxetane or hydrolysis of the dioxolane substituents gave alkyl and hydroxyalkyl substituted crown compounds. These types of crowns have three carbon bridges. The stability constants of their potassium complexes are reported to be lower than those of the corresponding two carbon bridged ligands.[27]

Table 1 contains a listing of functionalized derivatives of the simple crown ethers except the diester compounds(3. B.1.) which are reviewed elsewhere.[19]

Table 1. Functionalized derivatives of the simple cyclic oligomer of ethylene oxide (crown compounds)

Structure	Substituent(s)	No.	mp(bp)	Yield[a]	Ref
1-4	R				
	CH_3	1	--	41	15
	$n-C_4H_9$	2	(120-125/ 0.2)	20	21
	$n-C_6H_{13}$	3	(130-134/ 0.1)	11	21
	$CH_2OCH=CH_2$	4	--	41	15
5-16	R				
	CH_3	5	--	53	15
	$n-C_{10}H_{21}$	6	oil	41	20
	$n-C_{14}H_{29}$	7	oil	35	20
	$(CH_2)_9NHAc$	8	--	--	22
	$n-C_{20}H_{41}$	9	41-42	33	20
	$(CH_2)_9NHC_2H_5$	10	--	--	22
	$C(OH)(Ph)CH_2CH_2CO_2CH_3$	11	--	10	23
	$C(OH)(Ph)CH_2CH_2CN$	12	oil	17-20	23
	$C(OH)(Ph)CH_2CH_2CO_2H$	13	--	12	23
	$C(OH)(Ph)CH_2CH_2CO_2K$	14	--	21	23
	$C(OH)(Ph)CH_3$	15	oil	9	23

Table 1. (*Contd.*)
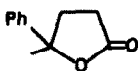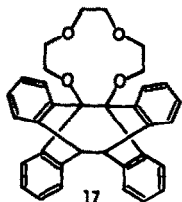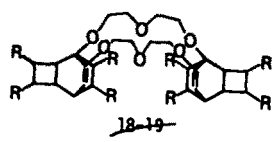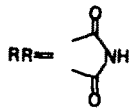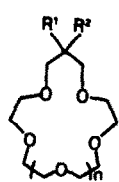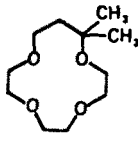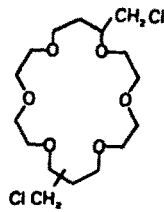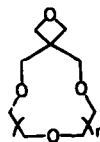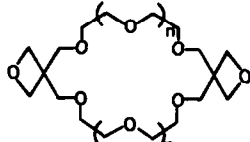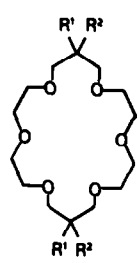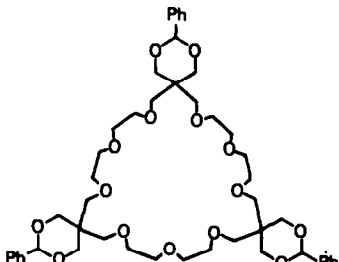
Structure	Substituent(s)	No.	mp(bp)	Yield[a]	Ref
		16	oil	--	23
		17	--	--	30
	RR==	18	--	--	31
		19	--	--	31

20-26

n=1

R[1]	R[2]	No.	mp(bp)	Yield	Ref
=CH2		20	(115-120/ .005)	45	24
H	CH2OH	21	oil	40	24
H	OH	22	--	good	32
			oil	27	24
CH3	OH	23	oil	35	24
=O		24	oil	44	24

n=2

| =CH2 | | 25 | (120-125/ .005) | 66 | 24 |
| CH3 | OH | 26 | -- | -- | 24 |

27

| | | 27 | -- | -- | 25 |

| | | 28 | -- | -- | 25 |

28

Table 1. (Contd.)

Structure	Substituent(s)	No.	mp(bp)	Yield[a]	Ref
29-35	n				
	0	29	(97-99/		
			10)	42	27
			oil	3	29
	1	30	(100-120/		
			.3)	.2	27
	2	31	(97-98/		
			6)	32	27
	3	32	28-30	53	27
	4	33	(136-37/		
			1)	60	27
	6	34	42-43	35	27
	8	35	(250-260/		
			1)	11	27
36-38	n				
	0	36	163-165	7	27
	1	37	85-86	8	29
			86-87	47	27
	2	38	52-53	26	27

Structure	R^1	R^2	No.	mp(bp)	Yield[a]	Ref
39-47			39	99	--	29
			40	--	--	29
	CH_2OH	CH_2OH	41	77	--	29
	syn CH_2OH	CH_2OCH_2Ph	42	--	--	29
	anti CH_2OH	CH_2OCH_2Ph	43	--	--	29
	syn CH_3	CH_2OCH_2Ph	44	--	--	29
	anti CH_3	CH_2OCH_2Ph	45	--	--	29
	syn CH_3	CH_2OH	46	--	--	29
	anti CH_3	CH_2OH	47	--	--	29
			48	86-87	--	29
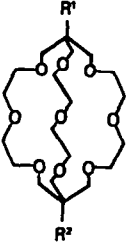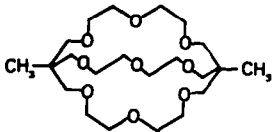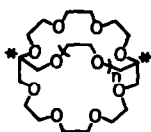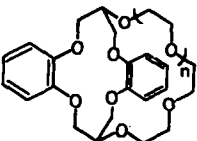
(C) *Bicyclic systems* (Table 2)

It was hypothesized that the addition of an oligoethylene oxide bridge across the cavity of the macrocycle would lead to increased stability constants for the macrocyclic ligand-cation complexes. The first report of such a system from pentaerythritol appeared in 1974.[28] Unlike the cryptands (see Section 5. D.), these ligands exhibited only weak tendencies to bind metal cations.[29] Two other systems prepared from glycerol have subsequently appeared.[33,34] Very high binding constants with cations are reported for one system.[34] Unlike the pentaerythritol based bicyclic compounds, those based on glycerol retain the repeating two carbon to one oxygen system of the simple crown ethers which were earlier shown to complex very strongly with cations.[3]

Table 2 contains a list of bicyclic oligoethylene oxide compounds.

Table 2. Bicyclic oligomers of ethylene oxide (and derivatives)

Structure	Substituent(s)		No.	mp(bp)	Yield[a]	Ref
	R^1	R^2				
	CH_2OH	CH_2OH	49	64-65	--	28,29
	CH_2OCH_2Ph	CH_2OCH_2Ph	50	48-49	30	28,29
	CH_2OMs	CH_2OMs	51	90-91	--	28,29
	CH_3	CH_3	52	59-60	--	28,29
	CH_3	CH_2OH	53	oil	--	28,29
49-53						
54			54	109-11	--	29
	n					
	2		55	--	1.5	33
	3		56	--	1.5	33
55,56	*note chiral centers					
	n					
	1		57	--	--	34
	2		58	--	--	34
57,58						

[a]Yields are overall and are based on readily available starting materials.

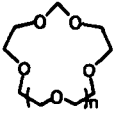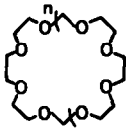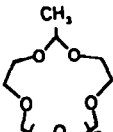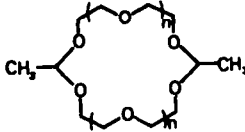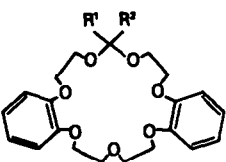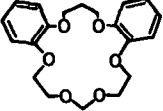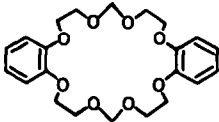## (D) Macrocyclic acetals of ethylene oxide oligomers (Table 3)

Pedersen intially prepared three macrocyclic formals and reported that they possessed only a weak affinity for alkali metal cations.[3,35] Very little interest was expressed in these compounds during the following decade. Another potential deficiency of these systems is their expected acid lability. Gold has recently demonstrated, however, that the rate of acid catalyzed hydrolysis of 78 can be diminished more than an order of magnitude by the addition of rubidium chloride.[36] Since macrocyclic ligands are

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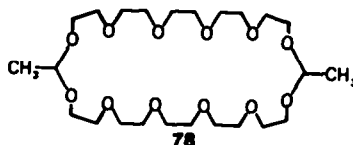
generally employed as their alkali metal complexes, acid lability may be less significant than earlier believed. Macrocyclic formals have been successfully used in the same manner as "normal" crown ethers to accelerate the conversion of butyl bromide to butyl acetate by reaction with potassium acetate.[37] Because they can be prepared in high yields from polyethylene glycols, renewed interest in this class of ligands may be justified.

Table 3 lists macrocyclic oligoethylene glycols which have been cyclized via formation of acetal or ketal linkages.

Table 3. Macrocyclic acetals, formals, and ketals of ethylene oxide oligomers[a]

| Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
59-63	n				
	0	59	27		
			(30/.001)	65	38,39
			--	--	37
	1	60	23.5		
			(51/.001)	47	38,39
			--	--	37
	2	61	--	--	37
	3	62	--	--	37
	4	63	--	--	37
64-70	n				
	1	64	88	18	38,39
	2	65	27	9.4	39
	3	66	56.5	6.4	39
	4	67	19	3.4	39
	5	68	38	2.0	39
	6	69	23	1.6	39
	7	70	28.5	1.4	39
71-74	n				
	0	71	(60/0.2)	2.5	36
	1	72	(82/0.15)	8.0	36
	2	73	(120/.1)	13	36
	3	74	(150/.05)	20	36
75-78	n				
	1	75	36-37	1.5	36
	2	76	61-62	4	36
	3	77	33-34	1	36
	4	78	52-53.5	1	36
79,80	$R^1 R^2 =$ ⬡	79	162	16	35,40
	$R^1 = R^2 = H$	80	151-2	62	35,40
81		81	118	31	35,40
82		82	166-167	8	35,40

[a]See Table 2 also.

4. FUSION TO AROMATIC DERIVATIVES

(A) 1,2-*Benzo and naphthaleno derivatives*

The first crown compounds prepared by Pedersen were derived from catechol (1, 2-dihydroxybenzene) and were thus fused onto an aromatic system.[3,40,41] A large number of such compounds were prepared with different glycols.[8,9] The related 2,3-dihydroxynaphthalene system was also used. The high yield of the medium sized macrocycles (15 and 18 members) was attributed to templating the acyclic intermediate about the alkali metal cations. Subsequently, Cram *et al.* used this template effect around much larger organic cations to produce larger ringer systems. For example, benzo-27-crown-9 can be readily prepared in the presence of guanidinium ion with guanidine acting as the base (eqn 9).[42] Potassium ions, however gave superior yields.[42,43]

$$\text{(9)}$$
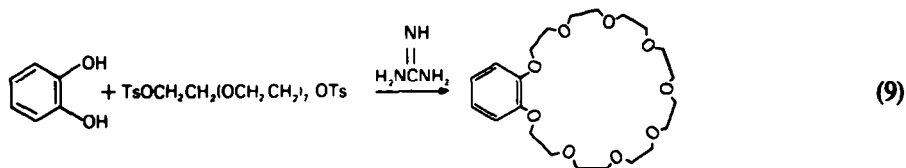
The preparation of 18-crown-6 and 21-crown-7, fused to benzene at every carbon, has also recently been reported.[44]
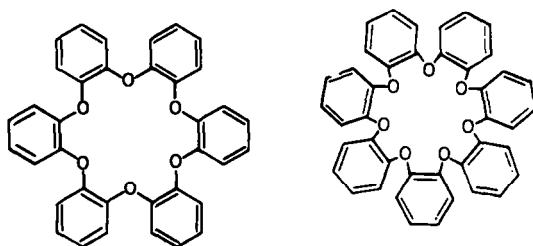

In his first papers, Pedersen reported the reduction of several of the benzo-fused crown compounds to the corresponding cyclohexano-fused systems via catalytic hydrogenation.[3,40,41] However, only two of the five possible isomers were obtained (*cis-syn-cis* and *cis-anti-cis*). The remaining isomers have been synthesized directly from *cis-*and *trans-* 1,2-cyclohexandiol.[45,46]

1. *Functionalization on the macrocyclic ring* (Table 4). Several derivatives bearing substituents on the macrocyclic ring have been prepared. All were synthesized from the corresponsing dihalo compounds and catechol or catechol derivatives. The di- and tetra-methylated compounds were used to study conformational changes during complexation.[47] Those with alkylidenyl and hydroxy functions were, or could be, utilized for further modification of the ligand.[24,34] For example, compound 97 was converted to a series of bicyclic ligands (see Section 3. C.).[34]

Table 4 lists functionalized derivatives of the 1,2-benzo macrocyclic oligoethylene oxides wherein the functional group is attached directly to the macrocylic ring.

Table 4. 1,2-Benzo fused macrocycles functionalized on the macrocyclic ring[a]
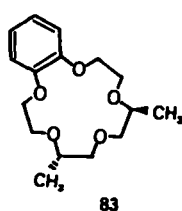
Structure	Substituent(s)	No.	mp(bp)	Yield[b]	Ref
	Isomer 8S, 12S	83	43	--	48
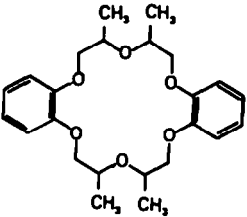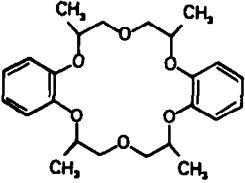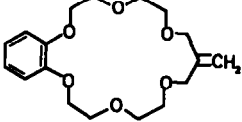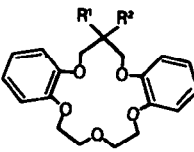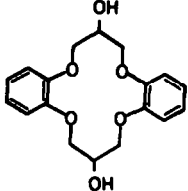
Table 4. (*Contd.*)

Structure	Substituent(s)	No.	mp(bp)	Yield[b]	Ref
	7R,9R,18S,20S	84	199-200	6.7	47
	7R,9R,18R,20R	85	134	3.8	47
	7R,9S,18R,20S	86	92	1.9	47
	7R,9S,18S,20R	87	160	8.4	47
	7R,9R,18R,20S	88	120-122	31.1	47

84-88

	6R,10S,17R,21S	89	109-110	6.5	47
	6R,10S,17S,21R	90	137	5.6	47
	6R,10R,17R,21R	91	136-137	3.0	47
	6R,10R,17S,21S	92	121-122	--	47
	6R,10R,17R,21S	93	84-86	--	47

89-93

| | | 94 | oil | 28 | 24 |

94

R^1 R^2					
$= CH_2$		95	94-95	30	24
H CH_2OH		96	110-111	50	24

95,96

syn isomer		97	160	--	34
anti isomer		98	164	--	34
			(hydrate)		

97,98

[a]See Tables 2 and 3 also.
[b]Yields are overall and are based on readily available starting materials.

2. *Functionalized on the aromatic ring(s)* (Tables 5 and 6). Because they can be prepared with such a large variety of substituents on the aromatic ring, the benzo derivatives are the most versatile of the crown compounds. The fused aromatic ring of the benzo crown ethers is isoelectronic with veratrole (1,2-dimethoxy benzene). As would be expected, it is therefore very reactive towards electrophilic aromatic substitution. Additionally, substituted crowns may be prepared by a ring closure of substituted catechols with the usual glycol derivatives. A few simple alkylated derivatives of catechol are commercially available and are typically used in the preparation of alkylated, benzo crown ethers. In most cases, however, the substitution of electrophiles onto the aromatic ring of the crown compound, has proven to be a superior approach to the preparation of such substituted benzo crowns.

The majority of the substituted benzo crowns are prepared by nitration or acylation of the simple preformed benzo crown compound.[49] The nitro derivatives are readily reduced to the corresponding amines.[50] These may participate in condensation reactions,[51] nucleophilic addition reactions,[49] diazonium reactions[50] or any reaction typical of the amine functional group. Although acylation of the aromatic rings has been done using aluminum chloride as a catalyst,[52,53] phosphorus pentaoxide in anhydrous methanesulfonic acid has proved to be a superior medium.[54] Acyl derivatives may be converted to oximes,[52] reduced to hydrocarbons[55,56] or alcohols,[55] or subjected to Grignard reagents.[57]

Substituted benzo derivatives have been used to study parameters affecting binding constants and kinetics,[49,58] transport through synthetic and biological membranes[56,59-64] and phase transfer catalysis.[55] They also provide reactive sites for attachment of additional binding sites,[49] spin labels,[65] or polymer supports.[50,57,66-68] Substituents have also been attached to provide specific biological activity.[51-53] In addition, numerous other modifications of the ligand can be made once reactive substituents are provided.

For convenience, substituted benzo crowns derived via the cyclization of substituted catechols are tabulated in Table 5. Those derived by substitution onto the preformed benzo crown compounds are in Table 6.

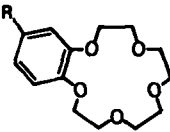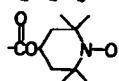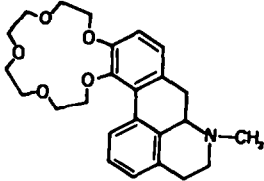Table 5. Benzo crown ethers prepared by the cyclization of substituted catechols[a]
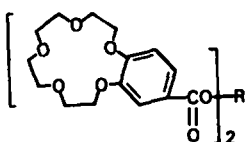
Structure	Substituent(s)	No.	mp(bp)	Yield[b]	Ref
99-111	**R**				
	CH_3	99	51.2-52	57	60,61
	t-Butyl	100	98[c]	61	3,41
	CH_3CO	101	96-97	22	66
	CH_3CHOH	102	65-66	17	66
			--	26	57
	$CH_2=CH$	103	43-44	10	66
			--	22	57
	CHO	104	oil	31	57
			78-79	40	49
	$CH(OH)CH_2NHCH_3$	105	61	--	69
	CO_2H	106	180	20	70
	CO_2CH_3	107	82	16	70
	COCl	108	--	--	70
	$CONH(CH_2)_4CO_2H$	109	--	--	49
	$CH_2CH_2NH_2$	110	90-92	--	69
		111	113-114	--	65
112		112	oil	--	69
113-117	**R**				
	CH_2CH_2	113	124-125	17.4	70
	$CH_2CH_2CH_2CH_2CH_2$	114	88-89	12.8	70
	$CH_2CH_2OCH_2CH_2$	115	89-91	12	70
	$(CH_2CH_2O)_2CH_2CH_2$	116	83-84	9.6	70
	$-(CH_2)_8-$	117	82	11.2	70

Table 5. (Contd.)

Structure	Substituent(s)	No.	mp(bp)	Yield[b]	Ref
118		118	104	25	71
119		119	109-110	20	71
120-128 R	CH$_3$	120	54-55	52	60,61
	t-Butyl	121	35-37	62	3,41
	CHO	122	60-62	25	49
	"		32	57
	CH(OH)CH$_3$	123	58-59	25	57
			58-59	11	66
	CH=CH$_2$	124	59-61	20	57
			61-62	8	66
	CH$_3$CO	125	77.5-78.5	16	66
	CO$_2$H	126	118-120	13	49
	COCl	127	--	--	49
	CONH(CH$_2$)$_3$CH$_3$	128	97-98	10.6	49
129-130	CH$_2$–N(morpholine)O	129	oil	29	72,73
	CH$_2$–N$^\oplus$(morpholine)O CH$_3$	130	--	--	72,73

	R^1	R^2	No.	mp(bp)	Yield[b]	Ref
131-146	CH$_3$	CH$_3$	131	132-135	40	55,74
				126-127	--	59
	n-C$_3$H$_7$	n-C$_3$H$_7$	132	109-112	--	59
	t-C$_4$H$_9$	t-C$_4$H$_9$	133	135-137	low	3
				132-134	--	41
	n-C$_{16}$H$_{33}$	n-C$_{16}$H$_{33}$	134	--	low	75
syn	CH$_3$CO	CH$_3$CO	135	218-220	--	63
anti	CH$_3$CO	CH$_3$CO	136	197-199	--	63
				213-215	3	63
syn	n-C$_3$H$_7$CO	n-C$_3$H$_7$CO	137	183-185	--	63
anti	n-C$_3$H$_7$CO	n-C$_3$H$_7$CO	138	158-161	--	63
	CH$_3$CO	H	139	169-171	27	66
	CH(OH)CH$_3$	H	140	141-143	25	66
	CH=CH$_2$	H	141	148-149	16.5	66

Table 5. (Contd.)

Structure	Substituent(s)		No.	mp(bp)	Yield[b]	Ref
	CH_3CO	CH_3	142	151–153	--	66
	$CH(OH)CH_3$	CH_3	143	135–139	--	66
	$CH=CH_2$	CH_3	144	144–147	--	66
	$CO_2C_2H_2$	$CO_2C_4H_9$	145	--	--	76
	$CO_2C_4H_9$	$CO_2C_4H_9$	146	--	--	76

	n	R				
	1	CH_3	147	68–70	--	59
	2	$CH(OH)CH_2NHCH_3$	148	190–192	--	69

147–148

		No.	mp(bp)	Yield	Ref
149		149	--	12	75

		No.	mp(bp)	Yield	Ref
150		150	149–152	--	41

[a]Table includes compounds obtained by further modification of substituted benzo crown ethers which were derived by cyclization of a substituted catechol.

[b]Yields are overall and are generally based on commercially available catechol derivatives.

[c]The melting point originally reported was 43.5–44.5°C.[3] This value has subsequently been found to be in error, and the value reported above was confirmed to be correct.

Table 6. Benzo crown ethers prepared by direct substitution onto the aromatic ring[a]

Structure	Substituent(s)		No.	mp(bp)	Yield[b]	Ref
151–159	R[1]	R[2]				
	NO_2	H	151	84–85	77	49
				70–80	50	
	NH_2	H	152	—	—	50
	$N_2^+BF_4^-$	H	153	—	—	50
	$CH=CH_2$	H	103	43.5–44.2	20–25	50
	Br	H	154	66–68	57	49
	NO_2	NO_2	155	168	20	49
	CH_3CO	H	156	95–96.5	63	54
	$C_6H_{13}CO$	H	157	49–51	55	54
	$C_6H_{13}CH(OH)$	H	158	wax	51	54
	$C_{13}H_{27}CO$	H	159	55–57	26	54
160, 161	R					
	NO_2		160	—	—	67
	NH_2		161	—	—	67

Table 6. (Contd.)
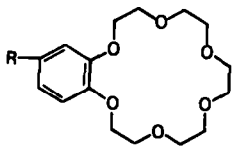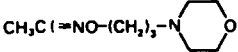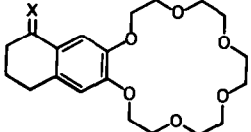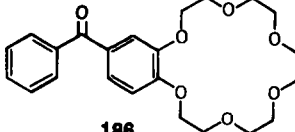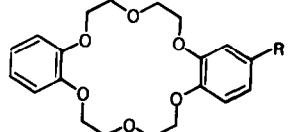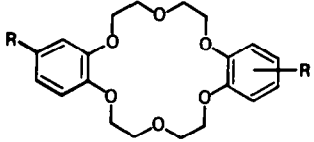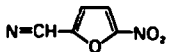
Structure	Substituent(s)	No.	mp(bp)	Yield[b]	Ref
162–183	**R** NO_2	162	70–72	56	49
	CHO	163	61–62	36	53
	CH_3CO	125	—	67	52
	n-C_3H_7CO	164	58–59	—	52
	cyclopropyl-CO	165	—	—	52
	C_2H_5CO	166	—	—	52
	cyclohexyl-CO	167	—	—	52
	$CH_3C(=NOH)$	168	110–111	ca 20	52
	n-$C_3H_7C(=NOH)$	169	104–105	—	52
	cyclopropyl-C(=NOH)	170	64–67	—	52
	$C_2H_5C(=NOH)$	171	77–82	—	52
	cyclohexyl-C(=NOH)	172	128–130	—	52
	$CH_3C(=NOCH_3)$	173	79–80	ca 40	52
	$CH_3C(=NOCH_2Ph)$	174	66–68	ca 30	52
	Phenyl-C(=$NOCH_3$)	175	70–71	ca 10	52
	Phenyl-C(=$NOCH_2Ph$)	176	—	—	52
	$CH_3C(=NO$-t-Butyl)	177	63–65	—	52
	$CH_3C(=NOC_2H_5)$	178	71–73	—	52
	$CH_3C(=NO$-n-hexyl)	179	47–48	—	52
	$CH_3C(=NO$-n-decyl)	180	42–43	—	52
	$CH_3C(=NO$-$COCH_3)$	181	66–67	—	52
	$CH_3C(=NO$-COPh)	182	66–80	—	52
$CH_3C(=NO-(CH_2)_3-N\langle O\rangle)$		183	113–114	ca 60	52
184–185	**X** =O	184	—	—	52
	=NOH	185	124–126	—	52
186		186	112–114	36	53

Note: References 52 and 53 contain 119 references to carbonyl and oxime substituted benzo-18-crown-6 compounds. We have given only a partial list of compounds.

Structure	Substituent(s)	No.	mp(bp)	Yield[b]	Ref
187–188	**R** $CH_3CH_2CH_2CH_2CO$	187	—	—	77
	$Cr(CO)_3$	188	123–24	—	58
189, 239	**R[c]** Br	189	—	—	78
	syn NO_2	190	245–248	—	58
			245–251	—	79
	anti NO_2	191	210–212	—	58
			208–213	—	79
	NO_2		177–236	64	41
	NO_2		—	88*	67
	NO_2		—	—	80
	NO_2		—	—	51
	NO_2		—	—	68
	SO_3H	192	139	75	41
	$Cr(CO)_3$	193	155–158	—	58
	syn NH_2	194	178–184	ca 30	58
	NH_2		177–178	—	81
	anti NH_2	195	196–200	ca 20	58
	NH_2		—	—	67
	NH_2		—	—	51
	NH_2		—	—	68
$N=CH-\langle furan\rangle-NO_2$		196	—	—	51

Table 6. (*Contd.*)
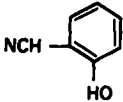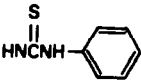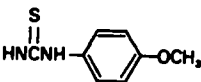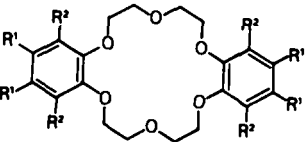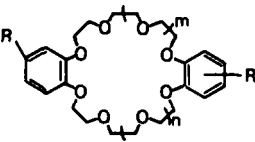
Structure	Substituent(s)	No.	mp(bp)	Yield[b]	Ref
NCH— (phenyl, HO)		197	—	—	51
S‖HNCNH— (phenyl)		198	—	—	51
S‖HNCNH— (phenyl)—OCH$_3$		199	—	—	51
	syn CH$_3$CO	135	213–215	—	63
	anti CH$_3$CO	136	197–199	—	63
	CH$_3$CO		194–201	85	63
	CH$_3$CO		200–208	84	54
	syn CH$_3$CH(OH)[d]	200	197–199	70	55
	anti CH$_3$CH(OH)[d]	201	164–167	—	55
	syn C$_2$H$_5$CO	202	195–196	—	63
	anti C$_2$H$_5$CO	203	182–184	—	63
	C$_2$H$_5$CO		173–179	70	63
	syn C$_3$H$_7$CO	137	183–185	—	63
	C$_3$H$_7$CO[d]		174–182	72	54
	anti C$_3$H$_7$CO	138	158–161	—	63
	C$_3$H$_7$CO		149–165	70	63
	C$_3$H$_7$CO[d]		148–157		55
	iso C$_3$H$_7$CO	204	154–160	88	54
	syn C$_4$H$_9$CO	205	170–171	—	63
	anti C$_4$H$_9$CO	206	150–152	—	63
	C$_4$H$_9$CO		136–148	72	63
	C$_4$H$_9$CO		144–150	100	55
	iso C$_4$H$_9$CO	207	129–132	80	55
	iso C$_4$H$_9$CH(OH)	208	129–132	75	55
	tert-C$_4$H$_9$CO	209	146–159	85	54
	syn Phenyl-CO	210	200–201	—	63
	Phenyl-CO[d]		197–198	100	54, 55
	anti Phenyl-CO	211	184–185	—	63
	Phenyl-CO		145–156	68	63
	Phenyl-CO[d]		178–184		55
	syn C$_5$H$_{11}$CO	212	152.5–153.5	—	56
	anti C$_5$H$_{11}$CO	213	142.5–143.5	—	56
	C$_5$H$_{11}$CO		—	43	56
	syn C$_6$H$_{13}$CO	214	143–145	—	56
	C$_6$H$_{13}$CO		125–141	37	56
	syn C$_6$H$_{13}$CO		119.5–122	86	54
	C$_6$H$_{13}$CH(OH)	215	134–137	—	55
	syn C$_7$H$_{15}$CO	216	141–143	—	56
	anti C$_7$H$_{15}$CO	217	126–128	—	56
	C$_7$H$_{15}$CO		—	37	56
	C$_9$H$_{19}$CO	218	117–129	74	54
	syn C$_9$H$_{19}$CH(OH)[d]	219	145–148	57	54, 55
	anti C$_9$H$_{19}$CH(OH)[d]	220	120–122	—	54, 55
	syn C$_{13}$H$_{27}$CO[d]	221	144–146	71–80	54, 55
	syn C$_{13}$H$_{27}$CH(OH)[d]	222	145.5–147	—	55
	anti C$_{13}$H$_{27}$CO[d]	223	123–127	—	54, 55
	anti C$_{13}$H$_{27}$CH(OH)[d]	224	129–134	—	55
	C$_{17}$H$_{35}$	225	116–120	75	54
	anti C$_2$H$_5$	226	121–123	ca 37	56
	anti C$_3$H$_7$	132	111–113	ca 28	56
	anti C$_4$H$_9$	227	96–98	ca 30	56
	syn C$_4$H$_9$	228	124–126	ca 35	56
	anti C$_5$H$_{11}$	229	111–113	ca 38	56
	C$_5$H$_{11}$		91–94	72	55
	iso C$_5$H$_{11}$	230	97–105	72	55
	anti C$_6$H$_{13}$	231	102–104	ca 23	56
	syn C$_6$H$_{13}$	232	109–111	ca 24	56
	anti C$_7$H$_{15}$	233	92–94	ca 21	56

Table 6. (Cond.)

Structure	Substituent(s)	No.	mp(bp)	Yield[b]	Ref
	C_7H_{15}	234	89–94	72	55
	anti C_8H_{17}	235	89–91	ca 19	56
	anti CH_2Ph	236	148–150	—	56
	$C_{10}H_{21}$	237	89.5–91.5	—	55
	syn $C_{14}H_{29d}$	238	100–100.5	76	55
	anti $C_{14}H_{29}$	239	96–97	—	55

240–242

	R^1	R^2	No.	mp(bp)	Yield[b]	Ref
	Br	H	240	212–215	50	58
	Cl	Cl	241	283	25	58
	NO_2	H	242	228–229	96	80

243–257

n	m	R	No.	mp(bp)	Yield[b]	Ref
0	1	NO_2	243	—	—	67
1	1	NO_2	244	—	—	67
1	2	NO_2	245	—	—	67
2	2	NO_2	246	—	—	67
0	1	NH_2	247	—	—	67
1	1	NH_2	248	—	—	67
1	2	NH_2	249	—	—	67
2	2	NH_2	250	—	—	67
1	1	CH_3CO	251	150–160	85	54
1	1	$CH_3CH(OH)$	252	wax	76	54
1	1	$C_6H_{13}CO$	253	89–91	66	55
1	1	$C_6H_{13}CH(OH)$	254	wax	—	55
1	1	$C_9H_{19}CO^d$	255	86–92	50–48	55
n	m	R				
1	1	$C_9H_{19}CO^d$		78–91	—	55
1	1	$C_9H_{19}CH(OH)$	256	88–91	—	55
1	1	$C_{10}H_{21}$	257	74.5–76	44	55

[a]Table includes compounds obtained by further modification of benzo crown ethers obtained by direct substitution onto the aromatic ring.
[b]Yields are on an overall basis and are based on commercially available benzo crown ethers.
[c]When no isomer is specified, a syn and anti mixture is assumed.
[d]The higher melting isomer is believed to be the syn form. The yield for the syn isomer is a total value for the crude product.

(B) o- and m-Xylyl derivatives (Table 7).

α,α'-Dihalo-m-xylenes bearing a large number of different substituents are readily available. These, in turn, can be cyclized with polyethyleneglycols to yield analogs of the crown ethers (eqn 10). The compounds are alternatively prepared from glycol diosylates and the a,a'-dihydroxyxylenes. The

(10)
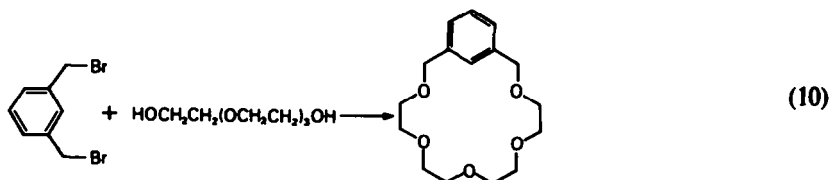
majority of the research of these classes of compounds has been carried out by three research groups: Cram et al. in the United States;[73,82–85] Vögtle, in Germany;[86] and Reinhoudt et al. in the Netherlands.[87–89] McKervey, in Ireland, has also performed research in this area.[90]

Several features of the system are immediately apparent. In the region of the aromatic fusion an unusually long carbon bridge exists. This has generally resulted in a lower binding constant for cations. Another characteristic of the system is the ease with which a large number of different substituents may be projected from the aromatic ring into the macrocyclic cavity. Such substituents may contain atoms capable of binding cations or may simply "crowd" the cavity. Models suggest that for complexation to occur, the aromatic ring must be tilted about 30° out of the plane of the macrocyclic ring.[82] This allows

the benzene substituent, which is projected into the cavity, to act as an additional binding site below the plane of the ether oxygens and gives the ligand a basket shape.[83]

A substantial amount of data regarding alkali metal complexation by these ligands is available.[82,84,85,91] In addition to the *m*-xylylene derivatives, *o*-xylylene derivatives are also known. Their structure, however, precludes the ability to project a substituent into the cavity, and they have received less attention.

Ester analogs of all these ligand types are also available from the reaction of phthaloyl chloride with the polyethylene glycols. These ester compounds have recently been reviewed.[19]

Table 7 is a listing of *ortho* and *meta*-xylyl crown compounds.

Table 7. *Ortho* and *Meta*-xylyl derivatives and related compounds
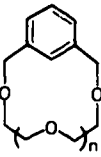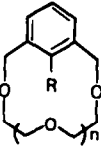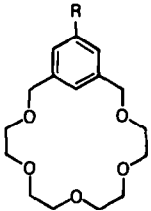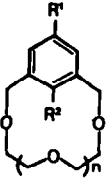
Structure	Substituent(s)			No.	mp(bp)	Yield[a]	Ref
258-264	n						
	1			258	--	2	87,88
	2			259	--	16	87,88
	3			260	85-88	67	87,88
	4			261	--	49	87,88
	5			262	(220/.01)	18	87,88
					44-46	60	83
	6			263	--	21	83,90
	7			264	--	21	83,90
265-281	n	R					
	2	OH		265	66-66.5	41	90
		OCH₃		266	oil	45	90
		CO₂CH₃		267	oil	34	85
		CO₂H		268	106-112	33	85
	3	OH		269	48-49	53	90
		OMe		270	oil	58	90
		Br		271	oil	7	83,85
		Cl		272	oil	53	83,85
		CN		273	oil	10	83,85
		CH₂OH		274	oil	65	83,85
		CH₂OMe		275	70-71	32	83,85
		CO₂CH₃		276	oil	82	83,85
		CO₂H		277	100-1	81	83,85
	4	CO₂CH₃		278	oil	68	83,85
		CO₂H		279	86-95	67	83,85
	7	CO₂CH₃		280	oil	34	83,85
		CO₂H		281	oil	33	83,85
282-287	R						
	Br			282	45-60	62	84
	CN			283	oil	38	84
	OCH₃			284	wax	53	84
	SCH₃			285	oil	19	84
	t-Butyl			286	--	61	84
	CO₂Et			287	glass	31	84
288-292	n	R¹	R²				
	2	CH₃	OCH₃	288	oil	58	82
		NO₂	OH	289	105-6	--	90
	3	CH₃	OCH₃	290	70-72	49	82
		NO₂	OH	291	91-91.5	--	90
	4	CH₃	OCH₃	292	71-73	59	82

Table 7. (Contd.)
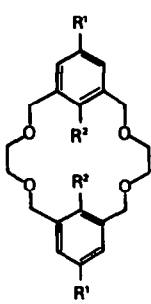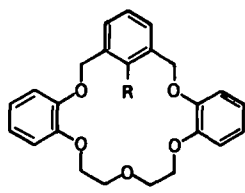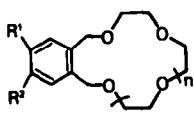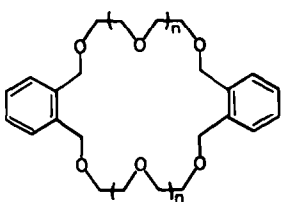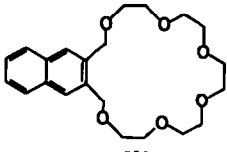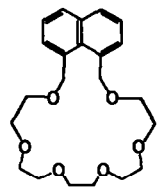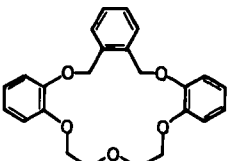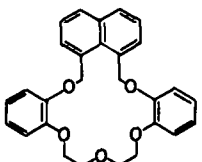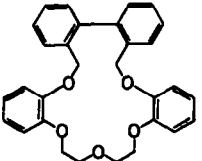
Structure	Substituent(s)			No.	mp(bp)	Yield[a]	Ref
	n	R^1	R^2				
	0	CH_3	OCH_3	293	148-151	14	82
	1	H	H	294		30	87,90
		CH_3	OCH_3	295	88-90	26	82
	2	H	H	296		9	87,90

293-296

	R		No.	mp(bp)	Yield	Ref
	H		297	158-160	5	86
	F		298	178-179	3	86
	OCH_3		299	215-216	9	86
	NO_2		300	179-180	36	86
	$SOCH_3$		301	273-274	8	80

247-301

	n	R^1	R^2	No.		Yield	Ref
	0	H	H	302	--	3	89
	1	H	H	303	--	13	89
	2	H	H	303a	--	48	89
				304	--	29	89
	3	H	H	305	--	63	89
	4	H	H	306	--	60	89
				307	--	25	89
	5	H	H	308	--	47	89
	6	H	H	309	--	36	89

302-309

	n	No.		Yield	Ref
	1	310	--	17	88
	2	311	--	24	88
	3	312	--	8	88

310-312

	No.	mp(bp)	Yield	Ref
	313	58-58.5	--	92

313

	No.	mp(bp)	Yield	Ref
	314	53.5-54.5	--	92

314

Table 7. (Contd.)

Structure	Substituent(s)	No.	mp(bp)	Yield[a]	Ref
 315		315	131-132	8	86
 316		316	152-153	10	86
 317		317	112-115	3	86

[a]Yields are on an overall basis and are based on bis (X-CH$_2$) aromatic starting material.

(C) p-Xylyl, p-Benzeno and cyclophano crown ethers: the π cloud as a binding site (Table 8)

Several researchers have examined the possibility that fusion of the crown ether to cyclophane systems or to p-xylyl or benzene systems would turn the face of the aromatic π cloud into the macrocyclic cavity and result in a cation-π cloud interaction during complexation. This affect has been verified by several groups. Kawashima et al. reported that the NMR chemical shifts of aromatic protons indicate that in some such systems the π cloud is involved in complexation and in others it is not.[93] Stoddart et al. have used the low temperature NMR technique to examine the kinetics of these interactions in complexes such as (341′).[94] Sousa and Larsen have shown that the photo excited states of the cesium complex (318′) are perturbed, indicating interaction of the cation with the π-face.[95] In addition, Cram et al. have obtained considerable data regarding the complexation of this ligand class with ammonium salts.[73]

Table 8 is a listing of p-xylyl, p-benzeno and cyclophano crown ethers.

341′

318′
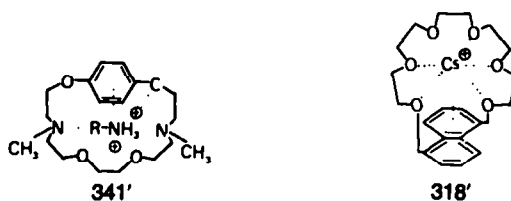
Table 8. p-Xylyl, p-benzo and cyclophano crown ethers: the π-cloud as a binding site
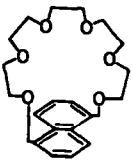
Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
 318		318	55-56	--	95

Table 8. (*Contd.*)
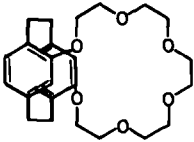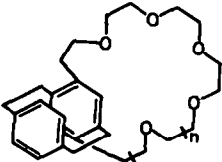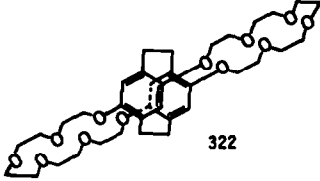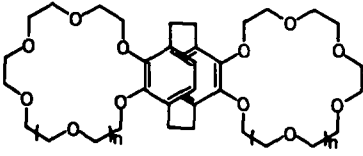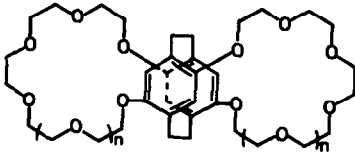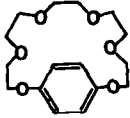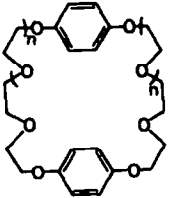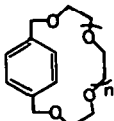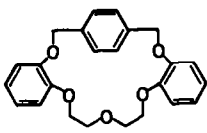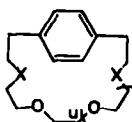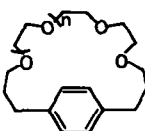
Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
 319		319	73-74	18	73,83
 320-321	n 1 2	320 321	oil 94-94.5	46 25	93 93
 322		322	133-134	23	73,83
 323,324		323 324	192-193 157-158	6 14	73,83 73,83
 325,326		325 326	118-119 121-122	3 25	73,83 73,83
 327		327	(120-130/ .01) oil	2 2.2	73,83 93
 323-330	n 1 2 3	328 329 330	95.5-96.5 93.5-94 67-68	7 8 7	73,83 73,83 73,83

Table 8. (Contd.)

Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
331-336	n				
	1	331	56-56.5	2.6	93
			--	4	88
	2	332	59-60	10	93
			--	35	88
	3	333	--	16	88
	4	334	--	6	88
	5	335	--	7	88
	6	336	--	13	88
337		337	121-122	2	86
338-342	n X				
	1 O	338	oil	17	93
	1 S	339	55.5-56	51	93
	1 $NCO_2C_2H_5$	340	(220/ .005)	15	94
	1 NCH_3	341	(175/ .005)	14	94
	2 O	342	oil	17	93
343,344	n				
	1	343	36-37	2.9	93
	2	344	oil	3	93

(D) Fusion to heterocyclic systems

Fusion of the crown to carbocyclic aromatic systems other than by 1,2 fusion results in an interruption of the normal two carbon to one heteroatom arrangement. The problem is typically avoided by replacement of the carbocyclic system by a heterocyclic one. The most common heterocycle used has been pyridine, which can be included by the reaction of dihalomethyl or dihydroxymethyl pyridine with the appropriate glycol derivative, or by direct attachment of the glycol oxygens to the aromatic nucleus by displacement of ring halogens. Alternatively, the glycols may be reacted with dicarbonyl chlorides to give the related macrocyclic ester; or α, ω-diamino glycol ethers may be condensed with dicarboxalde-hyde, or diketone derivatives to give imine type products. Furan and thiophene derivatives are also commonly employed.

Macrocyclic compounds containing heterocyclic subunits have been reviewed,[96] and crown ester compounds, including heterocyclic subunits, have also recently been reviewed.[19]

5. ALTERNATIVE HETEROATOMS

Until now we have primarily discussed modification of crown ethers by the attachment of various substituents to the macrocyclic ring or to aromatic subunits that are fused to the macrocycle. Another

obvious modification that can be made is the replacement of oxygen (or in some cases carbon) by alternative heteroatoms. An enormous amount of work has been reported in this area. Changing of even one heteroatom in the macrocycle can have a profound affect on its ability to bind cations.

(A) Sulfur

Even before Pedersen's all oxygen crown compounds had been reported, sulfur containing analogs of the crown ethers were known. For example, 1, 10-dithia-18-crown-6 was prepared in 1961.[97]

Bradshaw *et al.* prepared a large number of related macrocycles of various sizes and varying numbers of sulfur atoms.[98] Shortly after publication of his work with the benzo crown compounds, Pedersen investigated the preparation of analagous sulfur containing benzo crown compounds.[99]

In recent years there has been a marked decline in interest in the sulfur ligands and little new synthetic work has appeared. One exception is the work of Vögtle in the preparation of thia crowns fused to heterocyclic and other aromatic systems.[100-102]
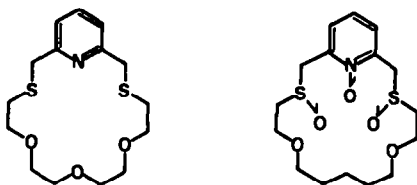
The older work has been reviewed both specifically[98] and as a part of larger reviews.[8,9] Several macrocyclic polyether-sulfide esters have also been reported and reviewed.[19]

The macrocyclic sulfides and ether-sulfides are generally poor complexing agents for the alkali and alkaline earth metal cations. They do exhibit strong interactions with mercury and silver,[103] but it should be recognized that simple alkyl sulfides also form strong complexes with these metals.

The introduction of sulfur into the macrocycle generally distorts the ring and often leaves the sulfur pointed out of, rather than into, the ring.[104] Indeed, the complex of 1, 4-dithia-18-crown-6 with mercuric chloride leaves the metal cation outside, rather than inside, the cavity of the ligand.[105]
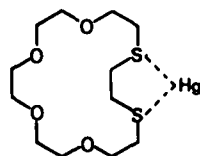
(B) Phosphorus

The preparation of macrocyclic phosphorous containing ligands has proven to be quite difficult. To date only a few compounds, wherein the phosphorous atoms form a true macrocyclic ligand, have been reported.[106] The products are usually air sensitive. Several complexes with nickel (II) and cobalt (II) salts were prepared.
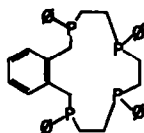

(C) Nitrogen

The heteroatom most often substituted for oxygen is nitrogen. Nitrogen is not only an excellent electron donor, but its trivalent nature and chemical reactivity make it very useful for further reactions. Macrocyclic azapolyethers have been further functionalized to improve ligand-cation binding,[107] provide secondary binding sites,[108] change ligand-cation selectivity,[107] and to prepare ion-selective dyes,[109] biologically active compounds,[110] bicyclic analogs[110] and polymer bound reagents.[111] The macrocycles may be cyclized with substituents on either carbon or nitrogen or both, and may be prepared from both aliphatic and aromatic amines. Some substituents on nitrogen, such as tosyl, may be removed to generate ligands containing secondary amines, or may be removed and then replaced by other substituents.

The tremendous variety of compounds prepared by the inclusion of a nitrogen atom in the macrocycle has made this class of ligand the most studied of all the crown ether types.

1. *Simple unsubstituted and N-substituted macrocyclic azapolyethers prepared by ring closure with the N-substituent(s) in place* (Table 9). The earliest workers to express an interest in crown ethers containing nitrogen heteroatoms were Lehn and Pedersen. Pedersen primarily worked with compounds fused to one or more benzene rings. These compounds will be discussed in a later section (Section 5.C.4.). Lehn *et al.* developed a generally useful procedure for the preparation of diaza derivatives. This synthesis is based on the high dilution reaction of a diamine and a diacid chloride to form a macrocyclic diamide. The amide carbonyls were subsequently reduced to form the diaza crown compound (eqn 11).[110, 112]

$$\tag{11}$$
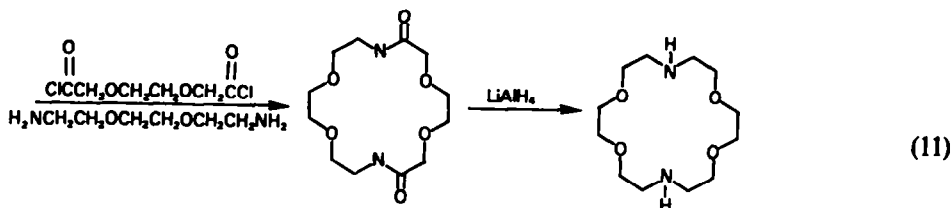
Subsequently Richman and Atkins found that alkylation of the sodium salts of a bis(toluenesulfonamide) with a bis(methanesulfonate ester) was a convenient procedure to form these compounds (eqn 12).[113] The latter procedure is particularly amenable to the synthesis of crown compounds where all the heteroatoms are nitrogen. Vögtle has improved the procedure and has demonstrated the viability of reductive as well as hydrolytic removal of the tosyl function.[114-116]

$$\tag{12}$$
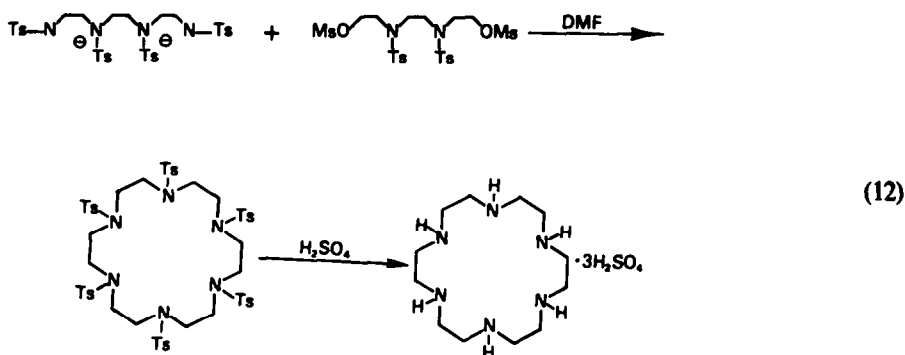
In the case of aromatic amines, direct alkylation with a bis(chloroethyl) ether derivative yields the aza macrocycle.[117,118]

A novel, but little explored approach to these compounds involves ring opening of a lactone by a diamine, ring closure of the resulting dihydroxy compound and reduction of the amide carbonyls.[119] The process has never been fully tested, however.

A final approach to the synthesis of the aza ligands is the replacement of diethylene glycol by *N*-alkyl diethanol amine in any of the "normal" crown ether preparations.[120]

Table 9 is a listing of unsubstituted and *N*-substituted macrocyclic azapolyethers prepared by ring closure with the *N*-substituent(s) in place.

Table 9. Simple unsubstituted and *N*-substituted macrocyclic azapolyethers prepared by ring closure with the *N*-substituents in place

Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
		345	199-201	32	121
			--	--	114

345

Table 9. (Contd.)
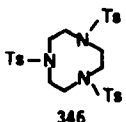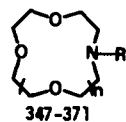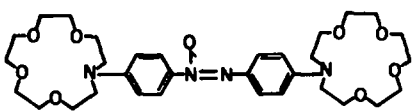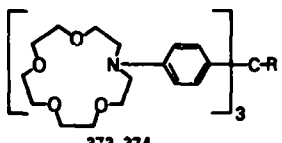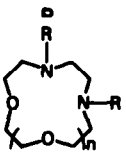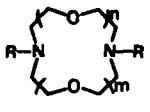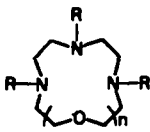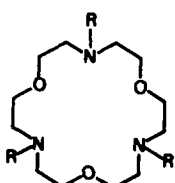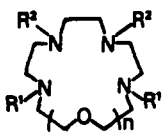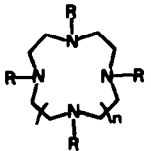
Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
		346	222-223	71	113
			--	--	114

346

	n	R	No.	mp(bp)	Yield	Ref
	1	o-HOPh	347	90	--	117
	2	CH_3	348	--	45	120
		C_2H_5	349	oil	75	120
		$n-C_4H_9$	350	--	58	120
		$CH_2CH=CH_2$	351	--	48	120
		Ph	352	44-45	--	109
		$p-NO_2Ph$	353	127	--	109

347-371

	n	R	No.	mp(bp)	Yield	Ref
		$p-NH_2Ph$	354	46	--	109
		p-CHOPh	355	80	--	109
		$p-SO_3NaPhN=NPh-$	356	136-145	--	109
		$p-NO_2PhN=NPh$	357	132-134	--	109
		$m-NO_2PhN=NPh-$	358	110	--	109
		$p-CO_2EtPhN=NPh-$	359	115	--	109
		$o-CO_2NaPhN=NPh-$	360	139-149	--	109
		$(p-Me_2NPh)_2(2,3,-$				
		$5,6-Cl_4-4-$				
		OHPhO) C-	361	--	--	109
	3	H	362	--	13	122
				--	28	14
		CH_3	363	--	55	120
		C_4H_9	364	--	67	120
		$CH_2CH=CH_2$	365	--	40	120
		CH_2Ph	366	--	25	122
		Ph	367	30-35	--	109
		Ph_3C	368	--	43	14
		$p-NO_2PhN=NPh-$	369	111-116	--	109
	4	H	370	oil	--	109
		$p-NO_2PhN=NPh-$	371	95-97	--	109
			372	145-151	--	109

372

	R	No.	mp(bp)	Yield	Ref
	H	373	125-127	--	109
	(chlorophenol ring)	374	--	--	109

373,374

	R^1	R^2	No.	mp(bp)	Yield	Ref
	H	H	375	80-85	--	109
	H	HOCOCOO	376	--	--	109
	H	Ph	377	117-121	--	109
	Ph	$4-OH-2,3,5,$				
		$6-Cl_4Ph-$	378	--	--	109
	H	$p-Me_2NPh-$	379	oil	--	109
	Cl	$p-Me_2NPh$	380	--	--	109

375-380

Table 9. (*Contd*).

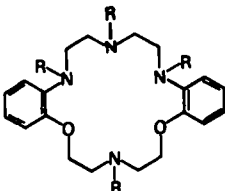| Structure	Substituent(s)			No.	mp(bp)	Yield	Ref
	n		**R**				
381-383	1		H	381	oil	--	121
					--	6	118
			Tosyl	382	--	--	114
					--	--	118
	2		Tosyl	383	201-207	23	121
	n	**m**	**R**				
384-390	1	1	H	384	83-84	45	110
			Tosyl	385	203-204	80	113
	1	2	H	386	oil	68	110
	2	2	H	387	115-116	80	110
			Tosyl	388	164-165	80	113
					--	--	114
	1	3	CH_3	389	--	--	120
	3	3	H	390	15	65	110
	n		**R**				
391-395	1		H	391	83-85	61	117
			Tosyl	392	200-204	63	121
	2		H	393	oil	19	115
			Tosyl	394	198-199	71	121
	3		Tosyl	395	196-198	14	121
	R		**R^1**				
396,397	H		H	396	135-136	--	123
	H		Tosyl	397	88-89	--	123
	n	**R^1**	**R^2**				
398-404	1	H	H	398	66-69	64	115
		Tosyl	Tosyl	399	253-255	52	121
	2	H	H	400	oil	74	115
		H	Tosyl	401	121	--	124
		Tosyl	Tosyl	402	93-96	25	121
	3	Tosyl	Tosyl	403	192-193	35	121
	5	Tosyl	Tosyl	404	192-194	12	121
	n		**R**				
405-411	1		Tosyl	405	--	80	113
			H·HCl	406	--	72	113
	2		Tosyl	407	278-280	83	113
			H·HCl	408	--	--	7
	3		Tosyl	409	311-312	60-75	113
			H·½H_2SO_4	410	280	--	7
	4		Tosyl	411	183-184	45	113

2. *Macrocyclic azapolyethers fused to an aromatic ring at nitrogen* (Table 10). *o*-Phenylenediamine, *o*-aminophenol and *o*-nitrophenol are all readily available raw materials that can be converted to the title compounds with relative ease. The first two can be cyclized by refluxing with bis(chloroethyl) ethers in dimethylformamide.[117,118] The latter starting material allows stepwise reaction to yield products fused to two benzene rings.[118,125] Both the Lehn (macrocyclic amide reduction) and Richman (toluenesulfonamide) methods have also been used successfully to prepare the fused aromatic ring systems.[108,125]

Meth–Cohn has alkylated benzimidazolone, a phenylenediamine derivative, with various bis(chloroethyl) ethers to produce diaza crown ethers which have a urea carbonyl pointed into the cavity.[126–128] The same technique is also successful with other cyclic diamides.

As in the case of the simple macrocyclic azapolyethers (Sect 5.V.1.), the nitrogen function may be further derivatized.

Table 10 contains a listing of macrocyclic azapolyethers fused to an aromatic ring at nitrogen.

Table 10. Macrocyclic azapolyethers fused to an aromatic ring at nitrogen
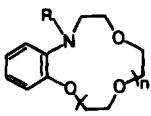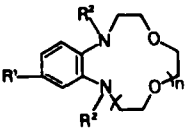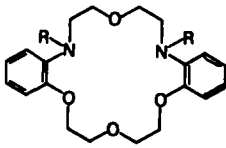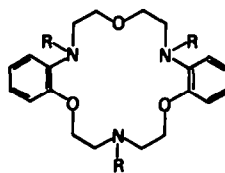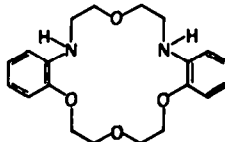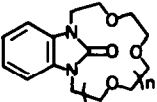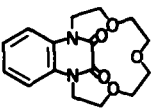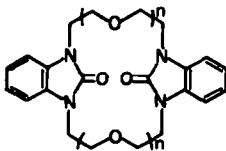
Structure	Substituent(s)		No.	mp(bp)	Yield[a]	Ref
	n	R				
412-423	1	H	412	80	--	108,117
	2	H	413	101.5	--	108,117
		n-C_3H_7	414	oil	--	108
		$CH_2CH_2CH_2OEt$	415	oil	--	108
		$CH_2CH_2CH_2Br$	416	solid	--	108
		$COCH_2CH_2Br$	417	oil	--	108
		$COCH_2CH_2CO_2H$	418	solid	--	108
	3	H	419	oil	--	108,118
		CH_3SO_2	420	91-92	32	125
	4	H	421	oil	--	108,118
	5	H	422	oil	--	108,118
	6	H	423	oil	--	108,118

Structure	n	R^1	R^2	No.	mp(bp)	Yield[a]	Ref
424-429	1	H	H	424	92-94	--	117,118
		H	$COCH_2CH_2CO_2H$	425	oil	--	108
	2	H	H	426	110	--	108,117
		CH_3	H	427	oil	--	108
	3	H	H	428	--	--	108
		H	CH_3SO_2	429	191-192	5	125

Structure	R	No.	mp(bp)	Yield[a]	Ref
430,431	H	430	203-204	20	125
	CH_3SO_2	431	200-202	28	125

Table 10. (*Contd.*)

Structure	Substituent(s)	No.	mp(bp)	Yield[a]	Ref
432,433	**R** H Tosyl	432 433	182-183 glass	6 18	125 125
434,435	**R** H Tosyl	434 435	198-200 150-153	43 52	125 125
436		436	117	31	108
437-439	**n** 1 2 3	437 438 439	117-118 -- (95-100/ 0.05)	13.7 41 79	126,127 128 126-128
44		440	184	7.2	126-128
441,442	**n** 1 2	441 442	197-199 114	14.8 12.4	126-128 126-128

[a]Yields are overall and are based on the starting aromatic amines.

3. *Functionalization of the nitrogen(s) of preformed macrocyclic azapolyethers* (Table 11). We have already seen that a wide variety of aza and polyaza macrocyclic polyethers may be prepared by several methods. In some cases, the nitrogen atoms are substituted before the macrocycle is formed, usually by an alkyl group or a sulfone. The sulfone and benzyl substituents can readily be removed. Thus, macrocyclic ligands containing one or more secondary nitrogen atoms are easily prepared. These secondary amines are reactive and can be further functionalized. Alkylation of the aza compound increases its cation binding,[107] increases its lipophilicity,[20] imparts biologcal activity to the macrocycle,[110] and may be used to attach the ligand to a polymer support.[111] These amines are also reactive towards acylation and electrophilic addition as well.[129] A large number of both simple and complex derivatives have been prepared.

Table 11 is a listing of macrocyclic azapolyethers which have been functionalized on nitrogen.

Table 11. Functionalization of the nitrogen (s) of preformed macrocyclic azapolyethers
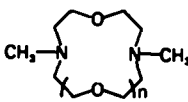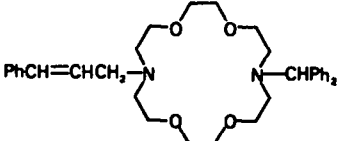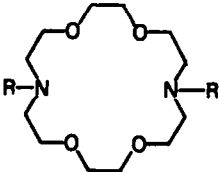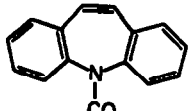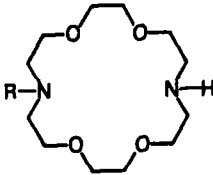
Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
443,444	**n** 1	443	(79/.02)	61	130
	2	444	--	--	131
445		445	oil	87	132
446-462	**R** CH_3	446	--	--	133
					131
	$CH_2C(CH_3)_3$	447	--	--	133
	CH_2Ph	448	--	--	133
	4-MeOPh	449	--	--	133
	n-$C_{10}H_{21}$	450	--	--	7
	n-$C_{16}H_{33}$	451	90-92	90	20
	n-$C_{15}H_{31}CO$	452	43-44	95	20
	CH_2CO_2Et	453	--	65	108
	CH_2CH_2CN	454	49	--	134
			oil	--	135
	$CH_2CH_2CO_2H$	455	128.5-130	65	135
	$CH_2CH_2CH_2NH_2$	456	--	--	134
	Ph_2CH	457	109-109.5	86	132
	CO_2Et	458	89	86	132
	$PhCH=CHCO$	459	148-150	72	132
	$PhCH_2CH_2CO$	460	76-79	94	132
	p-NO_2PhSO_2	461	197-199	86	132
		462	165-166	45	132

Table 11. (*Contd.*)

Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
463-466	R p-NH$_2$PhCO$_2$CH$_2$CH$_2$	463	oil	60	132
	p-NO$_2$PhCO$_2$CH$_2$CH$_2$	464	118-120	24	132
	p-CO$_2$HPhCO	465	170-173	65	132
	Ph$_2$CH	466	88-89	22	132

4. *Macrocyclic azapolyethers substituted on carbon* (Table 12). Many of the methods already discussed have been applied to cyclization reactions of glycols branched at carbon and their derivatives, or similar dihalo compounds. Substitution on carbon has generally been used is a method to change the solubility characteristics of the ligand.[20] Substituted diazamacrocycles may also be used as intermediates for the preparation of substituted cryptands (Section 5.D.).[136,137]

Macrocyclic azapolyethers substituted on carbon are listed in Table 12.

Table 12. Macrocyclic azapolyethers substituted on carbon (including attachment by fusion to another ring)
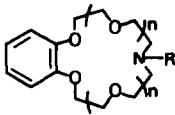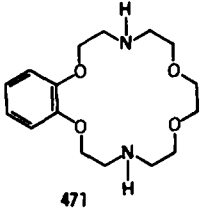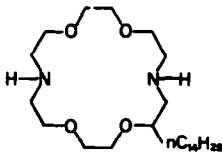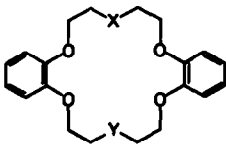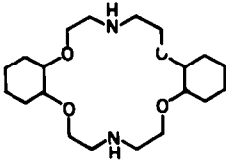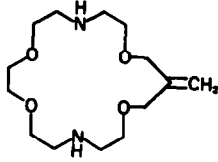
Structure	Substituent(s)		No.	mp(bp)	Yield	Ref
467-470	n	R				
	0	H	467	39-40	18	125
		Tosyl	468	174-175	35	125
	1	H	469	142-143	1.8	125
		Tosyl	470	136-137	36	125
471			471	--	--	138
472			472	38-39	60	20
473-477	X	Y				
	HN	O	473	150-152	12	125
				--	--	129
	TsN	O	474	158-160	34	125
	HN	HN	475	175-177	4.5	125
	TsN	TsN	476	215-216	10	125
	PhCH$_2$N	PhCH$_2$N	477	--	--	139

Table 12. (Contd.)

Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
		478	oil	13.5	140
478					
		479	(140-142/ .005)	35	24
479					

5. *Nitrogen in place of carbon* (Table 13). Generally nitrogen has been put into the macrocycle as an alternative to oxygen, however, two types of macrocyclic ligands have been reported in which the nitrogen is used as an alternative to one or more carbon atoms. The result is a nitrogen–oxygen bond. The first approach to this class of ligands is the cyclization of salicylaldehyde oxime or diacetyl dioxime by the usual methods.[141] However, the resulting macrocyclic mono- and dioximes show little tendency to bind alkali metal cations. The second type of ligand, which is a macrocyclic polyhydroxamate, is prepared by oligomerization of nitrile N-oxides. They are reported to bind cations but are thermally unstable and can decompose violently.[142,143]

Table 13 lists macrocyclic polyether compounds with nitrogen in place of carbon.

Table 13. Nitrogen in place of carbon
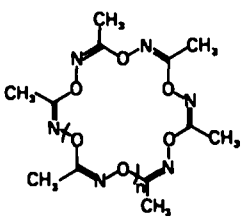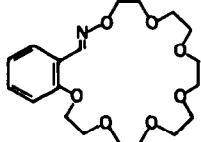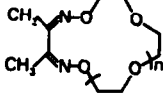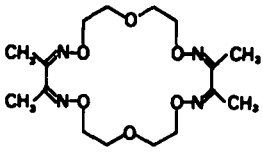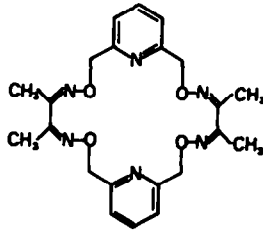
Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
	n				
	1	480	320	--	142,143
	2	481	174-176	6	142,143
	3	482	171	--	142,143
480-482					
		483	--	--	141
483					
	n				
	0	484	--	--	141
	1	485	--	--	141
	2	486	--	--	141
484-486					

Table 13. (*Contd.*)

Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
487		487	--	--	141
488		488	--	--	141

6. *Miscellaneous* (Table 14). A handful of macrocyclic azapolyethers do not fall neatly into any category discussed above and are listed in Table 14.

Table 14. Miscellaneous macrocyclic azapolyethers
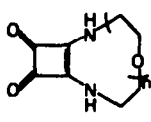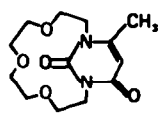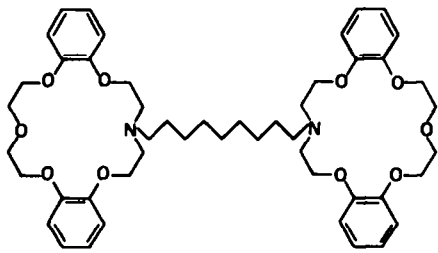
Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
489-491	n 1	489	240	78	144
	2	490	290-296	24	144
	3	491	190-200	39	144
492		492	92-94	0.2	126
493		493	--	--	129
			--	--	139

Table 14. (Contd.)
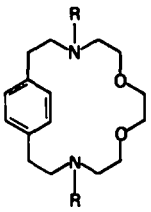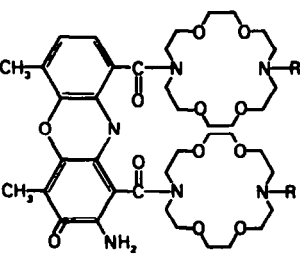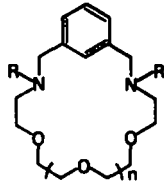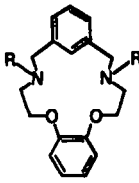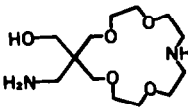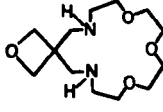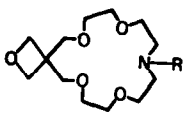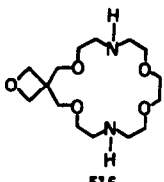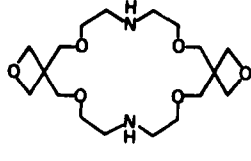
Structure	Substituent(s)	#	mp(bp)	Yield	Ref

	R				
	CO₂Et	340	135	72	94
	CH₃	341	(200/		
			.005)	20	94

340,341

	R				
	H	494	--	--	145
	CO₂CH₂Ph	495	--	--	145

494,495

n	R				
-1	CO₂Et	496	--	ca 40	146
-1	CH₃	497	oil	--	146
0	H	498	--	--	147
0	CO₂Et	499	--	ca 40	146
0	CH₃	500	oil	--	146
0	CO₂CH₂Ph	501	--	--	147
0	CH₂CH₂OH	502	--	--	147
0	CH₂CONMe₂	503	--	--	147
0	CH₂(2-pyridyl)	504	--	--	147
1	CO₂Et	505	--	ca 40	146
1	CH₃	506	oil	--	146

496-506

R				
H	507	--	--	147
CO₂CH₂Ph	508	--	--	147
CH₂CH₂OH	509	--	--	147
CH₂CONMe₂	510	--	--	147

507-510

	511	52-56	35	148

511

	512	--	--	148

512

Table 14. (*Contd.*)

Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
513,514	R H CH₂CH₂OH	513 514	80-81 oil	67 58	148 148
515		515	--	--	148
516		516	118.5-119	17	148

(D) *Cryptands (bi- and tricyclic polyazapolyethers): a special case of funcationalization on nitrogen*

Macrocyclic polyethers containing two or more secondary nitrogen atoms in the macroring may be alkylated with a dihalide compound[129] or acylated with a diacid chloride[110,113,144] to yield bicyclic ligands. The latter method is by far the most common procedure to make these bi- and tricyclic ligands. The macrobicyclic compounds are generally referred to as cryptands (the name originally proposed by Lehn), but have also been referred to as "lanterns" (the name originally proposed by Pedersen).

Three properties of the cryptands are particularly important; (1) binding constants for most cations are several orders of magnitude greater than with 18-crown-6 or other monocyclic ligands,[9] (2) the anion is completely separated from the cation,[108] and (3) decomplexation is extremely slow. Decomplexation may be made rapid however, by adding acid which protonates the tertiary nitrogen atoms.[110]

Tricyclic compounds can also be prepared if the appropriate starting materials and conditions are used.[123,150-153]
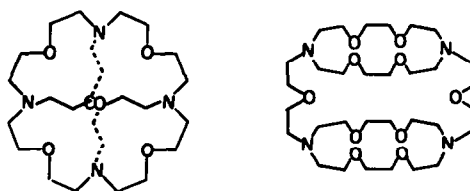
Because the cryptands have been known since 1969 and have proven to be both interesting and useful, they have been included in several reviews.[8,9,154] Therefore, Table 15 includes only cryptands that have not appeared in previous reviews. Nearly all have been prepared by the standard methods described in earlier literature. Substituted derivatives are generally prepared from substituted diacid chlorides, but sometimes from the substituted diaza crown ethers discussed earlier (Section 5.C.2,3 and 4). The substituents have generally been added to change solubility characteristics[136,137] or allow attachment to polymer supports.[22]

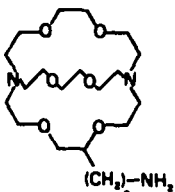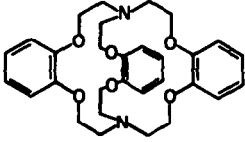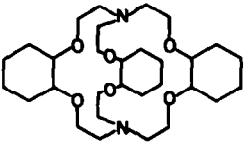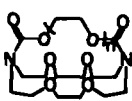Table 15. Cryptands: macrocyclic bi-and tricyloazapolyethers
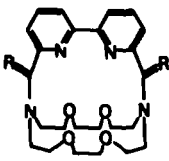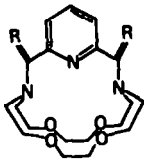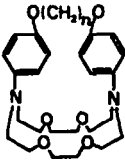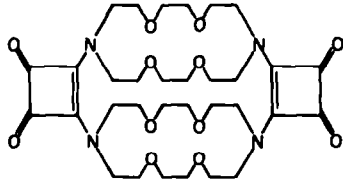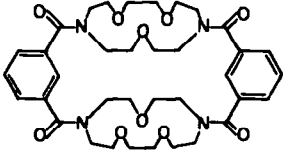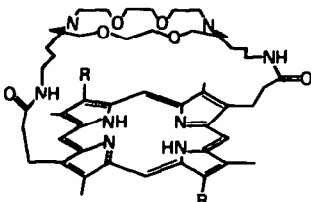
Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
517		517	--	--	22
518		518	--	--	129
519		519	oil	9	140
520-521	n 1 2	520 521	106 104-105	40 36	155 155
522,523	R= H$_2$ R= O	522 523	-- 264-266	-- 25	156 156
524,525	R= H$_2$ R= O	524 525	100-101 185-187	30 74	157 157
526	n=2-6	526 a-f	-- --	--	133

Table 15. (Contd.)

| Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
		527	229-230	12	144
		528	257-259	30	157
		529	--	--	134

527

528

529

6. CHIRAL CROWN ETHERS

Crown ethers which are chiral have been prepared by a number of different methods, often utilizing chiral natural products. When the chiral centers are close to, or are part of, the macrocyclic ring, selective binding of chiral substrates is possible. Thus chiral crown compounds can be used as stereo selective catalysts, enzyme models and for optical resolution of racemic substrates. Each of the several approaches to the synthesis of these types of compounds will be discussed separately.

(A) Chiral crown ethers derived from binaphthyl substrates

Because rotation about the single carbon–carbon bond of 2, 2′-dihydroxy-1, 1-binapthyl is hindered, it can be resolved into its (R) and (S) isomers. These may be cyclized with polyethylene glycol disulfonate esters to yield chiral macrocycles. Inclusion of one, two or three chiral binaphthyl subunits is thus possible.[158-160] An alternative approach is to resolve the macrocycle derived from the racemic binaphthyl diol by complexation to (S)-valine.[161] Such ligands may also be prepared with additional fusions to heterocyclic subunits[162] or with a large variety of substituents at the 3 and 3′-positions of the binaphthyl moeity.[163]

Selectivity ratios for the binding of these ligands to optical isomers in a racemic mixture of organic ammonium salts can be as high as eighteen.[158,164] This selective binding has been utilized in the total optical resolution of chiral ammonium salts.[165,166] If a 3, 3′-bis(mercaptomethyl) group is present, the chiral crown may behave as an enzyme. For example, the (S) isomer of the ligand hydrolyzes p-nitrophenyl-L-phenylalanine eight times faster than the corresponding (R) ligand. The reverse is true of the D-amino acid. Similar results are observed with other bulky amino acids, but no affect is observed with alanine itself.[167]
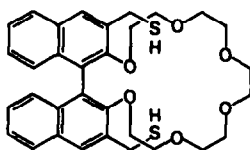
Bicyclic and tricyclic cryptand type compounds containing the binaphthyl moiety have also been prepared.[168,169] The tricyclic compound provides a particular advantage in that the lateral cavities may first bind an alkali metal cation. The anion may then be subsequently bound inside the central cavity. This allows selective binding of chiral anions as well as cations. The alkali metal employed may have a dramatic affect on this selective binding.[169]
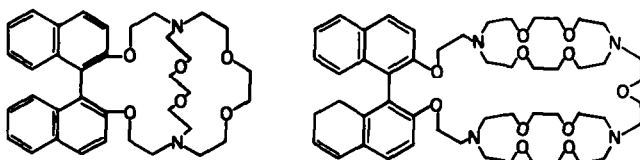
With the exception of Lehn's work on the bi- and tri-cyclic systems, vitrually all work an the binaphthyl system has been performed by Cram *et al.* Three recent articles by them constitute a very thorough review of the subject.[170-172]

(B) *Chiral crown ethers derived from tartaric acid* (Table 16)

Tartaric acid has proven to be an ideal candidate for preparing chiral crown compounds. Both (+) and (−) isomers are readily available and the resulting crown ethers contain versatile functional groups. They can be prepared with either one or two tartrate moieties in the macrocycle,[173-177] and may also be fused to heterocyclic subunits.[173]

Primary interest in these ligands has been as enzyme models. A large number of different amino and mercapto containing side chains have been included in both the mono- and ditartrate ligands. Selective hydrolysis of the *p*-nitrophenyl esters of a large number of amino acids and dipeptides has been studied, and a high degree of selectivity is observed.[178] The specific selectivity varies greatly depending on the length of the side arm.[175]

Table 16 condains a list of the chiral macrocyclic polyethers derived from tartaric acid.

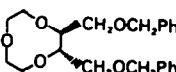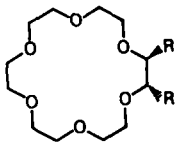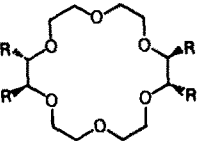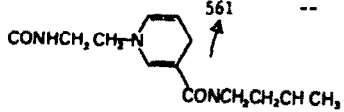Table 16. Chiral macrocyclic polyethers derived from tartaric
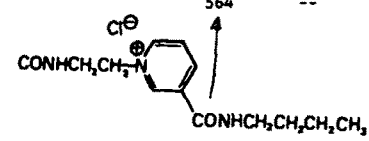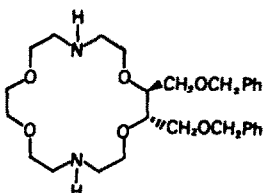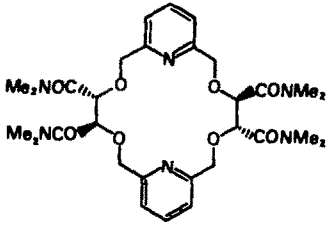
Structure	Substituent(s)	No.	[α]D	mp(bp)	Yield	Ref
530		530	+19.3	40	<<1	174
531-546	R					
	CH_2OCH_2Ph	531	+5.0	oil	7.5	177
			--	--	--	175
	CH_2OH	532	--	--	--	177
			--	--	--	175
	CH_2OCOCH_3	533	-9.6	--	4.6	177
	CH_2OTs	534	--	--	--	175
	CH_2SCOPh	535	--	--	--	175
	CH_2SH	536	-10.8	--	--	175
	$CH_2OCH_2CH_2OCH_2Ph$	537	--	--	--	175
	$CH_2OCH_2CH_2OH$	538	--	--	--	175
	$CH_2OCH_2CH_2OTs$	539	--	--	--	175
	$CH_2OCH_2CH_2SCOPh$	540	--	--	--	175
	$CH_2OCH_2CH_2SH$	541	+2.9	--	--	175

Table 16. (Contd.)

Structure	Substituent(s)	No.	$[\alpha]_D$	mp(bp)	Yield	Ref
	$CH_2CH_2CH_2OCH_2Ph$	542	--	--	--	175
	$CH_2CH_2CH_2OH$	543	--	--	--	175
	$CH_2CH_2CH_2OTs$	544	--	--	--	175
	$CH_2CH_2CH_2SCOPh$	545	--	--	--	175
	$CH_2CH_2CH_2SH$	546	-26.9	--	--	175
547–564	R					
	$CONMe_2$	547	+108.0	--	--	173,178
	CH_2OH	548	--	oil	.85	174
	CH_2OCH_2Ph	549	+5.8	--	--	174
	CH_2COCH_3	550	-20.5	--	--	174
	CH_2OCPh_3	551	--	--	--	174
	CO_2H	552	--	211	--	176,178
	$COCl$	553	--	180	--	176,178
	L-CONHCH-(3-indole) CO_2Me	554	--	135-138	--	176
	L-CONHCH-(3-indole) $CO_2^-NMe_4^+$	555	--	--	--	176
	$CONHCH_2CO_2Me$	556	--	188	--	176
	$CONHCH_2CO_2^-NMe_4^+$	557	--	--	--	176
	$CONHCH_2CH_2$ (4-imidazole)	558	--	--	--	176
	L-CONHCH$_2$CHCH$_2$SH CO_2Me	559	+41	204-205	--	176,178
	L-CONHCHCH$_2$SCH$_2$Ph CH_2CO_2Me	560	-44.5	139-140	--	178
		561	--	--	--	179
	$CONHCH_2CH_2NHCO_2CH_2Ph$	562	--	214-215	70	179
	$CONHCH_2CH_2NH_2$	563	--	174-177	65	179
		564	--	--	--	179
565		565	+17	oil	7.7	177
566		566	+107	224	15	173

(C) Chiral crown ethers derived from carbohydrates (Table 17)

Carbohydrates are another convenient source of natural chirality. A substantial number of chiral ligands have been prepared from D-manitol, D-glucose, D-galactose and combinations of these compounds. The carbohydrate is normally protected to yield a diol which is cyclized in the usual manner by reacting with a ditosyl ester of the polyethylene glycols,[174,180] however, one report of a novel closure by addition of a hydroxy function across the double bond of a vinyl ether has also appeared.[181]

Because carbohydrates often contain several chiral centers the choice of available compounds is limited to those of C2 symmetry if more than one carbohydrate unit is to be included in the ring. Otherwiše a large number of diasteriomers can result.

Carbohydrate based chiral ligands have not exhibited a high degree of chiral recognition.

A list of chiral macrocyclic compounds derived from carbohydrates is shown in Table 17.

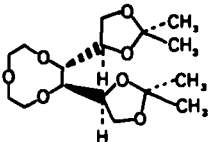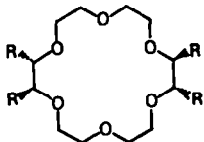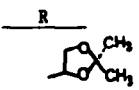Table 17. Chiral macrocyclic polyethers derived from carbohydrates
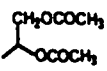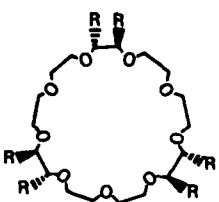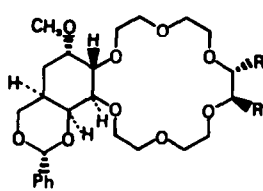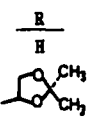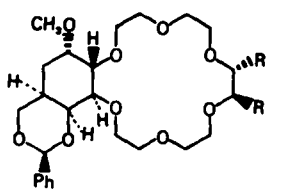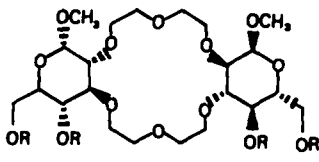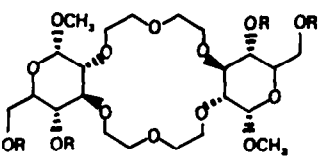
Structure	Substituent(s)	No.	$[\alpha]_D$	mp(bp)	Yield	Ref
567		567	--	oil	3.6	174
568-572		568	+7.6	oil	7.4	174
	CH₂OH / OH	569	+24.5	69-71	6.7	174
	CH₂OCOCH₃ / OCOCH₃	570	+48.4	--	6.4	174
	CH₂OCH₃ / OCH₃	571	+4.7	--	3.8	174
	CO₂OCOCH₃	572	+20.2	--	1.9	174
573		573	--	oil	3.1	174
574,575	R H CH₃ / CH₃	574 575	+37.6 +69.4	52-56 44-46	-- --	180 180

<div align="center">Table 17. (Contd.)</div>

Structure	Substituent(s)	No.	$[\alpha]_D$	mp(bp)	Yield	Ref
	R					
	H	576	+102.9	115	--	180
		577	+90	60-80	--	180
	R					
	H	578	--	--	--	181
	$COCH_3$	579	--	--	--	181
	R					
	H	580	--	--	--	181
	$COCH_3$	581	--	--	--	181

(D) *Chiral crown ethers derived from miscellaneous sources* (Table 18)

The classes of chiral ligands discussed thus far are the most common. Chiral ligands, however, may also be prepared from a great many other chiral starting materials, including glycercol derivatives,[33] optically active propylene glycol,[48] optically active cyclohexanediols[182] and L-proline and D-ephedrine[183] (see Table 18).

<div align="center">Table 18. Chiral macrocyclic polyethers derived from miscellaneous sources</div>
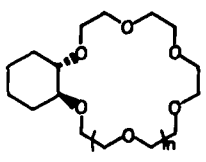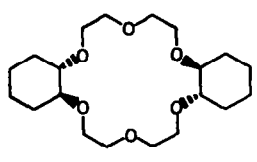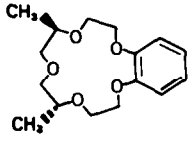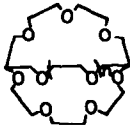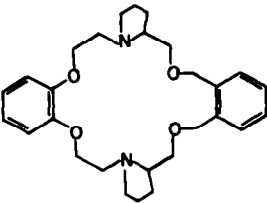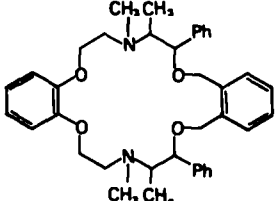
Structure	Substituent(s)	No.	$[\alpha]_D$	mp(bp)	Yield	Ref
	n					
	0	582	+36.5	oil	23	182
	1	583	+25.1	oil	20	182
		584	+39.2	77-80	12	182

Table 18. (Contd.)

Structure	Substituent(s)	No.	mp(bp)	Yield	Ref
		83	--	43	--	48

83

	n					
	1	55	-1.0	--	1.5	33
	2	56	--	--	1.5	33

55,56

| | | 585 | -- | 98-99 | -- | 183 |

585

| | | 586 | -- | 94-95 | 20 | 183 |

586

7. POLYMER-BOUND MACROCYCLIC POLYETHERS (TABLES 19 AND 20)

For several reasons it has been desirable to either attach crown ether compounds to polymers or to form polymers from crown ethers. The earliest efforts to bind macrocyclic polyether ligands to polymers utilized the reaction of the polyoxyaromatic compounds with formaldehyde.[41] Subsequently, several others have prepared similar formaldehyde polymers from a variety of benzo crown compounds.[184-187] These polymers involve the crown as an integral part of the polymer backbone. They have proven very effective in ion chromatography applications.[184] Mixed polymerization of monobenzo crowns with formaldehyde and some other reactive aromatic compound (i.e. phenol, toluene, resorcinol, etc.) provides some separation between the macrocycle and the polymer backbone.[184]

Vinyl benzo crown ethers and spiro oxetane crown compounds have also been polymerized,[26, 62, 66] but the monomer crown compounds are far more difficult to prepare.

Chloromethylated polystyrene can be used to alkylate a benzo crown compound or may be reacted with hydroxy or aza-crown compounds. Again only a short separation of the macrocycle from the backbone is obtained. All the polymer and polymer bound crown compounds mentioned thus far have been used almost exclusively in ion chromatography. In order to have efficient polymer bound phase transfer catalysts the macrocycle needs to be separated from the backbone.[188] This has been accomplished but only via a rather cumbersome multi-step process based on chloromethylated polystyrene and 2-(9-aminononyl)-18-crown-6.[22,188] Such polymers do appear to be useful as phase transfer catalysts.

$$n = 1, 2$$

635, 636
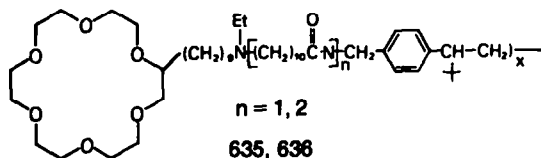
In addition to their use as phase transfer catalysts and in ion chromatography, polymer crown compounds have been used in reverse osmosis membranes. Dibenzo crown ethers are nitrated and reduced to the diamino benzo crown compounds. The diamines may be reacted with any diacid chloride or anhydride to yield polyimides, polyamides, polyamide ester, etc. which can be formed into membranes that allow the passage of water but only a slow migration of sodium and potassium ions.[67]

Table 19 lists polymers which have crown ethers as part of the polymer backbone. Table 20 lists polymers which have crown ether compounds as attachments.

Table 19. Polymers with macrocyclic polyethers as part of the polymer backbone

Structure	Substituent(s)	No.	References
587-592	n=1,2,3 m=1,2,3	587-592	41,184-187
593		593	184,185
594		594	184,185
595		595	184,185
596		596	111,184,185

Table 19. (Contd.)
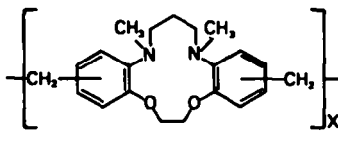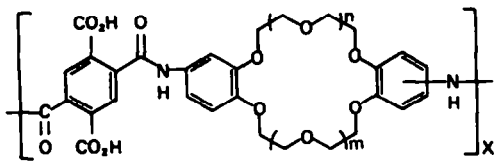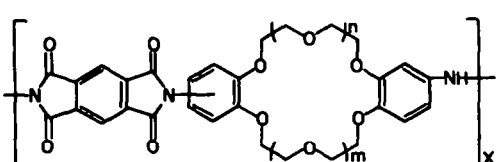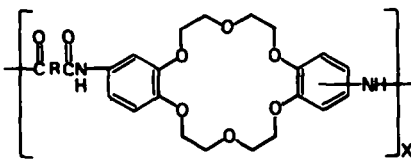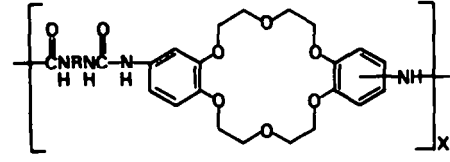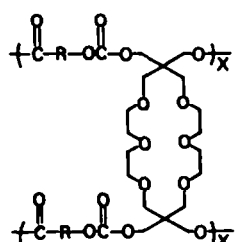
Structure	Substituent(s)	No.	References
		597	111,184,185

597

	m= 0-3 n= 1-3	598-603	67

598-603

| | m= 0-3
n= 1-3 | 604-609 | 67 |

604-609

| | | 610 | 189 |

610

| | | 611 | 189 |

611

| | | 612 | 26 |

612

Table 19. (Contd.)

Structure	Substituent(s)	No.	Ref.
		613	26

613

| | | 614 | 26 |

614

| | | 615 | 111,184,185 |

615

| | | 616 | 111,184,185 |

616

Table 20. Polymers bearing marocyclic polyether substituents

Structure [a]	Substituent(s)			No.	Ref.
	n	R^1	R^2		
	0	H	OH	617	184,185
	0	CH_3	H	618	184
	0	OH	OH	619	184
	0	CH_3	CH_3	620	184
	1	H	OH	621	184,185
	1	CH_3	H	622	184
	1	OH	OH	623	184
	1	CH_3	CH_3	624	184
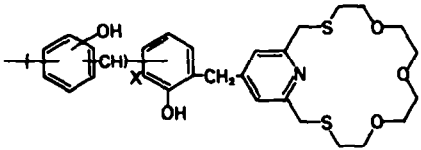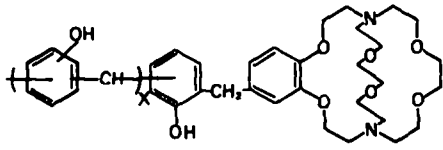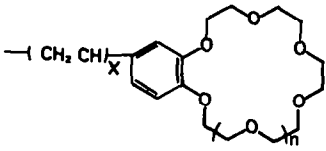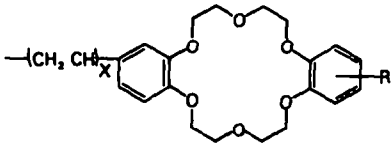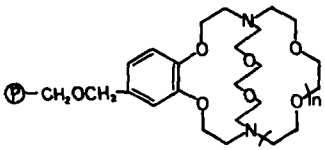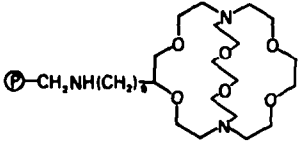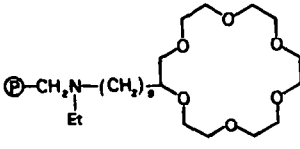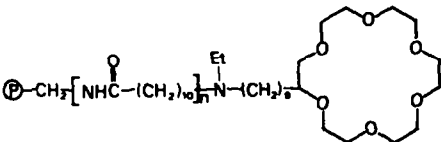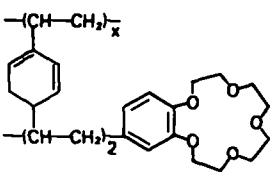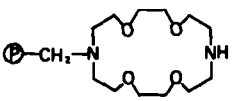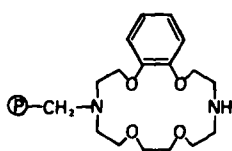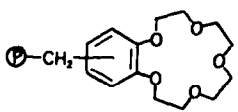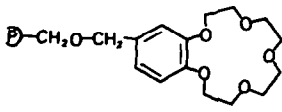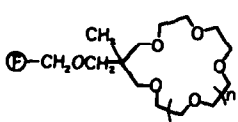
617–624

$P = \left(CH_2 \right)_n$

Table 20. (Contd.)

Structure[a]	Substituent(s)	No.	Ref.
625		625	184,185
626		626	111,184,185
627,628	n 0 1	627 628	62,66 62,66
629,630	R H CH₃	629 630	66 66
631,632	n 0 1	631 632	7 7
633		633	22
634		634	22,188

625

626

627,628

629,630

631,632

633

634

Table 20. (Contd.)

Structure [a]	Substituent(s)	No.	Ref.

635,636

	n		
	1	635	188
	2	636	188

637

| | | 637 | 184 |

638

| | | 638 | 111,184,185 |

639

| | | 639 | 111,184,185 |

640

| | | 640 | 184 |

641

| | | 641 | 184 |

642. 643

	n		
	1	642	24
	2	643	24

[a] Unless otherwise specified, Ⓟ represents polystyrene.

8. MISCELLANEOUS SYSTEMS

(A) *Novel ring closures* (Table 21)

Since Pedersen's first report of crown ether compounds, workers have tried closing diols with a variety of reactive, bifunctional reagents (generally acid halides). The results have not produced any useful products to date. Table 21 lists some these compounds.
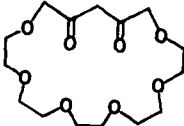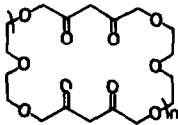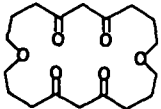
Table 21. Macrocyclic polyethers obtained via novel ring closure reactions

Structure	Substituent(s)		No.	Ref.
644-647	X			
	CO		644	35
	SO		645	35
	$P(O)CH_3$		646	190
	$SiMe_2$		647	191
648			648	190

(B) *Carbonyl oxygens in the macrocycle* (Table 22)

Cram has recently prepared a series of macrocyclic polyether-β-diketones which are reported to have high binding constants for a variety of metal cations.[192,193] The diaza macrocycles of Meth–Cohn and coworkers could be viewed as related compounds[126–128] (see Section 5.C.).

Table 22. Carbonyls in the macrocycle

Structure	Substituent(s)		No.	Ref.
649			649	192
650,651	n			
	1		650	192
	2		651	192
652			652	193

(C) Anion complexing agents

Until now, only cation complexation has been discussed. Polyaza crown compounds, however, can be protonated and, if large enough, they then can complex with anions. Both bicyclic and tricyclic[195] anion complexors have been studied.

More recently, a macrocyclic guanidinium compound has been prepared and studied as an anion complexor.[196]
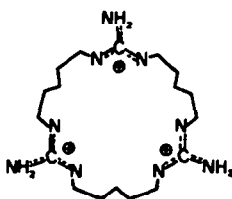
(D) Acyclic polyethylene glycol derivatives

Initial comparisons between various oligoethylene glycol dimethyl ethers (glymes) and various crown compounds indicated that the macrocyclic compounds bind sodium, potassium and alkylammonium cations several orders of magnitude more strongly than the open chain analogues.[197,198] Although more recent work with the glymes has continued to show that the macrocycles are stronger cation complexors, it has now been demonstrated that larger glymes do have significant binding constants for alkali metal cations[199] and diazonium salts[200] than the smaller glymes studied earlier. These, as well as polyethylene glycols capped with phenolic or nitrogen heterocycle moieties, have been shown to form stable complexes with a variety of cations.[201–205] In addition, they have been shown to operate effectively as phase transfer catalysts,[206] and in the transport of cations through lipid membranes.[207] Indeed, even the simple polyethylene glycols (Carbowaxes) have been shown to form complexes with alkali metals,[208] extract cations into organic solvents,[209] and to behave in a manner similar to the macrocyclic crown ethers when employed as phase transfer catalysts.[32,55,210–215]

Simon et al. have also shown that acyclic ligands that are very specific for the binding of certain cations can be prepared.[215–218]

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