THE SYNTHESIS OF A NEW CLASS OF MACROPOLYCYCLIC POLYETHER LIGANDS

A Thesis

by

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ABSTRACT

The Synthesis of a New Class
of Macropolycyclic Polyether Ligands.
(December 1979)
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A scheme for the synthesis of polyoxacyclophane polyether ligands is outlined. An improved synthesis for 5-bromobis(bromomethyl)benzene (14) is reported. The use of (14) with the appropiate glycol in a two step Williamson ether synthesis to give bis(5-bromo-1,3-xyleno)-18-crowns, intermediates for the syntheses of polyoxacyclophanes is described. Conversion of bis(5-bromo-1,3-xyleno)-18-crown-4 (22) to bis(5-bromomethyl-1,3-xyleno)-18-crown-4 (27) and the synthesis of 2,5,14,17,26,29-hexaoxa[6.6.6]-cyclophane (28) from 27 is reported. The special features of the ^{1}H and ^{13}C NMR spectra of 28 are discussed. The complexation of lithium picrate by 28 in chloroform is reported.

ACKNOWLEDGMENTS

I wish to thank Dr. Martin E. Newcomb for his support and guidance during my studies at Texas A&M University. I wish to thank the Department of Chemistry and the Robert A. Welch foundation for their financial support.

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INTRODUCTION

Macrocyclic polyether compounds have been known for many years. Lütringhaus and Ziegler first reported the synthesis of the cyclic tetramer of ethylene oxide, 1, in 1937[1]. The value of macrocyclic polyether compounds as agents for complexation of ions was not, however, recognized until recently. In 1967 Pedersen reported[2-5] that during the attempted synthesis of bis-phenol, 2, reaction of the incompletely protected catechol gave rise to a white fibrous material, 3, which he called dibenzo-18-crown-6 (eq 1). Subsequent studies have shown that 3 and related crown ethers such as 4 and 5 bind cations within the macrocyclic cavity with large complexation constants[6]. This large increase in binding constants as compared to the corresponding open chain compounds is termed the macrocyclic effect[7]. Since Pedersen's groundbreaking work hundreds of crowns and related compounds have been synthesized and studied. A comprehensive listing of those reported by July 1975 has been published by Bradshaw[8].

Lehn and co-workers have developed an important class of compounds related to the crowns which they have named "cryptands"[9] (latin crypto = cavity). Cryptands are macrobicyclic polyether amines such as [2.2.2]-crypt, 6, where the numbers within the brackets refer to the number of

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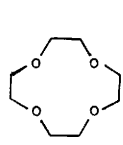

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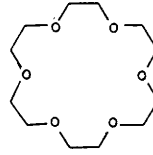

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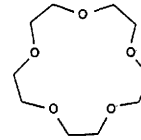

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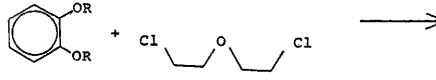

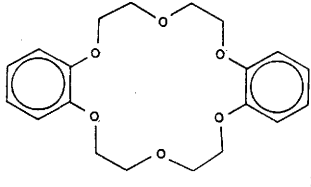

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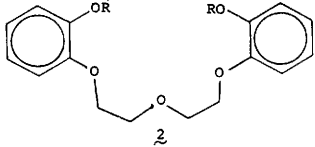
(1)



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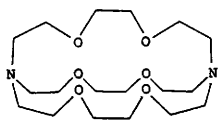
oxygen atoms in each of the bridges between the bridge-head nitrogen atoms. Cryptands form complexes ("cryptates") with alkali metal cations of the appropriate size which have much larger binding constants than those found in the crown complexes. This increase in binding constants in analogy to the previously mentioned macrocyclic effect has been termed the macrobicyclic effect. Cryptands also form cryptates with alkaline earth cations.

The cryptands are related to the "out-in" bicyclic amines, e.g. 7, reported by Simmons and Park[10], and the pentaerythritol-based bicyclic polyethers, e.g. 8, more recently reported by Coxon and Stoddard[11]. Lehn has published a review of the extensive investigations of the cryptands accomplished by his group[12].

Structural Effects in Cation Binding

The ability of macrocyclic polyether compounds to extract salts from aqueous solutions has been attributed to their ability to block access of competing solvent molecules to the complexation sites of cations[13]. The cryptands should be more effective than the crowns in the exclusion of solvent from complexed cations. This has been the rationalization for the larger binding constants of cryptates for appropriately sized cations. Binding constants for alkali metal cations of 6 and 18-crown-6, (4), are compared in Table I.



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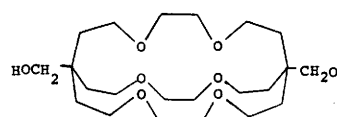

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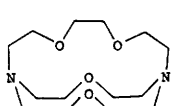
Figure 1. Bicyclic Polyether Compounds.



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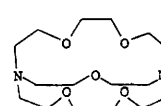

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Figure 2. [2.1.1]-crypt, 9, and [2.2.1]-crypt, 10.

Table I. Stability constants, Log K_S, for representive cryptate and crown ether complexes of alkali metal cations.

cation	Na^+	K^+	Rb^+	Tl^+	method
[2.2.2]-crypt	3.9	5.4	4.35	6.3	^1H nmr[14]
18-crown-6	0.8	2.06	1.56	2.27	ultrasound[15]

In addition to increased binding constants for cryptands over crowns, several groups have found that the cryptands are more selective in cation binding (e.g. Table I). This has been attributed to difficulty of over-sized cations entering the cryptand[16]. However, cryptands are flexible molecules and x-ray studies have shown that the ligand cavity can expand or contract slightly to accomodate large or small cations[17]; regardless of conformational change all of the heteroatoms of the cryptand are coordinated to the cation.

The selectivity of a ligand for various cations is setermined by the relative stability of its complexes with these cations. The stability of these complexes are in turn governed by the relative rates of complexation and decomplexation. Thus studies of structural effects on complexation and decomplexation can lead to better understanding of selectivity of ligand binding.

Shchori *et al.*[16] have suggested that the major barrier to the removal of Na^+ from dibenzo-18-crown-6 and its derivatives is that energy necessary for a conformational

rearrangement of the crown complex. This speculation derives from their observation that the activation energy for decomplexation of Na^+ from dibenzo-18-crown-6 is 12.6 ± 1.0 kcal/mol in dimethylformamide, methanol, and dimethoxyethane while the activation energy of the more flexible dicyclohexyl-18-crown-6 in methanol is only 8.3 kcal/mol.

Cryptands have shown similar phenomena. The decomplexation rates in water for the lithium complex of [2.1.1] - crypt, 9, (selective for lithium) is much slower (a factor of 10^3) than that for the potassium complex of [2.2.2] - crypt, 6, (selective for potassium). Decomplexation rates have been shown to be inversely related to stability constants by Loyola et al.[18] in their study of the complexation of Ca^{2+} with 6, 9, and 10. Of the two cryptates with a poor fit (6-Ca^{2+} and 9-Ca^{2+}) the more flexible 6 has rates of decomplexation and complexation which are greater than those of rigid 9. The fact that both rates are greater for 6 would argue against strict steric control of complexation since steric compression in the smaller cavity of 9 would be expected to enhance the decomplexation of Ca^{2+} in 9 as compared to 6.

From these complexation data and the high binding constants observed for the cryptands, it would seem logical to expect a rigid cryptand-type macropolycyclic polyether compound to have exceptional complexation and selectivity properties. The synthesis of such a compound, 11, was

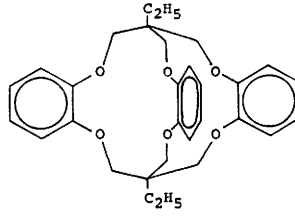

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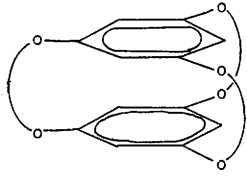
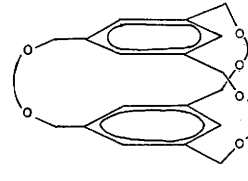
Figure 3. Pedersen's "Lantern".



A



B

Figure 4. Polyether Cyclophanes.

proposed and attempted by Pedersen[19]. Compound 11 would be closely related to the bicyclic polyether, 8, synthesized by Coxon and Stoddard. Pedersen was foiled in his attempts to make 11 by the low reactivity of trihalides of a neopentyl structure and by the difficulty of formin bridgehead carbon bonds.

Compound 11 would depend upon benzene rings for its rigidity. By the appropriate rearrangement of structural elements in 11 it is possible for the rings to also replace the troublesome bridgehead carbons. This leads to heterocyclophanes of the types shown in Figure 4, (A and B). The feature distinguishing between these two types of heterocyclophanes is the location of the ether linkages within the bridges. Type A has aryl ether linkages and aryl ethers have wide precedent in the crown ether field (including Pedersen's initial work). However, on consideration of this structure it will be noted that the lone electron pairs on the ether oxygen atoms are directed outward, away from the central cavity where complexation must occur. This problem is remedied in type B by the use of benzylic ether linkages which enjoy adequate, if not ubitiquious, precedent among the crown ethers[20]. In B the lone pairs of oxygen are directed inward to complex any cation in the central cavity.

Thioether analogues of type A and B compounds have been prepared by Lichtenthaler and Vogtle[21a&b]. They obtained complexes with Cu^{2+}, Hg^{2+}, and Au^{2+} but were unable

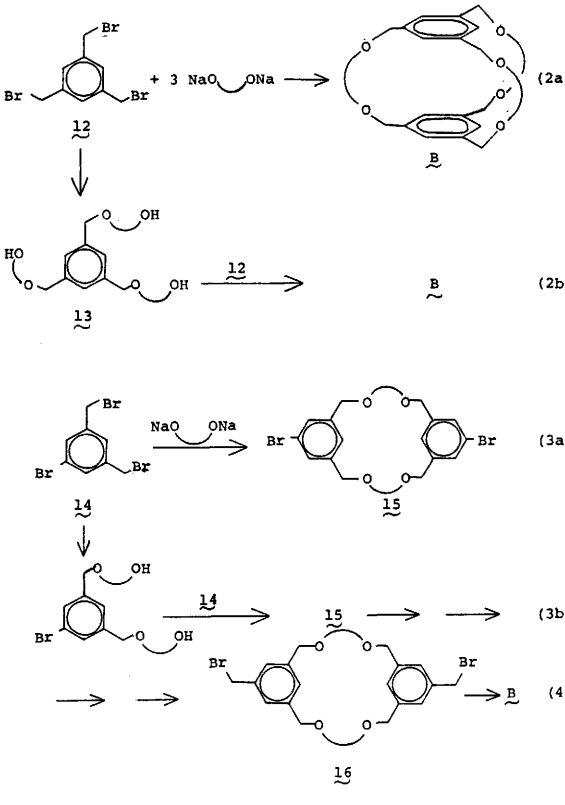
to obtain complexes with Ni^{2+}, Sn^{2+}, Zn^{2+}, Co^{2+}, Ag^{+}, Cd^{2+}, Pd^{2+}, Pt^{2+}, or any alkali metal cations.

Synthetic Approaches

Several approaches to the synthesis of group B compounds are available. In principle, a benzylic alkoxide and an aliphatic halide or a benzylic halide and an aliphatic alkoxide could be used to form the desired ether linkages. Since benzylic halides are more labile than primary aliphatic halides and α,ω-diols are more readily available and easier to work with than the corresponding α,ω-dihalides, I attempted the synthesis of type B compounds by the general scheme shown in Scheme I.

Within the context of Scheme I, there are several options for the synthesis of type B compounds. The most direct would be a "shotgun" approach wherein two moles of tris(bromomethyl)benzene, 12, and three moles of α,ω-dialkoxide react to give the heterocyclophane "cage" (eq 2a). While this method might work if a suitable template cation were found, it runs the risk of excessive or exclusive polymerization. This risk can be reduced by a two step synthesis (eq 2b). Analogous procedures could give the substituted crowns, 15 (eq 3a and 3b). Conversion of the substituents to bromomethyl gives 16 which can then be closed to give type B compounds (eq 4).

SCHEME I


Br
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Br
+ 3 NaO ONa
12
B
(2a)
HO
OH
OH
13
12
B
(2b)
NaO ONa
15
(3a)
14
14
15
(3b)
16
B
(4)

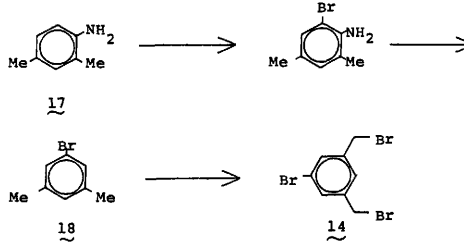
RESULTS

Synthesis

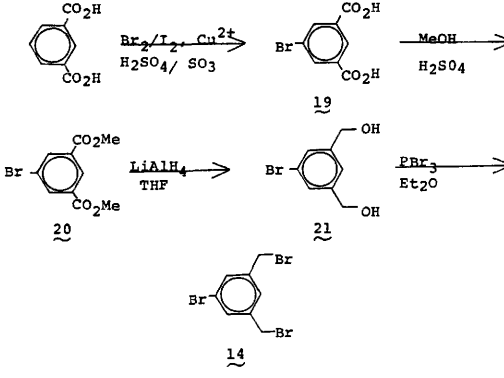
Newcomb obtained 5-bromo-1,3-bis(bromomethyl)benzene, 14, by a multistep and low yield route which involved aromatic bromination of 4-amino-m-xylene, 17, followed by diazotization to give 5-bromo-m-xylene, 18, and bromination of 18 with N-bromosuccinimide to give 14 (Scheme II)[22].

A better method was sought and a literature search revealed that iodine and/or certian metal salts directed aromatic substitution of bromide to the 5-position of isophthalic acid[23]. This seemed to be a promising approach since the diacid, 19, should be easily converted to the dibenzyl bromide, 14, (Scheme III). Bromination of isophthalic acid in fuming sulfuric acid with the presence of catalytic amounts of iodine and copper sulfate gave 5-bromoisophthalic acid, 19. Although esterification with methanol gave dimethyl 5-bromoisophthalate, 20, in only 68% yield, unreacted acid could easily be recovered by a basic wash of the crude product. Reduction of the diester, 20, with lithium aluminium hydride in tetrahydrofuran gave 5-bromo-1,3-bis(hydroxymethyl)benzene, 21, in 92% yield. Bromination with phosphorus tribromide in diethyl ether gave the dibenzylic bromide, 14, in 82% yield. Compound 14, the last common intermediate in the synthesis of type B

SCHEME II



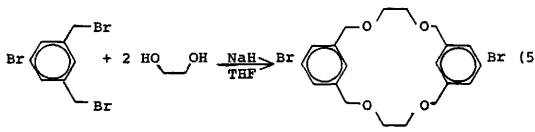
SCHEME III



compounds, was thus obtained from isophthalic acid, a very cheap starting material, in four steps with inexpensive reagents in good yield.

To obtain bis(5-bromo-1,3-xyleno)-18-crown-4, 22, an equimolar mixture of the dibenzylic bromide, 14, and ethylene glycol was added under high dilution conditions to a stirred suspension of sodium hydride in refluxing tetrahydrofuran (eq 5). The yield of 5% was unacceptably low since several steps remained en route to the cage. The alternative two step route was then tried. Compound 14 was added drop-wise to a stirred solution of the monosodium salt of ethylene glycol in tetrahydrofuran to give 5-bromo-1,3-bis(2'-hydroxyethoxymethyl)benzene, 23, in 96% yield. An equimolar mixture of 14 and 23 was then added under high dilution conditions to a stirred suspension of sodium hydride in refluxing tetrahydrofuran to give the bis(bromoxyleno)crown, 22, in 38% yield (eq 6).

With two of the three bridges constructed it was time to build the foundations of the third (Scheme IV). Aromatic nucleophilic substitution of crown 22 with cuprous cyanide in refluxing dimethyl formamide[24] gave bis(5-cyano-1,3-xyleno)-18-crown-4, 24, in 90% yield. Dinitrile 24 was stirred with Raney nickel alloy in refluxing 75% aqueous formic acid[25] to give bis(5-formyl-1,3-xyleno)-18-crown-4, 25, in 80% yield. Reduction of the dialdehyde 25 with sodium borohydride in ethanol gave bis(5-hydroxymethyl-



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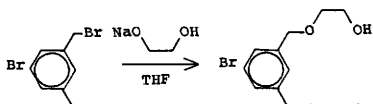
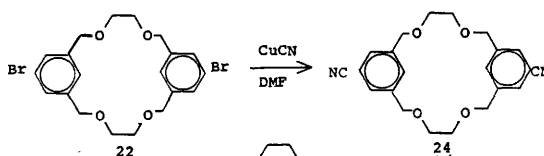


14 23

SCHEME IV



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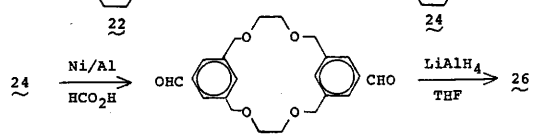

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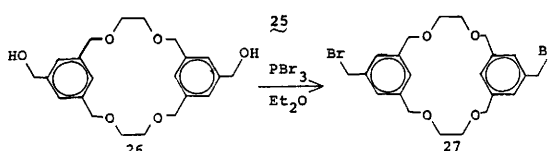


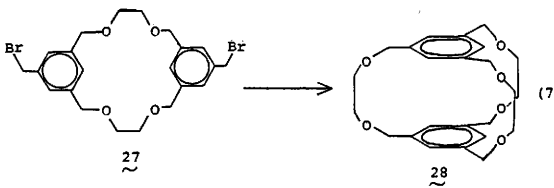
26 27

1,3-xyleno)-18-crown-4, 26, in 83% yield. Bromination of 26 with phosphorus tribromide in diethyl ether gave bis(5-bromomethyl-1,3-xyleno)-18-crown-4, 27, in 76% yield.

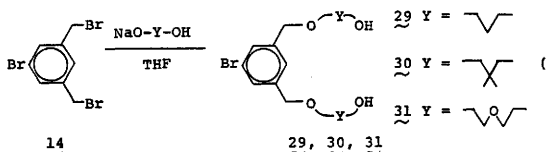
With the foundation laid all that remained was to close the cage door. Crown 27 and ethylene glycol were added under high dilution conditions to a stirred suspension of sodium hydride in tetrahydrofuran to give the hexaoxa-[6.6.6]-(1,3,5)cyclophane, 28, in 17% yield (eq 7).

Three other bis(bromoxyleno)crown compounds were synthesized by the route shown in equation 3b. Dibenzyl bromide, 14, was added to a stirred solution of monosodium propylene glycol salt in refluxing tetrahydrofuran to give 5-bromo-1,3-bis(3'-hydroxypropoxymethyl)benzene, 29, in 65% yield. By similar methods 5-bromobis(3'-hydroxy-2,2-dimethylpropoxymethyl)benzene, 30 was obtained in 72% yield and 5-bromobis(5'-hydroxy-3-oxapentoxymethyl)benzene, 31, was obtained in 71% yield (eq 8). Equimolar amounts of the resulting diols and dibromide, 14, were added under high dilution conditions to a stirred suspension of sodium hydride in refluxing tetrahydrofuran. This gave bis(5-bromoxyleno)-20-crown-4, 32, in 82% yield; bis(5-bromoxyleno)-3,3,13,13-tetramethyl-20-crown-4, 33, in 53% yield; and bis(5-bromoxyleno)-24-crown-6, 34, in 62% yield (eq 9).

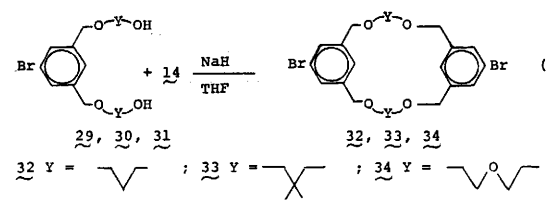
Compound 33 was stirred with cuprous cyanide in refluxing dimethyl formamide to give bis(5-cyanoxyleno)-3,3,13,13-tetramethyl-20-crown 4, 35, in 70% yield (eq 10).



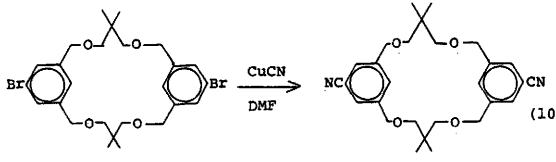
27 28 (7)



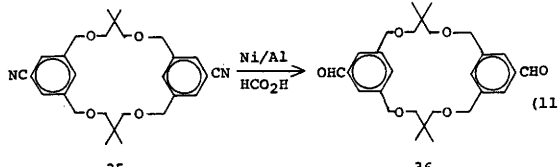
14 29, 30, 31 (8)



29, 30, 31 32, 33, 34 (9)



33 35



35 36

Compound 35 was stirred with Raney nickel alloy in refluxing 75% aqueous formic acid to give bis(5-formyl-1,3-xyleno)-3,3,13,13-tetramethyl-20-crown-4, 36, in 85% yield (eq 11).

Complexation.

The distribution coefficient of lithium picrate in a water:deuteriochloroform system is sufficiently low so that when a 0.08M aqueous solution of lithium picrate was shaken against an equal volume of the chloroform no color was apparent in the chloroform. However, when the same solution was shaken against an 0.08M solution of [2.2.2]-cage, 28, the chloroform solution acquired a strong yellow color from lithium picrate solubilized by the presence of the cage. The ^{1}H NMR spectrum of the complex was inconclusive. The peaks showed a slight downfield shift but this was within the reproducible error of the instrument used. There were also some small peaks downfield of each resonance attributable to impurities in the sample rather than to cage:lithium picrate complex.

EXPERIMENTAL

General.

^{1}H NMR spectra were recorded on a Varian T-60 spectrometer using deuteriochloroform as solvent with tetramethylsilane as an internal standard except where otherwise indicated. ^{13}C NMR spectra were recorded on a JEOL PFT-100 spectrometer. IR spectra were recorded on a Beckman IR-8 spectrometer using sodium chloride plates or sodium chloride cells. The high resolution mass spectrum was determined by Dr. Ronald Grigsby, Dept. of Biochemistry and Biophysics, Texas A&M University. Melting points were determined on a Thomas-Hoover capillary-type melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from a purple solution or suspension of disodium benzophenone dianion prior to use. Glycols were dried over 4 A molecular seives. All organic chemicals were purchased from Aldrich Chemical Co. or other commercial sources in reagent quality and were used as supplied. The high dilution conditions were obtained by use of the apparatus shown in Figure 5. A dilute solution of reactants was dropped by a precision dropping funnel (Ace Glass Co.) through a reflux condenser into a funnel within a cone. There the solution was further diluted by refluxing solvent and dropped into the reaction flask containing a large amount of solvent and any reagents

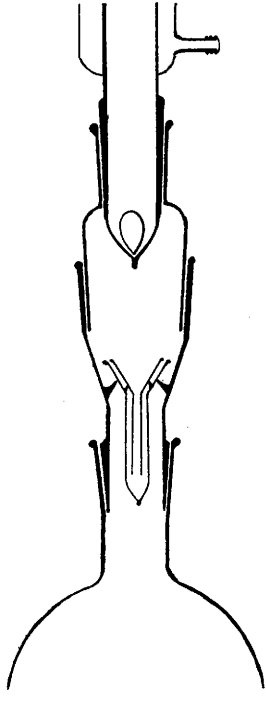


Figure 5. High Dilution Apparatus.

required. This method requires a reasonably fast reaction to avoid build-up of the reactants in the reaction flask. Gas chromatographic analyses were performed on a Varian Associates series 2400 chromatograph using an 1/8 in x 6 ft aluminium column packed with SE-30 (3% w/w) on Chromosorb G support (80-100 mesh). Gas chromatographic separations were carried out on a Varian model 920 chromatograph using a 1-4 in x 6 ft aliminium column packed with SE-30 (10% w/w) on Chromosorb W support.

Synthetic

5-Bromoisophthalic acid (19)

Isophthalic acid (109.5 g, 0.66 mole), cupric sulfate (1.65 g, 6.6 mmole), and iodine (0.87 g, 3 mmole) were added to fuming sulfuric acid (725 mL, 30% SO_3). After dissolution was complete, bromine (40 mL, 0.78 mole) was added dropwise. The reaction mixture was heated at reflux for 5 h. Completion of the reaction was indicated by the formation of a yellow suspension with concurrent disappearance of the brown gaseous bromine above the liquid. The reaction mixture was poured cautiously into 2 L of water resulting in a fine white precipitate. The precipitate was removed by filtration, washed with water, and dried by heating under aspirator vacuum to give 159 g of crude product as a white cake, mp 280-287° C (lit. mp[26] 282-283° C): ^{1}H NMR ($CDCl_3$/DMSO-d_6, 3:1): δ8.13-8.67 (m, 3H); 10.77 (broad s, 2H). Glc analysis (170° C) of the dimethyl ester prepared from

the product showed the 4,5-dibrominated acid as 30%.

Dimethyl 5-bromoisophthalate (20).

Crude 5-bromoisophthalic acid (159 g) from the previous reaction was added to methanol (1 L) and concentrated sulfuric acid (2 mL). This mixture was stirred and heated at reflux for 24 h with removal of water as a ternary azeotrope with chloroform (250 mL) at 2 h and at 18 h in the reaction period. The sulfuric acid was neutralized with sodium bicarbonate and the methanol was removed in a rotary evaporator to give a green oil which was distributed between water and dichloromethane. The aqueous layer was washed with dichloromethane and the combined dichloromethane layers were dried ($MgSO_4$). The dichloromethane was removed in a rotary evaporator to give 110 mL of oil which partially crystalized on standing. These crystals were removed by filtration (46.6 g, mp 110-120° C) and the remaining oil was recrystalized from methanol to yield an additional 75.5 g of 20 (68% crude yield). Distillation under vacuum gave 20 as a white crystaline solid: mp 139-140° C; ^1H NMR: δ4.00 (s, 6H), 8.37 (m, 1H), 8.60 (m, 2H). (See reference 27).

5-Bromo-1,3-bis(hydroxymethyl)benzene (21).

Dimethyl 5-bromoisophthalate (20) (26.2 g, 96.0 mmole) in diethyl ether (400 mL) was added dropwise to a suspension of lithium aluminium hydride (9.3 g, 245 mmole) in ether (500 mL). The reaction mixture was stirred and heated at reflux for 6 h, then water (250 mL) was cautiously added to

decompose the excess lithium aluminium hydride. Stirring was continued at room temperature overnight. Decantation of the ether layer and removal of solvent on a rotary evaporator gave 21 (18.2 g, mp 84-89° C; lit. mp[27] 90-91° C): ^{1}H NMR: δ1.7 (broad, 2H, hydroxyl), 4.70 (s, 4H), 7.33 (s, 1H), 7.50 (s, 2H). Repeated extraction of the lithium aluminium salts with ether increased the yield to 19.3 g (92.7%).

5-Bromo-1,3-bis(bromomethyl)benzene (14).

Phosphorus tribromide (19.5 g, 72.4 mmole) in diethyl ether (75 mL) was added slowly to a solution of 21 (18.2 g, 83.9 mmole) in ether (500 mL) maintained at 0° C. The reaction mixture was allowed to warm to room temperature over 4 h, and then the two layer mixture was poured over ice. The aqueous layer was separated and extracted with ether and the combined ether solutions were dried with Na_2SO_4. After removal of ether in a rotary evaporator, the ^{1}H NMR spectrum showed incomplete bromination by the presence of peaks at δ4.70 (ArC$\underline{H}_2$OH) and 2.67 (ArCH$_2$O$\underline{H}$, exchangeable with D_2O). The crude product was again subjected to the conditions above to give white crystals (21.6 g) and a yellow oil which was purified by chromatography on silica gel with dichloromethane elution to give an additional 2.1 g of crystaline material. Recrystalization from absolute ethanol gave 14 (21.2 g, mp 96-98° C and 2.4 g, mp 94-97° C; lit. mp[22] 97-98.5° C). ^{1}H NMR: δ4.45 (s, 4H), 7.40 (m, 1H), 7.55 (m, 2H)

5-Bromo-1,3-bis(2'-hydroxyethoxymethyl)benzene (23).

Ethylene glycol (22 mL, 0.39 mole) and sodium hydride (6 g, 50% in oil, 0.125 mole) were stirred in refluxing THF (100 mL) for 1.5 h. A solution of 14 (7.0 g, 20 mmole) in THF (50 mL) was added dropwise. Heating at reflux was continued overnight. Ammonium chloride (1 g) was added followed after 5 min by concentrated hydrochloric acid (1 mL). The reaction mixture was decanted and the solvent was removed in a rotary evaporator. The yellow, oily liquid was washed with hexane and dissolved in dichloromethane. This solution was extracted with water and dried (Na_2SO_4). Removal of solvent in a rotary evaporator gave 23 (5.88 g, 96%) as a pale yellow oil. ^1H NMR: δ3.63 (m, 10H), 4.50 (s, 4H), 7.30 (m, 1H), 7.41 (m, 2H).

5-Bromo-1,3-bis(3'-hydroxypropoxymethyl)benzene (29).

By the procedure described for 23 above, 1,3-propanediol (31 mL, 450 mmole) and 14 (7 g, 20 mmole) gave a yellow liquid which was distilled on a Kugelrohr apparatus (180-220° C, 1.5 mm Hg) to give 29 as a clear liquid (4.33 g, 65%) ^1H NMR: δ1.83 (m, 4H), 3.67 (m, 10H), 4.47 (s, 4H), 7.23 (m, 1H), 7.40 (m, 2H). IR: 3450 cm^{-1} (broad, medium), 1090 (broad, strong).

5-Bromo-1,3-bis(3'-hydroxy-2,2-dimethylpropoxymethyl)benzene (30).

By the procedure described for 23 above, 2,2-dimethyl-1,3-

propanediol (9.5 g, 91.3 mmole) and 14 (4.4 g, 12.8 mmole) gave 30 as a clear oil (3.58 g, 71.7%) bp 180° C (1.5 mm Hg), ^{1}H NMR: δ0.9 (s, 12H), 2.97 (s, 2H), 3.30 (s, 4H), 3.43 (s, 4H), 4.47 (s, 4H), 7.27 (m, 1H), 7.40 (m, 2H).

5-Bromo-1,3-bis(5'-hydroxy-3'-oxapentoxymethyl)benzene (31).

By the procedure described for 23 above, diethylene glycol (34 mL, 390 mmole) and 14 (7.0 g, 20 mmole) gave 31 (5.68 g, 70.8%) as a pale yellow syrup, bp 190-205° C (1mm Hg), ^{1}H NMR: δ3.63 (m, 20H), 4.55 (s, 4H), 7.30 (m, 1H), 7.45 (m, 2H), IR: 3500 cm^{-1} (broad, medium), 1100 (broad, strong).

Bis(5-bromo-1,3-xyleno)-18-crown-4 (22).

A solution of 14 (1.71 g, 5 mmole) and 23 (1.52 g, 5 mmole) in THF (110 mL) was added under high dilution conditions to a suspension of sodium hydride (1.8 g, 50% in oil, 37.5 mmole) in THF (80 mL) which was heated at reflux. The addition required 6 h, and heating at reflux was continued for an additional 2 h. The entire reaction was run under a nitrogen atmosphere. At the end of the reflux period, water (10 mL) was cautiously added followed by ammonium chloride (1 g) and concentrated hydrochloric acid (1 mL). The THF solution was decanted and the solvent was removed in a rotary evaporator. The residue was dissolved in dichloromethane, dried ($MgSO_4$), filtered, and the solvent again removed to give 22 as a yellow oil (2.92 g). This oil was purified by chromatography on silica gel. Elution with dichloromethane gave 14 and

mineral oil. Elution with a 1:1 mixture of methanol and dichloromethane gave an oily solid which was recrystalized from dichloromethane to give 22 (0.92 g, 1.9 mmole, 38%), ^{1}H NMR: δ3.74 (s, 8H), 4.57 (s, 8H), 7.30 (m, 4H), 7.67 (m, 2H).

Bis(5-bromo-1,3-xyleno)-20-crown-4 (32).

By the procedure described for 22 above, 29 (4.33 g, 13.0 mmole) and 14 (4.46 g, 13 mmole) gave 32 (5.47 g, 10.6 mmole, 82%) as a white solid, mp 97-99° C, ^{1}H NMR: δ1.90 (m, 4H), 3.53 (t, 8H), 4.40 (s, 8H), 7.17 (m, 2H), 7.34 (m, 4H).

Bis(5-bromo-1,3-xyleno)-3,3,13,13-tetramethyl-20-crown-4 (33).

By the procedure described for 22 above, 30 (3.58 g, 9.2 mmole) and 14 (3.16 g, 9.2 mmole) gave 33 (2.79 g, 4.9 mmole, 53%) as white crystals, ^{1}H NMR: δ0.93 (s, 12H), 3.27 (s, 8H), 4.43 (s, 8H), 7.17 (m, 2H), 7.37 (m, 4H).

Bis(5-bromo-1,3-xyleno)-24-crown-6 (34).

By the procedure described for 22 above, 31 (5.68 g, 14.4 mmole) and 14 (4.96 g, 14.4 mmole) gave 34 (5.16 g, 9.0 mmole, 62.4%) as white crystals, ^{1}H NMR: δ3.70 (s, 16H), 4.57 (s, 8H), 7.27 (m, 2H), 7.50 (m, 4H).

Bis(5-cyano-1,3-xyleno)-18-crown-4 (24).

Crown 22 (4.93 g, 10 mmole) and cuprous cyanide (2.34 g,

25 mmole) were stirred in dimethyl formamide (20 mL) which was heated at reflux. After 12 h the hot, dark reaction mixture was poured into a warm solution of potassium cyanide (20 g) in water (60 mL). This gave a creamy white suspension which was extracted with dichloromethane. The resulting stable emulsion was dispersed by addition of chloroform, and the organic solution was dried (Na_2SO_4). Removal of solvent in a rotary evaporator gave 24 (3.42g, 9.0 mmole, 89.2%) as a creamy white solid, mp 194-206° C, ^1H NMR: δ3.73 (s, 8H), 4.60 (s, 8H), 7.43 (m, 4H), 7.97 (m, 2H), IR: 2220 cm^{-1} (sharp, medium), 1120 (strong).

Bis(5-cyano-1,3-xyleno)-3,3,13,13-tetramethyl-20-crown-4 (35).

Crown 33 (2.79 g, 4.9 mmole) and cuprous cyanide (1.94 g, 21 mmole) were stirred in dimethyl formamide (20 mL) for 7 h. Acidic ferric chloride solution (40 g of $FeCl_3 \cdot 6H_2O$, 10 mL concentrated HCl, and 60 mL water) was added. The resulting mixture was stirred for 20 min without further heating. The mixture was extracted with dichloromethane (100 mL and three 20 mL portions). The combined dichloromethane solution was washed repeatedly with dilute hydrochloric acid to remove the residual ferric chloride and was neutralized ($NaHCO_3$). The solvent was removed in a rotary evaporator to give a brown oil (5.49 g), which partially crystalized on standing. Filtration gave 35 (0.92 g,

mp 142-145° C). Chromatography of the filtrate on silica gel with a 1:1 hexane and dichloromethane mixture gave a small amount of mineral oil. Elution with dichloromethane gave 35 (0.67 g) for a total yield of 1.59 g, 3.44 mmole, 70%. ^{1}H NMR: δ0.97 (s, 12H), 3.27 (s, 8H), 4.47 (s, 8H), 7.43 (s, 6H); ^{13}C NMR: 22.299, 36.215, 71.828, 75.663, 112.152, 118.672, 129.685, 130.123, 140.423 ppm relative to internal Me_4Si.

Bis(5-formyl-1,3-xyleno)-18-crown-4 (25).

Crown 24 (1.80 g, 4.71 mmole) and Raney nickel alloy (1:1 nickel/aluminium, Alfa Ventron)(2.3 g) were stirred in formic acid (75% aqueous, 100 mL) which was heated at reflux for 7 h. The reaction mixture was filtered and the solids were washed with hot ethanol. The combined filtrate was distributed between dichloromethane and water. The aqueous phase was extracted with dichloromethane (four 50 mL portions). The combined dichloromethane fractions were washed with 5% Na_2CO_3 and dried (K_2CO_3). Removal of solvent in a rotary evaporator gave 25 (1.46 g, 3.76 mmole, 79.8%) as a white solid, mp 167-170° C, ^{1}H NMR: δ3.77 (s, 8H), 4.73 (s, 8H), 7.73 (m, 4H), 8.07 (m, 2H), 10.1 (s, 2H), IR: 1700 and 1100 cm^{-1}.

Bis(5-formyl-1,3-xyleno)-3,3,13,13-tetramethyl-20-crown-4 (36).

By the procedure described for 25 above, 35 (1.45 g, 3.14

mmole) and Raney nickel alloy (1.55 g) gave 1.44 g of yellow oil. Column chromatography of silica gel with dichloromethane elution gave 36 (1.26 g, 2.69 mmole, 85.7%) as white crystals, ^{1}H NMR: δ0.93 (s, 12H), 3.23 (s, 8H), 4.50 (s, 8H), 7.43 (m, 2H), 7.60 (m, 4H), 9.9 (s, 2H).

Bis(5-hydroxymethyl-1,3-xyleno)-18-crown-4 (26).

Crown 25 (0.25 g, 0.64 mmole) and sodium borohydride (0.148 g, 3.9 mmole) were stirred in absolute ethanol (100 mL) for 0.5 h. The reaction mixture was acidified with 5% aqueous HCl and distributed between water and dichloromethane. The aqueous phase was washed with dichloromethane. The combined dichloromethane solution was washed with 5% $NaHCO_3$, dried (Na_2SO_4), and the solvent removed in a rotary evaporator to give 26 (0.21 g, 0.53 mmole, 83%) as a white powder, mp 138-144° C, only slightly soluble in CH_2Cl_2 or $CHCl_3$. ^{1}H NMR: δ2.48 (s, 2H), 3.75 (s, 8H), 4.67 (s, 8H), 4.73 (s, 4H), 7.23 (m, 4H), 7.73 (m, 2H).

Bis(5-bromomethyl-1,3-xyleno)-18-crown-4 (27).

Phosphorus tribromide (1 g, 3.7 mmole) in THF (20 mL) was added dropwise to a stirred solution of crown 26 (0.21 g, 0.54 mmole) in diethyl ether (20 mL) maintained at 0° C. Stirring was continued and the reaction mixture was allowed to warm slowly to room temperature. The mixture was poured over ice. The organic layer containing a fluffy white solid was decanted and the aqueous layer was extracted with

ether and with dichloromethane. The combined organic solution was dried (Na_2SO_4) and the solvent removed in a rotary evaporator to give a white solid which was recrystalized from ether to give 27 (0.21 g, 0.41 mmole, 75.7%) as white needles, mp 152-165° C[28]. ^1H NMR: δ3.70 (s, 8H), 4.47 (s, 4H), 4.60 (s, 8H), 7.2 (m, 4H), 7.70 (m, 2H).

2,5,14,17,26,29-Hexaoxa[6.6.6]-(1,3,5)cyclophane (28).[29]

Crown 27 (0.30 g, 0.58 mmole) and ethylene glycol (0.07 g, 1.1 mmole) in THF (50 mL) were added under high dilution conditions to a suspension of sodium hydride (2.35 g, 50% in oil) in THF (50 mL) which was heated at reflux. Aliquots taken at 5.7, 7.5, and 15 h showed increasing amounts of 28 by ^1H NMR. An $ArCH_2Br$ absorbance was present in the 5.7 and the 7.5 h aliquots but had disappeared after 15 h. At that time water (10 mL) was added followed by ammonium chloride (1 g) and concentrated hydrochloric acid (1 mL). The reaction mixture was distributed between water and dichloromethane and the aqueous phase was extracted with dichloromethane. The combined dichloromethane solution was dried (Na_2SO_4) and the solvent removed in a rotary evaporator. Chromatography on silica gel with dichloromethane elution gave a mixture of 27 and mineral oil. Elution with a 9:1 dichloromethane/acetone mixture gave 28 (0.041 g, 0.1 mmole, 17%) as a white solid, dec. pt. 190° C, ^1H NMR: δ3.40 (s, 12H), 4.40 (s, 12H), 7.08 (s, 6H), ^{13}C NMR: 68.135, 72.518, 125.986, 137.927 ppm

relative to Me_4Si, IR: 3000, 2920, 2860, 1090 cm^{-1}, high resolution mass spectrum contained a molecular ion a m/e 414.2030 (± 3.0 ppm, ± 0.0012), calcd. for $C_{24}H_{30}O_6$: m/e 414.2042.

1,3,5-tris(hydroxymethyl)benzene (40).

A solution of 1,3,5-benzenetricarboxylic acid chloride (10.0 g, 37.7 mmole) in THF (100 mL) was added dropwise under nitrogen (1.5 h) to lithium aluminium hydride (5.0 g, 139 mmole) suspended in THF (500 mL) stirred at reflux. Reflux was continued for 2.5 h then the mixture was cooled to room temperature and water (200 mL) was carefully added. The organic layer was separated and the THF removed in a rotary evaporator to give a pale yellow oil. Successive extractions of the aqueous suspension of the lithium aluminium salts with ether gave a clear oil after evaporation of the ether. The combined oils were crystalized from dichloromethane to give 40 (5.30 g, 31.5 mmole, 83%) as white crystals, mp 68-72° C (lit. mp 77° C[30]), ^1H NMR: δ4.5(s, 6H), 4.6 (s, 3H), 7.2 (s, 3H).

1,3,5-Tris(bromomethyl)benzene (12).

A solution of phosphorus tribromide (9.1 g, 33.6 mmole) in THF (35 mL) was added slowly to a stirred suspension of 40 (4.77 g, 28.4 mmole) in THF (100 mL) at 0° C. Stirring at 0° was continued for 4 h, then the reaction mixture was allowed to warm to room temperature. The

mixture was poured over ice and extracted with ether. The combined ether extracts were dried (Na_2SO_4) and the ether evaporated to give a yellow oil. Chromatography on silica gel (30 g, 80-100 mesh) with dichloromethane elution gave a yellow oil which was crystalized from cyclohexane and petroleum ether to give 12 (6.2 g, 17.4 mmole, 61%) as beige crystals, mp 91-92° C (lit. mp 93° C[30]), ^{1}H NMR: δ4.4 (s, 6H), 7.4 (s, 3H).

1,3,5-Tris(methoxymethyl)benzene (38).

A mixture of 12 (2.03 g, 5.7 mmole) and NaOMe (6.0 g, 111 mmole) was stirred overnight in methanol (260 mL). The reaction mixture was neutralized with ammonium chloride (1 g) and concentrated hydrochloric acid (1 mL). The methanol was removed in a rotary evaporator and the residue was distributed between water (100 mL) and dichloromethane (75 mL) and the aqueous layer was extracted with two portions of dichloromethane (50 mL). The combined organic solution was dried ($MgSO_4$) and the solvent removed in a rotary evaporator to give a yellow oil (1.25 g). Chromatography on silica gel with dichloromethane elution gave 38 as an oil, bp 250° C, ^{1}H NMR: δ3.30 (s, 9H), 4.70 (s, 6H), 7.15 (s, 3H).

Complexation of lithium picrate.

A solution of lithium picrate (0.08 M) was prepared by mixing lithium hydroxide (0.2 g, 8 mmole) and picric acid

(1.9 g, 8 mmole) in water (100.0 mL). An aliquot (1.0 mL) of this solution was shaken against $CDCl_3$ (1.0 mL). No color was visible in the $CDCl_3$. A second aliquot of the lithium picrate solution was shaken against a solution of heterocyclophane 28 (0.041 g, 0.1 mmole) in $CDCl_3$ (1.0 mL). A strong yellow color was transferred to the $CDCl_3$ solution. ^1H NMR: δ3.43 (s, 12H), 4.48 (s, 12H), 7.10 (s, 6H).

DISCUSSION AND SUMMARY

These experiments involve the synthesis of a new group of macropolycyclic polyether ligands which is expected to show enhancement of cation selectivity versus other polyether cryptands and crowns. One member of this new class, a hexaoxacyclophane, 28, was synthesized to develop the appropriate synthetic methods and these methods were applied to the partial synthesis of three other members of the class. These synthetic methods are discussed in the first of the following sections. The second section discusses the NMR spectra of 28. The third section discusses the complexation observed for compound 28 and the experiments which should be performed to determine if this new group of ligands does indeed have enhanced binding selectivity.

Synthetic Methods.

The synthesis of the [7.7.7]-(1,3,5)-heterocyclophane, 37, was attempted by the routes shown in Scheme I, equations 2a and 2b. Although the synthesis of tris(bromomethyl)-benzene, 12, (by a modification of the method of Cochrane, et al.[30]) and tris(3'-hydroxypropoxymethyl)benzene, 39, were readily accomplished, all attempts at cage closure resulted in intractable oils.

The nucleophilic bromination of isophthalic acid was derived from a patent disclosure by McGrath[23] and has not

been optimized in this laboratory. Although dibromination occured to some extent, it is probable that this problem could be corrected by reducing the excess of bromine used in the reaction.

The higher yields observed for the 20- and 24-membered crowns relative to the yield for the 18-membered crown may be attributable to a template effect with the sodium hydride cation. The effect of the two phenyl hydrogens jutting into the crown cavity would be expected to interfere more strongly with the complexation of the sodium cation in the 18-membered crown than in the larger ones. If this is so it is unclear whether this would affect the yield in the cage forming reaction since these hydrogens would not be in the cavity of the cage.

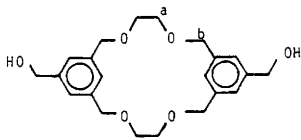
The cyanation reaction developed by Friedman and Schechter[24] gave the cyanocrown compounds in high yields but there was some difficulty in removing the solvent DMF with several aqueous washes required. It was also observed that the crowns seemed to complex the ferric ion resulting in difficulty in removing the ferric chloride after using it to decompose the complex formed by the cyano groups and the copper. This problem was avoided by the use of potassium cyanide to decompose the copper complex thereby removing the copper as water soluble potassium cuprocyanide.

In the cage forming reaction reported, a near two-fold excess of ethylene glycol was used. This was done because

a previous smaller scale reaction had about 90% of the bis(bromomethyl)crown remaining at workup and it was thought that some of the ethylene glycol might have been destroyed in a side reaction. However, that workup was at six hours and, as reported in the experimental section, the starting material was still present in recoverable amounts after 15 h. It is therefore probable that a return to equimolar amounts of crown and glycol with longer reaction times will result in higher yields of cage.

NMR Spectra.

The most striking feature of the NMR spectra of the cage 28 is their simplicity. There are only three singlets in the ^{1}H NMR spectrum and only four peaks in the ^{13}C NMR spectrum. This is due to the high symmetry of 28. The second significant feature is the upfield shift in the ^{1}H NMR spectrum compared to some related compounds. (Figure 6 and Table II). This shift was not observed in the sulfur analogs synthesized by Lichtenwahler and Vogtle [21a] who had speculated that such a shift would be observed if the ethylene units were in the conformation shown in Figure 7 which places the ethylene units within the sheilding cones of both benzene rings. Although an adequate NMR spectrum of the complex with lithium was not obtained, complexation within the central cavity would be expected to result in a downfield shift to the vicinity of the crown compounds. Although no up-field shift was observed



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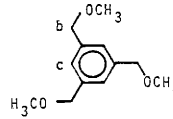

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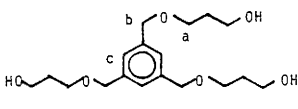

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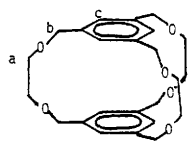

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Figure 6. Cyclophane 28 and some related compounds.

Table II. ^{1}H NMR Chemical Shifts (δ).

compound	a	b	c
26	3.75	4.73	----
38	----	4.70	7.15
39	3.63	4.50	7.27
28	3.40	4.40	7.08

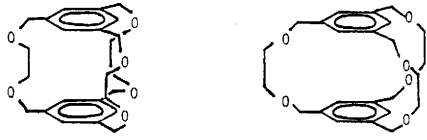
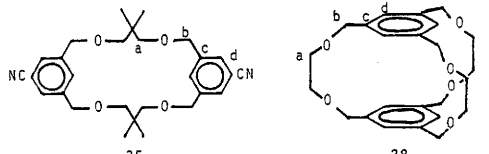


Figure 7. Possible conformations of cyclophane 28.



35 28

Figure 8. Cyclophane 28 and crown 35.

Table III. ^{13}C NMR Chemical Shifts (ppm).

compound	a	b	c	d
28	68.14	72.52	133.03	125.98
35	71.83	75.66	129.69	112.15

in the sulfur analogs, similar shifts have been observed in unsubstituted cyclophanes. Just why there is a shift in the cyclophanes and oxacyclophanes and not in the thiacyclophanes is not clear although the longer carbon-sulfur bonds could allow a different conformation than is possible in the cyclophanes and oxacyclophanes.

The ^{13}C NMR spectra of 26, 38, and 39 have not been determined for comparison with that of 28. However, the ^{13}C NMR spectrum of crown 35 was determined and some comparison can be made, especially in the alkyl bridges. (Figure 8 and Table III). The resonances of the carbons in the bridge of 28 are shifted upfield by about 3 ppm. The downfield shift of the ring carbon resonances may actually be an upfield shift in 35 due to the electronic effects of the cyano groups. The ^{13}C NMR spectra of compounds 38 and 39 would be useful to determine if this is indeed the case.

Complexation.

The complexation properties of the [6.6.6]-heterocyclophane, 28, were not extensively investigated. It was determined that 28 increases the solubility of lithium picrate in deuteriochloroform. However, no significant shift was observed in the ^{1}H NMR spectrum of 28, and so it may be possible that only a small amount of the 28 present in the deuteriochloroform solution was involved in the complexation. It was not determined if this was

due to a slow complexation step or to a low equilibrium between the complexed and uncomplexed cage. The picrate complexes should lend themselves to easy determination by colorimetric methods. More experimentation with a variety of cations is needed to determine the selectivity of 28 and other members of the class.

It was observed that the dicyanocrown compounds such as 35 appear to complex the ferric ion. The basis for this proposal is the difficulty observed in the removal of ferric chloride from dichloromethane solutions of these crowns. This apparent complexation was not investigated further.

Summary.

General methods for the synthesis of a new class of macropolycyclic polyether ligands were explored and applied to the synthesis of one member, 28, of this new class of compounds. Compound 28, an oxacyclophane, exhibited significant shifts in its NMR spectra when compared to open-chain and crown ethers with similar structural features. Compound 28 was shown to complex lithium picrate in chloroform although the extent of this complexation was not determined.

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(28) A sample of compound 27 recovered by chromatography of the reaction mixture from the synthesis of compound 28 had a mp of 163-169° C.

(29) The IUPAC nomenclature for compound 28 is: 5,7, 15, 17, 22, 24-hexaoxatetracyclo [10.10.6.1^{3,21}.1^{10,14}]-triaconta-1,3(29),10,12,14(30),21-hexaene.

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VITA

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