CHEMISTRY OF CROWN ETHERS

SYNTHESIS OF CROWN ETHERS BASED ON α,β-BIS(HALOMETHYL)- OR α,β-BIS(HYDROXYMETHYL)-SUBSTITUTED AROMATICS

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Abstract—Two types of novel crown ethers in which a polyether chain is linked, via C atoms, with two adjacent C atoms of an aromatic or heteroaromatic ring have been synthesized by reaction of α,β-bis(halomethyl)-substituted aromatics with polyethylene glycolates. Both 1:1 and 2:2 cyclic reaction products were formed, in yields varying from 1 to 53% and from 0 to 24%, respectively. The relatively high yields of these macrocyclic polyethers (rings containing from 11 to 34 atoms), obtained without operating at high dilution, depend both on the chain length of the glycol and on the nature of the cation. This can be explained in terms of a "template" effect of the cation in the cyclization step. Experimental evidence supporting such an effect was obtained from the relationship between the 1:1 product selectivity and the glycol chain length for cations with different ionic radii (Li$^+$, Na$^+$ and K$^+$). Furthermore, a correlation has been established between the ratio of the yields of 1:1 and 2:2 cyclic products from the reaction of 1,2-bis(bromomethyl)benzene and dipotassium triethylene glycolate and the ratio of the relative complexation constants of these compounds with potassium salts.

INTRODUCTION

Ever since Pedersen disclosed a method for the synthesis of macrocyclic polyethers—from catechol and α,ω-dihalides of polyethylene glycols[1]—crown ethers have received a great deal of attention because of their ability to form complexes with salts.[2,3] Up to now various crown ethers have been synthesized such as oligomers of ethylene oxide,[4,5] macrobicyclic polyethers[6] and crown ethers with additional functional groups.[7] In most cases the macrocyclic polyether ring is formed via the Williamson ether synthesis[8] as other methods, such as cyclo-oligomerization of ethylene oxide[9] or insertion of olefins into 1,3-dioxacycloalkanes,[10] are as yet unsuitable for the selective synthesis of crown ethers in acceptable yields. So far only crown ethers with ring sizes of 18–21 atoms, including 6 or 7 O atoms, have been obtained in reasonable yields. The fact that these compounds are formed under non-high-dilution conditions was attributed to the operation of a so-called "template" effect of the particular cation present in the base during the cyclization step.[4,5]

Complex formation occurs via incorporation of the cation in the cavity of the crown ether, as was shown by X-ray analysis of the crystalline complexes[11,12] and by spectroscopic measurements in solution.[2,3,13]

At present crown ethers are being applied in various areas of chemistry. They are excellent phase-transfer catalysts, generating highly reactive unsolvated anions.[14,15] Strong bases which result from charge-separated ion pairs[16] have been utilized to enhance the rate of anionic polymerization[17] and isomerization.[18] Not only salts but also metals are dissolved in organic solvents in the presence of crown ethers, a solvated electron being the counterion.[19]

A very promising field of application is the optical resolution of protonated amino-acid derivatives with the aid of crown ethers having a chiral cavity.

The objectives of the present study were (i) to develop a simple method for the preparation of crown ethers from easily accessible materials that gives high yields and can be used without operating under high-dilution conditions, and (ii) to examine the effect of various cations on the yield of the cyclization reaction.

The obvious way to prepare an unsymmetrical ether is by solvolysis of a halide or a tosylate with an alkoxide (Williamson synthesis[1]). This reaction has, however, two serious disadvantages: (i) the rate of solvolysis of alkyl halides is low, (ii) under the prevailing (strongly basic) reaction conditions elimination as well as substitution occurs. The latter is the more serious disadvantage because in a reaction with equimolar amounts of the reactants it has an adverse effect on the yield.

Therefore we have investigated the solvolysis of *activated* dihalides in which no competitive β-elimination with polyethylene glycol dialkoxides can occur. Examples of such compounds are bis(halomethyl)-substituted aromatics or heteroaromatics. The work reported here deals with the synthesis of crown ethers starting from α,β-bis(halomethyl)- or α,β-bis(hydroxymethyl)-substituted aromatics and polyethylene glycolates.

Starting materials. The lower polyethylene glycols (di, tri and tetra) were commercially available; the higher homologues (penta up to octa) were prepared by methods described by Cornforth *et al.*[21] and by Krespan.[7] The polyethylene glycol ditosylates were prepared using a method developed by Dale *et al.*[5] Both 1,2-bis(bromomethyl)- and 1,2-bis(chloromethyl)benzene were commercially available; 1,2-bis(hydroxymethyl)benzene was obtained by reduction of dimethyl phthalate with LAH. 3,4-Bis(chloromethyl)furan was synthesized starting from the corresponding diol, which in turn was obtained by reduction of 3,4-bis(methoxycarbonyl)furan with LAH.[22] 3,4-Bis(chloromethyl)-2,5-dimethylthiophene was prepared from 2,5-dimethylthiophene,[23] and 4,5-bis(chloromethyl)-benzo-1,3-dioxole was obtained by chloromethylation of benzo-1,3-dioxole.[24]

RESULTS

Synthesis of crown ethers. 1,2-Bis(bromomethyl)benzene (1)† was reacted with equimolar amounts of dipotassium salt of polyethylene glycol

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†1,2-Bis(chloromethyl)benzene gave similar results, but under more drastic reaction conditions (16 hr, 110°).
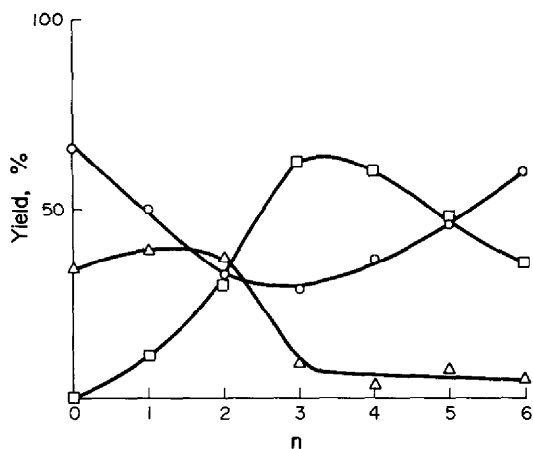
CH₂Br

+ HO[CH₂CH₂O]ₙ₊₂H $\xrightarrow[30-60°C]{2\ eq\ KOBu^t}$ **3 + 4 + polymer**

CH₂Br

1   **2**

3

a: n = 0	d: n = 3
b: n = 1	e: n = 4
c: n = 2	f: n = 5
	g: n = 6

4

a: n = 0
b: n = 1
c: n = 2

Scheme 1.

Table 1a. Reaction of 1,2-bis(bromomethyl)benzene with disodium and dipotassium polyethylene glycolates

Glycol (2)	Base	Prod. distribution,[a] % 3	4[b]	High mol. wt. prod.	1:1 Selectivity[c] (ring size)	Yield of 3, %	Yield of 4, %
n = 0	NaH	3	17	80	~0.01 (11)	1	17
	KOBu^t	-	34	66	-	-[d]	-[d]
n = 1	NaH	13	22	65	0.15 (14)	10	14
	KOBu^t	11	39	50	0.12 (14)	8	24
n = 2	NaH	48	11	41	0.92 (17)	34	-
	KOBu^t	30	37	33	0.43 (17)	24	8
n = 3	NaH	34	28	38	0.51 (20)	29	-
	KOBu^t	63	8	29	1.70 (20)	53	-
n = 4	NaH	32	22	46	0.47 (23)	18	-
	KOBu^t	60	3	37	1.50 (23)	50	-
n = 5	NaH	28	17	55	0.38 (26)	22	-
	KOBu^t	47	7	46	0.87 (26)	43	-
n = 6	NaH	22	25	53	0.26 (29)	16	-
	KOBu^t	36	4	60	0.56 (29)	28	-

a) Calculated from PMR spectroscopy.
b) Including some cyclic reaction products higher than 4 with b.p. > 250 °C/0.01 mm Hg.
c) Defined as [1:1 products]/[all other products].
d) Not isolated.

(2)—which were generated prior to the reaction by exchange in solution with potassium t-butoxide—in 0.1 M concentration in toluene at temperatures from 30 to 60°. A reaction time of 1 hr was sufficient in all cases to achieve complete conversion of the starting materials, as was inferred from the formation of two equivalents of potassium bromide and from the fact that the IR spectrum of the crude reaction mixture indicated the absence of OH groups. The crude mixture was separated into three fractions by chromatography over neutral alumina using THF as the eluent, followed by high-vacuum fractionation of the eluted materials.† The lower-boiling fraction consisted of the 1:1 cyclic products, the crown ethers **3**; the higher-boiling fractions were indentified as the 2:2 cyclic products **4** (Scheme 1). In the residues of the distillation various compounds of higher molecular weight (up to 4:4 cyclic products) were detected by mass spectrometry.

The results of these experiments are presented in Table

Table 1b. Reaction of 1,2-bis(bromomethyl)benzene with dilithium polyethylene glycolates

Glycol (2)	Crude product from solid residue,[a]	Yield of 3,[b] %	1:1 selectivity of 3[c]
n = 0	<2	<1	<0.01
n = 1	80	31	0.45
n = 2	69	23	0.30
n = 3	58	13	0.15
n = 4	36	10	0.11

a) Obtained by dissolving the solid residue in water/chloroform.
b) Calculated from PMR spectroscopy.
c) Defined as in Table 1a.

1a; the product distribution as a function of the glycol chain length is shown in Fig. 1. Considering the concentration of the reactants and the ring sizes of the macrocyclic products the amount of polymeric materials is surprisingly low, especially in the case of the tetra-, penta- and hexaethylene glycols (<40%). On the other hand, the yield of 1:1 cyclic product (**3**) is low for 11- and 14-membered rings but increases for larger rings (up to 63 and 60% for 20- and 23-membered rings, respectively). Considerable amounts of cyclic products other than **3** are

†The fraction obtained by chromatography is referred to as the "total cyclic products" as opposed to the "polymer fraction", which contains the reaction products of higher molecular weight together with traces of glycols.
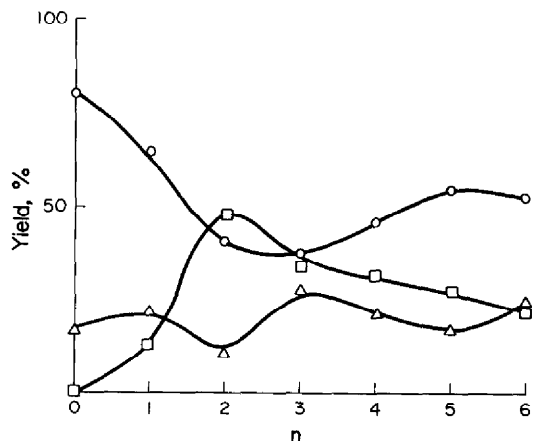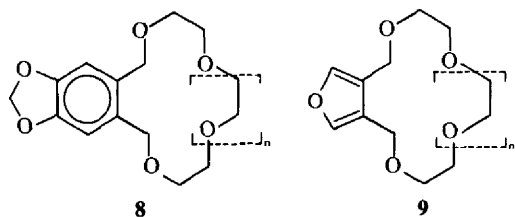
Fig. 1. Product distribution of reactions of 1,2-bis(bromomethyl)benzene with dipotassium polyethylene glycolates (K[OCH$_2$CH$_2$]$_{n+2}$OK). □, 1:1 cyclic product; △, other cyclic products; ○, high mol. wt.

formed only in the reactions of di- tri- and tetra-ethylene glycols, the major component of these products being the 2:2 cyclic product (4).

Reaction of 1 with di*sodium* polyethylene glycolates—generated prior to the reaction from 2 with sodium hydride or sodium t-butoxide—proceeded similarly, although the product distribution and the relationship between ring size and yields were different (Table 1 and Fig. 2). The highest yield of 1:1 cyclic product was obtained with disodium *tetra*ethylene glycolate instead of dipotassium *hexa*ethylene glycolate.

Reaction of 1 with dilithium polyethylene glycolates—generated with butyllithium prior to the reaction—required much longer reaction times (72 hr) for complete conversion of 1. In this case a crystalline compound was isolated containing lithium bromide, obviously a crown ether (3)-lithium bromide complex. Upon treatment with water the crown ethers 3 were isolated (Table 1b). The highest yield of 1:1 cyclic reaction product (31%) was obtained for the 14-membered ring (3b) using dilithium triethylene glycolate.

Compounds of type 3 with additional functionality were prepared either by starting from a modified 1,2-bis(halomethyl)benzene, e.g. 4,5-bis(chloromethyl)benzo-

1,3-dioxole (5), or by replacing the aromatic by a heteroaromatic ring (6 or 7).
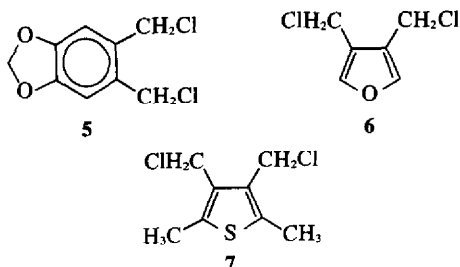
Reacting 5 with dipotassium and disodium tetraethylene glycolate yielded the corresponding crown ether 8a in yields of 19 and 29%, respectively. The yield of crown ether 8b, obtained by reaction with dipotassium hexaethylene glycolate, was 25%. In these cases only 1:1 reaction products could be isolated; other cyclic products did not distil at temperatures below 250° (1 Pa).

8
a: n = 2
b: n = 4

9
a: n = 0   d: n = 3
b: n = 1   e: n = 4
c: n = 2   f: n = 5

10
a: n = 0   e: n = 4
b: n = 1   f: n = 5
c: n = 2   g: n = 6
d: n = 3

11a: n = 0
b: n = 1
c: n = 2

12

Fig. 2. Product distribution of reactions of 1,2-bis(bromomethyl)benzene with disodium polyethylene glycolates (Na[OCH$_2$CH$_2$]$_{n+2}$ONa. □, 1:1 cyclic product; △, other cyclic products; ○, high mol. wt.
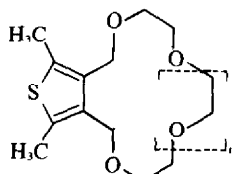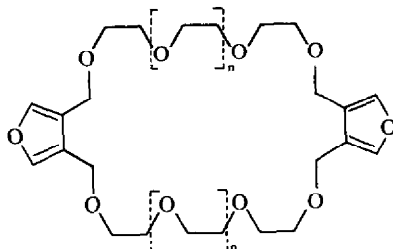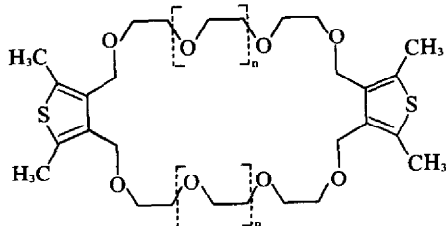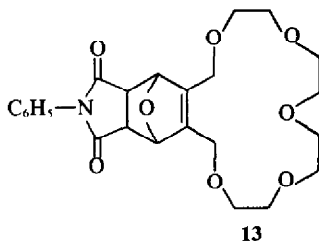
Table 2. Reaction of 3,4-bis(chloromethyl)furan with polyethylene glycolates

Glycol (2)	Base	Product distribution, %			1:1 Selectivity[c] (ring size)	Yield of 9, %	Yield of 11, %
		9	11[b]	High mol. wt. prod.			
n = 1	NaH	15	42	43	0.18 (14)	8	18
	KOBu^t	10	45	45	0.11 (14)	7	18
n = 2	NaH	43	11	46	0.75 (17)	31	1
	KOBu^t	34	22	44	0.52 (17)	19	8
n = 3	NaH	22	12	64	0.28 (20)	13	-
	KOBu^t	42	6	52	0.72 (20)	30	-
n = 4	NaH	45	28	27	0.82 (23)	28	-
	KOBu^t	61	3	36	1.56 (23)	44	-
n = 5	NaH	31	22	47	0.45 (26)	30	-
	KOBu^t	46	6	48	0.85 (26)	43	-

a) Calculated from PMR spectroscopy.
b) Including some cyclic reaction products higher than 11 with b.p. > 250 °C/0.01 mm Hg.
c) Defined as [1:1 product]/[all other products].

Table 3. Reactions of 3,4-bis(chloromethyl)-2,5-dimethylthiophene with polyethylene glycolates

Glycol (2)	Base	Prod. distribution,[a] %			1:1 Selectivity[c] (ring size)	Isolated yield of 10, %
		10	12[b]	High mol. wt. prod.		
n = 1	NaH	9	38	53	0.10 (14)	7
n = 2	NaH	40	25	35	0.67 (17)	35
n = 2	KOtBu	27	24	49	0.37 (17)	21
n = 3	KOtBu	37	13	50	0.59 (20)	38
n = 4	KOtBu	43	7	50	0.75 (23)	43
n = 5	KOtBu	43	8	49	0.75 (26)	42
n = 6	KOtBu	40	4	56	0.67 (29)	22

a) Calculated from PMR spectroscopy.
b) Including some cyclic reaction products higher than 12 with b.p. > 150 °C/0.01 mm Hg.
c) Defined as [1:1 product]/[all other products].

13

14: R = COOCH₃

15

TsO[CH₂CH₂O]ₙ₊₂Ts

16
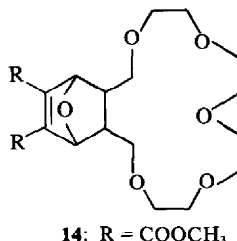
a: n = 0   e: n = 4
b: n = 1   f: n = 5
c: n = 2   g: n = 6
d: n = 3

Similar reactions of polyethylene glycolates (2) in refluxing toluene or THF for 16 hr fully converted the heteroaromatics 3,4-bis(chloromethyl)furan (6) and 3,4-bis(chloromethyl)-2,5-dimethylthiophene (7) into mixtures of 1:1 reaction products (9 or 10), 2:2 reaction products (11 or 12) and products of higher molecular weight. The results of these experiments were in line with those described above for 1,2-bis(bromomethyl)benzene.† Full details are given in Tables 2 and 3.

Compounds of type 9 have the advantage that they possess a reactive moiety that can be used for further reactions. For instance, the furan ring in 9c reacted with N-phenylmaleimide and with dimethyl acetylene-dicarboxylate at room temperature to give the Diels-Alder adducts 13 and 14, respectively.

We also investigated the synthesis of crown ethers from reactants with inversed reactivity, viz. the reactions of 1,2-bis(hydroxymethyl)benzene dialkoxides (15) with polyethylene glycol ditosylates (16).
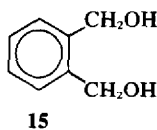
The reaction times required for conversion of the starting materials were as long as 48 hr. Crown ethers 3 and 4 (n ≤ 2), were isolated in yields considerably lower than those obtained with the other method.

Structural assignments. The structures of the crown ethers were identified on the basis of their mass spectrometric, and their PMR (Tables 4 and 5) and ¹³CMR (Tables 6 and 7) spectroscopic data. The mass spectrometric results will be discussed in detail separately, together with those from a wide range of macrocyclic polyethers.[25]

Generally, the mass spectra featured a strong parent peak and a fragmentation pattern in agreement with the proposed structures. With the MS technique reaction products up to 4:4 were identified.

†Products of type 12 could not be distilled at 1 pa and 250° without decomposition.

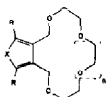Table 4. PMR spectroscopic data[a] of crown ethers 3 (X=CH=CH, R=H), 9 (X=O, R=H) and 10 (X=S, R=CH₃)
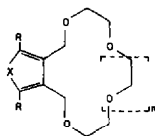
n	3			9			10		
	$\delta(H_{arom.})$	$\delta(CH_2O)$	$\delta(CH_2CH_2O)$	$\delta(H_{2,5})$	$\delta(CH_2O)$	$\delta(CH_2CH_2O)$	$\delta(CH_2O)$	$\delta(CH_2CH_2O)$	$\delta(CH_3)$
0	7.221	4.662	3.56–3.87	–	–	–	–	–	–
1	7.2–7.4	4.786	3.658–3.759	7.375	4.577	3.638–3.697	4.567	3.674–3.726	2.370
2	7.2–7.4	4.726	3.658–3.726	7.355	4.518	3.638–3.674	4.502	3.664–3.681	2.363
3	7.2–7.4	4.685	3.664–3.687	7.375	4.499	3.671	4.467	3.642	2.334
4	7.2–7.4	4.678	3.671	7.371	4.502	3.674	4.448	3.667	2.350
5	7.2–7.4	4.672	3.661	7.371	4.486	3.661	4.486	3.677	2.363
6	7.2–7.4	4.662	3.64–3.66	–	–	–	4.476	3.667	2.363

a) In CDCl₃ solutions; chemical shifts in ppm relative to TMS (T = 300 K).

Table 5. PMR spectroscopic data[a] of crown ethers 4 (X=CH=CH) and 11 (X=O)
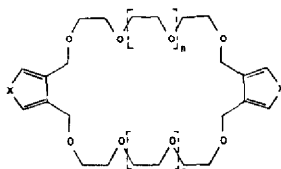
n	4			11		
	$\delta(H_{arom.})$	$\delta(CH_2O)$	$\delta(CH_2CH_2O)$	$\delta(H_{arom.})$	$\delta(CH_2O)$	$\delta(CH_2CH_2O)$
0	7.1–7.3	4.623	3.592	7.362	4.512	3.667
1	7.1–7.5	4.659	3.664	7.368	4.483	3.654
2	7.1–7.6	4.639	3.651	7.378	4.476	3.654

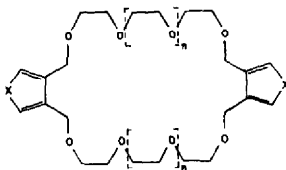a) In CDCl₃ solutions; chemical shifts in ppm relative to TMS (T = 300 K).

Table 6. ¹³CMR data of crown ethers 3 (X=CH=CH, R=H) 9 (X=O, R=H) and 10 (X=S, R=CH₃)

n	3			9			10*		
	$\delta(C_{arom.})$	$\delta(CH_2\ benzylic)$	$\delta(CH_2CH_2O)$	$\delta(C_{arom.})$	$\delta(CH_2\ benzylic)$	$\delta(CH_2CH_2O)$	$\delta(C_{arom.})$	$\delta(CH_2\ benzylic)$	$\delta(CH_2CH_2O)$
0	138.20 136.57 128.29	71.87	71.12 69.99	–	–	–	–	–	–
1	137.06 129.01 127.77	71.62	71.16 70.06 69.34	141.48 122.51	63.56	71.29 70.19 69.21	134.53 134.14	65.12	71.75 70.19 69.28
2	136.87 128.36 127.51	71.23	70.97 70.58 69.73	141.29 122.31	63.95	71.10 70.97 70.57 69.60	134.27 134.01	64.99	71.10 70.64 69.47
3	136.67 128.94 127.70	71.03	70.84 69.93	141.55 122.12	63.50	70.77 69.63	134.27 133.94	64.80	70.84 69.14
4	136.80 128.94 127.71	71.10	70.77 69.86	141.55 122.10	63.56	70.71 69.61	134.20 133.04	64.93	70.83 69.41
5	136.74 128.81 127.64	70.77	70.77 69.73	141.55 122.05	63.56	70.77 69.54	134.14 133.75	64.80	70.71 69.21
6	136.67 128.81 127.71	70.97	70.71 69.73	–	–	–	134.14 133.81	64.80	70.71 69.15

*δ(CH₃) 12.86–13.00 ppm

PMR spectroscopy allowed us to distinguish between 1:1 reaction products, 2:2 reaction products and products of higher molecular weight on the basis of the relative positions of the adsorption peaks of the benzylic protons. In all cases the absorption was at lower field for the 1:1 reaction product than for the 2:2 reaction product ($\Delta\delta = 0.05$–0.15 ppm) and for the products of higher molecular weight (Fig. 3a). The chemical shifts of the aromatic protons and of the methylene protons of the polyether ring were very similar for all the cyclic products

Table 7. ^{13}CMR data of crown ethers 4(X=CH=CH) and 11(X=O)

n	4			11		
	δ(C$_{arom.}$)	δ(CH$_2$ benzylic)	δ(CH$_2$CH$_2$O)	δ(C$_{arom.}$)	δ(CH$_2$ benzylic)	δ(CH$_2$CH$_2$O)
0	136.87 128.81 127.68	71.16	70.84 69.73	141.55 122.51	63.69	70.84 69.67
1	136.80 128.44 127.77	71.10	70.90 69.80	141.55 122.05	63.63	70.77 69.53
2	136.67 128.81 127.77	70.97	70.77 69.37	141.68 121.92	63.56	70.64 69.41

(i) Reaction of I with triethyl-
ene glycol

(ii) Reaction of I with hexaethyl-
ene glycol
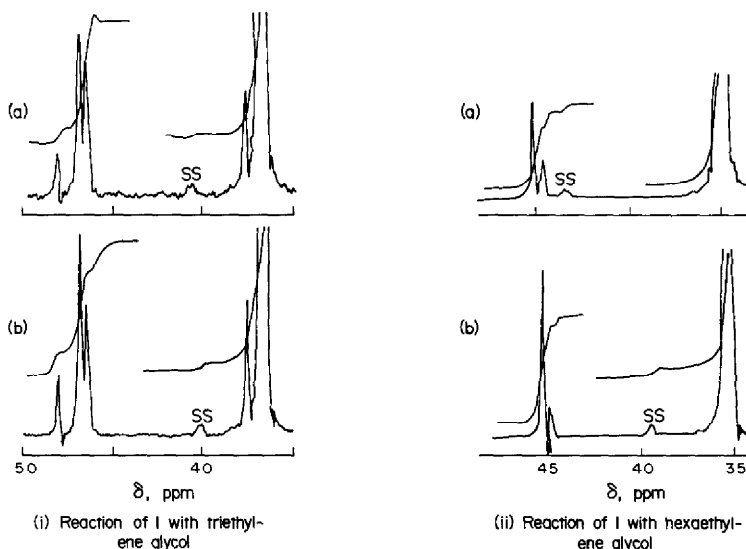
Fig. 3a. PMR spectra of reaction mixtures of 1,2-bis(bromomethyl)benzene with (i) triethylene glycol and with (ii) hexaethyleneglycol. (a) crude reaction product; (b) after chromatography.

of one particular reaction. In products containing large rings (>20 atoms) the methylene protons of the polyethylene glycol chain were magnetically almost equivalent, but in compounds with smaller rings they were different (e.g. Fig. 3b).

More detailed information about the polyether ring was provided by ^{13}CMR spectroscopy. All the C atoms of the smaller rings proved to have different absorptions (Fig. 4). However, with increasing ring size the signals of the individual carbon atoms gradually collapsed to a single absorption. The relevant data of these spectra are summarized in Tables 6 and 7. The benzylic carbon atoms in 3 and 4 showed an absorption between 71 and 73 ppm, in agreement with that of some benzyl ethers (e.g. 72.01 ppm for dibenzyl ether and 72.92 ppm for benzyl butyl ether). The absorptions of the other polyether carbon atoms were in line with those of the corresponding glycols.

DISCUSSION

The most significant result of this work is the fact that the yields of the 1:1 and in some cases of the 2:2 cyclic reaction products as well are exceptionally high considering the concentrations of the reactants and the ring size of the products. On the basis of results of other cyclization reactions one would expect yields lower than 1%. The fact that one of the reactants, the dihalide, has the preferred rigid *cis* configuration might be partially responsible because it is known that macrocyclic esters from *o*-phthalic acid and 1,2-bis(bromomethyl)-benzene can be obtained in reasonably high yields (3–13%).[26] However, a model reaction of 1,2-bis(bromomethyl)benzene with dipotassium dodecane-1,12-diol performed under the same conditions failed to give any 1:1 cyclic reaction product.

In 1972 Greene[4] and Dale *et al.*[5] suggested that such unexpectedly high yields of crown ethers might be explained by a "template" effect of the particular cation in the cyclization step. They based their assumptions on the finding that the highest yields of 18-crown-6 and 21-crown-7 were obtained by the solvolysis of ditosylates with di*potassium* polyethylene glycolates; it was also shown that the resulting crown ethers form the most stable crown ether complexes with potassium salts. On
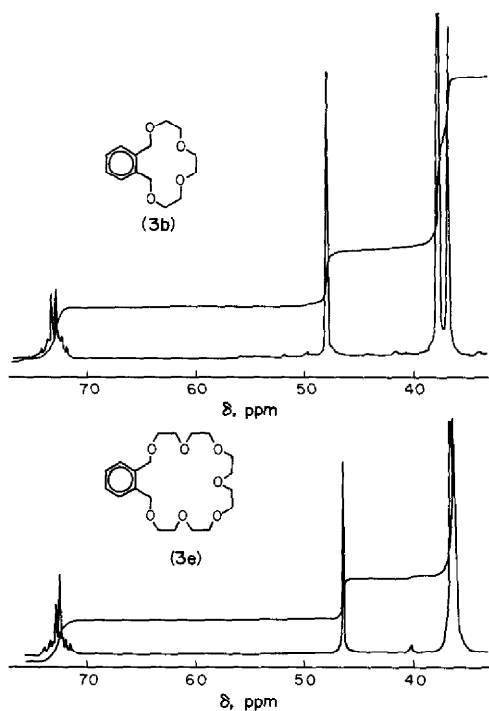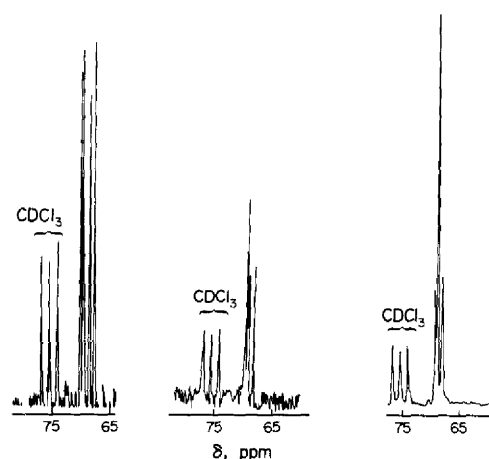
Fig. 3b. PMR spectra of crown ethers 3b and 3e.

Fig. 4. ^{13}CMR spectra of crown ethers 3b, 3c and 3e in CDCl$_3$
(polyethylene ring signals)

Table 8. Reactions of 1,2-bis(bromomethyl)benzene (1) with
dipotassium hexaethylene glycolate with variation of addition time

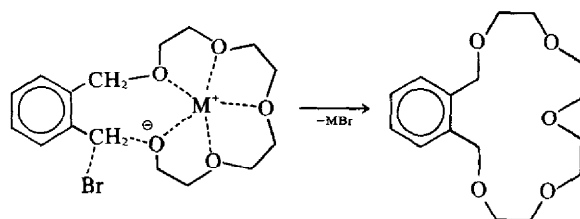| Addition time [a]	Prod. distribution [b], %		
	3e	4e	High mol. wt. prod.
<10 s	60	3	37
1 h	63	3	34
2 h	60	3	37

a) Of dibromide 1.

b) Calculated from PMR spectroscopy.

glycolate dialkoxides and found that the yields of 3 (and 4)
were greatly dependent on the combination of cation and
chain length of the particular glycol. Figure 5 shows that
the 1:1 selectivity, which is defined as the ratio of the
yield of 3 to the yield of all the other products formed,
reaches different maxima with different cations. For
lithium the maximum value for the 1:1 selectivity of 3 is
obtained with triethylene glycol (ring size 14), for sodium
with tetraethylene glycol (ring size 17) and for potassium
with pentaethylene glycol (ring size 20). Considering the
diameters of the crown ethers (CPK models)† and the
ionic radii the results point very strongly to a "template"
effect of the cation during the cyclization step (Scheme 3).

Secondly, in one particular reaction (with 1 and 2e) we
extended the period of addition of the dibromide to the
dipotassium hexaethylene glycolate from less than 10 sec
to 2 hr. As can be seen from Table 8, this had very little
effect on the yield of the reaction. This means that
although we created a situation which statistically favours
the *inter*molecular over the *intra*molecular reaction the
results are the same. Since both reactions involve the
nucleophilic displacement of a benzyl bromide by
alkoxide, we conclude that the rate of the second
(intramolecular) substitution is much faster than that of
the first (intermolecular) substitution. There are two
factors that may favour the occurrence of the in-
tramolecular reaction. First, there might be an enhanced
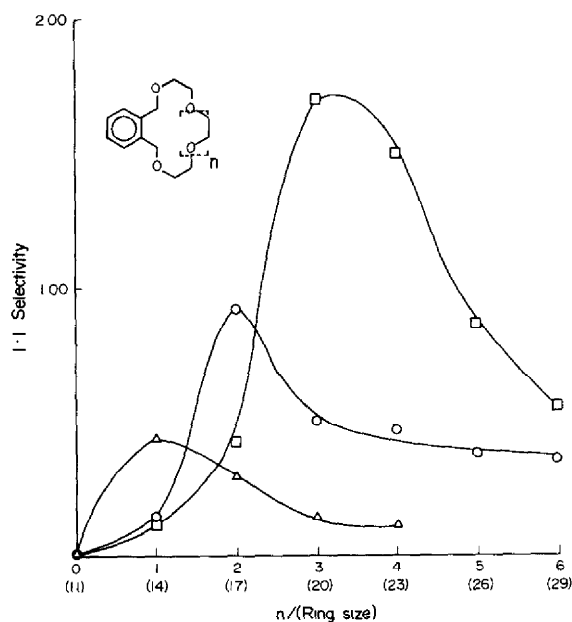
Fig. 5. 1:1 Selectivity of the reactions of 1,2-bis(bromo-
methyl)benzene and polyethylene glycolates (Li$^+$, Na$^+$, K$^+$). △,
lithium; ○, sodium; □, potassium.

the other hand, it has been demonstrated that complexes
of cations with *linear* polyethers are far less stable (by
several powers of 10) than those with *cyclic* polyethers of
the appropriate size.[27] In addition, other macrocycles, e.g.
cyclic polyamines have recently been obtained in high
yields from concentrated solutions under reaction condi-
tions that preclude the occurrence of a template effect.[28]
It thus remained unclear what factors are responsible for
the high yields of macrocyclic compounds in particular
cases.

Therefore, we investigated several reaction parameters
of the cyclization reaction in more detail. Firstly, we
studied   a   number   of   reactions   of   1,2-
bis(bromomethyl)benzene (1) with various polyethylene

†Corey-Pauling-Koltun models.

Scheme 3.

contribution of the activation entropy ($\Delta S^{\ddagger}$), which lowers the free energy of activation ($\Delta G^{\ddagger}$), and secondly, there might be a decrease in activation enthalpy due to a higher nucleophilicity of the alkoxide ion as a result of the formation of a charge-separated ion pair. Both arguments point to a highly rigid conformation of an intermediate complex (the so-called "pre-crown ether" complex) between the polyethylene glycol chain and the cation.

In another series of experiments (with 1 and 2c) the addition time was kept constant ($\leqslant 10$ s) and the initial concentrations were reduced from 0.2 to 0.025 M. Table 9 shows that, as might be expected, the total yield of cyclic product increased with decreasing concentration. However, the 1:1 selectivity remained constant. This means that the relative rates of the intra- and inter-molecular nucleophilic displacements of the second bromomethyl group are almost independent of the initial concentration (Table 9).

Should the high yields indeed be due to complexation of the "pre-crown ether" with the cation of the base, then the yields of cyclic products might be expected to depend on the relative complexation constants of the "pre-crown ethers". Since in the transition state of the cyclization reaction the conformation of the polyether chain will be very close to that of the resulting crown ether, the relative rates of formation of the 1:1 and 2:2 cyclic products will be related to the respective complexation constants of the final crown ethers with the same cation.

In one particular case, namely the reaction of 1 with dipotassium triethylene glycolate, the yields of the isolated 1:1 and 2:2 cyclic reaction products 3b and 4b were 8% and 24%, respectively. The relative complexation constants of the two crown ethers 3b and 4b with potassium ions were determined by a new method† and found to be 0.43 and 1.5, respectively. Furthermore, the ratio of the yields of the 1:1 cyclic adducts of different glycols is also in line' with the ratio of the relative complexation constants. The yields of 3b (from dipotassium triethylene glycolate) and of 3c (from dipotassium tetraethylene glycolate) were 8 and 24%, respectively, and

Table 9. Reaction of 1,2-bis(bromomethyl)benzene (1) with dipotassium tetraethylene glycolate in toluene[a]

Molar conc.	Prod. distribution[b], %		
	3c	4c	High mol. wt. products
0.2	26	23	51
0.1	27	24	49
0.05	27	34	39
0.025	26	42	32

a) Addition time of 1 ≤ 10 s.
b) Calculated from PMR spectroscopy.

†In this method, recently developed by us, Zeise's salt is used as the potassium salt.[29]

the ratio of the relative complexation constants with Zeise's salt was 0.17.

In view of the above we conclude that the high yields of crown ethers in our synthesis may very well be due to a template effect of the cation in the cyclization step.

For crown ethers with cavities much larger than the ionic radius of the cation present in the base we would expect very low yields. The results, as depicted in Fig. 5, however, show a surprisingly slow decrease of the selectivity for the higher polyethylene glycols. A possible explanation for this phenomenon was provided by the complexation experiments with Zeise's salt.[30] It was found that in the complex of the larger crown ethers the polyether ring folded itself around the potassium ion in a twisted conformation. This might also be the case in the cyclization step of the synthesis. The two reactive centres are directed towards each other although the cation is small relative to the diameter of the crown ether formed.

EXPERIMENTAL

PMR and ¹³CMR spectra were recorded on a Bruker WH90 instrument in deuteriochloroform with TMS as the internal reference compound.

IR spectra were obtained on a Perkin Elmer 457 spectrometer.

The mass spectra of all the compounds were recorded on an AEI-MS 902 spectrometer. In all cases they featured a parent peak and a fragmentation pattern in agreement with the proposed structures.

Reactions of 1,2-bis(bromomethyl)benzene (1) with polyethyleneglycolates (2). A soln of 2 (0.04 mol) in 300 ml toluene was stirred at 30–60° for 1 hr with freshly sublimed t-BuOK (9.40 g; 0.084 mol) or with NaH (2.16 g; 0.09 mol) in an atmosphere of dry argon. Subsequently the nearly homogeneous soln was cooled to room temp and a soln of 1 (10.56 g; 0.04 mol) in 100 ml dry toluene was added in one portion. This mixture was heated at 60° for 4 hr and then cooled down to 0°. The ppt formed was filtered off and the filtrate concentrated to a small volume. The residue was dissolved in THF. Chromatography over neutral alumina (160 g) with THF as the eluent yielded an oil, which was fractionated at 1 Pa. The results of these experiments are given in Table 1a. The PMR and ¹³CMR data of products 3 and 4 are summarized in Tables 4–7.

Reaction of 1,2-bis(chloromethyl)benzene with disodium tetraethylene glycolate. A soln of tetraethylene glycol (7.75 g; 0.04 mol) in 300 ml toluene was stirred at 60° for 1 hr with NaH (2.16 g; 0.09 mol) in an atmosphere of dry argon. Subsequently 1,2-bis(chloromethyl)benzene (7.00 g; 0.04 mol), dissolved in 100 ml toluene, was added. The resultant mixture was heated at 110° for 16 hr and then cooled down to 0°. The NaCl (4.70 g) was filtered off and the filtrate was concentrated to give 10.7 g (90%) of oil. Distillation at 1 Pa afforded a fraction at 160° of 3c (4.03 g; 34%) as a colourless oil.

Reaction of 1,2-bis(bromomethyl)benzene with dilithium polyethylene glycolates. A soln of 2 (0.02 mol) in 150 ml toluene was stirred for 1 hr under argon at room temp with BuLi (0.044 mol; 20% in n-hexane). Subsequently a soln of 1,2-bis(bromomethyl)benzene (5.28 g, 0.02 mol) in 50 ml toluene was added. The mixture was heated at reflux temp for 72 hr and then cooled down to 0°. A cream-coloured solid was filtered off, which was suspended in water (50 ml). This suspension was extracted

with chloroform. The combined extracts were dried over $MgSO_4$ and subsequently the filtrate was concentrated to a small volume to give an oil. The composition of the crude products and the yields are summarized in Table 1b. In the case of triethylene glycol the oil was distilled at 1 Pa to give 1.26 g (25%) of 3,4-benzo-1,6,9,12-tetraoxacyclotetradec-3-ene **3b** as a colourless oil, b.p. ~ 150°.

Reaction of disodium 1,2-bis(hydroxymethyl)benzene (15) with triethylene glycol ditosylate (16b). A soln of 1,2-bis(hydroxymethyl)benzene (1.38 g; 0.01 mol) in 75 ml toluene was heated with NaH (0.50 g; 0.021 mol) in 75 ml dry toluene for 1 hr at 50°. Subsequently, a soln of triethylene glycol ditosylate (4.58 g; 0.01 mol) in 25 ml dry toluene was added and the mixture was heated for 16 hr at reflux temp. After cooling down to room temp, the sodium *p*-toluenesulphonate was filtered off, the ppt washed with toluene and the filtrate concentrated. Chromatography over neutral alumina with THF as the eluent afforded 2.4 g (95%) of an oil. Distillation at 1 Pa yielded **3b** (0.18 g; 7%) boiling at 160°, and **4b** (0.45 g; 19%), boiling at 250°.

Reaction of 1,2-bis(chloromethyl)-4,5-methylene dioxybenzene (5) with dipotassium hexaethylene glycolate. A soln of dipotassium hexaethylene glycolate (0.01 mol) in 75 ml benzene was prepared as described above at 60°. To this soln **5** (2.18 g; 0.01 mol) dissolved in 25 ml toluene was added and this resultant mixture was heated under argon at 100° for 4 hr. The mixture was cooled to 0°, the KCl filtered off and the filtrate evaporated to give 3.91 g of an oil. Chromatography over alumina in THF and subsequent distillation at 1 Pa yielded **8b** (1.07 g; 25%).

Similarly, **8a** was prepared from **5** and dipotassium and disodium tetraethylene glycolate in yields of 19 and 29%, respectively. **8a**; PMR spectrum ($CDCl_3$): $\delta(H_{arom})$ 6.899 ppm, $\delta(OCH_2)$ 5.924 ppm, $\delta(CH_{2\,benzylic})$ 4.623 ppm, $\delta(CH_2CH_2O)$ 3.713 and 3.667 ppm. ^{13}CMR spectrum ($CDCl_3$): $\delta(C_{arom})$ 146.94, 130.76 and 109.12 ppm, $\delta(O\underline{C}H_2O)$ 100.93 ppm, $\delta(\underline{C}H_{2\,benzylic})$ 71.29 ppm, $\delta(\underline{C}H_2CH_2O)$ 71.03, 70.58 and 69.54 ppm. **8b**; PMR spectrum ($CDCl_3$): $\delta(H_{arom})$ 6.876 ppm, $\delta(OCH_2)$ 5.917 ppm, $\delta(CH_{2\,benzylic})$ 4.571 ppm, $\delta(CH_2CH_2O)$ 3.667 ppm. ^{13}CMR spectrum ($CDCl_3$): $\delta(C_{arom})$ 147.01, 130.76 and 109.64 ppm, $\delta(O\underline{C}H_2O)$ 100.99 ppm, $\delta(\underline{C}H_{2\,benzylic})$ 70.84 ppm, $\delta(\underline{C}H_2CH_2O)$ 70.84 and 69.60 ppm.

Reactions of 3,4-bis(chloromethyl)furan (6) with polyethylene glycolates. Solns of disodium or dipotassium polyethylene glycolates (0.04 mol) in 300 ml toluene were prepared as described. To each soln **6** (6.60 g; 0.04 mol) dissolved in 100 ml toluene was added in one portion and the mixture was stirred for 16 hr. Filtration of the ppt and concentration of the filtrate yielded an oil, which was fractionated at 1 Pa to give compounds **9** and (for the lower glycols) **11**. The results are given in Table 2. The PMR and ^{13}CMR data are presented in Tables 4-7.

Reactions of 3,4-bis(chloromethyl)-2,5-dimethylthiophene (7) with polyethylene glycolates. Solns of disodium or dipotassium polyethylene glycolates (0.05 mol) in 300 ml toluene were prepared as described. To each soln **7** (10.40 g; 0.05 mol) was added and the reactions were carried out as described for 3,4-bis(chloromethyl)furan. The results are given in Table 3. The spectroscopical data are presented in Tables 4 and 6.

Reaction of [3,4-c]furo-1,6,9,12,15-pentaoxacycloheptadec-3-ene (9c) with dimethyl acetylenedicarboxylate. A mixture of **9c** (1.43 g; 5.0 mmol) and dimethyl acetylenedicarboxylate (0.71 g; 5.0 mmol) in 20 ml toluene was refluxed for 16 hr under argon. Evaporation of the solvent yielded an oil, which was shown to be the Diels-Alder adduct **14**. On attempted distillation at 1 Pa **14** decomposed at 250° into **9c** and dimethyl acetylenedicarboxylate. PMR spectrum of **14** ($CDCl_3$): $\delta(H_{furyl})$ 5.625 ppm, $\delta(H_{benzylic})$ 4.533 ppm, $\delta(COOCH_3)$ 3.833 ppm. $\delta(CH_2CH_2O)$ 3.667 ppm.

Variation of the concentration of the reactions in the reaction of 1,2-bis(bromomethyl)benzene (1) with dipotassium tetraethylene glycolate. Mixtures of solns of dipotassium tetraethylene glycolate (0.01 mol) and **1** (0.01 mol) in toluene in concentrations of 0.2-0.025 M were reacted for 1 hr at 60°. The crude products were separated into three fractions by chromatography over alumina with THF as the eluent, followed by high-vacuum fractionation at 150° and 200° at 1 Pa. The results are given in Table 9.

Reactions of 1,2-bis(bromomethyl)benzene (1) with dipotassium hexaethylene glycolate with variation of the addition time of 1. A soln of **1** (1.32 g; 5.01 mmol) in 25 ml toluene was added at a constant rate to a soln of dipotassium hexaethylene glycolate (5.0 mmol) in 25 ml toluene (prepared in the usual manner) at 50-60°. Three experiments were performed with different rates of addition of **1** (∞ to 12 ml/hr). The reactions were complete 5 min after the end of the period of addition. The products were separated in the usual way. The results are given in Table 8.

REFERENCES

[1a]C. J. Pedersen and H. K. Frensdorff, *Angew. chem.* **84**, 16 (1972); [b]C. J. Pedersen. *J. Am. Chem. Soc.* **89**, 7017 (1967); [c]C. J. Pedersen, *Ibid.* **92**, 386 and 391 (1970).

[2a]H. K. Frensdorff, *Ibid.* **93**, 600 (1971); [b]H. K. Frensdorff, *Ibid.* **93**, 4684 (1971).

[3]J. J. Christensen, D. J. Eathough and R. M. Izatt, *Chem. Rev.* **74**, 351 (1974).

[4]R. N. Greene, *Tetrahedron Letters* 1793 (1972).

[5a]J. Dale and P. O. Kristiansen, *Acta Chem. Scand.* **26**, 1471 (1972); [b]J. Dale, P. O. Kristiansen, *J. Chem. Soc.* Chem. Comm. 670 (1971).

[6]A. C. Coxon and J. Fraser Stoddardt, *Ibid.* Chem. Comm. 537 (1974).

[7]C. G. Krespan, *J. Org. Chem.* **39**, 2351 (1974).

[8]H. Feuer and J. Hooz, *Chemistry of the Ether Linkage*, (Edited by S. Patai), p. 445. Interscience, London (1967).

[9]J. Dale, G. Borgen and K. Daasvaten, *Acta Chem. Scand.* **B28**, 378 (1974).

[10]J. Cooper and P. H. Plesch, *J. Chem. Soc.* Chem. Comm. 1017 (1974).

[11]D. Bright and M. R. Truter, *Nature* **225**, 176 (1970).

[12]M. R. Truter, *Structure and Bonding*, Vol. 16, p. 71, Springer-Verlag, Berlin (1973).

[13]D. Leibfritz, *Tetrahedron Letters* 4125 (1974).

[14a]D. J. Sam and H. E. Simmons, *J. Am. Chem. Soc.* **94**, 4024 (1972); [b]C. L. Liotta and H. P. Harris, *Ibid.* **96**, 2250 (1974).

[15a]M. Makosza and H. Ludwikow, *Angew. Chem.* **86**, 744 (1974); [b]D. Landini, F. Montanari and F. M. Pirisi, *J. Chem. Soc.* Chem. Comm. 879 (1974).

[16]U. Takaki, T. E. Hogen Esch and J. Smid, *J. Phys. Chem.* **76**, 2152 (1972).

[17]S. Boileau, B. Kaempf, J. M. Lehn and F. Schué, *Polymer Letters* **13**, 203 (1974).

[18]M. J. Maskornick, *Tetrahedron Letters* 1797 (1972).

[19]J. L. Dye, M. G. De Backer and V. A. Nicely, *J. Am. Chem. Soc.* **92**, 5226 (1970).

[20a]D. J. Cram and J. M. Cram, *Science* **183**, 803 (1974); [b]L. R. Sousa, D. H. Hoffman, L. Kaplan and D. J. Cram. *J. Am. Chem. Soc.* **96**, 7100 (1974).

[21]J. W. Cornforth, E. D. Morgan, K. T. Potts and R. J. W. Rees, *Tetrahedron* **29**, 1659 (1973).

[22]*Br. Pat.* 911, 211. Merck & Co., Inc.

[23]R. Gaertner and R. G. Tonkyn, *J. Am. Chem. Soc.* **73**, 5872 (1951).

[24a]W. Bonthrone and J. W. Cornforth, *J. Chem. Soc.* (C), 1202 (1969); [b]J. W. Cornforth, private communication.

[25]R. T. Gray, D. N. Reinhoudt, K. Spaargaren and Ms. J. F. de Bruyn, to be published.

[26a]S, E, Drewes and P. C. Coleman, *J. Chem. Soc.* Perkin I, 2148 (1972); [b]S. E. Drewes and B. G. Riphagen, *Ibid.* Perkin I, 323 (1974).

[27]J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel and D. J. Cram, *J. Am. Chem. Soc.* **96**, 7097 (1974).

[28]J. E. Richman and T. J. Atkins, *Ibid.* **96**, 2268 (1974); and ref. therein.

[29]R. T. Gray and D. N. Reinhoudt, *Tetrahedron Letters* 2109 (1975).

[30]D. N. Reinhoudt, R. T. Gray, F. de Jong and C. J. Smit, to be published.