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The Synthesis and Complexation of Open Chain Polyethers having Various End Groups

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The syntheses of a series of oxygen containing ligands of general formula o-$ROC_6H_4O(CH_2CH_2O)_n$-oC_6H_4OR' *are described; the complex formation of these ligands with alkali and alkaline earth metal cations has been investigated. Stability constants for sodium and potassium increase as n is increased from 1 to 3, as R is varied through the series, H,* $CH_2C_6H_5$, CH_2CH_2OH, $CH_2CO_2C_2H_5$, CH_2CO_2H. *When R and R' are different, the stability constant is intermediate between that found when both end groups are R and that when both are R'. In these compounds there is no evidence for the presence of internal hydrogen bonding contributing to the stability of the complexes.*

Introduction

Pedersen's synthesis of crown polyethers and his discovery that these oxygen ligands form complexes with alkali and alkaline earth metals [1] stimulated great interest in cyclic ligands where the oxygen atoms are able to form a cavity to provide a coordination sphere for cations.

Selectivity between the alkali metals is achieved by varying the size of the cavity, and these ligands mimic the neutral cyclic antibiotics such as nonactin [2]. Non-cyclic polyethers with hydroxy end groups, IIIa, IVa and Va of Fig. 1 were used by Pedersen as intermediates in synthesis of the cyclic ethers. He postulated [3] that their wrapping round sodium facilitated ring closure as in a template reaction. Non-cyclic polyethers themselves are of interest as possible analogues of antibiotics such as monensin and nigericin. Monensin is a monobasic acid and may complex either in the deprotonated form, as in the sodium salt mon$^-$Na$^+$ [4], or as the free acid as in its complex with sodium bromide, mon H·NaBr [5]. In both structures, intramolecular hydrogen bonding between a hydroxyl and a carboxy end group of the ligand help to hold it in a cyclic conformation round the metal ion. The synthetic diacid $CO_2HC_6H_4O[CH_2CH_2O]_4C_6H_4CO_2H$ shows no dissociation of the carboxylic protons on complexation with potassium and calcium salts, and it was suggested that there is intramolecular hydrogen bonding between the carboxyl groups, thus showing similarities to monensin [6]. Solution studies have also indicated that α-carboxy, ω-hydroxy open chain polyethers are much more effective alkali cation transporters than α,ω-dihydroxy polyethers, and suggest that the carboxy group is essential [7]. In this laboratory we studied the complexation of dicarboxyclic acids of the form $RC_6H_4O(CH_2CH_2O)_n$-

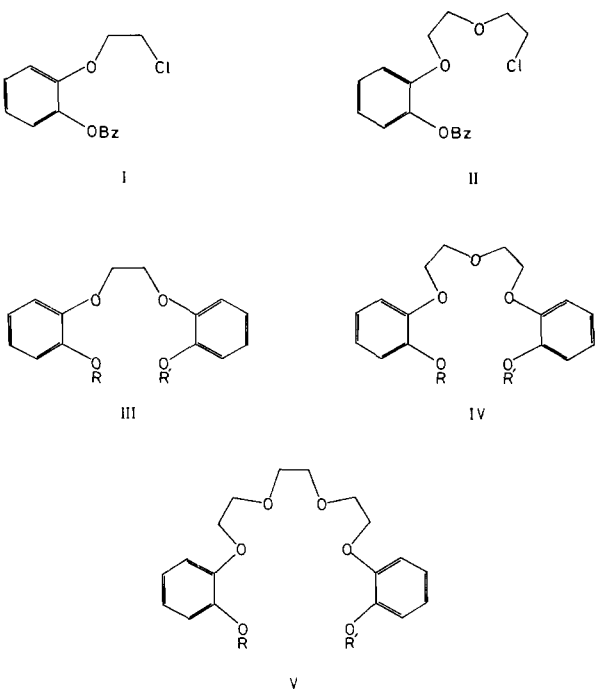

Fig. 1. a, R = R' = H; b, R = R' = $CH_2C_6H_5$ (Bz); c, R = R' = CH_2CO_2H; d, R = R' = $CH_2CO_2C_2H_5$; e, R = R' = CH_2CH_2OH; f, R = R' = $CH_2CH_2OCH_3$; g, R = $CH_2C_6H_5$, R' = CH_2CO_2H; h, R = H, R' = CH_2CO_2H; i, R = H, R' = $CH_2CO_2C_2H_5$.

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C_6H_4R (R = OCH_2CO_2H) and found that when n = 2, IVc, there is no dissociation of the carboxylic protons in the sodium and potassium picrate complexes [8]. The crystal structure of the potassium picrate complex however showed that although the ligand adopts a shallow helix around the cation, the molecule is a dimer where one carbonyl group from each ligand bridges the two potassium atoms [9]. There is no hydrogen bonding holding the two ends of the ligand together and the conformation of the ligand is held by ion-dipole interaction. We have similarly found that the sodium and potassium thiocyanate complexes of the diol $RC_6H_4OCH_2CH_2OC_6H_4R$ (R = OCH_2CH_2OH) IIIe, encircle the metal ions without exhibiting any intramolecular hydrogen bonding [10]. In this paper, we report the synthesis of a series of hydroxyacids of the form $RC_6H_4O(CH_2CH_2O)_nC_6H_4OH$ (R = OCH_2CO_2H) and also compare the stability constants of this series with those containing symmetrical end-groups. Labelling of the ligands is as indicated in Fig. 1.

Experimental

Preparation of I

o-Benzyloxyphenol (60 g) and 1,2-dichloroethane (180 g) were refluxed together in *n*-butanol (100 ml) with stirring. Sodium hydroxide pellets (24 g) were added portionwise during 30 minutes when the solution slowly became brown. Reflux was continued for 16 hr during which time a sodium chloride precipitate was formed. The solution was cooled to room temperature and sodium chloride removed by filtration. The filtrate was distilled under vacuum to give a mixture of unreacted *o*-benzyloxyphenol and product. This mixture was dissolved in chloroform (200 ml) and treated with sodium hydroxide pellets (12 g) in water (100 ml). A white precipitate of the sodium salt of *o*-benzyloxyphenol was formed, and this was removed by filtration. The chloroform layer was concentrated on a rotary evaporator, and the product fractionally distilled under vacuum to give a colourless liquid, b.p. 195–6 °C at 6 mm. Yield 37 g, 47%. II may similarly be prepared, b.p. 218–9 °C at 1 mm, yield 34%, and recrystallisation from diethyl ether/60–80 petrol ether gives colourless needles, m.p. 44 °C. *Anal.* $C_{17}H_{19}ClO_3$ requires: C, 66.55; H, 6.24. Found: C, 66.65; H, 6.31%.

Preparation of IIIg

I (26 g) and *o*-hydroxyphenoxyacetic acid (16.8 g) were heated together with stirring in dimethylsulphoxide (200 ml) at 90 °C. Sodium hydroxide pellets (8.1 g) in water (15 ml) were added at a rate to keep the temperature as nearly constant as possible as reaction took place. The solution became darker, and a white precipitate formed. Reaction was continued for 5 hr during which time the precipitate disappeared. The reaction mixture was cooled to room temperature, poured onto iced 4 *N* hydrochloric acid, and allowed to stand overnight. A buff solid was formed which was recrystallised from di-*n*-butyl ether to give small fluffy white needles, m.p. 134 °C, yield 17 g, 44%. *Anal.* $C_{23}H_{22}O_6$ req.: C, 70.04; H, 5.62. Found: C, 70.07; H, 5.72%. Similarly prepared as an oil was IVg yield 49% which exhibited a satisfactory ^1H NMR in $CDCl_3$ (CO_2H singlet 0.2, C_6H_5 multiplet 2.68, C_6H_4's singlet 3.14, CH_2-C_6H_5 singlet 4.93, CH_2CO_2H singlet 5.5, CH_2–CH_2 multiplet centred at 6.0). This product was used in the next step without further purification.

Preparation of IIIh

IIIg (15.5 g) was refluxed in ethyl alcohol (100 ml) with vigorous stirring in the presence of 5% palladium on charcoal (0.4 g) under a stream of hydrogen. Hydrogen uptake was rapid, and the reaction proceeded to completion in 1 hr. The solution was filtered hot, and alcohol removed on a rotary evaporator to give an oil. This was dissolved in diethyl ether/hexane to give colourless crystals, m.p. 123–5 °C, yield 9.3 g, 78%. $C_{16}H_{16}O_6$ requires: C, 63.15; H, 5.30; M, 304.3. Found: C, 63.15; H, 5.44%. X-ray M. Wt. 300.0.

IVh may similarly be obtained as an oil, and may be purified by treatment with potassium thiocyanate in methanol when the potassium thiocyanate complex separates and recrystallisation from methanol gives colourless crystals of the methanolate, m.p. 154–8 °C (loses solvent above 140 °C). $C_{18}H_{20}O_7 \cdot KSCN \cdot MeOH$ requires: C, 50.3; H, 5.01; N, 2.9. Found: C, 50.1; H, 5.10; N, 3.27%. The free ligand may be regenerated by boiling the complex in water and extracting into chloroform. Removal of solvent and recrystallisation from diethyl ether/cyclohexane gives the free ligand IV m.p. 95 °C. $C_{18}H_{20}O_7$ requires: C, 62.06; H, 5.79. Found: C, 61.95; H, 5.84%.

Vh may similarly be prepared in low yield (overall 5%) by preparing $BzOC_6H_4O(CH_2CH_2O)_2CH_2CH_2Cl$ as an oil, converting this to Vg by reaction with *o*-hydroxyphenoxyacetic acid and subsequent debenzylation of the oil. Recrystallisation from diethyl ether/cyclohexane gives a white solid, m.p. 78–9 °C. $C_{20}H_{24}O_8$, requires: C, 61.21; H, 6.16. Found: C, 60.94; H, 6.33%.

Preparation of Vh was also accompanied by some esterification of the carboxyl group. It was then necessary to hydrolyse with sodium hydroxide, reacidify, and then complete the hydrogenation. This, together with the use of an unpurified intermediate, Vg, contributes to the low yields.

Better yields of IVh and Vh may be obtained direct from the diol as indicated below.

TABLE I. Analytical Data.

Complex		Solvent	M.p. (°C)	Analysis					
				req.			found		
				C	H	N	C	H	N
IVb	$NaBPh_4$	methanol	215	79.81	6.19		79.37	6.11	
Vb	$NaBPh_4 \cdot MeOH$	methanol	57–9	77.02	6.58		77.23	6.67	
IVc	K picrate	methanol	148–9	46.36	3.59	6.24	46.22	3.59	6.81
IVc	Na picrate$\cdot H_2O$	methanol/ethylacetate		46.23	3.88	6.22	46.61	3.94	6.77
IVc	$KCl \cdot H_2O$	methanol	160	48.15	4.61		48.35	4.87	
IVc	RbNCS	methanol	165–70	46.58	4.00	2.52	46.03	4.22	3.02
IVc	RbBr	ethanol	188–91	42.02	3.88		42.09	3.92	
IIIe	$Ca(NCS)_2$	ethyl acetate	dec >250	48.97	4.52	5.71	49.16	4.68	5.86
IIIe	NaNCS	ethyl acetate	125	54.94	5.34	3.37	54.99	5.44	3.43
2IIIe	$KNCS \cdot \frac{1}{2}CHCl_3$	chloroform/carbon tetrachloride	109–10	54.56	5.43	1.70	54.57	5.73	1.69
IVe	KNCS			53.05	5.51	2.95	53.17	5.69	2.68
IVe	$Ca(NCS)_2$	ethyl acetate	235–7	49.43	4.90	5.24	49.39	5.10	5.31
IVf	$NaBPh_4$	methanol	140	73.8	6.68		73.15	6.89	
IVf	KNCS		97	54.85	6.01	2.78	55.00	6.02	2.61
IVh	KNCS·MeOH	methanol	154–8	50.3	5.01	2.93	50.1	5.10	3.27
IVi	KNCS	acetone/cyclohexane	121–2	53.27	5.11	2.96	53.23	5.19	3.19
IVi	$Ca(NCS)_2$	ethyl acetate	195–8	49.63	4.54	5.26	49.47	4.78	5.26

Alternative Preparation of IVh, *2-(o-Hydroxyphenoxy)2'-[o-(carboxymethoxy)phenoxy)] diethylether*

The diol, IVa, (5.0 g) in water (10 ml) was dissolved by addition of the minimum amount of 30% aqueous sodium hydroxide solution. Chloroacetic acid (1.0 g) was added and the precipitate which formed redissolved by addition of a little more sodium hydroxide solution; this mixture was stirred at 90–100 °C for 40 min. After cooling, the solid product was acidified (5 *N* HCl), the resulting product collected, and shaken with sodium bicarbonate solution. The filtrate, on acidification yielded a gummy product; this was extracted with dichloromethane to yield an orange oil. This oil was dissolved in ether and filtered to remove the dicarboxylic acid which separated and the filtrate concentrated to yield an orange oil which crystallised on standing. Extraction with a hot mixture of cyclohexane and ether removed the hydroxy acid which crystallised on cooling, yielding 1.3 g of product, m.p. 93–95 °C. The sodium bicarbonate insoluble material yielded 2.9 g of unchanged diol.

Esterification of the carboxylic acid groups is performed using concentrated sulphuric acid in ethanol, and a typical preparation is described below.

Preparation of IVd

Sulphuric acid (2 ml) in ethanol (20 ml) was added dropwise to a stirred refluxing solution of IVc (75 g) in ethanol (100 ml) and reaction continued for 2 hr. The resulting solution was cooled to room temperature and poured into iced cold excess aqueous sodium bicarbonate solution. The resultant precipitate was collected on a sinter, washed well with water and recrystallised from cyclohexane (50 ml) to give colourless crystals, m.p. 43–4 °C, yield 66 g 77%. $C_{24}H_{30}O_9$ req.: C, 62.32; H, 6.54. Found: C, 62.39; H, 6.62%. In similar reactions IIId is obtained as colourless needles, m.p. 106 °C, yield 92%. $C_{22}H_{26}O_8$ req.: C, 63.16; H, 6.22. Found: C, 63.15; H, 6.27%; Vd as a colourless oil (characterised by ^1H NMR in $CDCl_3$; CH_3 triplet 8.69, CH_2CH_3 quartet 5.65, CH_2CO_2 singlet 5.21, CH_2–CH_2's multiplet 5.65, 6.14, C_6H_4's singlet 2.91), and IVi as a colourless oil (characterised by ^1H NMR in $CDCl_3$). IVi is further characterised by formation of its potassium thiocyanate complex in methanol, which on recrystallisation from acetone/cyclohexane gives a fluffy white solid, m.p. 121–2 °C. IVi·KSCN req.: C, 53.27, H, 5.11; N, 2.96. Found C, 53.23; H, 5.19; N, 3.19%.

Treatment of IVi with calcium thiocyanate in ethyl acetate gives a white solid, m.p. 195–8 °C. Found: C, 49.47; H, 4.78; N, 5.26. IVi·$Ca(NCS)_2$ requires: C, 49.63; H, 4.54; N, 5.26%.

The groups $OCH_2CO_2C_2H_5$ were reduced to OCH_2CH_2OH by using lithium aluminium hydride in diethyl ether, and a representative reaction is described below.

TABLE II. Log_{10} Stability Constants Measured in Methanol at 25 °C with Sodium and Potassium Bromides.[a,b]

Ligand	Metal	
	Na^+	K^+
IVa		1.09
IIIc	–	2.23
IVc	2.21	3.07
Vc	2.30	3.21
IIId	1.48	2.09
IVd	1.89	2.79
Vd	2.38	3.42
IIIe	1.42	1.74
IVe	1.39	2.23
IIIh	1.48	1.55
IVh	1.69	2.24
Vh	1.91	2.47

[a]No interaction was detected by this method between sodium or potassium and IIIa. There was also no interaction between sodium bromide and the ligands IVa, IIIb, IVb and Vb. [b]Values quoted are the $log_{10}K$ where $K = [M \cdot polyether^+]/\{[M^+][polyether]\}$. Standard deviation from Miniquad programme of 0.01.

Preparation of IIIe

IIId (15.7 g) was added portionwise to a gently refluxing suspension of lithium aluminium hydride (4.7 g) in diethyl ether (250 ml). After 4 hr, the solution was cooled to room temperature and treated with i) water (10 ml), ii) 15% sodium hydroxide solution (10 ml), iii) water (30 ml). This was stirred for 1 hr, and then treated with 2 *N* HCl (450 ml) when a fluffy precipitate was formed. This was recrystallised from methanol, and the resulting white solid dried *in vacuo* at 65 °C for 5 hr to give the anhydrous ligand m.p. 99 °C. $C_{18}H_{22}O_6$ required: C, 64.65; H, 6.63. Found: C, 64.27; H, 6.61%.

Complexation of polyethers with alkali and alkaline earth metals

Stoicheiometric ratios of ligand and metal salt were heated in a suitable solvent to give a clear solution, and then filtered hot. Crystallisation of the complex generally occurred on cooling or on slow evaporation of the solvent. Isolated complexes and their relevant physical data are given in Table I. Melting points were determined on a Koffler hot stage melting point apparatus. Elemental analyses were carried out at the Microanalytical Laboratory, University College London. ^1H NMR spectra were recorded on a JEOL PMX 60 spectrometer; chemical shifts quoted are τ values with reference to TMS.

Measurement of stability constants

Stability constants were determined as previously described by titrations in Analar methanol at 25 °C by a potentiometric method using ion selective electrodes [11]. The titration curves were then converted to stability constants using the Miniquad program [12, 13], and the calculated values are listed in Table II.

Results and Discussion

The log_{10} values of stability constants of the various ligands with sodium and potassium ions in methanol are listed in Table II. Several trends may be noticed from these values. Firstly, for a given ligand, the formation constant for potassium is larger than that for sodium, and although the selectivity of potassium over sodium is smaller than that shown by some of the cyclic polyethers, it is still larger than that reported for linear polyethers with quinoline end groups [14]. The end groups in the ligands reported here are oxygen donors, and are expected to form stronger ion-dipole interactions with alkali metal cations than end groups containing nitrogen donors.

Secondly, as the number of OCH_2CH_2O groups linking the two benzene rings is increased from 1 to 3 so the binding constant also increases. A similar trend has been observed by proton nmr for sodium and potassium with polyethylene glycols in acetone and acetonitrile [15, 16]. This is almost certainly due to the increased number of coordination sites available in any one ligand, and also the increased flexibility of the larger ligands, which would allow an 'induced fit' conformation to be adopted more easily. The crystal structures of longer open chain polyether complexes all show the ligand to spiral round the cation [9, 10, 17–22] and a longer chain length may be necessary for good complexation.

The third feature, as noticed before [6, 23, 24] is the large change in stability constant with different end groups. For example, in the series of ligands III, IV, V where R = R′ = H and R = R = $CH_2C_6H_5$ only the titrations for IVa with potassium show deviations from dilution curves and hence allow a stability constant to be determined. However, it should be noted at this stage that whilst the e.m.f. titration method showed no detectable interaction between IVb or Vb and sodium bromide in methanol, crystals of the complex IVb $NaBPh_4 \cdot H_2O$ are readily obtained from methanol. This apparent disagreement between stability constant and ease of isolation of crystalline complexes is quite general because crystallisation depends upon the relative solubilities and lattice energies of the various species in solution and is often influenced by the anion;

examples include other open chain polyethers [6, 14] and the crown ethers (1). It emphasises the importance of not relying on one method alone for determining interactions between ligands and salts. If CH_3 groups are introduced into the bridge of IVb (to give the compound d, 1 *ortho*[*ortho*-C_6H_5-$CH_2OC_6H_4OCH_2CH(CH_3)OCH(CH_3)CH_2O$] C_6H_4-$OCH_2C_6H_5$ then this no longer forms a crystalline complex with sodium tetraphenylborate. No complexes have so far been isolated where R = R′ = H, but crystalline complexes have been characterised for V with R = R′ = CH_3 [25].

Incrasing the number of coordinating atoms in the end groups R and R′ makes the stability constants higher, and the diacids and diesters are more effective ligands than the diols (R = R′ = CH_2CH_2-OH). Esterification of the diacids to the diesters does not bring a uniform lowering of the stability constants throughout the series, and is an indication that intramolecular hydrogen bonding from the acid OH is not involved in holding the ends of the ligand together round the cation in solution. In the crystalline complexes neither IVc with potassium picrate [9] nor IIIe with sodium or with potassium thiocyanate [10] shows intramolecular hydrogen bonding between the carboxylic acid or hydroxy groups.

The hydroxy acid series IIIh, IVh and Vh may be considered to be analogous to the monensin series of ligands, but the stability constants determined in this study show no increase which would be expected for any intramolecular hydrogen bonding helping to hold the ligand in a coordinating position round the cation. In fact, the values lie between those obtained for IIIa, IVa, Va and IIIc, IVc and Vc.

The crystal structures of IIIe complexes show that with sodium thiocyanate a 1:1 ligand:metal compound is isolated, whereas with potassium thiocyanate, a 2:1 complex is obtained [10]. However, the e.m.f. titrations for this ligand with both sodium and potassium bromides fit 1:1 stoicheiometry reasonably well, and the Miniquad programme rejects the 2:1 stoicheiometry when a 1:1 and 2:1 model is refined. This phenomenon has also been observed for e.m.f. titrations of sodium bromide with dibenzo-24-crown-8 [26], whereas complexes of the ratio 1:2 (ligand to metal) are often isolated for sodium salts with this ligand [27, 28]. It is an indication that the complex which crystallises out of solution is the least soluble species present, and not necessarily the major solution species at equilibrium. However, when stability constants are small, it is difficult to fit curves for several species at a time.

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