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Note

Synthesis of some polyethers from carbohydrate derivatives and related compounds, and their interaction with sodium and potassium cations

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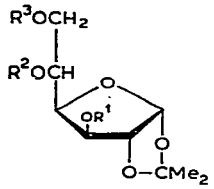
We have reported[1] on the interaction of some carbohydrate derivatives with sodium ions in acetone solution, and on the formation and structure of crystalline complexes of 1,4-anhydroerythritol with sodium perchlorate[2,3] and sodium iodide[4,5]. In an extension of our study in this area, we have prepared, from carbohydrate derivatives and from carbohydrate-related compounds, a group of polyethers all containing the O–C–C–O spacing favourable[6] for interaction with alkali-metal ions, and have investigated the ability of each polyether to interact with sodium and potassium cations.

Compounds **1** and **2** were prepared by acylation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and 1,2-*O*-isopropylidene-α-D-glucofuranose, respectively, with 3,6,9,12-tetraoxatridecanoyl chloride. The acid chloride was prepared by hydrolysis of ethyl 3,6,9,12-tetraoxatridecanoate (**3**) and treatment of the resulting oxa-acid with thionyl chloride*. In an attempt to synthesise another type of "multi-armed" ligand[7], pentaerythritol was treated with four molar equivalents of the acid chloride. Surprisingly, the product was the tri-ester (**4**), as indicated by spectroscopy and its elemental analysis. Resistance of the fourth hydroxymethyl group in **4** towards further acylation was confirmed when attempted acetylation at room temperature and at 100° yielded only unchanged starting material.

In a further attempt to prepare ligands from pentaerythritol, pentaerythritol tetra(toluene-*p*-sulphonate) was treated with the sodium alkoxides prepared from 2-(2-methoxyethoxy)ethanol and 2-[2-(2-methoxyethoxy)ethoxy]ethanol to give compounds **5** and **6** in yields of 9 and 15%, respectively. The low yields of these substitution reactions are not unexpected, in view of the similarity of adverse steric factors which operate here with those that retard substitution reactions in neopentyl

*The reaction of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with the oxa-acid chloride afforded material which gave i.r. and ^{1}H-n.m.r. spectra fully in accord with the expected 2,3-diester, but its elemental analysis for carbon was just outside acceptable limits of error (see Experimental). Nevertheless, details of the complexing properties of the material are reported here.



1 R^1 = $MeO(CH_2CH_2O)_3CH_2CO-$; R^2, R^3 = CMe_2
2 R^1 = R^2 = R^3 = $MeO(CH_2CH_2O)_3CH_2CO-$

$MeO(CH_2CH_2O)_3CH_2COOEt$

3

$HOCH_2C\left[CH_2OCO \cdot CH_2(OCH_2CH_2)_3OMe\right]_3$

4

$C(CH_2OR)_4$

5 R = $MeOCH_2CH_2OCH_2CH_2-$
6 R = $MeO(CH_2CH_2O)_2CH_2CH_2-$

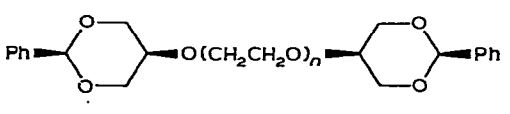
$HC(OR)_3$

7 R = $MeOCH_2CH_2OCH_2CH_2-$
8 R = $MeO(CH_2CH_2O)_2CH_2CH_2-$

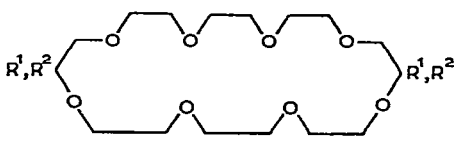
halides. Interestingly, polyethers related to **5** and **6** have been prepared by a different route[8] and have been used as phase-transfer catalysts.

Although a co-operative interaction of several chains of a "multi-armed" ligand with a cation might be expected to lead to more efficient complexation of the latter than a corresponding, single chain–cation association, it appears that, if the chains are attached to the same tetrahedral carbon atom, three is generally the maximum number of them that will be involved in complexation at any one instant. This consideration led us to synthesise and investigate some ligands of the orthoformate ester type. Trans-esterification of triethyl orthoformate with 2-(2-methoxyethoxy)ethanol and 2-[2-(2-methoxyethoxy)ethoxy]ethanol gave compounds **7** and **8**, respectively, as high-boiling liquids.

Polyethers **9** and **10**, readily prepared by the reaction of *cis*-1,3-*O*-benzylideneglycerol with diethylene glycol di(toluene-*p*-sulphonate) and triethylene glycol di(toluene-*p*-sulphonate), respectively, both contain a linear polyether chain, at each end of which are linked extra possible sites for complexation in the form of a 1,3-dioxane ring; the favourable O–C–C–O spacing may be traced from the central chain into each of these rings.



9 n = 2
10 n = 3



11 R^1 = H; R^2 = CH_2OCH_2Ph

The cyclic polyether **11**, prepared from **10** by cleavage of the acetal rings followed by intramolecular alkylation of the resulting diol with triethylene glycol di(toluene-*p*-sulphonate), is a mixture of the three possible stereoisomers*, and is

*The three stereoisomers are the *cis*, (+)-*trans*, and (−)-*trans* compounds.

included here to aid a comparison of the relative complexing abilities of acyclic and cyclic polyethers.

To assess the relative degree of interaction of polyethers **1**–**11** with sodium and potassium ions, we used Pedersen's extraction procedure[10], which measures the extent to which sodium and potassium picrate are extracted from aqueous solution into a dichloromethane solution of the polyether. The results are recorded in the Experimental section.

As might be expected, the extraction of a given cation with a given type of polyether ligand is more efficient with that ligand containing the greater number of O–C–C–O repeating-units. Thus, **6**, **8**, and **10** are more efficient at extracting sodium and potassium picrates into organic solution than **5**, **7**, and **9**, respectively. A comparison of extraction data for **1**, for the diester from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, and for **2** (compounds that contain one, two and three tetraoxatridecanoyl residues, respectively), indicates that the number of polyether chains within a potential ligand is an important factor governing the degree of interaction.

The superior complexing ability shown by **11** over all of the other polyethers described here is very apparent, and is in agreement with other work[11] which compares the complexation properties of acyclic and cyclic polyethers. Quite clearly, efficient complexation is aided, in general, by placing a restriction on the conformational freedom of the polyether chain, since it requires the ligand to adopt an arrangement that allows a cooperative interaction between many oxygen atoms and the metal cation.

It is noteworthy that, in each case, the potassium salt is more effectively extracted than the sodium salt into the organic medium. Such a selectivity might reasonably be expected for cyclic ether **11**, from a consideration of the cavity and cation size-relationships[11,12], but it is more surprising that such a selectivity appears with ligands containing acyclic polyether chains.

It is clear that the compounds described here, except **11**, do not interact strongly with sodium and potassium cations. However, the reasonable degree of interaction found to occur between potassium cations and compounds **2**, **4**, **6**, and **8** suggests that the complexing ability of oxygen-containing compounds may be increased significantly towards potassium ions by their conversion into relatively simple polyether derivatives. It is possible that such substances may have some biological interest.

EXPERIMENTAL

Proton n.m.r. spectra were recorded for solutions in $CDCl_3$, unless stated otherwise, with Varian HA-100 or Perkin–Elmer R-12 instruments (Me_4Si as internal standard). Rotations were measured for solutions in chloroform at ambient temperature with a Perkin–Elmer 141 polarimeter. U.v. spectra were recorded with a Unicam SP 800A spectrophotometer (1-cm quartz cells). Preparative layer chromatography (p.l.c.) was performed on Kieselgel PF_{254}. The preparation of compounds **10** and **11** is described elsewhere[9].

Ethyl 3,6,9,12-tetraoxatridecanoate (3). — To a stirred solution of 2-[2-(2-methoxyethoxy)ethoxy]ethanol (8.2 g) in 1,2-dimethoxyethane (30 ml) was added sodium hydride (1.2 g) in portions. After 2 h, ethyl bromoacetate (8.4 g) was added and the mixture was stirred for a further 1 h. Following the addition of methanol (5 ml), the reaction mixture was concentrated to a thick slurry which was partitioned between chloroform (150 ml) and water (100 ml). The aqueous layer was extracted with chloroform (2 × 150 ml), and the combined organic extracts were washed with water (100 ml), dried, and concentrated. Distillation of the residue gave 3 (5.3 g, 42%), b.p. 126–128°/0.07 mmHg; ν_{max}^{film} 1740 cm^{-1} (C=O). N.m.r. data: δ 1.24 (t, J 6 Hz, CH_3CH_2), 3.32 (s, OMe), 3.44–3.74 (complex, 6 CH_2), 4.08 (s, CH_2CO), and 4.18 (q, CH_2CH_3).

Anal. Calc. for $C_{11}H_{22}O_6$: C, 52.8; H, 8.9. Found: C, 52.6; H, 8.85.

3,6,9,12-Tetraoxatridecanoyl chloride. — A solution of ester 3 (4 g) in 0.352M aqueous sodium hydroxide (45.4 ml; 1 molar equivalent) was heated under reflux for 4 h, cooled, and concentrated to a thick syrup. Toluene (25 ml) was added to, and evaporated from, the residue, yielding the sodium salt of the oxa-acid as a syrup (3.8 g, 97%). To a stirred solution of the salt (3.5 g) in water (30 ml) was added aqueous sulphuric acid (50%) until the mixture just became acidic to litmus; then more acid (5 ml) was added. The aqueous solution was extracted with chloroform (3 × 75 ml), and the combined extracts were dried and concentrated, to afford the oxa-acid as a thick syrup (3 g, 94%). A solution of this acid (3 g) in thionyl chloride (10 ml) was heated under reflux for 4 h, toluene (10 ml) was then added, and the mixture was concentrated to dryness. The addition and removal of toluene was repeated, to remove final traces of thionyl chloride, yielding the crude acid chloride as a liquid (3.4 g, 97%), ν_{max}^{film} 1800 cm^{-1} (C=O), sufficiently pure for further reactions. N.m.r. data: δ 3.40 (s, OMe), 3.50–3.80 (complex, 6 CH_2), and 4.54 (s, CH_2CO).

Preparation of various esters of 3,6,9,12-tetraoxatridecanoic acid. — (*a*) *1,2:5,6-Di-O-isopropylidene-3-O-(3,6,9,12-tetraoxatridecanoyl)-α-D-glucofuranose* (1). To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (1.3 g) in pyridine (5 ml) was added dropwise 3,6,9,12-tetraoxatridecanoyl chloride (1.4 g; 1.2 molar equivalents). After storage for 24 h at room temperature, the mixture was poured into ice–water (50 ml) and extracted with chloroform (3 × 75 ml). The combined extracts were washed with water, dried, and concentrated, to give a syrupy residue which was subjected to p.l.c. (pyridine–di-isopropyl ether, 1:9) to give **1** (1.5 g, 65%), $[\alpha]_D$ −21°.

Anal. Calc. for $C_{21}H_{36}O_{11}$: C, 54.3; H, 7.8. Found: 53.9; H, 7.9.

(*b*) *1,2-O-Isopropylidene-3,5,6-tri-O-(3,6,9,12-tetraoxatridecanoyl)-α-D-glucofuranose* (2). Treatment of 1,2-*O*-isopropylidene-α-D-glucofuranose with 10 molar equivalents of the acid chloride, essentially as described in (*a*) and with purification of the reaction product by p.l.c. (chloroform–methanol, 19:1), gave **2** (74%), $[\alpha]_D$ +1.2°.

Anal. Calc. for $C_{36}H_{64}O_{21}$: C, 51.9; H, 7.75. Found: C, 51.7; H, 7.9.

(*c*) *From methyl 4,6-O-benzylidene-α-D-glucopyranoside.* Treatment of the diol

with 4 molar equivalents of the acid chloride, essentially as described in (*a*), gave, after p.l.c. (ethyl acetate) of the crude product, a syrupy residue (86%), $[\alpha]_D$ +42°, which had spectroscopic properties in agreement with its being methyl 4,6-*O*-benzylidene-2,3-di-*O*-(3,6,9,12-tetraoxatridecanoyl)-α-D-glucopyranoside; ν_{max}^{film} 1765 cm^{-1} (C=O). N.m.r. data: δ 3.35 (s, 2 CH_2OMe), 3.40 (s, $CHOMe$), 3.50–3.90 (complex, 12 CH_2 and H-6,6'), 4.05–4.50 (complex, H-4,5, 2 CH_2CO), 4.80–5.10 (complex, H-1,3), 5.50 (s, PhC*H*), 5.40–5.70 (complex, H-2), and 7.36 (s, Ar-H).

Anal. Calc. for $C_{32}H_{50}O_{16}$: C, 55.6; H, 7.3. Found: C, 55.1; H, 7.3.

(*d*) *Pentaerythritol tris(3,6,9,12-tetraoxatridecanoate)* (**4**). Pentaerythritol (0.42 g) was treated with the acid chloride (4.7 g, 6.3 molar equivalents) at room temperature for 24 h. Isolation of the product, essentially as described in (*a*), yielded liquid **4** (1.5 g, 65%), ν_{max}^{film} 3690–3300 (OH) and 1755 cm^{-1} (C=O). N.m.r. data: δ 2.18 (br.s, OH), 3.35 (s, 3 OMe), 3.44–3.70 (complex, 18 CH_2O- and CH_2OH), and 4.08–4.24 (complex, 3 OCH_2CO and 3 C-CH_2OCO).

Treatment of **4** (0.3 g) with acetic anhydride (5 ml) in pyridine (5 ml) at 100° for 12 h gave, after the usual work-up procedure, **4** (0.2 g). A similar result was obtained on reaction at room temperature.

Pentaerythritol tetra[2-(2-methoxyethoxy)ethyl] ether (**5**). — To a stirred suspension of sodium hydride (1 g) in *N,N*-dimethylformamide (DMF) (10 ml) was added, in portions, a solution of 2-(2-methoxyethoxy)ethanol (4.8 g) in DMF (20 ml) during 0.5 h. Pentaerythritol tetra(toluene-*p*-sulphonate)[13] (7.5 g) in DMF (30 ml) was added and the mixture was then heated and stirred at 120° for 24 h. The mixture was cooled, and methanol (0.5 ml) and dichloromethane (50 ml) were added. After removal of sodium toluene-*p*-sulphonate by filtration, the mixture was concentrated and the resulting slurry was partitioned between chloroform (60 ml) and water (30 ml). The aqueous layer was extracted with chloroform (2 × 30 ml), and the combined organic extracts were dried and concentrated to a syrup, which was subjected to column chromatography on aluminium oxide (300 g) with dichloromethane. Combination of appropriate fractions gave the major product, which was distilled to afford **5** (0.5 g, 9%), b.p. 140° (bath)/0.5 mmHg. N.m.r. data: δ 3.35 (s, 4 OMe) and 3.42–3.74 (complex, 20 CH_2).

Anal. Calc. for $C_{25}H_{52}O_{12}$: C, 55.1; H, 9.6. Found: C, 55.1; H, 10.0.

Pentaerythritol tetra{2-[2-(2-methoxyethoxy)ethoxy]ethyl} ether (**6**). — Treatment of pentaerythritol tetra(toluene-*p*-sulphonate) with the sodium salt of 2-[2-(2-methoxyethoxy)ethoxy]ethanol in dimethyl sulphoxide at 50° for 70 h, with isolation of the product in a manner similar to that described for **5**, gave **6** (15%), b.p. 170–175°/0.15 mmHg. N.m.r. data (neat): δ 3.36 (s, 4 OMe) and 3.41–3.84 (complex, 28 CH_2).

Anal. Calc. for $C_{33}H_{68}O_{16}$: C, 55.0; H, 9.5. Found: C, 54.8; H, 9.45.

Tris[2-(2-methoxyethoxy)ethyl] orthoformate (**7**). — Triethyl orthoformate (29.6 g) and 2-(2-methoxyethoxy)ethanol (72 g) were heated under reflux in the presence of toluene-*p*-sulphonic acid for 18 h. Ethanol that was formed in the reaction was then distilled from the mixture. The residue was heated at 100° for a further 18 h,

and then concentrated to a syrup which was distilled to give **7** (20.2 g, 27%), b.p. 170–190°/0.5 mmHg. N.m.r. data (neat): δ 3.28 (s, 3 OMe), 3.40–3.70 (complex, 12 CH_2), and 5.22 (s, CH).

Anal. Calc. for $C_{16}H_{34}O_9$: C, 51.9; H, 9.25. Found: C, 51.6; H, 9.1.

Tris{2-[2-(2-methoxyethoxy)ethoxy]ethyl} orthoformate (**8**). — Treatment of triethyl orthoformate (14.8 g) with 2-[2-(2-methoxyethoxy)ethoxy]ethanol (49.2 g) in the presence of toluene-*p*-sulphonic acid, and distillation of the crude product, yielded **8** (11.5 g, 23%), b.p. 210–215°/0.15 mmHg. N.m.r. data: δ 3.35 (s, 3 OMe), 3.50–3.70 (complex, 18 CH_2), and 5.20 (s, CH).

Anal. Calc. for $C_{22}H_{46}O_{12}$: C, 52.6; H, 9.2. Found: C, 52.3; H, 9.2.

5,5'-Oxybis(ethyleneoxy)bis(cis-*2-phenyl-1,3-dioxane*) (**9**). — To a stirred solution of *cis*-5-hydroxy-2-phenyl-1,3-dioxane[14] (9.0 g) and diethylene glycol di(toluene-*p*-sulphonate) (8.3 g) in dimethyl sulphoxide (30 ml) was added, in portions, sodium hydride (1.2 g) during 0.5 h, and the mixture was then heated at 50° for 72 h. To the cooled mixture were added methanol (0.5 ml) and dichloromethane (250 ml), and the precipitated sodium toluene-*p*-sulphonate was removed. The filtrate was extracted with water (2 × 100 ml), the organic layer was dried and concentrated, and the crude material so obtained was crystallised from benzene–light petroleum to give **9** (3.2 g, 37%), m.p. 78–80°. N.m.r. data: δ 3.4 (complex, H-5,5'), 3.70 (s, 4 CH_2), 3.94 (dd, $J_{4a,4e}$ 13, $J_{4a,5}$ 2 Hz, H-4a,6a,4'a,6'a), 4.30 (dd, $J_{4e,5}$ 2 Hz, H-4e,6e,4'e,6'e), 5.46 (s, 2 PhC*H*), and 7.20–7.60 (complex, 10 Ar-H).

Anal. Calc. for $C_{24}H_{30}O_7$: C, 67.0; H, 7.0. Found: C, 66.7; H, 6.9.

Extraction of sodium and potassium picrate from aqueous solutions into dichloromethane solutions of polyethers. — The method used is essentially that described by Pedersen[10]. A 0.5mM solution of the polyether in CH_2Cl_2 (50 ml) was shaken one hundred times with an equal volume of a 50 μM solution of the alkali metal picrate in 0.1M alkali metal hydroxide. The phases were separated, and the concentration of the picrate anion in the organic phase was determined by u.v. spectroscopy (λ_{max} 375 nm; ε, 18,000). The initial concentration of picrate in the aqueous solution was similarly determined (λ_{max} 357 nm; ε, 15,000). The extraction data are given in the following format: compound, % extraction of Na picrate, % extraction of K picrate; **1**, 0.4, 1.5; **2**, 4.5, 14.8; **3**, 0, 1.5; **4**, 3.4, 11.2; **5**, 2.2, 2.4; **6**, 4.5, 17.1; **7**, 0, 1.1; **8**, 1.7, 14.4; **9**, 0.6, 1.6; **10**, 1.1, 3.7; **11**, 36.1, 67.3; and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2,3-bis(3,6,9,12-tetra-oxatridecanoate), 2.2, 6.3.

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