Benzo-15-crown-5 Derivatives. Synthesis and Properties as Ion-extraction and Ion-transport Agents

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The preparation of some derivatives of benzo-15-crown-5 is described, each containing a carbohydrate moiety attached through either an ester or an ether linkage. The ion-extraction properties into dichloromethane of these and other related benzo-15-crown-5 derivatives towards lithium, sodium, and potassium picrate in aqueous solution have been measured, together with their ability to transport the alkali-metal picrates through a dichloromethane membrane.

There is considerable interest in the effect of ionophores on biological systems,[1,2] and this has led to their administration to intact animals.[3] The use of some polyether antibiotics as coccidostats has been patented.[4,5] However, the therapeutic potential of such compounds is still unclear in view of the broad spectrum of physiological response which they induce. Properties of ionophores which are significant in this respect are (*a*) their ability to transport biologically significant cations across membranes, (*b*) their ability to differentiate in their complexation properties between related, biologically important cations, (*c*) their influence on oxidative phosphorylation, and (*d*) their ability to stimulate heart muscle and cardiovascular responses.

Although polyethers of the crown-type [6] generally are toxic, their structure provides a possible basis for the development of pharmacologically active compounds. We have been interested in the possibility of modifying the complexing ability and selectivity of such macrocyclic polyethers towards metal cations, and in varying the lipid solubility of these ethers in a controlled fashion. To this end we have prepared derivatives of benzo-15-crown-5 (1) which contain a carbohydrate residue.† The latter moiety could provide several extra co-operative, oxygen binding sites in a relatively fixed spatial array which would be capable of variation on changing the type of carbohydrate residue, and a variation in the number and type of substituents on the carbohydrate hydroxy-groups should allow a series of derivatives, ranging from water soluble to lipid soluble, to be prepared. We describe the synthesis of representatives of such compounds and the results of ion-extraction and ion-transport experiments on them and related benzo-15-crown-5 derivatives.

Attachment of the crown-ether to a carbohydrate residue was made through an ester, an ether, and a glycosidic link. The ether link has the attraction of hydrolytic stability, relative to the other two types, in biological systems. Suitable starting materials for this work were 4′-carboxybenzo-15-crown-5 (2) and 4′-hydroxymethylbenzo-15-crown-5 (3), both of which were readily prepared from 4′-formylbenzo-15-crown-5 (4).[8] The acid (2) has been synthesised through etherification of methyl 3,4-dihydroxybenzoate,[9] and by a haloform reaction [10] on 4′-acetylbenzo-15-crown-5 (5) which is itself prepared [11] from 3,4-dihydroxyacetophenone. Unfortunately the latter compound is not commercially available and it is tedious to prepare in quantity from pyrocatechol diacetate [11] or by de-methylation of acetovanillone.[12,13] We find that the acid (2) is most conveniently prepared, in good yield, by oxidation with potassium permanganate of 4′-formylbenzo-15-crown-5 (4), which is itself readily prepared [8] from the commercially available 3,4-dihydroxybenzaldehyde.

Sodium borohydride reduction of (4) yielded, in good yield, 4′-hydroxymethylbenzo-15-crown-5 (3), which was characterized as its *p*-nitrobenzoate (6). Reduction with this reagent is preferable to that with lithium aluminium hydride,[14] since in the latter case a substantial portion of the corresponding dibenzyl ether is formed concomitantly.

The esters (7), (11), (12), (16), and (18) were obtained by reaction of the acid chloride (8) with the appropriate alcohol. The mono-ester (18), whose structure was confirmed by comparison of its ^{13}C n.m.r. spectrum with those of the 2- and 3-benzoates of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, was the major product obtained on reaction of the parent diol, with two molar equivalents of the acid chloride.

Treatment of the alcohol (3) with thionyl chloride afforded the crystalline chloromethyl-compound (9) and reaction of this with the sodium alkoxides of the appropriate alcohols gave 4′-methoxymethylbenzo-15-crown-5 (10), and the carbohydrate ethers (13), (14), (17), and (19). Reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with (3) under Koenigs-Knorr conditions gave the acetylated glycoside (20), which was de-*O*-acetylated to yield glycoside (21) as a monohydrate.

Extraction Measurements.—The equilibrium extraction of metal salts into organic solvents by neutral, ion-binding molecules has been analysed by Frensdorff [15] and by Eisenman and co-workers [16] in terms of the constituent equilibria. The treatment by Frensdorff [15] for a 1 : 1 alkali metal ion-crown complex allows evaluation by a non-linear regression, curve-fitting technique of the extraction constant, K_e, defined by equilibrium (1), and of the dissociation constant, K_d, for equilibrium (2), if the partition coefficient, P_e, for equilibrium (3) and the equilibrium constant, K_s, for complexation in the aqueous phase according to equilibrium (4) are known. In

$$M^+ + A^- + Cr^* \overset{K_e}{\rightleftharpoons} M^+, Cr, A^{-*} \quad (1)$$

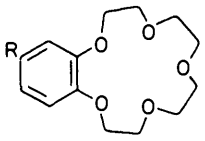
$$M^+, Cr, A^{-*} \overset{K_d}{\rightleftharpoons} M^+, Cr^* + A^{-*} \quad (2)$$

$$Cr^* \overset{P_e}{\rightleftharpoons} Cr \quad (3)$$

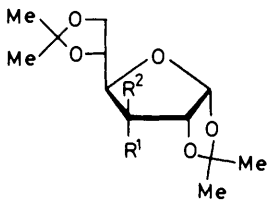
$$M^+ + Cr \overset{K_s}{\rightleftharpoons} M^+, Cr \quad (4)$$

these equations the metal salt is M^+A^-, the ionophore is Cr and species present in the organic phase are denoted by an asterisk.

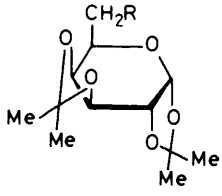
† Interestingly, the reaction of the polyether antibiotic monensin with D-glucose to form a glycoside is claimed in the patent literature.[7]



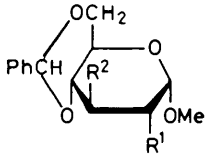
(1) R = H
(2) R = CO_2H
(3) R = CH_2OH
(4) R = CHO
(5) R = Ac
(6) R = $CH_2OCO{\cdot}C_6H_4{\cdot}pNO_2$
(7) R = CO_2Me
(8) R = COCl
(9) R = CH_2Cl
(10) R = CH_2OMe



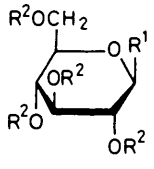
(11) R^1 = H, R^2 = A
(12) R^1 = A, R^2 = H
(13) R^1 = H, R^2 = B
(14) R^1 = B, R^2 = H
(15) R^1 = H, R^2 = OCOPh



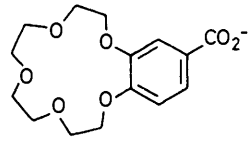
(16) R = A
(17) R = B

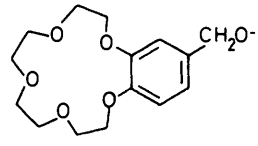


(18) R^1 = A, R^2 = OH
(19) R^1 = R^2 = B



(20) R^1 = B, R^2 = Ac
(21) R^1 = B, R^2 = H

A = 

B = 

The equations developed by Eisenman and his co-workers [16] afforded an expression for the total uptake of the lipid compatible anion, A^-, into the organic layer, as indicated in equation (5). This total uptake of A^- is seen to be a function

$$\{[M^+, Cr, A^-*] + [A^-*]\} = \{K_eK_d[M^+][A^-][Cr^*]\}^{\frac{1}{2}} + K_e[M^+][A^-][Cr^*] \quad (5)$$

of the single variable $[M^+][A^-][Cr^*]$. If the value of K_d is sufficiently small, that is dissociation of the complex M^+, Cr, A^- in the organic layer may be neglected, then the first term on the right-hand side in equation (5) is negligible compared to the second one, and equation (6) is obtained. Equation (6)

$$[M^+, Cr, A^-*] = K_e[M^+][A^-][Cr^*] \quad (6)$$

describes the equilibrium (1) above and has been used for the calculation of K_e values by other workers, with [17-21] and, apparently, sometimes without [22,23] full justification.*

If the amount of the ionophore in the aqueous layer is negligible compared to that in the organic phase,† then measurement of the total amount of salt transferred to the organic layer, together with a knowledge of the initial concentration of the salt, $[M^+A_0^-] = [M_0^+] = [A_0^-]$, the ionophore, $[Cr_0]$, and the value of K_d, allows a simple calculation of K_e by use of the relationship in equation (5).‡

For stoicheiometry of the type shown in equilibrium (7),

$$M^+ + A^- + 2Cr^* \overset{K_e(2)}{\rightleftharpoons} M^+, Cr_2, A^-* \quad (7)$$

which describes the complexation between potassium ions and mono-benzo-15-crown-5 derivatives in the presence of excess of ionophore,[10,11,24] then the equilibrium constant, $K_e(2)$, may be calculated in a similar way, using a suitably modified equation.§

Finally, in the case where two ionophoric groups are present within the same molecule and they simultaneously interact with a single metal ion as a single kinetic entity, equation (5) can again be used to define the corresponding extraction constant.[21]

We have measured the ability of dichloromethane solutions of benzo-15-crown-5 derivatives prepared in this work to extract alkali-metal picrates from aqueous solution, using the procedure described by Pedersen.[25] The results are given in

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* Obviously, equation (6) is valid only under conditions where $[A^-*]$ is negligible compared to $[M^+, Cr, A^-*]$. In dichloromethane, K_d has been evaluated [15] as 3.7×10^{-5} and 10^{-4}M for the complexes between the mixed isomers of dicyclohexano-18-crown-6 and potassium and sodium picrate, respectively, which means that at concentrations of *ca.* 10^{-5}M, the complexed picrate salts in dichloromethane solution are appreciably ionized. However, in chloroform, the value [12] of K_d for a benzo-18-crown-6/potassium picrate complex is *ca.* 10^{-9}. This difference of a factor of 10^4 between the values K_d is reasonable [12] considering the difference in dielectric constants of dichloromethane (9.08) and chloroform (4.80). It is clear that the analysis of the extraction equilibrium is simplified considerably if chloroform (or a less polar solvent) is used as the organic medium. Extractions involving dichloromethane should take into account dissociation in the organic phase for dilute solutions.

† That this is the case, with the exception of the 4′-hydroxymethyl derivative (3), for compounds studied here was confirmed by determination (u.v. spectroscopy) of their partition between dichloromethane (initially 7×10^{-4}M in crown ether) and water, and between dichloromethane and 0.1M aqueous solutions of lithium, sodium, and potassium hydroxide. The amount of crown ether transferred to the aqueous layer did not exceed 5% and in most cases it was considerably less than this. However, the 4′-hydroxymethyl derivative (3) was extracted to the extent of 19.5—21% into the aqueous layer.

‡ Rearrangement of equation (5) affords the equation:

$$[M^+][A^-][Cr^*]K_e + \{K_d[M^+][A^-][Cr^*]\}^{\frac{1}{2}}K_e^{\frac{1}{2}} - \{[M^+, Cr, A^-*] + [A^-*]\} = 0$$

which may be solved in the usual way for a quadratic equation to yield $K_e^{\frac{1}{2}}$. If x = the fraction of salt transferred to the organic layer when equal volumes of aqueous and organic media are equilibrated, then $[M^+] = [M_0^+](1 - x)$, $[A^-] = [A_0^-](1 - x)$, $[Cr^*] = [Cr^*_0] - x[A^-_0]$, $[M, Cr, A^-*] + [A^-*] = x[A^-_0]$, K_d = an assumed value, and $x = (Abs_0 - Abs_x)/Abs_0$, where Abs_0 = original u.v. absorbance of aqueous salt solution at a certain wavelength and Abs_x is the u.v. absorbance of the aqueous salt solution after equilibration with an equal volume of organic solvent containing the ionophore. In experiments containing an added common ion, M^+, in the aqueous phase, the original concentration of the metal ion, $[M_0^+]$, must be adjusted accordingly and a suitable activity coefficient used to convert the concentration of the metal ion, $[M^+]$ into its corresponding activity.

§ In equation (5), $[Cr^*]$ is replaced [16] by $[Cr^*]^2$ and the quadratic equation in $K_e(2)^{\frac{1}{2}}$ is: $[M^+][A^-][Cr^*]^2K_e(2) + \{[M^+][A^-][Cr^*]^2K_d\}^{\frac{1}{2}}K_e(2)^{\frac{1}{2}} - \{[M^+, Cr, A^-*] + [A^-*]\} = 0$ and in this case $[Cr^*] = [Cr_0] - 2xA_0$.

Table 1 in the form % extraction and K_e [or $K_e(2)$] values, the extraction constants being calculated through equation (5) (or its modified form for a 1 : 2 metal : crown complex), using K_d values reported by Smid and his co-workers [11] for sodium and potassium picrate complexes with 4′-vinylbenzo-15-crown-5. For the corresponding lithium picrate complex, no such K_d value was reported and therefore we have used the value of K_d evaluated [11] for the lithium picrate–poly(4′-vinylbenzo-15-crown-5) complex.

Our original hope was that the carbohydrate portion of our benzo-15-crown-5 derivatives would provide additional, geometrically defined, oxygen binding sites for metal ions complexed with the crown polyether ring. Secondary donor groups attached to a macrocyclic polyether can enhance the cation binding power of that ring.[26-32] However, it is clear that such co-operative complexation effects are not of great importance in the mono-substituted carbohydrate derivatives. In the series of ester derivatives, 4′-methoxycarbonylbenzo-15-crown-5 (7) may be taken as the model compound against whose complexing properties the complexing abilities of the carbohydrate derivatives (11), (12), (16), and (18) may be measured. A comparison of the extraction data for (7) with those of the carbohydrate crown esters for each of the three metal ions show only small differences in extracting ability [maximum difference 7.5% for (16) with sodium cation] and, strangely, for extraction of potassium picrate, the esters (11), (12), and (18) are less efficient than the model compound (7). It may be significant that these three carbohydrate derivatives are all esters involving a secondary alcohol group. The primary ester (16) is marginally better at extracting potassium picrate than (7) and considerably better at extracting sodium picrate. The poor ability shown by 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (15) to extract any of the three metal picrates is noteworthy.

In the ether series, 4′-methoxymethylbenzo-15-crown-5 (10) serves as the model compound. The greater complexing ability of this and related compounds over the 4′-methoxycarbonyl compound (7) for the potassium and sodium salts may be rationalized [8,22,33] in terms of the relative electron-releasing properties of alkoxymethyl compared to carboxyalkyl substituents, and the dependence of the electron density on the oxygen atoms directly attached to the aromatic ring on such substituent effects. Strangely, the 4′-hydroxymethyl derivative (3) extracts potassium picrate about as effectively as the 4′-methoxycarbonyl compound (7) although it is more efficient in extracting sodium picrate. The comparisons may be complicated here by the significant solubility differences between the hydroxylic compound (3) and the lipophilic compound (7) in the aqueous media.

The D-glucose 3-ether (13) is a little more efficient at extracting all three metal picrates than is (10), the difference being most noticeable with the potassium salt (13.5%). For the D-allose 3-ether (14) and the D-galactose 6-ether (17) the extraction abilities for potassium and sodium picrate are marginally less (2—7%) than for (10), but they are both slightly better (3—9%) than the model compound in extracting lithium picrate.

The most striking extraction data are for the 2,3-bis-ether (19). Potassium and sodium picrates are extracted with high efficiency (83 and 74% respectively), and, most surprisingly, the bis-ether is very effective in extracting lithium picrate (67%). All the other benzo-15-crown-5 derivatives are noticeably inefficient in extracting the lithium salt (<11%).* Further consideration of these properties is given below, but we note here that a co-operative interaction between the two adjacent crown ether rings might be the most likely cause. There is now considerable evidence that, in a bis(crown ether) or a poly(crown ether), two suitably disposed crown ether rings can provide, jointly, a superior binding capability for certain metal cations than can either of the rings singly, leading to a 2 : 1 crown ether : metal cation complex.[10-12,21,24,35-43] Also, it appears that extraction abilities of bis(crown ethers) are much greater than those of the corresponding mono(crown ethers) for cations which are larger than the size (diameter) of the crown ring.[21,37,39-43] It is in just such a situation regarding the relative size of cation and crown ether that a 2 : 1 ether to cation stoicheiometry is favoured.[40] It is not surprising, therefore, that the bis(benzo-15-crown-5) ether (19) (crown hole-diameter 1.7—2.2 Å) [44] is so effective in extracting potassium picrate (cation diameter 2.66 Å) into organic solution; more surprising is the large increase in complexing ability of (19), compared to 4′-methoxymethylbenzo-15-crown-5 (10), towards sodium picrate (cation diameter 1.94 Å) and lithium picrate (cation diameter 1.36 Å).† Studies [40] into the nature of the complex between sodium picrate and a bis(benzo-15-crown-5) ether, and between sodium, potassium, and rubidium picrates and a bis(benzo-18-crown-6) ether (cation : ether combinations in which the ions are able to fit inside the cavity) by conductometric measurements were inconclusive as regards whether a 1 : 1 or 2 : 1 ether : cation complex was formed. However, a u.v. spectroscopic study [41] on a related system suggested that in all such cases a 1 : 1 complex was preferred. Also, little difference in extractive power for sodium picrate was observed [41] between two bis(benzo-15-crown-5) ethers in one of which the two rings could, and in the other could not, interact in a co-operative manner. This latter result stands in contrast to our own for compound (19).

The crown ether glucoside (20) shows complexing properties closer to those of the ester than the ether series, which may be a result of the electron-withdrawing properties of the anomeric centre.

An examination of CPK models of the D-glucose-3-ester (11) or 3-ether (13) suggests that for cation complexation a co-operative interaction between a carbohydrate oxygen atom and the benzo-15-crown-5 ether ring would best be possible with O-5, whereas for the D-allose 3-ester (12) or 3-ether (14), either O-5 or O-6 could provide an extra co-ordination site. With the D-galactose 6-ester (16) or 6-ether (17), O-1 could, in principle, be involved in complexing a cation already co-ordinated with the crown ether ring. Conformational freedom of the molecule would be curtailed if such co-operative complexation occurred and it would be predicted that certain carbohydrate protons would be subjected to significant shielding effects resulting from the diamagnetic anisotropy of the benzene ring. However, no significant changes were apparent in the chemical shifts of the carbohydrate protons in (14) on the addition of potassium iodide to a solution of the ether in acetone.

A CPK model of the bis(crown ether) (19) indicates that certain conformations are available which allow a close, parallel alignment of the mean planes of the two crown ether rings such that a cation could be completely enveloped. The uptake of an ion can be envisaged as involving the opening of the bis-ether unit, much in the way an alligator's jaws open to

* The *X*-ray crystal structure of a hydrated lithium picrate–benzo-15-crown-5 complex showed that lithium ion is not bound to the crown ether oxygens directly, but through a water molecule co-ordinated with the crown ether.[34]

† In contrast, a bis(benzo-18-crown-6) ether (hole size 2.6—3.2 Å) showed [39] little increased complexing ability towards sodium picrate (cation diameter 1.94 Å) over that of the corresponding mono(benzo-18-crown-6) ether. Unfortunately, few extraction experiments have been made using lithium picrate.

entrap its prey.* Smid and his co-workers reported [10] that a bis(benzo-15-crown-5) ester derivative of ethane-1,2-diol was less effective in complexing ability towards potassium picrate in tetrahydrofuran than a related derivative from pentane-1,5-diol, and rationalized this in terms of a favoured molecular geometry for complexation in the latter case. Similarly, extraction studies [21] with a series of bis(benzo-15-crown-5) ethers derived from (3) and ethane-1,2-diol, 3-oxapentane-1,5-diol, and 3,4-dioxaoctane-1,8-diol indicated that for potassium, rubidium, and cesium picrates the minimum extraction constants are obtained with the ethane-1,2-derivative. Other workers [37,41] have reported the superior extracting ability for some cations (and therefore presumed complexing ability) shown by a bis(benzo-15-crown-5) ester derivative in which the two polyether rings are constrained to close proximity by incorporating them into a maleic rather than a fumaric acid framework but noted [41] no great advantage for the former bis-ester over the bis-ester derived from succinic acid. In the case of the bis(benzo-15-crown-5) ether (19) the two polyether rings although not conformationally fixed, with respect to each other, are held in relatively closer proximity than those in the ethane-1,2-diol ester [10] and ether [21] derivative by the equatorial-equatorial nature of the linkages to the carbohydrate ring which itself has a fixed conformation.

Measurement of the u.v. spectra of dichloromethane solutions of the bis-ether (19) containing lithium, sodium, and potassium picrates ($\lambda_{max.}$ *ca.* 372 nm in each case) suggests that there are greater proportions of crown ether separated ion pairs present than in corresponding solutions containing 4′-methoxymethylbenzo-15-crown-5 ($\lambda_{max.}$ 362, 356, and 368 nm, respectively). It is known that in tetrahydrofuran [10,24,39,41] and chloroform [12,21] the conversion of a crown ether-metal picrate tight, ion-pair complex into a separated ion-pair complex is accompanied by a bathochromic shift in the picrate absorption, originally in the region 350—360 nm, and that bis(benzo-15-crown-5) esters of certain α,ω-diols afford [10] only a crown-separated ion pair ($\lambda_{max.}$ 380 nm) with potassium picrate in tetrahydrofuran. With bis(benzo-15-crown-5) ethers of a series of α,ω-diols [21] in chloroform solution, potassium and rubidinium picrate gave crown-separated ion pairs ($\lambda_{max.}$ 378) but sodium picrate afforded only crown-complexed tight ion pairs ($\lambda_{max.}$ 356 nm), resembling those formed with 4′-methylbenzo-15-crown-5 ($\lambda_{max.}$ 356 nm). Of the metal ions studied here, only potassium cations are thought to form a 2 : 1 ether : cation complex with benzo-15-crown-5 but it is intriguing that the $\lambda_{max.}$ values of all three complexes of (19) are the same; it is tempting to speculate that this similarity might reflect a similar structure of the complexes.†

Transport Measurements.—The ability of the benzo-15-crown-5 derivatives to transport lithium, sodium, and potassium picrate through a dichloromethane solution separating the two aqueous phases was examined and the transport rates and cation selectivities are recorded in Table 2. The obvious conclusion that can be drawn is that the linking of one benzo-15-crown-5 residue to a carbohydrate derivative produces relatively unimportant changes in the transporting abilities of the parent crown ether. Thus, for the model compounds 4′-methoxycarbonylbenzo-15-crown-5 (7) and 4′-methoxymethylbenzo-15-crown-5 (10), sodium and potassium ions are transported between 7 and 11 times more quickly than lithium cations. With the carbohydrate esters, sodium and potassium cations are transported between 7 and 26 times more effectively than lithium cations and for the mono-ethers, between 5 and 14 times more effectively. The glycoside (20) shows a similar behaviour.

Within the series of model compounds, mono-esters, and mono-ethers, excepting three compounds, potassium cations are transported more efficiently (between 1.1 and 2.5 times) than sodium cations. For the three mono-ethers (13), (14), and (17), however, the differences in transport rates for sodium and potassium picrates are minimal. Interestingly, the glycoside (20) does show a distinct selectivity for the transport of sodium compared to potassium picrate.

As in the extraction experiments the most unusual results were obtained with the bis(crown ether) (19). Transport of lithium picrate was remarkably more efficient than that mediated by the mono-substituted derivatives and the rate was comparable to that for potassium picrate. Also, the rate for sodium cation transport was approximately twice that for lithium and potassium cations.

It has been shown [12] in transport experiments on sodium and potassium picrates in a water–chloroform–water system mediated by certain benzo-crown ethers that the selectivity of cation transport is determined by the extraction equilibrium constant if migration of the salt is diffusion controlled and if the extraction equilibrium across the interphase is rapidly established. However, other workers have noted [45] that for a given polyether, selective transport of a metal picrate through an organic medium is not necessarily reflected in the preferential extraction of that metal picrate into the medium from water. The relative rate of uptake and release of the metal ion from and into the aqueous phase, respectively, is important [23,46] and is dependent on the cation. In our work it is noteworthy that sodium picrate is more effectively transported yet less efficiently extracted than potassium picrate by the bis-ether (19). On the other hand, the rates of transport of lithium and potassium picrates are similar yet the former is extracted considerably less efficiently than the latter. With macrobicyclic ligands, an optimum complex stability for the efficient transport of metal ions has been demonstrated.[46]

Transport Measurements with Chiral Amine Salts.—In view of the success of Cram and his co-workers [47] in differentiating between salts of enantiomeric amines in transport experiments through an organic membrane, we have measured the rate of transport of (+)- and (−)-α-phenylethylamine hexafluorophosphate across a dichloromethane membrane containing the dissolved chiral crown compound (17). However, the rates of transport for the enantiomeric salts were equal within the experimental error, a result which is not surprising in view of the fact that there was little indication from other experiments of any co-operative interaction during cation complexation between the chiral carbohydrate moiety of the crown-ether derivatives and the crown-ether ring.

Biological Testing.—Compounds (4), (11), (12), (16), and (21) were inactive in a broad screen antibacterial test against nine organisms and against the fungus *Candida abicans*. Compounds (4), (11), and (16) showed no insectidal activity. Compound (11) showed no activity against nine other types of fungi.

Experimental

^{13}C N.m.r. spectra were recorded at *ca.* 27 °C using a JEOL FX-100 spectrometer at 25.05 MHz in [^2H]chloroform unless stated otherwise. Spectra were recorded at a sweep width of

* Certain macrocycles prepared by Cram and co-workers [38] possess a jaws-like shape and complex with a cation to afford a sandwich structure.

† However, it should be noted that the addition of a macrocyclic polyether to lithium picrate in chloroform led to 1 : 1 complex formation and caused the replacement of the absorption originally with $\lambda_{max.}$ 334 nm by a new absorption with $\lambda_{max.}$ 375.5 nm.[45]

5 000 Hz and FIDs were accumulated into 8 K addresses giving a digital resolution of 1.22 Hz, equivalent to 0.048 p.p.m. Chemical shifts (δ_C) are measured from $SiMe_4$. ^1H N.m.r. spectra were recorded at 99.6 MHz on the same spectrometer in [^2H]chloroform unless stated otherwise, or at 100 MHz on a Varian HA-100 spectrometer, or at 60 MHz on a Perkin-Elmer R12 spectrometer, and chemical shifts (δ_H) are from $SiMe_4$. U.v. spectra were recorded on a Unicam SP 800A spectrophotometer (1-cm quartz cells), and i.r. spectra on a Perkin-Elmer 257 spectrophotometer. The high-resolution mass spectrum was obtained on an AEI MS 902 spectrometer.

Column chromatography was performed on Merck Kieselgel 60 (70—230 mesh). Light petroleum refers to the fraction b.p. 60—80 °C unless indicated otherwise. Rotations were measured in chloroform unless stated otherwise. 1,2-Dimethoxyethane was dried over calcium hydride and stored over sodium. Methyl 2-*O*-benzoyl-[48] and 3-*O*-benzoyl-4,6-*O*-benzylidene-α-*O*-glycopyranose,[49] and 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-*O*-glucofuranose (15) [50] were prepared by literature procedures.

4′-Carboxybenzo-15-crown-5 (2).—(a) *From 4′-acetylbenzo-15-crown-5* (5).—Following the procedure of Bourgoin and his co-workers [10] 4′-acetylbenzo-15-crown-5 [11] (1 g) was added portionwise at 0—10 °C with stirring to a solution prepared previously by adding bromine (0.7 ml) to a solution of sodium hydroxide (2.2 g) in water (15 ml). After acidification of the reaction mixture with concentrated hydrochloric acid to pH *ca.* 1, a white solid was obtained, m.p. 183—197 °C, which on recrystallisation from water gave the acid (2) (0.78 g, 89%), m.p. 183—185 °C (lit.,[9] m.p. 180 °C from ethanol, lit.,[10] m.p. 184—186 °C) (Found: C, 57.8; H, 6.4. Calc. for $C_{15}H_{20}O_7$: C, 57.7; H, 6.5%). Failure to collect the recrystallised acid within *ca.* 3 h led to isolation of material having a m.p. >183°, with a wide melting range. Dissolution of a sample, m.p. 183—185 °C, in water and estimation of sodium ion content by flame photometry showed it contained 0.018% by weight of Na^+. Similar treatment of material having m.p, 183—197 °C showed it to contain 1.2% by weight of Na^+.

(b) *From 4′-formylbenzo-15-crown-5* (4). 4′-Formylbenzo-15-crown-5[8] (4) (2 g) was added to a solution of sodium carbonate (0.2 g) in water (5 ml), maintained at 0 °C, and a solution of potassium permanganate (1.8 g) in water (30 ml) was added slowly, with stirring during 2 h. The stirred reaction mixture was allowed to come to room temperature and after *ca.* 12 h was centrifuged. The supernatant liquid was separated from the brown precipitate of manganese dioxide and brought to pH 1 by the addition of concentrated sulphuric acid. Cooling of the solution to 0 °C afforded a precipitate which was collected, dried, and then recrystallised from water to afford the acid (1.55 g, 75%), m.p. 184—186 °C; δ_H [$(CD_3)_2SO$] 3.60—4.30 (16 H, complex, 8 × CH_2), 7.10 (1 H, d, $J_{5',6'}$ 8.6 Hz, 6′-H), 7.50—7.70 (2 H, m, 3′,5′-H); δ_C [$(CD_3)_2SO$] 6.83, 68.5 (2),* 68.7, 69.6, 69.7 70.5 (2) (CH_2O), 112.3 (C-6′), 113.9 (C-3′), 123.1 (C-4′), 123.4 (C-5′), 147.9 (C-2′), 152.4 (C-1′), and 167.0 (CO_2H).

4′-Hydroxymethylbenzo-15-crown-5 (3).—To a stirred solution of 4-formylbenzo-15-crown-5 (4) (3 g) in a mixture of water (20 ml) and ethanol (40 ml) was added sodium borohydride (0.6 g). After 12 h, the solution was acidified with dilute hydrochloric acid (8 ml) then made alkaline with saturated sodium hydrogen carbonate solution. Water was added (40 ml) and solvent (*ca.* 50 ml) removed on a rotatory evaporator. The remaining aqueous solution was extracted with dichloromethane (2 × 30 ml) and the combined extracts were dried and concentrated to yield an oil (2.6 g) which crystallised on storage. This material was crystallised from ether acetate–light petroleum to yield crude product (2.13 g, 72%), m.p. 48—50 °C; recrystallisation of this material from propan-2-ol–light petroleum (1 : 1, v/v) gave the alcohol, m.p. 52—53 °C (lit.,[14] m.p. 52—54 °C) (Found: C, 60.05; H, 7.3%; M^+, 298.1431. Calc. for $C_{15}H_{22}O_6$: C, 60.4; H, 7.4%; M^+, 298.1410); δ_H 3.05br (1 H, s, OH), 3.70—4.20 (16 H, complex, 8 × CH_2), 4.50 (2 H, s, CH_2OH), 6.85br (3 H, s, 3′-, 5′-, 6′-H); δ_C 64.9 (CH_2OH), 68.7, 69.0, 69.5 (2), 70.4 (2), 70.9 (2) (CH_2O), 112.8 (C-3′), 113.8 (C-6′), 119.8 (C-5′), 134.7 (C-4′), 148.3 (C-1′), and 149.0 (C-2′).

The alcohol gave a 4-nitrobenzoate (6), m.p. 87—89 °C (Found: C, 58.8; H, 5.5; N, 3.0. $C_{22}H_{25}NO_9$ requires C, 59.1; H, 5.6; N, 3.1%); δ_H 3.65—4.25 (16 H, complex, 8 × CH_2), 5.30 (2 H, s, CH_2OCO), 6.95 (3 H, m, 3′-, 5′-, 6′-H), 8.20 (4 H, s, *p*-$O_2NC_6H_4CO$); δ_C 67.7 ($ArCH_2$), 69.0, 69.2, 69.5 (2), 70.5 (2), 71.1 (2), (CH_2O), 113.7 (C-3′), 114.8 (C-6′), 122.1 (C-5′), 123.5 (C-3″,5″), 128.1 (C-4′), 130.8 (C-2″,6″), 135.6 (C-1″), 149.2 (C-1′), 149.6 (C-2′), 150.5 (C-4″), and 164.5 (COO).

Esterification of Various Alcohols with 4′-Chlorocarbonylbenzo-15-crown-5 (8).—(a) *Preparation of* (8). 4′-Carboxybenzo-15-crown-5 (0.78) was stirred with a solution of oxalyl chloride (1 ml) in dichloromethane (15 ml) containing dry pyridine (1 drop) for 4 h at room temperature; during this time complete dissolution of the solid occurred. The solvent was removed using an oil pump, without heating. Further portions of dichloromethane (2 × 10 ml) were added to the residue and removed in the same way to yield a solid (0.82 g, 99%) to which was added the required alcohol dissolved in pyridine (see below).

(b) *Reaction of* (8) *with an alcohol.* A solution of the monohydric alcohol (1 mmol) in dry pyridine (1 ml) was added to the acid chloride (8) (1.1 mmol) prepared as described above, and after 18 h at room temperature, water (0.5 ml) was added to the mixture. After 0.5 h, the mixture was added to saturated aqueous sodium hydrogen carbonate containing ice (20 ml) and the aqueous solution extracted with dichloromethane (2 × 20 ml). The combined, dried extracts were concentrated to afford a residue from which pyridine was removed by the repeated addition and evaporation of toluene; material so obtained was crystallised from an appropriate solvent or purified by column chromatography. The following esters of 4′-carboxybenzo-15-crown-5 were prepared.

The methanol ester (7) (80%), from ether, had m.p. 82—84 °C (lit.,[9] 81—83 °C; lit.,[10] m.p. 82 °C) (Found: C, 59.1; H, 6.9. Calc. for $C_{16}H_{22}O_7$: C, 58.9; H, 6.8%); δ_H 3.70—4.70 (19 H, complex, 8 × CH_2 and OMe), 6.85 (1 H, d, $J_{5',6'}$ 8 Hz, 6′-H), 7.50—7.70 (2 H, complex, 3′, 5′-H); δ_C 51.9 (OMe), 68.6, 69.0, 69.2, 69.3, 70.3, 70.4, 71.1 (2) (CH_2O), 112.0 (C-6′), 114.4 (C-3′), 122.8 (C-4′), 123.9 (C-5′), 148.4 (C-2′), 153.1 (C-1′), and 166.7 (COO).

The 1,2:5,6-*di*-O-*isopropylidene*-α-D-*glucofuranose ester* (11) (87%), from ethyl acetate–light petroleum, had m.p. 94—96 °C; $[\alpha]_D$ −43° (*c* 0.56) (Found: C, 58.6; H, 6.8. $C_{27}H_{38}O_{12}$ requires C, 58.5; H, 6.9%); δ_H 1.25, 1.30, 1.40, 1.50 (4 × 3 H, 4 × s, 2 × CMe_2), 3.70—4.40 (20 H, complex), 4.55 (1 H, d, $J_{1,2}$ 3.5 Hz, 2-H), 5.45 (1 H, s, 3-H), 5.90 (1 H, d, 1-H), 6.80 (1 H, d, $J_{5',6'}$, 9 Hz, 6′-H), and 7.40—7.70 (2 H, m, 3′,5′-H); δ_C 25.2 (Me), 26.2 (Me), 26.8 (2 × Me), 67.2, 68.6, 69.2 (2), 69.3, 70.3, 70.4, 71.2 (2), 72.7, 76.5, 79.9, 83.4 [CH_2O, CH(OR)], 105.1 (C-1), 109.3 (OCO), 112.0 (C-6′), 112.3 (OCO), 114.8 (C-3′), 122.0 (C-4′), 124.1 (C-5′), 148.6 (C-2′), 153.7 (C-1′), and 164.9 (COO).

The 1,2:5,6-*di*-O-*isopropylidene*-α-D-*allofuranose ester* (12),

* The number in brackets indicates the intensity of the peak relative to others in the spectrum and gives an indication of the number of resonances coincident at that chemical shift.

purified by column chromatography (ethyl acetate) to afford an oil (56%) had $[\alpha]_D$ −40° (*c*, 0.58) (Found: C, 58.4; H, 7.1. $C_{27}H_{38}O_{12}$ requires C, 58.5; H, 6.9%); δ_H 1.35 (6 H, s, 2 × CMe), 1.40, 1.55 (2 × 3 H, 2 × s, 2 × CMe), 3.70—5.20 (22 H, complex), 5.90 (1 H, complex), 6.90 (1 H, d, $J_{5',6'}$ 10 Hz, 6'-H), and 7.10—7.25 (2 H, m, 3',5'-H); δ_C 25.1, 26.4, 26.7, 26.8 (4 × Me), 65.8, 68.7, 69.1, 69.2, 69.4, 70.3, 70.4, 71.2 (2), 73.1, 74.3, 77.9 (2) (CH_2O, CH(OR), 104.3 (C-1), 109.9 (OCO), 112.1 (C-6'), 113.1 (OCO), 114.9 (C-3'), 122.0 C-4'), 124.3 (C-5'), 148.5 (C-2'), 153.4 (C-1'), and 164.3 (COO).

The 1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactopyranose ester* (16) (72%), from methanol or ethyl acetate–light petroleum, had m.p. 145—146 °C; $[\alpha]_D$ +80.5° (*c*, 0.65) (Found: C, 58.4; H, 7.1. $C_{27}H_{38}O_{12}$ requires C, 58.5; H, 6.9%); δ_H 1.25, 1.30, 1.40, 1.45 (4 × 3 H, 4 × s, 2 × CMe_2), 3.50—4.60 (20 H, complex), 5.45 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), 6.75 (1 H, d, $J_{5',6'}$ 8 Hz, 6'-H), 7.40—7.70 (2 H, m, 3',5'-H); δ_C 24.5 (Me), 25.0 (Me), 26.0 (2 × Me), 63.7, 66.2, 68.6, 69.0, 69.3, 69.4, 70.4, 70.6, 70.7, 71.2 (3) [CH_2, CH(OR)], 96.3 (C-1), 108.7 (OCO), 109.6 (OCO), 112.0 (C-6'), 114.7 (C-3'), 122.7 (C-4'), 124.1 (C-5'), 148.4 (C-2'), 153.2 (C-1'), and 166.1 (COO).

The 2-*ester of methyl* 4,6-O-*benzylidene*-α-D-*glucopyranoside* (19). Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (0.3 g, 1.06 mmol) in pyridine (2 ml) was added to (8) which had been prepared from 4'-carboxybenzo-15-crown-5 (0.7 g, 2.24 mmol) and the reaction mixture was stirred for 48 h. Isolation of the product in the usual manner gave an oil, shown by t.l.c. (ethyl acetate) to contain a mixture of products including the starting material (R_F 0.55) and a major component (R_F 0.4) which was u.v. active and which charred on development of the chromatogram with concentrated sulphuric acid. Column chromatography (ethyl acetate) afforded the component with R_F 0.4, and this product was crystallised from ethyl acetate–light petroleum to give the *mono-ester* (18) (0.35 g, 58%), m.p. 161—163 °C; $[\alpha]_D$ +80° (*c*, 0.23) (Found: C, 60.3; H, 6.4. $C_{29}H_{36}O_{12}$ requires C, 60.4; H, 6.3%); $\nu_{max.}$ ($CHBr_3$) 3 600—3 200 (OH), and 1 710 cm^{-1} (C:O); δ_H 2.50br (1 H, OH), 3.35 (3 H, s, OMe), 3.55—4.40 (20 H, complex), 4.50—5.05 (3 H, complex), 5.50 (1 H, s, PhC*H*), 6.80 (1 H, d, $J_{5',6'}$ 8 Hz, 6'-H), and 7.20—7.70 (7 H, complex, ArH); δ_C 55.5 (OMe), 62.0, 68.5, 68.8, 68.9, 69.0, 69.1, 69.3, 70.2, 70.3, 71.1 (2), 74.0, 81.5 [CH_2O, CH(OR)], 97.8 (C-1), 102.0 (Ph*C*H), 111.9 (C-6'), 114.8 (C-3'), 122.0 (C-4'), 124.5 (C-5'), 126.3 (C-2'', 6''), 128.3 (C-3'', 5''), 129.2 (C-4''), 137.0 (C-1''), 148.4 (C-2'), 153.5 (C-1'), and 165.9 (COO).

The product was identified as the 2-ester by comparison of its ^{13}C n.m.r. spectrum with that of the 2-[48] and 3-benzoates[49] of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, on which data are given below. The chemical shift of C-1 in (18) is particularly indicative of 2-substitution (note substituent effects for OH and OCOPh in cyclohexane[51]). Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 2-benzoate: δ_C 55.5 (OMe), 62.0, 68.8 (2), 74.1, 81.4 [CH_2O, CH(OR)], 97.8 (C-1), 102.0 (Ph*C*H), 126.3 (C-2',6'), 128.3 (C-3',5'), 128.4 (C-3'',5''), 129.2 (C-4'), 129.5 (C-1''), 129.9 (C-2'',6''), 133.3 (C-4''), 137.0 (C-1'), and 166.2 (COO) (C' refers to benzylidene aromatic carbons). Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 3-benzoate: δ_C 55.6 (OMe), 62.8, 68.9, 71.9, 73.0, 78.9 [CH_2O, CH(OR)], 100.2 (C-1), 101.5 (Ph*C*H), 126.1 (C-2',6'), 128.1 (C-3',5'), 128.2 (C-3'',5''), 128.9 (C-4'), 129.8 (C-2'',6''), 133.0 (C-4''), 136.9 (C-1'), and 166.6 (COO).

4'-*Chloromethylbenzo*-15-*crown*-5 (9).—A suspension of 4-hydroxymethylbenzo-15-crown-5 (3) (1.1 g) in dry benzene (20 ml) was heated under reflux in an oil-bath whilst thionyl chloride (1 ml) was added dropwise. Dissolution occurred and heating was continued for 2 h, after which time the volume of solvent was reduced to *ca.* 10 ml by distillation. The remaining solvent was removed on a rotatory evaporator and the oily residue taken up in a further portion (20 ml) of benzene which was removed under reduced pressure. The residue was crystallised from light petroleum (b.p. 40—60 °C) to afford the title compound (0.94 g, 80%), m.p. 60—61 °C (lit.,[14] m.p. 65—66 °C, lit.,[36] m.p. 67—68 °C) (Found: C, 57.15; H, 6.7; Cl, 11.5. Calc. for $C_{15}H_{21}ClO_5$: C, 56.9; H, 6.7; Cl, 11.2%); δ_H 3.65—4.25 (16 H, complex, 8 × CH_2), 4.50 (2 H, s, CH_2Cl), 6.85—6.95br (3 H, 3'-, 5'-, 6'-H); δ_C 46.5 (CH_2Cl), 67.0 (2), 69.5 (2), 70.5 (2), 71.0 (2) (CH_2O), 113.6 (C-3'), 114.4 (C-6'), 121.6 (C-5'), 130.4 (C-4'), 149.1, and 149.2 (C-1', C-2').

Etherification of Various Alcohols with 4'-*Chloromethylbenzo*-15-*crown*-5 (9).—*General procedure.* To a stirred solution of the monohydric alcohol (5 mmol) in 1,2-dimethoxyethane (25 ml) was added sodium hydride (0.5 g; 4 molar equivalents) followed by tetra-n-butylammonium iodide (0.02 g). After 20 min, the chloro-compound (9) (5 mmol) was added and the reaction mixture was stirred overnight at room temperature. Methanol (2 ml) was added to the stirred solution followed, after 0.5 h, by solid dioxide. Concentration of the solution gave a residue which was taken up in water and extracted with dichloromethane (3 × 25ml). The combined organic extracts were dried and then concentrated to give a product which was recrystallised from light petroleum or ethyl acetate–light petroleum or which, in the case of an oil, was purified by column chromatography in ethyl acetate. The following mono-ethers were prepared.

The *methanol ether* (10) (75%), had m.p. 45—47 °C (Found: C, 61.6; H, 7.8. $C_{16}H_{24}O_6$ requires C, 61.5; 7.7%); δ_H 3.30 (3 H, s, OMe), 3.65—4.25 (16 H, complex, 8 × CH_2), 4.30 (2 H, s, CH_2Ph), 6.85br (3 H, s, 3'-, 5'-, 6'-H); δ_C 57.8 (OMe), 68.9, 69.1, 69.6 (2), 70.5 (2), 71.1 (2), (CH_2O), 74.5 (CH_2Ph), 113.7, 113.8 (C-3', C-6'), 120.8 (C-5'), 131.3 (C-4'), 148.7 (C-1'), or 149.2 (C-2').

The 1,2:5,6-*di*-O-*isopropylidene*-α-D-*glucofuranose ether* (13) (78%) an oil, had $[\alpha]_D$ −17° (*c*, 0.41) (Found: C, 58.25; H, 7.5. $C_{27}H_{40}O_{11}\cdot H_2O$ requires C, 58.0; H, 7.6%) (Found: M^+, 540.2639. $C_{27}H_{40}O_{11}$ requires M^+, 540.2571); $\nu_{max.}$ (film) 3 680 and 3 620 cm^{-1} (weak, OH); δ_H 1.25, 1.35, 1.40, 1.45 (4 × 3 H, 4 × s, 2 × CMe), 3.65—4.55 (24 H, complex), 5.85 (1 H, d, $J_{1,2}$ 4 Hz, 1-H), 6.85br (3 H, s, 3'-, 5'-, 6'-H); δ_C 25.5 (Me), 26.3 (Me), 26.8 (2 × Me), 67.3 (CH_2Ar), 69.1 (2), 69.6 (2), 70.5 (2), 71.1 (2), 72.3, 72.6, 81.3, 81.4, 82.7 [CH_2O, CH(OR)], 105.2 (C-1), 108.9 (OCO), 111.7 (OCO), 113.8, 113.9 (C-3', C-6'), 120.9 (C-5'), 130.7 (C-4'), 148.9 (C-1'), and 149.2 (C-2').

The 1,2:5,6-*di*-O-*isopropylidene*-α-D-*allofuranose ether* (14) (56%), had m.p. 90—92 °C; $[\alpha]_D$ +6° (*c*, 0.43) (Found: C, 60.1; H, 7.3. $C_{27}H_{40}O_{11}$ requires C, 60.0; H, 7.5%); δ_H 1.40 (6 H, s, 2 × Me), 1.45, 1.60 (2 × 3 H, 2 × s, 2 × Me), 3.70—4.65 (24 H, complex), 5.75 (1 H, d, $J_{1,2}$ 4 Hz, 1-H), 6.90br (2 H, m, 3'-, 5'-H), and 7.00 (1 H, d, $J_{5',6'}$ 2 Hz, 6'-H); δ_C 25.0, 26.2, 26.6, 26.9 (4 × CH_3), 65.1 (CH_2Ar), 68.9, 69.2, 69.6 (2), 70.5 (2), 71.1 (2), 72.2, 74.8, 77.4, 78.0 (2) [CH_2O, CH(OR)], 103.8 (C-1), 109.6 (OCO), 112.8 (OCO), 113.8 (C-3'), 114.1 (C-6'), 121.2 (C-5'), 130.6 (C-4'), 149.0 (C-1'), and 149.2 (C-2').

The 1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactopyranose ether* (17) (53%), had m.p. 84—85 °C; $[\alpha]_D$ −40° (*c* 0.70) (Found: C, 60.0; H, 7.4. $C_{27}H_{40}O_{11}$ requires C, 60.0; H, 7.5%); δ_H 1.30 (6 H, s, 2 × Me); 1.40, 1.50 (2 × 3 H, 2 × s, 2 × Me), 3.60—4.55 (24 H, complex), 5.50 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), and 6.85br (3 H, m, 3'-, 5'-, 6'-H); δ_C 24.4, 24.9, 26.0, 26.1 (4 × Me), 66.9 (CH_2Ar), 68.6, 69.0, 69.2, 69.6 (2), 70.5 (2), 71.1 (2), 71.2 (2), 73.1 [CH_2O, CH(OR)], 96.3 (C-1), 108.5 (OCO), 109.2 (OCO), 113.8 (2) (C-3', 6'), 120.7 (C-5'), 131.5 (C-4'), 148.6 (C-1'), and 149.1 (C-2').

The methyl 4,6-O-*benzylidene*-α-D-*glucopyranoside bis-ether* (19). Reaction of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside [52] with 8 molar equivalents of sodium hydride and 2 molar equivalents of chloro-compound (9) in the presence of tetra-n-butylammonium iodide, essentially as described in the general procedure above, gave the *bis-ether* (19) (59%), had m.p. 141—143 °C; $[\alpha]_D$ −44° (*c* 0.41) (Found: C, 62.6; H, 7.0. $C_{44}H_{58}O_{16}$ requires 62.7; H, 6.95%); δ_H 3.38 (3 H, s, OMe), 3.48—4.07 (38 H, complex), 4.50—4.77 (5 H, complex), 5.54 (1 H, s, OC*H*O), 6.82—6.95 (5 H, m, C_6H_5), and 7.35—7.55 (6 H, m, 2 × C_6H_3); δ_C (55.3 (OMe), 62.3, (CH_2Ar), 69.0, 69.1, 69.6, 70.5, 71.0, 71.6, 82.1 [CH_2O, CH(OR)], 99.2 (C-1), 101.4 (OCHO), 113.9 (C-3′, 6′), 121.0 (C-5′), 126.1 (C-2″, 6″), 128.2 (C-3″, 5″), 128.9 (C-4″), 131.4 (C-4′), 137.4 (C-1″), 148.7 (C-1′), and 149.2 (C-2′).

Glycoside from Reaction of the Alcohol (3) *and* 2,3,4,6-*Tetra*-O-*acetyl*-α-D-*glucopyranosyl Bromide*.—A mixture of 4′-hydroxymethylbenzo-15-crown-5 (3) (0.6 g), anhydrous calcium sulphate (2.0 g), and silver oxide (0.5 g) in ethanol-free chloroform (7 ml) were stirred together, protected from light, for 1 h, before iodine (0.1 g) was added. A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.8 g) in alcohol-free chloroform (10 ml) was added to the reaction mixture during a period of 1 h and stirring was continued for 72 h; the suspension was then filtered and the filtrate concentrated to give a yellow oil. Chromatographic purification (ethyl acetate) gave as a syrup the *acetylated glycoside* (20) (0.65 g, 52%); $[\alpha]_D$ −28.7° (*c* 0.35) (Found: C, 55.2; H, 6.6. $C_{29}H_{40}O_{15}$ requires C, 55.4; H, 6.4%); δ_H 1.95 (6 H, s, 2 × Ac), 2.05, 2.10 (2 × 3 H, 2 × s, 2 × Ac), 3.50—5.30 (25 H, complex), 6.80br (3 H, s, 3′,- 5′-, 6′-H); δ_C 20.6, 20.7 (2 × 2 Ac), 62.0 (CH_2Ar), 68.4, 69.1 (2), 69.5 (2), 70.5 (2), 71.1 (2), 71.3, 71.8, 72.9 [CH_2O, CH(OR)], 99.1 (C-1), 113.7 (C-3′), 114.1 (C-6′), 121.0 (C-5′), 129.6 (C-4′), 149.0, 149.2 (C-1′, C-2′), 169.3, 169.4, 170.2, and 170.6 (4 × COO).

Deacetylation of the acetylated glycoside (20) in the usual manner with methanol containing sodium methoxide afforded, from ethyl acetate–light petroleum, the glycoside (21) (79%), m.p. 114—115 °C; $[\alpha]_D$ −29° (*c* 0.38 in H_2O) (Found: C, 52.4; H, 6.9. $C_{21}H_{32}O_{11}\cdot H_2O$ requires C, 52.7; H, 7.2%), δ_C (CD_3OD) 62.8 (CH_2Ar), 70.0, 70.2, 70.6 (2), 71.4 (2), 71.7 (2), 71.8 (2), 75.1, 77.9, 78.1, 102.9 (C-1), 115.0, 115.6 (C-3′, C-6′), 122.4 (C-5′), 132.2 (C-4′), 149.9 (C-1′), and 150.3 (C-2′).

Hydrochlorides of (+)- *and* (−)-α-*Methylbenzylamine*.—Through a solution of (+)- or (−)-α-methylbenzylamine (Aldrich) in diethyl ether was passed a stream of hydrogen chloride until precipitation of the hydrochloride was complete. The salt was collected, washed with ether, and dried over phosphorus pentaoxide. (+)-Isomer, $[\alpha]_D$ +3° (*c* 2 in H_2O); (−)-isomer, $[\alpha]_D$ −4° (*c* 2 in H_2O) {lit.,[53] (+)-isomer, $[\alpha]_D^{15}$ +3.5° (*c* 3 in H_2O); lit.,[54] (−)-isomer, $[\alpha]_D$ −3.5° (*c* 4 in H_2O)}.

Extraction Measurements.—Picric acid (*ca.* 7 × 10^{-5} mol) was dissolved in 0.1M-aqueous solutions of lithium, sodium, and potassium hydroxide, and a 7 × 10^{-4}M-solution of the crown ether was prepared in dichloromethane. Equal volumes of the crown ether solution and the required alkali-metal picrate solution were placed in a separating funnel and the contents were vigorously shaken 100 times. The absorbance, *A*, of the aqueous layer before and after the extraction experiment, A_0 and A_e, respectively, was measured at the position of maximum absorption at 354 nm and the percentage extraction of alkali-metal picrate into the organic layer was calculated by the expression $100(A_0 - A_e)/A_0$. Results are recorded in Table 1.

Table 1. % Extraction of metal picrates from aqueous to organic phase and extraction constants (K_e) [a]

	Metal cation					
	Li^+		Na^+		K^+	
Compd.	%	$10^{-2}K_e$ [b] / l^2 mol^{-2}	%	$10^{-2}K_e$ [b] / l^2 mol^{-2}	%	$10^{-6}K_e(2)$ [c] / l^3 mol^{-3}
(1)	4.5	6.0	24	52.2	42	7.3
(3)	3.5	*d*	19.5	*d*	28.5	*d*
(4)	0	0	10	17.1	21	1.7
(5)	0	0	3.5	5.0	20	1.5
(7)	2	2.2	10.5	18.1	28	3.0
(10)	2	2.2	29	68.6	45	8.7
(11)	2	2.2	11.5	20.2	21	1.7
(12)	2	2.2	15	28.1	21	1.7
(13)	7	10.3	37	100.1	58.5	18.0
(14)	11	18.0	22	46.3	38.5	6 0
(15)	0	0	0	0	4	0 07
(16)	4.5	6.0	18	35.5	31	3.7
(17)	5	6.8	27	61.8	42	7.3
(18)	4.5	6.0	11.5	20.2	23	2.0
(19)	67	357.1 [e]	74	522.8 [e]	83	0.043 [f]
(20)	2.5	2.9	13	23.5	23	2.0

[a] For calculation of K_e, assumed [11] K_d values are: Li^+ complex, $K_d = 0.4 \times 10^{-6}$ mol l^{-1}; Na^+ complex, $K_d = 0.2 \times 10^{-6}$ ml l^{-1}; for calculation of $K_e(2)$ assumed [11] K_d value for K^+ complex = 40×10^{-6} mol l^{-1}. Mean activity coefficient for 0.1M-metal hydroxide = 0.798. [b] Calculated for equilibrium (1); the pair of crown ether rings in (19) are assumed to behave as a single kinetic entity. [c] Calculated for equilibrium (7), except for bis-ether (19). [d] K_e Value omitted because of significant solubility of (3) in aqueous medium. [e] K_d Values assumed the same as for 1 : 1 crown-ether ring : metal-ion complex. [f] Calculated for equilibrium (1), assuming the pair of crown-ether rings in (19) behave as a single kinetic entity and $K_d = 40 \times 10^{-6}$ mol l^{-1}.

Ion Transport Experiments.—For all the transport experiments involving alkali-metal picrates, a cell similar to one previously described [45] was used, which consisted of a glass cylinder (i.d. 5 cm, height 3.2 cm) in which was held by three radial glass rod supports an inner glass tube (i.d. 2.5 cm) such that the bottom of the latter was 3 mm above the bottom of the outer vessel. A portion (25 ml) of a 7 × 10^{-5}M solution of the crown ether in dichloromethane was placed in the bottom of the cell, and this organic layer isolated the inner and outer compartments formed by the two cylinders. In the inner compartment was placed an aqueous solution (4 ml) which was 2 × 10^{-4}M in alkali-metal picrate and 0.1M in the corresponding alkali-metal nitrate. In the outer annular compartment was placed water (12 ml). The organic layer was stirred magnetically at a steady rate, and at known times, a sample was withdrawn from the outer compartment and the concentration of alkali-metal picrate therein was determined by u.v. spectroscopy using the following constants for lithium, sodium, and potassium picrates: $\varepsilon_{max.}$ 15 000 at $\lambda_{max.}$ 354 nm. After each determination the aqueous aliquot was returned to the outer layer. Results are recorded in Table 2.

In the case of transport experiments with the chiral amines, a U-tube (i.d. 2 cm, height 10 cm) was used and aqueous phases in the two side arms were separated by a stirred dichloromethane solution (15 ml), 0.001M in crown ether (17). In the one arm, A, was placed an aqueous solution (8 ml) 0.05M in the amine hydrochloride and 0.05M in lithium hexafluorophosphate, and in the other arm, B, was placed water (8 ml). The concentration of α-methylbenzylamine salt in the aqueous layer in arm B was determined by u.v. spectroscopy ($\varepsilon_{max.}$ 450

Table 2. Transport rates and selectivity ratios of alkali-metal picrates through dichloromethane membrane

Carrier	$10^7 \times$ Transport rate (mol l^{-1} h^{-1})			Transport selectivity	
	Li^+	Na^+	K^+	Li^+/Na^+	Na^+/K^+
(1)	4.24	40.88	60.8	0.10	0.67
(7)	4.78	36.32	48.68	0.13	0.75
(10)	5.06	36.96	41.48	0.14	0.89
(11)	1.46	13.88	26.00	0.15	0.53
(12)	1.71	12.04	16.8	0.14	0.72
(13)	2.76	36.52	36.4	0.08	1.0
(14)	5.86	32.36	29.96	0.18	1.08
(16)	2.04	24.60	39.08	0.08	0.63
(17)	7.01	41.8	45.6	0.17	0.92
(18)	1.67	16.48	41.92	0.10	0.39
(19)	40.04	76.48	40.12	0.52	1.91
(20)	3.36	60.48	37.28	0.05	1.62

at $\lambda_{max.}$ 255 nm). The initial rate of transport (repeat measurement given in brackets) of the (+)-amine salt and the (−)-amine salt into the aqueous layer in arm B was 1.89×10^{-4} (2.02×10^{-4}) and 1.99×10^{-4} (2.16×10^{-4}) mol l^{-1} h^{-1}, respectively.

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