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Elaboration of a Chiral 20-Crown-6 from a Glucofuranose Derivative and Its Complex Formation with Alkali Cations

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ABSTRACT

*The synthesis of bis-(1,2-O-isopropylidene-6-O-triphenylmethyl-α-D-glucofuranosyl)-20-crown-6 (**1**) and its complexing ability with alkali and ammonium cations are described. The crown ether **1** was synthesized in a stepwise manner via the "half-crown" (**2**) using a blocking-deblocking procedure, in which the 3,3'-bridge was formed, followed after suitable manipulations, by formation of the 5,5'-bridge. An unusual feature of the complexing ability of the crown ether is that, although potassium and ammonium ions most closely approach the size of the complexing cavity, it is the sodium ion which forms the most stable complex. Compound **1** does not show chiral recognition toward two alkylammonium salts.*

INTRODUCTION

It is known that chiral crown ethers functioning as hosts in complexation exhibit chiral recognition of enantiomers of alkylammonium salts as guests [1–6]. Certain macrocyclic compounds incorporating a sugar moiety show some enantiomer selectivity toward an (RS)-α-phenylethylammonium salt [2]. Compounds having *bis*-dinaphthyl units have a very high enantiomer selectivity for 1,2-diphenylethylamine and other amines [3,4]. Enantiomer selectivity of the chiral crown ethers was evaluated by a membrane electrode method [5,6].

Chiral crown ethers in which the chirality is carried by carbohydrate molecules incorporated into the macrocycle form a very important class of compounds [7–9]. Protected sugars bearing acetals, such as isopropylidene [10,11] and benzylidene [12–15] derivatives, have been used in the synthesis of several such chiral crown ethers, and the sugar moieties may be in the form of the open chain [10], the pyranose [12–15] or, more rarely, the furanose [11] ring.

In the majority of syntheses, the macrocycle has been constructed in a regioselective manner using one sugar residue and conventional ring formation or template ring closure, in which a metal ion participates. In those cases where two sugar residues are incorporated into the macrocycle, the ring closure reaction is often not regioselective, and stereoisomeric products result [13–15]. Similar preparative difficulties have been encountered in syntheses of the related aza crown compounds derived from amino sugars [16–18].

In order to increase the number of chiral compounds having different ring sizes and lipophilicities, we planned to synthesize chiral compounds with a 20-membered ring similarly to the chiral 18-crown-6 compounds synthesized and published earlier by us [14,15]. This new crown

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TABLE 1 Effect of Different Bases on Yield of Half-Crown **2** and Formation of Monotosyl Ether **4**

Base	*Solvent*	*Yield% of* **2**	*Formation of* **4**
aq KOH	THF	50	yes
$NaOBu^t$	THF-Bu^tOH	4.7	yes
NaH	THF	45	no
NaH	DMF	62	no

TABLE 2 Complex Formation Constants for Chiral Crown **1** with Ions in Chloroform at Room Temperature

Ion	*Log Ka*[a]
Li^+	3.85
Na^+	4.46
K^+	4.06
NH_4^+	3.92

[a]Error limit: ±0.03; the results are the average of triplet runs.

ether contains only six oxygen atoms in the ring. As a result, the complex-forming ability of the new ring of this type changes and may even be decreased compared to the 18-crown-6 compounds.

There are enantioselective reactions in which the chiral crown ether is being used as a phase transfer catalyst; e.g., carbohydrate-containing crown ethers have been used as catalysts in asymmetric Michael additions [19–21]. We have also obtained significant results in this field using 18-crown-6 incorporating glucopyranoside units [22]. Compared with the 20-membered ring, they may have other influences on the measure and direction of their enantioface differentiating ability in asymmetric reactions. Bradshaw et al. have found that the molecular conformation and flexibility play important roles in enantiomer recognition and in its function as a catalyst [23,24].

RESULTS AND DISCUSSION

Synthesis

The present article describes the regioselective synthesis of the chiral 20-crown-6 (**1**) from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**3**), in a stepwise manner using a blocking-deblocking process via the "half-crown" (**2**), in which the 3,3′-bridge is first formed, followed, after suitable manipulations, by formation of the 5,5′-bridge.

The protected sugar **3** contains a secondary hydroxyl group at position-3, which, as is well known, has a low reactivity. Since two molecules of **3** were to be coupled through this hydroxyl group using a base-catalyzed condensation with diethyleneglycol ditosylate, various base-solvent combinations were examined (see Table 1).

Using our earlier process [15] involving concentrated potassium hydroxide in tetrahydrofuran gave a reasonable yield (50%) of the desired half-crown **2**, but an additional by-product was formed, from which it could be separated only by chromatography. Isolation and characterization proved the by-product to be the monotosyl intermediate (**4**). On the other hand, a good yield of the 3,3′-bridged product **2** was obtained free from by-products using sodium hydride in dimethylformamide, the only contaminant being unreacted starting material from which **2** was easily separated by solvent extraction.

In the next stage, the 5,6-O-isopropylidene groups of **2** were removed using ethanoic acid in dioxane [26] to give the *bis*-diol (**5**) in 90% yield. In order to carry out the next stage of cyclization using the 5- and 5′-hydroxyl groups, it was necessary to protect the primary alcohol groups. Because it was intended to re-expose these groups after formation of the crown ether, triphenylmethyl protection was employed; the ditrityl derivative (**6**) was obtained in 95% yield using trityl chloride in dichloromethane in the presence of triethylamine.

Intramolecular ring closure leading to the target 20-crown-6 **1** was carried out by reaction of **6** with diethylene glycol ditosylate. This step proceeded in very poor yield, even with use of sodium hydride in dimethylformamide, chromatographic purification giving a 4% yield of the product. A probable reason for the difficulty of cyclization is steric inhibition by the triphenylmethyl groups.

COMPLEX FORMATION

The complex-forming properties of the crown **1** with lithium, sodium, potassium, and ammonium picrates were measured by the method of Cram [27]. The logarithms of the complex-formation constants (log K_a) in chloroform at room temperature are shown in Table 2. These values are of a similar order of magnitude to the values of 18-crown-6 having two glucopyranoside units (log K_a = 4–5) [25], and the ion selectivity is low; but, in spite of the large size of the ring, the most stable complex is formed with the sodium cation, even though the sizes of the potassium and ammonium ions most closely approach the diameter of the crown ring cavity (ion diameter of cations: Li^+ 1.2; Na^+ 1.9; K^+ 2.66; NH_4^+ 2.84 Å; the hole size of crown ethers: 12-crown-4 1.0–1.3; 15-crown-5 1.7–2.2; 18-crown-6 2.6–3.2 Å). The ionic diameter of K^+ corresponds to the inner dimensions of the 18-crown-6 ring. The hole of our ligand **1** is larger than that of 18-crown-6. The investigated cations are too small in comparison to the hole size of the 20-membered ring, and this is why they have play in the ring of **1**. The complex formation can be explained by the

flexibility of **1**, the cations being "wrapped up" by the crown ring.

The chiral recognition power of compounds can be measured by the membrane-transport process of racemic ammonium salts [28,29]. We have performed experiments using our new crown ether **1** to carry the enantiomers of a racemic mixture of 2-phenylethylammonium chloride or phenylglycine methyl ester hydrochloride, respectively, from the aqueous solution through chloroform (membrane) to the other aqueous phase, by Cram's method [29] in a co-axial cylinder cell apparatus. Compound **1** was able to transport the ammonium salts (49 and 42%, respectively, after 3 hours), but it did not show chiral recognition; we obtained the racemic mixture in the receiving phase.

The application of the new crown ether as a stereoselective catalyst in asymmetric reactions will be reported in a subsequent article.

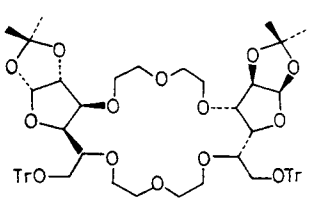
EXPERIMENTAL

1H NMR spectra: Perkin-Elmer R12 and JEOL FX-100 (in CDCl3), TMS as internal standard. UV spectra: Hitachi-Perkin-Elmer 124. Mass spectra: JEOL JMS-OL SG-2. Elemental analysis: Perkin-Elmer 240 automatic analyzer. TLC: Kieselgel 60 F254 or Al203 150 F254 Type T (Merck), eluent toluene/methanol mixtures (10:1–10:5); detection with Dragendorff's reagent [30]. Column chromatography: Kieselgel 60 (0.2–0.063 mm) (Merck).

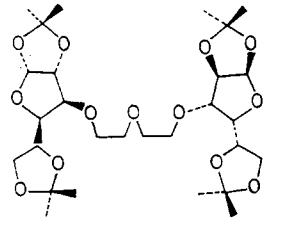
Preparation of 2,2'-di-O-(1,2:5,6-di-O-isopropylidene-D-glucofuranos-3-yl)diethylene Glycol **2** *Using Potassium Hydroxide as Base: Isolation of 3-O-(5'-p-toluenesulphonyloxy-3'-oxapentyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose* **4**

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (31.2 g, 0.12 mol) dissolved in tetrahydrofuran (450 mL) was placed in a round-bottomed flask equipped with a magnetic stirrer. Potassium hydroxide (20.2 g, 0.36 mol) in water (40.4 mL) was added and the mixture stirred under reflux for 2 hours. Diethyleneglycol ditosylate (24.8 g, 0.06 mol) was added, and the mixture was stirred under reflux for an additional 40 hours. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in methylene chloride (750 mL) and washed, respectively, with 2M hydrochloric acid (2 × 300 mL), 10% $NaHCO_3$ solution (300 mL), and saturated NaCl solution (300 mL). The solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to give a yellow syrup (27.5 g), which contained four components according to tlc. The product mixture was subjected to column chromatography on Kieselgel 60 using toluene-ethyl acetate (5:1) as eluent, giving three fractions: fraction 1 consisted of ethyleneglycol ditosylate (3.20 g); fraction 2 contained a by-product (3.45 g); fraction 3 contained a mixture of the unchanged di-O-isopropylidene-glucose **3** and the dissolved half-crown product **2**.

The syrupy mixture (18.70 g) obtained by evaporation of fraction 3 was boiled with petroleum ether for 0.5 hours, and the resulting suspension was allowed to stand for 10 hours at room temperature. Filtration gave unchanged 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (1.2 g). Evaporation of the filtrate gave the ethyleneglycol *bis*-glucose derivative (**2**) as a pale syrup (17.5 g, 50% yield). Evaporation of fraction 2 gave 3-O-[5'-*p*-toluenesulphonyloxy-3-oxapentyl]-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose as a pale syrup (3.45 g, 11.5%), $[\alpha]_D^{22} = -16.0°$ (c 5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.25 (12H, d, J = 10 Hz, isopropylidene CH_3). 2.30 (3H, s, C_6H_4–CH_3), 3.3–4.5 (14H, m, sugar protons), 3.5 (8H, s, 4 × crown–CH_2), 5.7 (1H, d, J = 4 Hz, 1-H), 7.2–7.7 (4H, m, aromatic-H). Anal. calcd. for $C_{23}H_{34}O_{11}S$ (518): C, 53.27; H, 6.61; S, 6.18. Found: C, 53.57; H, 6.58; S, 6.03.



1



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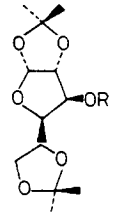
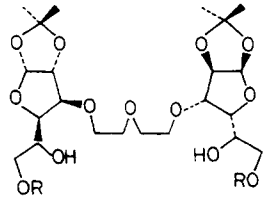


3 R = H

4 R = $(CH_2)_2O(CH_2)_2OTs$



5 R = H

6 R = CPh_3

Preparation of the Half-Crown **2** *Using Sodium tert- Butoxide as Base*

Metallic sodium (1.4 g, 0.06 mol) was caused to react with absolute *tert*-butyl alcohol (50 mL) under stirring and reflux, and a solution of the diacetal **3** (5.2 g, 0.02 mol) in absolute tetrahydrofuran (10 mL) was added. The mixture was maintained under reflux and stirring for an additional 2 hours, after which diethylene glycol ditosylate (4.14 g, 0.01 mol) in absolute tetrahydrofuran was added. After 25 hours at reflux, the reaction mixture was poured

into ice-water (100 mL), and the resulting suspension was evaporated to dryness in vacuo. The residue was extracted with chloroform (200 mL) and the extracts washed successively with 10% $NaHCO_3$ solution (100 mL) and water (100 mL). Drying of the chloroform extract over Na_2SO_4 gave, on evaporation, a yellow oil, from which was obtained by column chromatography, as before, the half-crown **2** (0.28 g, 4.7%). One of the two other compounds of the product mixture was shown to be the monotosyl by-product **4**.

Preparation of 2,2'-Di-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl)diethylene Glycol **2** *without Formation of* **4**

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose **3** (2.84 g, 0.011 mol) was dissolved in absolute DMF (30 mL), and 55% paraffin-free sodium hydride (3.02 g, 0.069 mol) was added. After the mixture had been stirred for 1 hour at 60°C, a solution of diethylene glycol ditosylate (2.28 g, 0.006 mol) in absolute DMF (30 mL) was added. The reaction mixture was further diluted with DMF (20 mL), and the solution was maintained at 60°C for 30 hours. The reaction mixture was cooled, water (60 mL) added, and the resultant solution extracted with chloroform (3 × 50 mL). The combined chloroform phases were washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated to yield the title compound, as a thick syrup (2.0 g, 62%), $[\alpha]_D^{20} = -27.05°$ (c 5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28, 1.32, 1.40, 1.45 (8 × CH_3, 4 × s), 3.55–4.32 (18H, m, OCH_2CH_2O and other CH and CH_2 groups), 4.48 (2H, d, 2, 2^1-H J = 4 Hz), 5.88 (2H, d, anomeric-H, J = 4 Hz); **ms** *m/z* 575 (83.9), 474 (6.0), 373 (10.9), 101 (100), 59 (18.2), 45 (27.2%). Anal. calcd. for $C_{28}H_{46}O_{13}$ (590): C, 56.95; H, 7.80; O, 35.25. Found: C, 57.12; H, 7.60; O, 35.20.

Preparation of 2,2'-Di-O-(1,2-O-isopropylidene-α-D- glucofuranos-3-yl)diethylene Glycol **5**

The *bis*-diacetal **2** (6.81 g) was dissolved in dioxane (20 mL), and a solution of ethanoic acid (33 mL) in water (14 mL) was added. The reaction mixture was maintained under stirring at 65° for 2 hours. The solution was concentrated in vacuo, the residue dissolved in water (100 mL) and extracted with chloroform (2 × 10 mL). The aqueous phase was again concentrated and the acetic acid removed by azeotropic distillation with toluene to yield the title compound as a yellow syrup. (5.4 g, 92%), $[\alpha]_D^{20} = 16.2$ (c 5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 (6H, s, 2 × CH_3), 1.45 (6H, s, 2 × CH_3); 3.55–4.12 (18H, m, OCH_2CH_2O, CH2, CH), 4.50 (2H, d, 2,2'-H, J = 4 Hz), 5.87 (2H, d, 2 × 1-H, J = 4 Hz) Anal. calcd. for $C_{22}H_{38}O_{13}$ (510): C, 51.67; H, 7.45. Found: C, 52.21; H, 7.30.

Preparation of 2,2'-Di-O-(1,2-O-isopropylidene-6-O-triphenylmethyl-α-D-glucofuranos-3-yl)diethylene Glycol **6**

Diethylene glycol-di-(1,2-O-isopropylidene-α-D-glucofuranos-3-yl) **5** (1.26 g, 2.5 mmol) dissolved in a mixture of dichloromethane (10 mL) and triethylamine (3 mL) was treated with triphenylmethyl chloride (1.38 g, 5.0 mmol) and stirred for 5 hours at room temperature. The reaction mixture was washed successively with water (10 mL), 2M HCl (10 mL), and 10% aq $NaHCO_3$ solution (10 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was digested with hot petroleum ether (10 mL), and the residue was dried in a vacuum desiccator to yield the title compound as a yellow amorphous solid (1.90 g, 78.5%), $[\alpha]_D^{20} = 20.1$ (c 5, $CHCl_3$), mp 96–101°; ^1H NMR ($CDCl_3$) δ 1.26 (6H, s, 2 × CH_3), 1.44 (6H, s, 2 × CH_3), 3.25–4.05 (18H, m, OCH_2CH_2O, CH, CH2), 4.46 (2H, d, 2,2'-H, J = 4 Hz), 5.78 (2H, d, C1-H, J = 4 Hz), 7.10–7.52 (30H, m, aromatic-H). Anal. calcd. for $C_{60}H_{64}O_{13}$ (992): C, 72.59; H, 6.45. Found: C, 72.50; H, 6.40 MS (70 eV) $m/z(M^+$ 992).

Preparation of bis-(1,2,-O-Isopropylidene-6-O-triphenylmethyl-α-D-glucofuranos-3,5-diyl)-20-crown-6 **1**

The diethylene glycol glucose derivative **5** (4.78 g, 4.9 mmol) was dissolved in absolute tetrahydrofuran (40 mL), and 55% petroleum-washed sodium hydride (1.28 g, 28.4 mmol) was added. The resulting suspension was stirred for 1 hour at 60°C, and diethyleneglycol ditosylate (2.03 g, 4.9 mmol) in absolute tetrahydrofuran (10 mL) was added. The mixture was stirred for an additional 40 hours at 60°C. The cooled solution was added dropwise into water (5 mL) to decompose unreacted sodium hydride. The mixture was filtered and the filtrate evaporated in vacuo. The residue was washed successively with water, 2M HCl, 10% aq $NaHCO_3$ solution, and finally dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using Kieselgel 60 with toluene-ethyl acetate (5:3) as eluent. The title crown ether was obtained as a white amorphous solid (0.21 g, 4%), mp 62–67°C. $[\alpha]_D^{20} = -17.2$ (c 3.0 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.27 (6H, d, J = 4 Hz, 2 × CH3), 1.44 (6H, s, 2 × CH_3), 3.25–4.08 (26H, m, OCH_2CH_2O, CH; other CH_2), 4.48 (2H, d, J = 4 Hz, 2,2'-H), 5.75 (2H, d, J = 4 Hz, 2 × anomeric H), 7.10–7.52 (30H, m, Ph). Anal. calcd. for $C_{64}H_{22}O_{14}$ (1066): C, 72.18; H, 6.77. Found: C, 71.77; H, 6.91.

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