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The formation of a cyclic diacetal of methyl α-D-mannopyranoside with a 16-membered macrocyclic loop

Jolanta Maslinska-Solich,*[a] Nikodem Kuznik,[b] Maciej Kubicki[c] and Sylwia Kukowka[a]

[a] *Institute of Physico-Chemistry and Polymer Technology, Silesian University of Technology, Strzody 9, 44-101 Gliwice, Poland. E-mail: jms1acet@zeus.polsl.gliwice.pl*

[b] *Institute of Inorganic Chemistry, Technology and Electrochemistry, Silesian University of Technology, Krzywoustego 6, 44-101 Gliwice, Poland. E-mail: nikodem@zeus.polsl.gliwice.pl*

[c] *Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznan, Poland*

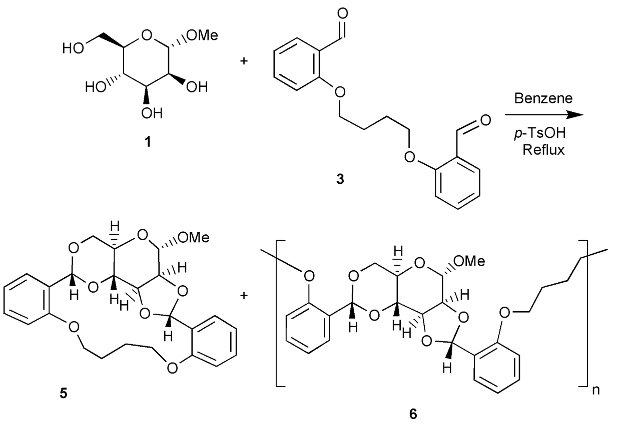
Received (in Cambridge, UK) 4th March 2002, Accepted 21st March 2002
First published as an Advance Article on the web 5th April 2002

The X-ray structure of a diacetal with a 16-membered macrocyclic loop, which was obtained as a product of the condensation of methyl α-D-mannopyranoside and 1,4-bis(2-formylphenoxy)butane is presented together with polymeric compounds resulting from polycondensation; a similar polymer was formed in the reaction of methyl 2,3:4,6-di-*O*-salicylidene-α-D-mannopyranoside with 1,4-dibromobutane.

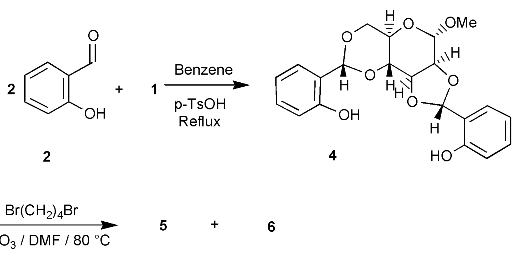
Over the past two decades numerous macrocycles have been synthesized, with much attention focused on the systems derived from carbohydrates.[1] The sources of chiral crowns[2] and cryptands[3,4] are monosaccharide derivatives, frequently methyl 4,6-*O*-benzylidene-α-gluco-, α-D-galacto- and α-D-mannopyranosides. Chiral crown ethers and cryptands originating from derivatives of the methyl hexopyranoside residue were found to show chiral recognition of primary amine[5,6] and aminoester salts.[7-9] Kakuchi *et al.*[10] described syntheses of chiral poly(crown ether)s *via* cyclopolymerization of divinyl ethers containing altro- galacto-, gluco- and mannopyranoside moieties. The enantioselective transport of methyl esters of phenylglycine and phenylalanine through bulk and solution of chiral polymers[10] was examined.

Recently, our investigations have been focused on polyacetals derived from methyl α-D-mannopyranoside **1** and dialdehyde.[11] The polycondensation of **1** with terephthaldehyde under selected reaction conditions gave polymers with molecular weights ranging from 1000 to 7000 g mol^{-1}. It has been confirmed that the polymer chain is constructed of cyclic (5- and 6-membered) acetal rings of dialdehyde and **1**. Their transformation into polyesters was achieved in the oxidation reaction with *N*-bromosuccinimide.[11]

In this paper we report the synthesis, structure and spectroscopic data of the products formed in the acetalation of **1** with salicyldehyde **2** or 1,4-bis(2-formylphenoxy)butane **3**. The condensation or polycondensation of **1** with **3** was performed in solution in the presence of a catalytic amount of toluene-*p*-sulfonic acid. If the molar ratio of co-monomers was 1 : 1, the major product[12] was cyclic diacetal **5** (57% yield) and polymer **6**. Evidence for the cyclic diacetal compound **5** is demonstrated in the NMR spectra. The characteristic signals due to methoxy protons at 3.41 ppm, acetal protons in the region of 5.89 and 6.54 ppm and aromatic protons at 6.55–7.02, 7.2–7.50 and 7.50–7.52 ppm, which exist in the ratio 3 : 2 : 8 respectively, confirmed that the condensation product **5** consists of two cyclic acetal rings bridged by a di-*O*-[2,2′(1,4-butoxy)]phenylidene unit. Although the spectral and analytical data were generally consistent with compound **5**, its structure could be determined unambiguously by X-ray crystallographic analysis. These X-ray studies of **5** are to our knowledge, the first analysis report of a cyclic diacetal of methyl α-D-mannopyranoside with a 16-membered macrocyclic loop.



Scheme 1 Synthesis of macrocyclic and polymeric compounds.



Scheme 2 Alternative synthetic path of polycondensation.

The asymmetric part of the unit cell contains two symmetry-independent molecules; one of them is slightly disordered in the alkyl chain, refined in two positions. As is depicted in Fig. 1, compound **5**†‡ adopts a *trans*-decaline-like conformation which places the phenoxy group attached to the 1,3-dioxane ring in an equatorial orientation. The conformation of the five-membered 1,3-dioxolane rings is different in the two symmetry-independent molecules: in one of the molecules it is close to an envelope, while in the other—to a distorted half-chair. Both

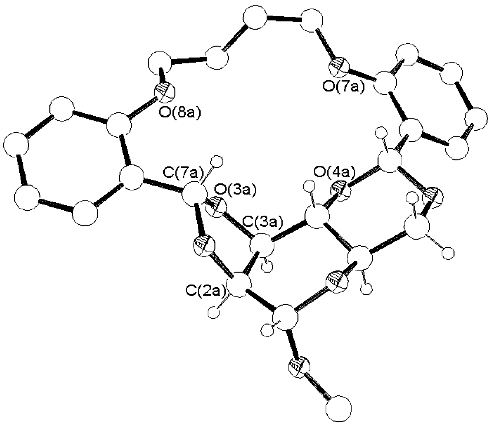


Fig. 1 Molecular structure of one of the two independent molecules of **5** (40% displacement ellipsoids).

DOI: 10.1039/b202273g

symmetry-independent molecules are H-*endo* isomers [at C(7)]. Similar isomers[13] of benzylidene-, alkenylidene-acetals of **1** have been reported. The macrocyclic 16-membered ring can be expected to accommodate small molecules. Its diagonals (defined by the O···O distances) range from 4.646(4) to 4.847(4) Å. The macrocyclic 16-membered loop confines a bent tetragon of shape close to a trapezium with the sides: O(7a)···O(8a): 4.435(4); O(4a)···O(3a): 3.057(4); O(7a)···O(4a): 3.059(4); O(8a)···O(3a): 2.963(4) Å.

The oligomer and polymer fractions were obtained by two alternative synthetic paths. The acetalation of **1** with salicylaldehyde **2** under acid-catalysed (PVP–TsOH) conditions yields a mixture of diastereoisomers at the acetal position of 1,3-dioxolane rings (in approximately equal amounts).[14] Alkaline-catalysed condensation of methyl 2,3:4,6-di-*O*-salicylidene-α-D-mannopyranoside[14] **4** with 1,4-dibromobutane under standard conditions (K_2CO_3)[15] in butyl acetate gave the expected polycondensates in high yield (87%). A small amount of **5** (5%) was also isolated after flash column chromatography purification. The evidence for polymer **6** was confirmed by SEC analysis (Mn = 800–2100 g mol^{-1}). The NMR data of polymer **6** have been used to establish the configuration of a five-membered acetal ring at C(2) and C(3) of the methyl α-D-mannopyranoside units in the polymer chain. The ^{1}H-NMR spectrum of **6** consists of several sets of bands produced by acetal protons at 5.4–5.6 and 5.8–6.0 ppm (1,3-dioxane), 6.1–6.2 ppm (H-2 *exo* 1,3-dioxolane) and 6.4–6.6 ppm (H-*endo* 1,3-dioxolane). The relative intensities of *endo*-H and *exo*-H (in the 1,3-dioxolan-2yl ring) were 2 : 1. The characteristic signals of methoxy, acetal and aromatic protons provide evidence that the repeating units in the polymer chain consist of one molecule of **1** and one of **3**.

The formation of the macrocycle **5** and polymer **6** can be discussed on the basis of the dynamic chemistry.[16,17] Direct acid-catalysed acetalation of two bifunctional building blocks **1** and **3** is driven to macrocycle **5** (57% yield) and polymer **6**. Macrocycle formation was efficient under thermodynamic conditions, whereas the polymer was formed under kinetically controlled conditions which led to mixture of *exo*-H and *endo*-H (in 1,3-dioxolane) units.

Further investigations are in progress in order to confirm the binding selectivity of methyl α-D-mannopyranoside with 1,ω-dialdehyde in the formation of macrocyclic diacetals and new class of sugar polymers.

Notes and references

† *Spectral data of* **5**: ^{1}H NMR ($CDCl_3$, 300 MHz, $SiMe_4$) δ 1.9–2.2 (m, 4H), 3.4 (s, 3H), 3.8–3.83 (m, 2H), 3.91–4.03 (m, 3H), 4.05–4.15 (m, 3H), 4.24–4.22 (d, J 5.7Hz, 1H), 4.59–4.54 (dd, J5.7 and 8.2 Hz, 1H), 5.07 (s, 1H), 5.89 (s, 1H), 6.54 (s, 1H), 6.86–6.96 (m, 4H), 7.27–7.3 (m, 2H), 7.59–7.52 (dd, 2H) ^{13}C NMR($CDCl_3$, 75 MHz) δ 27.52, 55.09, 59.89, 69.74, 69.87, 75.25, 75.86, 76.34, 98..43, 98.75, 99.29, 113.49, 120.64, 120.94, 125.56, 125.89, 130.24, 157.50, 157.80; satisfactory elemental analysis obtained.

‡ *Crystal data for compound* **5**: $C_{25}H_{28}O_8$, M = 456.47, monoclinic, space group $P2_1$, a = 11.955(2), b = 16.560(3), c = 12.578(3) Å, β = 113.83(3)°, U = 2277.8(8) Å^3, Z = 4, T = 293(2) K, μ(Cu-Kα) = 0.825 mm^{-1}, D_c = 1.331, 3997 reflections measured, of which 3791 independent (R_{int} = 0.0288) R_f = 0.0402 [3570 data $F_o > 4\sigma(F_o)$], $wR(F^2)$ = 0.0980, S = 1.00. Largest residual density peak (0.32 e Å^{-3}) is located close to atom C7B (1.33 Å). CCDC 166041. See http://www.rsc.org/suppdata/cc/b2/b202273g/ for crystallographic files in .cif or other electronic format.

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12 *Synthesis of methyl 2,3(R);4,6(R)-di-O-[2,2(1,4-butoxy)]phenylidene-α-D-mannopyranoside* **5**. A mixture of **1** (0.01 mol, 1.94 g) and **3** (0.01 mol 2.98 g) in benzene (50–100 ml), TsOH (0.05–0.1 g), was subjected to azeotropic distillation (Dean-Stark). After 20 h the catalyst was deactivated with CaO and the solvent was removed under reduced pressure. The white powder of the products was filtered off (analyzed by TLC, NMR). A mixture of compounds was fractionated on silica gel ($CHCl_3$:CH_3OH 20:1). The solutions were concentrated and the residue was subjected to low pressure at 80–100 °C/3 mmHg. Appropriate crystals were obtained by crystallization from ethyl acetate : chloroform (8 : 1) and by diffusion of heptane to the 1,4-dioxane solution, mp.229.6 °C, $[\alpha]^{25}{}_{546}$ = −56.0° (c.1 $CHCl_3$). The residue of polycondensation products was purified by reprecipitation in THF–ethanol, SEC 800–2100 g mol^{-1}; $[\alpha]_{546}{}^{25}$ = +16 to −25.0° (c.1 $CHCl_3$).

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15 *Polycondensation of methyl 2,3 : 4,6-di-O-salicylidene-α-D-mannopyranoside* **4** *with 1,4-dibromobutane*. A mixture of **4** (6.3 mmol, 2.55 g), 1,4-dibromobutane (6.3 mmol, 1.36 g) and 1.80 g of K_2CO_3 in 50 ml of a mixture of DMF–butyl acetate (1 : 10) was heated at 80 to 100 °C. After 20 h the mixture was filtered off and solvents were removed under reduced pressure. The residue **6** was purified by flash chromatography.^{1}H NMR ($CDCl_3$) of **6** δ 1.80–2.10 (m, CH_2), 3.36–3.43(m., OCH_3), 3.80–4.85 (m, OCH, OCH_2), 4.98–5.09(m., $OCHO_{anom}$), 5.3–5.6 and 5.8–6.0(m OCHO, H-2 dioxan-2-yl), 6.10–6.24(m, OCHO, H-2 dioxolan-2-yl, *exo*), 6.42–6.60(m, OCHO, H-2 dioxolan-2-yl, *endo*), 6.89–7.04(m., Ar), 7.20–7.42(m, Ar), 7.43–7.72 (m, Ar), 7.80–7.82 (m, Ar), 10.49–10.5 (m, CHO).

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