Synthesis of Functional Polymers with Acetal-Monosaccharide Moieties

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Summary: The polycondensation of methyl α-D-mannopyranoside (**1**) with 1,n-bis(formylphenoxy)alkanes (**2**), using acidic catalysts, leads to the formation of linear polymers and macrocyclic compounds. The structure of the polymer and macrocycles was determined by ^{1}H, ^{13}C NMR spectroscopy and ESI-MS analysis.

Keywords: acetal; dialdehydes; macrocycle; methyl α-D-hexopyranoside; polycondensation

Introduction

The monosaccharides are probably the most densely functionalized naturally occurring organic molecules and are undoubtedly among the most important molecules in the biochemistry of all living things. Synthetic polymers combined with carbohydrates are of great interest in the applications as polymeric protecting groups, polymer support in the asymmetric synthesis or polymer-supported phase transfer catalysts.[1]

Recently, our investigations have been focused on the polyacetals derived from methyl D-hexopyranosides with terephthaldehyde[2] or 1,4-bis(2-formylphenoxy)butane.[3] It was found that in the polymer syntheses the equilibrium of macrocycles and linear macromolecules are occurred. Polymer of **1** with terephthaldehyde was tested as a polymeric phase transfer catalyst in the polyetherification reactions.[4]

In this paper, we report the results of studies on the equilibration reactions in the polycondensation of methyl α-D-mannopyranoside (**1**) with 1,n-bis(formylphenoxy)alkanes (**2**).

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Experimental

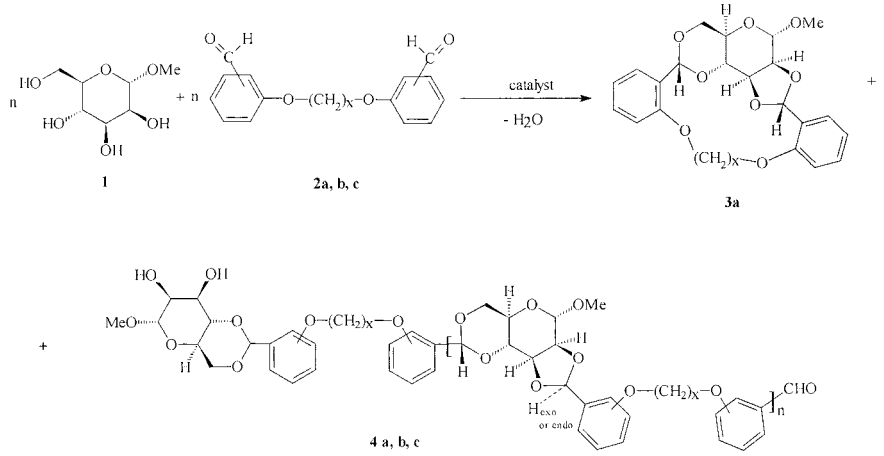
Measurements

^{1}H and ^{13}C NMR spectra were recorded using a Varian Unity/Inova spectrometer (300 MHz and 75 MHz, respectively) in deuterated chloroform with tetramethylsilane as an internal standard.

Gel permeation chromatography (GPC) analyses were performed in tetrahydrofuran using Waters System equipped with a refractive index detector. Two (300 x 7.5) PL-gel mixed E (3 μm) columns were used and maintained at 40 ^{0}C. Polystyrene standards (Polymer Laboratories) were used to calibrate the system. ESI MS experiments were carried out using a Finnigan MAT TSQ 700 triple stage quadrupole mass spectrometer equipped with an electrospray ionization (ESI) source (Finnigan, San Jose, CA, US).

Optical rotation measurements were made in chloroform solution using a Carl-Zeiss Jena Polamat A spectropolarimeter with a sensitivity $\pm 0.01^{o}$.

Polycondensation of 1 with 2



Scheme 1. Polyacetalising of methyl α-D-mannopyranoside (**1**) with 1,n-bis(formylphenoxy)alkanes (**2**)

General procedure:

A mixture of **1** (0.05 mol) and **2(a,b,c)** (0.05 mol) in solution (benzene/dioxane, benzene/DMF, benzene/DMSO) containing TsOH (0.2-0.05 g), or PVP-TsOH (0.6-1.5 g) was subjected to azeotropic distillation (Dean-Stark). After 8-27 h the catalyst was filtered off (or deactivated with $CaCO_3$) and the solvent was removed under reduced pressure. The residue was extracted with chloroform, the organic layer was washed with a solution of $NaHSO_3$, water (3-4 times), and dried over anh. $MgSO_4$ and filtered off. The chloroform was removed under reduced pressure and the residue was analyzed by TLC, NMR. The reaction mixture of compounds was fractionated on silicagel (flash chromatography). The polymeric materials were purified by reprecipitation in THF/ ethanol.

For **4a** (where x = 4), $[\alpha]^{20}_{546}$ (c. 1, $CHCl_3$)= +16.5 deg · dm^{-1} · g^{-1} · cm^3.

^{1}H NMR ($CDCl_3$): δ [ppm] = 1.70–2.20 (m, -C**H**$_2$-); 3.30–3.50 (m, -OC**H**$_3$); 3.60–4.71 (m, -OC**H**-, -OC**H**$_2$-); 4.76–5.20 (m, -OC**H**O $_{anom}$); 5.80–6.04 (m, -OC**H**O-, H-2 dioxan-2-yl); 6.12–6.36 (m, -OC**H**O-, H-2 dioxolan-2-yl, *exo*), 6.54–6.68 (m, -OC**H**O-, H-2 dioxolan-2-yl, *endo*), 6.70–7.90 (m, **H**$_{Ar}$, Ar-O**H**), 10.40–10.60 (m, -C**H**O)

^{13}C NMR ($CDCl_3$): δ[ppm] = 24.0–27.6 (-**C**H$_2$-); 55.1–82.0 (-O**C**H$_3$, -**C**H$_2$O-, -O**C**H-); 96.0–102.0 (-O**C**HO-acetal); 110.0–136.0 (**C**$_{Ar}$); 155.0–160.0 (**C**$_{Ar}$-O-); 190.0 (-**C**HO).

For **4b** (where x = 4), $[\alpha]^{20}_{546}$ (c. 2.5, $CHCl_3$) = -2.5 deg · dm^{-1} · g^{-1} · cm^3.

^{1}H NMR ($CDCl_3$): δ [ppm] = 1.80–2.10 (m, -C**H**$_2$-); 3.30–3.50 (m, -OC**H**$_3$); 3.63–4.66 (m, -OC**H**-, -OC**H**$_2$-); 4.70–5.08 (m, -OC**H**O $_{anom}$); 5.44–5.63 (m, -OC**H**O-, H-2 dioxan-2-yl); 5.85–5.94 (m, -OC**H**O-, H-2 dioxolan-2-yl, *exo*), 6.09–6.25 (m, -OC**H**O-, H-2 dioxolan-2-yl, *endo*), 6.84–7.48 (m, **H**$_{Ar}$, Ar-O**H**), 9.92–10.00 (m, -C**H**O).

^{13}C NMR ($CDCl_3$): δ[ppm] = 26.0–26.4 (-**C**H$_2$-); 55.1–80.6 (-O**C**H$_3$, -**C**H$_2$O-, -O**C**H-); 99.9–104.1 (-O**C**HO-acetal); 112.0–140.4 (**C**$_{Ar}$); 159.0–159.8 (**C**$_{Ar}$-O-); 192.4 (-**C**HO).

For **4c** (where x = 4), $[\alpha]^{20}_{546}$ (c. 2.5, $CHCl_3$) = -17.6 deg · dm^{-1} · g^{-1} · cm^3.

^{1}H NMR ($CDCl_3$): δ [ppm] = 1.84–2.04 (m, -C**H**$_2$-); 3.31–3.42 (m, -OC**H**$_3$); 3.64–4.64 (m, -OC**H**-, -OC**H**$_2$-); 4.76–5.06 (m, -OC**H**O $_{anom}$); 5.45–5.60 (m, -OC**H**O-, H-2 dioxan-2-yl); 5.86–5.90 (m, -OC**H**O-, H-2 dioxolan-2-yl, *exo*), 6.11–6.24 (m, -OC**H**O-, H-2 dioxolan-2-yl, *endo*), 6.80–7.84 (m, **H**$_{Ar}$, Ar-O**H**), 9.93–9.92 (m, -C**H**O)

^{13}C NMR ($CDCl_3$): δ[ppm] = 25.8–26.0 (-**C**H$_2$-); 55.0–80.6 (-O**C**H$_3$, -**C**H$_2$O-, -O**C**H-); 98.7–

104.1 (-O**C**HO-acetal); 114.1–132.0 ($\mathbf{C}_{Ar}$); 164.0 ($\mathbf{C}_{Ar}$-O-); 190.8 (-**C**HO).

Results and discussion

The polycondensation of **1** with dialdehyde **2** (**a,b,c**) was performed in solution (benzene/dioxane, benzene/DMF, benzene/DMSO) in the presence of a catalytic amount of p-toluenesulfonic acid (TsOH) or its complex with poly(4-vinylpyridine) PVP-TsOH under azeotropic removal of water.

The formation of macrocycles and polymers was followed by ^{1}H NMR spectroscopy.

In case of a 1:1 molar ratio of comonomers **1** and **2a** (**x = 4, 8, 10, 12**), in benzene/DMSO as solvent, the major products were cyclic diacetals **3a** (where **x = 4, 8, 10, 12**) and linear polymers **4a** (see Table 1).

Table 1. Formation of macrocycles as a function of dialdehyde **2** structure.

-$(CH_2)_x$-	Macrocycles 3a [%]	Polymer 4a [%]
4	69.8 [1+1] [2+2]	30.2
8	58.9 [1+1]	41.1
10	50.1[1+1]	48.1
12	29.7 [1+1]	70.3

$[M_1]$= $[M_2]$=0.1 mole/dm^3; benzene-DMSO (4:1),TsOH as catalyst; 12h

The evidence of the cyclic diacetal **3a** is demonstrated in the NMR spectrum (Figure 1, for **3a** where x = 8).

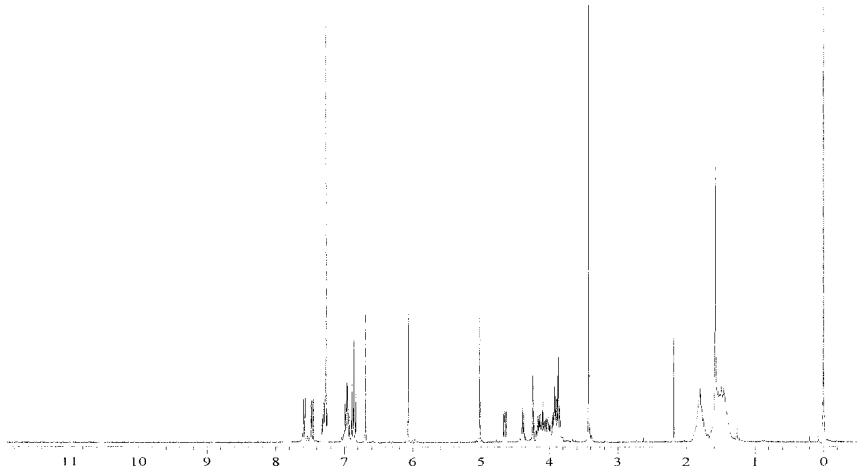


Figure 1. ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of the macrocyclic compound **3a** (x = 8).

The characteristic signals due to methoxy protons at 3.41 ppm, acetal protons in the region of 5.89–6.06 and 6.54–6.68 ppm and aromatic protons at 6.55-7.52 ppm, confirmed that the condensation product **3a** consists of two cyclic acetal rings bridged by a di-O-[2,2'(1,n-alkoxy)]phenylidene unit (Table 2).

Table 2. Chemical shifts of acetals and C^1 (anomeric) protons of selected macrocyclic compounds **3a**.

	Chemical shifts [ppm]		
	2,3-acetal	4,6-acetal	OCHO anom.
Methyl 2,3:4,6-di-O-[2,2(1,4-butoxy)]phenylidene-α-D-mannopyranoside	6.54 H *endo*	5.89	5.08
Methyl 2,3:4,6-di-O-[2,2(1,8-octoxy)]phenylidene-α-D-mannopyranoside	6.68 H *endo*	6.06	5.01
Methyl 2,3:4,6-di-O-[2,2(1,10-decoxy)]phenylidene-α-D-mannopyranoside	6.65 H *endo*	6.01	5.02
Methyl 2,3:4,6-di-O-[2,2(1,12-dodecoxy)]phenylidene-α-D-mannopyranoside	6.67 H *endo*	6.04	5.01

A detailed ^{1}H NMR and X-ray analysis of **3a** (x = 4) confirmed that the conformation of five-membered 1,3-dioxolane rings is different in two symmetry-independent molecules: in one of the molecules it is close to an envelope, while the other one has a distorted half chair. Both symmetry-independent molecules are H-*endo* isomers. Whereas the substituent at C-2 (in 1,3-dioxane) is in equatorial orientation with respect to the chair-shaped dioxane ring fused to a tetrahydropyran ring.[3]

Moreover the presence of macrocycles were detected by ESI mass spectrometry (Figure 2). Analyses of ESI MS **3a** (where x = 4) revealed the presence of potassium adduct ions with m/z values 495.5 and 950.9 that correspond to the individual macrocycles [1+1] and [2+2].

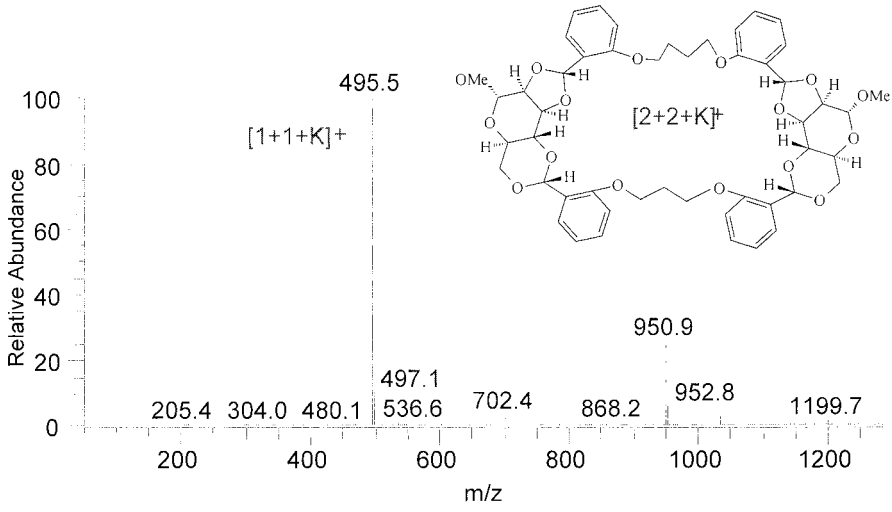


Figure 2. ESI MS macrocycles [1+1] and [2+2] of **3a** (x = 4).

It has shown the ability of co-monomers to form also the linear macromolecules that co-exit with macrocyclic structure. The polymers were soluble in THF, $CHCl_3$, DMSO but insoluble in alcohols, aliphatic and aromatic hydrocarbons. The polymers were purified by repeated precipitation with ethanol from solution in THF. It was noted that the specific rotation, the molecular weight and molecular weight distribution depends on the structure of 1,n-bis(formylphenoxy)alkanes (**2**).

The polycondensation of **1** with 1,4-bis(3-formylphenoxy)butane **2b** or 1,4-bis(4-formylphenoxy)butane **2c** leads to the formation only of linear polymers with molecular range from 2500 to 4500 g · mol^{-1} (M_w, GPC).

The NMR data of polymer have been used to establish the configuration of a five-membered acetal ring at C (2) and C (3) of **1** in the polymer chain of **4**.

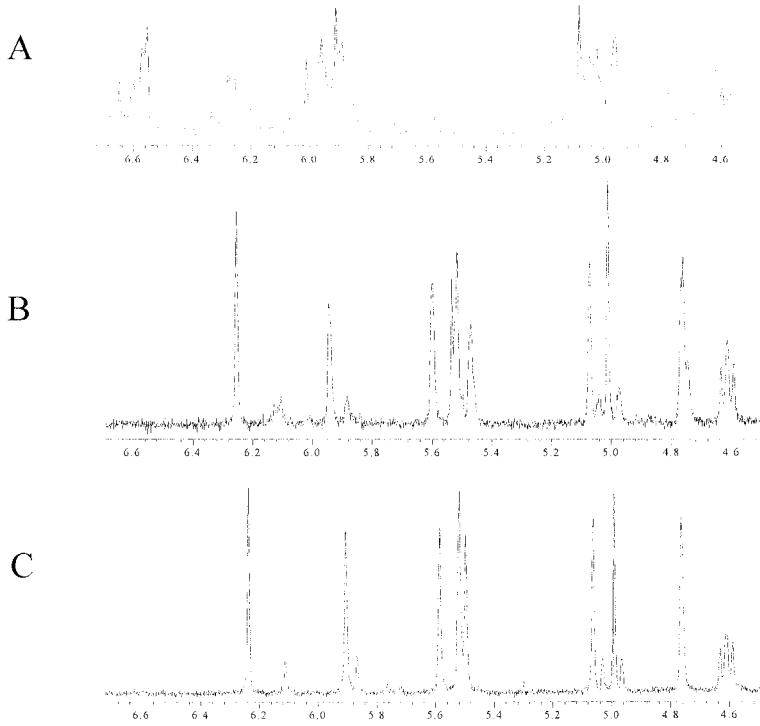


Figure 3. ^{1}H NMR (300 MHz, $CDCl_3$) spectra (expansion of the region 4.6 to 6.6 ppm) of polymers A - **4a,** B - **4b,**C - **4c**.

^{1}H NMR spectra (expansion region of OCHO protons) show characteristic signals of anomeric C-1 protons at 4.7-5.2 ppm, the acetal protons at 5.8-6.0 ppm (1,3-dioxane), 6.1-6.4 ppm (H-*exo* 1,3-dioxolane) and 6.5-6.7 ppm (H-*endo* 1,3-dioxolane) for polymer **4a** (x = 4).

The influence of steric factors caused by five-membered acetal rings (which adopt a suitable half-

chair or twist conformation) with six-membered acetal rings in a sugar unit has been considered as an interpretation of multi-set signals of acetal protons (**4a**, Fig. 3 A). However, slight sterically effect in polymers **4b** and **4c** is shielded the acetal protons as can be seen in Figure 3(B and C). The characteristic signals due to the OCHO protons appear at 5.4-5.6 ppm (1,3-dioxane), 5.8-5.9 ppm (H-2 *exo* 1,3-dioxolane) and 6.1-6.3 ppm (H-*endo* 1,3-dioxolane).

It is known that methyl 2,3:4,6-di-O-benzylidene-α-D-mannopyranoside exists in C1 conformation where the 1,3-dioxolane (at C-2 and C-3) system shows a strong preference for the *endo*-H (*exo*-phenyl) isomer.[5]. The *exo*-H diastereomer was only formed by benzylidenation of **1** with benzylidene bromide under basic-catalyzed (potassium tert-butoxide) conditions.[6] Clode[7] postulated that the acid-catalyzed acetal formation might be divided into a kinetic and a thermodynamic phase. Then, *endo*-phenyl diastereomer of methyl 2,3:4,6-di-O-benzylidene-α-D-mannopyranoside was formed acid catalyzed under kinetically controlled conditions.

The formation of **3a** (x = 4, 8, 10, 12) may need thermodynamically rather than kinetically controlled conditions for the given reaction. Thus, although there are theoretically four possible intramolecular condensations of **1** with **2a**, only one compound **3a** (highly favored H-2 *endo*-5-membered ring and H-2 *axial*-6-membered ring) is produced.

The presence of *endo*-H and *exo*-H isomers of five-membered rings in the polymer chains **4** can be explained by less sterically interactions between methyl α-mannopyranosyl and arylidene groups in the kinetically controlled polycondensation.

All these results confirm that the polymer **4** is constructed of the cyclic acetal rings (five and six-membered) of dialdehyde **2** and methyl α-D-mannopyranoside. The chemical analysis has also established the presence of macromolecular chains containing formyl and hydroxyl end groups.

From the experimental data one can conclude that macrocycle formation was efficient under thermodynamic conditions (*endo*-H isomer), whereas the polymer was formed under kinetically controlled conditions which led to a mixture of *exo*-H and *endo*-H (in 1,3-dioxolane) units.

The relative quantities of *endo*-H and *exo*-H (in 1,3-dioxolan-2yl ring) units in the linear macromolecules are equal 1:1. This relationship is valid for the polymers with molecular weights $M_w \sim 2000\ g \cdot mol^{-1}$.

In spite of the moderate stability of these new compounds, their transformation into functional polymers has been achieved in thermal or chemical conditions. Further investigations are in

progress in order to explore the synthetic potential of this new class of sugar polymers as chiral catalysts.

Conclusion

The results of this work indicate that the polycondensation of methyl α-D-mannopyranoside (**1**) with 1,n-bis(formylphenoxy)alkanes (**2**) in the presence of acidic catalyst yields polyacetals. It was demonstrated that the intramolecular cyclization reactions [1+1] of **1** with 1,n-bis(2-formylphenoxy)alkanes decrease with the elongation of an alkane spacer between phenoxyaldehyde units. The formation of linear macromolecules with *endo*-H and *exo*-H isomers of five-membered rings in the polymer chain supports the regioselective character of this reaction.

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