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Synthesis of macrocyclic and linear oligomers of methyl α-D-mannopyranoside**)

Summary — The polycondensation of methyl α-D-mannopyranoside (I) with 1,x-bis(2-formylphenoxy)alkanes (II) using various acid catalysts leads to the formation of macrocyclic compounds [1+1] and [2+2] and linear copolymer. NMR and ESI-MS studies demonstrated the evidence of structure of macrocyclic compounds. The structure of dialdehyde, the nature of the catalyst, and in particular, the molar ratio of catalyst to dialdehyde, show a very pronounced effects on yield of the resulting macrocycles.

Key words: polycondensation, polyacetals, macrocycles, methyl α-D-mannopyranoside.

Macrocyclic compounds are now used for a variety of applications [1] such as sensors, imaging agents, catalysts, and for ion analysis, providing further impetus for the development of this area. In particular, the incorporation of carbohydrate subunits into a macrocyclic ring has been the focus of much attention due to the unusual chemical, physical and biological properties that such systems exhibit.

In 1912 Ruggli [2] published the first syntheses of macrocycles under conditions which were later called "Ruggli—Ziegler dilution method" (RZDM) [3]. This RZDM then became the standard procedure for the preparation of macrocycles. This method is based on the consideration that difunctional monomer under conditions allowing for a clean and rapid reaction has the choice to undergo cyclization or dimerization. Analogously, higher oligomers have the choice between cyclization and polycondensation. However, this approach is expensive and makes it difficult to synthesize larger quantities of macrocycles.

The important role of cyclization in polycondensation has not been demonstrated until very recently by Kricheldorf *et al.* [4]. In the classical theory of polycondensation as developed by Carothers [5] and Flory [6, 7] cyclization reactions do not play any role, and no differentiation between kinetically controlled and thermodynamically controlled polycondensations (TCP) was made. In 1950 Jacobson and Stockmayer [8] modified this theory, demonstrating that in TCP cyclic oligomers and polymers may be formed by "back-biting degradation". Thermodynamically controlled polycondensation concerns polycondensation involving "back-biting degradation" and other equilibrium reactions (also called transreactions or interchange reactions). In contrast, the kinetically controlled polycondensation (KCP) is characterized by the absence of equilibrium and "back-biting" reactions and the resulting reaction mixtures do not necessarily represent thermodynamically the most stable situation. It is still accepted in all textbooks that according to the equation of Carothers a clean TCP and KCP running up to 100 % conversion will yield one gigantic polymer chain with a low weight percentage of cyclic oligomers as byproduct of the "back-biting equilibrium". Meanwhile, the recent mathematical and experimental treatment of KCPs [4] has shown cyclization to compete with propagation at any concentration and at any stage of the polycondensation process.

Many macrocyclic polyether systems have been prepared since Pedersen's earlier syntheses of derivatives of crown ether [9]. The method exploits spontaneous self-assembly of the substrates, that proceeds their linking *via* covalent bond(s), on regio- and stereochemistry of the occurring processes with the special attention being paid to the role of so-called "templates", determining the orientation of the substrates due to the stabilization of particular transition states. Hydrogen bonding, lipophilic, hydrophilic interactions or combination of them in a molecule have proven to be particularly prevalent in design efforts to control a self-assembly [10].

Our interest has been focused on the synthesis, structure and stereochemistry of polyacetals formed in the

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acetalization of methyl D-hexopyranisides with dialdehyde. Early studies in our laboratory demonstrate that the reaction of methyl α-D-mannopyranoside [Formula (I) on Scheme A] with dialdehydes (terephthalaldehyde [11] or 1,x-bis(2-formylphenoxy)alkanes [Formula (II) on Scheme A] [12—15]) leads to the formation of macrocycles and linear macromolecules. The present paper deals with studies on parameters that could control the content of macrocyclic compounds in the polycondensation of (I) and (II).

EXPERIMENTAL

Materials

The following materials were used:

— Methyl α-D-mannopyranoside — Fluka, BioChemika for microbiology ≥99.0 % (sum of enantiomers, HPLC), $[\alpha]_D^{20}$ = +79±2° (*c* = 10 in H_2O), melting point 187—189 °C.

— 1,x-Bis(2-formylphenoxy)alkanes — alkylation of 2-hydroxybenzaldehyde (Fluka) was accomplished *via* Williamson etherification with 1,x-dibromoalkane (Fluka) [16].

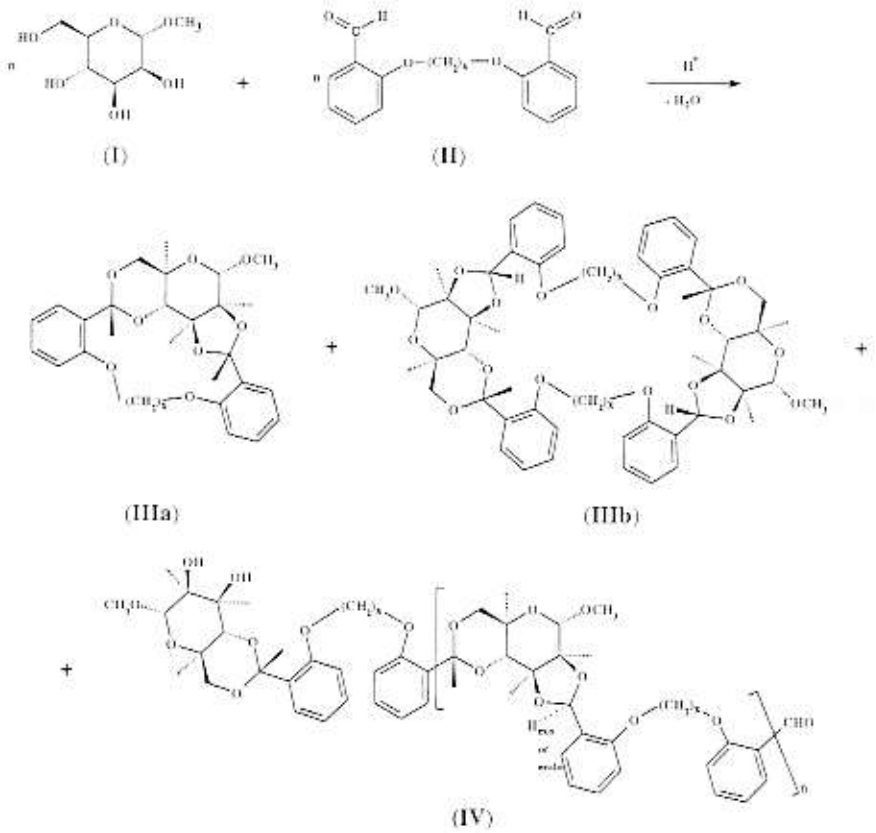
— Catalysts — *p*-Toluenesulfonic acid monohydrate (*p*-TsOH; Fluka); β-cyclodextrin (β-CD; Fluka), $[\alpha]_D^{20}$ = +162±3° (*c* = 1.5 in H_2O), melting point 290—300 °C; (1S)-(+)-camphor-10-sulfonic acid (CSA; Aldrich), 99 %, $[\alpha]_D^{20}$ = +19.9° (*c* = 2 in H_2O), melting point 196—200 °C; Amberlyst®15 (Fluka).

— Solvents — benzene, dimethylsulfoxide (DMSO), chloroform, acetone, pyridine anhydrous 99.8 % (POCh, Gliwice, analitycal grade products).

Polycondensation

A mixture of (I) (0.05 mole) and (II) (0.05 mole) in solution (benzene/DMSO) containing selected acidic catalyst was subjected to azeotropic distillation (Dean-Stark). After the reaction, 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 extract was washed with a solution of $NaHCO_3$, water (3—4 times), dried over anhydrous $MgSO_4$, filtered off and chloroform was removed under reduced pressure. The product was analyzed by NMR and ESI-MS spectroscopy.

The fraction insoluble in acetone [Formula (III) on Scheme A where x = 4, 5, 6, 8] was purified by crystallization from ethyl acetate:chloroform (8:1). The structure of (III) was identified by ^1H NMR, ^{13}C NMR spectra.



where x: 4, 5, 6, 8, 9, 10 or 12

Scheme A. Polycondensation of methyl α-D-mannopyranoside (I) with 1,x-bis(2-formylphenoxy)alkanes (II)

After evaporation of acetone, the oligomeric residue [Formula (IV)] was dried under vacuum.

Methods

^1H 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.

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). The sample was dissolved in methanol at a concentration of 0.5 mg·mL^{-1}, and introduced into the ESI source by continuous infusion by means of the instrument syringe pump at a rate of 3 mL·min^{-1}. The ESI source was operated at 4.5 kV, with the capillary heater held at 200 °C, under gas pressure (N_2) of 40 psi. Mass spectrum was acquired over the range of *m/z* 50—2000 in positive ion mode.

Table 1. Chemical shifts of acetals anomeric and methoxy protons of methyl 2,3:4,6-di-*O*-[2,2(1,x-buthoxy)]phenylidene-α-D--mannopyranoside [macrocyclic compound (IIIa)]

Methyl 2,3:4,6-di-O-[2,2(1,x-buthoxy)]phenylidene-α-D-mannopyranoside, where n:	Chemical shifts, ppm			
	2,3-acetal ^1H NMR (H_{endo}) (^{13}C NMR)	4,6-acetal ^1H NMR (^{13}C NMR)	OCHO an. ^1H NMR (H_{ax}) (^{13}C NMR)	-OCH_3 (acetal) ^1H NMR (^{13}C NMR)
4	6.54 (99.3)	5.89 (98.8)	5.08 (98.4)	3.44 (55.1)
5	6.62 (99.2)	6.01 (98.1)	5.08 (97.6)	3.45 (55.1)
6	6.60 (99.0)	6.01 (98.4)	5.08 (97.7)	3.45 (55.1)
8	6.68 (99.0)	6.06 (98.4)	5.01 (97.7)	3.42 (55.1)
9	6.56	5.94	4.93	3.32
10	6.65	6.01	5.02	3.40
12	6.67	6.04	5.01	3.39

RESULTS AND DISCUSSION

The signals in Figure 1 of (**IIIa**) (where x = 6) are particularly noteworthy, the signal at 6.60 ppm is characteristic for the acetal proton in 1,3-dioxolane ring in their *endo* (H_{endo}) position, the acetal proton at 6.01 ppm in 1,3-dioxane ring is characteristic for the axial position (*ax*; in its chair conformation); the signal at 5.08 ppm is due to the presence of anomeric proton of mannopyranoside ring.

The characteristic signals due to methoxy protons, acetal protons and aromatic protons, which exist in the ratio 3:2:8, respectively, confirm that all condensation products (**IIIa**) consist of two cyclic acetal rings bridged by a di-*O*-[2,2'(1,x-alkoxy)]phenylidene unit. The acetal protons of 1,3-dioxolane ring in all macrocycles exist in *endo* orientation.

The ^{13}C NMR spectrum (Fig. 2) confirmed the macrocyclic structure of (**IIIa**) compound.

The appropriate chemical shifts of acetals H-2 dioxolan-2-yl (H_{endo}) and H-2 dioxan-2-yl (H_{ax}) and C^1 (anomeric) protons (H_{an}) of particular macrocyclic com-

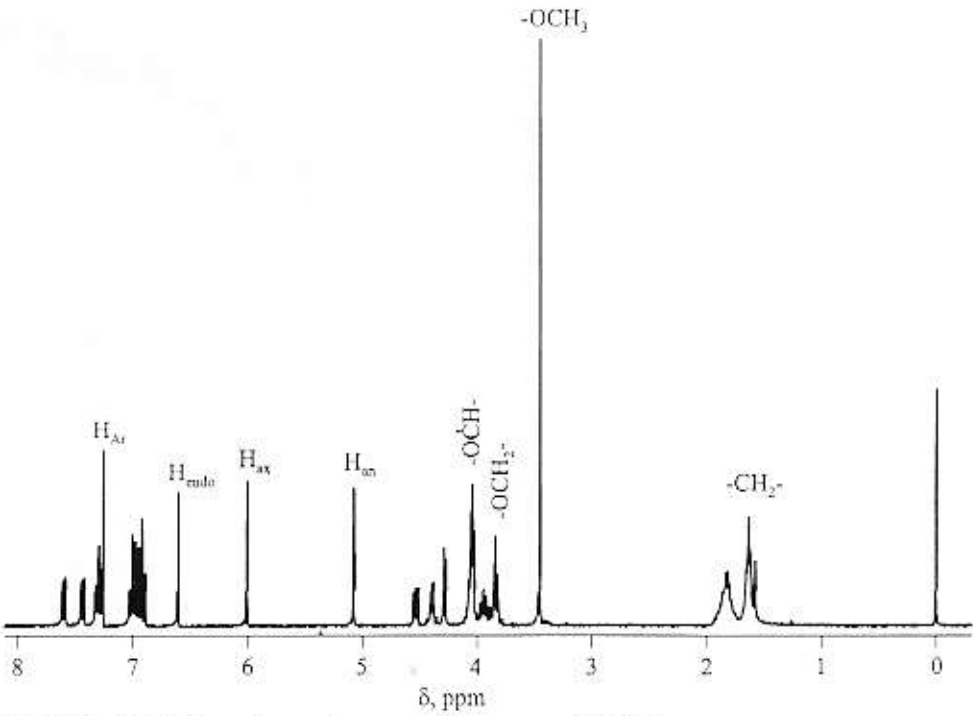


Fig. 1. ^1H NMR (300 MHz, $CDCl_3$) spectrum of macrocyclic compound (IIIa)

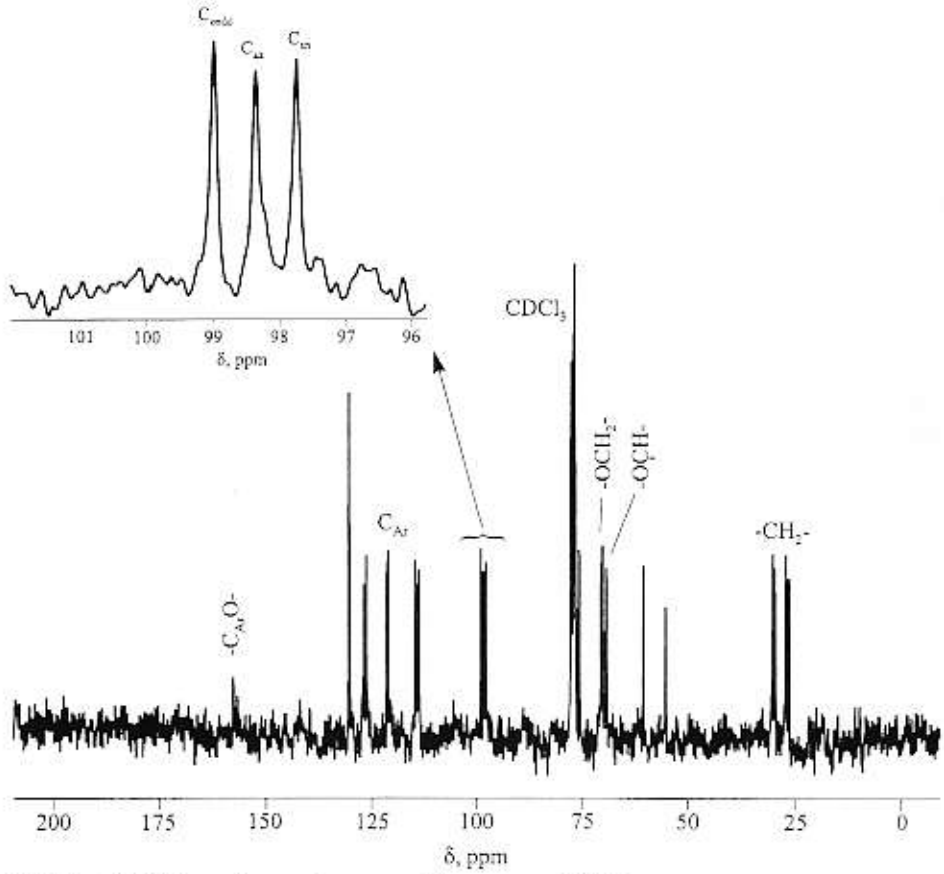


Fig. 2. ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of macrocyclic compound (IIIa)

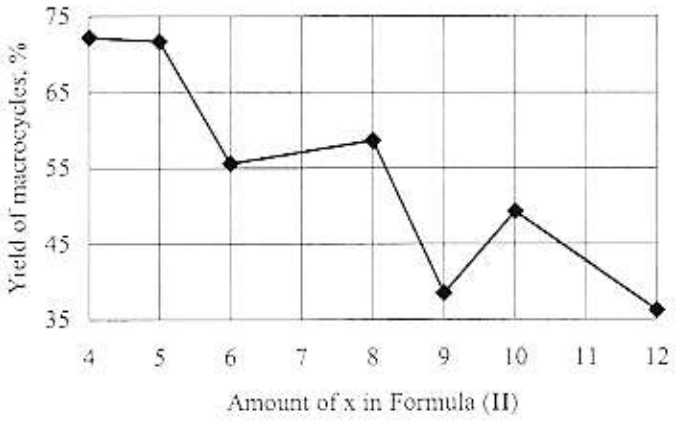


Fig. 3. Effect of dialkoxy spacer length [amount of (x)] in (II) on the yield of macrocycles (p-TsOH, benzene:DMSO = 4:1, t = 12 h)

pounds let calculate their amounts in mixture of products (Table 1). This approach allows controlling and estimating every experimental data without their separation.

Special attention was paid to structural effects of dialdehydes: the position of CHO groups in the aromatic ring and the length of dialkoxy spacer between aromatic rings.

A successful synthesis of macrocycles can be achieved from (I) and dialdehydes in which formyl groups exist in *ortho* position. Condensation of dialdehydes with -CHO in *meta* and *para* positions with (I) leads to formation of linear macromolecule only [14].

Figure 3 presents the relationship between the length of the dialkoxy spacer in (II) and the yields of macrocycles.

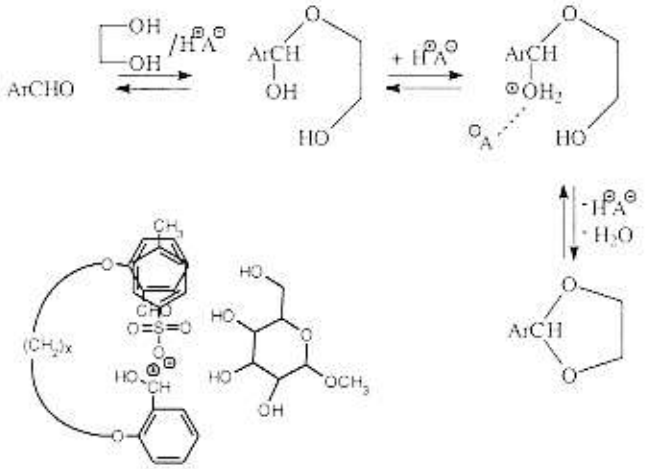
From the theoretical point of view a flexible chain of compound can adopt a high number of conformations. When the number of flexible conformation decreases the yield of cyclization increases.

The efficiency of cyclization depends on the flexibility (length) of spacer in dialdehydes. A very pronounced effect on the cyclization has been observed, when the alkoxy spacer between aromatic rings was short, *e.g.* $O(CH_2)_4O$ and $O(CH_2)_5O$.

The appropriate mixture of solvents in the reaction could control the formation of macrocyclic compounds. Benzene:DMSO (4:1) was selected as reaction medium, because homogenous reaction conditions and the highest conversion of macrocyclic compounds were observed.

The nature of catalyst, and in particular, the molar ratio catalyst:dialdehyde, show a very pronounced effect on yield of the resulting macrocycles. A plausible mechanism of the formation of cyclic acetals catalyzed by acids is outlined in Scheme B.

In particular, the relationship between the nature of selected acidic catalyst and content of macrocycles



Scheme B. Mechanism of the formation of cyclic acetals catalyzed by acids

formed in the polycondensation of (**I**) with 1,8-bis(2-formylphenoxy)octane (**1,8-*O*-dial**) has been examined. The reactions were performed in a mixture of solvents benzene:DMSO = 4:1, at the molar ratio of 1:1 for 12 h. Experimental data are presented in Table 2.

The predominance of macrocycle [1+1] with 53.6 % yield was observed when the condensation of (**I**) with 1,8-*O*-dial was catalyzed by *p*-toluenesulfonic acid (*p*-TsOH).

However, pyridine *p*-toluenesulfonate and camphor-10-sulfonic acid (CSA) demonstrate relatively lower catalytic activities in comparison with *p*-TsOH in the cyclization process. Contrary to our expectations, it was found that polycondensation of these substrates in the presence of Amberlyst 15 [(styrene-*co*-divinylbenzene-SO_3H)] led to the products of linear structure. The yield of macrocycles was very small (2.2 %) insufficient to identify the structure.

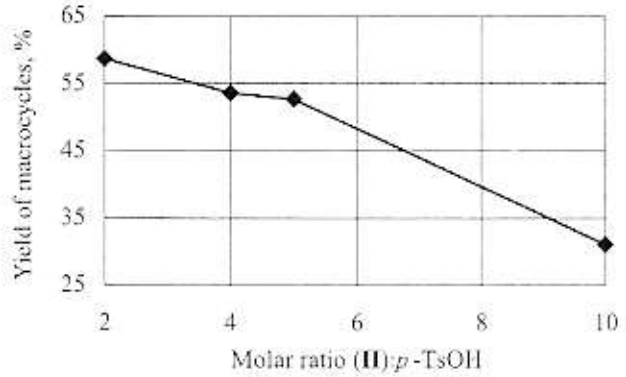


Fig. 4. Effect of the molar ratio of 1,8-bis(2-formylphenoxy)octane (II) and p-TsOH on the yield of macrocycles (benzene:DMSO = 4:1, t = 12 h)

T a b l e 2. Influence of kind of catalyst on content of macrocycles in polyacetals with (I) and 1,8-*O*-diol (benzene:DMSO = 4:1, *t* = 12h)

Catalyst	Macrocycles, %	Total conv., %
p-TsOH	53.6	73.0
CSA	28.7	71.0
p-TsOH/β-CD	53.2	88.7
CSA/β-CD	45.7	88.3
p-TsOH + pyridine	22.9	79.4
Amberlyst® 15	2.7	75.4

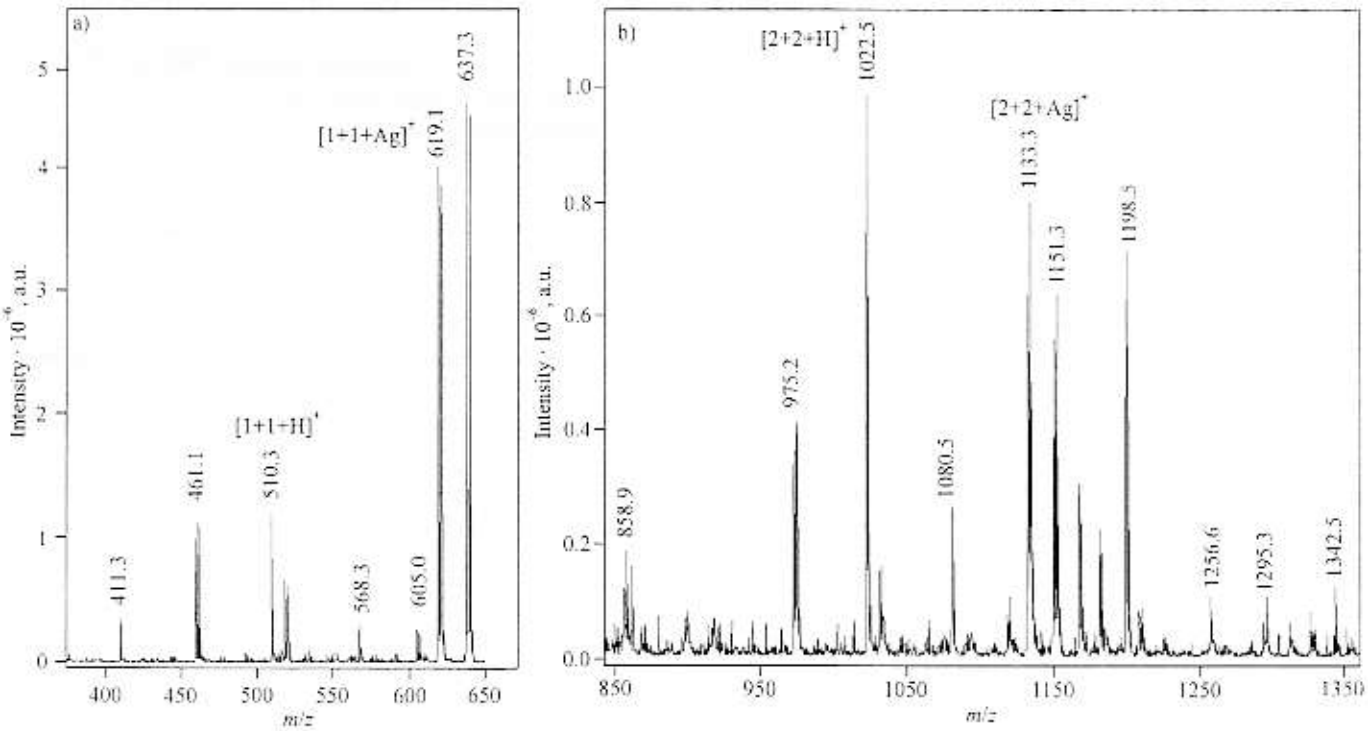


Fig. 5. ESI-MS spectra (in positive ion mode) of macrocycles [1+1] (a) and [2+2] (b), x = 8

This effect can be explained on the basis of non-covalent bonding interactions of anionic part of catalysts during the reaction. Thus, *p*-TsOH is not only the catalyst of acetalization, but also efficient and cooperative self-assembly template in the process of construction of novel compounds (macrocycles). Pyridine *p*-toluenesulfonate and camphor-10-sulfonic acids have relatively larger groups in comparison with *p*-TsOH and thus the yield of macrocycles was lower. In the case of polymeric catalyst — Amberlyst® 15, the interactions between anions and molecules containing both reactive groups probably do not exist.

The influence of the nature of catalyst and comonomer (dialdehyde) in this reaction have been observed in the relationship of molar ratio of (II) and catalyst.

As depicted in Fig. 4 the fraction of macrocycles decreases with increasing of monomer (dial)/catalyst molar ratio.

ESI-MS is important tool in the studies on structure of polymer chain and macrocyclic compounds [17].

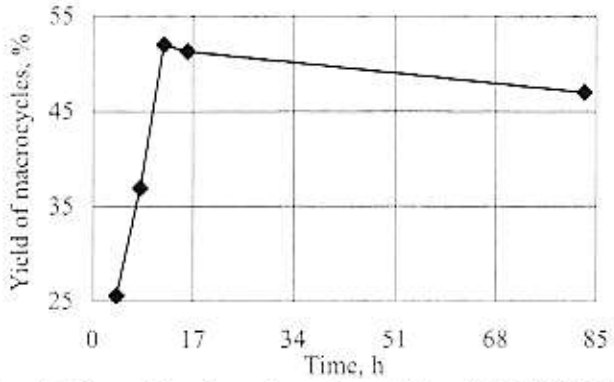


Fig. 6. Effect of the time of reaction of (I) with 1,8-bis(2-formylphenoxy)octane on the yield of macrocycles (p-TsOH, benzene:DMSO = 4:1)

ESI-MS analysis of polycondensation product (I) with 1,8-*O*-dial revealed the presence of protonated ions with *m/z* values of 510.3 and 1022.5, and their values of silver adduct ions with *m/z* values of 619.1 and 1133.3. These values correspond to the individual macrocycles [1+1] and [2+2] (Fig. 5).

It was found that the fraction of macrocycles (Fig. 6) increases during the polycondensation reaching the equilibrium of ring-chain at very high conversion.

CONCLUSIONS

As shown in our previous papers [12—15] at this work the polycondensation of methyl α-D-mannopyranoside (I) and dialdehydes (1,x-bis(2-formylphenoxy)alkanes (II) is a rather clean thermodynamically controlled step growth polymerization with a high extent of cyclization.

The nature of catalyst, and in particular, the molar ratio of catalyst and dialdehyde, show a very pronounced effect on yield of the resulting macrocycles. This effect can be explained on the basis of non-covalent bonding (self-assembly process) between catalyst and monomer compounds. Thus, *p*-toluenesulfonic acid is not only the catalyst of acetalization, but also efficient and cooperative self-assembly template in the process of construction of novel compounds (macrocycles).

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