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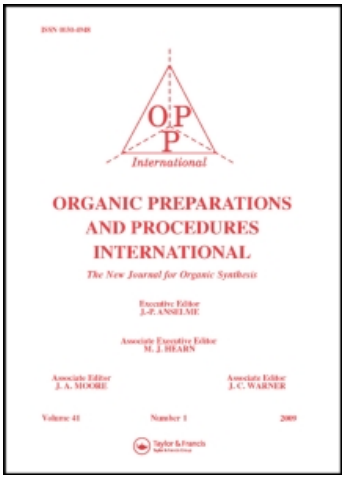

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A GENERAL SYNTHESIS OF MACROCYCLIC ESTERS

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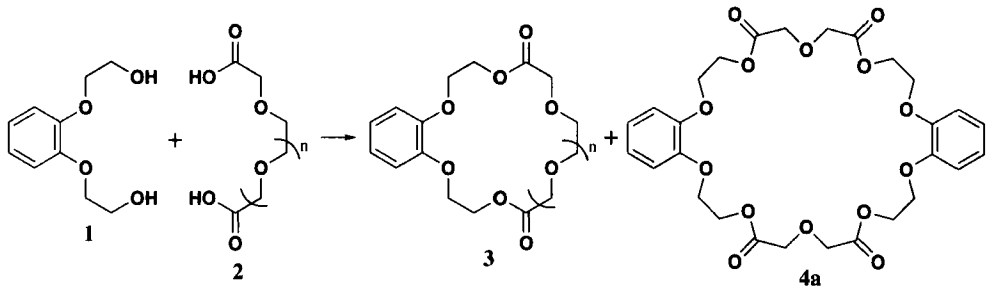
Synthetic ionophores are of great interest for various applications in the life sciences.[1] For example they can be used for the removal of heavy metals from living organisms. For this purpose, ionophores possessing hydrolytically-labile groups, which decrease their own toxicity, are of interest. Macrocyclic polyether esters are interesting potential receptors for heavy metal ions. Macrocyclic polyether diesters and tetraesters of the structure (**3** and **4**, respectively) were selected as target compounds. Their toxicity should decrease due to the presence of hydrolytically-labile esters, and the size of macrocyclic cavity can be easily adjusted by the length of the diacid **2** unit.

Several methods are commonly used for the synthesis of macrocyclic esters. The high-dilution method based on the reaction of dicarboxylic acid chlorides with α,ω-diols requires large volumes of anhydrous solvents and simultaneous addition of both reagents.[2] Better results were obtained with the base-catalysed transesterification procedure for preparation of macrocyclic diesters.[3] The systematic studies[4] on macrocyclic oligomerization of simple lactones showed a marked difference between acidic and basic catalysts. Only an acidic catalyst (BF_3/CH_2Cl_2) converts β-propiolactone cleanly to the cyclic oligomers.[4] Several attempts were also made to perform base-catalysed oligomerization of β-lactones.[5] Based on the literature data, we decided to use a *p*-toluenesulfonic acid-catalyzed esterification for preparation of macrocyclic esters. In order to achieve good cavity size for complexation of toxic metal cations, only the compounds of structure **3**, derived from acids **2b** and **2c** are of interest, as well as crown **4a** derived from **2a**.



a) n = O b) n = 1 c) n = 2

We found that the esterification of diol **1** with diacid **2a** without any catalyst proceeds very slowly. Addition of *p*-toluenesulfonic acid (4.4 mol%), under azeotropic conditions, leads to a mixture of products **3a** and **4a** (see Table). The reaction progress was monitored by TLC, and heating was continued until diol **1** was not detected in the reaction mixture. Pure products **3a** and **4a** were obtained

after conventional work-up followed by column chromatography. This procedure gave fully reproducible results, irrespective of the solvent used. In the initial stage of our studies, the influence of a catalyst on the reaction course was investigated. We found that increasing amount of *p*-toluenesulfonic acid (from 2.2 to 10%) led to a decrease of reaction time from 19.5 to 6 h, respectively. For larger amount of catalyst, separation of both products **3a** and **4a** became troublesome, whereas the yield was nearly the same. Therefore, we decided to perform further experiments using 4.4% of the catalyst since the amount of catalyst did not influence the reaction selectivity. Among the aromatic solvents, benzene seemed to be the best one. In this solvent, the highest yield of both products, **3a** and **4a**, was obtained, although a period of 8.5 hours is required for complete reaction (entry 1). In more polar aromatic solvents, the yield of both products decreases with increasing solvent polarity (entries 2, 3 and 4). In dichloromethane, the reaction proceeds very slowly and a period of 21 hours is required to complete the reaction but the yield of diester **3a** increased to 61% (entry 5). A smaller amount of dimeric product **4a** (15%) is formed in this reaction. In chloroform, the reaction is completed within 14.5 hours and the yield of both products is unchanged. In 1,2-dichloroethane, a higher yield of diester **3a** was obtained while that of corresponding tetraester **4a** was practically the same (entry 7). 1,2-Dichloroethane seems to be the best solvent for the reaction aimed to macrocyclic diesters (**3a**).

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Table. The influence of Solvent on the Macrocyclization Reaction between **1** and **2a**

Entry	Solvent	Time (h)	Yield of **3a** (%)	Yield of **4a** (%)
1	Benzene	8.5	48	21
2	Toluene	5.5	45	16
3	Xylene	4.5	36	12
4	*sec*-Butylbenzene	3.5	34	11
5	Dichloromethane	21.0	61	15
6	Chloroform	14.5	61	15
7	1,2-Dichloroethane	6.0	67	14

It is known that the acid catalyst can cause ring enlargement of several macrocylic esters.[5d] We investigated this phenomenon in detail, since it could be used for the synthesis of large size macrocyclic esters which are not available in a one-step synthesis. Compounds **3a** and **4a** were dissolved in toluene in the presence of 4.4% of *p*-toluenesulfonic acid and heated to reflux. The results were unexpected. Pure **3a** under these conditions is stable for 5.5 hours and only traces of compound **4a** were observed on TLC. When the reaction mixture was heated for 26 hours, the starting material was recovered in 77% yield and the dimeric product **4b** was obtained in 18% yield. Tetraester **4a**, under the same reaction conditions, gave diester **3a** in 29% yield and 54% of **4a** was recovered. These results suggest that thermodynamic processes leading to ring enlargement or ring contraction did not influence substantially the course of esterification reaction for the compounds studied. Therefore, the reactions leading to formation of macrocyclic diesters and tetraester are primarily kinetically controlled.

In conclusion, a new method for preparation of hydrolytically-labile diesters and tetraester was established. For the synthesis of macrocyclic tetraesters, eg., **4a**, benzene is the best solvent. The reaction aimed to macrocyclic diesters should be performed in 1,2-dichloroethane.

EXPERIMENTAL SECTION

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Varian 200 Gemini spectrometer in $CDCl_3$ with TMS as an internal standard. EI-MS and liquid SIMS spectra were determined on an AMD 604 spectrometer (Cs^+, 10 keV). Diol **1** was prepared according to the literature procedure.[6]

One-step Synthesis of Macrocylic Esters. General Procedure: A solution of diol **1** (990 mg, 5 mmol) and the respective diacid **2** (5 mmol) in 100 mL of respective organic solvent containing a catalytic amount of *p*-toluenesulfonic acid (see Table) was refluxed, the water was collected in a Dean-Stark trap. Reaction progress was monitored by TLC and then mixture was cooled to 25°. To this solution 10 g of silica gel was added and the solvent was evaporated. The products adsorbed on the surface of silica gel were placed on a top of silica-gel column and separated by flash chromatography using the mixture of chloroform-hexane (8/2, v/v) for **3** and chloroform for **4a**.

Crown 3a, colorless oil, R_f = 0.76 ($CHCl_3$/MeOH 95:5 v/v). ^{1}H NMR ($CDCl_3$): δ 4.21-4.30 (m, 8H); 4.54-4.59 (m, 4H); 6.85-6.97 (m, 4H). ^{13}C NMR: δ 62.6; 66.8; 68.9; 114.1; 121.8; 148.3; 169.4. IR ($CHCl_3$, cm^{-1}): $\nu_{C=O}$ 1764, 1740. EI-MS *m/z* 296 ([M]$^+$, 47%), 136 (31%), 101 (100%). HR-MS *m/z* 296.090 (296.090 Calcd. for $C_{14}H_{16}O_7$ [M]$^+$).

Anal. Calcd for $C_{14}H_{16}O_7 \cdot H_2O$: C, 53.50; H, 5.77. Found: C, 53.75; H, 5.72

Crown 4a, white solid, mp. 138-142° (PhH). R_f = 0.69 ($CHCl_3$/MeOH 95:5 v/v). ^{1}H NMR ($CDCl_3$): δ 4.18-4.31 (m, 16H); 4.48-4.55 (m, 8H); 6.86-6.97 (m, 8H). ^{13}C NMR: δ 63.3; 67.4; 67.8; 115.4; 122.3; 148.7; 169.7. IR ($CHCl_3$, cm^{-1}): $\nu_{C=O}$ 1756. EI-MS *m/z* 592 ([M]$^+$, 49%), 136 (13%), 121 (19%), 101 (100%). HR-MS *m/z* 592.183 (592.179 Calcd. for $C_{14}H_{16}O_7$ [M]$^+$).

Anal. Calcd for $C_{28}H_{32}O_{14}$: C, 56.76; H, 5.44. Found: C, 56.81; H, 5.65

Crown 3b, white solid, mp. 118-120° (PhH). R_f = 0.44 ($CHCl_3$/MeOH, 95:5 v/v). ^{1}H NMR ($CDCl_3$): δ 3.76 (s, 4H); 4.19-4.25 (m, 8H); 4.54-4.58 (m, 4H); 6.85-6.94 (m, 4H). ^{13}C NMR: δ 62.93; 66.85; 68.87; 71.09; 114.20; 121.78; 148.41; 170.42. IR ($CHCl_3$, cm^{-1}): $\nu_{C=O}$ 1737. EI-MS *m/z* 340 ([M]$^+$, 77%), 239 (21%), 137 (100%), 121 (44%), 101 (67%).

Anal. Calcd for $C_{16}H_{20}O_8$: C, 56.45; H, 5.93. Found: C, 56.41; H, 6.08

Crown 3c, white solid, mp. 80-81° (PhH). R_f = 0.37 ($CHCl_3$/MeOH, 95:5 v/v). ^{1}H NMR ($CDCl_3$): δ 3.67-3.71 (m, 4H); 3.77-3.81 (m, 4H); 4.23-4.28 (m, 4H); 4.34 (s, 4H); 4.55-4.60 (m, 4H); 6.88-7.01 (m, 4H). ^{13}C NMR: δ 63.64; 67.83; 69.56; 71.40; 72.27; 115.45; 122.57; 149.18; 171.10. IR ($CHCl_3$, cm^{-1}): $\nu_{C=O}$ 1754. EI-MS *m/z* 384 ([M]$^+$, 100%), 137 (66%), 136 (66%), 102 (79%). HR-MS *m/z* 384.143 (384.142 Calcd. for $C_{18}H_{24}O_9$ [M]$^+$).

Anal. Calcd for $C_{18}H_{24}O_9$: C, 56.25; H, 6.29. Found: C, 56.1; H, 6.52

Ring Enlargement of Crown 3a.- A solution of crown **3a** (296 mg, 1 mmol) in toluene (100 mL),

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containing a catalytic amount of *p*-toluenesulfonic acid (6.6 mg, 0.044 μmol) was refluxed. The progress was monitored by TLC. After 26 h, the reaction was cooled to 25° and compounds **3a** and **4b** were separated by flash chromatography. The starting crown was recovered in 77% yield. Dimeric product **4b** was obtained in 18% yield.

Ring Contraction of Crown 4a.- A solution of crown **4a** (295 mg, 0.5 mmol) in toluene (100 mL) containing catalytic amount of *p*-toluenesulfonic acid (6.6 mg, 44 μmol) was refluxed. The progress was monitored by TLC. After 26 h, the reaction was cooled to 25° and compounds **3a** and **4b** were separated by flash chromatography. The starting crown was recovered in 55% yield. Crown **3a** was obtained in 29% yield.

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