

Stereochemistry of Macrocyclization of *cis*-4-Cyclohexene-1,2-dicarboxylic Acid with Dihalogen Derivatives

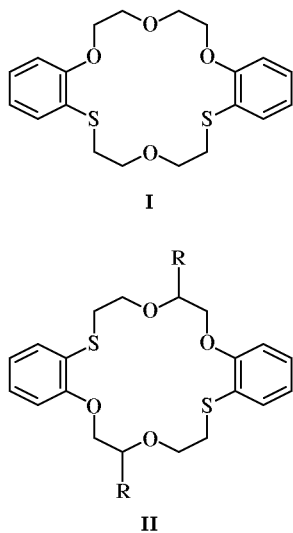
A. L. Shabanov, M. M. Gasanova, and Ch. I. Mamedov

“Geotechnology Problems of Petroleum, Gas, and Chemistry” Research Institute, Azerbaijan State Petroleum Academy, pr. Azadlyg 20, Baku, 370601 Azerbaijan

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Abstract—Stereochemistry of [2+2]- and [1+1]-macrocyclization of *cis*-4-cyclohexene-1,2-dicarboxylic acid with 1,2-dibromoethane, 1,3-dichloro-2-propanol, and 1,5-dichloro-3-oxapentane was studied. The reaction of *cis*-4-cyclohexene-1,2-dicarboxylic acid with 1,2-dibromoethane according to the [2+2]-cyclization scheme gave a mixture of stereoisomeric macroheterocycles with *cis,syn,cis*- and *cis,anti,cis*-junction of the polyether and cyclohexene rings. In the reaction of *cis*-4-cyclohexene-1,2-dicarboxylic acid with 1,5-dichloro-3-oxapentane, a mixture of crown compounds with *cis,anti,cis*- and *cis*-junction of the polyether and cyclohexene rings was obtained. The structure of the products was established on the basis of their chemical transformations and spectral data.

We previously found that *o*-mercaptophenols react with symmetric 2,2'-dichloro- and 2,2'-dibromodiethyl ethers according to the [2+2]-cyclization scheme, leading to formation of compound **I** with symmetric arrangement of the sulfur atoms [1, 2]. By contrast, reactions of *o*-mercaptophenols with unsymmetrical 2-haloethyl 2-halo-1-alkylethyl ethers give macroheterocycles **II** with unsymmetrical arrangement of the sulfide sulfur atoms and alkyl groups [2].



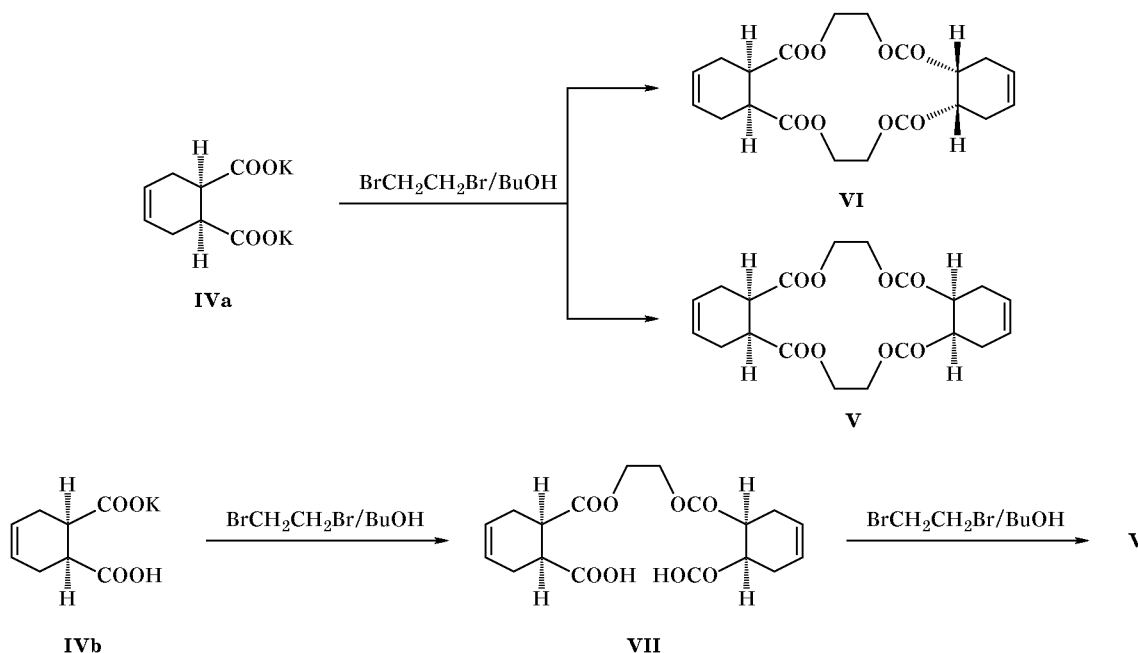
We have studied the stereochemistry of macrocyclization of *cis*-4-cyclohexene-1,2-dicarboxylic acid

(**III**) with 1,2-dibromoethane, 1,3-dichloro-2-propanol, and 1,5-dichloro-3-oxapentane. The reaction of dipotassium *cis*-4-cyclohexene-1,2-dicarboxylate with 1,2-bromoethane in anhydrous butanol follows the [2+2]-cyclization scheme and gives a mixture of *cis,syn,cis*- and *cis,anti,cis*-polyesters **V** and **VI** (Scheme 1). Isomers **V** and **VI** were isolated by vacuum distillation in combination with column chromatography (R_f 0.23 and 0.30, respectively; Silufol plates, hexane–chloroform, 2:1). The isomer ratio is 1:1. Compound **V** crystallizes on storage.

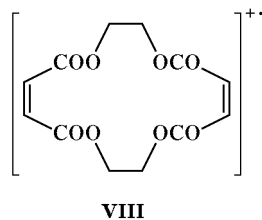
The IR spectra of **V** and **VI** contain strong absorption bands at 1732 and 1736 cm^{-1} , respectively, which belong to the ester fragments. The double bonds in *cis,syn,cis*-isomer **V** give only one IR absorption band with its maximum at 1642 cm^{-1} , whereas in the spectrum of *cis,anti,cis* isomer **VI** two strong bands are observed at 1640 and 1660 cm^{-1} due to steric non-equivalence of the double bonds.

Both isomers **V** and **VI** undergo hydrolysis in alkaline medium to afford *cis*-dicarboxylic acid **III** which is almost quantitatively converted into the corresponding *cis*-anhydride by heating in boiling acetyl chloride [4]. These data indicate that no *cis*–*trans* isomerization of **III** occurs in the course of formation of macroheterocycles **V** and **VI**. The molecular weight of isomeric products **V** and **VI** was determined by mass spectrometry (M^+ 392 amu). Their fragmentation under electron impact follows the retro-Diels–Alder

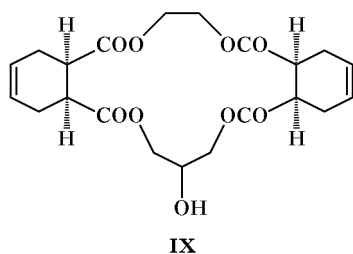
Scheme 1.



decomposition scheme and gives rise to macrocyclic fragment ion **VIII** with m/z 284 [5]. The molecular weights of **V** and **VI** were also determined by iodometric titration.

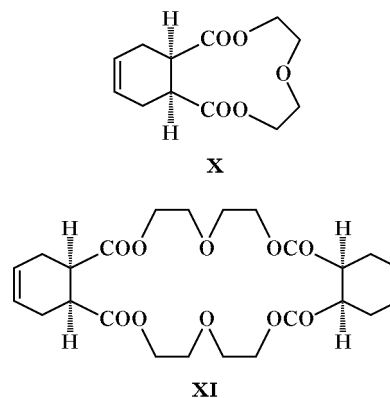


Unlike the reaction of dipotassium salt **IVa** with 1,2-dibromoethane ([2+2]-cyclization scheme), monopotassium salt **IVb** reacts 1,2-dibromoethane in two steps according to the [1+1] scheme to afford only one *cis*,*syn*,*cis* isomer **V** (Scheme 1). As might be expected, the reaction of dicarboxylic acid **VII** with 1,3-dichloro-2-propanol was strictly stereoselective; as a result, crown compound **IX** with *cis*,*syn*,*cis*-junction of the polyester and cyclohexene rings was obtained.



The purity of compound **IX** was checked by TLC on Silufol plates, and its structure and configuration were confirmed by physical methods and chemical transformations. The IR spectrum of **IX** contains strong absorption bands at 3744 and 3456 cm^{-1} , which are typical of hydroxy group. A strong absorption band with its maximum at 1736 cm^{-1} belongs to stretching vibrations of the lactone carbonyl groups. Alkaline hydrolysis of compound **IX** gave only *cis*-4-cyclohexene-1,2-dicarboxylic acid (**III**) which was identical to a sample obtained by heating of the corresponding anhydride in boiling water [3, 5].

We also examined the reaction of dipotassium salt **IVa** with 1,5-dichloro-3-oxapentane which followed the [2+2]-cyclization scheme. Unlike the reaction with 1,2-dibromoethane, we obtained a mixture of macrocyclic compounds **X** and **XI** with *cis*- and



Yields, boiling points, refractive indices, elemental analyses, and IR spectra of compounds **V–VII** and **IX–XI**

Comp. no.	Yield, %	bp, °C (<i>p</i> , mm)	n_D^{20}	Found, %		Formula	Calculated, %		IR spectrum (KBr), ν , cm^{-1}
				C	H		C	H	
V	34.6	155 (2) mp 31	–	61.08	6.28	$\text{C}_{20}\text{H}_{24}\text{O}_8$	61.22	6.12	1722 (C=O); 1642 (C=C); 1196, 1280, 1296 (C–O _{ester})
VI	27.6	162 (2)	1.4202	61.19	6.25	$\text{C}_{20}\text{H}_{24}\text{O}_8$	61.22	6.12	1736 (C=O); 1640, 1660 (C=C); 1064, 1088, 1296 (C–O _{ester})
VII	76.34	135 (2)	1.4632	59.08	6.21	$\text{C}_{18}\text{H}_{22}\text{O}_8$	59.01	6.01	1702 (COOH), 1728 (C=O), 1640 (C=C)
IX	32.03	110 (1)	1.4659	59.26	5.93	$\text{C}_{21}\text{H}_{26}\text{O}_9$	59.71	6.16	3792, 3744, 3456 (OH); 1736 (C=O); 1660, 1636 (C=C); 1180, 1208, 1248, 1280 (C–O _{ester})
X	11.2	125 (2)	1.4778	60.23	6.43	$\text{C}_{12}\text{H}_{16}\text{O}_5$	60.0	6.66	1728 (C=O), 1637 (C=C)
XI	26.2	163 (1.5)	1.4864	60.26	6.41	$\text{C}_{24}\text{H}_{32}\text{O}_{10}$	60.0	6.66	1724 (C=O), 1644 (C=C)

cis,syn,cis-junction of the rings, respectively. The isomeric products were separated by vacuum distillation in combination with column chromatography. Their structure was established on the basis of the IR spectra and chemical transformations, and the molecular weight was determined by iodometric titration. The hydrolysis of macroheterocycles **X** and **XI** gave *cis*-diacid **III** and diethylene glycol which were identified by both chemical and spectral methods.

Taking into account that compound **XI** shows in the IR spectrum only one absorption band from the double bonds ($\nu_{\text{C}=\text{C}}$ 1644 cm^{-1}), *cis,syn,cis*-junction of the cyclohexene and polyester rings therein may be assumed.

EXPERIMENTAL

The IR spectra were recorded on Beckmann and UR-20 spectrometers from samples pelleted with KBr. The mass spectra (70 eV) of compounds **V** and **VI** were recorded on an MKh-1310 spectrometer, batch inlet temperature 235°C. The progress of reactions and the purity of products were monitored by TLC on Silufol plates. Mono- and dipotassium salts of *cis*-4-cyclohexene-1,2-dicarboxylic acid were obtained by potentiometric titration in 1-butanol using glass and silver chloride electrodes; the pH was measured with the aid of a pH-340 instrument. Standard solutions of iodine (0.01 M) and sodium thiosulfate (0.005 M) were used in the iodometric titration of compounds **V**, **VI**, and **IX–XI**. Stereoisomers **V** and **VI** were separated by vacuum distillation followed by column chromatography using a glass column ($h = 100$ mm,

$d = 10$ mm) charged with aluminum oxide of activity grade II (according to Brockman); a 1:2 (by volume) chloroform–hexane mixture was used as eluent.

[2 + 2]-Macrocyclization of *cis*-4-cyclohexene-1,2-dicarboxylic acid (III) with 1,2-dibromoethane. Diacid **III**, 8.5 g (0.05 mol), was dissolved in 150 ml of 1-butanol, and the solution was neutralized with 5.6 g (0.1 mol) of powdered potassium hydroxide. The released water was removed by azeotrope distillation, the solution was heated to the boiling point, and 9.4 g (0.05 mol) of 1,2-dibromoethane was added with stirring over a period of 2 h. The mixture was stirred for 20 h under reflux. When the reaction was complete (TLC), the solvent was removed under reduced pressure (25 mm), the residue was treated with octane (5 × 50 ml), the extract was evaporated, and the residue was distilled in a high vacuum. Two fractions were thus obtained and were subjected to column chromatography on Al_2O_3 to isolate *cis*-2,3:10,11-bis(1,2,3,6-tetrahydrobenzo)-1,4,9,12-tetraoxo-5,8,13,16-tetraoxa-*syn*-cyclohexadecane (**V**) and *cis*-2,3:10,11-bis(1,2,3,6-tetrahydrobenzo)-1,4,9,12-tetraoxo-5,8,13,16-tetraoxa-*anti*-cyclohexadecane (**VI**) (see table).

1,2-Bis(2-carboxy-1,2,3,6-tetrahydrobenzoyloxy)-ethane (VII) was synthesized in a similar way from 8.5 g (0.05 mol) of diacid **III**, 2.8 g (0.05 mol) of powdered potassium hydroxide, and 4.7 g (0.025 mol) of 1,2-dibromoethane. The properties of product **VII** are given in table.

Following the above procedure, from 18.3 g (0.05 mol) of compound **VII** and 9.4 g (0.05 mol) of

1,2-dibromoethane we obtained 34.6% of *cis,syn,cis* isomer **V**.

***cis*-2,3:10,11-Bis(1,2,3,6-tetrahydrobenzo)-1-hydroxy-1,4,9,12-tetraoxo-5,8,13,16-tetraoxa-syn-cycloheptadecane (IX)**. Following the above procedure, from 9.15 g (0.025 mol) of compound **VII** and 3.225 g (0.025 mol) of 1,3-dichloro-2-propanol we obtained 32% of compound **IX**.

Macrocyclization of *cis*-4-cyclohexene-1,2-dicarboxylic acid (III) with 1,5-dichloro-3-oxapentane. Following the above procedure, the reaction of 8.5 g (0.05 mol) of diacid **III**, 5.6 g (0.1 mol) of powdered KOH, and 7.16 g (0.05 mol) of 1,5-dichloro-3-oxapentane gave *cis*-2,3-(1,2,3,6-tetrahydrobenzo)-1,4-dioxo-5,8,11-trioxacycloundecane (**X**) and *cis*-2,3:13,14-bis(1,2,3,6-tetrahydrobenzo)-1,4,12,15-tetraoxo-5,8,11,16,19,22-hexaoxa-*syn*-cyclodocosane (**XI**) (see table).

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