Synthesis of Macrocyclic Oligomers of Pivalolactone. Crystal Structure and Properties of Tetrolide†

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Synthesis of cyclic oligomers of pivalolactone has been performed by a cyclooligomerization strategy promoted by a simple catalytic system: potassium alkoxides. The thermodynamic control of macrocyclic oligomerization and yields of macrolides of pivalolactone depend on the reaction conditions, specifically temperature and concentration. In dilute solution, the yield of macrocyclic oligomers is around 75%, in which the trimer and tetramer are the major products. The 16-membered tetrolide has been isolated in crystalline form and its structure has been proven by X-ray crystal structure analysis. The mechanism of the cyclooligomerization is discussed. The strategy of cyclooligomerization with an anionic catalyst offers a unique, simple synthesis of pivalolactone cyclic oligomers, which are potential ligands for metal complexation.

Introduction

The chemistry of β-lactones (2-oxetanones) has attracted considerable attention because of its utility in the synthesis of biologically active materials. Studies of the base alcoholysis of α,α-diphenyl-β-propiolactone have been aimed at preparation of analogues of tropic acid esters, which exhibit antispasmodic activity.[1] The low molecular weight polymers of β-butyrolactone (100–200 units) in the form of complexes with calcium polyphosphate have been found in the ion channels of cell membranes and as well as with proteins in the human blood plasma.[2] The natural 16-membered tetrolide of 3-hydroxybutyric acid is of interest because of its potential antibiotic activity.[3] Therefore, many attempts have been made to synthesize analogues of these natural, biologically active compounds, first the tetrolide of 3-hydroxybutyric acid, utilizing the Yamaguchi reaction.[4,5] Another method has recently been developed, which is based on either β-propiolactone or (*S*)-β-butyrolactone oligomerization in a dilute chloroform solution with 2,2-dibutyl-1,3,2-dioxastannolane dibutyltin dichloride as catalyst.[6] The equilibrium of cyclooligomers and open-chain oligo-esters in these syntheses was achieved at low substrate concentration. The observed product distribution was evaluated by fitting with modified Jacobson–Stockmayer theory.[7] However, the yield of tetramer was rather low (ca. 10%). A somewhat higher yield of triolide of (*R*)-3-hydroxybutyric acid was obtained *via* acid hydrolysis of polyhydroxybutyrate.[8]

We have now found that a simple catalyst, potassium alkoxide, under proper reaction conditions, promotes the formation of cyclic oligomers of pivalolactone. Thus, synthesis of cyclic oligomers of pivalolactone *via* cyclooligomerization, as well as some properties and crystal structure of the tetrolide, are herein discussed. The aim of this study was to better understand the chemistry of β-lactone cyclooligomerization and its evaluation for potential applications in organic synthesis.

Results and Discussion

Results of experiments indicate that oligomerization of pivalolactone with potassium alkoxides, e.g. potassium methoxide, proceeds smoothly, yielding cyclic oligomers, in particular its triolide and tetrolide. The general course of this reaction is shown in Scheme 1.

The acyl–oxygen bonds of pivalolactone are cleaved and the cyclic as well as open-chain oligomers are produced (Scheme 1). The cyclooligomerization of α-unsubstituted four-membered lactones, e.g. β-propiolactone or β-butyrolactone with an alkali metal alkoxide as catalyst, is impossible, because carboxylate not alkoxide anions are formed as the active anionic species.[9,10] The carboxylate anions, which are weak nucleophiles, are unable to attack their own chain *via* a "back biting" reaction to form cyclic oligomers. Thus, only open-chain oligomers and polymers were produced. On the contrary, the polymerization of α,α-disubsituted β-lactone with an alkali metal alkoxide as catalyst involves acyl–oxygen bond scission with formation of alkoxide anion; a rela-

† 3,3,7,7,11,11,15,15-Octamethyl-1,5,9,13-tetraoxacyclohexadecane-2,6,10,14-tetraone.

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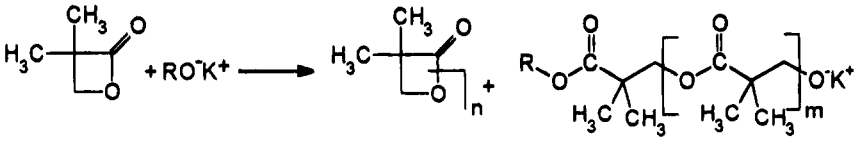
Scheme 1



Where:
R: -Me or -t-Bu

tively high yield of cyclic oligomers can be obtained. The reaction follows the Jacobson–Stockmayer theory[11] and, in dilute solutions, the main products are cyclic oligomers (yield >75%).

The mixture of oligomers from the reaction conducted at 0.2 M pivalolactone and 0.02 M catalyst concentration in THF at 20 °C was carefully separated by precipitation with hexane–THF and then analyzed by GC-MS technique and crystallized (see Experimental Section). According to the analytical data, the trimer and tetramer were main isolated products. The tetrolide of pivalolactone was characterized by a X-ray crystal determination.

As evidenced by X-ray crystal data (Figure 1), the shape of the tetrolide of pivalaloctone indicates an almost square, 16-membered macrocycle. It has approximate $\bar{4}$ symmetry with the carbonyl oxygens situated alternately up and down relative to the main plane of the molecule. The distance between the nearest pairs of oxygens O(13)–O(33) and O(23)–O(43) is 4.283 and 4.531.1 Å, respectively; whereas taking into account the van der Waals radii of 1.40 Å, the distance is 1.48 and 1.73 Å, respectively. The distance between H(13)–H(33) and H(23)–H(43) equals 3.68(3) and 3.82(3) Å, respectively, which corresponds to van der Waals distance 1.7–1.8 Å. Therefore, a 1.5 Å diameter hole should be assumed within this macrocycle. The four sides of the nearly square molecule form almost planar chains with the torsion angles C–C–C(O)–O equal to about 176° and C–C–C(O)–C to about 178°. The conformation of tetrolide of pivalolactone presented here is different from that of cyclic oligomer of β-butyrolactone described by Plattner et al.,[5] who found fragments of helices along 16-membered ring in the molecule possessing four external methyl groups.

Roelens et al.[6] found the same strain in the 16-membered tetrolide of β-butyrolactone. The authors[5,6] explain the decreased yield of tetrolide, synthesized from β-butyrolactone, when compared with that of tetrolide of unsubstituted β-propiolactone, in terms of restricted freedom of rotation in β-butyrolactone tetramer caused by the presence of four methyl groups. However, as herein demonstrated, even the presence of 8-methyl groups in the α-position does not influence the rotational freedom of the 16-membered tetramer of pivalolactone. The different conformation, as evidenced by X-ray crystal structures, seems to be responsible for different behavior of tetrolides of β-butyrolactone and pivalolactone. We have shown, that anionic cyclooligomerization of α,α-disubstituted β-propiolactones, e.g. pivalolactone, with potassium alkali metal alkoxide catalyst affords the cyclic trimer and tetramer oligomers, in good yield. The previous observation,[12] that a mixture of such oligomers is produced by thermal degradation of poly(pivalolactone),

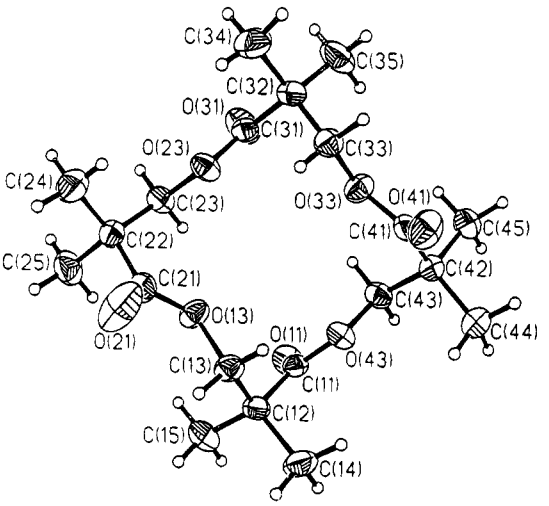


Figure 1. Crystal structure of the tetrolide (3,3,7,7,11,11,-15,15-octamethyl-1,5,9,13-tetraoxacyclohexadecane-2,6,10,14-tetraone). A view showing the atom-numbering system.

is not very useful from the point of view of its synthetic utility. Thus the cyclooligomerization of pivalolactone with alkali metal alkoxide is a suitable strategy for the synthesis of macrocyclic oligomers. The tetrolide seems to be a useful potential ligand for complexation of metals: due to its good solubility in polar and nonpolar solvents.

Experimental Section

General. Pivalolactone (PVL) was distilled twice over calcium hydride. The fraction boiling at 48–49 °C (9 mmHg) was collected (99.8% purity by GC). Potassium methoxide was obtained by reacting dry MeOH with a potassium mirror. The excess MeOH was removed in vacuo. THF (tetrahydrofuran) was purifed as described[13] and then distilled over a sodium–potassium alloy in a dry argon atmosphere. ^{1}H-NMR spectra were recorded using a Varian VXR-300 spectrometer in $CDCl_3$ with TMS as the internal standard. GC-MS analyses were run on a 30 m long DB-5 fused silica capillary column, using a Varian 3400 chromatograph connected with SSQ-700 Finnigan MAT mass spectrometer. X-ray analyses were performed on a K-M4 KUMA-DIFFRACTION.

General Procedure for the Preparation of Macrocyclic Oligomers. The cyclooligomerization was conducted at 25 °C in THF solution. The monomer concentration varied from 0.5 to 0.1 mol × dm^{-3}, and the concentration of potassium alkoxide varied from 0.05 to 0.01 mol × dm^{-3}. After 30 min the reaction was accomplished, and the polymer formed was precipitated by addition of hexane. In the filtrates obtained, after polymer separation, the presence of cyclic oligomers was detected by GC-MS spectroscopy. The acquired mass spectra of cyclic trimer and tetramer were in good agreement with those described in literature[12,14,15] for respective cyclic oligo-

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mers formed *via* thermal degradation of polypivalolactone. The solvent was partly evaporated, and crystallization of oligomers was observed. Then the selected crystals were analyzed by ^{1}H-NMR and GC-MS (in THF solution).

3,3,7,7,11,11-Hexamethyl-1,5,9-trioxacyclododecane-2,6,10-trione (cyclic trimer): ^{1}H-NMR δ 1.24 (s, 6H), 4.07 (s, 2H); MS m/z 301 ($M^+ + 1$), 282 ($M^+ - H_2O$), 270 ($M^+ - CH_2O$), 242 (270 − CO), 201 (301 − $C_5H_8O_2$), 182 (282 − $C_5H_8O_2$), 170 (270 − $C_5H_8O_2$), 142 (242 − $C_5H_8O_2$), 101 (201 − $C_5H_8O_2$), 82 (182 − $C_5H_8O_2$), 70 (170 − $C_5H_8O_2$), 42 (142 − $C_5H_8O_2$) (where $C_5H_8O_2$ is the unit with molecular weight equal to pivalolactone monomer MW = 100).

3,3,7,7,11,11,15,15-Octamethyl-1,5,9,13-tetraoxacyclohexadecane-2,6,10,14-tetraone (cyclic tetramer): ^{1}H-NMR δ 1.21 (s, 6H), 3.97 (s, 2H); MS m/z 401 ($M^+ + 1$), 382 ($M^+ - H_2O$), 370 ($M^+ - CH_2O$), 342 (370 − CO), 301 (401 − $C_5H_8O_2$), 282 (382 − $C_5H_8O_2$), 270 (370 − $C_5H_8O_2$), 242 (342 − $C_5H_8O_2$), 201 (301 − $C_5H_8O_2$), 182 (282 − $C_5H_8O_2$), 170 (270 − $C_5H_8O_2$), 142 (242 − $C_5H_8O_2$), 101 (201 − $C_5H_8O_2$), 82 (182 − $C_5H_8O_2$), 70 (170 − $C_5H_8O_2$), 42 (142 − $C_5H_8O_2$) (where $C_5H_8O_2$ is the unit with molecular weight equal to pivalolactone monomer, MW = 100).

Crystal Data. The needle-shape crystals of tetramer were analyzed by X-ray crystal structure methods. A single crystal from hexane–THF: $C_{20}H_{32}O_8$, MW = 400.46, monoclinic, space group $P2_1/c$, a = 15.487(1), b=12.381(1), c = 11.833(1) Å, β = 100.40(1)°, V = 2231.6(3) Å^3, D_x = 1.192 g/cm^3, D_m =1.18 g/cm^3, Z = 4, μ = 0.76 mm^{-1}, λCu(K) = 1.54178 Å, $F(000)$ = 864, T = 295 K. Specimen 0.35 × 0.33 × 0.20 mm, KM-4 diffractometer, 4125 reflections for 2.9 < ω <70.2°, of which 3940 with $F^2 > 2\sigma$ (F2) were used in refinement. The crystal structure was evaluated using SHELXS-86,[16] as well as SHELXS-93,[17] R = 0.041, wR = 0.123 at S = 1.061. Atomic coordinates, bond lengths and angles, thermal parameters, and $F_o - F_c$ tables have been deposited at the Cambridge Crystallographic Data Centre, which can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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Supporting Information Available: Space-filling model and stereoview of tetrolide and ^{1}H-NMR spectrum of cyclic tetramer (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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