# Petroleum and Coal

## Synthesis of L-lactide supplemented with stage-wise analytical control

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### Abstract

L-lactide synthesis from an aqueous solution of L-lactic acid under different conditions in the presence or absence of a catalyst (zinc oxide, stannous octoate or magnesium ethoxide) has been studied. Synthe-sis of L-lactide is accompanied by analytical control. The glass transition temperature of lactic acid oligo-mers, i.e. a product of polycondensation at the first stage of the process, has been investigated using differential scanning calorimetry (DSC). Identification and quantitative deter-mination of lactic acid and L-lactide at different stages of the synthesis have been performed by HPLC. A residual solvent in L-lactide after its recrystallization has been determined by gas chromatography-mass spectrometry (GC-MS).

*Keywords:* lactide; lactic acid oligomer; recrystallization.

## 1. Introduction

Lactide (3,6-dimethyl-1,4-dioxane-2,5-dione) is a dehydrated cyclic dimer of lactic acid. Since it has two asymmetric carbon atoms, lactide may exist in three different stereo-isomers: L-lactide, D-lactide, and meso-lactide [1]. Lactide is a monomer for the synthesis of poly(lactic acid) (PLA). It is biodegradable and biocompatible with a human body. The poly-mer is easily processed using standard plastics equipment yielding molded parts, films or fibers [1-2].Plastic PLA films are used in packaging of, e.g. food, medical and hygienic pro-ducts; PLA items find applications in food industry, agriculture, electronics [3-7]. The poly-mer may potentially be used for medical and pharmaceutical applications: sutures, scaffolds, implants, artificial tissues and organs in transplantation, orthopedic devices and drug deli-very systems [8-14].

There are two major synthetic ways to obtain PLA: the direct polycondensation of lactic acid and the ring-opening polymerization (ROP) of L-lactide. The preparation of the L-lactide mono-mer for ROP includes the following steps:

- L-lactic acid polycondensationfor obtaining oligo(L-lactic acid) (OLLA);
- OLLA depolymerization for producing crude lactide;
- Crude lactidepurification [1-2, 15-19].

As a rule, polycondensation of lactic acid is carried out for 3 to 5 hours in two stages, the dehydration of lactic acid and its oligomerization [17- 25]. Generally, the stannous- or zinc-contai-ning mineral compounds are used as catalysts in oligomerization [19-20,27]. The dehydration of lactic acid is carried out using an entrainer (azeotropic distillation), for example, xylene [24]. After the polycondensation, the depolymerization of the lactic acid oligomer is conducted. This process is carried out in the presence of similar catalysts at an elevated temperature under vacuum [18-19, 26].

## 2. Experimental part

### 2.1 Materials

85% aqueous L-lactic acid solution, tin(II) 2-ethylhexanoate (stannous octoate) with purity 92.5-100% and magnesiumethylat (magnesium ethoxide) with purity 98% ($(C_2H_5)_2Mg$) were purchased from Sigma-Aldrich, USA, and used without additional treatment. 80% the aqueous L-lactic acid solution was purchased from Lach-Ner, Czech Republic. Zinc oxide Red Seal (purity 99.5%) was purchased from Numinor Chemical Indus-tries Ltd., Israel.

### 2.2. Methods

#### 2.2.1. Polycondensation

L-Lactic acid was placed in a 500 ml two-necked flask equipped with a stirrer, a vacuum system and a capillary inlet for argon. The flask was heated at a low-melting eutectic alloy bath (Belmont). Between the flask and the pressure controller, the vacuum line was intercepted by a trap cooled with a dry ice/ethanol mixture. The reactor was heated from 120 to 160-200°C for 80 min. Subsequently, the pressure was reduced gradually from 500 to 5-30 torr using a vacuum controller. The polycondensation was carried out in the presence or absence of a catalyst (Tab. 1).

Table 1. Conditions of the L-lactide synthesis and the yields of crude lactide

| No. of experiment | LA | Polycondensation | | | | | | Depolymerization | | | | | | η, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cat. | $T_{in}$, °C | $T_{fin}$, °C | $P_{in}$, torr | $P_{fin}$, torr | t, min | Cat. | $T_{in}$, °C | $T_{fin}$, °C | $P_{in}$, torr | $P_{fin}$, torr | t, min | |
| 1 | ALD. | - | 122 | 160 | 90 | 5 | 150 | ZnO | 160 | 200 | 500 | 0,22 | 60 | 27 |
| 2 | ALD. | - | 120 | 200 | 500 | 6 | 175 | ZnO | 200 | 250 | 10 | 10 | 60 | 43 |
| 3 | ALD. | - | 120 | 200 | 500 | 10 | 160 | ZnO | 200 | 250 | 10 | 2 | 80 | 57 |
| 4 | ALD. | ZnO | 120 | 200 | 500 | 15 | 170 | - | 200 | 250 | 10 | 1 | 65 | 31 |
| 5 | ALD. | - | 120 | 200 | 500 | 25 | 150 | SnOct | 200 | 250 | 25 | 2 | 80 | 49 |
| 6 | ALD. | SnOct | 120 | 200 | 500 | 25 | 150 | - | 200 | 250 | 25 | 1 | 80 | 54 |
| 7 | ALD. | - | 120 | 200 | 500 | 25 | 150 | - | 200 | 250 | 25 | 2 | 90 | 59 |
| 8 | ALD. | SnOct | 120 | 200 | 500 | 25 | 150 | SnOct | 200 | 250 | 7.5-11 | | 80 | 56 |
| 9 | ALD. | ZnO | 120 | 200 | 500 | 19 | 240 | SnOct | 200 | 250 | 7.5-11 | | 80 | 52 |
| 10 | ALD. | SnOct | 120 | 200 | 500 | 19 | 240 | SnOct | 200 | 250 | 7.5-11 | | 80 | 64 |
| 11 | LAC. | - | 120 | 200 | 500 | 25 | 150 | ZnO | 200 | 250 | 10 | 2 | 80 | 76 |
| 12 | LAC. | - | 120 | 200 | 500 | 25 | 150 | - | 200 | 250 | 25 | 2 | 90 | 54 |
| 13 | LAC. | - | 120 | 200 | 500 | 25 | 150 | MgOEt | 200 | 250 | 25 | 2 | 90 | 82 |
| 14 | LAC. | ZnO | 120 | 160 | 500 | 30 | 240 | - | 200 | 250 | 25 | 2 | 85 | 72 |

The thermodynamic parameters of the obtained OLLA were identified by differential scanning calorimetry (DSC). The purity of the products was analysed using high performance liquid chromatography (HPLC) (see below for the details). Four samples of lactic acid oligomers were selected for 40 (LA1), 80 (LA2), 120 (LA3) and 150 (LA4) min time of the polycondensation reaction for analysis using HPLC.

#### 2.2.2. Depolymerization of lactic acid oligomer

Depolymerization of the OLLA resulting in the production of a lactide monomer was carried out using the same laboratory setup with replacing a receiver flask. The residual pressure in the reactor was further reduced from 10-25 to 1-2torr for 20-30 min. Subsequently, the temperature was increased gradually from 200 to 250°C. The process conditions are given in tab. 1.

The obtained product, crude lactide, once removed from the reactor, was recrystallized once in three routes using various solvents - ethyl acetate, toluene, and benzene. After recrystallization, L-lactide was dried and stored in an evacuated desiccator.

The contents of lactic acid and L-lactide were determined by HPLC. The residual solvent in L-lactide after its recrystallization was quantified using gas chromatography-mass spectrometry (GC-MS).

## 2.3. Measurements

Glass-transition temperatures of the OLLA were identified using a DSC Q100 model (TA Instruments, New Castle, DE, USA).The dry material in an amount of 5 mg was placed to a hermetic aluminium panin the closed compartment filled with nitrogen. Heating was applied to the pan at the rate of 10°C min$^{-1}$ from -60 to 190°C.The heating rate for the analysis was chosen in accordance with the literature [27-28].

The reversed phase HPLC analysis was carried out using a YL9100 HPLC system (Young Lin Clarity, South Korea). The chromatographic columns Tracer Excel 120 ODSA (250 mm × 4.6 mm × 5 µm) and Zorbax Eclipse XDB-C18 (250 mm × 4.6 mm × 5 µm) were connected consecutively. Chromatographic separation was carried out at the column oven temperature of 40 ± 2 °C with a mobile phase flow rate 1.2 mLmin$^{-1}$. The mobile phase consisted of acetonitrile (HPLC grade) and an aqueous solution of ortho-phosphoric acid containing 1 g L$^{-1}$. The gradient profile of the mobile phase, applied in the analysis, started from 88 vol.% of aqueous solution of ortho-phosphoric acid and 12 vol.% of acetonitrile. In 15 minutes the acetonitrile concentration was ramped linearly to 100 vol.% within 0.2 min, maintained for 4.8 min and returned back to 88 vol.% aqueous solution of ortho-phosphoric acid and 12 vol.% of acetonitrile. The injected sample volume was 20 µL. The wavelength in the UV-detector was set at 210 nm.The conditions of HPLC analysis were chosen in accordance with [29].

The GC-MS analysis was carried out using a gas chromatograph Agilent 7820 equipped with a mass spectrometer Agilent 5975 as a detector. Chromatographic separation was performed in a capillary column DB-5MS filled with 5% phenyl and 95% methyl polysiloxane (30 m × 250 µм id × 0.25 µm). The temperature was held for 7 min at 60°C with subsequent ramping to 190°C with a heating rate of 10°C min$^{-1}$. Helium was used as a carrier gas at a flow rate of 20 mLmin$^{-1}$. Detection was carried out using electron impact ionization at 70 eV in selec-ted ion monitoring (SIM) mode at *m/z* of 45, 56, 61, 78, 84, and 91 amu. Tridecane was added to the samples as an internal standard [30].

## 3. Results and Discussion

The condensation reaction of L-lactic acid results in the formation of OLLA. L-lactide is prepared via the depolymerization of OLLA (fig. 1). The obtained data on the synthesis both of OLLA and L-lactide and reaction conditions are shown in the tab. 1.
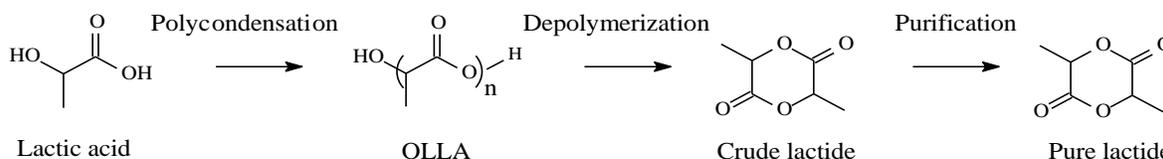


Fig. 1. The scheme of lactide production

## 3.1. Impact of the synthesis conditions on the yield of crude lactide

The pressure at the stage of lactic acid polycondensation can be reduced to 19-20 torr. Lower pressure promotes the early oligomers depolymerization and loss of lactidethat lead to low yields of the crude lactide during the stage of the OLLA depolymerization (expe-riments 1-4).

It should be noted that under equal conditions, the yield of L-lactide depends strongly on the choice of the initial lactic acid (producer) (Tab. 2).

Table 2. Glass-transition temperature of OLLA

| No. of experiment (see Table 1) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Glass-transition temperature, °C | -21 | -7 | -11 | -13 | -8 | 2 | -2 | 3 | -1 | -2 | -14 |

The presence of a catalyst in the OLLA depolymerization has a greater impact on the yield of crude lactide than only in the oligomer synthesis (experiments 1-3, 5, 8-11 and 13). The highest yields of lactide are observed when using 80% aqueous lactic acid solution from LACH-NER in the presence of zinc oxide and magnesium ethoxide (experiments 11, 13, and 14).

## 3.2. Analysis of OLLA

The glass-transition temperature of the OLLA is determined using DSC. The results are given in tab. 2. The high-molecular weight poly(L-lactic acid) having molar mass $M_v$= 153000g/mol has a glass-transition temperature of about 64°C [14].Poly(L-lactic acid) prepared by poly-condensation and purified by precipitation of dichloromethane solution into methanol ($M_v$=6200 g/mol) has 54°C [14].Low-molecular weight oligomers act as inherent plasticizers significantly reducing a glass-transition temperature (Tab. 2).

The results of HPLC analysis at the stage of samples polycondensation are shown in the tab. 3. It can be seen that the content of lactic acid significantly decreases at about 120 min of the polycondensation reaction with an insignificant change afterwards.

Table 3. Results of HPLC analysis of samples polycondensation

| No. of experiment (see Table 1) | Sample | Lactic acid content, % mass. |
|---|---|---|
| 8 | LA1 | 59 ± 1 |
| | LA2 | 18.0 ± 0.3 |
| | LA3 | 11.0 ± 0.2 |
| | LA4 | 1.01 ± 0.2 |
| 9 | LA1 | 33.0 ± 0.6 |
| | LA2 | 19.0 ± 0.3 |
| | LA3 | 2.00 ± 0.04 |
| | LA4 | 2.00 ± 0.04 |

## 3.3. Analysis of L-lactide

The L-lactide samples are analysed by HPLC and GC-MS methods (fig.2).
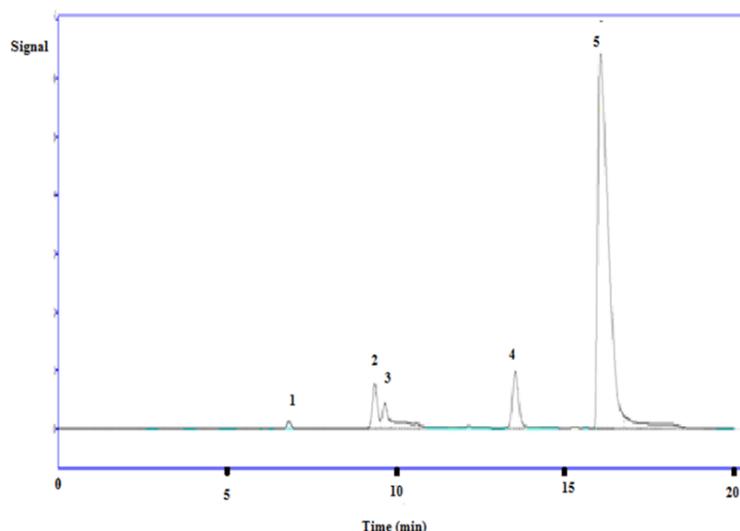


Fig. 2. HPLC chromatogram of lactide after its recrystallization from ethyl acetate: 1 – lactic acid; 2-4 – unknown impurities; 5 – L-lactide

The content of lactic acid, L-lactide, and solvents in samples are presented in the tab. 4. Ethyl acetate is the most volatile among the three solvents; its residual content in L-lactide after recrystallization was only 0.08 ± 0.003% mass. However, the lactic acid content in L-lactide decreases to 0.7 ± 0.01 % mass and the L-lactide content increases up to 95 ± 0.2 % mass when recrystallized from toluene.

Table 4. HPLC analysis of L-lactide

| Sample | | Content, % mass. | | |
|---|---|---|---|---|
| | | Lactic acid | L-lactide | Solvent |
| Crude-lactide | | 1.60 ± 0.03 | 65.0 ± 0.1 | - |
| Recrystallized L-lactide from | ethyl acetate | 1.40 ± 0.02 | 93.0 ± 0.2 | 0.08 ± 0.003 |
| | toluene | 0.70 ± 0.01 | 95.0 ± 0.2 | 0.33 ± 0.004 |
| | benzene | 1.10 ± 0.02 | 81.0 ± 0.2 | 0.37 ± 0.006 |

## 4. Conclusion

1. It has been shown that the yield of crude lactide depends on the quality of the initial lactic acid (producer).
2. It has been found that the yield of crude lactide depends on the presence and catalyst type during the depolymerization more than only during the oligomer synthesis.
3. The analytical techniques to control L-lactide synthesis and its purification using methods of DSC, HPLC and GC-MS, which allow tracing the processes of lactic acid polycondensation, L-lactide synthesis, and L-lactide purification, have been selected.

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