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Mendeleev Commun., 2019, **29**, 648–650

Mendeleev Communications

Synthesis of lactide from alkyl lactates catalyzed by lanthanide salts

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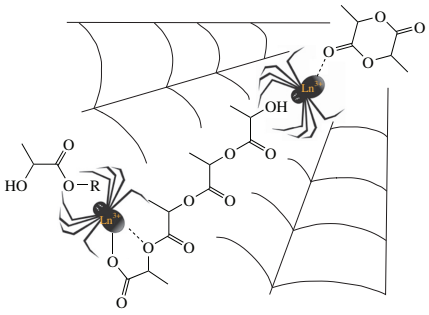
DOI: 10.1016/j.mencom.2019.11.014

Cerium salt exhibited a highest catalytic activity in the conversion of ethyl and isopropyl oligolactates into lactide. A maximum yield of the target product was reached at the concentration of $CeCl_3 \cdot 7H_2O$ ranging from 1 to 4 mol% relative to the lactide units in ethyl and isopropyl oligolactates. A gradual reduction of the pressure from 50 to 5 Torr along with the temperature increase from 180 to 230 °C during depolymerization resulted in the product containing up to 94% lactide.



There is an increasing need for polymer materials capable of degradation upon the contact with a biological media *via* hydrolytic decomposition and/or zymolysis to monomers with their subsequent transformation into CO_2 and H_2O.[1] Due to their biodegradability and biocompatibility, such polymers may be employed as starting materials for manufacturing high-tech medical products, *e.g.* implants, pins, and inventive surgical suture materials.[2–4] Polylactic acid (polylactide, PLA) is especially suitable for this purpose since its desired physical and mechanical properties along with the rate of biodegradation can be finely tuned by varying the PLA microstructure (sequence and ratio of stereoisomeric L- and D-forms of monomer units), molecular weight, and polydispersity.[5–8]

Polylactides can be synthesized either *via* a polycondensation of lactic acid, *e.g.* azeotropic distillation of water, or by the ring-opening polymerization (ROP) of lactide that is the cyclic dimer of lactic acid.[2] The second approach is preferable for producing a high molecular weight PLA with a low polydispersity.[9–11] Lactide can be obtained either directly from lactic acid or from alkyl lactates. The current synthetic approach to lactide involves the use of compounds containing heavy metal ions as the catalysts. Thus, a design of goods obtained from such polymers is undesirable in medicine.[12–16] Some highly efficient one-step methods for producing lactides from lactic acid in the presence of zeolites[17] or Cs_2CO_3[18] as the catalysts were reported. However, a disadvantage of those methods is the need for water removal from the reaction mixture by the circular azeotropic distillation with organic solvents. Another method for the lactide production is a gas-phase transesterification of methyl lactate in a flow-type reactor containing a heterogeneous titanium-based catalyst.[19,20] In spite of a high degree of conversion of raw materials and a high selectivity towards the target product, this method requires a high flow rate of N_2 carrier, while the flow rate and concentration of methyl lactate in the gas-raw streams are low. Therefore, the search for new methods for the lactide production, based on low toxic as well as easy-to-handle catalysts and appropriate for both laboratory and industrial scales, is a crucial challenge.

Recently we have demonstrated that lactide can be produced either from lactic acid, or its ethyl ester, or its oligomers in the presence of Y^{III} and Pr^{III} oxides or $CeCl_3 \cdot 7H_2O$.[21] In the presence of catalytic amount of $CeCl_3$, a mixture of ethyl lactate and oligoesters can be converted into the desired product in a yield of up to 84%, which is comparable to the yields achieved using tin and lead containing catalysts.[15,16] The production of lactide from lactic acid esters is known as minimizing the undesired racemization[19,20] catalyzed by water.[22] The development and further optimization of catalytic methods for the conversion of alkyl lactates into lactide are preferable. Here, we report on the lactide synthesis from lactic acid esters in the presence of catalytic amounts of Ce^{III}, Nd^{III} and Sm^{III} chlorides. The dependence of product yield on the catalyst concentration and pressure has also been investigated.

Lactide was synthesized in two steps including the oligomerization of alkyl lactates and subsequent deoligomerization of the mixture of oligoesters. Figure 1 shows the supposed reaction mechanism. According to the modern concepts, the mechanism of lactide ROP includes the formation of metal lactates.[23–26] We assume that the lactide formation proceeds *via* a reversible ROP mechanism.

Lactic acid was esterified with aliphatic alcohols. A distillation of alcohol excess from the reaction mixtures resulted in a crude product containing alkyl lactate (*ca.* 65%) and alkyl oligolactates (*ca.* 30%). Unreacted lactic acid and its oligomers were present in the crude product along with other admixtures. A total conversion of lactic acid was *ca.* 95%. The further oligomerization of crude product to alkyl oligolactates was carried out by a gradual increase in the temperature from 160 to 190 °C under N_2 atmosphere in the presence of $LnCl_3 \cdot nH_2O$ (1.6 mol%; Ln = Ce, n = 7; Ln = Nd, Sm, n = 6). Some experimental results on oligomerization and depolymerization processes are given in Table 1.

The selected lanthanide salts exhibited different catalytic activity that can be evaluated by the degree of polymerization (DP_n) of crude product to the alkyl oligolactate. These DP_ns

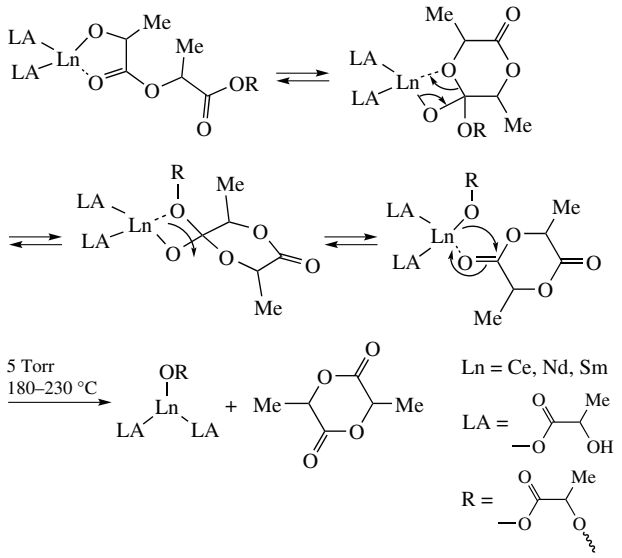
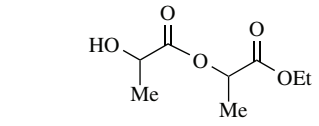
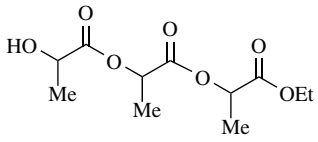


Figure 1 Proposed reaction mechanism for the lactide formation.

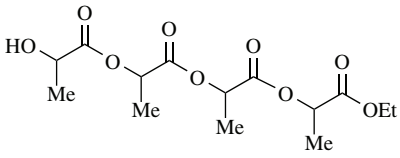
were determined by the ^{1}H NMR spectroscopy according to the known approach.[21] To obtain the desired lactide, the oligomer mixtures were heated (200 °C) under reduced pressure (5 Torr) in the presence of a catalyst. At the elevated temperature, the depolymerization occurred affording the lactide, although not quantitatively. In all the experiments, lactide has been isolated as the mixture of L-, D- and *meso*-lactides. During the depolymerization, lactide was sublimed together with other low molecular weight products. In the absence of lanthanide salt, the thermal depolymerization of oligomer mixture did not afford lactide in any detectable quantities. The GC/MS analysis revealed the presence of ethyl dilactate as the major component (55 wt%). Ethyl trilactate and ethyl tetralactate have been also found in the sublimed product.



Ethyl dilactate



Ethyl trilactate



Ethyl tetralactate

Table 1 Conversion of lactic acid esterification products into lactide in the presence of different catalysts.

Entry	Catalyst[a]	DP_n	Lactide yield (%)	Selectivity (%)		
				L-lactide[b]	D-lactide[b]	*meso*-lactide
1	$CeCl_3·7H_2O$	3.9	46	91.8	0.2	8
2	$NdCl_3·6H_2O$	2.4	21	82.1	0.9	17
3	$SmCl_3·6H_2O$	3.1	34	77.6	1.4	21
4	–	1.7	0[c]	–	–	–

[a] Amount of the catalyst: 1.6 mol%. [b] The L- and D-lactide selectivities were calculated according to the known method.[22] [c] GC/MS analysis confirmed the absence of lactide in the sublimate along with the presence of ethyl di-, tri- and tetralactates.

In the case of cerium salts, the DP_n value and lactide yield (3.9 and 46%, respectively) were the highest ones among all the used lanthanide compounds, while the D- and *meso*-lactides contents were lower (0.2 and 8%, respectively) (see Table 1). In all the cases, the racemization was probably catalyzed[22] by water that was present in the lanthanide chlorides.

Thus, Ce^{III} salt was selected as the catalyst to investigate the impact of ester substituent in alkyl lactates on the lactide formation. The oligomerization of three lactic acid esters, *viz.* isopropyl, *n*-butyl and isobutyl lactates was attempted under the same conditions applied previously for the oligomerization of ethyl lactate (N_2, 160–190 °C). No oligomerization was observed for the two latter esters, while the mixture of oligomers (DP_n = 3.3) was obtained from isopropyl lactate. One can suggest that a lack of oligomerization products in the case of butyl lactates is caused by a steric hindrance of the carboxylate group due to the bulkier butyl groups. A thermal depolymerization of the mixture of isopropyl oligolactates (5 Torr, 180 °C) afforded lactide in the yield of 40% and the content of D- and *meso*-lactides of 0.5 and 13%, respectively.

The impact of amount of $CeCl_3·7H_2O$ on the conversion of ethyl- and isopropyl oligolactates (Et-oligo-LA and Pr^i-oligo-LA, respectively) into lactide was also estimated (Table S1, Online Supplementary Materials). An increase in the catalyst concentration did not affect the DP_n of Pr^i-oligo-LA, while for Et-oligo-LA, it was changed from 3.3 to 4.5 upon raising the $CeCl_3$ concentration from 1 to 3 mol%. Meantime, there was a pronounced effect of the amount of $CeCl_3·7H_2O$ on the lactide yield and its racemization. Increase in the catalyst concentration for Et-oligo-LA (up to 3 mol%) and for Pr^i-oligo-LA (up to 2 mol%) allowed us to increase the target product yields up to 59 and 58%, respectively. Consequently, the total content of D- and *meso*-lactides increased to 12.4 and 16.8% for Et-oligo-LA and Pr^i-oligo-LA, respectively. This can be explained by a higher water content in the mixtures due to the higher amount of $CeCl_3·7H_2O$ used. A further increase in the concentration of cerium catalyst (up to 4 and 3 mol% for Et-oligo-LA and Pr^i-oligo-LA, respectively) led to the decreased yield of lactide.

According to the GC-MS analysis data, the mixture of products obtained by the depolymerization of alkyl oligolactates contained alkyl lactates with $DP_n \leqslant 4$ in addition to L-, D- and *meso*-lactides. This fact indicates that the oligomeric components at 5 Torr were removed from the reaction area faster than they were converted into lactide. Thus, we started the depolymerization under the pressure of 50 Torr with its reduction to 5 Torr at the rate of 22.5 Torr h^{-1}, as well as at the temperature increased from 180 to 230 °C at the rate of 25 °C h^{-1}. The implemented modification of the process resulted in a significantly higher lactide yield (Table S2). Thus, Pr^i-oligo-LA was converted into the mixture of lactides in the yield of 94% using 2 mol% of $CeCl_3·7H_2O$.

In conclusion, we have demonstrated that lanthanide salts can be employed as the catalysts for the conversion of alkyl lactates into alkyl oligolactates. The latter can be successfully depolymerized to lactide. The desired lactide was obtained in the yield of 94% starting from L-lactic acid, although a partial racemization to D- and *meso*-lactides was also observed. The ring-opening polymerization of prepared lactides has been carried out using main group metal-based catalysts, and these results will be reported elsewhere.

This work was supported by the Russian Foundation for Basic Research (grant no. 18-43-520006) and performed within the framework of the Russian State Assignment using the equipment of the Analytical Center at the G. A. Razuvaev Institute of Organometallic Chemistry of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.11.014.

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Received: 11th April 2019; Com. 19/5882