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Kinetic Study of the Effect of Catalyst in the Polycondensation of Lactic Acid to Produce Low Molecular Weight Polymers

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The synthesis of low molecular weight (less than 30000 Da) lactic acid polymers (PLA) by polycondensation of a racemic mixture of D and L lactic acid was investigated. All polymerizations were carried out in the melt both in the absence and presence of catalysts at various temperatures. The obtained polymers were characterized by viscosimetry GPC and titrimetric methods. As catalysts it has been adopted both protic (sulphuric and phosphoric acid) and aprotic ($SnCl_2$, $SnCl_4$, $AlCl_3$, AlF_3, $FeCl_3$, $NiCl_2$, Al_2O_3) acids. Since it is known that these reacting systems can reach the equilibrium, different experiments were carried out in closed conditions to estimate the equilibrium constants for these reactions. According to our results, the best polycondensation catalyst was $SnCl_2$, that produced the highest molecular weights in the operating conditions (reaction time of 24 hours at 180 °C). Successively we studied the polycondensation of lactic acid adopting $SnCl_2$ as catalyst under different operating conditions. In particular we focalized our research on the temperature and residence time effect after being optimized the pre-treatment of the reactants.

1. Introduction

Polymers based on lactic acid have received a large amount of attention in the field of medical applications because these polyesters degrade in the body by simple hydrolysis of the ester backbone to non-harmful and non-toxic compounds. In particular suture materials have a long history regarding their excellent safety and biocompatibility as biomaterials. These compounds are used as starting materials in the production of implantable medical devices, in dental applications and, in more experimental applications, as scaffolds for autografted new skin, wound covers, anastomose systems and stents (Benedix 1998, Sodergard 2002).

The present work was focused on estimating the kinetic and equilibrium constants for the direct polycondensation of lactic acid to produce low molecular wieght PLA under different operating conditions. Experiments in both open (under nitrogen flow) and closed (equilibrium reactions) systems were carried out. A mathematical model for the polycondensation of lactic acid through a generalized reversible step-growth polycondensation scheme was developed. The model was validated by comparing with experimental results.

2. Experimental

2.1 Chemicals

D, L-lactic acid (50:50, 90% by weight) was purchased from Fluka Chemicals. The catalyst, $SnCl_2$ (98% pure), was purchased from Sigma-Aldrich. Titanium butoxide $(TiBuO)_4$ [98% pure], was obtained from ABCR GmbH & Co. KG. The catalysts, $SnCl_4.5H_2O$, $NiCl_2.6H_2O$ and Al_2O_3 98.5%, were produced by Carlo Erba. $MnCl_2.4H_2O$, $MoCl_5$, WCl_6, $FeCl_3.6H_2O$ and ortho phosphoric acid 98% were purchased from Merck. The catalyst $AlF_3.H_2O$ was by BDH.

2.2 Apparatus

All reactions were carried in a glass reactor (250 ml). The reactor was equipped with a magnetic coupling, joining motor and mechanical stirrer and ensuring no-leak conditions in the system. The magnetic coupling (MRK1/20 NS29/32) was purchased from Premex AG, Switzerland. One neck of the reactor was used to pump in nitrogen for the first stage of the reaction while the other neck was connected to a pump capable of achieving 15 mbar pressure in the suction side through a digital vacuum controller. A digital vacuum controller (DVR-300-MR) with multi-ramp meter (9500P, 58 programs and each program with 32 segments can be set at a time), capable of controlling the pressure in the range ± 0.5 mbar, over a range of 0-760 mbar, supplied by K-JEM Scientific Inc., USA, was used to control vacuum in the reactor. The PLA sample was heated with a thermostatic bath HBR 4 Digital, IKA Labortechnik; the vapours were condensed with a Claisen tube and were picked into a distillation flask

2.3 Experimental procedure

2.3.1 Closed system reactions

For equilibrium reactions, the reactor was connected to a condenser, which was intended for complete recycling of the vaporized water and monomer to the reaction mixture and all reactor inlets and outlets were closed.

To carry out the reaction, 50 ml of lactic acid were initially charged to the reactor and temperature was increased from ambient to the target value. The time required to increase the temperature was in the range of 45 to 90 minutes depending on the target temperature. The reaction was continued for 48 hours at the same temperature to ensure that the equilibrium is reached. The reaction mixture was weighed before and after the reaction to account for the loss of material from the reacting mixture through small leaks.

2.3.2 Open system reactions

Initially, experiments were carried out to find the most efficient catalyst from various catalysts. For each experiment definite amount of catalyst (0.1 % w/w) was added to lactic acid at the reaction start. The reaction mixture was pretreated by heating to 100 ^oC under vacuum (100 mbar) for 3 h to remove most of the initial water present in the reactant. After this pre-treatment, connection to vacuum was closed and reaction temperature was increased to the operating value. Then reaction was carried at constant temperature under nitrogen flow and samples were taken at different time intervals.

2.4 Analysis techniques

2.4.1 Gel permeation chromatography

Polymer properties of all samples were estimated by a Gel Permeation Chromatography (GPC) device (Agilent 1100 series) equipped with two detectors, namely, ultraviolet (UV) and differential refractive index (RI), three PLgel columns (two with pore sizes of MXC type and one with oligopore; column length: 300 mm; column diameter: 7.5 mm) and a pre-column. Chloroform was used as solvent with 1 ml/min flow rate and analysis temperature of 30 °C.

2.4.2 Karl Fischer

The amount of water present in a polymer sample was estimated by the Karl Fischer equipment (633 Karl Fischer-Automat and 645 Multi-dosimat), capable of measuring low concentration of water. About 0.5 g of polymer in 10 ml of CH_2Cl_2 was used. Merck combititrant 5 was used as the titrant and Merck combimehtanol was used as solvent.

2.4.3 Electron spray ionization

To analyze the oligomers produced in the closed system reactions, ESI mass-spectroscopy technique (Finnigan Mat TSQ 7000) was used. Approximately 10 mg of polymer sample was dissolved in 500 µl of THF. After that, 5 µl solution was diluted with methanol to make 1000 µl of final sample. For the analysis nano-ESI source with separation voltage of 2-2.3 kV was used. Capillary temperature was set to 100 °C and samples were scanned in the MS mode with the scan range of 10-1000 Da.

3. Results and Discussion

3.1 Catalyst selection: Selection of the most efficient catalyst

Reactions were carried out with different catalysts under the same operating conditions (reaction time, temperature, pressure, catalyst amount, etc.) with open system conditions, i.e. under flow of nitrogen. The performance of different catalysts on the basis of polymer properties (number and weight average molecular weights) is shown in Table 1. It can be seen that $SnCl_2$ is the most effective catalyst, leading to highest molecular weights under the given set of operating conditions.

Table 1: Polymer properties corresponding to different catalysts (reaction time: 24 h, reaction temperature: 180 °C)

Catalyst	M_n [Da]	M_w [Da]
$AlCl_3$	2340	3828
$SnCl_4$	3219	5033
$FeCl_3$	3179	5226
H_3PO_4	2845	4518
$SnCl_2$	3842	7013
$Ti(BuO)_4$	2664	5247

3.1.1 Closed system reactions: Estimation of the equilibrium constant

To estimate the equilibrium constant for the polycondensation of lactic acid, equilibrium imposed reactions were carried out at three reaction temperatures, 110, 150 and 180 °C for 48 h. For all reactions the final reaction mixture was found as a viscous liquid at room temperature as the degree of polymerization was very low. The reaction mixture was weighed before and after the reaction. It was found that very small amount of material was released through the leaks, thus indicating reaction conditions close to those of a completely closed system. The reaction mixture was analyzed by GPC and ESI to estimate the polymer properties and corresponding monomer conversion.

After estimating the number average molecular weight, the degree of polymerization, and hence the monomer conversion were estimated easily. It was found that the equilibrium constant is very weak function of the reaction temperature, changing from 1.25 to 1.21 when temperature changes from 110 °C to 180 °C. So, a constant value of the equilibrium constant equal to 1.25 was then used for all simulations in the present work, i.e. in the complete temperature range of 110-180 °C.

3.1.2 Open system reaction:

After performing the equilibrium limited reactions (no water removal), the aim was to estimate the polymerization rate constant under different reaction temperatures. Therefore, reactions were carried under nitrogen flow using two different catalysts [$SnCl_2$ and $Ti(BuO)_4$] and without catalyst at reaction conditions given in Table 2.

Table 2: List of experiments performed in open system

Reaction run	Temperature [°C]	Catalyst
1	110	$SnCl_2$
2	130	
3	150	
4	170	
5	110	$Ti(BuO)_4$
6	150	
7	180	
8	150	---
9	180	

Table 3: Polymerization rate constant estimated from the reaction profile at 180 oC using $SnCl_2$ as catalyst

Reaction time [h]	DP_n	k_1x10^5 l/mol/s
8	6.79	1.96
16	17.24	2.49
20	21.01	2.43
40	34.26	1.98

For each case, samples were taken at different time intervals and analyzed by GPC. The values of the polymerization rate constant estimated at 180 °C for different reaction times for reaction run 7 in Table 2 are presented in Table 3. It should be noted that the reaction time also includes the time required to reach the final reaction temperature from ambient temperature, it was typically in the range of 45 to 90 minutes depending on the operating temperature. Although the temperature profile experienced in the initial stage of the reaction does not affect the reaction samples at large reaction times, the samples taken at small reaction times may be affected. However, it can be seen from the table that the estimated values of the apparent polymerization rate constant at different reaction times are reasonably constant, being the observed scattering reflecting the experimental inaccuracies involved. Similar estimations were performed for all reactions carried out at different temperatures and catalysts from Table and the same behaviour was found. The following relations were found for the dependence of the polymerization rate constant on temperature for $Ti(BuO)_4$ and $SnCl_2$ as catalysts:

$$\ln(k_1) = -\left(\frac{3741.1}{T}\right) - 2.4781 \qquad (1)$$

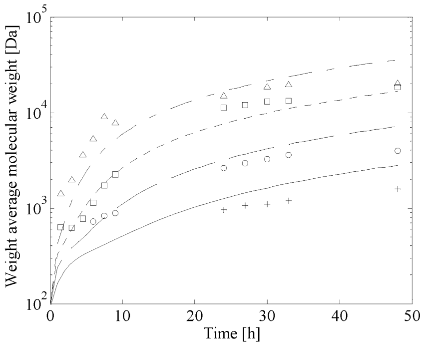
for Ti(BuO)4

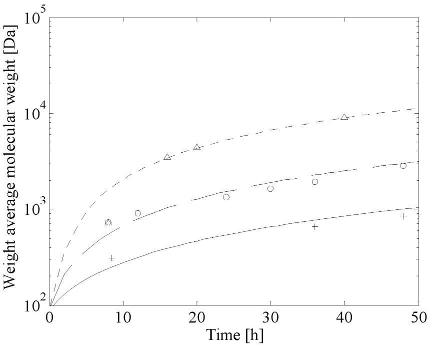
$$\ln(k_1) = -\left(\frac{6810.3}{T}\right) + 6.1928 \qquad (2)$$

for SnCl2

The only parameter that was evaluated by direct fitting of the model predictions to the experimental results was the overall mass transfer coefficient for water, $K_{y,w}$. Such fitting was carried out for the reaction with $Ti(BuO)_4$ as the catalyst at 180 °C and a $K_{y,w}$ of $5x10^{-4}$ [mol/l/s] has been determined. As the model predictions fit fairly well with the reported value of the overall mass transfer coefficient, such value was used for all simulations presented in the present work.

Using the estimated values of the model parameters, the model was used to simulate all the reactions specified in Table 2. The reaction profiles in terms of the weight average molecular weight as a function of time as predicted by the model at different temperatures with $SnCl_2$ (runs 1 to 4), $Ti(BuO)_4$ (runs 5 to 7) and without any catalyst (runs 8 and 9) are compared with the experimental reaction profiles in Figure 1, Figure 2, and Figure 3, respectively. It can be concluded that reasonable agreements were found in all cases. The discrepancy in the results could be due to the side reactions (e.g. trans-esterification, polymer degradation, etc.) and/or difference in the reactivities of the functional groups, which were not accounted for in the model (Kumar et al., 1982; Dotson et al., 1996). Further, the broadening of the experimental MWD increases with in the reaction time, thus is indicating a dependence of the corresponding side reactions upon the polymer concentration.





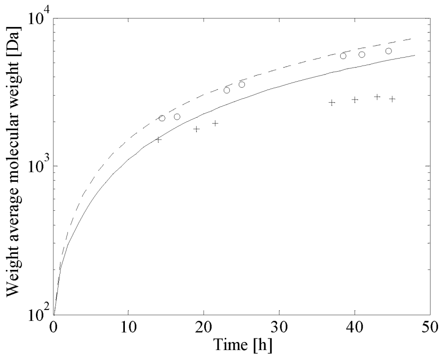


Figure 1: Comparison of model and experimental results for runs 1 to 4 from Table (points: experiments, lines: model: + , —: reaction run 1; ○, — — : reaction run 2; □, ---: reaction run 3; Δ, — – —: reaction run 4).

Figure 2 : Comparison of model and experimental results for runs 5 to 7 from Table (points: experiments, lines: model: + , —: reaction run 5; ○, — — : reaction run 6; Δ, ----: reaction run 7).

Figure 3 : Comparison of model and experimental results for runs 8 and 9 from Table (points: experiments, lines: model: +, —: reaction run 8; ○, ----: reaction run 9

4. Conclusion

Polycondensation of lactic acid with and without catalyst under closed and open conditions was studied at different temperatures. The experimental results were used to estimate the polymerization rate constant and the equilibrium constant. The mathematical model developed with the assumption of simple kinetic scheme and estimated kinetic parameters, was useful to understand and to predict effects of different operating conditions on the polymer properties. Though the model results differed from the experimental results in terms of the polymer MWDs, the model predicted average polymer properties were fairly good agreement with the experimental values. To improve the model predictions more emphasis should be focused on studying the involved reaction chemistry.

5. References

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