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# Scaleup of Lipase-Catalyzed Polyester Synthesis

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## Abstract:

**One of the critical steps for the commercialization of new enzyme-based products is the successful scaleup of the catalyzed reaction. In the study presented here, we achieved a scaleup for the enzymatic production of glycerol adipate on a 500 g scale in a heated, solvent-free system. The influence of various reaction conditions (i.e., temperature, pressure, enzyme concentration, reactants ratio, stirrer type, stirring rate, and reaction time) on the substrate conversion and molecular weight of the product was investigated. Conversions were higher than 0.9, and molecular weights were in the desired range of 2000−3000 Da. Space time yields of 370 g $d^{-1}$ $L^{-1}$ could be achieved. Maximal polymer yield was achieved at 60 °C, < 20 mbar, 3 wt % Novozym 435, glycerol:adipic acid ratio 1.1:1, <48 h while stirring at 100 rpm.**

## Introduction

Enzymes, which are catalysts derived from living organisms, are already successfully used in many fields of organic synthesis. Some first examples for industrial enzyme applications were amino acylases, penicillin acylases, lactases, and D-amino acid oxidases.[1,2] Main advantages are higher-product quality, better raw material exploitation, lower production costs, and lower environmental impact. As biocatalysts could already replace chemical catalysts in many fields, such as synthesis of acrylamide using nitrile hydratase in whole cells of *Rhodococcus rhodochrous*,[3] L-*tert*-Leucine by leucine dehydrogenase[4] or surfactant production by Novozym 435,[5] research is also done with the aim of using enzymes as catalysts in polymer synthesis.[6] Generally, enzymes used as catalysts can offer the following advantages: high enantio- and regioselectivity,[7] possible catalyst recycling,[8,9] no organic solvents needed,[10] low reaction temperatures,[11,12] replacement of potentially toxic catalysts and no protection/deprotection steps.[13] Especially peroxidases,[14] cellulases and lipases can be used in order to prepare well-defined polymeric structures. A first example of lipase catalyzed polymerization is the reaction of divinylsebacate with glycerol carried out by Kobayashi and co-workers.[15] In general, lipases have the advantage that many of them are commercially available in larger quantities.[16]

As stated before, the production of polyesters with lipases has advantages in comparison with the chemical synthesis. However, to the best of our knowledge, no lipase catalyzed industrial process for the production of polyesters is known. There are different reasons responsible for this finding. The chemical synthesis of polyesters is a well established process in the chemical industry and new process technologies may lead to many changes in the current manufacturing protocols. Another reason is also that only a few academic groups are active in polymer synthesis using enzymes and only very few feasibility studies for the enzyme catalyzed preparation of larger quantities of polymers are published. The aim of this study was to investigate the synthesis of polyesters in preparative scale (>500 g) as a feasibility study for industrial production.

A recent approach is the lipase-catalyzed polyester synthesis in a biphasic reaction system starting from sebacic acid and 1,4-butanediol.[17] Instead, we carried out bulk polymerizations applying the commercially available immobilized lipase B from *Candida antarctica*, Novozym 435, for production of polyesters containing glycerol and adipic acid (Scheme 1), because here higher space time yields[18] can be obtained. In the literature, polyesters from glycerol and adipic acid were produced by Gross et al. only on a small scale (~5 g).[19] Here, at a temperature of 70−90 °C Novozym 435 beads (10 wt % relative to monomers, 600 mg, dried at 25 °C/10 mmHg/24 h) were used. The flask was sealed with a rubber septum, and the

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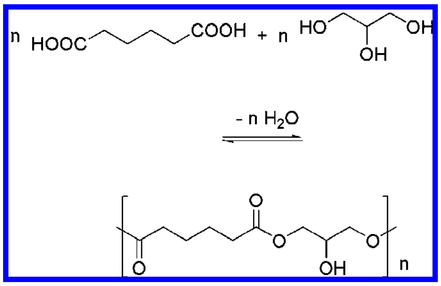
***Scheme 1.*** **Scaled up bulk polymerization of adipic acid and glycerol**



reaction was maintained at 70 or 90 °C, respectively, with mixing. Furthermore, after the first 2 h of the reaction, the contents of the reaction were maintained under reduced pressure (53 mbar). The $M_n$ and $M_w$ values of the resulting poly(glyceryl adipate), determined by SEC-MALLS in THF, were 2500 and 3700 g/mol, respectively. These polyesters offer high hydroxyl functionality and thus should also show different properties than conventional polyesters based on diols and diacids.

## Results

Polycondensation reactions are step-growth reactions. In the beginning of the reaction short oligomers are formed, while polymers with higher molecular weight are formed at high conversions at the end of the reaction.[20,21] To obtain high molecular weights and, beyond that, to avoid the separation of unreacted monomer high conversion is important.[22,16] In this study, polyesters with a weight average molecular weight between 500 to 3000 Da were desired, most favorably between 2000 to 3000 Da.

Basic reaction parameters like temperature, pressure and enzyme amount are of great importance because they directly influence the reaction rate and the conversion of the reaction. An optimal temperature for an enzymatic reaction was found where the biocatalyst shows high activity and good stability. While in the literature[19] a temperature of 90 °C was used by Gross et al. for the enzymatic bulk polymerization, we varied the temperature from 60 to 80 °C as shown in Figure 1.

At a temperature of 60 °C a conversion of 0.97 can be achieved. At temperatures of 70 and 80 °C conversions of only 0.34 and 0.17, respectively, were obtained (Figure 2). Hence, temperatures from 70 °C upwards have a negative effect on the stability of the enzyme. This was also previously reported for the acylation of polyglycerol by Novozym 435.[5] The polyesterification of adipic acid (AA) and glycerol (Gly) will therefore be carried out at 60 °C in all future experiments.

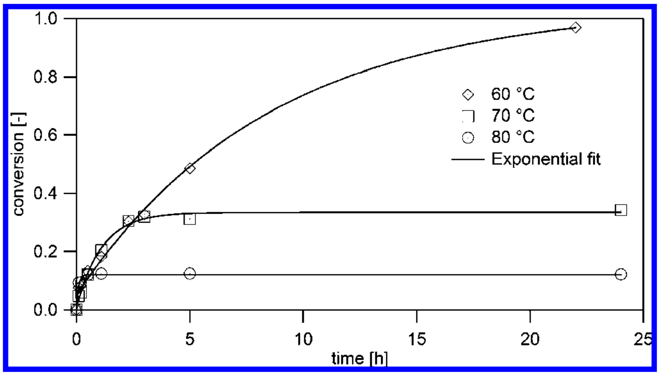


***Figure 1.*** **Conversion time plot for the enzymatic bulk polymerization carried out at temperatures from 60 to 80 °C. Reaction conditions: 7 mbar, 3 wt % Novozym 435, Gly:AA = 1.6, half moon stirrer, 100 rpm, 20 g.**

The polycondensation is an equilibrium reaction. At first, oligomers are formed, while in the course of the reaction these oligomers react and polyesters with higher molecular weight are obtained. This means that the there is a strong impact of the conversion level on the molecular weight. In order to reach high conversion, the formed water must be removed, e.g. by applying a vacuum. The vapor pressure of water at a temperature of 60 °C is 199.5 mbar.[23] Therefore, a pressure of 20 mbar is already sufficient for evaporation of the water. However, the lower the pressure in the reactor, the higher the driving force, and the faster the evaporation. From this point of view, the highest vacuum possible should be utilized since no substrate or product is removed. This is also of high importance when dealing with the scaleup of reactions. Here the ratio of gas/liquid interface to bulk volume gets smaller, and thus lower pressure is advantageous in large-scale reactions. Figure 2 (inlet) shows the conversion as a function of pressure. For pressures of 7, 10, and 20 mbar a conversion of 0.97 was achieved after 22 h on a 20 g scale. The results show that a vacuum of 20 mbar is a suitable pressure for future experiments because conversion after 22 h is not higher for lower pressures of 10 or 7 mbar. However, a slight difference in mass specific activity in the beginning of the reaction was observed.

Figure 3 shows the conversion as a function of time and enzyme concentration. With a concentration of 3 wt % Novozym 435, a conversion of 0.95 was achieved after 48 h. For 1 wt % a conversion of 0.89 was obtained after 46.5 h. Mass specific activity in the beginning of the reaction was 330 U/g for 3 wt % and 300 U/g for 1 wt %. In an industrial process the catalyst price is a crucial factor. However, conversion is the crucial point in polycondensation reactions. Therefore, in all further experiments, an enzyme concentration of 3 wt % was chosen because of the faster achievement of higher conversion. Blank tests at 60 °C and 7 mbar with the halfmoon stirrer at 100 rpm in a 20 g scale without Novozym 435 showed no conversion after 22 h.

Mixing influences the mass transport in the reaction mixture. Mass transport, diffusive as well as convective, is important because the substrate has to reach the active site of the enzyme immobilized on a porous carrier. Therefore, an influence of mixing on reaction rate was expected. The reaction parameters important for a homogeneous mixture (stirrer type and stirring rate) were investigated. Pitched blade, anchor, and helicon ribbon stirrers were tested. Figure 4 shows that conversion is not affected by the stirrer type. For all stirrers a conversion of approximately 0.93 and 0.94 was achieved after 24 and 48 h of reaction time, respectively. Although conversion is not

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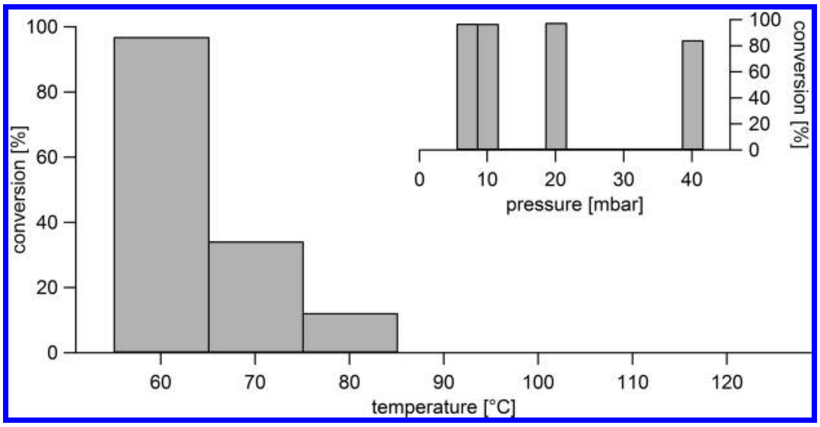

***Figure 2.*** **Conversion after 22 h versus temperature and pressure. Reaction conditions for temperature variation: 7 mbar, 3 wt % Novozym 435, Gly:AA = 1.6, half moon stirrer, 100 rpm, 20 g. Reaction conditions for pressure variation: 60 °C, 3 wt % Novozym 435, Gly:AA = 1.6, half moon stirrer, 100 rpm, 20 g.**

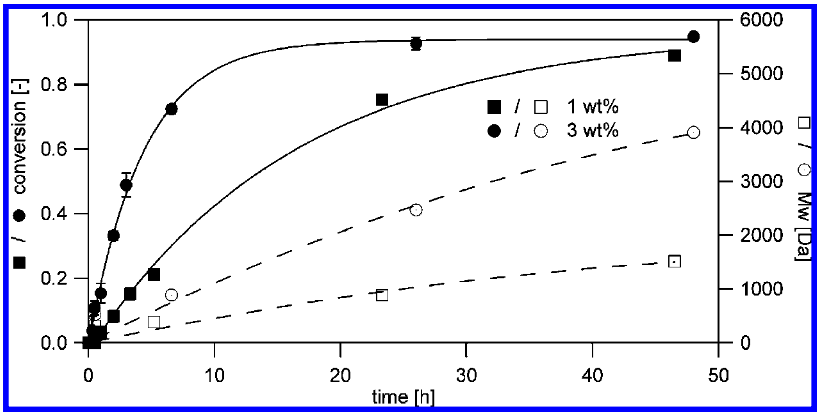

***Figure 3.*** **Variation of enzyme concentration, reaction conditions: 60 °C, <7 mbar, Novozym 435, Gly:AA = 1.1, helicon ribbon stirrer, 100 rpm, 500 g.**

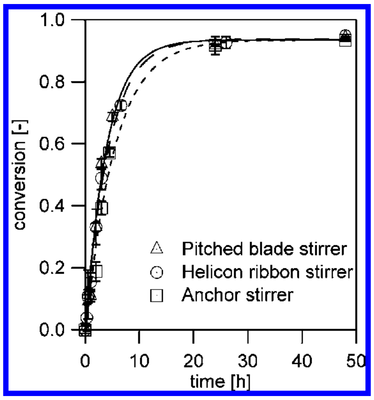

***Figure 4.*** **Variation of stirrer geometry, reaction conditions: 60 °C, < 7 mbar, 3 wt % Novozym 435, G:AA = 1.1, 500 g; pitched blade stirrer: 500 rpm; anchor stirrer and helicon ribbon stirrer: 100 rpm.**

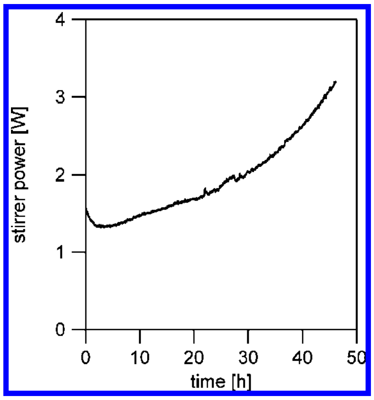

***Figure 5.*** **Stirrer power, reaction conditions: 60 °C, $10^{-2}$ mbar, 3 wt % Novozym 435, Gly:AA = 1.1, anchor stirrer, 100 rpm, 300 g, weight average molecular weight after 48.3 h: 17000 ± 2700 Da.**

affected by the stirrer type, mixing itself is strongly influenced by the stirrer type. Only with the helicon ribbon stirrer is a uniform convection of the substrate and the catalyst in the vessel observed. When agitating with the anchor and the pitched blade stirrer, convection near to the stirrer is higher than in distant volumina, although intermixing of the enzyme is simplified because viscosity reaches a minimum after 2 h of reaction progress. Additional mixing by bubbles is introduced to the system by evaporating water. Therefore, the bad mixing capacity of the pitched blade and anchor stirrer is partly compensated.

That viscosity is running through a minimum could be verified by an experiment carried out in a reactor with torque recording. Figure 5 shows the stirrer power as a function of time. Alterations in temperature influence the viscosity and thus cause minor fluctuations in power consumption. The influence of stirring rate on conversion is shown in Figure 6. A conversion of 0.95 was achieved after 26 h with a stirring rate of 200 rpm. There was a slightly higher reaction rate at 200 rpm compared with experiments carried out at 100 rpm. However, during the enzyme separation small particles resulting from the destruction of the enzyme carrier were found in the product. Therefore,

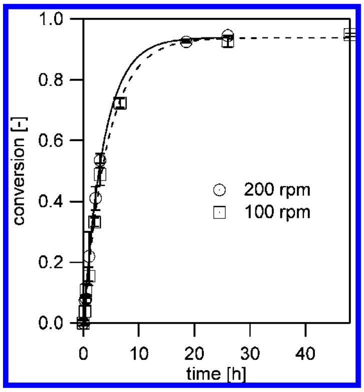

***Figure 6.*** **Variation of stirring rate, reaction conditions: 60 °C, <7 mbar, 3 wt % Novozym 435 (LC 200230), Gly:AA = 1.1, helicon ribbon stirrer, 500 g.**

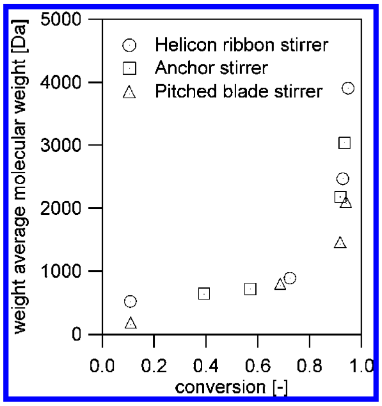

***Figure 7.*** **Weight average molecular weights as a function of conversion: Influence of stirrer geometry on molecular weight, reaction conditions: 60 °C, <7 mbar, 3 wt % Novozym 435 (LC 200230), Gly:AA = 1.1, 500 g, pitched blade stirrer: 500 rpm, anchor stirrer and helicon ribbon stirrer: 100 rpm.**

further experiments were carried out at 100 rpm to reduce abrasion of the enzyme carrier.

It could be shown that pressure, homogeneity of mixture, and enzyme concentration influence conversion. This is important as high conversions are necessary because of the step-growth mechanism of a polycondensation reaction, and the aim of this study was to synthesize polyesters with molecular weights of 2000−3000 Da. Figure 7 shows the weight average molecular weight as a function of conversion for different stirrer types. Here, the influence of the mixture's homogeneity on molecular weight was studied. These weight average molecular weights correspond to the conversion−time curves shown in Figure 4. Low influence of stirrer type on conversion was found, although badly mixed regions were observed. Figure 7 shows the dependency of weight average molecular weight on conversion. At a conversion of 95% with a helicon ribbon stirrer weight, average molecular weights of 3900 Da were achieved in experiments carried out at <7 mbar, while in contrast to this, with an anchor stirrer, molecular weights of 3000 Da were obtained. At the same conversion using a pitched blade stirrer resulted in an average molecular weight of only 2100 Da. The polydispersity index (PDI) of the polymer obtained by using the pitched blade stirrer was the highest (PDI 2.2). The PDI products obtained by using the anchor and the helicon ribbon stirrer were both 1.7. By decreasing the pressure down to $10^{-2}$ mbar, significantly higher weight average molecular weights of 17000 ± 2700 Da were achieved (data not shown). The final product was slightly yellow and showed no specific odor.

Information about branching of the produced polyesters is important, because the applications of polyesters in polyurethane industry differ, depending on their degree of branching. In order to analyze the branching behavior with gel permeation chromatography (GPC) measurements, chemically similar linear polymers with the same molecular weight are needed. Therefore, linear polymers consisting of 1,3-propanediol and adipic acid were synthesized with Novozym 435. Mass specific activity in the beginning of the reaction was 554 U/g. A molecular weight of 11800 Da was achieved after 48 h. This is consistent with results from literature. Here, molecular weight of glycerol copolyesters is rising slower than with other monomers like 1,8-octanediol or sorbitol.[24] For branching analysis the propanediol adipate sample with a weight average molecular weight of 5700 Da was taken. In the Mark−Houwink plot of this sample, a linear region can be observed for logarithm of molecular weight values between log M = 3.3 and log M = 3.8, a slope of 0.8 and an axis intercept of −4 are derived. Figure 8 shows the Mark−Houwink plot of the glycerol adipate sample and a straight line with the slope 0.8 and axis intercept of −4 representing the linear polyester.

When the intrinsic viscosity and the molecular weight are known, structural information such as the hydrodynamic radius of the molecules and the number of branches per molecule can be derived. The hydrodynamic radius of the molecules can be calculated, and branching analysis is possible using the Mark−Houwink equation:[25,26]

$$[\eta] = K \cdot M^{a} \Leftrightarrow \log[\eta] = \log K + a \cdot \log M$$

with the Mark−Houwink parameters log K (axis intercept) and a (slope).

When plotting log $[\eta]$ over log $M$ (Mark−Houwink plot) a linear function with the slope $a$ and the axis intercept log $K$ for a linear polymer is obtained. For a branched sample that is structurally similar, the intrinsic viscosity rises less with increasing molecular weights. From this it follows that the density of the polymer molecules is higher. Thus, with increasing molecular weight, the number of branches is rising.

## Discussion and Conclusions

Results for conversion and average molecular weight distribution of the produced polymer are not independent. Important parameters such as pressure, enzyme concentration, and reaction time influence conversion as well as molecular weight. In Table 1 the different experiments are summarized, including the variable experimental parameters pressure, stirrer type, batch volume, and temperature as well as the important final characteristics molecular weight, polydispersity, and conversion.

The desired specifications, a molecular weight between 2000 and 3000 Da, are only met if high conversions are achieved. Temperature as a basic parameter in view of conversion is a

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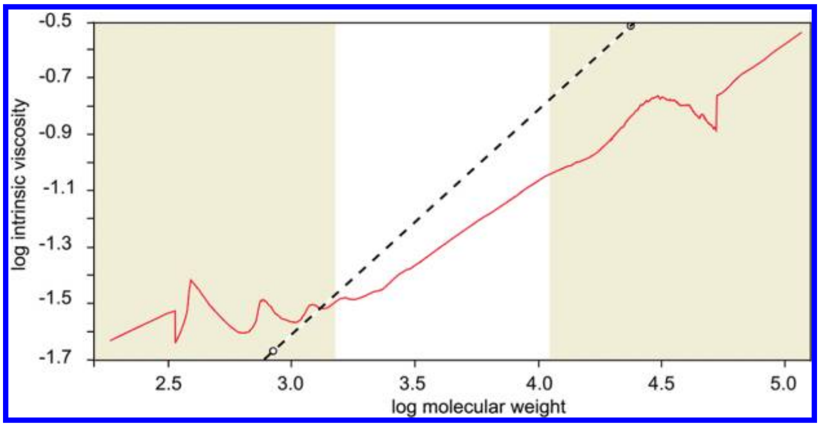

***Figure 8.*** **Mark−Houwink plot, dashed line: linear polyester with slope 0.8 and axis intercept of −4, solid curve: logarithm of intrinsic viscosity of glycerol adipate with a weight average molecular weight of 4400 Da and a conversion of 0.95.**

***Table 1.*** **Summary of experiments carried out**[a]

| no. | pressure [mbar] | stirrer type | batch volume [g] | temperature [°C] | molecular weight [Da] | polydispersity | conversion |
|---|---|---|---|---|---|---|---|
| 1 | 7 | HM | 20 | 60 | n.d. | n.d. | 0.97 |
| 2 | 7 | HM | 20 | 70 | n.d. | n.d. | 0.34 |
| 3 | 7 | HM | 20 | 80 | n.d. | n.d. | 0.17 |
| 4 | 10 | HM | 20 | 60 | n.d. | n.d. | 0.97 |
| 5 | 20 | HM | 20 | 60 | n.d. | n.d. | 0.97 |
| 6 | 40 | HM | 20 | 60 | n.d. | n.d. | 0.80 |
| 7 | 7 | HR | 500 | 60 | 3900 | 1.7 | 0.95 |
| 8 | 7 | A | 500 | 60 | 3000 | 1.7 | 0.94 |
| 9 | 7 | PB | 500 | 60 | 2100 | 2.2 | 0.94 |
| 10 | 0.01 | A | 300 | 60 | 17000 | n.d. | 0.95 |

[a] HM = half moon stirrer; HR = helicon ribbon stirrer; A = anchor stirrer; PB = pitched blade stirrer; n.d.= not determined.

prerequisite for high activity and good stability of the enzyme and should be kept in the range of 60 °C, and with enzyme concentrations between 1 and 3 wt % sufficient conversion was achieved after 48 h. The change in pressure from 20 to 40 mbar had an influence on the equilibrium of the reaction, and thus conversion was increased. By decreasing the pressure from 20 down to 7 mbar, no further improvement of conversion was achieved. Parameters influencing the molecular weight are pressure, homogeneity of mixture, reaction time and enzyme concentration. The desired molecular weights of 2000−3000 Da were also obtained with pitched blade and anchor stirrers. However, in order to obtain a product with a low polydispersity, the helical ribbon stirrer is necessary. The molecular weight can be controlled by choosing a pressure between 0.01 and 20 mbar and an enzyme concentration between 1 and 3 wt %. At a conversion of approximately 0.95, desired polymers are formed from the oligomers. No further separation of unreacted monomer is necessary. The branching analysis of the produced glycerol adipate showed that with increasing molecular weight, the number of branches rises. In this work, a polydispersity index (PDI) of 1.7 was achieved for a polyester with a molecular weight of 1800 Da and a PDI of 2.7 at a molecular weight of 2800 Da.

In this paper, it is demonstrated that Novozym 435 is active up to 80 °C; however, stability of the enzyme is only given at 60 °C for 48 h. This reactivity optimum at 60 °C is in agreement with the work of Kobayashia who used Novozym 435 within in the reaction of divinylsebacate with glycerol. Until now, polyesters from glycerol and adipic acid were produced only in small scale (<5 g)[19] at a reaction temperature of 70−90 °C, a reactants ratio of Gly:AA = 1 and using 9.2 wt % Novozym 435. Pressure was reduced (53−80 mbar) after 2 h of reaction time, while the total reaction time was 42 h. Glycerol adipate with a weight average molecular weight of 3700 Da (absolute weight) and a polydispersity index of 1.4 was produced. In comparison to our work, higher temperature was applied and enzyme concentration was 9 times higher. The different enzyme concentration could be a possible explanation for the differing findings regarding reaction temperature. Enzyme deactivation probably also occurred in the experiments of Gross et al.,[19] but enzyme concentration was chosen high enough to compensate the activity loss over reaction time. We carried out experiments at 70 and 80 °C, applying 3 wt % Novozym, and determined conversion time plots. Lower final conversions compared with experiments at 60 °C were found. These findings support that the stability of the enzyme within the reaction system glycerol and adipic acid is given up to a temperature of 60 °C. A possible further explanation could be the different enzyme charges applied in the different studies.

The synthesis of glycerol adipate is also possible using a chemical catalyst. In literature, glycerol adipate was produced using a dibutyltin oxide catalyst.[27] Reaction temperature was 150 °C and 0.15 wt % of catalyst was used. Water formed during the reaction was distilled off. The pressure was 100 mbar. With a reactants ratio of Gly:AA = 1, polyesters with a weight average molecular weight of 3060 and a PDI of 1.75 were obtained after 8 h of reaction time. Conversion calculated by the acid value was 0.86. The catalyst was not removed from

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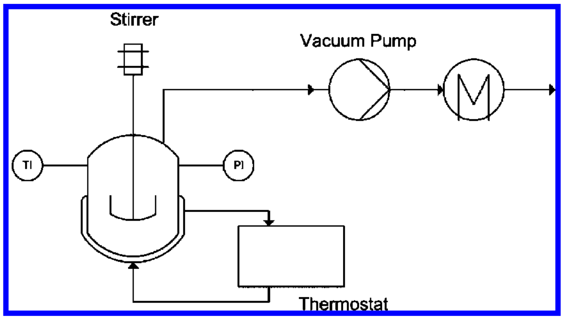

***Figure 9.*** **Flowsheet for the production of polyesters.**

the final product and could cause problems in subsequent polyurethane reactions. In comparison with the process developed in this work, reaction time is 3 times shorter, temperature is 250% higher, and pressure is 5 times higher. The polydispersity of the chemically catalyzed product was lower. Since the mixture is very viscous, high energy input by the mixture is necessary, which influences the integrity of the Novozym 435. Recent work from Ansorge-Schumacher et al. suggests that this might be a major problem.[28] The diameter of Novozym 435 beads is in the range of 300−900 $\mu$m.[29] To quantify particles surviving the reaction, the content of enzyme in the final product—which was filtrated by a filter with pores of 200 $\mu$m—was determined. Assuming a protein content of 3 wt % on the Novozym 435 beads, a maximum of 1.07 g/kg could be found in the final product if all enzyme beads were to be destroyed. Our results show a protein content of 0.48 g/kg final product, implying that 45% of the enzyme carrier was destroyed after the reaction. Therefore, in the future process development, the increase of mechanical stability must to be taken into account.[30]

## Experimental Section

A batch process in a stirred tank reactor was chosen for the production of the polyesters. A general flowsheet is shown in Figure 9. The polymerization was carried out solvent-free as mass polymerization. Reaction temperature was provided by a heating jacket in combination with a Lauda RC6 thermostat. Water formed during the reaction was removed by applying a vacuum to the system. The vacuum pump consisted of a vacubrand CVC 2 pressure sensor and a PC 511 pump. The agitator drive was an IKA Werke RW 20. Specific amounts of liquid polyol and solid adipic acid crystals were filled in the reactor. They were heated up to reaction temperature and mixed in the reactor in a vacuum. Before starting the reaction by adding Novozym 435, the homogeneity of the mixture was controlled by determination of the acid value. This value was compared with the theoretical acid value. Temperature was measured before starting the reaction in order to ensure that reaction temperature was achieved. The polycondensation was carried out in a 20, 30, 300, and 500 g scale, respectively, regarding the reactants initial weight. For the 20 and 30 g scales, the reaction was carried out in a round-bottom flask with a heating jacket, for the 300 g scale in a wide-necked Schott bottle inside the thermostat, and for the 500 g scale in a tailor-made glass reactor with heating jacket. The temperature was measured by a type K thermocouple plugged to a Voltcraft Data Logger Thermometer. Pressure was recorded with a Center one sensor from Leybold Vakuum.

Different stirrer geometries were tested regarding their mixing results. In the round-bottom flask (100 mL) a half moon stirrer was used, in the glass reactor (500 mL) an anchor stirrer and a tailor-made helicon ribbon stirrer were used, and in the glass reactor (1 L) a pitched blade stirrer with 4 blades inclined by 45°, the anchor stirrer, and the helicon ribbon stirrer were compared (see Scheme 2 for illustrations of each stirrer). The halfmoon, pitched blade, and anchor stirrers were purchased from Bola. They were made of polytetrafluoroethylene. The halfmoon and anchor stirrers were cut to size in order to fit exactly into the reactors. The helicon ribbon stirrer was produced in-house. Chosen material was AISI 3042. Table 2 shows important aspect ratios of the stirrers inside the reactors.

Samples were withdrawn after specific time intervals and analyzed without further purification by determination of acid value. In case of GPC, value samples were dissolved in THF and filtered to remove the heterogeneous catalyst. The acid value AV is determined according to DIN 53402. The samples were dissolved in ethanol and titrated with 0.1 M ethanolic potassium hydroxide solution. The titration was done with a Brand Titrette on a 1 L Schott bottle. The sample solution was stirred and heated up to 50 °C with an IKA MAG RET-G magnetic stirrer. Indicator was phenolphthalein. The acid value was calculated according to eq 1.

$$\mathrm{AV} = \frac{V \cdot c \cdot 56.1}{M} \tag{1}$$

with

$V$ = volume of potassium hydroxide solution [mL]
$c$ = concentration of potassium hydroxide solution [mol/L]
$m$ = mass of sample [g]

The acid value was used in order to determine the conversion, $X$ (eq 2).

$$X = \frac{\mathrm{AV}_0 - \mathrm{AV}}{\mathrm{AV}_0} \tag{2}$$

with

$X$ = conversion [-]
$\mathrm{AV}_0$ = acid value of initial reactants mixture [mg/g]
$\mathrm{AV}$ = acid value at reaction time $t$ [mg/g]

The mass specific activity "$a$" of the enzyme was calculated according to eq 3 by reading off the values from the conversion vs time curves.

$$a = \frac{\frac{\Delta X}{\Delta t} \cdot n_\mathrm{s}}{m_\mathrm{e}} \tag{3}$$

with

$a$ = mass specific activity [U/g]
$\Delta X$ = conversion for period of time [-]

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***Scheme 2.*** **Illustration of the applied stirrer types: (a) half moon stirrer; (b) pitched blade stirrer; (c) anchor stirrer; (d) helicon ribbon stirrer**

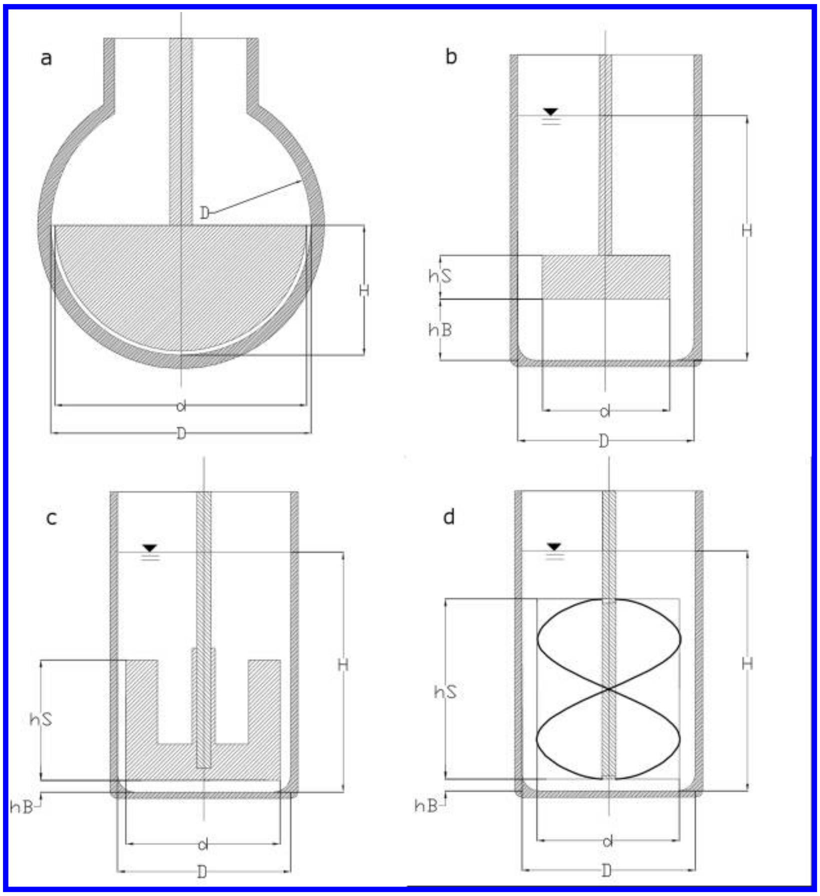

***Table 2.*** **Stirrer aspect ratios**

| stirrer | $d/D$ | $H/D$ | $h_B/D$ | $h_s/D$ |
|---|---|---|---|---|
| halfmoon | 0.97 | – | – | – |
| pitched blade | 0.74 | 1.39 | 0.35 | 0.25 |
| anchor | 0.89 | 1.39 | 0.07 | 0.69 |
| helicon ribbon | 0.82 | 1.39 | 0.07 | 1.04 |

$\Delta t$ = period of time for conversion [min]
$n_s$ = amount of substrate [$\mu$mol]
$m_e$ = mass of enzyme [g]

The space time yield (STY) is the mass of product synthesized per reactor volume and time:

$$\mathrm{STY} = \frac{m_p}{t \cdot V_R} \qquad (4)$$

with

STY = space time yield [g/(L d)]
$m_p$ = mass of synthesized product [g]
$t$ = reaction time [d]
$V_R$ = reactor volume [L]

The GPC measurements were carried out with a system consisting of an LC-20AT pump from SHIMADZU, a MARATHON autosampler from Spark Holland, a GMHHR-L Mixed Bed column from Viscotek in series with a PLgel 3_ MIXED-E 30 K column from Latek, a K-2301 refractive index detector from Knauer, and a 270 Dual Detector from Viscotek. Tetrahydrofuran (THF) was used as a solvent with a flow rate of 1 mL/min. Calculations were done with the OmniSEC 4.6.1 software from Viscotek. Universal calibration was done with seven narrow polystyrene standards. Polystyrene samples with the molecular weight of 29600, 13400, 6040, 2790, and 1050 Da were purchased from Viscotek; polystyrene samples with the molecular weight of 2170 and 575 Da were purchased from Varian. The refractive index increment d$n$ = d$c$ of the polyesters was determined to be 0.0624 mL/g for glycerol adipate, 0.0658 mL/g for glycerol propanediol adipate, and 0.0671 mL/g for propanediol adipate.

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## Supporting Information Available

Reagent bottle of glycerol adipate. This material is available free of charge via the Internet at http://pubs.acs.org.

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