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Isosorbide Polyesters from Enzymatic Catalysis

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ABSTRACT: The synthesis of isosorbide aliphatic polyesters is demonstrated by the use of Novozym 435, a catalyst consisting of *Candida antarctica* lipase B immobilized on a macroporous support. Several experimental procedures were tested and azeotropic distillation was most effective in removing low mass byproduct. Furthermore, the use of diethyl ester derivatives of diacid comonomers gave isosorbide copolyesters with highest isolated yield and molecular weights. The length of the diacid aliphatic chain was less restrictive, but with a clear preference for longer aliphatic chains. The molecular mass values of the obtained products were equivalent or higher than those obtained by nonenzymatic polymerizations, a clear illustration of the potential of enzymatic over conventional catalysis. The ability of Novozym 435 to catalyze the synthesis of isosorbide polyester with weight-average molecular weights in excess of 40 000 Da was unexpected given that isosorbide has two chemically distinct secondary hydroxyl groups. This is the first example in which isosorbide polyesters were synthesized by enzyme catalysis, opening a large array of possibilities for this important class of biomass-derived building blocks. Because these polymers are potential biomaterials, the total absence of conventional Lewis acid catalyst residues represents a major improvement in the toxicity of the material.

Introduction

One of the most important items on the agenda of the global chemical industry is the substitution of petroleum-based feedstocks by those from renewable sources. Hence, the use of biomass-derived building blocks has been investigated in the chemical and commodity industries.

Isosorbide is an example of a building block already used in both markets: isosorbide dinitrate and 5-mononitrite are used as vasodilators[1] and also as comonomers in the production of a modified poly(ethylene terephthalate) with improved thermal properties.[2]

Isosorbide (1,4:3,6-dianhydro-D-glucitol) is the product of the double dehydration of sorbitol. It contains four stereocenters and two five-membered rings fused through carbons 3 and 4 in the *Z* configuration with an angle of approximately 120°, where two hydroxy groups are attached at positions 2 (exo) and 5 (endo). Isosorbide is classified by the US Food and Drug Administration as a GRAS ("generally recognized as safe") material.[3] As a generic diol monomer, it has been considered in several polymer systems like polyester,[4] polyether,[5] polycarbonate[6] and polyurethane,[7] among others.

The known synthesis of isosorbide-derived polyesters is often dependent on activated diacid derivatives and/or the use of Lewis acid catalysts coupled with the removal of low mass condensation products. Its aliphatic polyester derivatives have proven to be biodegradable, thereby making them appealing for use in biomaterial applications.[8,9] Okada showed that isosorbide, isomannide and isoidide aliphatic polyesters are readily hydrolyzed by a series of esterases, with very distinct specificity among them.[9]

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The obvious conclusion from these results is that, if esterases can hydrolyze these polyesters, their synthesis through enzymatic catalysis can be anticipated. To our knowledge, there are no other reported attempts of enzymatic synthesis of isosorbide-derived polyesters. The sterically hindered hydroxyl groups in isosorbide have likely discouraged others from attempting enzyme-catalyzed condensation polymerizations.

The successful use of lipase to catalyze polymerizations through either ring-opening or condensation reactions has been established by several groups.[10,11] Not only can activated diacid and diol derivatives be used, but also inactivated monomers,[12] showing the commercial potential of the method.

Novozym 435 (immobilized lipase B from *Candida antarctica*) is one of the most studied commercial lipases and is used for several tasks, including polymerization reactions.[13] This lipase is robust and presents activity under a large array of conditions.

On the basis of the information above, we decided to evaluate the synthesis of a series of isosorbide-derived polyesters catalyzed by Novozym 435 CAL-B. Several parameters were varied in order to establish successful conditions for polyester synthesis. Azeotropic distillation of the low mass condensation products proved to be an efficient method to obtain high molecular mass polyesters.

Experimental Section

Materials. All solvents (Merck) were dried and distilled prior to use. All dicarboxylic acid esters (Aldrich) were used as received. Adipic acid (Aldrich) was recrystallized from ethanol:H_2O (2:1) and dried in a vacuum desiccator for the polymer synthesis. Isosorbide (Cerestar) was recrystallized from ethyl acetate and dried under vacuum in the presence of P_2O_5 until constant mass. Its final purity was better than 99.8% by GC. Special care was taken in the weighing of the dried isosorbide due its highly hygroscopic character. Immobilized *C. antarctica*

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lipase Novozym 435 (CAL-B; declared specific activity 360 BAT/g) was a gift from Novozymes Latin America.

Enzyme Catalyzed Bulk Polymerization. First, 10 mmol of isosorbide and 10 mmol of the corresponding dialkyl diester were added to a 50 mL round bottomed flask containing 10% (w/w) of Novozym 435 relative to total monomer mass. The mixture was heated in an oil bath at 85 °C in two phases: phase A at atmospheric pressure and phase B under a 2 mmHg vacuum. The final mixture was dissolved in chloroform; the enzyme was filtered off and the solvent was evaporated.

Enzyme-Catalyzed Azeotropic Polymerization. A total of 10 mmol of isosorbide and 10 mmol of the diacid derivative were added to an 80 mL round bottomed flask containing 65 mL of solvent and 10% (w/w) of Novozym 435 relative to the total monomer mass. The flask was attached to a Dean−Stark apparatus adapted to receive 5 g of activated molecular sieves (4 Å). The molecular sieves were replaced every 24 h. The mixture was magnetically stirred and heated in an oil bath until a gentle reflux was attained. The distillate vapor temperature typically stabilized at a few degrees (2−5 °C) below the expected boiling temperature of the solvent. The products were formed as an insoluble material that adhered to the flask wall. The final mixture was dissolved in 50 mL of chloroform, the enzyme was filtered off and the solvent was evaporated. If needed, the products were purified by dissolution in a minimal amount of hot chloroform and precipitated by adding methanol (typically 10× v/v), filtered and dried under vacuum for 48 h.

Enzymatic Activity. The lipase activity in organic media was determined by lipase catalyzed esterification of lauric acid with propanol.[12] Catalytic assays were performed with CAL-B unused and recovered from poly(isosorbide adipate) synthesis. Briefly, 2 g (10 mmol) of lauric acid and 750 μL (10 mmol) of *n*-propanol were added to a 50 mL round bottomed flask containing 10 mL of toluene, 200 mg of Novozym 435 and 1 g of activated molecular sieves (3 Å). A condenser was attached and the mixture was stirred at 85 °C for 3 h. After filtering off the enzyme, the products were analyzed for propyl laurate by gas chromatography (GC) (Shimadzu GC-2010 connected to a DB5 column (dimensions), flame ionization detector (FID), nitrogen as carrier gas at a flow rate of 15 mL/min, temperature program 40 °C (hold 1 min) to 100 at 7 °C/min (hold 10 min) to 280 at 10 °C/min (hold 4 min), injector temperature 350 °C). From the GC data, the recovered enzyme activity was calculated as follows:[12] residual activity = [(peak area (propyl laurate) of the recovered catalyst)/(peak area (propyl laurate) of the unused catalyst)] × 100.

Table 1. Enzymatic Synthesis of Poly(isosorbide adipate) by Solventless Polymerization[a]

time (h)			
phase A	Phase B	$\overline{M}_w$ (Da)	P_d
4.5	48	630	1.6
24	48	1700	1.9
86	36	2100	1.9
72		2000	2.3
168		3800	3.9

[a] Conditions: monomers, isosorbide and diethyl adipate; catalyst, 10% Novozym 435 (w/w); bath temperature, 85 °C; pressure in phase A, 760 mmHg; pressure in phase B, 2 mmHg.

Solvent Effect. The "shake flask" method was employed in order to determine log *P* for the solvent mixtures cyclohexane:benzene (6:1) and cyclohexane:toluene (6:1) because this is an important physical chemistry parameter that drives lipase catalysis.[12] The partition coefficient, *P*, was determined by adding an aliquot of solvent mixture samples to a presaturated mixture of *n*-octanol/water (1:1). After reaching equilibrium, the solvent concentrations in each phase were determined by GC, and *P* (and log *P*) was calculated from: $P_{ow} = c_{n\text{-}octanol}/c_{water}$. Values of log *P* for the binary mixture were 3.0 for cyclohexane:benzene (6:1) and 3.1 for cyclohexane:toluene (6:1).

Polymer Characterization. Size exclusion chromatography was used to evaluate $\overline{M}_n$ and $\overline{M}_w$ on a Shimadzu HPLC/SEC class-VP system connected to a Shimadzu RID 10A differential refractive index detector and four Styragel columns (10^2, 10^3, 10^4, and 10^5 Å; Waters), using chloroform at a flow rate of 1 mL × min^{-1} as the mobile phase. For calibration, low polydispersity polystyrene standards (Aldrich/Waters; $\overline{M}_w$ = 820, 2460, 5120, 13200, 29300, 47500, and 216000 Da) were used. The ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ using TMS as a standard and recorded on a Bruker DPX 300 (300 and 75 MHz, respectively). FT-IR spectra were recorded from films on a Bomem MB 100 spectrometer. Differential scanning calorimetry (DSC) measurements were performed on a TA Instruments DSC2920 calorimeter using In as a reference. Thermogravimetry (TG) analyses were carried out in a TA Instruments TGA 2950 using a Pt crucible under an N_2 atmosphere. The diffraction patterns of wide-angle X-ray diffraction (WAXD) were recorded on a Rigaku Miniflex powder X-ray diffractometer, using a monochromatic beam with emission at 0.194 nm (Fe Kα), a voltage of 30 kV and an electric current of 15 mA. The intensities were collected from a 2θ range of $3-80^o$ with step scanning mode of 0.02^o. The powdered samples were annealed in a vacuum-oven at 90 °C for 48 h prior to analysis.

Results and Discussion

Solventless Polymerization. The enzymatic synthesis of poly(isosorbide adipate) from isosorbide and diethyladipate was investigated under solventless (bulk) conditions. The production of oligomers with $\overline{M}_w$ values of up to 2000 Da was observed with or without a vacuum reaction phase, while the total time of reaction was usually high. Typically, an initial phase at room pressure is necessary for preoligomerization to avoid vacuum removal of the starting monomers. However,

Table 2. Enzymatic Synthesis of Poly(isosorbide adipate) by Azeotropic Distillation[a]

monomer A	solvent[b] (log *P*)[c]	$\overline{M}_w$ (Da)	P_d	S^d(mg × mL^{-1})
adipic acid	benzene (2.0)	230	1.1	18
	chloroform (2.0)	420	1.7	298
	MEK: *n*-hexane 4:1 (0.86:3.5)	2700	2.5	n.d.
diethyl adipate	dichloromethane (1.01)	900	1.0	n.d.
	benzene (2.0)	760	1.1	18
	chloroform (2.0)	820	1.5	298
	carbon tetrachloride (2.86)	430	1.7	n.d.
	cyclohexane (3.2)	21 000	2.6	< 0.1
	n-hexane (3.5)	6400	2.0	< 0.1
	cyclohexane:benzene 6:1 (3.0[e])	37 000	2.2	0.6
	cyclohexane:toluene 6:1 (3.1[e])	20 000	2.3	n.d.

[a] Conditions: monomer B, isosorbide; initial monomer concentration, 0.15 mol × L^{-1}; catalyst, 10% Novozym 435:monomer (w/w); reaction time, 168 h; apparatus, Dean−Stark apparatus containing molecular sieves. [b] Solvent mixtures are in v/v. [c] From ref 22. [d] Solubility of a sample of poly(isosorbide adipate) $\overline{M}_w \sim$ 30 kDa. [e] This work (see Experimental Section).

Table 1 shows that vacuum did not improve progress in molecular weight increase. Aside from the low $\overline{M}_w$ values obtained, we found it rather surprising that CAL-B was able to catalyze the condensation of isosorbide, a hindered secondary alcohol. This result prompted us to investigate other polymerization methods using enzymatic catalysis.

Enzymatic Polymerization by Azeotropic Distillation:Solvent Effect. Azeotropic distillation has been used in several types of condensation reactions as a driving force to push the equilibrium toward the product.[14] In these cases, the condensations are carried out in a solvent that forms an azeotrope with the byproducts formed, typically water or alcohol. This includes condensations catalyzed by enzymes[15,16] and polycondensation reactions.[17] PLLA produced from lactic acid is by far the most studied case of a polymerization reaction with azeotropic distillation. This method was chosen by Toatsu for the large scale production of PLLA.[18,19] To further improve removal of byproducts, drying agents such as molecular sieves are often used.[20,21]

In this work, several pure solvents and solvent mixtures were used in an attempt to achieve high $\overline{M}_w$ polymers. In all cases, the reaction was run over long time periods, typically up to 7 days. The reaction temperature was chosen to attain a steady reflux, but temperatures higher than 90 °C were avoided to prevent enzyme denaturation. Additionally, in all cases, molecular sieves were placed in the Dean−Stark apparatus and renewed daily. Isosorbide was the diol and its copolymerization with adipic acid and diethyl adipate was studied. Table 2 shows the results of copolymerizations in various solvent mixtures, all having known azeotropes with the byproducts.

In the case of adipic acid as monomer A, its poor solubility in the solvent systems is largely responsible for the low $\overline{M}_w$ of corresponding copolyesters. While benzene and chloroform, two solvents typically used to extract water through azeotropic distillation, did not show satisfactory results, a mixture of MEK and *n*-hexane formed oligomers with $\overline{M}_w$ up to 2700 Da. In contrast, the ethyl ester derivative was soluble in all solvents used.

According to Table 2, there appeared to be a correlation of log *P* values with the formation of poly(isosorbide adipate), where cyclohexane, cycholexane:toluene and cyclohexane:benzene mixtures showed polymers with high $\overline{M}_w$, with values of up to 37 000 Da. While diethyl adipate and isosorbide were very soluble in all solvents used, the product poly(isosorbide adipate), PIA, had reduced solubility, especially in the higher log *P* solvents. In fact, after 12 h of reaction, a phase-separated solid material was already noticeable, which increased in content as the reaction proceeded. The addition of 14% (w/w) benzene to the solvent had a positive effect on the polymer $\overline{M}_w$ that is attributed to improved solubility of PIA in the reaction media (see Table 2).

Benzene is a toxic solvent and its use has been banned from most industrial processes. Toluene is the typical substitute for benzene and presents much lower toxicity. Like benzene, it also forms a binary azeotrope with ethanol, but with a BP of 76.6 °C. However, the cyclohexane:ethanol binary azeotrope has a lower BP, at 64.8 °C. Its log *P* is on the order of 2.5, still much lower than aliphatic hydrocarbons, but very close to the log *P* of benzene. Surprisingly, the addition of toluene in cyclohexane did not provide the same improvement as benzene, producing a polymer with an $\overline{M}_w$ of the same order of magnitude as pure cyclohexane.

Notwithstanding, a critical balance between the solvent log *P* value and the solubility of the reagents and products seemed to control the growth of the polymer chain. What's most surpising is that, despite the low solubility of PIA in reaction media, the polymerization depended on the dissolution dynamics of the growing product which likely explains the need for long reaction times. This is supported by the observed increase in $\overline{M}_w$ by decreasing the concentration of isosorbide and diethyl adipate in the reaction media (Table 3).

Another example of the balance of solubility and log *P* was the dependence of $\overline{M}_w$ on the amount of benzene added to cyclohexane. In Table 4, the $\overline{M}_w$ increased by adding up to 14% w/w benzene relative to cycloexane which increased PIA solubility. However, above 14% benzene, the log *P* value decreased which negatively influenced PIA $\overline{M}_w$ values attained.

The synthesis of PIA in the 6:1 cyclohexane:benzene mixture was followed over a period of 8 days (Figure 1). Consumption of monomers occurs rapidly so that within the first 12 h, a polymer with $\overline{M}_w$ of 5000 Da formed in 60% yield. This indicates that the reaction proceeds mainly through condensation step polymerization reactions. The isolated yields at the end of days 7 and 8 reached 87%, showing that the content of remaining monomer or oligomer in reaction mixtures had reached a plateau value. Furthermore, as the isolated yield increased slowly from 60% in 12 h to 87% in 7 days, PIA $\overline{M}_w$ increased regularly over time reaching a maximum value of ~33,000. Thus, condensation step reactions between chain segments continue regardless of the low solubility of PIA in the reaction media.

The decay of Novozym 435 catalytic activity over long reaction times used herein was a concern. Thus, the residual activity of Novozym 435 recovered from reactions was determined by an assay consisting of measuring the rate of

Table 3. Effect of the Reaction Dilution[a]

isosorbide to solvent ratio[b]	$\overline{M}_w$ (Da)	P_d	ϕ^c (%)
1:20	17 000	3.5	82
1:30	18 000	2.1	85
1:40	20 000	2.3	82
1:50	31 000	2.3	83
1:60	40 000	2.1	92
1:80	45 000	2.5	92

[a] Conditions: monomers, isosorbide and diethyl adipate; solvent, cyclohexane: benzene (6:1 v/v); catalyst, 10% Novozym 435:monomer (w/w); reaction time, 168 h; apparatus, Dean−Stark apparatus containing molecular sieves. [b] In g of isosorbide to mL of solvent. [c] Isolated reaction yield.

Table 4. Effect of the Ratio of Benzene to Cyclohexane and Toluene to Cyclohexane as Solvent Mixtures[a]

benzene concentration (v/v) [%]	$\overline{M}_w$ (Da)	P_d	ϕ^b (%)	Toluene concentration (v/v) [%]	$\overline{M}_w$ (Da)	P_d	ϕ^b (%)
20 (1:4)	31 000	2.4	61	20 (1:4)	19 200	2.1	57
14 (1:6)	40 000	2.2	76	14 (1:6)	20 000	2.3	78
11 (1:8)	36 000	2.2	76	11 (1:8)	7300	1.8	70
9 (1:10)	32 000	2.3	86	9 (1:10)	11 200	1.6	75

[a] Conditions: monomers, isosorbide and diethyl adipate; total initial monomer concentration, 0.15 mol × L^{-1}; catalyst, 10% Novozym 435:monomer (w/w); reaction time, 168 h; apparatus, Dean−Stark apparatus containing molecular sieves. [b] Isolated reaction yield.

esterification by GC of lauric acid and propanol.[12] Results of this work showed that, after 168 h, the residual catalytic activity of Novozym 435 was 62% and 78% in cyclohexane:benzene (6:1) and cyclohexane:toluene (6:1), respectively. It was therefore concluded that observation of plateau values in PIA yield and molecular weight, such as described in Figure 1, is not due to loss in enzyme activity.

Enzymatic Polymerization by Azeotropic Distillation: Effect of Diacid Monomer. The control of material properties is made through variation of molecular structure and molecular weight. While the diol in all reactions studied was isosorbide, the influence on diacid structure on polymer formation was investigated.

Table 5 shows results of enzyme-catalyzed condensation polymerizations to prepare a series of isosorbide polyesters using Novozym 435 as catalyst, azeotropic distillation to remove byproduct formed, and diacid esters differing in chain length. Diacid ethyl esters studied included those from succinate, glutarate, adipate, suberate, sebacate and dodecanedioate having 4, 5, 6, 8, 10, and 12 carbons, respectively. In all cases, isosorbide polyesters were formed. Most extraordinary is the general observation that isosorbide polyesters were formed with higher $\overline{M}_w$ and isolated yield values by carrying out polymerizations in cyclohexane:benzene 6/1 relative to in media consisting of cyclohexane or cyclohexane:toluene 6/1. In all of the solvents studied, increasing the length of diethyl ester from 4 to 5 and 6 carbons resulted in isosorbide polyesters of higher $\overline{M}_w$. For reasons that are unclear to the authors further increases in diester chain lengths resulted in less regular trends in $\overline{M}_w$ values. By conducting reactions in cyclohexane:benzene 6:1, isorbide polyesters synthesized from diacids with chain lengths from C6 to C12 had $\overline{M}_w$ and isolated yield values ranging from 33 000 to 47 000 and 76−92%, respectively.

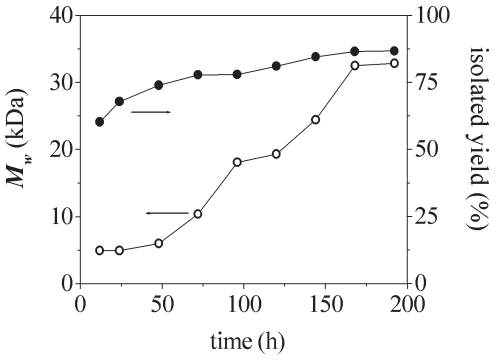

Figure 1. Changes in poly(isosorbide adipate) yield and molecular weight as a function of reaction time. Condiditons: monomers, isosorbide and diethyl adipate; initial monomer concentration, 0.15 mol × L^{-1}; solvent, cyclohexane:benzene (6:1 v/v); catalyst, 10% Novozym 435:monomer (w/w); apparatus, Dean−Stark apparatus containing molecular sieves.

Table 5 also lists glass transition (T_g) values measured for isosorbide polyesters prepared from diacid esters differing in chain length. Experimental values obtained herein were compared to those reported by Okada et al.[8] from the same polymer structures with similar molecular weight that were prepared by chemically catalyzed polymerizations between diacyl dichloride and isosorbide. The high reactivity of acyl chlorides precludes any selectivity between the endo and exo hydroxyl groups of isosorbide, thereby producing two different initial AB monomers (hydroxyacids AB_{endo} and AB_{exo}) that lead to a random copolymer structure. Conversely, during initial stages of CAL-B catalyzed polymerizations between isosorbide and diesters, it may be that enzyme-catalysis provides selectivity resulting in preferential exo- or endoacylation of isosorbide producing either hydroxyacid AB_{exo} or AB_{endo}, respectively. Formation of blocks of one of these hydroxyacids during the initial phase of polymer synthesis would provide higher order along chains relative to chemical polymerizations and could explain the higher T_g values of isosorbide polyester prepared herein relative to those reported in ref8.

The above hypothesis is supported by literature reports by others that describe regioselective esterification of isosorbide. For example, Chalecki and Guibé-Jampel[23] used Novozym 435 (e.g., CAL-B) and Lipozyme (lipase from *Mucor miehei*) as catalysts to prepare a series of isosorbide fatty monoesters under solvent-free conditions at 60 °C. These authors observed that, after 1 h, Novozym 435 gave 63% conversion of isosorbide with 30% endosubstituted, 13% exosubstituted, and 20% disubstituted isosorbide. In contrast, Lipozyme yielded the endo monoester of isosorbide as the sole product in 90% yield. Therefore, it may be that during the formation of isosorbide polyesters by CAL-B catalysis chain segments having some stereoregularity might be formed. Furthermore, it is well established that tacticity along polymer chains is an important structural parameter that determines T_g of those polymers.[24]

Finally, the nature of the leaving byproduct of the condensation reaction was investigated for Novozym 435 catalyzed polymerizations conducted in cyclohexane:benzene 6:1 (v/v) (Table 6). The alkanol molecules of dialkyladipate esters studied included methanol, ethanol, *n*-propanol and *n*-butanol. While ethanol, *n*-propanol and *n*-butanol form a known ternary azeotrope with cyclohexane and benzene, methanol forms a zeotropic mixture. Nevertheless, methanol is continually removed due its lower boiling point. Results in Table 6 show that diethyladipate was converted to PIA of highest molecular weight and isolated yield. The origin of this result could be 2-fold: (i) *n*-propanol and *n*-butanol have (in this order) less adsorptivity on the molecular sieves as compared to ethanol and methanol, and (ii) the efficiency of the byproduct removal from the equilibrium is reduced by its low proportion in the ternary azeotrope distillate.

Table 5. Enzymatic Synthesis of Isosorbide Polyesters by Azeotropic Distillation: Effect of Diacid Chain[a]

	cyclohexane				cyclohexane:benzene 6:1				cyclohexane:toluene 6:1				
monomer A	$\overline{M}_w$ (Da)	P_d	$\overline{x}_w$	ϕ^b (%)	$\overline{M}_w$ (Da)	P_d	$\overline{x}_w$	ϕ^b (%)	$\overline{M}_w$ (Da)	P_d	$\overline{x}_w$	ϕ^b (%)	T_g (°C)
diethyl succinate	3000	1.9	13	71	4300	2.1	19	72	6100	1.8	26	67	56 (36[c])
diethyl glutarate	16 000	1.7	67	56	17 000	2.3	70	68	11 700	1.5	48	64	29 (28[c])
diethyl adipate	21 000	2.5	81	74	37 000	2.2	142	76	20 000	2.3	74	78	35 (40[c])
diethyl suberate	10 000	2.5	35	61	40 000	2.2	142	82	12 000	1.7	42	39	16
diethyl sebacate	9000	2.3	29	51	47 000	2.2	152	79	24 000	2.1	77	70	−2 (−10[c])
diethyl dodecanedioate	21 000	2.0	63	75	33 000	1.8	98	92	4300	1.1	13	60	−7

[a] Conditions: monomer B, isosorbide; initial monomer concentration, 0.15 mol × L^{-1}; catalyst, 10% Novozym 435:monomer (w/w); reaction time, 168 h; apparatus, Dean−Stark apparatus containing molecular sieves. [b] Isolated reaction yield. [c] From ref 8

Table 6. Effect of the Reaction Byproduct

monomer A	byproduct	azeotrope[a]	$\overline{M}_w$ (Da)	P_d	ϕ^b (%)
dimethyladipate	methanol	(zeotrope)	28 000	2.6	79
diethyladipate	ethanol	64.7 °C (29.6%)	37 000	2.2	75
di-*n*-propyladipate	*n*-propanol	73.8 °C (5.5%)	4800	1.8	59
di-*n*-butyladipate	*n*-butanol	77.4 °C (4%)	500	1.4	30

[a] Conditions: monomer B, isosorbide; initial monomer concentration, 0.15 mol × L^{-1}; solvent, cyclohexane, benzene (6:1 v/v); catalyst, 10% Novozym 435:monomer (w/w); reaction time, 168 h; apparatus, Dean−Stark apparatus containing molecular sieves. [b] Isolated reaction yield; azeotrope boiling point from ref 22; in parentheses is the percent of byproduct in the distillate.

Conclusions

Aliphatic polyesters of isosorbide were prepared by use of Novozym 435 that consists of *C. antarctica* Lipase B physically adsorbed on a macroporous support. To our knowledge, this is the first example of an isosorbide-derived polymer prepared through enzymatic catalysis. The total absence of solvent resulted in low molecular weight isosorbide polyesters, with $\overline{M}_w$ values of up to 3800 Da. The presence of a solvent or solvent mixture that can accelerate the removal of ethanol leaving groups via azeotropic distillation proved to be an effective method for obtaining isosorbide polyesters of high $\overline{M}_w$ values. Several solvents were tested in the synthesis of poly(isosorbide adipate), and a 6:1 mixture of cyclohexane:benzene was most efficient, producing isosorbide polyesters with $\overline{M}_w$ values above 40 000 Da. The product had low solubility in this solvent, which reflects a serious limitation with respect to substrate diffusion and effective collisions with the heterogeneous immobilized lipase catalyst, both of which are necessary for efficient chain propagation and molecular weight increase. Consistent with this logic, lower concentrations of monomers and therefore propagating chains in cyclohexane:benzene were preferred for formation of higher molecular weight poly(isosorbide adipate). The use of ethyl esters relative to shorter and longer alkanol leaving groups on diacid ester monomers was preferred to achieve higher poly(isosorbide adipate) yields and $\overline{M}_w$ values. Furthermore, increasing the length of diethyl ester from 4 to 5 and 6 carbons resulted in isosorbide polyesters of higher $\overline{M}_w$.

This is the first example using isosorbide, a sterically hindered diol, as a monomer for enzyme-catalyzed polyester synthesis. The fact that this complex monomer bearing two chemically distinct secondary alcohols can be polymerized by CAL-B to polyesters with molecular weights of ~40 000 Da is surprising given that CAL-B is well-known to function with far better kinetics for reactions between primary hydroxyl and acyl donor molecules. Furthermore, it is also unexpected that isosorbide polyester synthesis would proceed under the present conditions in which both the immobilized lipase catalyst and propagating chain have poor solubility in the reaction solvent. Nevertheless, the obtained molecular masses were equivalent or higher than that obtained by nonenzymatic polymerizations. Even though isosorbide polyester synthesis catalyzed by Novozym 435 required long reaction times and was performed in nonattractive reaction media, this work represents an important starting point showing the feasibility of such a polymerization. Future work will address improving the efficiency of enzyme-catalyzed isosorbide polyester synthesis.

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Supporting Information Available: Text giving ^{1}H NMR and ^{13}C NMR data for compounds prepared and structures of those compounds and a table of FTIR characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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