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Lipase-catalyzed acetylation of methacrylic polymers containing OH-groups

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SUMMARY

In the present paper the synthesis of N-Methacryloyl-11-aminoundecanoyl-N'-(1-amino-2-propanol) and the corresponding copolymer with styrene is described. The stereoselective enzyme-catalyzed acetylation of the monomers and copolymers in the presence of vinylacetate by two lipases was investigated.

INTRODUCTION

Recently, growing interest has been directed to the enzymatically catalyzed synthesis and modification of polymers. In this area the lipase-catalyzed oligomerization of hydroxyacids has been investigated. (1)
Some studies were published concerning the cleavage of polymer side chains by special enzymes. (2), (3) We have investigated stereochemicals effects of esterase (PLE)-catalyzed hydrolysis of polymeric side chains ester groups. (4), (5) Usually, enzymes have been used for the cleavage of chemicals bonds. Considering the equilibrium situation, a catalysis of covalent bond formation is also possible by the same enzymes. (6) In the fact, we found a formation of peptide bonds by methacrylic polymers containing phenylalanine moieties in the side chains using α-chymotrypsin. (7)
In the present paper we describe the lipase-catalyzed acetylation of methacrylic polymers containing OH-groups.

RESULTS AND DISCUSSION

Synthesis of Monomers and Polymers

N-Methacryloyl-11-amino-undecanoic acid was activated with ethylchloroformate and the product reacted with 1-amino-2-propanol yielding the monomer N-methacryloyl-11-amino-N'-(1-amino-2-propanol) **1**. For the investigations the racemic form **1a** and the pure R-(**1b**) resp. S-(**1c**) enantiomers have been synthesized. The monomer N-methacryloyl-11-amino-undecanoyl-N'-(1-amino-2-acetoxy-propane) **2** was prepared by acetylation of **1** with acetic anhydride. The specific rotation angles are summarized in tab. 1.

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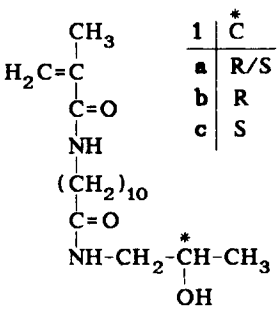
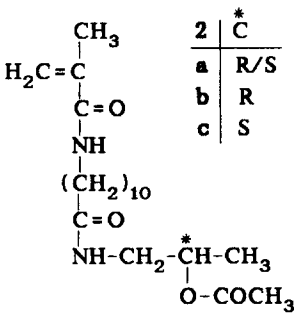
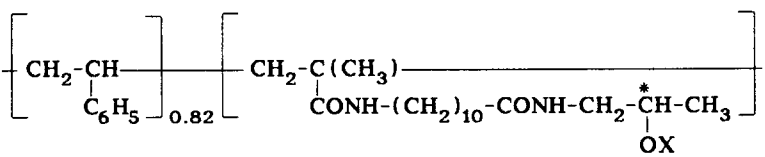


1	* C
a	R/S
b	R
c	S



2	* C
a	R/S
b	R
c	S

The monomers **1** have been polymerized radically with styrene yielding the copolymer **3**. The chemical composition was calculated from elementary analysis. The reaction of **3** with acetic anhydride yielded the polymer **4**. Tab. 1 shows, that in different solvents the rotations angles of the polymer increases upon acetylation, while esterification of the monomer results in a decrease of optical activity.



3	a	b	c
* C	R/S	R	S

X = H

4	a	b	c
* C	R/S	R	S

X = OCO-CH_3

Table 1 Comparison of specific rotation angles of monomers **1**, **2** (CH_2Cl_2) and of polymers **3** and **4** (CH_3OH)

Substrate		1b	2b	3b	4b
		1c	2c	3c	4c
$[\alpha]_{546}^{20°}$	R	-2.08	-1.05	-2.28	-3.29
	S	+2.01	+1.05	+2.22	+3.32

Enzymatically catalyzed acetylation

Recently, the lipase-catalyzed transesterification of low molecular weight alcohols with vinyl acetate was described. The reaction proceedes enantioselectively with high yields.(8)

$$\overset{*}{R}\text{-OH} + H_2C{=}CH\text{-}OCO\text{-}CH_3 \xrightarrow{\text{Lipase}} \overset{*}{R}\text{-}OCO\text{-}CH_3 + H_3C\text{-}CHO$$

According to these results our investigations were directed to the acetylation of monomer **1** and copolymer **3**. Stereochemical effects were verified by measuring the corresponding rotation angles. It was found, that the racemic monomer **1a** can be transformed partially to optically active **2**. The results are summarized in tab. 2.

Table 2 Specific rotation angles of monomer compounds seperated by thin layer chromatography after six days of enzymatically acetylation with lipase L_I resp. L_{II}. (yield in percent)

Substrate	$[\alpha]^{20°}_{546}$ L_I	$[\alpha]^{20°}_{546}$ L_{II}
residual component **1**	+0.19	+0.36
Acetate **2**	-0.04 (45)	-0.07 (25)

Comparing the rotation angles of the separated monomer components (tab. 2) with the pure model compounds summarized in tab. 1 a low kinetic preference of the R-enantiomer by lipases can be formulated:

$$\mathbf{1a}\ (c_R{=}c_S) + \text{vinyl acetate} + \text{lipase} \xrightarrow{K_R > K_S} \mathbf{2a'}\ (c_R{>}c_S) + \mathbf{1a'}\ (c_S{>}c_R)$$

c: concentration of enantiomers
K: rate constante

In analogy, the acetylation of the polymer **3a** containing racemic side chains can be performed in an organic solvent in the presence of vinyl acetate and lipase. The course of the reaction has been observed by IR-spectroscopy (fig. 1) and the quantitative amount of acetylation was determined from elementary analysis results. The resulting acetylated polymers show a low degree of optical activity:

Table 3 Optical activity and yield of lipase-catalyzed acetylation of polymer **3a**

lipase	L_I			L_{II}		
time in days	2	4	6	5	10	15
yield in percent	23	44	71	25	30	31
$[\alpha]^{20°}_{546}$	+0.02	+0.04	+0.06	+0.42	+0.52	+0.56

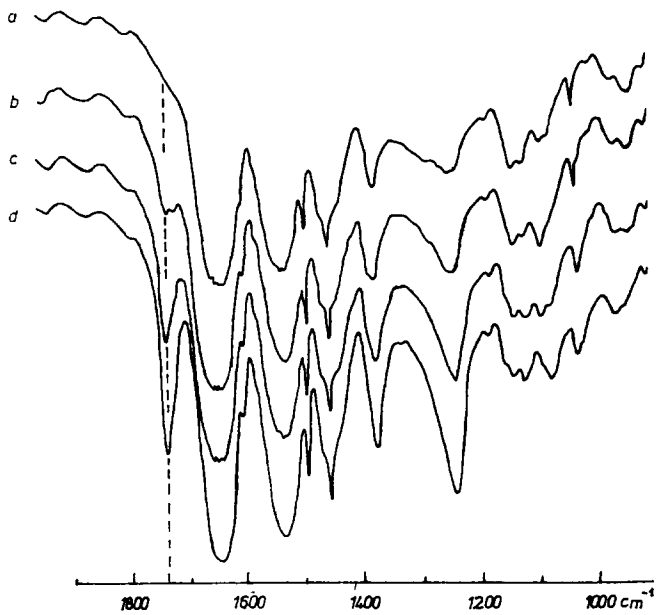


Figure 1 IR-spectra for verifying the enzymatically catalyzed acetylation of the copolymer **3a** with vinyl acetate in dependence of time with lipase L_I: a) Staring material; b) after 2 days c) after 4 days d) after 6 days of enzymatic influence

EXPERIMENTAL

N-Metharyloyl-11-aminoundecanoyl-N'-(1-amino-2-propanol) **1** :

To a solution of 10.76g (0.04 mol) N-methacryloyl-11-aminoundecanoic acid, 4.04g (0.04 mol) triethylamine and 0.1ml pyridine in 30ml THF 4.32g (0.04 mol) ethylchloroformate is added at -10°C, while triethylammoniumchloride precipitates. To the reaction mixture a solution of 3.0g (0.04 mol) 1-amino-2-propanol, 4.04g (0.04 mol) triethylamine in 30ml THF is slowly added at 0-5°C. After stirring for 20hrs at ambient temperature the suspension is poured into a mixture of 400ml water and 400ml methylenchloride. The organic layer is separated, washed twice with 100ml water and dried over $MgSO_4$. Evaporating the solvent and recrystallisation from ethylacetate gives a colourless product. Yield: 9.10g (70%), m.p.: 80-81°C

IR (KBr): 3440 (OH), 3300 (NH), 1640 (amid I), 1605 (C=O), 1535 (amid II).

^{1}H-NMR (CDCl): δ=1.17 (d; 3H, -CH-C$\underline{H}_3$), 1.33 (m; 16H, -$(CH_2)_8$-), 1.93 (s; 3H, C$\underline{H}_3$-(C=CH_2)-), 5.27 resp. 5.63 (2s; 1H, CH_3-(C=C$\underline{H}_2$)-).

$C_{18}H_{34}N_2O_3$ (326.48) calc. C 66.25 H 10.43 N 8.58
found C 66.03 H 10.50 N 8.56

N-Methacryloyl-11-aminoundecanoyl-N'-1(1-amino-2-acetoxy-propane) **2** :
A mixture of 1.0g (3.10 mmol)**1**, 5ml ethylacetate, 5ml acetic anhydride and 50mg sodium acetate is heated 10 min under refluxing conditions. The hot mixture is filtrated, and to the filtrate 50ml ether are added. The resulting precipitate product is filtrated and washed with ether.
Yield: 0.83g (75%), m.p. 79-80°C
IR (KBr): 3300 (NH), 1725 (C=O), 1640 (amid I), 1600 (C=C), 1525 (amid II).
^{1}H-NMR ($CDCl_3$): δ=1.20 (d; 3H, -CH-C$\underline{H}_3$), 1.37 (m; 16H, -$(CH_2)_8$-), 1.93 (s; 3H, C$\underline{H}_3$-(C=CH_2)-), 2.07 (s; 3H, CH_3-(CO)-), 5.27 resp. 5.63 (2s; 1H, CH_3-(C=C$\underline{H}_2$)-).
$C_{20}H_{36}N_2O_4$ (368.52) calc. C 65.18 H 10.30 N 8.47
found C 65.58 H 10.01 N 8.27

Enzymatically catalyzed acetylation of **1** :
A mixture of 1.50g (4.60 mmol) **1a**, 8.60g vinyl acetate and 120mg lipase in 40ml methylenchloride is stirred for 5d at ambient temperature and daily 120mg lipase L_I resp. L_{II} is added. The mixture of acetate **2** and primary product **1a** is separated by preparative thin layer chromatography using ethylacetate as flowing medium. The components are extracted with hot THF (Tab. 2).

Poly[-N-methacryloyl-11-aminoundecanoyl-N'-(1-amino-2-propanol)-co-styrene] **3** :
A mixture of 3.22g (10 mmol) **1**, 1.04g (10 mmol) styrene, 1.64mg (1 mmol) AIBN and 7.0g abs. THF is stirred 24h at 60°C under nitrogen. The solution is poured in a mixture of 200ml acetone/ether (1:1, vol). The obtained polymer is soluble in MeOH, THF, DMSO, DMF. [η] = 8.136ml/g (MeOH)
IR (KBr): 3500-3300 (OH; NH), 1630 (amid I), 1525 (amid II).
Found C 52.34 H 8.30 N 6.78

Poly[-N-methacryloyl-11-aminoundecanoyl-N'-(1-amino-2-acetoxy-propane)-co-styrene] **4** :
The acetylation of **3** with acetic anhydride is performed analogously as described for the monomer **1**. The product is soluble in MeOH, THF, DMSO, DMF.
IR (KBr): 3500-3300 (OH; NH), 1730 (C=O), 1640 (amid I), 1530 (amid).

Enzymatically catalyzed acetylation of the copolymer **3** :
A mixture of 400mg (1.09 mmol) **3**, 3.20g vinyl acetate and 7ml THF is stirred at ambient temperature adding daily 20mg lipase L_I resp. L_{II}. Finally the reaction mixture is diluted with 10ml methanol, filtrated, and the solvent is evaporated partially. The polymer is obtained by pouring the solution in a mixture of acetone/ether (1:1, vol).

Applied lipases:
L_I: lipase L 701 of GGUmbH
Department Enzymes
In der Schildwacht 13
6230 Frankfurt - 80
100mg (1500 u; standard: tributyrin)

L_{II}: lipase from pork pancreas liver (EC 3.1.1.3)
1mg (10 u; standard: oilic acid)

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