NEW ALTERNATING POLY(AMIDE-ESTER)S: SYNTHESIS AND PROPERTIES

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SUMMARY: New alternating poly(amide-ester)s derived from β-hydroxy acids and α-amino acids **3a,b** or ε-aminocaproic acid **4a-c** were prepared. Two approaches were considered: (i) polycondensation of N-(β-hydroxyacyl)-amino acids **1a,b** and **2b,c** and (ii) ring-opening polymerization of cyclic amide-esters **5a-c** and **6a-c**. For all the linear precursors polycondensation reactions result in oligomers with number average molecular weights lower than 5000. The ring-opening polymerization of the cyclic precursors is substrate specific and is sensitive to changes in the polymerization conditions. For N-(3-hydroxybutyroyl)-ε-aminocaproic acid lactone [c(3HB-εAC); **5b**] (IUPAC nomenclature: 2-methyl-5-aza-1-oxa-cycloundecan-4,11-dione) bulk and solution polymerizations result in oligomers with an alternating ester amide microstructure. Polymerization of N-(3-hydroxypropionyl)-ε-aminocaproic acid lactone [c(3HP-εAC); **5a**] (IUPAC nomenclature: 5-aza-1-oxa-cycloundecan-4-11-dione) in dimethylformamide solution and with $Bu_2Sn(OMe)_2$ as initiator high molecular weight linear, semi-crystalline polymers were obtained (T_m = 145.9°C). Polymerization of N-(hydroxypivaloyl)-ε-aminocaproic acid lactone [c(HPv-εAC); **5c**] (IUPAC nomenclature: 3,3-dimethyl-5-aza-1-oxa-cycloundecan-4-11-dione) in bulk results in amorphous alternating poly(amide-ester)s with cyclic structure (T_g = 6.8°C). The fourteen membered cyclo(diamide-diester)s **6a-c** (IUPAC nomenclatures: : 4,11-diaza-1,8-dioxa-cyclotetradecan-2,5,9,12-tetraone (**6a**), 7,14 dimethyl-4,11-diaza-1,8-dioxa-cyclotetradecan-2,5,9,12-tetraone (**6b**), 3,10-dimethyl-4,11-diaza-1,8-dioxa-cyclotetradecan-2,5,9,12-tetraone (**6c**) based on β-hydroxy acids and α-aminoacids could not be polymerized.

Introduction

Biomaterials often are surface modified polymeric materials in which the bulk is responsible for the mechanical properties and the surface is responsible for the biocompatibility. Effective modifications of the surface are achieved by chemical modifications[1]. However, interaction of the biosystem with the surface modified biomaterial may cause degradation of the surface which is associated with a loss of its biocompatibility. As a consequence, materials have to be developed in which the bulk and the surface are equally suitable for the contact with the

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biosystem. In this case a degradation of the surface does not lead to a loss of biocompatibility. Such materials are expected when suitable naturally occurring building blocks are used, when well defined and regular chain architectures are synthesised and well defined morphologies are achieved for copolymers.

Poly(amide-ester)s (polydepsipeptides) with strictly alternating building blocks are expected to show a high degree of order determined by hydrogen bonding. For polydepsipeptides with lactic acid and valine repeating units (poly[(S)Lac-*alt*-(S)Val]) semicrystalline materials with high melting points were obtained. However, the melting points and melting enthalpies are dependent on the optical purity of the building blocks[2].

In order to fulfill the various demands on the properties of biomaterials new types of polymers were developed. This paper will present our results with respect to the synthesis of strictly alternating poly(amide-ester)s based on α-amino acids and ε-aminocaproic acid in combination with β-hydroxy acids as the repeating units.

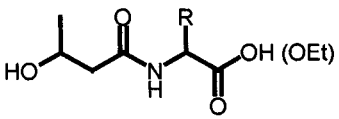
Results and discussions

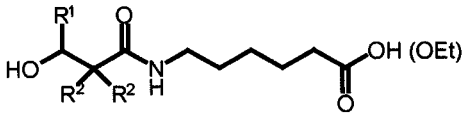
Alternating poly(amide-ester)s based on α-hydroxy acids and α-amino acids were obtained either by ring-opening bulk polymerization of morpholine-2,5-diones or by polycondensation of N-(α-hydroxyacyl)-α-amino acids (or esters)[2,3]. The linear amide precursors were obtained by aminolysis of α-hydroxy acid esters with α-amino acid salts without the use of protecting and activating groups, under mild conditions and with an easy work-up procedure[4,5]. Cyclization of N-(α-hydroxyacyl)-α-amino acids (or esters) according to Hartwig and Schöllkopf[6] under high dilution conditions with acidic catalysts results in cyclo(amide-ester)s (cyclic depsipeptides, morpholine-2,5-diones) with yields of 20 to 60% depending on the substitution pattern of the α-hydroxy acid and the α-amino acid.

In the following results of the same strategy, i.e., synthesis of linear precursors and polycondensation, and synthesis of cyclic precursors and ring-opening polymerization will be presented for β-hydroxy acids and α-amino acids or ε-aminocaproic acid.

Synthesis and polycondensation of N-(β-hydroxyacyl)-α-amino acid esters **1a,b** *and N-(β-hydroxyacyl)-ε-aminocaproic acid esters* **2b,c**.

For the synthesis of the linear precursors **1a,b** and **2b,c** based on α-amino acids and ε-amino caproic acid in combination with β-hydroxy acids three routes were followed.

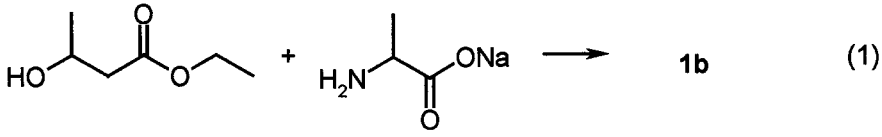




1a,b a: R = H
b: R = CH_3

2b,c b: $R^1 = CH_3$; $R^2 = H$
c: $R^1 = H$; $R^2 = CH_3$

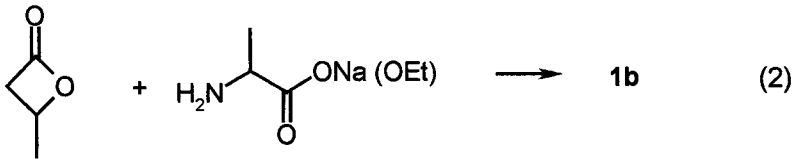
(i) The aminolysis of ethyl β-hydroxybutyrate with α-amino acid salts was realized in the presence of $BF_3 \cdot Et_2O$ as activating agent for the ester carbonyl (Eq.1). The β-hydoxy esters show much lower reactivity than the α-hydroxy esters due to the formation of a six-membered chelate structure. The linear precursors **1a,b** were obtained in yields of ≈ 50% when the reaction was performed at 80°C for 18 h.



(1)

(ii) The second route comprises the aminolysis of β-butyrolactone with amino acid salts or with amino acid esters (Eq.2). The reactivity of β-lactones was studied intensively by Greshom et al[7]. They have shown that strong nucleophiles induce an acyl-oxygen cleavage while with weak nucleophiles an alkyl oxygen cleavage is induced in β-butyrolactone. In addition the nature of the solvent and the sequence in which the reagents are supplied is important for the course of reaction.

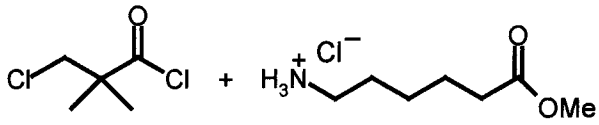
We performed the aminolysis of β-butyrolactone with amino acid salts in water at 0°C in order to avoid polymerization of the lactone and obtained N-(β-hydroxyacyl) amino acids **1a,b** and **2b** in yields ≥ 90%. The aminolysis of β-butyrolactone succeeded also with amino acid esters in acetonitrile at 0°C (Eq.2), however, an excess of lactone was necessary in order



(2)

to avoid the homocondensation reaction of the amino acid[8]. The linear hydroxy ester precursors **1a,b** and **2b** were obtained in yields ≥ 90%.

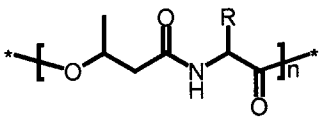
(iii) N-(Hydroxypivaloyl)-ε-aminocapronic acid ester **2c** was prepared starting from 3-chloro-2,2-dimethylpropionylchloride and the hydrochloride of ε-aminocaproic acid ester in the presence of triethylamine (Eq.3). A sequence of well established reactions (NaI/acetone, NaOH, HCl) leads to the linear precursor in 33% yield and excellent purity[9].



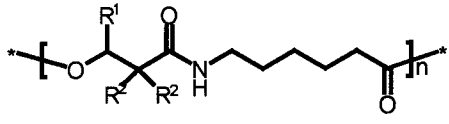
(3)

Polycondensation of the linear hydroxy acid and hydroxy ester precursors **1a,b** and **2b,c** were performed in bulk and in solution with transesterification catalysts as for example $Bu_2Sn(OMe)_2$ and $Ti(OiPr)_4$ and with acidic catalysts, e.g., toluene- and methanesulfonic acid in concentrations of 1-5 mol% at temperatures from 100 to 160°C for 3 to 115 h. Polymers **3a,b** and **4b,c** were obtained with number average molecular weights below 5000.

Polycondensation of the ethylesters **1b** or **2b** in bulk below 160°C results in a low polycondensation rate; after 24 h the conversion of the linear precursor is ≈ 50% and the number average molecular weight (M_n) below 2000. (Tab.1). Above this temperature conversions up to 95% were obtained, however, M_n does not increase indicating that chain degradation occurs predominantly at these high temperatures.



3a,b a: R = H
b: R = CH_3



4a-c a: R^1 = H; R^2 = H
b: R^1 = CH_3; R^2 = H
c: R^1 = H; R^2 = CH_3

Fig. 1 shows the ^{1}H NMR spectrum of the oligomeric mixture **3b** (Tab.1 entry 2) in which the ethylester endgroup on one hand and the crotonate or N-(3-hydroxybutyryl) endgroup on the other hand can clearly be identified. At these high temperatures ester pyrolysis reactions are predominant.

Tab. 1: Polycondensation of N-(hydroxyacyl)-amino acid esters **1b** and **2b**: initial conditions, monomer conversion (X_p) and number average molecular weights (M_n)

Mon.	Catalyst	[cat.][a]	T	t	p	X_p[b]	M_n[c]
		mol%	°C	h	mbar	Wt.%	
1b	$Ti(O\text{-}i.Pr)_4$	5	140	24	1013		
				24	10	40	1.400
1b	$Ti(O\text{-}i.Pr)_4$	0,2	160	3	1013		
				3	10		
				24	0,005	95	1.800
2b	$Bu_2Sn(OMe)_2$	1	120	115	1013		
				115	10	52	650
2b	$Bu_2Sn(OMe)_2$	5	140	24	1013		
				24	10	47	1700

[a] with respect to the monomer; [b] determined by means of ^1H NMR spectroscopy (integration of the CH-resonance lines of the hydroxybutyryl moiety and the crotonate endgroups; [c] GPC in DMAC, 1,2202 g/L LiCl, polystyrene standards.

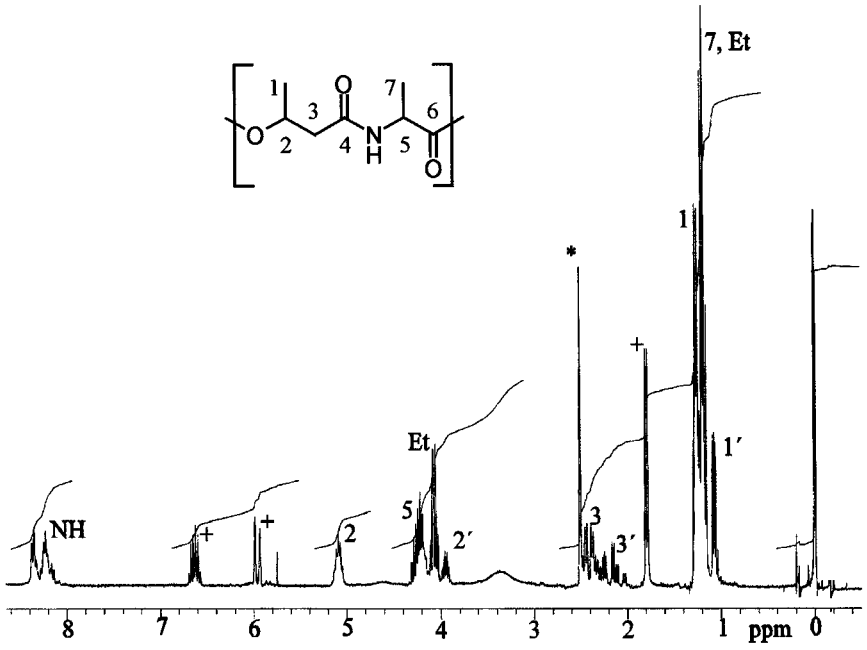


Fig.1. ^1H NMR spectrum of the oligomeric mixture **3b** (Tab.1 entry 2)

(solvent: * DMSO; internal standard TMS). 1-5 resonance lines of the repeating unit; + crotonate endgroups, 1′ -3′ N(3-hydroxybutyroyl) endgroup, Et ethylester endgroup

The polycondensation of the free acids **1a,b** in solution was performed in solvents which form an azeotrop with water in order to remove the water during polycondensation. The phenol is added to the reaction mixture to enhance the polycondensation by intermediate formation of an activated ester. ^{1}H NMR analysis of the product obtained after the linear precursor was consumed revealed that oligomers with crotonate and phenylester endgroups are obtained. The intermediate formation of the phenylester was documented also by GPC measurements: all oligomers show UV absorption which is in accord with phenylester endgroups. Nevertheless, the M_n values do not increase significantly.

Tab. 2: Polycondensation of N(hydroxyacyl)-amino acids **1a** and **1b** in solution: initial conditions, yields and number average molecular weights (M_n)

Mon.	Solvent	[M]	[phenol]	Catalyst	[cat.]	t	T	Yield in %	M_n[b]
		wt.%	mol%[a]		mol%[a]	h	^{0}C		
1a	C_2HCl_3	10	1*	TosOH	1	150	88	88	2.400
1a	C_2HCl_3	10	110	$MeSO_3H$	5	41	88	98	3.500
1b	$C_2H_4Cl_2$	10	10*	$MeSO_3H$	5	150	84	n. b.	1.000
1b	$EtNO_2$	75	10*	TosOH	1	150	115	74	1.400
1b	$CHCl_3$	10	200	$MeSO_3H$	5	150	61		
	-	-	--			260[c]	100	95	1.700

* p-nitrophenol was used
[a] with respect to the monomer; [b] GPC in DMAC, 1,2202 g/L LiCl, polystyrene standards;
[c] at 0,005 mbar.

Polycondensation experiments of the free acids **1a,b** in bulk in the presence of phenol (Tab.3) result in oligomers **3a,b** with phenylester and crotonate endgroups. Obviously the high concentration of endgroups does not lead to higher molecular weights. For the free acid precursor **2c** higher temperatures were selected for the polycondensation reaction since the substitution pattern does not allow ester cleavage as a side reaction. For this substrate the highest M_n-values were obtained .

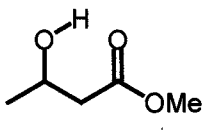
Tab. 3: Polycondensation of N(hydroxyacyl)-amino acids **1a,b** and **2c** in bulk: initial conditions, yields and number average molecular weights (M_n)

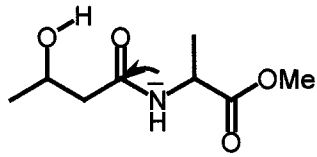
Mon.	[phenol] mol%[a)]	Catalyst	[cat.] mol%[a)]	t h	T ^{0}C	p mbar	Yield in %	M_n[c)]
1a	100*	TosOH	1	69	100	1013	95[b)]	1.440
1b	500	$MeSO_3H$	5	69	100	1013		
	--			168	100	0,005	95[b)]	1.900
2c	--	TosOH	5	1	140	1013		
				69		0,005	95[b)]	3.300

* p-nitrophenol was used
[a)] with respect to the monomer; [b)] after precipitation in Et_2O; [c)] GPC in DMAC, 1,2202 g/L LiCl, polystyrene standards.

In all cases and independently of conversion of the linear precursor the oligomers **3a,b** and **4b,c** were obtained with number average molecular weights lower than 5000 (Tab.1-3).
Three reasons for the low molecular weight of the poly(amide-ester)s **3a,b** and **4b,c** will be discussed:

(i) β-Hydroxy esters like methyl-3-hydroxy-butyrate show much lower reactivity than their α-homologes. This lower reactivity is explained by the formation of a six-membered chelate structure as shown for methyl-3-hydroxybutyrate. For N-(3-hydroxybutyroyl)-α- or ε-aminoacids the chelate stability is even increased by the electron donating effect of the adjacent amide nitrogen.





(ii) As a consequence of the low reactivity of the 3-hydroxy-butyroyl unit the reaction temperatures and times must be increased, which causes side reactions as there are ester pyrolysis and water elimination reactions which lead to α,β-unsaturated ester or amide endgroups.

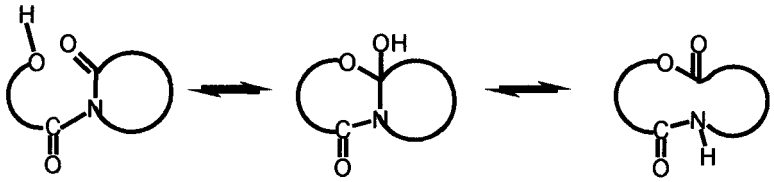
(iii) Experimental support for these explanations come from polycondensation experiments performed with methyl-3-hydroxybutyrate with the catalysts mentioned above and

temperatures up to 180°C. The polyhydroxybutyrate samples show low molecular weights with crotonate endgroups[10].

Finally it should be mentioned that cyclization experiments of the linear precursors **1a,b** and **2b,c** under high dilution conditions and with various activation agents did not result in cyclo(amide-ester)s[9].

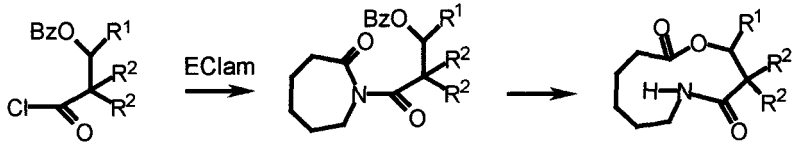
Synthesis of cyclic precursors

In the literature an alternative route to cyclo(amide-ester)s was described[11]. N-Hydroxyacyl lactames result in cyclic ester amides via the formation of cyclols. The course of the reaction depends on (i) the nucleophilicity of the hydroxyl group, (ii) the electrophilicity of the amid-carbon, (iii) the ring-size of both the starting lactam ring and the ring formed, (iv) and the steric accessibility of the acylamide carbon. Finally the energetic preference of the cyclic ester-amide over the cyclol structure is a prerequisite for a successful synthesis (Eq.4).



(4)

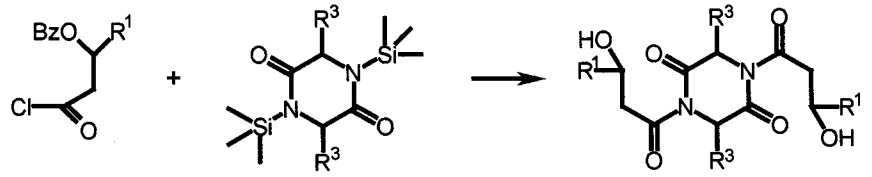
The initial N-acylamides may be readily prepared by acylation of ε-caprolactam (EClam) (or N-trimethylsilyl ε-caprolactam) with an acyl chloride containing a protected hydroxyl group (Eq.5). The presence of an acid scavenger as for example triethylamine favours the acylation of lactames and increases the yield. Removal of the protective group by hydrogenation over Pd in THF solution results in the spontaneous formation of the cyclic ester amides in relative good yields and high purity: **5a** 57%, **5b** 83%, **5c** 47%. The cyclic amide-esters are crystalline substances with relatively high melting points: **5a** 142°C, **5b** 137°C, and **5c** 165°C.



(5)

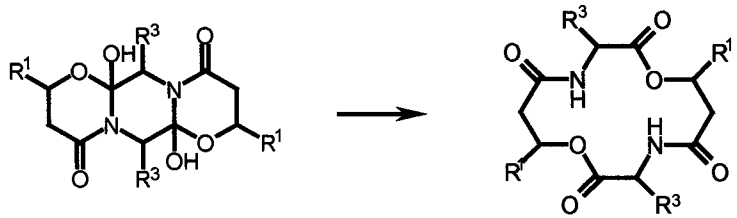
5a-c a: $R^1 = R^2 = H$
b: $R^1 = CH_3$, $R^2 = H$
c: $R^1 = H$, $R^2 = CH_3$

Ring-expansion reactions can be performed also with N,N'-bis(β-hydroxyacyl)-2,5-diketopiperazines (Scheme 1). The synthesis starts with the acylation of the silylated diketopiperazines with the corresponding acylchlorides in toluene solution at room temperature in nearly quantitative yields. Upon deprotection of the hydroxyl groups (H_2/Pd/C), however, ring-expansion does not take place spontaneously; heating in ethylacetate in the presence of triethylamine is necessary in order to produce the cyclic di(ester-amides). The yields depend on the substitution pattern: **6a** 48%, **6b** 19%, **6c** 26%. The 14-membered cyclic di(ester-amide)s are high melting crystalline materials with melting points of 258°C (**6a**), 232°C (**6b**) and 251°C (**6c**). It should be mentioned that the ring-expansion in N,N'-bis(α-hydroxyacyl)-2,5-diketopiperazines does not occur for with the corresponding α-hydroxy acid derivatives. In this case the equilibrium is completely shifted to the cyclol.



a: $R^1 = H$
b: $R^1 = CH_3$

a: $R^3 = H$
b: $R^3 = CH_3$



6a-c a: $R^1 = R^3 = H$
b: $R^1 = CH_3$, $R^3 = H$
c: $R^1 = H$, $R^3 = CH_3$

Scheme 1. Synthesis of 4,11-diaza-1,8-dioxa-tetradecan-2,5,9,12-tetraones **2a**, **2b** and **2c**

Polymerization of the cyclic precursors

The polymerization of N-(3-hydroxybutyroyl)-ε-aminocaproic acid lactone [c(3HB-εAC)] **5b** was performed in bulk at temperatures around the melting point of the cyclic monomer

(137°C), and in dimethylformamide (DMF) solution where lower polymerization temperatures could be employed (Tab.4). Several initiators were used and in all cases oligomers were obtained and no polymers. It should be mentioned that the alternating structure of 3-hydroxybutyrate units and ε-caproic acid units in the oligomers was confirmed by means of NMR-spectroscopy. In addition, from ^1H NMR data 3-hydroxybutyryl and crotonyl endgroups were detected. The GPC data (Fig.2) reveals an oligomeric series of to linear oligomers.

Tab.4 Polymerization of c(3HB-εAC) with various catalysts, polymerization conditions and GPC results.

Initiator	$[M]_0/[I]_0$	Medium	T / °C	t / h	GPC-results[a)]
NaH	100	melt	200	87	oligomers, n = 1 - 8
tert.-BuOK	100	melt	135	135	oligomers, n = 1 -3
NaphK	100	melt	140	672[b)]	oligomers, n = 1 - 8
$Bu_2Sn(OMe)_2$	100	melt	130	135	edukt
$Bu_2Sn(OMe)_2$	33	DMF[c)]	100	120	oligomers, n = 1 - 5
$Ti(O\text{-}i.Pr)_4$	100	melt	180	160	oligomers, n = 1 - 6
$Ti(O\text{-}i.Pr)_4$	100	melt	140	672[a)]	oligomers, n = 1 - 8
$Ti(O\text{-}i.Pr)_4$	33	DMF[c)]	100	120	oligomers, n = 1 - 8
CF_3SO_3Me	100	melt	130	135	oligomers, n = 1- 6

a) GPC in DMAC, 1,2202 g/L LiCl, polystyrene standards, b) polymerization in closed ampullae, c) [Mon.] = 58 Gew.%

As a reason for the formation of low molecular weight material the following arguments are presented:

(i) Due to transannular interactions in the 11-membered ring between the amide nitrogen and the ester carbon the electrophilicity of the ester carbon decreases and the stability of the ring structure increases.

(ii) In addition the methyl substituent induces some steric hindrance, e.g., introduction of a methyl group in ε-caprolacton reduces drastically the polymerizability of the 7-membered ring.

(iii) The susceptibility of the ester bond in the polymer to cleavage is increased, since α,β-unsaturated carbonyl species (crotonyl groups) with increased stability are the reaction products.

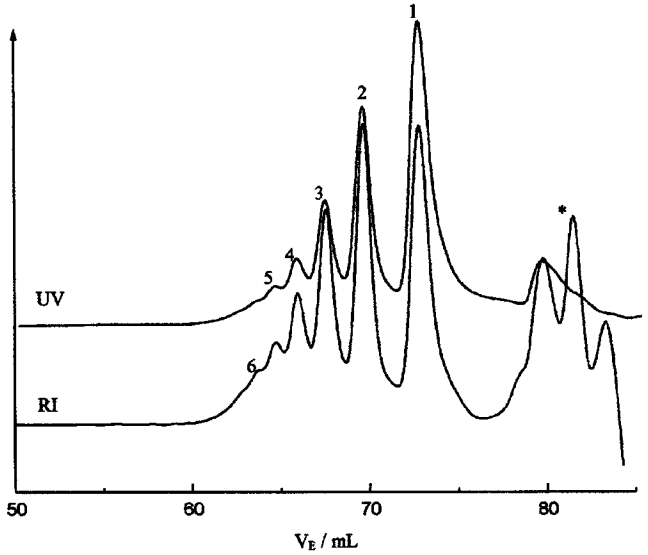


Fig. 2 GPC-trace of oligo(3HB-*alt*-εAC) **4b** (sample preparation according to Tab.4 entry 6).

The polymerization of N-(3-hydroxypropionyl)-ε-aminocaproic acid lactone [c(3HP-εAC)] was performed in DMF solution with $Bu_2Sn(OMe)_2$ as initiator. The polymerization rate is low, high monomer conversions are reached after 120h at a polymerization temperature of 100°C. The molecular weights of the polymer increase with the monomer to initiator molar ratio.

Polymerization experiments in DMF solution with initiators based on Ti, K, Mg show either no conversion or the formation of oligomers with low conversion of the monomer. Bulk polymerizations lead to a crosslinked product independent of the initiator used.

GPC-traces of the polymeric product (Fig.3) show beside polymer a homologous series of oligomers which can be partly removed by reprecipitation of the crude product from DMF solution into CH_2Cl_2.

The ^{13}C NMR spectrum obtained at 100°C in DMSO-d_6 (Fig.4) shows well resolved resonance lines for all carbon atoms of the repeating unit. For all methylene groups and especially for the carbonyl carbons a single resonance line is observed, indicating the alternating structure of ε-aminocaproic acid units and 3-hydroxypropionic acid units. Beside

these heterodiads no trace of homodiads is obsorved. The ^{1}H NMR spectrum supports the proposed alternating structure; integration of the methylene groups reveals a 1 : 1 ratio of the repeating units.

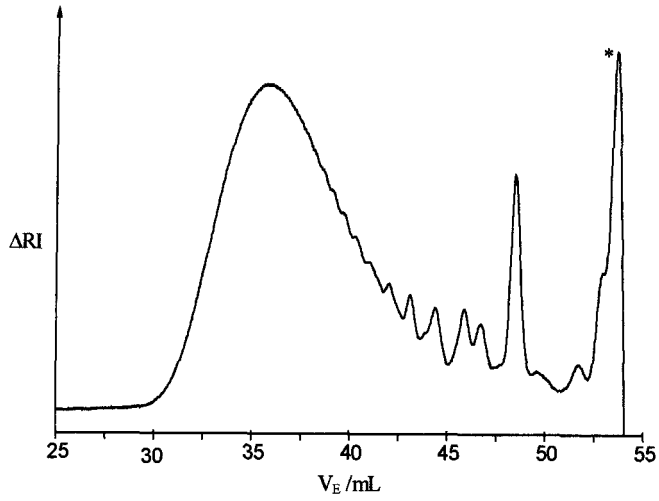


Fig.3 GPC-trace of poly(3HP-*alt*-εAC) **4a:** polymerisation conditions: solvent DMF, $[c(3HP\text{-}\varepsilon AC)]_o = [M]_o = 33$ wt.%, $[M]_o/[I]_o = 50$, T = 100°C, t = 120 h.
GPC in dimethylacetamide with 1.2202 g/L LiCl.

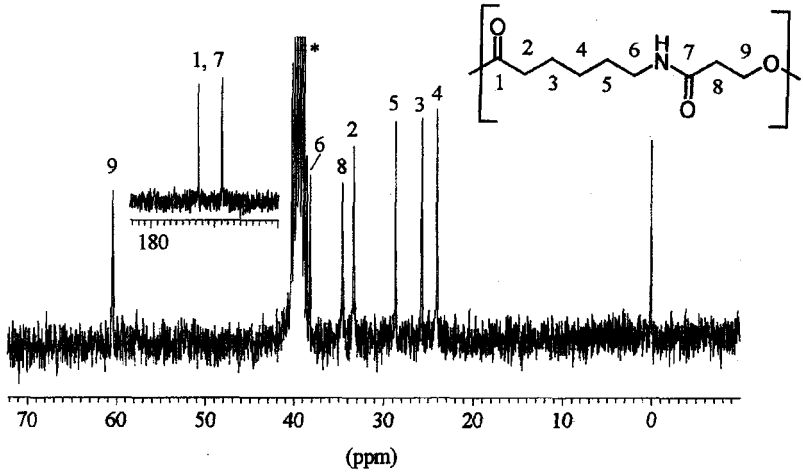


Fig. 4 ^{13}C NMR spectrum of poly(3HP-*alt*-εAC) **4a** in DMSO-d_6 at 100°C. (*DMSO-d_6)

The polymerization of N-(hydroxypivaloyl)-ε-aminocaproic acid lactone c(HPv-εCA) **5c** in bulk at 170°C was performed with a variety of initiating systems, e.g., Bu_2Mg, Al(O-*sec*Bu)$_3$, Ti(O-*i*Pr)$_4$. Dependent on the initiator used the polymerization exhibits different rates of polymerization. In addition with some initiators, e.g., Al(OsecBu)$_3$ a high concentration of low molecular weight material is formed, while for other initiators, e.g., Ti(O-*i*Pr)$_4$ no oligomers can be detected in the GPC (Fig.5). By reprecipitation the oligomers are only partly removed, a complete removal is possible by dialysis (ethanol/water = 3/1). During dialysis no hydrolytic degradation is observed.

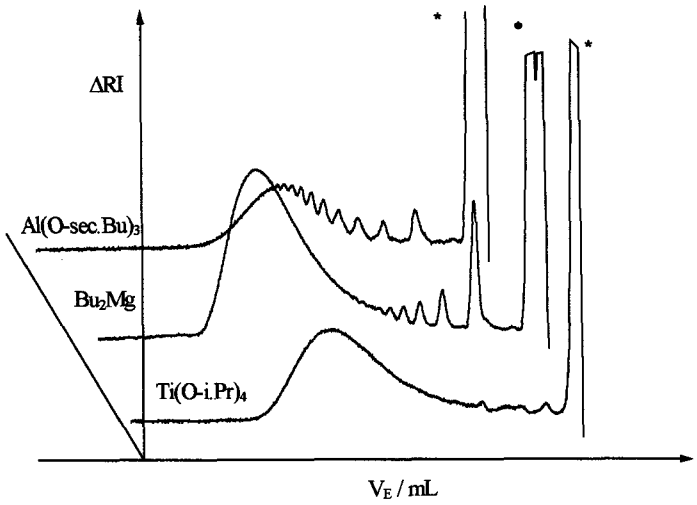


Fig.5 GPC-trace of poly(HPv-*alt*-εAC) **4c:** polymerisation conditions: in bulk, $[Al(O\text{-}sec Bu)_3]_o/[I]_o = [Bu_2Mg]_o/[I]_o = 143$, $[Ti(O\text{-}iPr)_4)]_o/[I]_o = 48$, T = 170°C, t = 2.5 h. GPC in dimethylacetamide with 1.2202 g/L LiCl (* = monomer and water)

The ^{1}H NMR spectrum of the polymer, shows well resolved resonance lines for all methylene groups independent of the molecular weight; no resonance lines for endgroups are detected. The spectrum of the polymer is very similar to the spectrum of the monomer, indicating the alternating structure of the repeat units in the polymer. The ^{13}C NMR spectrum (Fig.6) shows in the carbonyl region only two resonance lines, one for an ester carbonyl, the other for an amide carbonyl carbon; no ester-ester or amide-amide homodiads are observed.

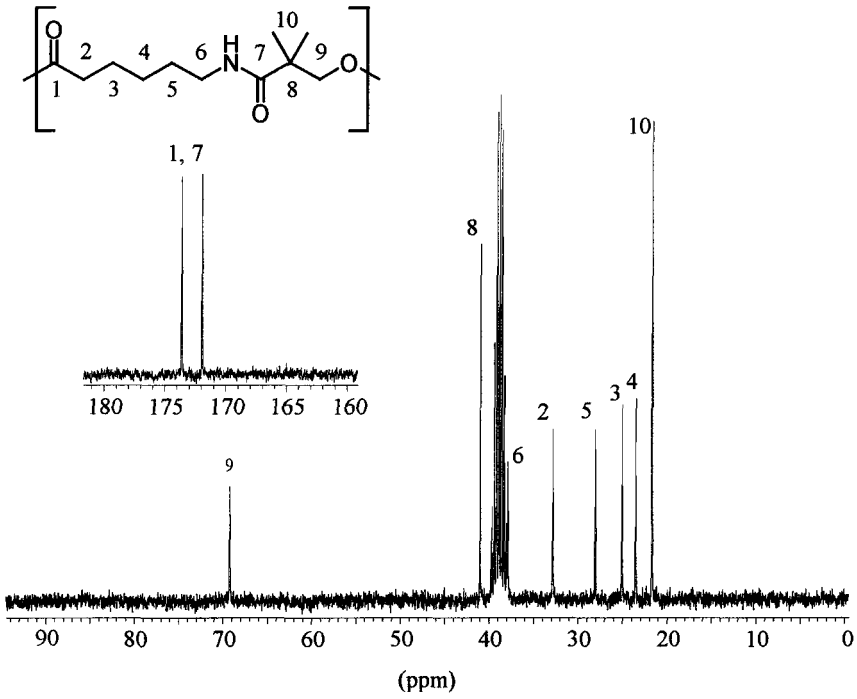
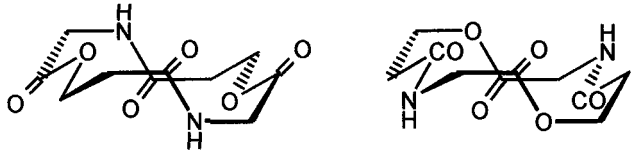


Fig. 6 ^{13}C NMR spectrum of poly(HPv-*alt*-εAC) **4c** in DMSO-d_6

Polymerization experiments with the cyclic diamide-diesters **6a-c** under a variety of polymerization conditions were unsuccessful; the starting materials were recovered.



Scheme 2. Conformation of 14-membered cyclo(diamide-diester)s

This result indicates the high thermodynamic stability of the 14-membered cyclo(amide-ester)s. Hassal et al.[12] suggested two favored conformations (Scheme 2) in which the positions of amide and ester groups correspond to the favored trans planar conformation. Molecular models show that the ring systems are strain-free and have a rigid conformation. In

addition intramolecular transannular hydrogen bonding results in an additional contribution to the ring stability.

Conclusions

Polymerization of cyclic ester amides **5a-c** revealed that under selected polymerization conditions high molecular weight polymers are obtained for c[3HP-εAC] (**5a**) and c[HPv-εAC] (**5c**) while for [3HB-εAC] (**5b**) a homologous series of oligomers is obtained. The polymerization mechanism is still under investigation. Poly(3HP-*alt*-εAC) is a linear, alternating, semicrystalline poly(amide-ester) with a higher stability to hydrolysis than poly(amide-ester)s based on α-hydroxy and α-amino acids. Poly(HPv-*alt*-εAC) is an alternating, amorphous poly(amide-ester) with a cyclic structure[9]. Since degradation of polypeptides in vivo often occur from the chain ends these polymers are expected to show a reduced tendency to hydrolysis.

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