Copolymerization of ε-caprolactone and morpholine-2,5-dione derivatives

*Peter J. A. in't Veld, Ye Wei-ping, Richard Klap, Pieter J. Dijkstra, Jan Feijen**

Department of Chemical Technology, University of Twente,
P. O. Box 217, 7500 AE Enschede, The Netherlands

(Date of receipt: September 30, 1991)

SUMMARY:

Novel biodegradable poly(ester-amide)s were prepared by ring-opening copolymerization of ε-caprolactone and 3- and/or 6-alkyl-substituted morpholine-2,5-dione derivatives. The copolymerizations were carried out in the bulk using stannous octoate as an initiator. Molecular weights of the copolymers ranged from $1{,}0 \cdot 10^4$ to $8{,}3 \cdot 10^4$ and decreased with increasing mole fractions of morpholine-2,5-dione derivatives in the feed. ^{13}C NMR sequence analysis indicated that the copolymers had a random distribution of ε-oxycaproyl and depsipeptide units, which resulted from the occurrence of transesterification reactions during copolymerization. The results of the DSC measurements and ^{13}C NMR sequence analysis showed a close relationship between the crystallinity and average length of ε-oxycaproyl blocks. Copolymers with a mole fraction of depsipeptide units smaller than 0,20 were semi-crystalline, whereas incorporation of larger amounts of depsipeptide units resulted in amorphous copolymers. The melting point depression as a function of the molar composition of the semi-crystalline copolymers was in good agreement with the melting point depression predicted by the Baur equation, which indicated the rejection of depsipeptide units from crystals consisting of ε-oxycaproyl units.

Introduction

Aliphatic homo- and copolymers of hydroxy acids such as glycolic acid, lactic acid and 6-hydroxyhexanoic acid are well known examples of biodegradable polyesters, and have been extensively studied and reported in the literature[1–4]. These (co)polymers are most effectively synthesized by ring-opening (co)polymerization of the corresponding cyclic dimers and monomers glycolide, lactide and ε-caprolactone, respectively. Copolymerization of ε-caprolactone with glycolide[5,6], DL-lactide[6–9] or L-lactide[10–12] yields biodegradable polymers with a broad variation in chemical and physical properties.

We have investigated the ring-opening polymerization of several 3- and/or 6-alkyl-substituted morpholine-2,5-dione derivatives to the corresponding alternating polydepsipeptides (copolymers of α-amino acids and α-hydroxy acids) as a method to synthesize novel biodegradable polymers[13]. Analogous to the synthesis of aliphatic copolyesters, morpholine-2,5-dione derivatives can be copolymerized with lactones to provide copoly(ester-amide)s with a range of chemical and physical properties. Previously we reported the synthesis of glycine-DL-lactic acid copolymers by copolymerizations of DL-lactide and (6*RS*)-methylmorpholine-2,5-dione using different mole ratios of monomers[14]. It was shown that the hydrolysis rate constants only varied from $5 \cdot 10^{-2}$ to $7 \cdot 10^{-2}$ day^{-1}, implying that the degradation rate was not significantly influenced by the composition of the copolymers. However, copolymers with a high glycine content showed weight loss at an earlier stage than copolymers with a low

 CCC 0025-116X/92/$05.00

glycine content. Therefore, the observed differences in degradation times were ascribed to the higher solubility of the degradation products rich in glycine [15]. The objective of increasing the rate of degradation of poly(ε-caprolactone) without compromising its excellent permeability for hydrophobic drugs [2, 8] prompted us to investigate novel copoly(ester-amide)s of ε-caprolactone and morpholine-2,5-dione derivatives. Only a few copoly(ester-amide)s synthesized by anionic ring-opening copolymerization of ε-caprolactone and lactams have been reported [16–18].

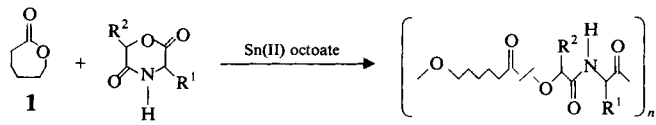
In the present paper the synthesis of copolymers of ε-caprolactone and morpholine-2,5-dione derivatives is described. The copolymers were characterized by ^{1}H NMR (monomer conversion, molar composition), ^{13}C NMR (sequence analysis), GPC/LALLS (apparent molecular weight) and DSC (glass transition temperatures, melting temperatures and heats of fusion).

Results and discussion

Copolymerizations

Previously we described the ring-opening polymerization of morpholine-2,5-dione derivatives **2a–e** [13] (*Scheme 1*) and the copolymerization of **2a** and DL-lactide [14]. On the basis of the results of these studies, initial copolymerizations of ε-caprolactone (**1**) with morpholine-2,5-dione derivative **2a** were performed in the bulk using stannous bis(2-ethylhexanoate) (stannous octoate) as an initiator (mole ratio M/I = 1000) and a mole fraction of **2a** in the feed of 0,10. In order to determine optimal reaction

Scheme 1:



1 **2a–e** **3a–e**

a: R^1 = H, R^2 = CH_3
b: R^1 = CH_3, R^2 = CH_3
c: R^1 = $CH(CH_3)_2$, R^2 = CH_3
d: R^1 = CH_3, R^2 = H
e: R^1 = $CH(CH_3)_2$, R^2 = H

conditions, both the reaction temperature and the reaction time were varied. The results listed in Tab. 1 indicate that a decrease in the reaction temperature results in a decrease of the ε-caprolactone conversion, despite the longer reaction time used at low reaction temperatures. In this series the highest molecular weight of the copolymer was found using a reaction temperature of 130 °C and a reaction time of 48 h. Based on these results the ring-opening copolymerization of ε-caprolactone with five different morpholine-2,5-dione derivatives **2a–e** was performed in the bulk at a temperature of 130 °C and a reaction time of 48 h. Stannous octoate was used as an initiator with a mole ratio M/I = 1000. The mole fraction of morpholine-2,5-dione derivative in the

Tab. 1. Copolymerization of ε-caprolactone and **2a** in the bulk using different reaction temperatures and times (mole fraction of **2a** in the feed x_M = 0,10); initiator: stannous octoate, mole ratio M/I = 1000 ($\bar{M}_{w,app}$: apparent weight-average mol. wt.)

Temp. in °C	Time in h	Conv. of ε-cap. [a] in %	Yield in %	$10^{-4} \cdot \bar{M}_{w,app}$ [b]
150	48	100	91	3,8
130	48	100	94	5,0
110	60	100	94	3,6
90	118	98	92	3,8
70	287	76	72	2,8

[a] Determined by ^{1}H NMR.
[b] Determined by GPC/LALLS.

feed was varied from 0,05 to 0,50. In this way five series of copolymers were obtained (Tab. 2).

The conversion of the monomers was determined from the ^{1}H NMR spectra of the crude reaction products by comparing the intensities of the OCH_2 signal of ε-caprolactone (δ = 4,00, $CDCl_3$) and the OCH or OCH_2 signal of the morpholine-2,5-dione derivatives (δ = 4,8–5,0, $CDCl_3$) with the intensities of the corresponding signals in the copolymers (Tab. 3). The ε-caprolactone conversion for all five series of copolymers was 100%. The conversions of the morpholine-2,5-dione derivatives **2a, 2b, 2d** and **2e** varied from 88 to 100% (Tab. 2), whereas the conversions of morpholine-2,5-dione derivative **2c** were lower (73–85%). The differences in conversions of morpholine-2,5-dione derivatives used in the copolymerizations can be attributed to differences in reactivity of the monomers, which has already been observed in the homopolymerization of morpholine-2,5-dione derivatives[13]. From Tab. 2 it is also observed that the conversions of the morpholine-2,5-dione derivatives decrease with increasing mole fraction of morpholine-2,5-dione derivatives in the feed of the copolymerizations.

The composition of the copolymers was calculated from the ^{1}H NMR spectra of the purified products using the OCH_2 signal intensities of the ε-oxycaproyl moieties and the OCH or OCH_2 signal intensities of the depsipeptide moieties (Tab. 3). Tab. 2 shows that the mole fractions of depsipeptide units in the copolymers (X_M) **3a, 3b, 3d** and **3e** are equal to the mole fractions of the corresponding morpholine-2,5-dione derivatives in the feed of the copolymerization reactions (x_M). For copolymer **3c**, X_M values smaller than x_M are found, which is caused by the lower conversion of the morpholine-2,5-dione derivative **2c** in the copolymerizations.

Tab. 2 also shows that the apparent molecular weights of the copolymers ($\bar{M}_{n,app}$, $\bar{M}_{w,app}$) decrease with increasing x_M, except for copolymer series **3c**. The differences in molecular weights in each series of copolymers result from the reaction conditions used in the copolymerizations, which apparently are not optimal for the morpholine-2,5-dione derivatives and molar compositions used, as will be illustrated hereafter.

The influence of the stannous octoate concentration on $\bar{M}_{w,app}$ of copolymer **3a** was investigated with a mole fraction of **2a** in the feed (x_M) of 0,10 and 0,50, respectively. Fig. 1 illustrates that for x_M = 0,50 the $\bar{M}_{w,app}$ values decrease with

Tab. 2. Copolymerization of ε-caprolactone with morpholine-2,5-dione derivatives carried out at 130 °C in the bulk using stannous octoate as an initiator, mole ratio M/I = 1 000, reaction time: 48 h (x_M: mole fraction morph. der. **2a–e** in the feed, X_M: mole fraction morph. der. in copolymer, $\bar{M}_{n,app}$ and $\bar{M}_{w,app}$: apparent number-average and apparent weight-average mol. wt., respectively, L_C and L_M: average block length of ε-oxycaproyl and depsipeptide units, respectively, T_g: glass transition temperature, T_m: melting temperature, ΔH: heat of fusion)

Copolymer	x_M	^{1}H NMR		GPC/LALLS		^{13}C NMR			DSC		
		X_M [a]	conv. of M in %	$10^{-4} \cdot \bar{M}_{n,app}$	$10^{-4} \cdot \bar{M}_{w,app}$	X_M [a]	L_C	L_M	T_g °C	T_m °C	ΔH J/g
3a	0	0	—	4,1	5,7	0	—	—	−53	65	68
3a	0,05	0,048	100	4,8	6,4	0,048	20	1	−48	58	54
3a	0,10	0,095	100	4,7	6,5	0,084	11	1	−46	45	38
3a	0,15	0,15	100	3,9	5,7	0,15	6,3	1,1	−44	37	4
3a	0,25	0,24	100	3,7	5,3	0,27	3,3	1,2	−31	—	—
3a	0,40	0,41	100	2,0	3,6	0,42	2,2	1,6	−4	—	—
3a	0,49	0,52	96	2,4	4,4	0,53	1,8	2,0	15	—	—
3b	0,05	0,046	100	2,1	4,8	0,045	21	1	−46	57	54
3b	0,10	0,088	92	2,0	3,1	0,083	11	1	−38	54	39
3b	0,15	0,14	88	1,5	2,2	0,13	7,0	1	−39	44	34
3b	0,25	0,24	93	1,2	1,7	0,23	4,3	1,3	−27	—	—
3b	0,40	0,37	93	0,59	1,0	0,37	2,6	1,5	−8	—	—
3b	0,49	0,49	92	0,88	1,4	0,50	2,1	2,1	4	—	—
3c	0,05	0,043	84	2,7	4,0	0,043	22	1	−56	58	48
3c	0,10	0,083	83	3,4	5,1	0,083	11	1	−38	49	37
3c	0,15	0,12	85	5,8	8,3	0,12	7,6	1	−39	40	2
3c	0,25	0,21	82	4,2	5,5	0,21	5,0	1,3	−33	—	—
3c	0,40	0,34	78	4,4	6,2	0,34	2,9	1,5	−3	—	—
3c	0,49	0,44	73	3,5	5,1	0,44	2,2	1,7	6	—	—

Tab. 2. Continued

Copolymer	x_M	^{1}H NMR		GPC/LALLS		^{13}C NMR			DSC		
		X_M [a]	conv. of M in %	$10^{-4} \cdot \bar{M}_{n,app}$	$10^{-4} \cdot \bar{M}_{w,app}$	X_M [a]	L_C	L_M	T_g °C	T_m °C	ΔH J/g
3d	0,05	0,049	98	4,2	5,6	0,050	19	1	−54	53	57
3d	0,10	0,097	97	3,0	4,0	0,091	10	1	−46	48	47
3d	0,15	0,14	97	1,7	3,3	0,14	6,2	1	−46	41	33
3d	0,25	0,23	93	1,2	2,0	0,25	3,9	1,3	−35	—	—
3d	0,40	0,39	97	1,2	1,8	0,40	2,1	1,4	−19	—	—
3d	0,50	0,52	95	0,82	1,4	0,50	1,7	1,7	−4	—	—
3e	0,05	0,051	96	4,5	5,7	0,059	16	1	−53	53	56
3e	0,10	0,099	93	1,6	3,5	0,091	10	1	−45	44	44
3e	0,15	0,14	96	1,4	2,4	0,14	6,0	1	−48	36	25
3e	0,26	0,25	95	1,2	1,8	0,24	4,5	1,4	−29	—	—
3e	0,39	0,39	92	0,92	1,6	0,40	2,7	1,8	−14	—	—
3e	0,49	0,47	88	1,2	1,7	0,48	2,3	2,1	−4	—	—

[a] The accuracy of the X_M values is within 3%.

Tab. 3. ^{1}H NMR chemical shifts ($CDCl_3$) of copolymers of ε-caprolactone and morpholine-2,5-dione derivatives (see also Fig. 2)

Copolymer	Chemical shifts δ (in ppm) of depsipeptide units
3a	1,48 (d, J = 6,8 Hz, CH_3), 4,04 (J = 6,4 Hz, CH_2), 5,25 (q, J = 6,8 Hz, CH), 6,7 (br s, NH)
3b	1,45 (m, CH_3 (2×)), 4,56 (m, NHC<u>H</u>), 5,21 (m, OCH), 6,75 (br d, NH)
3c	0,93 (m, $CH(C\underline{H}_3)_2$), 1,47 (m, $OCHC\underline{H}_3$), 2,20 (m, $C\underline{H}(CH_3)_2$), 4,54 (double d, J_1 = 8,8 Hz, J_2 = 4,7 Hz, NHC<u>H</u>), 5,22 (m, OCH), 6,6–6,8 (m, NH)
3d	1,44 (d, J = 7,2 Hz, CH_3), 4,59 (s, CH_2), 4,62 (m, CH), 6,8 (br d, NH)
3e	0,91 (d, J = 7,1 Hz, CH_3), 0,95 (d, J = 7,1 Hz, CH_3), 2,21 (m, $C\underline{H}(CH_3)_2$), 4,55 (t, J = 4,7 Hz, NH(C<u>H</u>), 4,59 and 4,62 (AB_q, J_{AB} = 6,0 Hz, CH_2), 6,7 (br d, NH)
	Chemical shifts δ (in ppm) of ε-oxycaproyl units
3a–e	1,3–1,8 (m, H_r), 2,31 (t, J = 7,4 Hz, H_s), 2,44 (t, J = 7,4 Hz, $H_{s'}$), 4,06 (t, J = 6,6 Hz, H_p), 4,15 (t, J = 6,6 Hz, $H_{p'}$)

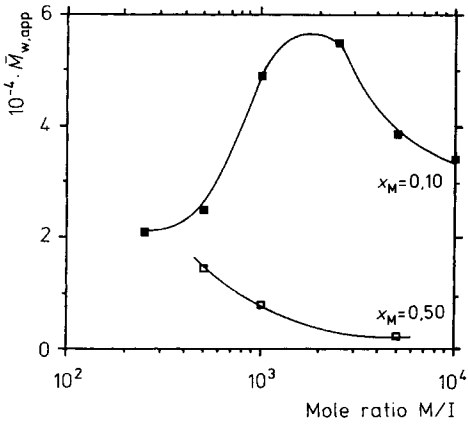


Fig. 1. Apparent weight-average mol. wt. ($\bar{M}_{w,app}$) of copolymers of ε-caprolactone and morpholine-2,5-dione **2a** as a function of the stannous octoate concentration (mole ratio M/I) for two different mole fractions of **2a** in the feed (x_M) of the copolymerization of ε-caprolactone and **2a** (T = 130 °C, t = 48 h)

decreasing initiator concentration. On the other hand, for the x_M = 0,10, the $\bar{M}_{w,app}$ values increase with decreasing initiator concentrations up to a monomer/initiator mole ratio (M/I) of circa 2500, whereafter the $\bar{M}_{w,app}$ values decrease again. For the copolymerization of ε-caprolactone with **2a** (x_M = 0,10), the influence of the reaction time on the conversion of ε-caprolactone, the mole fraction of **2a** in the copolymer, the yield and $\bar{M}_{w,app}$ of the copolymers was investigated. Tab. 4 shows that the optimal reaction time at 130 °C and M/I = 2500 was in between 45 and 60 h. Using these conditions in the copolymerization, the highest conversion, yield and $\bar{M}_{w,app}$ were obtained. The experiments illustrate that optimal reaction conditions are dependent on the molar composition of the feed in the copolymerization. Furthermore, the reaction conditions will also vary with the morpholine-2,5-dione derivative employed in the

Tab. 4. Copolymerization of ε-caprolactone and **2a** (x_M = 0,10) in the bulk at 130 °C using different reaction times; initiator: stannous octoate, mole ratio M/I = 2500 (X_M: mole fraction of morph. der. in the feed, $\bar{M}_{w,app}$: apparent weight-average mol. wt., L_C and L_M: average block length of ε-oxycaproyl units and depsipeptide units)

Time in h	X_M [a]	Conv. of ε-cap. in %	Yield in %	$10^{-4} \cdot \bar{M}_{w,app}$ [b]	L_C [c]	L_M [c]
5,5	0,15	52	41	2,1	6	1,2
11	0,13	81	76	3,7	8	1
29	0,09	100	87	4,7	9	1
45	0,10	100	94	5,0	9	1
53	0,09	100	94	5,7	10	1
60	0,11	100	93	5,5	10	1
70	0,10	100	93	4,8	9	1

[a] Determined by ^{1}H NMR.
[b] Determined by GPC/LALLS.
[c] Determined by ^{13}C NMR.

copolymerization. For each morpholine-2,5-dione derivative and feed composition used in the copolymerization reaction, further optimization of the reaction conditions may be performed to increase the conversion, yields and $\bar{M}_{w,app}$.

Sequence analysis

The sequence analysis of the copolymers prepared from ε-caprolactone and morpholine-2,5-dione derivatives was studied both by ^{1}H and ^{13}C NMR spectroscopy. ^{13}C NMR spectroscopy has been extensively applied for the sequence analysis of polyamides, polyesters and poly(ester-amide)s[5, 11, 12, 19–21]. ^{1}H NMR spectroscopy is less sensitive to sequence effects and has only been reported occasionally as a sequence analysis technique.

In the ^{1}H NMR spectra of the copolymers the α- (s, s') and ε-methylene protons (p, p') of the ε-oxycaproyl moieties showed a diad sensitivity, whereas the β-, γ- and δ-methylene protons (r) were insensitive to sequence effects (Fig. 2 and Tab. 3). The α-methylene protons appeared sensitive to the comonomer unit coupled to the carbonyl group of the ε-oxycaproyl unit (C), whereas they were insensitive to the comonomer unit coupled to the ε-oxygen atom. The triplet s at δ = 2,31 was assigned to the C-C sequence comparing the chemical shift of the α-methylene protons in poly(ε-caprolactone). The depsipeptide unit (M) in the C-M sequence caused a downfield chemical shift on the α-methylene protons s'. The ε-methylene protons of the ε-oxycaproyl unit only showed a sensitivity to the comonomer unit connected to the ε-oxygen atom and were shifted downfield. Analogous to the assignment of the α-methylene proton signals, the ε-methylene proton signals p and p' could be assigned to the C-C and M-C sequence, respectively. In contrast with the α- and ε-methylene protons of the ε-oxycaproyl unit, the α-methylene/methine protons of the depsipeptide units appeared insensitive to sequence effects. The integral ratio of the proton signals p/p' or s/s' was

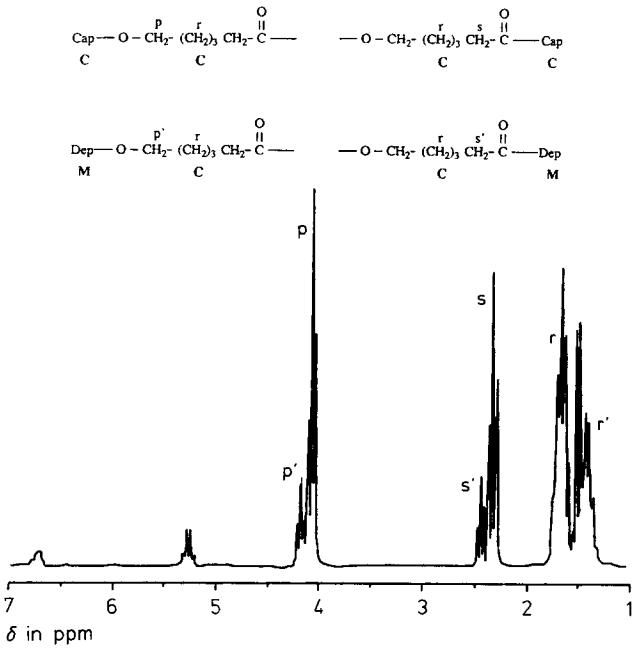


Fig. 2. ^{1}H NMR spectrum ($CDCl_3$) of copolymer **3a** (X_M = 0,24)

equal to the monomer feed composition in all copolymerization reactions performed. This indicates that the copolymers had a random distribution of the ε-oxycaproyl and depsipeptide units. The absence or presence of M-M sequences could not be proven on basis of the ^{1}H NMR data.

^{13}C NMR spectroscopy proved to be a suitable sequence analysis technique. The carbonyl signals in the ^{13}C NMR spectra of the copolymers **3a–c** appeared to be most sensitive to sequence effects, which is consistent with the sequence analysis of polyesters and poly(ester-amide)s reported in the literature. Both amide- and ester carbonyl signals of the depsipeptide units and the ester carbonyl signals of the ε-oxycaproyl units exhibited a triad sensitivity. The use of deuterated trifluoroacetic acid as a solvent in the ^{13}C NMR measurements proved to be advantageous over deuterated chloroform, because a higher resolution of the triad carbonyl signals was obtained.

The assignment of the carbonyl signals of copolymer **3a** will be discussed as an example to illustrate the sequence analysis of the different copolymers **3a–e**. The triad carbonyl peaks of copolymer **3a** (Fig. 3 and Tab. 5) were assigned on the basis of the following chemical and spectroscopic considerations. Previously we showed that the ring-opening polymerization of morpholine-2,5-dione derivatives in the melt using stannous octoate as an initiator proceeds exclusively by cleavage of the ester bond [13]. On the basis of this observation the triads presented in Fig. 3 have to be distinguished. Both the amide and ester carbonyl carbon atoms a–a‴ and b–b‴, respectively, in the sequences M-M-M, C-M-M, M-M-C and C-M-C of the central depsipeptide unit are

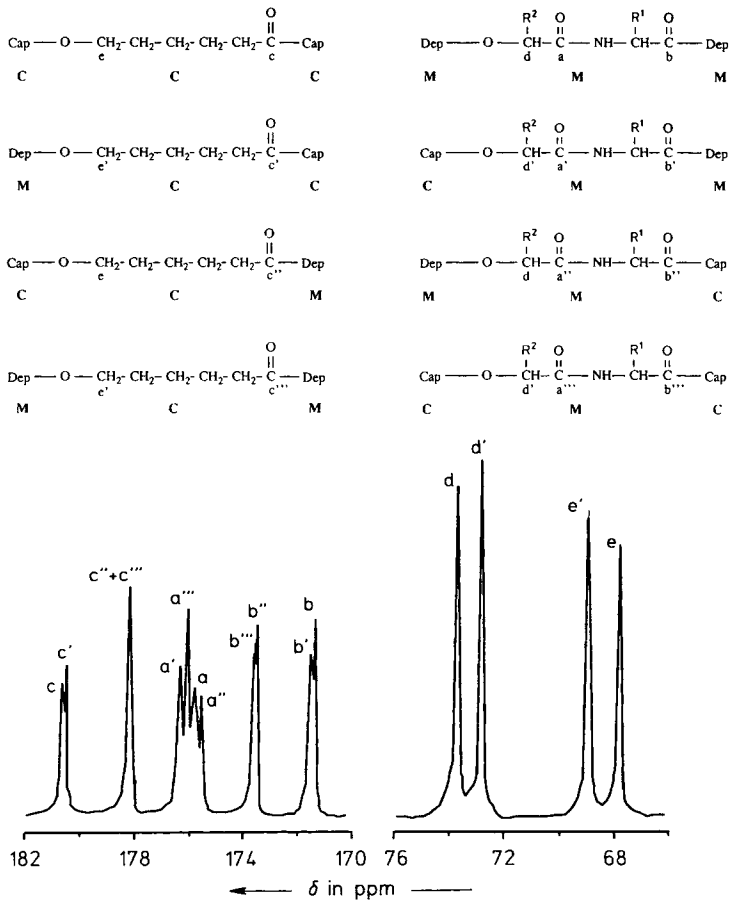


Fig. 3. Expanded ^{13}C NMR spectrum (TFA-d_1) of copolymer **3a** (X_M = 0,52)

considered. The peaks a and b in the M-M-M sequence were assigned on the basis of the chemical shifts of the ester and amide carbonyl carbon atoms found in the ^{13}C NMR spectra of the corresponding alternating polydepsipeptide (poly-(glycine-*alt*-DL-lactic acid)). Copolymers with a small mole fraction of depsipeptide units (X_M < 0,15) only showed peaks a''' and b''' in their ^{13}C NMR spectra. These carbonyl carbon signals were attributed to the C-M-C sequence, because this sequence will predominantly be present in random copolymers with small X_M values. Replacing a depsipeptide unit for an ε-oxycaproyl unit caused a downfield shift on the ester carbonyl carbon atoms of the central depsipeptide units. The downfield shift will be larger in M-M-C (peak b'') than in C-M-M (peak b'), for in the case of M-M-C the ε-oxycaproyl unit is directly bound to the ester carbonyl carbon atom of the central depsipeptide unit. The same effects were observed by Kricheldorf et al. in the sequence analysis of

copolymers of ε-caprolactone and glycolide[5]. Applying the considerations given above to the amide carbonyl carbon signals, peak a' was assigned in the C-M-M sequence and the remaining peak a'' to the M-M-C sequence.

The carbonyl carbon signals of the central ε-oxycaproyl unit in the sequences C-C-C, M-C-C, C-C-M and M-C-M were assigned as follows. Peak c could be assigned to the C-C-C sequence by comparison of the carbonyl chemical shift in poly(ε-caprolactone). In the sequences M-C-C, C-C-M and M-C-M the depsipeptide unit effected an upfield chemical shift on the carbonyl atoms c', c'' and c'''. While the influence of the depsipeptide unit was small on the carbonyl carbon atom c', the upfield chemical shift on c'' and c''' was much larger, because the depsipeptide unit is directly connected to the central ε-oxycaproyl carbonyl carbon atom. Accidently peaks c'' and c''' coincided for copolymer **3a**, whereas they were well resolved in the ^{13}C NMR spectra of the copolymers **3b–e** (Tab. 5).

The amide and ester carbonyl signals of the depsipeptide unit could be assigned for copolymers **3a, 3d** and **3e** on the basis of equal chemical shifts for the carbonyl carbon atoms in the racemic comonomers **2a, 2d** and **2e**. However, the comonomers **2b** and **2c** used in the copolymerization reactions consisted of a mixture of diastereomers. The synthesis of the monomers **2a–e** was performed by the cyclization of the corresponding *N*-(halogenacyl)-amino acids[13]. This method does not control the stereochemistry on the C-6 carbon atom of the morpholine-2,5-dione derivatives and results in the formation of a diastereomeric mixture of (3*S*, 6*R*) and (3*S*, 6*S*) monomers. As a result the ^{13}C NMR spectra of copolymers **3b** and **3c** showed multiple carbonyl signals due to the different shifts of the diastereomeric depsipeptide units, as was also observed in the ^{13}C NMR spectra of the homopolymers derived from the corresponding diastereomeric alternating polydepsipeptide. However, an adequate sequence analysis using the diad splitting of the ε-oxymethylene (OCH_2) carbon signals of the ε-oxycaproyl moieties and the oxymethine or oxymethylene (OCH/OCH_2) carbon signals of the depsipeptide moieties appeared possible.

The OCH_2 carbon signals of the ε-oxycaproyl units and the OCH/OCH_2 carbon signals of the depsipeptide units exhibited a diad sensitivity and were assigned to the possible diads (Fig. 3 and Tab. 5), analogous to the procedure described above to assign the carbonyl signals. According to Fig. 3 the OCH_2 carbon atoms of the ε-oxycaproyl unit in the sequences C-C and M-C are considered. Comparing the OCH_2 carbon chemical shift in poly(ε-caprolactone), peak e was assigned to the C-C sequence. The depsipeptide unit in the M-C sequence caused a downfield chemical shift on the carbon atom e'. Considering the OCH carbon atoms of the depsipeptide units in the sequences M-M and C-M (Fig. 3), peak d was assigned to the M-M sequence by comparison of the OCH carbon chemical shift in the alternating polydepsipeptide. The ε-oxycaproyl unit in the C-M sequence effected an upfield chemical shift on the carbon atom d'. In contrast with the problems encountered in the assignment of the carbonyl signals of the diastereomeric depsipeptide units of the copolymers **3b** and **3c**, the OCH signals were resolved well in the ^{13}C NMR spectra and could be assigned without difficulties. The results of the sequence analysis of copolymers **3a, 3d** and **3e** obtained from the OCH/OCH_2 signals were in good agreement with the results obtained from the carbonyl signals in the ^{13}C NMR spectra.

Tab. 5. ^{13}C NMR chemical shifts (TFA-d_1) used for the sequence analysis of copolymers of ε-caprolactone and morpholine-2,5-dione derivatives (see also Fig. 3)

Copolymer	Carbon atom and chemical shift δ (in ppm)															
	a	a′	a″	a‴	b	b′	b″	b‴	c	c′	c″	c‴	d	d′	e	e′
3a	176,3	176,6	175,8	176,5	171,9	172,0	174,0	174,1	180,7	180,6	178,4	178,4	73,7	72,8	67,8	68,9
3b	—[a]	—	—	—	—	—	—	—	180,7	180,6	178,8	178,7	74,0	73,1	67,9	69,1
3c	—	—	—	—	—	—	—	—	180,7	180,6	178,8	178,7	74,1	73,0	67,8	68,8
3d	175,1	175,2	176,9	177,0	171,7	171,5	172,3	172,1	180,7	180,6	178,4	178,3	65,0	64,4	67,9	69,1
3e	174,3	174,5	176,1	176,2	171,8	171,9	172,6	172,5	180,7	180,6	178,5	178,4	65,0	64,7	67,9	68,9

[a] Not assigned due to multiple signals in the spectra (see text).

For a true copolymerization, the two crossover steps C-M and M-C must be identical. Considering the carbonyl signals, this implies that the number of sequences C-C-M (or M-C-M) and M-M-C (or C-M-C) must be identical, resulting in equal intensities for the peaks c'' (or c''') and b'' (or b'''), respectively. The same applies to the oxymethylene and oxymethine carbon signals. The intensities of the peaks d' and e' must be equal, because the number of sequences C-M and M-C, respectively, are identical. All ^{13}C NMR spectra of the copolymers synthesized showed this behavior, confirming a true copolymerization.

The average lengths of homogeneous ε-oxycaproyl blocks (L_C) and depsipeptide blocks (L_M) (Tab. 2) were calculated according to Eqs. (1) and (2)[5]:

$$L_C = \frac{I_c + I_{c'}}{I_{c''} + I_{c'''}} + 1 = \frac{I_c}{I_{e'}} + 1 \tag{1}$$

$$L_M = \frac{I_a + I_{a'}}{I_{a''} + I_{a'''}} + 1 = \frac{I_b + I_{b'}}{I_{b''} + I_{b'''}} + 1 = \frac{I_d}{I_{d'}} + 1 \tag{2}$$

where I_n is the intensity of peak n, representing the corresponding sequence. The mole fractions of morpholine-2,5-dione derivative in the copolymer (X_M) determined by ^1H NMR were compared with the molar compositions as calculated by Eq. (3):

$$X_M = \frac{L_M}{L_M + L_C} \tag{3}$$

Tab. 2 shows that the X_M values determined by ^1H NMR and ^{13}C NMR are in good agreement, confirming the interpretation of the ^{13}C NMR spectra.

The influence of the molar composition used in the feed of the copolymerization reactions on the average block lengths in the copolymers is significant. For all copolymers, L_C values decrease and L_M values increase with increasing depsipeptide content. For copolymers with $X_M < 0{,}15$, signals belonging to the M-M sequences were absent in the ^{13}C NMR spectra of the copolymers. Thus $I_a + I_{a'} = I_b + I_{b'} = I_d = 0$, and according to Eq. (2) the L_M values are exactly equal to 1. It is concluded that for $X_M < 0{,}15$ the copolymers are composed of homogeneous blocks of ε-oxycaproyl units, subdivided by single depsipeptide units. Copolymers with $X_M = 0{,}50$ showed L_C and L_M values around 2,0, indicating a random sequence distribution. However, from Tab. 4 it is observed that in the early stage of the copolymerization reaction of ε-caprolactone with **2a** ($x_M = 0{,}10$) X_M exceeds x_M, and, as the reaction proceeded, X_M becomes equal to x_M. This would mean that the copolymer had a heterogeneous blocks length distribution, with shorter ε-oxycaproyl blocks formed at the beginning of the copolymerization and relatively longer ε-oxycaproyl blocks formed at the end of the reaction. However, after the initial stage of the copolymerization reaction the L_M value decreased from 1,2 to 1, implying that M-M sequences which were present at first had completely disappeared after prolonged reaction times. This can only be explained by the occurrence of transesterification reactions during the copolymerization. Transesterification results in a constant redistribution of sequences, finally leading to a homogeneous random copolymer. This suggests that if transesterifi-

cation accompanies the copolymerization of ε-caprolactone and morpholine-2,5-dione derivatives and using different molar compositions, all copolymers have a truly random sequence distribution.

Thermal analysis

The thermal transitions of the copolymer prepared in this study were examined by differential scanning calorimetry (DSC). Copolymerization of ε-caprolactone with increasing amounts of morpholine-2,5-dione comonomers strongly effects the glass transition temperature (T_g), melting temperature (T_m) and heat of fusion (ΔH) of the copolymers (Tab. 2 and Fig. 4). The T_g values of the copolymers increased with increasing mole fraction of morpholine-2,5-dione derivative in the copolymers (X_M). The single T_g values observed in the DSC scans indicate the presence of a continuous amorphous phase. The copolymers exhibited a melting behavior which is typical for

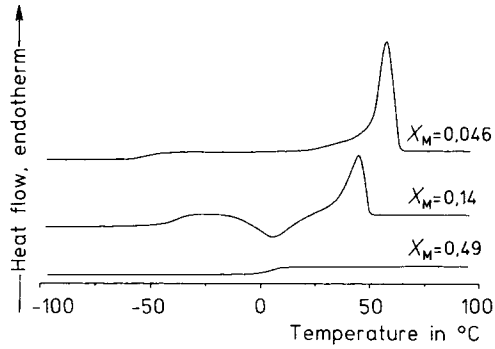


Fig. 4. DSC traces of copolymer **3b** with three different X_M values obtained at a heating rate of 10 °C/min after heating to 110 °C and subsequent cooling to −100 °C at a rate of 10 °C/min

random copolymers in which only one comonomer (ε-oxycaproyl) is able to crystallize. The T_m and ΔH values both decreased with increasing X_M up to $X_M \approx 0{,}15$. For $X_M > 0{,}15$, the copolymers were completely amorphous, as indicated by the absence of melting endotherms in the DSC curves. As illustrated by Fig. 4, copolymers with $X_M \approx 0{,}15$ showed a recrystallization peak prior to the melting peak in the DSC scans. No recrystallization was observed when copolymers with $X_M \approx 0{,}15$ were cooled down from the melt at a lower rate of 2 °C/min and heated again at a rate of 10 °C/min. Obviously, the crystallization of the ε-oxycaproyl blocks becomes more difficult with increasing X_M.

The results of the DSC measurements are in good agreement with the results obtained from the sequence analysis by ^{13}C NMR. With increasing X_M the average block length of ε-oxycaproyl units (L_C) decreases, resulting in a decreasing T_m and ΔH. For $X_M > 0{,}15$, L_C becomes too small to allow the crystallization of ε-oxycaproyl blocks. Both the sequence analysis and DSC measurements revealed that the copolymers investigated were truly random copolymers.

As has been described above, copolymerization of ε-caprolactone with increasing amounts of morpholine-2,5-dione comonomers caused a decrease in T_m values. The

melting point depression for random AB copolymers with A units which are able to crystallize and B units which cannot crystallize and are rejected from the crystal can be described by the Flory equation[22] (Eq. (4)) or by the equation derived by Baur[23] (Eq. (5)):

$$\frac{1}{T_m} - \frac{1}{T_m^0} = \frac{-R}{\Delta H_m} \ln x \tag{4}$$

$$\frac{1}{T_m} - \frac{1}{T_m^0} = \frac{-R}{\Delta H_m} \left(\ln x - \frac{1}{L} \right) \tag{5}$$

where T_m is the melting temperature of a random copolymer with mole fraction x of crystallizable comonomer, T_m^0 is the equilibrium melting temperature of an ideal crystal of the corresponding homopolymer of infinite chain length, R is the gas constant and ΔH_m is the molar heat of fusion. In the derivation of the Baur equation it is also assumed that the copolymer melt must be treated as a mixture of sequences of A and B units, each sequence of A units being only able to grow onto crystals of its own length. This assumption leads to an increased lowering of the melting point, as is expressed in Eq. (5) by the term $1/L$, where L is the average sequence length of the A and B units. For a random copolymer, L is equal to $1/(2x(1 - x))$. Fig. 5 shows that there is a close relationship between the melting point depression of the copolymers **3a–e** and the melting point depression according to Eq. (5) ($L = 1/(2x(1 - x))$), whereas the melting point depression predicted by Eq. (4) is too small. Obviously, the depsipeptide units are rejected from the crystals consisting of ε-oxycaproyl units, as might be expected from the dissimilarity in chemical structure between the ε-oxycaproyl and depsipeptide units. These findings are in agreement with the melting point depression reported for copolymers of ε-caprolactone and L-lactide[10].

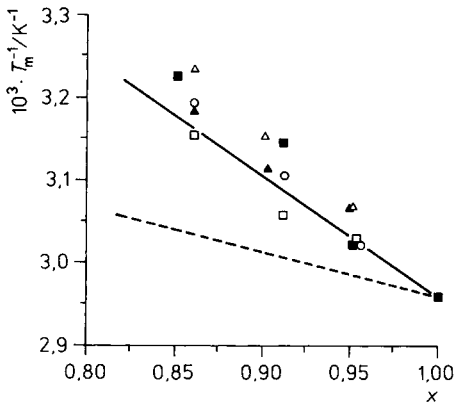


Fig. 5. Melting point (T_m) depression of copolymers **3a** (■), **3b** (□), **3c** (○), **3d** (▲) and **3e** (△) as a function of copolymer composition ($x = 1 - X_M$), and the melting point depression according to Eq. (4) (– – –) and Eq. (5) (———); (ΔH_m = 16,0 kJ/mol[24])

Conclusions

Biodegradable poly(ester-amide)s can be prepared by ring-opening copolymerization of ε-caprolactone and 3- and/or 6-alkyl-substituted morpholine-2,5-dione derivatives. The molecular weights of the copolymers decrease with increasing mole fractions of morpholine-2,5-dione derivatives in the feed of the copolymerizations. Both ^{13}C NMR sequence analysis and DSC measurements show that the copolymers have a random distribution of ε-oxycaproyl and depsipeptide units, which results from the occurrence of transesterification reactions during the copolymerizations. The morphology of the copolymers can be controlled from semi-crystalline to amorphous by increasing the mole fraction of depsipeptide units in the copolymers.

Experimental part

Materials: Reagents were purchased from Merck (Darmstadt, Germany). ε-Caprolactone was distilled under reduced pressure (P = 0,02 mbar, b.p. = 54 °C) and stored in a dry argon atmosphere. Morpholine-2,5-dione derivatives (**2a–e**) were prepared as described previously [13] and purified by repeated recrystallization. Stannous octoate was purchased from Sigma Chem. Corp. (St. Louis, USA). Toluene was dried over molecular sieves (4 Å).

Polymerizations: Polymerization tubes were silanized using trimethylsilyl chloride (20 vol.-% in toluene), followed by repeated washings with toluene and methanol. The tubes were equipped with a stirring bar and dried at 110 °C for 18 h. Subsequently the tubes were cooled to room temperature i. vac. and refilled with dry argon. Totally 20 mmol of ε-caprolactone and the appropriate morpholine-2,5-dione derivative was placed in the tubes. The required amount (50–200 μL) of a freshly prepared solution of stannous octoate in toluene (0,4 mol/L) was added using a glass syringe, to give the desired mole ratio M/I. The solvent was removed by evaporation i. vac. The tubes were refilled with dry argon and sealed with a rubber septum. Thereafter the tubes were purged with dry argon through the rubber septums using stainless steel capillaries. The tubes were placed in an oil bath at the desired reaction temperature, and the homogeneous polymerization mixtures were stirred until the increasing viscosity of the reaction mixtures prevented stirring. After the required reaction time the tubes were removed from the oil bath and allowed to cool to room temperature. The copolymers were isolated by cooling the tubes in liquid nitrogen, breaking the tubes and collecting the products. The crude polymerization products were dissolved in 20 mL of chloroform, filtered and precipitated in 400 mL of diethyl ether or hexane. The copolymers were collected and dried i. vac. at 65 °C for 4 h. Yields of the copolymers varied from 80–95%.

Measurements: ^1H NMR and ^{13}C NMR spectroscopy was performed with a Nicolet NT 200-WB spectrometer. Chloroform-d_1 ($CDCl_3$) and trifluoroacetic acid-d_1 (TFA-d_1) were used as solvents, and tetramethylsilane was used as an internal standard.

The apparent number-average molecular weight ($\bar{M}_{n,app}$) and apparent weight-average molecular weight ($\bar{M}_{w,app}$) of the copolymers were determined by gel-permeation chromatography combined with low-angle laser light scattering (GPC/LALLS). The GPC/LALLS measurements were carried out with chloroform as the eluent (2,0 mL/min) using a Waters 510 pump, a Waters U6K injector, three Waters μStyragel columns (10^5, 10^4 and 10^3 Å) in series, a Waters 411 differential refractometer and a Chromatix KMX-6 LALLS apparatus (λ = 633 nm). The refractive index increments (dn/dc) were measured at 633 nm using a Brice-Phoenix BP-2000-V differential refractometer.

Differential scanning calorimetry (DSC) measurements were performed with a Perkin-Elmer DSC-7 apparatus calibrated with indium and gallium. In order to have a uniform thermal history for all copolymers, the samples were heated to 110 °C and held at this temperature for 5 min. The samples were subsequently cooled at a rate of 10 °C/min to −100 °C. Finally the samples were heated at a rate of 10 °C/min to 110 °C. The thermal transitions (glass transition temperature, melting temperature and heat of fusion) were determined from the last scan.

We wish to thank the *Netherlands Organization for Scientific Research (NWO)* for financially supporting the research.

[1] D. K. Gilding, in *'Biocompatibility of Implant Materials'*, ed. by D. F. Williams, CRC Press, Boca Raton (Florida, USA) 1980, Vol. 2, p. 209
[2] S. J. Holland, B. J. Tighe, P. L. Gould, *J. Controlled Release* **4**, 155 (1986)
[3] D. L. Wise, D. J. Trantolo, R. T. Marino, J. P. Kitchell, *Adv. Drug Delivery Rev.* **1**, 19 (1987)
[4] M. Vert, *Angew. Makromol. Chem.* **166/167**, 155 (1989)
[5] H. R. Kricheldorf, T. Mang, J. M. Jonté, *Macromolecules* **17**, 2173 (1984)
[6] A. S. Sawhney, J. A. Hubbell, *J. Biomed. Mater. Res.* **24**, 1397 (1990)
[7] A. Schindler, R. Jeffcoat, G. L. Kimmel, C. G. Pitt, M. E. Wall, R. Zweidinger, in *'Contemporary Topics in Polymer Science'*, ed. by E. M. Pierce and J. R. Schaefgen, Plenum, New York 1977, p. 251
[8] C. G. Pitt, A. R. Jeffcoat, R. A. Zweidinger, A. Schindler, *J. Biomed. Mater. Res.* **13**, 497 (1979)
[9] X. D. Feng, C. X. Song, W. Y. Chen, *J. Polym. Sci., Polym. Lett. Ed.* **21**, 593 (1983)
[10] J. M. Vion, R. Jérôme, P. Teyssié, M. Aubin, R. E. Prud'homme, *Macromolecules* **19**, 1828 (1986)
[11] H. R. Kricheldorf, J. M. Jonté, M. Berl, *Makromol. Chem., Suppl.* **12**, 25 (1985)
[12] H. Fukuzaki, M. Yoshida, M. Asano, M. Kamakura, T. Mashimo, H. Yuasa, K. Imai, H. Yamanaka, *Polymer* **31**, 2006 (1990)
[13] P. J. A. in't Veld, P. J. Dijkstra, J. H. van Lochem, J. Feijen, *Makromol. Chem.* **191**, 1813 (1990)
[14] J. Helder, S. J. Lee, S. W. Kim, J. Feijen, *Makromol. Chem., Rapid Commun.* **7**, 193 (1986)
[15] J. Helder, P. J. Dijkstra, J. Feijen, *J. Biomed. Mater. Res.* **24**, 1005 (1990)
[16] H. Komoto, *Makromol. Chem.* **115**, 33 (1968)
[17] I. Goodman, A. Valavanidis, *Eur. Polym. J.* **20**, 241 (1984)
[18] I. Goodman, R. N. Vachon, *Eur. Polym. J.* **20**, 529 (1984)
[19] H. R. Kricheldorf, J. Kaschig, *Eur. Polym.* **14**, 923 (1978)
[20] H. R. Kricheldorf, B. Coutin, H. Sekiguchi, *J. Polym. Sci., Polym. Chem. Ed.* **20**, 2353 (1982)
[21] H. R. Kricheldorf, T. Mang, J. M. Jonté, *Makromol. Chem.* **186**, 955 (1985)
[22] P. J. Flory, *Trans. Faraday Soc.* **51**, 848 (1955)
[23] H. Baur, *Makromol. Chem.* **98**, 297 (1966)
[24] V. Crescenzi, G. Manzini, G. Calzolari, C. Borri, *Eur. Polym. J.* **8**, 449 (1972)