Synthesis of biodegradable polyesteramides with pendant functional groups

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SUMMARY:

Morpholine-2,5-dione derivatives having substituents with benzyl-protected carboxylic acid, benzyloxycarbonyl-protected amine and *p*-methoxy-protected thiol groups, respectively, were prepared in 29–58% yield by cyclization of the corresponding *N*-[(2*RS*)-bromopropionyl]-L-amino acids. Polyesteramides with protected pendant functional groups were obtained by ring-opening copolymerization of either ε-caprolactone or DL-lactide with morpholine-2,5-dione derivatives having protected functional substituents. The copolymerizations were carried out in the bulk at 130 °C using stannous octoate as an initiator and using low mole fractions (0,05, 0,10 and 0,20) of morpholine-2,5-dione derivatives in the feed. The molecular weight of the resulting copolymers ranged from 1,4 to $8{,}3 \cdot 10^4$. The ring-opening homopolymerization of morpholine-2,5-dione derivatives with protected functional substituents was not successful. Polyesteramides with either pendant carboxylic acid groups or pendant amine groups were prepared by catalytic hydrogenation of the corresponding protected copolymers. Treatment of copolymers having pendant *p*-methoxybenzyl-protected thiol groups with trifluoromethanesulfonic acid resulted not only in the removal of the *p*-methoxybenzyl group but also in severe degradation of the copolymers, due to acidolysis of main-chain ester bonds.

Introduction

Synthetic biodegradable polymers are important for the development of temporary surgical and pharmaceutical devices like sutures, absorbable bone plates and devices for the controlled release of drugs[1–4]. For each of these applications different material properties are required. Therefore, biodegradable polymers with a variation in hydrophilicity/hydrophobicity, permeability, morphology, degradation rates and mechanical properties are needed. Suitable material properties may be achieved by copolymerization, functionalization, crosslinking, blending and polymer processing conditions.

An important limitation in the use of degradable polymers for biomedical applications is the possible toxicity of the degradations products. Therefore, research towards biodegradable polymers is mainly focussed on materials composed of building blocks which already occur in the human body. Poly(α-hydroxy acid)s like poly(lactic acid) and poly(glycolic acid) are well known examples of biodegradable polyesters[1,3]. Poly(α-amino acid)s have been investigated for possible use in a wide variety of biomedical applications, e. g., for artificial skin substitutes, hemodialysis membranes, but especially as drug delivery systems[5–7].

Several investigations on the design of drug carrier systems consisting of a polyester backbone with pendant functional groups to which drugs can be covalently attached have been reported[8–15]. Furthermore the functionalization of polyesters by the

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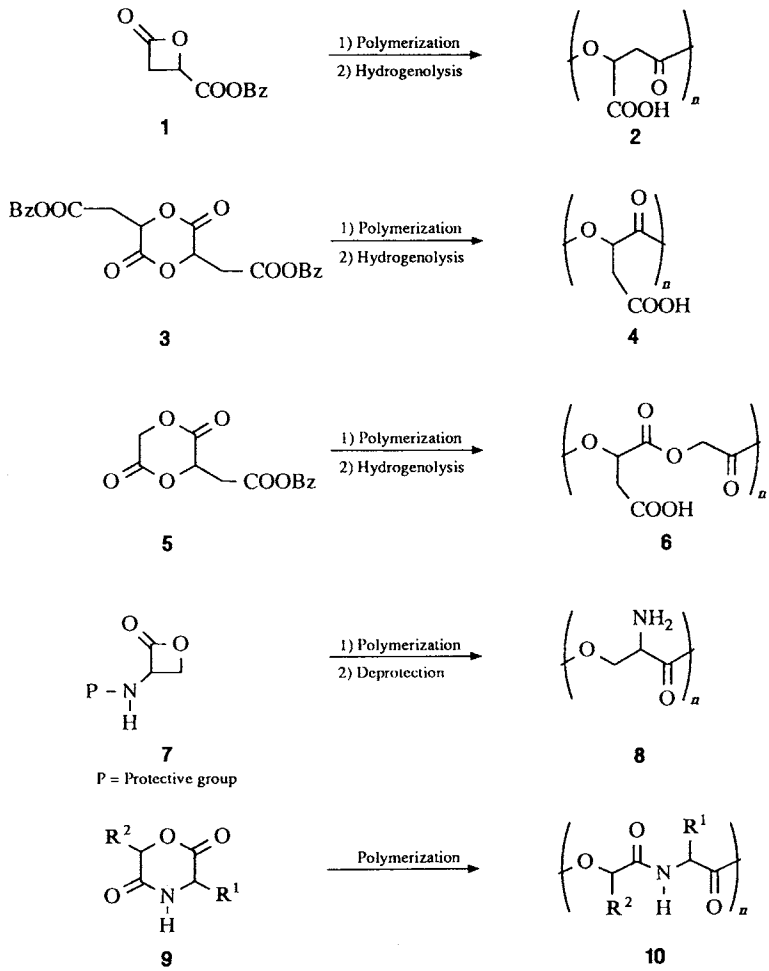
introduction of pendant carboxylic acid groups may be used in the development of so-called "self-destroying polymers". It may be expected that these modified polyesters will show an increased degradation rate due to the catalytic effect of the pendant carboxylic acid groups on the hydrolytic scission of the ester bonds[3, 16, 17].

Up to now a limited number of polyesters containing pendant carboxylic acid groups have been synthesized. Vert et al.[8-10] and Lenz et al.[8, 10, 11] prepared poly(β-malic acid) (**2**) (*Scheme 1*) by ring-opening polymerization of benzyl malolactonate (**1**) and subsequent hydrogenolytic debenzylation of the intermediate polymer. Copolymers of β-malic acid and α-alkyl esters of β-malic acid have been reported by Arnold and Lenz[11].

Scheme 1. Synthesis of biodegradable polymers with pendant functional groups



Poly(α-malic acid) (**4**), which can be regarded as a functionalized analogue of poly(lactic acid), has been prepared by Ouchi and Fujino [12] by ring-opening polymerization of malide dibenzyl ester (**3**) and subsequent debenzylation. Analogously, Kimura et al. [13] prepared poly(α-malic acid-*alt*-glycolic acid) (**6**) from the cyclic monomer **5**.

Recently the synthesis of poly(L-serine ester) (**8**) has been described. This polyester contains pendant amine groups and is a structural analogue of the polyamide poly(L-serine). Such structural analogues of poly(α-amino acid)s have now been termed pseudopoly(α-amino acid)s. Zhou and Kohn [14] and Fiétier et al. [15] synthesized poly(L-serine ester) by ring-opening polymerization of *N*-protected L-serine β-lactones **7**, followed by removal of the *N*-protective group.

Previously we reported on the synthesis of alternating polydepsipeptides **10** (copolymers of α-hydroxy and α-amino acids) by ring-opening polymerization of morpholine-2,5-dione derivatives **9** which had different alkyl substituents R^1 and R^2 [18–20]. Copolymerization of morpholine-2,5-dione derivatives with DL-lactic acid [21] or ε-caprolactone [22] provided a series of biodegradable polyesteramides with a wide range of chemical and physical properties. Based on these results, the ring-opening (co)polymerization of morpholine-2,5-dione derivatives with pendant functional groups was considered. The use of trifunctional α-amino acids like L-aspartic acid, L-lysine and L-cysteine in the synthesis of morpholine-2,5-dione derivatives offers a synthetic route to biodegradable polymers with pendant carboxylic acid, amine and thiol groups, respectively. Different α-amino acid residues with protected side-chain functional groups can be incorporated into morpholine-2,5-dione derivatives, which can be ring-opening (co)polymerized, followed by deprotection of the pendant functional groups.

In this paper the synthesis of morpholine-2,5-dione derivatives **9**, in which R^1 is a protected side-chain carboxylic acid, amine or thiol group, will be reported. The ring-opening homopolymerization as well as the ring-opening copolymerization of these morpholine-2,5-dione derivatives with DL-lactide or ε-caprolactone and the deprotection of pendant protected functional groups of the intermediate copolymers will be discussed.

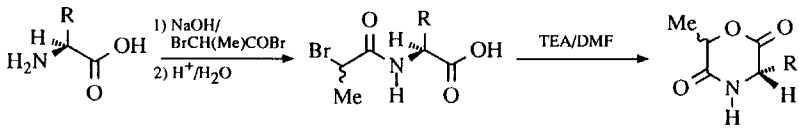
Results and discussion

Monomer synthesis

The synthesis of morpholine-2,5-dione derivatives with functional substituents **13a–c** is outlined in *Scheme 2*. To avoid side reactions at the pendant functional groups of the trifunctional amino acid residues, these groups had to be temporarily blocked by protective groups which are stable to the projected reactions outlined in *Scheme 2*. Moreover, the protective groups have to be stable during the reaction conditions used in the polymerization reaction of the morpholine-2,5-dione derivatives **13a–c**. Subsequently the protective groups must be selectively removed without cleavage of ester and/or amide bonds of the polymer main chains. Previously the benzyl ester group has been successfully employed in the preparation of homo- and copolymers

based on malic acid[8-13]. The protective group could easily be removed by catalytic hydrogenolysis. Therefore, the benzyl group was selected as a protective group for the β-carboxylic acid function of L-aspartic acid (**11a**). The ε-amine group of L-lysine was protected by the benzyloxycarbonyl group. On the basis of literature data it was expected that the benzyloxycarbonyl group could be selectively removed by catalytic hydrogenation[23]. The selection of a suitable protective group for the thiol group of L-cysteine proved to be less straightforward. Although many protective groups for the thiol group are known in the literature[23], only the *p*-methoxybenzyl group appeared to be suitable, because most thiol protective groups either are not stable to strong basic and/or strong acidic reaction conditions (*Scheme 2*), or they require deprotection conditions which might cause ester and/or amide bond cleavage in the polymer main chain. The *p*-methoxybenzyl group can be removed by treatment with trifluoromethanesulfonic acid[24].

Scheme 2. Synthesis of morpholine-2,5-dione derivatives with functional substituents



11a-c **12a-c** **13a-c**

a R = CH_2-COO-Bz Bz = benzyl

b R = $(CH_2)_4$-NH-Z Z = benzyloxycarbonyl

c R = CH_2-S-MBz MBz = *p*-methoxybenzyl

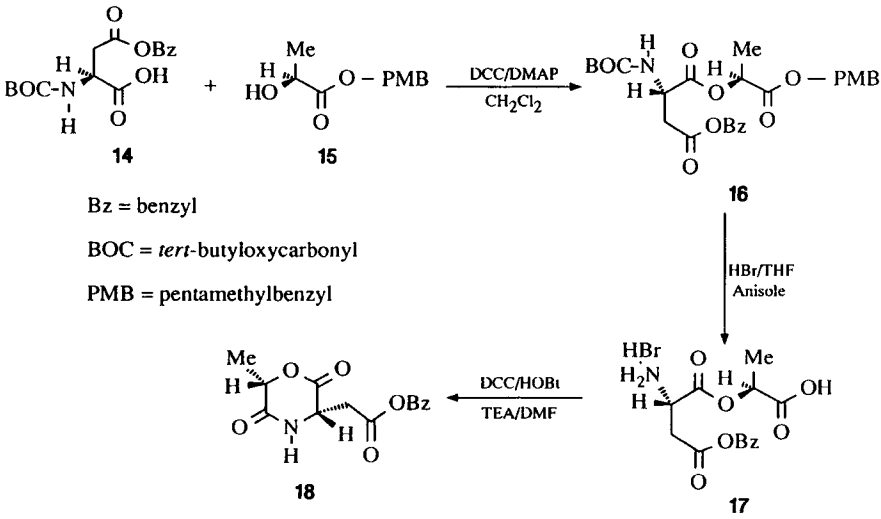
Reaction of the side-chain-protected trifunctional amino acids **11a–c** with (2*RS*)-bromopropionyl bromide under Schotten-Bauman conditions[25] afforded the *N*-[(2*RS*)-bromopropionyl]amino acids **12a–c** in 54–60% yields. The conventional Schotten-Bauman procedure was slightly modified by the addition of *p*-dioxane to the reaction mixture, in order to dissolve the sodium salts of **11a–c** and **12a–c** present in the reaction mixture.

Previously we reported on the synthesis of several (3- and) 6-alkyl substituted morpholine-2,5-dione derivatives[20]. These monomers were prepared in 23–83% yields by dry heating i. vac. of *N*-(2-halogenoacyl)amino acid sodium salts on a matrix of Celite, whereupon the morpholine-2,5-dione derivatives sublimed from the reaction mixture. When the synthesis of these alkyl-substituted morpholine-2,5-dione derivatives was accomplished by reaction of *N*-(2-halogenoacyl)-amino acids with triethylamine (TEA) in *N,N*-dimethylformamide (DMF) at 100 °C, generally lower yields (3–34%) were obtained. Therefore, initially the synthesis of morpholine-2,5-dione derivative **13a** was investigated by dry heating of the sodium salt of **12a** on a matrix of Celite

i. vac. at temperatures ranging from 100 to 150 °C. Although the monomer **13a** was formed, as was shown by ^{1}H NMR and TLC analysis of the reaction mixture, it was not possible to sublime the compound from the reaction mixture. Consequently, the desired product had to be extracted from the reaction mixture. However, the crude product obtained was contaminated with side products, which could not be removed by recrystallization or column chromatography (SiO_2, ethyl acetate/hexane (vol. ratio 1 : 2)). Most probably the side products resulted from reactions at the protective benzyl ester group of the sodium salt of **12a** during the dry heating procedure. The difficulties encountered in the synthesis of morpholine-2,5-dione derivative **13a** made further attempts to prepare monomers **13b** and **13c** by the same method less attractive and prompted us to investigate the cyclization of **12a–c** by reaction with TEA and DMF as an alternative method.

Morpholine-2,5-dione derivatives **13a** and **13b** were obtained in 55 and 38% yield, respectively, by the reaction of *N*-[(2*RS*)-bromopropionyl]amino acids **12a** and **12b** with TEA in DMF for 3 h at 100 °C[26]. Treatment of *N*-[(2*RS*)-bromopropionyl]amino acid **12c** with TEA in DMF using the same reaction conditions resulted in low yields of **13c** and the formation of several side products. The formation of side products might be due to partial deprotection of the thiol group, caused by the relatively high reaction temperatures employed. When the reaction was repeated at lower reaction temperatures and prolonged reaction times, the formation of side products could be depressed and higher yields of **13c** were obtained. Morpholine-2,5-dione derivative **13c** was eventually prepared in 29% yield by reaction of **12c** with TEA in DMF for 18 h at room temperature.

Scheme 3. Synthetic strategy used in the preparation of optically pure morpholine-2,5-dione derivative **18**, composed of a β-benzyl-protected L-aspartic acid residue and a L-lactic acid residue



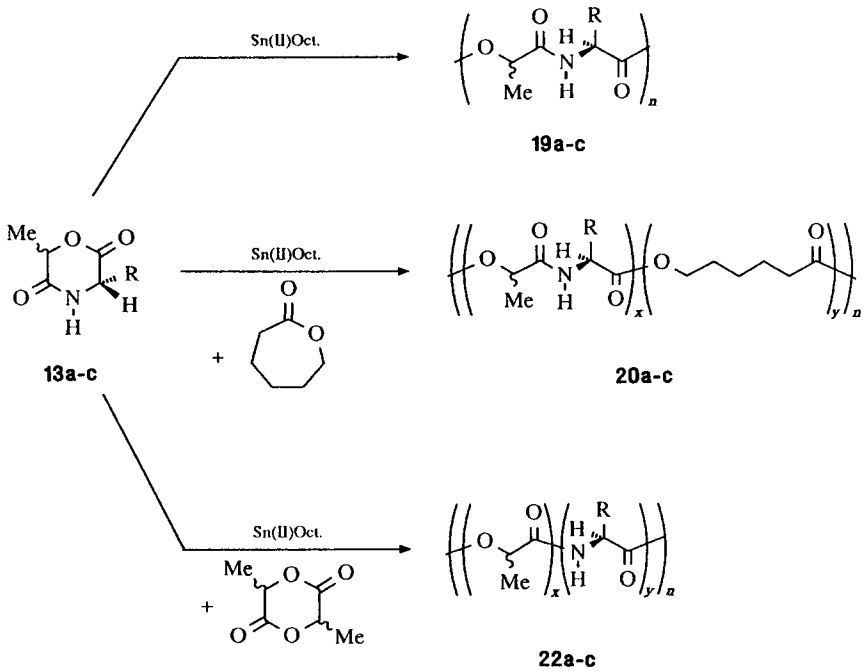
The treatment of the *N*-[(2*RS*)-bromopropionyl]amino acids **12a–c** with TEA in DMF afforded the morpholine-2,5-dione derivatives **13a–c** as mixtures of (3*S*, 6*R*) and (3*S*, 6*S*) diastereomers. The diastereomers could neither be separated by repeated recrystallization nor by column chromatography. In order to prepare the pure (3*S*, 6*S*) diastereomer of morpholine-2,5-dione derivative **13a**, the synthetic route as presented in *Scheme 3* was investigated. In contrast to the preparation of morpholine-2,5-dione derivatives **13a–c** by ring-closure at the ester bond (*Scheme 2*), the synthetic strategy outlined in *Scheme 3* utilizes ring-closure at the amide bond. The synthesis of the optically pure morpholine-2,5-dione derivative **18** was accomplished using protection-deprotection procedures commonly applied in peptide chemistry. *β*-Benzyl *N*-(*tert*-butoxycarbonyl)-L-asparate (**14**) was coupled with L-lactic acid pentamethylbenzyl ester (**15**) using *N,N'*-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in dichloromethane to afford the protected aminoacyl hydroxy acid **16** in 90% yield. The protective *tert*-butoxycarbonyl and pentamethylbenzyl groups were both removed by treatment of **16** with HBr in the presence of anisole, which functioned as a scavenger for the pentamethylbenzyl carbocations formed. Reaction of **17** with 1-hydroxybenzotriazole (HOBt) and DCC in the presence of TEA gave the optically pure morpholine-2,5-dione derivative **18** in 8% yield, based on **16**. Compared to the preparation of morpholine-2,5-dione derivative **13a** from **11a** by cyclization at the ester bond (30% overall yield), the synthesis of morpholine-2,5-dione derivative **18** by ring-closure at the amide bond required a larger number of reaction steps and resulted in a lower overall yield (7%).

Polymer synthesis

The reaction conditions used in the ring-opening (co)polymerization of morpholine-2,5-dione derivatives **13a–c** were selected on the basis of earlier work on the ring-opening polymerization of 3- and/or 6-alkyl-substituted morpholine-2,5-dione derivatives (**9**) and the copolymerization of these monomers with DL-lactide or *ε*-caprolactone[18,22]. The homopolymerization of monomers **13a–c** (*Scheme 4*) and the copolymerization with *ε*-caprolactone or DL-lactide was carried out in the bulk at 130 °C for 48 h using tin bis(2-ethylhexanoate) (stannous octoate) as an initiator (mole ratio M/I = 1000). The results of the ring-opening (co)polymerizations are summarized in Tab. 1.

The ring-opening homopolymerization of monomers **13a–c** resulted in the formation of the corresponding alternating polydepsipeptides **19a–c**, as was shown by the shift of the methyl proton signals of the lactic acid residue of the morpholine-2,5-dione derivatives from δ = 1,6 to δ = 1,4 ($CDCl_3$). Previously this upfield shift was also found for the methyl protons of the lactic acid residue present in polydepsipeptides[20]. However, the monomer conversions were low (36–57%). Attempts to isolate the polymers by dissolving the crude reaction mixture in chloroform and precipitation of the polymers from the resulting solution in diethyl ether/hexane failed. Apparently, the reactivity of the morpholine-2,5-dione derivatives is low,

Scheme 4. Synthesis of biodegradable polyesteramides with pendant functional groups



13, 19, 20, 22a: R = CH_2-COO-Bz

b: R = $(CH_2)_4$-NH-Z

c: R = CH_2-S-MBz

20a $\xrightarrow{i}$ **21a** R = CH_2-COOH

20b $\xrightarrow{i}$ **21b** R = $(CH_2)_4$-NH_2

20c $\xrightarrow{ii}$ **21c** R = CH_2-SH

22a $\xrightarrow{i}$ **23a** R = CH_2-COOH

22b $\xrightarrow{i}$ **23b** R = $(CH_2)_4$-NH_2

22c $\xrightarrow{ii}$ **23c** R = CH_2-SH

(i) H_2/Pd-C, ethyl acetate/methanol

(ii) CF_3SO_3H, TFA/anisole

resulting in relatively low monomer conversions and oligomeric products. These results are consistent with earlier reported observations, which showed that the reactivity of 3- and/or 6-alkyl-substituted morpholine-2,5-dione derivatives (**9**) decreases with increasing number and size of the alkyl substituents using the same reaction conditions[20]. This decrease in reactivity can be attributed to an increase in steric

Tab. 1. Results of the homopolymerization of morpholine-2,5-dione derivatives **13a–c** (**19a–c**) and their copolymerization with either ε-caprolactone (**20a–c**) or DL-lactide (**22a–c**). Polymerizations were carried out in the bulk at 130 °C using stannous octoate as an initiator, mole ratio M/I = 1 000, reaction time 48 h (x_M: mole fraction morph. der. in the feed, X_M: mole fraction morph. der. in copolymer, $\bar{M}_{n,app}$ and $\bar{M}_{w,app}$: apparent number-average and weight-average mol. wt., respectively, n.d.: not determined)

Polymer	^{1}H NMR			Yield in %	GPC	
	x_M	X_M	conv. of depsipeptide in %		$10^{-4} \cdot \bar{M}_{n,app}$	$10^{-4} \cdot \bar{M}_{w,app}$
19a	1	1	56	0	—	—
19b	1	1	57	0	—	—
19c	1	1	36	0	—	—
20a	0,20	0,18	96	85	1,1	2,5
20a	0,10	0,084	98	81	2,4	8,3
20b	0,20	0,17	85	91	0,76	2,0
20b	0,10	0,073	76	82	2,0	4,9
20c	0,20	n.d.	62	0	—	—
20c	0,10	0,088	96	70	1,3	2,5
20c	0,05	0,047	98	79	1,9	3,6
22a	0,20	0,15	75	65	1,4	3,9
22a	0,10	0,087	90	73	3,1	8,7
22b	0,20	0,13	81	39	0,54	1,4
22b	0,10	0,067	90	47	1,0	2,3
22c	0,20	n.d.	58	0	—	—
22c	0,10	0,051	74	47	2,1	4,6

hindrance and stability of the ring structure with an increase in the number and size of ring substituents[27]. Moreover, the introduction of an additional functional group in the morpholine-2,5-dione derivatives may result in an additional reduction of the reactivity, caused by an interaction between the stannous octoate and the pendant functional group. This interaction may cause side reactions at the pendant functional groups, resulting in removal of the protective group and the formation of branched polymers. However, in the ^{1}H NMR and ^{13}C NMR spectra of the crude reaction products no additional signals indicating the occurrence of side reactions at the pendant functional groups of both the monomers and polymers could be detected.

Because of the much lower overall yields in the synthesis of the optically pure morpholine-2,5-dione derivative **18** and the low monomer conversions observed in the polymerization of **13a–c**, the homopolymerization of **18** was not considered.

It was expected that, due to the observed low reactivities of the morpholine-2,5-dione derivatives, large mole fractions of these monomers in the copolymerization with other lactones would result in low monomer conversions and the formation of low-molecular-weight copolymers. Therefore, the ring-opening copolymerization of **13a–c** with either ε-caprolactone or DL-lactide was performed with relatively small mole fractions of morpholine-2,5-dione derivatives in the feed of the polymerization reac-

tion (x_M = 0,05, 0,10 and 0,20). The conversions of the morpholine-2,5-dione derivatives ranged from 74 to 98%, considerably higher as found in the homopolymerizations (Tab. 1). As expected, morpholine-2,5-dione derivative conversions and the apparent molecular weights of the copolymers **20a–c** and **22a–c** decreased with increasing x_M values. The mole fractions of depsipeptide units in the copolymers (X_M) are lower than the mole fractions of morpholine-2,5-dione derivatives in the feed of the copolymerization (x_M). In all copolymerization reactions the ε-caprolactone and DL-lactide conversions are over 98%. However, one exception has to be made for the copolymerization of **13c** and ε-caprolactone or DL-lactide with x_M = 0,20. In this case the conversions of the morpholine-2,5-dione derivative (58–62%), ε-caprolactone (90%) and DL-lactide (92%) are lower, and only oligomeric products were formed.

Copolymers **20a–c** and **22a–c** were analyzed by ^{1}H NMR and ^{13}C NMR, in order to determine to which extent the protective groups of the pendant functional groups were preserved during the copolymerization reactions. Because the spectra of the copolymers showed no additional signals, it was concluded that the copolymerization of morpholine-2,5-dione derivatives **13a–c** with either ε-caprolactone or DL-lactide proceeded without side reactions at the pendant functional groups.

Recently we reported on the ^{13}C NMR sequence analysis of copolymers of morpholine-2,5-dione derivatives with alkyl substituents and ε-caprolactone using the carbonyl carbon (CO) signals (triads) and methine/methylene carbon (OCH/OCH_2) signals (triads) of the possible sequences[22]. It was shown that these copolymers consisted of randomly distributed depsipeptide and ε-oxycaproyl units. Analogously, copolymers **20a–c** obtained by copolymerization of morpholine-2,5-dione derivatives **13a–c** and ε-caprolactone with x_M = 0,10 were analyzed by ^{13}C NMR sequence analysis. We compared the OCH/OCH_2 signals of copolymers **20a–c** with the corresponding signals of the copolymers of morpholine-2,5-dione derivatives with alkyl substituents and ε-caprolactone[22]. The OCH signals at δ =72,8 (TFA-d_1) belonging to the depsipeptide unit (M) in the M—C sequence (C = ε-oxycaproyl unit) were present, while the OCH signals at δ = 73,7 originating from the M—M sequence were absent. In addition, the OCH_2 signals at δ = 67,8 and δ = 69,3 resulting from the ε-oxycaproyl unit in the C—C and C—M sequences, respectively, were present. These results indicate that copolymers **20a–c** with x_M = 0,10 consist of blocks of ε-oxycaproyl units subdivided by single depsipeptide units. Determination of the sequence distribution of DL-lactyl units and peptide units in copolymers **22a–c** was not possible, because multiple CO and OCH signals were present in the ^{13}C NMR spectra. The multiple CO and OCH signals are due to the presence of both D and L enantiomeric forms of the lactic acid residues in copolymers **22a–c**.

The benzyl protective groups of copolymers **20a** and **22a** and the benzyloxycarbonyl protective groups of copolymers **20b** and **22b** were removed by catalytic hydrogenation using palladium/carbon as a catalyst. ^{1}H NMR analysis of the resulting copolymers **21a, 21b** (Fig. 1), **23a** and **23b** demonstrated the complete removal of the protecting groups, by the absence of the proton signals of the benzyl group at δ = 5,10, 5,12 and 7,34 ($CDCl_3$). The X_M values and the apparent molecular weights of the deprotected copolymers (Tab. 2) are somewhat lower compared to the values of the corresponding protected copolymers (Tab. 1). The catalytic hydrogenation thus appeared a selective

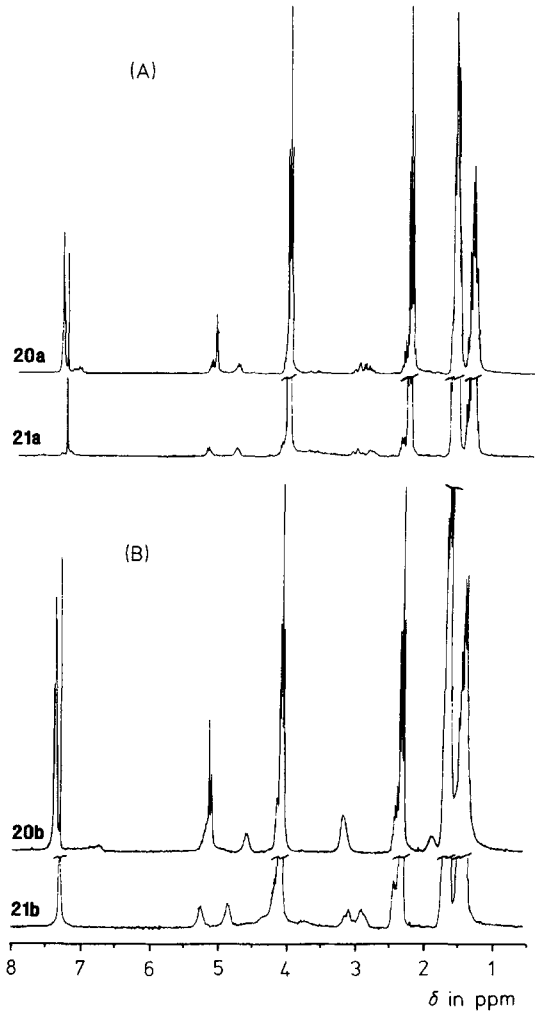


Fig. 1. ^{1}H NMR spectra ($CDCl_3$) of copolymers before and after hydrogenolysis; (A): **20a** (X_M = 0,084) and **21a** (X_M = 0,081), (B): **20b** (X_M = 0,17) and **21b** (X_M = 0,16)

and facile method to remove the pendant benzyl and benzyloxycarbonyl protective groups present in copolymers **20a–b** and **22a–b**.

Treatment of copolymers **20c** and **22c** with trifluoromethanesulfonic acid and anisole in trifluoroacetic acid (TFA)[24] for 5 min at room temperature resulted in the quantitative removal of the *p*-methoxybenzyl protective groups. The proton signals of the *p*-methoxybenzyl group at δ = 3,68, 3,72, 3,79, 3,84 and 7,23 ($CDCl_3$) as observed in the ^{1}H NMR spectra of **20c** and **22c** were absent in the ^{1}H NMR spectra of the corresponding deprotected copolymers **21c** and **23c** (Fig. 2). However, the deprotection reaction gave very low yields (5–8%) for copolymer **21c** and moderate yields (59%) for copolymer **23c**. In addition, the apparent molecular weights of the

Tab. 2. Characterization of copolymers after deprotection (for explanation see Tab. 1, T_g: glass transition temperature, T_m: melting temperature)

Polymer	^{1}H NMR X_M	Yield in %	GPC		DSC	
			$10^{-4} \cdot \bar{M}_{n,app}$	$10^{-4} \cdot \bar{M}_{w,app}$	T_g °C	T_m °C
21a	0,16	85	0,49	1,2	−26	41
21a	0,081	92	2,0	6,4	−30	50
21b	0,16	86	0,44	1,6	−21	41
21b	0,073	89	1,3	3,5	−32	52
21c	0,060	5	0,47	1,2	n.d.	n.d.
21c	0,021	8	0,89	2,3	−43	67
23a	0,11	81	0,90	2,1	51	—
23a	0,081	85	2,1	4,5	52	—
23b	0,12	85	0,62	1,3	43	—
23b	0,065	88	0,92	2,7	48	—
23c	0,049	59	1,1	2,2	49	—

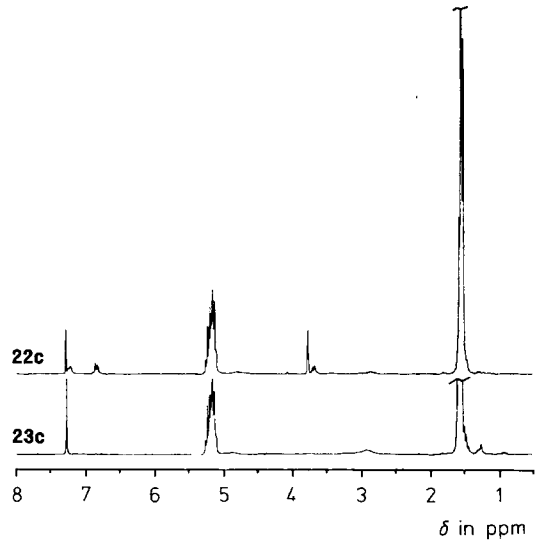


Fig. 2. ^{1}H NMR spectra ($CDCl_3$) of copolymer **22c** (X_M = 0,051) before and after trifluoromethanesulfonic acid treatment (=copolymer **23c** (X_M = 0,049))

deprotected copolymers (Tab. 2) were considerably lower than those of the corresponding protected copolymers. It appeared that the removal of the *p*-methoxybenzyl groups was accompanied by severe degradation of the polymers, which is most probably caused by acidolysis of the main-chain ester bonds by trifluoromethanesulfonic acid and trifluoroacetic acid (TFA).

The thermal transitions of the deprotected copolymers were determined by differential scanning calorimetry (DSC) (Tab. 2). Copolymers **21a–c** have glass transition temperatures (T_g) ranging from −32 to −21 °C and melting temperatures (T_m) ranging from 41 to 67 °C. The increase in T_g and the decrease in T_m is in the same order of magnitude as observed for copolymers of (3,6)-alkyl-substituted morpholine-2,5-diones and ε-caprolactone with similar molar compositions[22]. Copolymers of DL-lactic acid and amino acids with pendant functional groups (**23a–c**) have lower T_g values (43–51 °C) compared to poly(DL-lactic acid) (53 °C). This is in contrast to the previously observed increase in T_g for glycine/DL-lactic acid copolymers with regard to the T_g value of poly(DL-lactic acid)[21].

Conclusions

Morpholine-2,5-dione derivatives having substituents with benzyl-protected carboxylic acid, benzyloxycarbonyl-protected amine and *p*-methoxybenzyl-protected thiol groups, respectively, were prepared by reaction of *N*-[(2*RS*)-bromopropionyl]amino acids with TEA and DMF. The ring-opening homopolymerization of morpholine-2,5-dione derivatives with protected functional substituents failed, due to the low reactivity of the monomers. However, these derivatives could be copolymerized with ε-caprolactone and DL-lactide, to give polyesteramides with pendant protected functional groups. The selective removal of the benzyl and benzyloxycarbonyl protective groups by catalytic hydrogenation yielded copolymers with pendant carboxylic acid and amine groups, respectively. The removal of the *p*-methoxybenzyl protective group by treatment with trifluoromethanesulfonic acid was accompanied by severe degradation of the copolymers, which presumably was caused by acidolysis of the main-chain ester bonds.

The present study demonstrates that the copolymerization of morpholine-2,5-dione derivatives with functional substituents and ε-caprolactone or DL-lactide, followed by deprotection of the pendant functional groups of the intermediate copolymers, is a suitable method to prepare biodegradable polyesteramides with pendant carboxylic acid, amine and thiol groups, respectively.

Experimental part

Materials: β-Benzyl L-aspartate, N^{ε}-(benzyloxycarbonyl)-L-lysine, L-cysteine and stannous octoate were purchased from Sigma Chem. Corp. (St. Louis, USA). ε-Caprolactone (Merck, Darmstadt, Germany) was distilled under reduced pressure (P = 0,02 mbar, b.p. = 54 °C) and subsequently stored under a dry argon atmosphere. DL-Lactide (Boehringer Ingelheim, Germany) was recrystallized from dry toluene and dried over P_2O_5 i.vac. before use. Dry toluene and dry tetrahydrofuran (THF) were obtained by distillation from calcium hydride and metallic sodium, respectively, and stored on molecular sieves (4 Å). All other reagents were purchased from Merck and used as received.

Monomer synthesis

β-Benzyl N-[(2RS)-bromopropionyl]-L-aspartate (**12a**): To a cooled suspension (5–10 °C) of β-benzyl-L-aspartate (**11a**) (26,8 g; 0,12 mol) in 250 mL *p*-dioxane/water (1/1 (v/v)) was added 40 mL of a 3 M aqueous NaOH solution. The resulting solution was vigorously stirred and 50 mL

of a *p*-dioxane solution containing 13,8 mL (0,13 mol) of (2*RS*)-bromopropionyl bromide was added in 5-mL portions, simultaneously with ten portions of 10 mL of a 0,14 M aqueous NaOH solution, while maintaining the reaction temperature at 0 ± 1 °C by cooling with an ice/salt mixture. After the addition was completed the reaction mixture was stirred for another 5 min, whereafter the mixture was acidified to pH 2 with 20 mL of a concentrated HCl solution. The mixture was extracted with two 200-mL portions of diethyl ether. The combined organic layers were washed with a saturated aqueous NaCl solution, dried ($MgSO_4$) and concentrated i. vac. The crude product was recrystallized from toluene/hexane to give 23,2 g (54%) of **12a**. M. p. 120,5–122 °C, $[\alpha]_D^{25} = 46°$ (c = 0,2 g/dL in chloroform).

^{1}H NMR ($CDCl_3$): δ = 1,84 and 1,89 (two d, J = 7,1 Hz, 3H, CH_3), 2,89–3,18 (m, 2H, CH_2COOBz), 4,40 and 4,43 (two q, J = 7,1 Hz, 1H, BrCH), 4,88 (m, 1H, NHCH), 5,14 (s, 2H, CH_2Ph), 7,33 (s, 5H, Ph), 7,43 and 7,48 (two d, J = 8,2 Hz, 1H, NH), 10,70 (br s, 1H, COOH).

$C_{14}H_{16}BrNO_5$ (358,19)	Calc.	C 46,95	H 4,50	N 3,91
	Found	C 47,06	H 4,47	N 3,87

N^{α}-[(2RS)-bromopropionyl]-N^{ε}-(benzyloxycarbonyl)-L-lysine (**12b**): This compound was prepared by reaction of N^{ε}-(benzyloxycarbonyl)-L-lysine (**11b**) with (2*RS*)-bromopropionyl bromide following the procedure described above for the preparation of compound **12a**. The resulting oil (30,0 g; 60%) was used without further purification in the next step.

^{1}H NMR ($CDCl_3$): δ = 1,3–2,0 (m, 6H, $(CH_2)_3CH_2NH$), 1,85 (d, J = 7,1 Hz, 3H, CH_3), 3,20 (m, 2H, CH_2NH), 4,40 (q, J = 7,1 Hz, 1H, BrCH), 4,58 (m, 1H, NHCH), 5,11 (s, 2H, CH_2Ph), 5,13 (br d, J = 8 Hz, 1H, $NHCH_2Ph$), 7,16 (br s, 1H, NHCH), 7,34 (s, 5H, Ph), 8,27 (br s, 1H, COOH).

N-[(2RS)-bromopropionyl]-S-(p-methoxybenzyl)-L-cysteine (**12c**): This compound was prepared in 55% yield by reaction of *S*-(*p*-methoxybenzyl)-L-cysteine (**11c**) with (2*RS*)-bromopropionyl bromide according to the procedure described for the preparation of compound **12a**. The resulting **12c** was obtained as an oil, and was used without further purification in the next step.

^{1}H NMR ($CDCl_3$): δ = 1,84 and 1,89 (two d, J = 7,1 Hz, 3H, $CHCH_3$), 2,93 (m, 2H, $CHCH_2S$), 3,70 (s, 2H, SCH_2Ph), 3,79 (s, 3H, OCH_3), 4,39 and 4,42 (two q, J = 7,1 Hz, 1H, BrCH), 4,74 (m, 1H, NHCH), 6,84 and 7,22 (AB_q, J_{AB} = 8,6 Hz, 4H, Ph), 7,14 (br s, 1H, NH), 9,23 (br s, 1H, COOH).

(3S, 6RS)-3-[(Benzyloxycarbonyl)methyl]-6-methylmorpholine-2,5-dione (**13a**): To a solution of 17,9 g (0,050 mol) of **12a** in 150 mL of DMF was added 5,06 g (0,050 mol) of TEA. The reaction mixture was heated at 100 °C for 3 h. After removal of the solvent i. vac., the residue was partitioned between ethyl acetate and water. The organic layer was separated and subsequently extracted with water and a saturated aqueous NaCl solution, dried ($MgSO_4$) and concentrated i. vac. to yield a brown oil. Purification by column chromatography on silica gel using ethyl acetate as the eluent and recrystallization from toluene afforded 7,6 g (55%) of **13a**. M. p. 82–107 °C. $[\alpha]_D^{25} = -49°$ (c = 0,2 d/dL in chloroform).

^{1}H NMR ($CDCl_3$): δ = 1,57 (d, J = 6,8 Hz, 3H, CH_3), 2,82–3,17 (m, 2H, CH_2COOBz), 4,47–4,57 (m, 1H, NHCH), 4,90 and 4,96 (two q, J = 6,8 Hz, 1H, $CHCH_3$), 5,15 and 5,16 (two s, 2H, CH_2Ph), 7,35 (s, 5H, Ph), 7,63 and 7,73 (two br s, 1H, NH).

$C_{14}H_{15}NO_5$ (277,28)	Calc.	C 60,64	H 5,45	N 5,05
	Found	C 60,32	H 5,39	N 4,96

(3S,6RS)-3-[4-(Benzyloxycarbonylamino)butyl]-6-methylmorpholine-2,5-dione (**13b**): This compound was prepared in 38% yield from compound **12b** (20,8 g; 0,050 mol) by reaction with TEA in DMF following the procedure described for the synthesis of compound **13a**. M. p. 95–120 °C. $[\alpha]_D^{25} = -61°$ (c = 0,2 g/dL in chloroform).

^{1}H NMR ($CDCl_3$): δ = 1,58 (d, J = 6,9 Hz, 3H, CH_3), 1,4–2,1 (m, 6H, $(CH_2)_3CH_2NH$), 3,22 (m, 2H, CH_2NH), 4,10 (t, J = 7 Hz, 1H, NHCH), 4,84 and 4,88 (two q, J = 6,9 Hz, 1H, $CHCH_3$), 5,10 (s, 2H, CH_2Ph), 5,13 (br d, J = 8 Hz, 1H, $NHCH_2Ph$), 7,33 (s, 5H, Ph), 7,63 and 7,76 (two br s, 1H, NHCH).

$C_{17}H_{22}N_2O_5$ (234,37)	Calc.	C 61,07	H 6,63	N 8,38
	Found	C 61,15	H 6,84	N 8,21

(3S,6RS)-3-[(p-Methoxybenzyl)thiomethyl]-6-methylmorpholine-2,5-dione (**13c**): The title compound was prepared from compound **12c** (18,8 g; 0,050 mol) by reaction with TEA (5,06 g; 0,050 mol) in 150 mL of DMF at room temperature for 18 h. The precipitated TEA · HBr was filtered off and the solvent evaporated i. vac. The residue was partitioned between ethyl acetate and water. The organic layer was separated and subsequently washed with water and a saturated aqueous NaCl solution, dried ($MgSO_4$) and concentrated i. vac. to afford a yellow solid. The crude product was purified by column chromatography on silica gel (eluent hexane/ethyl acetate, 2:3) and subsequent recrystallization from toluene/diisopropyl ether gave 4,28 g (29%) of **13c**. M. p. 74–128 °C. $[\alpha]_D^{25} = -111°$ (c = 0,2 g/dL in chloroform).

^{1}H NMR ($CDCl_3$): δ = 1,58 and 1,61 (two d, J = 6,9 Hz, 3H, $CHCH_3$), 2,72–3,16 (m, 2H, $CHCH_2S$), 3,72 (s, 2H, CH_2Ph), 3,79 (s, 3H, OCH_3), 4,04–4,16 (m, 1H, NHCH), 4,83 and 5,00 (two q, J = 6,9 Hz, 1H, $CHCH_3$), 6,85 and 7,23 (AB_q, J_{AB} = 8,6 Hz, 4H, Ph), 6,93 and 7,21 (two br s, 1H, NH).

$C_{14}H_{17}NO_4S$ (295,36)	Calc.	C 56,93	H 5,80	N 4,74	S 10,86
	Found	C 56,58	H 5,77	N 4,58	S 10,71

*N-(tert-Butoxycarbonyl)-β-benzyl-*L*-aspartyl-*L-lactic acid pentamethylbenzyl ester (**16**): To a cooled solution (5–10 °C) of L-lactic acid pentamethylbenzyl ester (**15**)[28] (27,1 g; 0,108 mol), β-benzyl *N*-(*tert*-butoxycarbonyl)-L-aspartate (**14**)[29] (35,0 g; 0,108 mol) and DMAP (0,12 g; 0,001 mol) in 300 mL of dichloromethane was added dropwise a solution of DCC (22,3 g; 0,108 mol) in 100 mL of dichloromethane. After completion of the addition the reaction was stirred for 18 h at room temperature. Next the precipitated *N,N'*-dicyclohexylurea (DCU) was filtered off and the filtrate evaporated to dryness. The residue was dissolved in ethyl acetate, stirred for 1 h at 0 °C, and the precipitated DCU removed by filtration. The filtrate was washed with an aqueous 5% $NaHCO_3$ solution and a saturated aqueous NaCl solution, dried ($MgSO_4$) and concentrated i. vac. The crude product was recrystallized from diisopropyl ether to afford 53,9 g (90%) of **16**. M. p. 88–89,5 °C, $[\alpha]_D^{25} = -0{,}6°$ (c = 0,2 g/dL in chloroform).

^{1}H NMR ($CDCl_3$): δ = 1,43 (s, 9H, *tert*-Bu), 1,47 (d, J = 7,0 Hz, 3H, $OCHCH_3$), 2,21–2,26 (m, 15H, $Ph(CH_3)_5$), 2,91 (m, 2H, $NHCHCH_2$), 4,68 (m, 1H, NHCH), 5,11 (s, 2H, CH_2Ph), 5,12 (q, J = 7,0 Hz, 1H, $OCHCH_3$), 5,28 (s, 2H, $CH_2Ph(CH_3)_5$), 5,47 (d, J = 6,7 Hz, 1H, NH), 7,34 (s, 5H, Ph).

$C_{31}H_{41}NO_8$ (555,67)	Calc.	C 67,00	H 7,44	N 2,52
	Found	C 67,20	H 7,59	N 2,54

(3S, 6RS)-3-[(Benzyloxycarbonyl)methyl]-6-methylmorpholine-2,5-dione (**18**): To a cooled solution (0 °C) of **16** (55,5 g; 0,100 mol) and 60 mL of anisole in 100 mL of dry THF under a dry nitrogen atmosphere was added 75 mL of a cooled (0 °C) 33% HBr solution in acetic acid. The reaction mixture was stirred for 2 h at room temperature. Subsequently a large excess of diethyl ether was added, whereupon an oily precipitate formed. The supernatant was decanted, the residue was stirred three times with 100-mL portions of diethyl ether and dried on KOH i. vac. to give 31,3 g (83%) of the hygroscopic aminoacyl hydroxy acid **17**. A solution of **17** (31,3 g; 0,083 mol) in 200 mL of DMF was adjusted to pH 7–8 by addition of TEA (ca. 8,3 g; 0,083 mol). The mixture was cooled to 0 °C and HOBt · H_2O (14,0 g; 0,092 mol) was added. The mixture was stirred for 5 min, whereafter DCC (16,5 g; 0,080 mol) was added. The cooling bath was removed and stirring was continued for 2 h. Thereafter, the reaction mixture was left for 18 h at 6 °C in a refrigerator. The precipitate formed was filtered off and the filtrate evaporated i. vac. The residue was dissolved in ethyl acetate, stirred for 1 h at 0 °C and the precipitate removed by filtration. The filtrate was washed with an aqueous 0,5 M $KHSO_4$ solution, an aqueous 5% $NaHCO_3$ solution, water, a saturated aqueous NaCl solution and dried ($MgSO_4$). The solution was concentrated i. vac. and the crude product was purified by column chromatography on silica gel (eluent ethyl

acetate/hexane, 3:2), followed by recrystallization from toluene/diisopropyl ether, to afford 2,1 g (8%) of **18**. M.p. 98–100 °C. $[\alpha]_D^{25} = -98°$ (c = 0,2 g/dL in chloroform).

^{1}H NMR ($CDCl_3$): δ = 1,58 (d, J = 6,8 Hz, 3H, CH_3), 2,87 and 3,14 (AB part of ABX spectrum, 8 lines J_{AX} = 4,3 Hz, J_{BX} = 7,9 Hz, J_{AB} = 17,5 Hz, 2H, NHCHC$\underline{H}_2$), 4,53–4,58 (X part of ABX spectrum, 4 lines, J_{AX} = 4,3 Hz, J_{BX} = 7,9 Hz, 1H, NHC$\underline{H}$), 4,91 (q, J = 6,8 Hz, 1H, OC$\underline{H}$CH$_3$), 5,17 (s, 2H, CH_2Ph), 7,35 (s, 5H, Ph), 7,59 (s, 1H, NH).

$C_{14}H_{15}NO_5$ (277,28)	Calc.	C 60,64	H 5,45	N 5,05
	Found	C 60,38	H 5,35	N 4,97

Polymer synthesis

Polymerization: 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 10 mmol of the appropriate morpholine-2,5-dione derivative and ε-caprolactone or DL-lactide was placed in the tubes, and 50 µl of a freshly prepared 0,2 M solution of stannous octoate in dry toluene was added using a dry glass syringe to give a mole ratio M/I = 1000. 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 130 °C and the homogeneous polymerization mixtures were stirred until the increasing viscosity of the reaction mixtures prevented stirring. After 48 h the tubes were removed from the oil bath and allowed to cool to room temperature. The tubes were broken, the products collected and dissolved in 10 mL of chloroform. The resulting solutions were filtered to remove pieces of glass and precipitated in 200 mL of diethyl ether/hexane, 2:1. The (co)polymers were collected and dried i. vac. at 40 °C for 5 h.

^{1}H NMR: see Tab. 3.

Tab. 3. ^{1}H NMR chemical shifts ($CDCl_3$) of protected copolymers **20a–c** and **22a–c**

Polymer	Chemical shifts in ppm
	ε-Oxycaproyl units:
20a–c	1,3–1,8 (m, $CH_2(C\underline{H}_2)_3CH_2$), 2,3–2,5 (m, CH_2COO), 4,0–4,2 (m, OCH_2)
	Depsipeptide units:
20a	1,48 (m, CH_3), 2,8–3,1 (m, NHCHC$\underline{H}_2$), 4,82 (m, NHC$\underline{H}$), 5,10 and 5,12 (two s, CH_2Ph), 5,19 (m, OCH), 7,1–7,2 (m, NH), 7,34 (s, Ph)
20b	1,48 (m, CH_3), 1,2–2,0 (m, C$\underline{H}_2)_3CH_2NH$), 3,18 (m, C$\underline{H}_2$NH), 4,58 (m, NHC$\underline{H}$), 5,10 and 5,12 (two s, CH_2Ph), 5,13 (m, N$\underline{H}CH_2$Ph), 5,17 (m, OCH), 6,65–6,85 (m, N$\underline{H}$CH), 7,35 (s, Ph)
20c	1,49 (m, CH_3), 2,8–3,0 (m, CHC$\underline{H}_2$S), 3,64 and 3,68 (two s, CH_2Ph), 3,79 (s, OCH_3), 4,77 (m, NHC$\underline{H}$), 5,1–5,2 (m, OCH), 6,85 and 7,23 (AB_q, J = 8,6 Hz, Ph), 7,15–7,25 (m, NH)
22a	1,53 (m, CH_3), 2,85–3,2 (m, NHCHC$\underline{H}_2$), 4,8–5,0 (m, NHC$\underline{H}$), 5,1–5,3 (m, OCH and CH_2Ph), 7,0–7,2 (m, NH), 7,34 (s, Ph)
22b	1,2–2,0 (m, C$\underline{H}_2)_3CH_2NH$), 1,55 (m, CH_3), 3,17 (m, C$\underline{H}_2$NH), 4,87 (m, NHC$\underline{H}$), 5,0–5,2 (m, OCH, $CH_2N\underline{H}$ and CH_2Ph), 6,9–7,1 (m, N$\underline{H}$CH), 7,32 (s, Ph)
22c	1,55 (m, CH_3), 2,8–3,1 (m, CHC$\underline{H}_2$S), 3,68 and 3,72 (two s, CH_2Ph), 3,79 (s, OCH_3), 4,80 (m, NHC$\underline{H}$), 5,1–5,3 (m, OCH), 6,84 and 7,23 (AB_q, J = 8,6 Hz, Ph), 7,15–7,25 (m, NH)

Elemental analyses: $((C_aH_bN_cO_d)_y\ (C_eH_fO_g)_{1-y})_n$ with $y = X_M$, where X_M is the mole fraction of depsipeptide units present in the copolymers determined by ^{1}H NMR (see Tab. 1). The composition of copolymers of morpholine-2,5-dione derivatives and ε-caprolactone with $X_M > 0{,}15$ was only determined by ^{1}H NMR, because these polymers were pasty, which prevented the accurate weighing of samples for elemental analysis.

20a: $((C_{14}H_{15}NO_5)_{0,084}\ (C_6H_{10}O_2)_{0,916})_n$ (127,8)$_n$	Calc.	C 62,68	H 8,21	N 0,92
	Found	C 61,74	H 8,22	N 0,91
22b: $((C_{17}H_{22}N_2O_5)_{0,073}\ (C_6H_{10}O_2)_{0,927})_n$ (130,2)$_n$	Calc.	C 62,74	H 8,42	N 1,57
	Found	C 61,59	H 8,44	N 1,91
20c: $((C_{14}H_{17}NO_4S)_{0,088}\ (C_6H_{10}O_2)_{0,912})_n$ (130,1)$_n$	Calc.	C 61,90	H 8,22	N 0,95
	Found	C 61,23	H 8,54	N 0,90
20c: $((C_{14}H_{17}NO_4S)_{0,047}\ (C_6H_{10}O_2)_{0,953})_n$ (122,7)$_n$	Calc.	C 62,43	H 8,49	N 0,54
	Found	C 61,74	H 8,70	N 0,41
22a: $((C_{14}H_{15}NO_5)_{0,15}\ (C_6H_8O_4)_{0,95})_n$ (164,1)$_n$	Calc.	C 52,70	H 5,56	N 1,28
	Found	C 51,63	H 5,34	N 1,22
22a: $((C_{14}H_{15}NO_5)_{0,087}\ (C_6H_8O_4)_{0,913})_n$ (155,7)$_n$	Calc.	C 51,65	H 5,57	N 0,78
	Found	C 50,50	H 5,46	N 0,65
22b: $((C_{17}H_{22}N_2O_5)_{0,13}\ (C_6H_8O_4)_{0,97})_n$ (168,9)$_n$	Calc.	C 52,85	H 5,86	N 2,16
	Found	C 52,35	H 5,89	N 2,84
22b: $((C_{17}H_{22}N_2O_5)_{0,067}\ (C_6H_8O_4)_{0,933})_n$ (156,9)$_n$	Calc.	C 51,58	H 5,74	N 1,20
	Found	C 51,05	H 5,69	N 1,60
22c: $((C_{14}H_{17}NO_4S)_{0,051}\ (C_6H_8O_4)_{0,949})_n$ (151,8)$_n$	Calc.	C 50,69	H 5,62	N 0,47
	Found	C 50,10	H 5,58	N 0,41

Deprotection of copolymers **20a, 20b, 22a** *and* **22b:** The copolymers (1,0 g) were dissolved in 10 mL of ethyl acetate, whereafter 5 mL of methanol and 50 mg of 10% Pd-C were added. For copolymers **20a** and **22a**, the suspensions were vigorously stirred in a hydrogen atmosphere at atmospheric pressure for 18 h. In the case of copolymers **20b** and **22b** hydrogen was bubbled through the suspensions with stirring for 18 h. The catalyst was removed by filtration over Celite 545. The filtrate was added dropwise to a twenty-fold excess of diethyl ether/hexane, 2:1. The precipitated polymer was collected and dried i. vac. at 40 °C for 5 h.

^{1}H NMR ($CDCl_3$):

21a: δ = 1,3–1,8 (m, $CH_2(C\underline{H}_2)_3CH_2$), 1,49 (m, CH_3), 2,3–2,5 (m, CH_2COO (ε-cap.)), 2,8–3,2 (m, $C\underline{H}_2COOH$), 4,0–4,2 (m, OCH_2), 4,85 (m, $NHC\underline{H}$), 5,25 (m, OCH).

21b: δ = 1,3–1,8 (m, $CH_2(C\underline{H}_2)_3CH_2$ and $(C\underline{H}_2)_3CH_2NH_2$), 1,48 (m, CH_3), 2,3–2,5 (m, CH_2COO), 2,7–3,2 (m, $C\underline{H}_2NH_2$), 4,0–4,2 (m, OCH_2), 4,82 (m, $NHC\underline{H}$), 5,23 (m, OCH).

23a: δ = 1,54 (m, CH_3), 2,8–3,2 (m, $C\underline{H}_2COOH$), 4,57 (m, $NHC\underline{H}$), 5,14 (m, OCH).

23b: δ = 1,2–2,0 (m, $(C\underline{H}_2)_3CH_2NH_2$), 1,55 (m, CH_3), 3,0–3,3 (m, $C\underline{H}_2NH_2$), 4,56 (m, $NHC\underline{H}$), 5,16 (m, OCH).

Elemental analysis: $((C_aH_bN_cO_d)_y(C_eH_fO_g)_{1-y})_n$ with $y = X_M$, where X_M is the mole fraction of depsipeptide units present in the copolymers determined by ^{1}H NMR (see Tab. 2). Pasty copolymers of morpholine-2,5-dione derivatives and ε-caprolactone could not be accurately analyzed.

21a: $((C_7H_9NO_5)_{0,081}\ (C_6H_{10}O_2)_{0,919})_n$ (120,1)$_n$	Calc.	C 57,35	H 8,02	N 0,89
	Found	C 60,13	H 8,47	N 1,06
23a: $((C_7H_9NO_5)_{0,11}\ (C_6H_8O_4)_{0,89})_n$ (148,9)$_n$	Calc.	C 49,30	H 5,49	N 1,04
	Found	C 50,15	H 5,98	N 1,31
23a: $((C_7H_7NO_5)_{0,081}\ (C_6H_8O_4)_{0,919})_n$ (147,6)$_n$	Calc.	C 49,48	H 5,52	N 0,77
	Found	C 49,76	H 5,74	N 0,94
23b: $((C_9H_{16}N_2O_3)_{0,12}\ (C_6H_8O_4)_{0,98})_n$ (150,9)$_n$	Calc.	C 50,63	H 5,99	N 2,23
	Found	C 50,12	H 6,35	N 2,88
23b: $((C_9H_{16}N_2O_3)_{0,065}\ (C_6H_8O_4)_{0,935})_n$ (147,8)$_n$	Calc.	C 50,35	H 5,81	N 1,23
	Found	C 50,02	H 5,83	N 1,61

Deprotection of copolymers **20c** *and* **22c**: To a stirred solution of copolymer **20c** or **22c** (ca. 1–2 g, equivalent with 0,80 mmol of S-MBz groups) in 10 mL of trifluoroacetic acid under a dry argon atmosphere (in order to prevent air oxidation of the resulting thiol groups to disulfide groups) was added anisole (0,35 g; 3,2 mmol), followed by trifluoromethanesulfonic acid (0,70 mL; 8,0 mmol). The reaction mixture was stirred for 5 min at room temperature, whereafter 100 mL of methanol (through which previously a stream of dry argon had been led) was added. The precipitated polymer was collected and dried i. vac. at 40 °C for 5 h. The polymers were stored under an argon atmosphere.

^{1}H NMR ($CDCl_3$):

21c: δ = 1,3–1,8 (m, $CH_2(C\underline{H}_2)_3CH_2$), 1,50 (m, CH_3), 2,3–2,5 (m, CH_2COO), 2,9–3,1 (m, $C\underline{H}_2SH$), 4,0–4,2 (m, OCH_2), 4,81 (m, $NHC\underline{H}$), 5,19 (m, OCH).

23c: δ = 1,55 (m, CH_3), 2,8–3,1 (m, ($C\underline{H}_2SH$), 4,87 (m, $NHC\underline{H}$), 5,1–5,3 (m, OCH).

Elemental analysis: $((C_aH_bN_cO_d)_y(C_eH_fO_g)_{1-y})_n$ with $y = X_M$, where X_M is the mole fraction of depsipeptide units present in the copolymers determined by ^{1}H NMR (see Tab. 2).

21c: $((C_6H_9NO_3S)_{0,060}\ (C_6H_{10}O_2)_{0,94})_n$ (117,8)$_n$	Calc.	C 61,17	H 8,50	N 0,71
	Found	C 59,89	H 8,49	N 0,31
23c: $((C_6H_9NO_3S)_{0,049}\ (C_6H_8O_4)_{0,951})_n$ (145,6)$_n$	Calc.	C 49,48	H 5,57	N 0,47
	Found	C 48,30	H 5,54	N 0,38

Methods

Preparative column chromatography: For column chromatography Merck Silica Gel 60 was used. Thin layer chromatography (TLC) was performed with Merck percoated Silica 60 F-254 plastic sheets (thickness 0,2 mm). Spots were visualized with an UV lamp or Cl_2-TDM[30].

Measurements: Melting points were determined on a Reichert melting point apparatus and are uncorrected.

Specific rotations ($[\alpha]_D^{25}$ were measured with a Perkin-Elmer 241 polarimeter.

^{1}H NMR and ^{13}C NMR spectroscopy was performed with a Bruker AC 250 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.

Elemental analyses were carried out by the Laboratory of Chemical Analysis of the University of Twente.

The apparent number-average molecular weight ($\bar{M}_{n,app}$) and apparent weight-average molecular weight ($\bar{M}_{w,app}$) of the polymers were determined by gel-permeation chromatography (GPC). The GPC 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 and a Waters 411 differential refractometer. The columns were calibrated with polystyrene standards having a narrow molecular-weight distribution.

Differential scanning calorimetry (DSC) measurements were performed with a Perkin-Elmer DSC-7 apparatus calibrated with indium and gallium. Samples of copolymers **21a–c** were quenched to −80 °C and kept at this temperature for 5 min. Subsequently, the samples were heated to 80 °C at a rate of 20 °C/min. Samples of copolymers **23a–c** were quenched to 0 °C, kept at this temperature for 5 min and heated at a rate of 20 °C/min.

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