Synthesis of alternating polydepsipeptides by ring-opening polymerization of morpholine-2,5-dione derivatives

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SUMMARY:
   Polydepsipeptides with alternating α-hydroxy acid and α-amino acid residues were synthesized by ring-opening polymerization of morpholine-2,5-dione derivatives. The polymerizations were performed in the melt using stannous octoate as an initiator. Molecular weights of the polydepsipeptides obtained ranged from $0,9 \cdot 10^4$ to $7,4 \cdot 10^4$. Morpholine-2,5-dione derivatives unsubstituted at the 6-position gave polymers with the highest molecular weights. Poly((*S*)-alanine-*alt*-glycolic acid) was semi-crystalline, whereas all other polydepsipeptides synthesized were amorphous. Morpholine-2,5-dione derivatives were synthesized by *N*-acylation of glycine, (*S*)-alanine or (*S*)-valine with chloroacetyl chloride or (*R,S*)-2-bromopropionyl bromide, followed by ring-closure of *N*-(2-halogenacyl)-amino acid sodium salts in the melt in 4 to 83% yield. Low yields in the cyclization reaction of *N*-(2-halogenacyl)-(*S*)-valine were accompanied by the formation of the corresponding polydepsipeptides in 13 to 46% yield, with molecular weights ranging from $3,3 \cdot 10^4$ to $4,9 \cdot 10^4$.

Introduction

   Biodegradable polymers are receiving increasing attention for possible use in a wide variety of surgical and pharmaceutical applications, such as absorbable bone plates and other surgical fixation devices, artificial skin substitutes and carrier systems for the controlled release of drugs[1]. For the various applications a wide range of polymer degradation times and profiles, permeabilities and mechanical properties is required, which cannot be achieved with the existing materials. Therefore, the development of new biodegradable materials and improvement of the existing materials is necessary.

   Two important classes of biodegradable polymers are poly(α-hydroxy acids) and poly(α-amino acids). Although the properties of homo- and copolymers of both classes have been extensively studied, the polymers containing both α-hydroxy acid and α-amino acid residues have received minor attention. These copolymers, called polydepsipeptides, may be a valuable addition to the existing synthetic biodegradable polymers.

   Sequential polydepsipeptides have been prepared on a small scale by polymerization of tetra-, tri- or didepsipeptide activated esters, which were synthesized via a multi-step synthetic route[2].

   High-molecular-weight polymers of lactic acid and glycolic acid can easily be obtained by ring-opening polymerization in the melt of the cyclic monomers, lactide and glycolide, respectively. Ring-opening polymerization of morpholine-2,5-dione derivatives could be an attractive route to obtain various alternating polydepsipeptides in a more facile way (*Scheme 1*).

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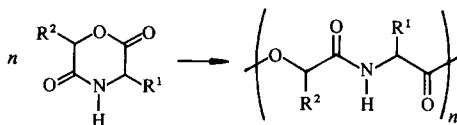
Scheme 1.   Synthesis of alternating polydepsipeptides by ring-opening polymerization of morpholine-2,5-dione derivatives

We confirmed this by the synthesis of poly(glycine-(R,S)-lactic acid) (*Scheme 1*, R^1 = H, R^2 = CH_3) and the ring-opening polymerization in the melt of (R,S)-6-methyl-morpholine-2,5-dione using tin bis(2-ethylhexanoate) (stannous octoate) as an initiator[3]. Thereafter, the synthesis of various other alternating polydepsipeptides by ring-opening polymerization of the corresponding morpholine-2,5-dione derivatives has been reported[4-6].

Copolymerization of morpholine-2,5-dione derivatives with lactide or glycolide provides the possibility to prepare materials with a wide range of properties which depend on the composition of the copolymers[4-7].

Synthesis of alternating polydepsipeptides consisting of different combinations of an α-amino acid (e. g., glycine, alanine or valine) and an α-hydroxy acid (e. g., glycolic acid or lactic acid) may give new materials with a range of hydrophilicity, crystallinity, degradation times and mechanical properties. To obtain semi-crystalline alternating polydepsipeptides, an enantiospecific synthetic route is required.

In this paper we report the synthesis and characterization of various morpholine-2,5-dione derivatives and their ring-opening polymerization to the corresponding alternating polydepsipeptides.

Results and discussion
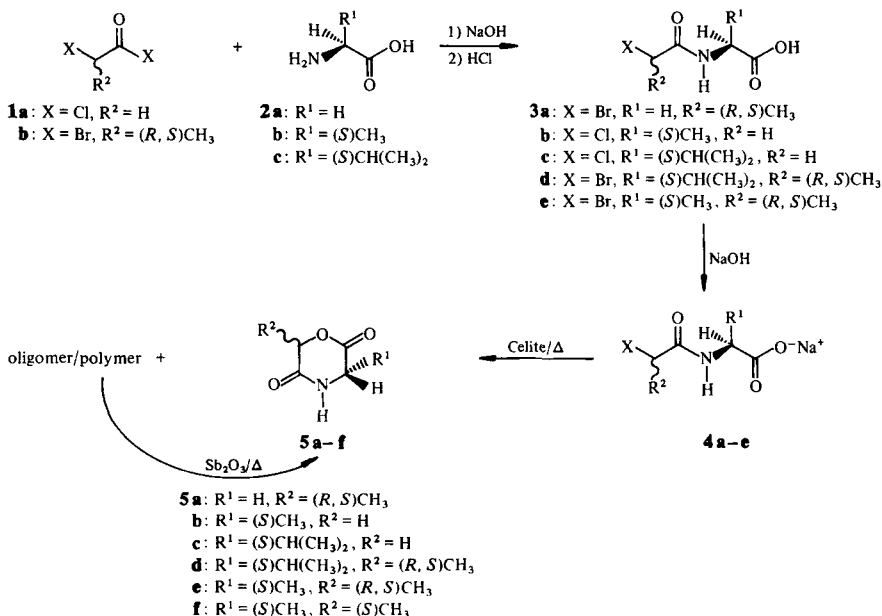
Synthesis of morpholine-2,5-dione derivatives

Morpholine-2,5-dione derivatives have only been mentioned occasionally in the literature. Goodman et al.[2c] reported that (3S,6S)-3,6-dimethylmorpholine-2,5-dione (5f) and (3S,6S)-3-isopropyl-6-methylmorpholine-2,5-dione were obtained as the main product in the attempted polymerization of the trifluoroacetate salts of the corresponding didepsipeptide pentachlorophenyl esters. The unsubstituted morpholine-2,5-dione[8,9], (S)-3-methylmorpholine-2,5-dione[5,9], (R,S)-6-methylmorpholine-2,5-dione[3,10] and (R,S)-6-isopropylmorpholine-2,5-dione[11] have been prepared from N-(2-halogenacyl)-amino acids by dry heating of the corresponding sodium salts. Fung and Glowaky[6] reported the synthesis of 3-substituted morpholine-2,5-dione derivatives by reaction of N-(2-chloroacetyl)-amino acids with triethylamine in DMF.

In previous papers we have described the synthesis of (R,S)-6-methylmorpholine-2,5-dione by dry heating of the sodium salt of N-((R,S)-2-bromopropionyl)glycine. The intermediate N-(R,S)-2-bromopropionyl)glycine was synthesized using the Schotten-Baumann procedure described by Greenstein and Winitz[13]. In order to

improve the low yields obtained, both in the Schotten-Baumann reaction and in the cyclization reaction, we reinvestigated the procedures as previously used.

Morpholine-2,5-dione derivatives 5a−f were synthesized as outlined in *Scheme 2*. Following the procedures described by Fischer et al.[12], reaction of chloroacetyl chloride (1a) or (R,S)-2-bromopropionyl bromide (1b) with glycine (2a), (S)-alanine (2b) or (S)-valine (2c) afforded the N-(2-halogenacyl)-amino acids 3a−e in 60−80% yields. The much better yields now obtained in the Schotten-Baumann procedure result from the difference in bases used. In the method described by Fischer et al. sodium hydroxide is used as a base to capture the hydrogen chloride formed during the reaction and to keep the amine group unprotonated. The method described by Greenstein and Winitz uses sodium hydrogencarbonate as a base. Obviously, the sodium hydrogencarbonate is too weak a base to fully deprotonate the amine group, resulting in a lower reactivity towards the acid halogenide, which causes lower yields of N-(2-halogenacyl)-amino acids.

The N-(2-halogenacyl)-amino acids 3a−e were quantitatively converted into the corresponding sodium salts 4a−e by treatment with sodium hydroxide. Morpholine-2,5-dione derivatives 5a−e were obtained by dry heating under reduced pressure of the sodium salts 4a−e on a matrix of Celite, whereupon the morpholine-2,5-dione derivatives sublimed from the reaction mixture. Yields and properties of the different morpholine-2,5-dione derivatives synthesized are summarized in Tab. 1. The addition of Celite to the sodium salts of the N-(2-halogenacyl)-amino acids enlarges the surface of the reaction mixture, which promotes the sublimation of the morpholine-2,5-dione

1a: X = Cl, R² = H
  b: X = Br, R² = (R, S)CH₃

2a: R¹ = H
  b: R¹ = (S)CH₃
  c: R¹ = (S)CH(CH₃)₂

3a: X = Br, R¹ = H, R² = (R, S)CH₃
  b: X = Cl, R¹ = (S)CH₃, R² = H
  c: X = Cl, R¹ = (S)CH(CH₃)₂, R² = H
  d: X = Br, R¹ = (S)CH(CH₃)₂, R² = (R, S)CH₃
  e: X = Br, R¹ = (S)CH₃, R² = (R, S)CH₃

5a: R¹ = H, R² = (R, S)CH₃
  b: R¹ = (S)CH₃, R² = H
  c: R¹ = (S)CH(CH₃)₂, R² = H
  d: R¹ = (S)CH(CH₃)₂, R² = (R, S)CH₃
  e: R¹ = (S)CH₃, R² = (R, S)CH₃
  f: R¹ = (S)CH₃, R² = (S)CH₃

Scheme 2.   Synthetic scheme for the preparation of morpholine-2,5-dione derivatives

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Tab. 1. Morpholine-2,5-dione derivatives obtained by cyclization of sodium salts of N-(2-halogenacyl)-amino acids

No.	Compound R¹	R²	Yield in %	m.p. in °C (recryst. solv.)	$[\alpha]_D^{25}$ [a]	Formula (mol. wt.)		Elemental analyses		
								C	H	N
5a	H	(R,S)CH$_3$	30	98,5–100 [b] (EtOAc)	—	C$_5$H$_7$NO$_3$ (129,11)	Calc.	46,51	5,46	10,85
							Found	46,61	5,52	10,74
5b	(S)CH$_3$	H	5	141,5–142,5 [c] (CH$_3$CN)	−69°	C$_5$H$_7$NO$_3$ (129,11)	Calc.	46,51	5,46	10,85
							Found	46,22	5,58	11,02
5c	(S)CH(CH$_3$)$_2$	H	4	95,5–96,5 (toluene)	+37°	C$_7$H$_{11}$NO$_3$ (157,17)	Calc.	53,49	7,05	8,91
							Found	53,19	7,25	8,95
5d	(S)CH(CH$_3$)$_2$	(R,S)CH$_3$	23	110–125 (toluene)	−54°	C$_8$H$_{13}$NO$_3$ (171,12)	Calc.	56,13	7,65	8,18
							Found	56,17	7,59	8,09
5e	(S)CH$_3$	(R,S)CH$_3$	83	129–137 (toluene)	−130°	C$_6$H$_9$NO$_3$ (143,14)	Calc.	50,35	6,34	9,79
							Found	50,65	6,29	9,51
5f [d]	(S)CH$_3$	(S)CH$_3$	28	162–163 [e] (EtOAc)	−165° [f]	C$_6$H$_9$NO$_3$ (143,14)	Calc.	50,35	6,34	9,79
							Found	50,59	6,26	9,58

[a] c = 0,2 g/dl in CHCl$_3$.
[b] Lit. [3a]; m.p. = 99–100 °C.
[c] Lit. [9]; m.p. = 139–141 °C.
[d] Obtained from the diastereomeric mixture 5e by fractionated recrystallization from ethyl acetate (EtOAc).
[e] Lit. [2c]; m.p. = 161–165 °C.
[f] Lit. [2c]; $[\alpha]_D^{20}$ = −161° (c = 0,5 g/dl in CHCl$_3$).
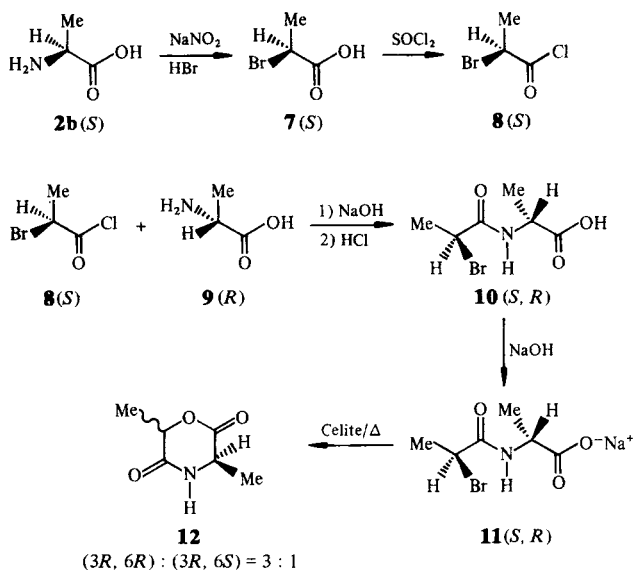
Scheme 3. Synthesis and cyclization reaction of N-((S)-2-bromopropionyl)-(R)-alanine (10)

derivatives formed. In this way pure morpholine-2,5-dione derivatives were obtained. This is in contrast with the previously reported extended work-up procedure[3a], which gave morpholine-2,5-dione derivatives with 2−3 times lower yields. However, using the methods described above, the morpholine-2,5-dione derivatives 5b and 5c still only could be obtained in low yields (4−5%). The preparation of morpholine-2,5-dione derivatives 5a and 5b was also attempted by treatment of the corresponding N-(2-halogenacyl)-amino acids with triethylamine[6] or cesium carbonate[14] in DMF at 100°C, or silver oxide in 1,4-dioxane[15] at 100°C. Only very low yields (<5%) of morpholine-2,5-dione derivatives 5a and 5b were obtained. Recently Fung and Glowaky[6] reported that (S)-3-methylmorpholine-2,5-dione (5b) was synthesized in 50% yield by reaction of N-(chloroacetyl)-(S)-alanine (3b) with triethylamine in DMF at 100°C.

The low yields observed in the cyclization reaction obviously are due to the high trans-cis barrier for the non-alkylated amide bond. The barrier to rotation for the C—N bond is about 90 kJ/mol[16]. In most acyclic amides the trans-configuration of the CONH-group is predominant. In order to form the cyclic compounds 5a−f, the linear precursors 4a−e should adopt a folded conformation with a cis amide bond, rather than the more extended form with the favoured trans amide bond, and thus drastic conditions are required for the formation of morpholine-2,5-dione derivatives.

Cyclization of the sodium salts of N-((R,S)-2-bromopropionyl)-(S)-valine (4d) and N-((R,S)-2-bromopropionyl)-(S)-alanine (4e) afforded the morpholine-2,5-dione derivatives 5d and 5e, respectively, as mixtures of the (3S,6S) and (3S,6R) diastereomers. In the synthesis of 5d one of the diastereomers is formed preferentially

$((3S,6S):(3S,6R) = 3:2$ or $2:3$, determined by ^{1}H NMR from the ratios of the NH or NHC$\underline{H}$-signal intensities), but neither the $(3S,6S)$ nor $(3S,6R)$ diastereomer could be separated from the mixture. However, from the 1:1 diastereomeric mixture of $(3S,6S)$- and $(3S,6R)$-3,6-dimethylmorpholine-2,5-dione (5e) the $(3S,6S)$ diastereomer (5f) could be isolated by fractionated recrystallization from ethyl acetate. The optical rotation of 5f, $[\alpha]_D^{25} = -165°$ $(c = 0,2$ g/dl, CHCl$_3$) is in agreement with the value reported by Goodman et al.[2c] $([\alpha]_D^{20} = -161°$ $(c = 0,5$ g/dl, CHCl$_3$)) who synthesized 5f by an enantiospecific route. This implicates that during the cyclization reaction no racemization occurs at the chiral centre of the amino acid residue.

Cyclization of N-((S)-2-bromopropionyl)-(R)-alanine (10) was performed to investigate whether inversion of configuration or (partly) racemization at the chiral centre of the hydroxy acid residue occurred during the cyclization reaction. Compound 10 was synthesized by an enantiospecific synthesis, as outlined in Scheme 3. (S)-Alanine (2b) was converted into (S)-2-bromopropionic acid (7) with retention of configuration by treatment with nitrosyl bromide[17, 18]. Upon reaction with thionyl chloride, 7 was converted into the acid chloride 8. Reaction of 8 with (R)-alanine (9) using methods described by Fischer et al.[12e] yielded N-((S)-2-bromopropionyl)-(R)-alanine (10). Treatment of 10 with sodium hydroxide gave the corresponding sodium salt 11, which was dry heated to give a mixture of $(3R,6R)$ and $(3R,6S)$ 12 in a ratio of 3:1, as determined from the ratio of the integrals of the NH-signals in the ^{1}H NMR spectrum of 12. The synthesis of the sodium salt 11 from 10 may cause racemization at the chiral centre of the 2-bromopropionic acid residue. However, ^{13}C NMR analysis of the sodium salt showed no additional signals for the carbonyl carbon atoms besides the two signals found at $\delta = 179,1$ and $\delta = 170,9$ (CD$_3$OD). From the results described above it was concluded that the cyclization reaction preferentially takes place via inversion of configuration.

The low yields obtained in the cyclization reactions to give 5b and 5c prompted us to a further analysis of the residue remaining after the reaction. ^{1}H NMR analysis of the residues remaining after the reaction revealed the formation of oligomeric products. However, extraction of the residual material obtained in the cyclization reaction of 4c and 4d with DMF and precipitation of the DMF extracts in water showed the formation of the corresponding polydepsipeptides 6c (46%) and 6d (13%), respectively. The molecular weights of the polymers ranged from 3,3 to $4,9 \cdot 10^4$ (Tab. 3). This means that polydepsipeptides 6c and 6d can be synthesized by a simple two-step synthesis. Possibly the presence of the isopropyl group causes steric hindrance and keeps the sodium salt in a more linear conformation which promotes the formation of linear polymer rather than cyclization to the corresponding morpholine-2,5-dione derivative.

δ-Lactones like glycolide and lactide can be synthesized by depolymerization of the low-molecular-weight polymer produced by dehydration of glycolic acid and lactic acid, respectively, on heating under reduced pressure[19, 20]. We studied the depolymerization of the residue obtained during the cyclization reaction containing oligomeric and polymeric depsipeptides by addition of a catalytic amount of antimony trioxide and heating to $230-250$ °C in vacuo in a sublimator. Using this methodology, morpholine-2,5-dione derivatives 5b and 5c were obtained in $25-30$% yields. However, the extreme reaction conditions required for the depolymerization resulted in considerable

racemization, as illustrated by the optical purities of **5 b** (opt. purity 51%) and **5 c** (opt. purity 70%). Depolymerization of residues with $R^2 = CH_3$ resulted in decomposition products which could not be further characterized.

Ring-opening polymerization of morpholine-2,5-dione derivatives

To elucidate the polymerizability of the morpholine-2,5-dione derivatives, initial experiments were carried out using polymerization conditions and procedures chosen on the basis of earlier work[3]. The ring-opening polymerization of morpholine-2,5-dione derivatives **5 a – f** (*Scheme 4*) was carried out in the melt using stannous octoate as an initiator (mole ratio M/I = 250) at temperatures of 5 °C above the melting point of the monomers. The results are summarized in Tab. 2 and Tab. 3.
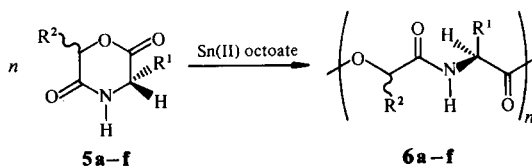
Scheme 4.   Synthesis of alternating polydepsipeptides by ring-opening polymerization of morpholine-2,5-dione derivatives

Molecular weights of the polydepsipeptides varied from $0,9 \cdot 10^4$ for **6 e** to $7,4 \cdot 10^4$ for **6 c**, as determined by LALLS measurements. Ring-opening polymerization of morpholine-2,5-dione derivatives with $R^2 = H$ (**5 b, 5 c**) gave polymers with higher molecular weights compared with morpholine-2,5-dione derivatives with $R^2 = CH_3$ (**5 a, 5 d** and **5 e**). First attempts to polymerize **5 b** resulted in the formation of oligomer with complete conversion of monomer after 48 h reaction time. However, already after 30 min the reaction mixture had turned into a solid, suggesting the fast formation of polymer. When the polymerization was terminated after 90 min, high-molecular-weight polymer was obtained with 95% conversion. Obviously, monomer **5 b** is much more reactive than the other monomers.

Morpholine-2,5-dione derivatives can be considered both as a 6-membered lactone and as a 6-membered lactam. Contrary to the polymerization of 6-membered lactones the polymerization of 6-membered lactams is rather difficult[21,22]. This implies that ring-opening polymerization of morpholine-2,5-dione derivatives most probably proceeds by cleavage of the ester bond. This was confirmed by ^{13}C NMR analysis of the polymers **6 b** and **6 c**. If, besides cleavage of the ester bond, cleavage of the amide bond should occur during the polymerization of **5 b** and **5 c**, this would lead to additional carbonyl signals due to a random distribution of amino acid and hydroxy acid residues. Because only two carbonyl signals were found at $\delta = 175,2$ and $\delta = 171,9$ (TFA-d_1) for **6 b** and at $\delta = 170,2$ and $\delta = 168,8$ (CDCl$_3$) for **6 c** in the ^{13}C NMR spectra, it was concluded that a completely alternating polydepsipeptide was formed.

Tab. 2.   Results obtained from the ring-opening polymerization of morpholine-2,5-dione deriva-
tives in the melt. Initiator: stannous octoate, mole ratio M/I = 250. Reaction time: 48 h

Polymer	Compound		Temp.	Conv. [a]	Yield
	R^1	R^2	in °C	in %	in %
6a	H	(R,S)CH$_3$	105	70	22
6b	(S)CH$_3$	H	147[b]	95	65
6c	(S)CH(CH$_3$)$_2$	H	100	70	40
6d	(S)CH(CH$_3$)$_2$	(R,S)CH$_3$	125	60	33
6e	(S)CH$_3$	(R,S)CH$_3$	134	70	55
6f	(S)CH$_3$	(S)CH$_3$	165	65	0

[a]   Determined by ^{1}H NMR.
[b]   Reaction time: 90 min.

Tab. 3.   Characterization of alternating polydepsipeptides ($\overline{M}_w$: weight-average mol. wt., $[a]_D^{25}$:
specific rotation, T_g: glass transition temperature)

Polymer	Compound		Method [a]	$10^{-4} \cdot \overline{M}_w$ [b]	$[a]_D^{25}$ [c]	T_g [d]
	R^1	R^2				°C
6a	H	(R,S)CH$_3$	RO	2,3 [e]	—	117 [f]
6b	(S)CH$_3$	H	RO	4,5 [e]	−29° [g]	103 [h]
6c	(S)CH(CH$_3$)$_2$	H	RO	7,4	+44°	99
	(S)CH(CH$_3$)$_2$	H	Matrix	3,5	+43°	93
	(R)CH(CH$_3$)$_2$	H	Matrix	4,9	−40°	93
6d	(S)CH(CH$_3$)$_2$	(R,S)CH$_3$	RO	2,5	−24°	93
	(S)CH(CH$_3$)$_2$	(R,S)CH$_3$	Matrix	3,3	+3°	99
6e	(S)CH$_3$	(R,S)CH$_3$	RO	0,90	−30°	94

[a]   Polymers synthesized by ring-opening polymerization (= RO) and polymerization of sodium
       salts of N-(2-halogenacyl)-amino acids (= matrix).
[b]   Determined by GPC/LALLS in CH$_2$Cl$_2$.
[c]   c = 0,2 g/dl in CHCl$_3$.
[d] T_g-values determined by DSC.
[e]   Determined by static LALLS in 2,2,2-trifluoroethanol.
[f]   Lit. [3b]: T_g = 110 °C.
[g]   c = 0,2 g/dl in 2,2,2-trifluoroethanol.
[h]   Melting temperature T_m = 221 °C (lit. [6]: T_m = 232 °C).

    Although stannous octoate is a well-known initiator for lactone polymerization, the
actual reaction mechanism by which polymerization occurs has not yet been elucidated.
Kricheldorf et al. [23] suggested that the stannous octoate-initiated ring-opening poly-
merization of glycolide and lactide proceeds via a coordinated insertion mechanism.
Presumably, this mechanism also applies for the ring-opening polymerization of mor-
pholine-2,5-dione derivatives. However, there may be an interaction between the

Tab. 4. ^{1}H NMR data of morpholine-2,5-dione derivatives (5a−f) and polydepsipeptides (6a−e)

Compound	^{1}H NMR data
5a	(DMSO-d_6) δ = 1,35 (d, J = 6,9 Hz; 3 H, CH$_3$) 3,93 and 4,13 (AB$_q$, J_{AB} = 17,7 Hz; 2 H, CH$_2$), 4,95 (q, J = 6,9 Hz; 1 H, CH), 8,35 (br s; 1 H, NH)
5b	(DMSO-d_6) δ = 1,33 (d, J = 7,0 Hz; 3 H, CH$_3$) 4,30 (q, J = 7,0 Hz; 1 H, CH), 4,62 and 4,86 (AB$_q$, J_{AB} = 15,4 Hz; 2 H, CH$_2$), 8,55 (br s; 1 H, NH)
5c	(DMSO-d_6) δ = 0,93 (d, J = 8,6 Hz; 3 H, CH$_3$), 0,96 (d, J = 8,6 Hz; 3 H, CH$_3$), 2,18 (m; 1 H, CH(CH$_3$)$_2$), 3,96 (double d, J_1 = 4,7 Hz, J_2 = 2,6 Hz; 1 H, NHCH), 4,69 and 4,78 (AB$_q$, J_{AB} = 15,9 Hz; 2 H, CH$_2$), 8,62 (br s; 1 H, NH)
5d	(DMSO-d_6) δ = 0,95 (m; 12 H, CH(CH$_3$)$_2$), 1,39 (d, J = 6,9 Hz; 3 H, OCHCH$_3$) 1,41 (d, J = 6,9 Hz; 3 H, OCHCH$_3$), 2,18 (m; 2 H, CH(CH$_3$)$_2$, 3,86 (double d, J_1 = 6,3 Hz, J_2 = 3,5 Hz; 1 H, NHCH), 4,21 (d, J = 3,0 Hz; 1 H, NHCH), 5,03 (q, J = 6,9 Hz; 1 H, OCH), 5,07 (q, J = 6,9 Hz; 1 H, OCH), 8,43 and 8,63 (two br s; 2 H, NH)
5e	(CDCl$_3$) δ = 1,56 (m; 6 H, CH$_3$), 4,25 (q, J = 6,9 Hz; 1 H, NHCH), 4,92 (q, J = 6,8 Hz; 1 H, OCH), 7,74 and 7,93 (two br s; 1 H, NH)
5f	(CDCl$_3$) δ = 1,57 (d, J = 6,8 Hz; 3 H, OCHCH$_3$), 1,61 (d, J = 6,9 Hz; 3 H, NHCHCH$_3$), 4,25 (q, J = 6,9 Hz; 1 H, NHCH), 4,91 (q, J = 6,8 Hz; 1 H, OCH), 7,27 (br s; 1 H, NH)
6a	(TFA-d_1) δ = 1,68 (d, J = 6,9 Hz; 3 H, CH$_3$), 4,41 (m; 2 H, CH$_2$), 5,55 (q, J = 6,9 Hz; 1 H, CH)
6b	(TFA-d_1) δ = 1,68 (d, J = 7,2 Hz; 3 H, CH$_3$), 5,06 and 5,21 (AB$_q$, J_{AB} = 15,9 Hz; 2 H, CH$_2$), 5,07 (q, J = 7,2 Hz; 1 H, CH)
6c	(CDCl$_3$) δ = 0,98 (d, J = 6,6 Hz; 3 H, CH$_3$), 1,04 (d, J = 6,6 Hz; 3 H, CH$_3$), 2,23 (m; 1 H, CH(CH$_3$)$_2$), 4,20 (t, J = 6,5 Hz; 1 H, NHCH), 4,48 and 4,86 (AB$_q$, J_{AB} = 15,8 Hz; 2 H, CH$_2$), 7,66 (d, J = 6,6 Hz; 1 H, NH)
6d	(CDCl$_3$) δ = 1,03 (m; 6 H, CH(CH$_3$)$_2$), 1,50 (m; 3 H, OCHCH$_3$), 2,32 (m; 1 H, CH(CH$_3$)$_2$), 3,9−4,4 (m; 1 H, NHCH), 5,14 and 5,38 (two m; 1 H, OCH), 7,1−7,8 (br m; 1 H, NH)
6e	(CDCl$_3$) δ = 1,50 (m; 6 H, CH$_3$), 4,32 (m; 1 H, NHCH), 5,16 (m; 1 H, OCH), 7,5−8,1 (br m; 1 H, NH)

stannous octoate and the amide function of the morpholine-2,5-diones and polydepsipeptides. This interaction may be hindered in morpholine-2,5-diones with R^1 = CH(CH$_3$)$_2$ (5c and 5d) for steric reasons, and explains the higher molecular weight obtained for polymer 6c compared with 6b.

Comparison of the optical rotations (Tab. 3) of polymer 6c obtained by ring-opening polymerization and dry heating of the sodium salt of N-(2-chloroacetyl)-(S)-valine (=matrix polymerization), with $[\alpha]_D^{25}$ = +44° and +43°, respectively, indicates that both polymerizations proceed without racemization at the chiral centre of amino acid residue.

Investigation whether racemization occurred at the chiral centre of the lactic acid residue could not be performed, because polymerization of the optically pure morpholine-2,5-dione derivative 5f failed. Compound 5f requires elevated reaction temperatures to perform the polymerization in the melt. At a temperature of 165 °C, brown

reaction products were obtained, indicating severe decomposition, which was confirmed by ^{1}H NMR analysis. On the other hand, the diastereomeric mixture (**5e**) consisting of (3S,6S) **5f** and its (3S,6R) diastereomer in a ratio of 1:1 could be polymerized at 134 °C (see **6e**, Tab. 2) because of its lower melting point of 129 – 137 °C. Thus, reaction temperatures cannot be raised too high because an increase of the temperature gives an increased rate of depolymerization and side reactions resulting in lower molecular weight of the polymer. In addition, elevated reaction temperatures may lead to racemization, as has been reported by Kricheldorf et al. for the bulk polymerization of (S)-lactide using stannous octoate as an initiator[24]. Higher reaction temperatures may however be necessary to accomplish higher conversions (Tab. 2). To reach higher conversions, longer reaction times may be considered, but prolonged reaction times will lead to depolymerization and side reactions. To improve conversions and molecular weights, polymerization conditions like reaction temperature, reaction time and monomer/initiator ratio will have to be optimized.

Polydepsipeptides **6c**, **6d** and **6e** were soluble in dichloromethane, chloroform, DMF, methanol, 2,2,2-trifluoroethanol and trifluoroacetic acid. Polymers **6a** and **6b** were soluble in 2,2,2-trifluoroethanol and trifluoroacetic acid.

Glass transition temperatures (T_g) (Tab. 3) of the polydepsipeptides varied from 93 to 117 °C, as measured by DSC. T_g-values decreased with increasing number and size of substituents (CH$_3$, CH(CH$_3$)$_2$). Polymer **6c** obtained by ring-opening polymerization and by matrix polymerization had different T_g-values, 99 and 93 °C, respectively. Probably, this is due to different molecular weight distributions, as indicated by GPC/LALLS measurements. The discrepancy in T_g-values for polymer **6d** obtained by ring-opening polymerization and by matrix polymerization can be explained by different ratios of (R)- and (S)-lactic acid in both polymers.

DSC analysis of the polymers **6a**, **6d** and **6e**, which contain racemic lactic acid moieties, showed no crystallinity, e. g., no melting point was observed. Polymer **6b** is optically pure, and therefore the occurrence of crystallinity was expected, which was confirmed by its melting point (T_m = 221 °C (lit.[6]: T_m = 232 °C)). On the other hand, polymer **6c**, which is also optically pure, revealed no melting point. Moreover, when a sample of **6c** was cooled from the liquid phase (T = 250 °C) to room temperature, a completely transparent polymer was obtained. Obviously, polymer **6c**, despite its optical purity, is unable to crystallize.

Conclusion

Morpholine-2,5-dione derivatives can be synthesized with good to moderate yields by cyclization of sodium salts of N-(2-halogenacyl)-amino acids and/or by depolymerization of the oligomeric and polymeric depsipeptides obtained in the cyclization reaction. Lactone ring-opening polymerization in the melt of morpholine-2,5-diones using stannous octoate as an initiator is a suitable route for the synthesis of alternating polydepsipeptides. Polymerization of (S)-3-methylmorpholine-2,5-dione (**5b**) and (S)-3-isopropylmorpholine-2,5-dione (**5c**) is most promising, e. g., giving polymers with the highest molecular weights. The alternating polydepsipeptides synthesized are amorphous, except for poly((S)-alanine-*alt*-glycolic acid) (**6b**), which is semi-crystalline.

Our current research involves optimization of the polymerization conditions for the various morpholine-2,5-dione derivatives and evaluation of the polydepsipeptides towards their degradation behaviour.

Experimental part

Materials: Reagents used were purchased from Merck (Darmstadt, W.-Germany), except for stannous octoate which was purchased from Sigma Chem. Corp. (St. Louis, USA). Thionyl chloride was distilled from triphenylphosphite before use. Dry toluene was obtained by distillation from calcium hydride.

Monomer synthesis

N-(2-Halogenoacyl)amino acids **3a−e**: These compounds were prepared according to the procedures described by Fischer et al. [12a−e] in 60−80% yields.

Morpholine-2,5-dione derivatives **5a−f** *(Tab. 1) (Procedure A):* A solution of the appropriate *N*-(2-halogenoacyl)amino acid (**3a−e**) (0,15 mol) in 200 ml of water was adjusted to pH 7,0 by slow addition of a 1 M NaOH solution. The solution was subsequently concentrated i. vac. to give a syrup. The syrup was stripped three times with ethanol to yield the hygroscopic sodium salt. The salt was dissolved in 300 ml of methanol, whereupon 50 g of Celite® 545 was added and the methanol was evaporated. To the residue, 300 ml of methanol was added and the solvent was evaporated again. This procedure was repeated once more. After drying for 48 h in an exsiccator on KOH, the product was transferred to a large sublimator. The mixture was dried for another 2 h at 80 °C ($P = 0,05 - 0,08$ mbar). Next, the temperature was raised to 130 °C, whereupon the reaction started and the morpholine-2,5-dione derivative formed sublimated. After 4 h, the temperature was raised to 150 °C and the reaction was continued until no more of the reaction product sublimed. The crude morpholine-2,5-dione derivative was collected and recrystallized from the appropiate solvent (Tab. 1).

^{1}H NMR: see Tab. 4.

Morpholine-2,5-dione derivatives **5b** *and* **5c** *(Procedure B):* *N*-(chloroacetyl)-(*S*)-alanine (**3b**) (24,8 g; 0,15 mol) or *N*-(chloroacetyl)-(*S*)-valine (**3c**) (29,0 g; 0,15 mol) were submitted to procedure A. The residue which remained after sublimation of the morpholine-2,5-dione derivative was mixed with 1,50 g of Sb$_2$O$_3$ and heated to 230−250 °C i. vac. ($P = 0,05 - 0,08$ mbar) in a sublimator until no more reaction product sublimed from the reaction mixture (ca. 2 h). The crude sublimate was collected and resublimed i. vac. at 145 °C for **5b** and at 100 °C for **5c**. The sublimate was collected and recrystallized from the appropiate solvent (see Tab. 1) to give 5,80 g (30%) of **5b** or 5,90 g (25%) of **5c**.

^{1}H NMR: see Tab. 4.

5b: $[a]_D^{25} = -35°$ ($c = 0,2$ g/dl in CHCl$_3$), opt. purity: 51%.

5c: $[a]_D^{25} = 26°$ ($c = 0,2$ g/dl in CHCl$_3$), opt. purity: 70%.

(S)-2-Bromopropionic acid **(7)**: This compound was prepared as described by Harfenist et al. [17] for the preparation of the *R* enantiomer. Yield: 60%, $[a]_D^{25} = -45,5°$ (neat) (Lit. [17] for the *R* enantiomer: $[a]_D^{20} = +45,6°$ (neat)).

(S)-2-Bromopropionyl chloride **(8)**: A solution of 25,4 g (0,166 mol) of **7** in 20,7 g (0,174 mol) of thionyl chloride was heated at 60 °C for 8 h. The reaction mixture was distilled and the fraction distilling at 52−53 °C ($P = 65$ mbar) collected to yield 16,0 g (58%) of **8** as a colorless oil.

N-((S)-2-Bromopropionyl)-(R)-alanine **(10)**: Reaction of (*R*)-alanine **(9)** and **8** following the procedure described by Fischer et al. [12e] for the preparation of *N*-((*R*,*S*)-2-bromopropionyl)-(*S*)-alanine (**3e**) yielded 5,50 g (60%) of **10** after recrystallization from acetonitrile. M. p. 170 °C (dec.). $[a]_D^{25} = -5,5°$ ($c = 0,2$ g/dl in EtOH).

^{1}H NMR (CD$_3$OD): $\delta = 1,41$ (d, $J = 7,3$ Hz; 3 H, NHCHC$\underline{H}_3$), 1,76 (d, $J = 6,8$ Hz; 3 H, BrCHC$\underline{H}_3$), 4,37 (q, $J = 7,3$ Hz; 1 H, NHC$\underline{H}$CH$_3$), 4,51 (q, $J = 6,8$ Hz; 1 H, BrC$\underline{H}$CH$_3$).

$C_6H_{10}BrNO_3$ (224,06)	Calc.	C 32,16	H 4,50	N 6,25
	Found	C 32,20	H 4,45	N 6,26

Diastereomeric mixture of (3R,6S) and (3R,6R)-3,6-dimethylmorpholine-2,5-dione (**12**): 4,80 g (21,4 mmol) of **10** was submitted to procedure A to give a mixture of diastereomers **12** (ratio (3R,6S):(3R,6R) = 1:3). The yield after recrystallization from toluene was 1,70 g (56%). ¹H NMR: see compound **5e**. $[a]_D^{25}$ = +116° (c = 0,2 g/dl in CHCl₃).

Polymerizations

Matrix polymerization of sodium salts of N-(chloroacetyl)-(S)-valine (**4c**) *and (R,S)-2-bromo-propionyl)-(S)-valine* (**4d**): N-(chloroacetyl)-(S)-valine (**3c**) (27,0 g; 0,139 mol) or N-((R,S)-2-bromopropionyl)-(S)-valine (**3d**) (42,7 g; 0,169 mol) were submitted to Procedure A. The residue which remained after sublimation of the morpholine-2,5-dione derivative was stirred with DMF and filtrated. The filtrate was added dropwise to a twenty-fold excess of water with stirring. The precipitated polymer was collected and dried i. vac. The dried polymer was dissolved in chloroform, precipitated in a twenty-fold excess of diethyl ether, collected by filtration and dried i. vac. at 60 °C for 4 h to give 10,0 g (46%) of poly((S)-valine-*alt*-glycolic acid) (**6c**) or 3,8 g (13%) of poly((S)-valine-*alt*-(R,S)-lactic acid) (**6d**). For characterization of the polymers see Tab. 3.

Ring-opening polymerization of **5a** − **f** (Tabs. 2, 3): Polymerization tubes (10 ml) were silanized using trimethylsilyl chloride (20 vol.-% in toluene), followed by washing with toluene and methanol. The tubes were dried at 80 °C i. vac. for 3 h and subsequently cooled to room temperature in a dry argon atmosphere. 8 mmol of the appropiate morpholine-2,5-dione derivative was placed in the tube, and 50 μl of a 6,40 · 10⁻³ M solution of stannous octoate (to give mole ratio M/I = 250) in dry toluene was added. The solvent was removed by evaporation i. vac. and the tube purged with dry argon for several times. The tube was sealed i. vac. (P = 0,08 mbar) and placed in an oil bath at the desired temperature (Tab. 2). After 48 h, the tube was cooled to room temperature and opened. Polymers **6a** and **6b** were dissolved in trifluoroacetic acid (TFA) and precipitated in a twenty-fold excess of ethanol. Polymer **6c** − **f** were dissolved in chloroform and precipitated in a twenty-fold excess of ethanol. Polymers **6c** − **f** were dissolved in chloroform and precipitated in a twenty-fold excess of diethyl ether. The polymers were collected and dried i. vac. at 60 °C for 4 h.

¹H NMR see Tab. 4.

Methods

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

¹H NMR and ¹³C NMR spectra were recorded with a Nicolet NT 200-WB spectrometer with tetramethylsilane as an internal standard.

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

Elemental analyses were carried out by A. M. Montanaro-Christenhusz of the Laboratory of Chemical Analysis of the University of Twente.

Gel permeation chromatography (GPC)/low-angle laser light scattering (LALLS) measurements were carried out with dichloromethane as the eluent using a Waters Model GPC-200 apparatus and a Chromatix KMX-6 light scattering photometer operating at 633 nm. The GPC apparatus was equipped with four series of styragel colums, 10⁵, 10⁴, 10³ and 500 Å in pore size. Static LALLS measurements were performed in 2,2,2-trifluoroethanol using a Chromatix KMX-6 light scattering photometer operating at 633 nm. The necessary refractive increments (dn/dc) were determined with a Brice-Phoenix differential refractometer at 633 nm.

DSC measurements were carried out with a Du Pont 990 thermal analyzer and cell base. The samples (5 mg) were heated at a rate of 10 °C/min to 250 °C and kept at 250 °C for 5 min. Thereafter the samples were cooled at a rate of 10 °C/min to 40 °C and heated for a second time at a rate of 10 °C/min. Glass transition temperatures (T_g) and melting points (T_m) were determined from the second heating run.

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