Synthesis of Copolymers of Isocyanides Derived from Alanylserine and Alanylhistidine

H. G. J. Visser, R. J. M. Nolte,* J. W. Zwikker, and W. Drenth*

Laboratory for Organic Chemistry of the University, 3522 AD Utrecht, The Netherlands

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Three optically active isocyanides were synthesized from the dipeptides L-Ala-L-Ser, L-Ala-D-Ser, and L-Ala-L-His by converting the amino group of these compounds into an isocyanato function. These isocyanides, as well as n-dodecyl isocyanide, were mixed in various monomeric ratios and polymerized with catalytic amounts of nickel(II) chloride. The resulting optically active copolymers have left-handed helical configurations. Their molecular weights are in the \( M_n \) range 70000–250000. The number of imidazole, carboxyl, and hydroxymethyl functions in the copolymers were determined by potentiometric titration. Two types of imidazolyl functions are present in the copolymers:

The parts concerning the esterolytic activity and enantioselectivity have been described before by Van der Eijk et al.1-3 In the preceding paper2 we reported on the advantages of synthesizing polymers of isocyanides that combine imidazolyl, carboxyl, and hydroxymethyl groups in one molecule. In that paper the synthesis of three isocyanides derived from diastereomeric alanylhistidinylserine tripeptides is described. Homopolymerization afforded the corresponding polymers.

In the work described in the present paper, the desired combination of functional groups is obtained by copolymerization of isocyanides derived from dipeptides. The parts concerning the esterolytic activity and enantioselectivity will be published separately.4 The surprising effect of surfactants on these properties has been described in preliminary communications.4,6

Results and Discussion

Two types of protected isocyanide monomers were synthesized, one containing a carboxylic acid and an imidazole residue, 5c, the other containing a carboxylic acid and a hydroxymethyl residue. The latter monomer was prepared in two diastereomeric forms, 5a and 5b. The synthetic route is given in Scheme I.

Copolymerization was achieved by mixing appropriate molar ratios of the monomers in the starting mixtures are listed in Table I. For comparison, isocyanides 5 were also prepared in order to study the effect of a hydrophobic moiety in the polymer.

Copolymerization was achieved by mixing appropriate amounts of various isocyanides 5 and dodecyl isocyanide 6, dissolved in chloroform and subsequently adding 0.1 mol% of nickel(II) chloride dissolved in methanol. The molar ratios of the monomers in the starting mixtures are listed in Table I. For comparison, isocyanides 5 were also homopolymerized.

The polymerizations were followed by observing the disappearance of the isocyanides in TLC and in the infrared absorption spectra of the reaction mixtures. The isocyanide absorptions in the infrared spectra were suf-
Synthesis of Copolymers of Isocyanides


Table I. Homopolymerization and Copolymerization of Isocyanides 5 and 6

<table>
<thead>
<tr>
<th>monomer ratio in starting mixture</th>
<th>5a</th>
<th>5b</th>
<th>5c</th>
<th>6</th>
<th>react time, h</th>
<th>product</th>
<th>yield %</th>
<th>polymer composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>&lt;0.5</td>
<td>7</td>
<td>86</td>
<td>5a</td>
</tr>
<tr>
<td>1:2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>&lt;0.5</td>
<td>7</td>
<td>86</td>
<td>5a</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>&lt;0.5</td>
<td>12</td>
<td>65</td>
<td>5a, 5b</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>1.5</td>
<td>13</td>
<td>53</td>
<td>5a, 5b</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>1.5</td>
<td>14</td>
<td>90</td>
<td>5a, 5b</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 0.1 mol % of NiCl₂·6H₂O in chloroform–methanol, 4:3:1 v/v, 25 °C. * Ratio of repeating units derived from 5 and 6 in the deprotected polymers as determined by both elemental analysis and potentiometric titration. * See ref 10.

The N(Im)-tosyl group in compounds 6p–14p was removed by treatment with acetic anhydride and pyridine. In order to remove the remaining protective groups, these polymers as well as 7p and 8p were subsequently treated for 2 days with 0.5 M aqueous NaOH or KOH at 40 °C. During this reaction no hydrolysis of the polymer imino functions occurred, as we checked separately. After ultrafiltration and freeze-drying, polymers 7dp and 8dp (dp stands for deprotected) were obtained as sodium salts and polymers 11dp–14dp as potassium salts. Polymers 9dp and 10dp were isolated as hydrochloric acid salts from their acidified aqueous solutions. Compounds 7dp, 9dp, and 11dp are spongy solids, varying in color from light-brown to brown; the other compounds are dark-brown powdery solids. From elemental analyses and potentiometric titrations the ratios of the various repeating units in the copolymers were calculated. These ratios are presented in Table I. All deprotected polymers contained crystal water in varying amounts. In addition, 8dp contained small amounts of acetyl groups. Polymers 7dp and 8dp are completely soluble in water at pH's >6. Below pH 6 precipitation occurs. In the pH range 3–11, homopolymer 9dp and the copolymers 10dp–14dp are soluble in water.

In Table II the intrinsic viscosities of the protected and deprotected polymers are given. The intrinsic viscosity is the intercept at \( c = 0 \) of the reduced viscosity vs. concentration plot. For all protected polymers except 11p these plots are linear.

By applying the Mark–Houwink equation as determined for poly(1-methylpentyliminomethylene), the molecular weights of the polymers are estimated to be in the range of 60 000–250 000 (Table II). It is noteworthy, that in the series of the protected compounds 7p–14p, there seems to

Table II. Viscosity and Optical Rotation Data of Polymers and Copolymers of Isocyanides 5 and 6

<table>
<thead>
<tr>
<th>no.</th>
<th>$\eta$, $\text{dL/g}^0$</th>
<th>$10^{-5} M$, $^b$</th>
<th>$[\alpha]^{20D}_D$ deg</th>
<th>screw sense</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>4.1</td>
<td>0.15</td>
<td>2.5</td>
<td>$+205$ - $63$</td>
</tr>
<tr>
<td>8</td>
<td>0.35</td>
<td>0.63</td>
<td>3.1</td>
<td>$-33$ - $57$</td>
</tr>
<tr>
<td>9</td>
<td>1.0</td>
<td>0.05</td>
<td>1.15</td>
<td>$+139$ + $126$</td>
</tr>
<tr>
<td>10</td>
<td>3.1</td>
<td>0.60</td>
<td>2.2</td>
<td>$+134$ - $43$</td>
</tr>
<tr>
<td>11</td>
<td>3.9</td>
<td>0.42</td>
<td>2.5</td>
<td>$+174$ - $130$</td>
</tr>
<tr>
<td>12</td>
<td>3.1</td>
<td>0.55</td>
<td>2.2</td>
<td>$+115$ - $30$</td>
</tr>
<tr>
<td>13</td>
<td>1.0</td>
<td>0.20</td>
<td>1.15</td>
<td>$+59$ - $87$</td>
</tr>
<tr>
<td>14</td>
<td>0.45</td>
<td>0.08</td>
<td>0.73</td>
<td>$+28$ - $82$</td>
</tr>
</tbody>
</table>

*Measured at 30.00 °C in CHCl$_3$-MeOH 5:2 v/v (p) or in 0.02 M Tris buffer pH 8.0 (dp). $^b$Calculated from viscosity data of protected polymers.

Figure 2. (A). CD spectra of homopolymer 8p and copolymer 14p in chloroform–methanol, 5:2 v/v. (B). CD spectra of homopolymer 7p and copolymers 10p–13p in chloroform–methanol, 5:2 v/v.

to the n–π* transition of the N=C chromophore of the polymer main chain.\(^{15}\) Except for 14dp an n–π* transition of the N=C chromophore is not clearly visible in the UV spectra of the unprotected polymers. The spectra of all the deprotected polymers, except for 14u, look alike and do not show pronounced peaks or shoulders.

CD spectra of poly(iminomethylenes) often reveal which screw sense is in excess.\(^{14,15}\) In many cases, so-called exciton coupled can be detected which give information about the screw sense.\(^{16}\) These exciton coupled are often partly or completely masked by bands due to the chiral side chains of the polymers. The CD spectra of polymers 8p and 14p are depicted in Figure 2, part A. In both spectra a positive couplet is visible, indicative of a predominantly left-handed (M) helical configuration.\(^{15}\) The CD spectrum of 14p the couplet is partly masked by the band due to the side chain contribution to the n–π* transition. The CD spectra of the polymers 7p, 10p–13p (Figure 2, part B) show a great similarity in shape. The couplet is not visible at all. On first sight, the high intensity in Δε at approximately 310 nm might be ascribed to the tosyl group. However, this cannot be true since this peak is also present in the spectrum of 7p. The latter compound does not have a tosyl group. We assume that the side chain contributions to the n–π* transition of the C=N chromophore are responsible for the observed CD bands. Apparently, these side chain contributions are much larger than the contribution of the helical main chain. The Δε values of copolymers 10p–12p are lower than those of homopolymer 7p. Noteworthy is the increase in Δε of copolymer 13p compared to the closely related 11p from which it only differs by the presence of the dodecyl moiety. This phenomenon is not yet understood. In Figure 1, part B the Δε values at 307 nm of the polymers 10p, 11p, and 12p are compared with those of the homopolymers 7p and 9p and their mixtures. The figure clearly shows that the polymers are real copolymers.

The CD spectra of the deprotected polymers are given in Figure 3. There is a qualitative similarity regarding the CD spectral shape of the deprotected polymers 7dp, 8dp, 10dp–14dp. This similarity suggests the same screw sense in these polymers, i.e., an M screw based on the presence of a positive couplet at ~300 nm. The CD


Figure 1. (A). Specific optical rotation of copolymers (●) and mixtures of homopolymers (○) as a function of polymer composition. (B). A* at 307 nm in the CD spectrum of copolymers (●) and mixtures of homopolymers (○) as a function of polymer composition. be a correlation between the intrinsic viscosity and the rate of polymerization. The most striking examples of this are 7p and 8p and 11p and 14p. Apparently, the side chains of the monomers leading to 7p and 11p fit more easily into the developing polymer helix than those leading to 8p and 14p.

The intrinsic viscosities of aqueous solutions of the unprotected polymers are considerably lower than those of the protected ones (Table II). Apparently, the viscosity behavior in water is quite different from that in chloroform–methanol, 5:2 v/v.

The optical rotation data (Table II) support the view that we are dealing with copolymers. With block polymers or a mixture of homopolymers a proportional behavior between specific rotation and molar ratio would be expected. The polymers 10p–12p did not show such a behavior, whereas the corresponding mixtures of homopolymers did, as we separately checked (Figure 1, part A).

On deprotection, all polymers in Table II show a shift in their [α]$^{20D}$/'s in a negative direction. Although sometimes optical rotation data can be used to answer the question which screw sense is in excess, it is more reliable to consider the circular dichroism (CD) spectra.

The ultraviolet (UV) spectra of each of the protected polymers 7p–14p in chloroform–methanol 5:2 v/v showed a shoulder at about 310 nm on the onset of a much larger band in the far UV region. This shoulder can be attributed...
Table III. pKₐ and n Values of Carboxylic Acid and Imidazole Functions of Polymers 7dp–14dp

<table>
<thead>
<tr>
<th>no.</th>
<th>COOH pKₐ</th>
<th>A ImH⁺</th>
<th>B ImH⁺</th>
<th>fraction of L-Ala-L-Ser in polymer</th>
<th>fraction of imidazole B in polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7dp</td>
<td>5.2</td>
<td>2.0</td>
<td>5.4</td>
<td>0.20</td>
<td>1.00</td>
</tr>
<tr>
<td>8dp</td>
<td>4.9</td>
<td>1.0</td>
<td>5.4</td>
<td>0.54</td>
<td>0.33</td>
</tr>
<tr>
<td>9dp</td>
<td>3.1</td>
<td>1.4</td>
<td>5.4</td>
<td>0.33</td>
<td>0.43</td>
</tr>
<tr>
<td>10dp</td>
<td>4.6</td>
<td>1.8</td>
<td>7.2</td>
<td>1.0</td>
<td>5.6</td>
</tr>
<tr>
<td>11dp</td>
<td>3.8</td>
<td>2.3</td>
<td>7.2</td>
<td>1.0</td>
<td>5.6</td>
</tr>
<tr>
<td>12dp</td>
<td>4.7</td>
<td>1.3</td>
<td>7.1</td>
<td>0.6</td>
<td>5.6</td>
</tr>
<tr>
<td>13dp</td>
<td>5.4</td>
<td>1.8</td>
<td>8.4</td>
<td>1.3</td>
<td>5.6</td>
</tr>
<tr>
<td>14dp</td>
<td>5.3</td>
<td>1.7</td>
<td>8.4</td>
<td>1.2</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*Isoeopoint. †Calculated from elemental analysis and titration data. ‡Calculated from titration data.

Figure 3. CD spectra of deprotected polymers 7dp, 8dp, and 10dp–14dp in Tris buffer.

Figure 4. Titration curve of copolymer 11dp.

spectra of 9p and 9dp have been discussed by van der Eijk. From optical rotation data it was concluded that polymers 9 predominantly have an M helical configuration, i.e., the same configuration as the other polymers mentioned above.

The ionization state of polymers 7dp–14dp as a function of pH was determined by potentiometric titration. These titration experiments revealed that the imino functions of the polymer main chain have a low basicity and remain unprotonated even at pH's <2. From the titration curves the fractions of unprotonated imidazole, αim, and of carboxylate functions, αcoo, were calculated by using the modified Henderson–Hasselbach equation:

\[
pH = pK_a - n \log \left( \frac{1 - \alpha}{\alpha} \right)
\]

The values calculated for \( pK_a(\text{ImH}^+) \) and \( pK_a(\text{COOH}) \) are presented in Table III. The titration curves give the impression that copolymers 10dp, 11dp, and 12dp have two different imidazole groups, A and B. Imidazole groups A have a normal \( pK_a(\text{ImH}^+) \) value of about 8.4. Thus, apparent values of \( pK_a(\text{ImH}^+) \) 8.4 are calculated from these curves, intermediate to those of imidazole groups A and B.

Experimental Section

Melting points were determined on a Mettler FP5/FP51 photoelectric melting point apparatus. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Infrared (IR) spectra were recorded on a Varian EM 390 instrument. Chemical shifts (δ) are given in ppm downfield from internal tetramethylsilane or sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate. Abbreviations used: s = singlet, d = doublet, q = quartet, m = multiplet, b = broad. Elemental analyses were carried out by the Elemental Analytical Section of the Institute of Chemistry TNO, Utrecht, The Netherlands. TLC was performed on silica (Schleicher and Schuell TLC Ready Plastic Foil FR-1500) and detection was effected by UV and/or iodide vapor. Column chromatography was performed on silica (Merck Kieselgel 60, 230–400 mesh). CD spectra were recorded on a home built apparatus. This instrument measures the differential absorbance (ΔA) with a sensitivity better than \( 1 \times 10^{-6} \). Solution viscosities were obtained with a Cannon-Ubbelohde viscometer. Intrinsic viscosities, optical rotation, and CD data for solutions of the deprotected polymers were obtained in 0.023 M Tris buffer, pH 8.0–8.1. Titrations were performed on Mettler automatic titrator devices types DV 10, DK 12, DK 14, and DK 25.

1-L-Histidine monohydrochloride, \([\alpha]_D^{20} +9.2^\circ (c 5, 5 M \text{HCl})\), was purchased from Fluka; L-alanine, \([\alpha]_D^{20} +9.7^\circ\), and D-alanine, \([\alpha]_D^{20} -9.4^\circ (c 2, 1 M \text{HCl})\) were purchased from BDH; L-serine, \([\alpha]_D^{20} -6.8^\circ\), and D-serine \([\alpha]_D^{20} +6.5^\circ (c 2, \text{water})\), were purchased from Aldrich.

**N-Formyl-L-alanine** (1) was prepared by formylating L-alanine with a mixture of formic acid and acetic anhydride as described previously.10

**L-Serine methyl ester hydrochloride (2a)** and **D-serine methyl ester hydrochloride (2b)** were synthesized from L-serine and D-serine through esterification with thionyl chloride in

The synthesis of this dipeptide was performed as described before. Recrystallization of the crude product from methanol–ether gave white crystals: yield 80%; mp 127–128 °C (lit. 107 mp 127–128 °C; [α]D0 −38.9° (c 1, methanol).

N-Formyl-L-allyl-1-histidine Methyl Ester (3c).
An amount of 10 g (39.8 mmol) of 2a was suspended in 150 mL of acetonitrile. After the reaction mixture was cooled to 0 °C, 4 g of triethylamine and 4.7 g (40.2 mmol) of 1 were added. After stirring this mixture at 0 °C for 15 min, coupling of 1 and 2a was effected by adding 9 g (44 mmol) of dicyclohexylcarbodiimide (DCC). The reaction mixture was subsequently stirred for 3 h at 0 °C. After standing overnight at room temperature, the dicyclohexylurea was filtered off and the remaining solution concentrated in vacuum to yield a light-yellow oil. The product was obtained by crystallization from methanol–ether as a white crystalline product: yield 7.9% (75%); mp 110–111 °C; [α]D0 −33.1° (c 2, methanol); IR (KBr) 3320 (NH), 1740 (C=O), 1665 (CH=N); 1H NMR 5:2 v/v, 30.00 °C; [α]D0 +174° (c 0.2, chloroform–methanol, 5:2 v/v); ν 3142 cm−1 (NH), 1740 (OCOCH3), 1670 (NHCO), 1600 (C=O), 1580 (C=O), 1525 (N=C). This polymer was synthesized as described previously.

Polymerization.
The following stock solutions were prepared: A, 0.5 M of 5a in chloroform; B, 0.5 M of 5b in chloroform; C, 0.5 M of 5c in chloroform–methanol (9:1 v/v); D, 0.5 M of 6 in chloroform; E, 2 × 10−3 M of NiCl2.6H2O in methanol.

Homopolymer 7p. Isocyanide 5a was polymerized by adding 0.7 mL of stock solution E to 3 mL of stock solution A. The reaction was completed within 0.5 h. The solvent was removed in vacuum and the dark-yellow residue dissolved in 5 mL of hot chloroform. While stirring, the solution was added dropwise to a 50-fold excess of methanol–water 1:3 v/v. The precipitate was filtered off, washed with ether and water and dried in vacuum to yield 320 mg (87%) of 7p as a pale yellow solid: [α]D0 +205° (c 0.2, chloroform–methanol, 5:2 v/v); ν 3142 cm−1 (NH) [α]D0 +7.6° (c 0.2, chloroform–methanol, 5:2 v/v), 30.00 °C; IR (KBr) 3320 (NH), 1740 (OCOCH3), 1670 cm−1 (NHCO). This polymer was synthesized as described previously.

Copolymer 11p. This polymer was synthesized as described for 7p by using 0.7 mL of stock solution E and 3 mL of stock solution B. The polymerization took 4 h and yielded 285 mg (78%) of 8p as a light-brown powder: [α]D0 +33° (c 0.2, chloroform–methanol, 5:2 v/v); ν 3142 cm−1 (NH) [α]D0 +174° (c 0.2, chloroform–methanol, 5:2 v/v), 30.00 °C; IR (KBr) 3320 (NH), 1740 (OCOCH3, COOCH3), 1670 cm−1 (NHCO). This polymer was synthesized as described previously.
Manganese(III) γ-Lactone Annulation with Substituted Acids

William E. Fristad,* John R. Peterson, and Andreas B. Ernst

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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Manganese(III) acetate oxidation of several HOOCCH₂X, X = electron withdrawing group, in the presence of alkenes led to the formation of α-substituted γ-lactones. Chloroacetic acid gave α-chloro γ-lactones, which were converted in two steps to the corresponding α,β-unsaturated γ-lactones. 3-Chloropropionic acid led to the α-methylene γ-lactone after base induced elimination of HCl. Cyanooic acid produced α-cyan γ-lactones which could be hydrolytically decyanated or converted to the α-methylene γ-lactones in two steps. Potassium methyl malonate was oxidized and annulated onto alkenes to give α-carboxymethoxy γ-lactones in reasonable yields. The method demonstrates a general route into several useful types of substituted γ-lactones.

The annulation of a γ-lactone ring onto an alkene by manganese(III) acetate, [Mn₃O(OAc)₉(OAc)₃(HOAc)₃]H₂O = [Mn₃O], according to eq 1 has been examined by us and others. In addition, limited studies of substituted acetic acid, XCH₂COOH, X = Me,CHO, CN, have been reported (1-3).


Polymer 7dp was obtained as a voluminous, spongy, yellow-brown solid: yield 190 mg (95%); [α]₀D = -130° (c 0.2, Tris buffer); [7] 0.42 dl/g (Tris buffer 30.00 °C). Anal. Calc. for C₁₅H₂₀N₃O₅K₅O₄(H₂O)₃: C, 44.4; H, 5.4; N, 18.0; O, 30.0; K, 2.2. Found: C, 44.6; H, 5.2; N, 18.0; O, 30.1; K, 2.1. IR (KBr) data as for 5dp in 5 cm⁻¹.

Polymer 12dp was obtained as a dark-brown powdery solid: yield 256 mg (50%); [α]₀D = -87° (c 0.2, Tris buffer); [7] 0.55 dl/g (Tris buffer, 30.00 °C). Anal. Calc. for C₃₇H₄₁N₉O₁₀₂K₉O₄(H₂O)₆: C, 42.5; H, 5.4; N, 18.3; O, 29.3; K, 4.5. Found: C, 42.7; H, 5.2; N, 18.2; O, 29.6; K, 4.3. IR (KBr) data as for 5dp in 5 cm⁻¹.