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 isocyano 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 \( M_u \) range 70,000–250,000. The number of imidazolyl, carboxyl, and hydroxymethyl functions in the copolymers were determined by potentiometric titration. Two types of imidazolyl functions are present in the copolymers:

- Type A with \( pK_a (\text{ImH}^+) \approx 7 \) and type B with \( pK_a (\text{ImH}^+) \approx 9.5 \). The fraction of imidazole groups B increases with decreasing amounts of Ala-Ser residues in the copolymers.

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.

Coupling of \( N \)-formyl-L-alanine, 1, and compounds 2 by applying the dicyclohexylcarbodiimide method afforded compound 3. Group X of 3 had to be protected prior to the synthesis of 5. The imidazolyl function of 3c was protected by the tosyl group (Tos) and the hydroxyl function of 3a and 3b by the easily removable acetyl group. The isocyanides 5a and 5b were obtained by the phosphorus oxychloride/triethylamine procedure at low temperatures. The synthesis of isocyanide 5c has been described before by Van der Eijk.

procedure by using phosphorus oxychloride and triethylamine instead of trichloroformate and \( N \)-methylmorpholine as the dehydrating agent and base.

The structures of the formamides 4 and the isocyanides 5 were confirmed by spectroscopic techniques. From \( ^1H \) NMR it appeared that no racemization had occurred within the limits of detection. The infrared absorption spectra of the various isocyanides showed characteristic isocyanide vibrations at 2145 cm\(^{-1} \) (5a,5b) and 2148 cm\(^{-1} \) (5c). \( n \)-Dodecyl isocyanide 6 was 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 sufficiently distinct to permit accurate determination of the monomer feed.

In the preceding paper 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. The surprising effect of surfactants on these properties has been described in preliminary communications.

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.

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The structures of the formamides 4 and the isocyanides 5 were confirmed by spectroscopic techniques. From \( ^1H \) NMR it appeared that no racemization had occurred within the limits of detection. The infrared absorption spectra of the various isocyanides showed characteristic isocyanide vibrations at 2145 cm\(^{-1} \) (5a,5b) and 2148 cm\(^{-1} \) (5c). \( n \)-Dodecyl isocyanide 6 was 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  

\[
H_2N-CH-COOH \rightarrow OCH-NH-CH-COOH
\]

\[
H_2N-CH-CO-CH_3 \rightarrow H_2N-CH-CO-CH_3
\]

\[
H_2N-CH-CO-CH_3 \rightarrow H_2N-CH-CO-CH_3
\]

Scheme I

\[
\text{Table I. Homopolymerization and Copolymerization of Isocyanides 5 and 6}
\]

<table>
<thead>
<tr>
<th>monomer ratio in starting mixture</th>
<th>reactn(^b) time, h</th>
<th>product</th>
<th>yield %</th>
<th>polymer composition(^c)</th>
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<tbody>
<tr>
<td>5a 5b 5c 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 1</td>
<td>&lt;0.5</td>
<td>7</td>
<td>87</td>
<td>1.00 1.00</td>
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<tr>
<td>2 1</td>
<td>&lt;0.5</td>
<td>9</td>
<td>90</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>1 1</td>
<td>&lt;0.5</td>
<td>10</td>
<td>76</td>
<td>2 1.07</td>
</tr>
<tr>
<td>1 2</td>
<td>1.5</td>
<td>13</td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>2 1</td>
<td>1.5</td>
<td>14</td>
<td>90</td>
<td>2 1.07</td>
</tr>
</tbody>
</table>

\(^{a}\) Reaction conditions: 0.1 mol % of NiCl\(_2\).6H\(_2\)O in chloroform-methanol, 4.3:1 v/v, 25 °C. \(^{b}\) Reaction time for complete conversion of isocyanide. \(^{c}\) Ratio of repeating units derived from 5 and 6 in the depolymerized polymers as determined by both elemental analysis and potentiometric titration. \(^{d}\) See ref 10.

The polymeric synthesis leading to 7, 10, 11, and 12 are very fast, even when compared to the high rate of polymerization of certain aliphatic isocyanides.\(^{13}\) The protected (p) polymers were isolated in good yields as solids varying in color from white to light-brown. The homopolymers 7p 8p and 9p are soluble in chloroform, slightly soluble in methanol, and insoluble in water, ether, benzene, and the lower straight-chain hydrocarbons. The copolymers 10p–14p are slightly soluble in chloroform and methanol, soluble in chloroform-methanol mixtures ranging from 10:1–5:2 v/v, and insoluble in water, ether, and the lower straight-chain hydrocarbons.

The N(Im)-tosyl group in compounds 9p–14p was removed by treatment with acetic anhydride and pyridine.\(^{7}\) 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 depolymerized 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 depolymerized 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-methylheptyliminomethylene),\(^{14}\) the molecular weights of the polymers are estimated to be in the range of 60000–250000 (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></th>
<th>[η], Dl/g°</th>
<th>10−5 M, b</th>
<th>[α]°p, c deg</th>
<th>screw sense</th>
</tr>
</thead>
<tbody>
<tr>
<td>no.</td>
<td>p</td>
<td>dp</td>
<td></td>
<td></td>
</tr>
<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>-33</td>
<td>-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>

a Measured at 30.00 °C in CHCl₃-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.

d: Figure 1. (A). Specific optical rotation of copolymers (●) and mixtures of homopolymers (○) as a function of polymer composition. (B). Δε at 307 nm in the CD spectrum of copolymers (●) and mixtures of homopolymers (○) as a function of polymer composition.

e: 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(aminomethylenes) often reveal which screw sense is in excess.\(14,15\) In many cases, so-called exciton couplings can be detected which give information about the screw sense.\(16\) These exciton couplings 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.\(15\) In 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


Table III. pKₐ and n Values of Carboxylic Acid and Imidazole Functions of Polymers 7dp–14dp

<table>
<thead>
<tr>
<th>no.</th>
<th>pKₐ</th>
<th>n</th>
<th>pKₐ</th>
<th>n</th>
<th>ImH⁺</th>
<th>pKₐ</th>
<th>n</th>
<th>ImH⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>7dp</td>
<td>5.2</td>
<td>2.0</td>
<td></td>
<td></td>
<td>7.2</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8dp</td>
<td>4.9</td>
<td>1.0</td>
<td></td>
<td></td>
<td>7.2</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9dp</td>
<td>3.1</td>
<td>1.4</td>
<td></td>
<td></td>
<td>7.1</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10dp</td>
<td>4.6</td>
<td>1.8</td>
<td>9.6</td>
<td>0.6</td>
<td>5.2</td>
<td></td>
<td>0.65</td>
<td>0.20</td>
</tr>
<tr>
<td>11dp</td>
<td>3.8</td>
<td>2.3</td>
<td>9.7</td>
<td>0.5</td>
<td>5.2</td>
<td></td>
<td>0.32</td>
<td>0.33</td>
</tr>
<tr>
<td>12dp</td>
<td>4.7</td>
<td>1.3</td>
<td>9.6</td>
<td>0.7</td>
<td>5.2</td>
<td></td>
<td>0.32</td>
<td>0.43</td>
</tr>
<tr>
<td>13dp</td>
<td>5.4</td>
<td>1.8</td>
<td>8.4</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14dp</td>
<td>5.3</td>
<td>1.7</td>
<td>8.4</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Isoelectric point. 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 predominately 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, α_{μναι}, and of carboxylate ions, α_{COOH}, were calculated by using the modified Henderson-Hasselbach equation: pH = pKₐ - n log ((1 - α) / α). The values calculated for n, pKₐ(ImH⁺) and pKₐ(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 pKₐ(ImH⁺) value of about 9.5. An example of such a titration is given in Figure 4.

The fraction of imidazole groups B increases with decreasing amounts of L-Ala-L-Ser residues in the polymers, as can be seen from Table III. The high value of pKₐ(ImH⁺) of imidazole groups B suggests that these groups strongly interact with neighboring carboxylate ions, for instance along the stacks of the side chains, as indicated below. When L-Ala-L-Ser residues (Table III) are inserted in these stacks the regular packing of imidazolyl and carboxylate functions is destroyed, giving rise to new sites of imidazole groups A with a lower pKₐ(ImH⁺) value. In line with this theory, homopolymer 9dp should only possess type B imidazole groups, which is indeed the case as can be concluded from Table III. The titration data for polymers 13dp and 14dp suggest that in these copolymers two types of imidazole groups are also present, which are, however, not clearly separated in the titration curves. Thus, apparent values of pKₐ(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 × 10⁻⁶. Solution viscosities were obtained with a Cannon-Ubbelohde viscometer. Intrinsinc 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.

N-Formyl-L-alanine (1) was prepared by formylating L-alanine with a mixture of formic acid and acetic anhydride as described previously. 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 presence of anhydrous pyridine.
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methanol.\textsuperscript{2} L-Histidine methyl ester dihydrochloride (2c) was obtained from L-histidine monohydrochloride by treatment with hydrogen chloride gas in methanol.\textsuperscript{10} It was used without further purification for the synthesis of Compound 5a.

N-Formyl-L-alanyl-L-histidine Methyl Ester (3c). The synthesis of this dipeptide was performed as described before.\textsuperscript{10} Recrystallization of the crude product from methanol-ether gave white crystals: yield 80%; mp 127-128 °C (lit. 11°C).

Recrystallization of the crude product from methanol-ether gave 4.8 g (q, 1, CHCH\(_3\)), 4.4 (d, 2, H, CH\(_2\)), 3.8 (s, 3, H, OCH\(_3\)), 2.1 (s, 3, H, CH\(_2\)). Isocyanide 5a is a labile compound. When kept at room temperature it decomposes within a week. However, when stored in a refrigerator under nitrogen it could be kept for about a week without appreciable decomposition.

L-Carbarylalanoyl-O-acetyl-L-serine Methyl Ester (5b). This isocyanide was synthesized from 3.4 g (13.1 mmol) of 4b as described for 5a. The product was obtained as a light yellow oil: yield 2.3 g (75%); TLC (CHCl\(_3\)-acetone, 4:1 v/v) R\(_f\) 5b 0.48, R\(_f\) 4b 0.13; [\(\alpha\)]\(_D\) -12.0° (c, 1, chloroform); IR (neat) 2145 cm\(^{-1}\) (N=C) other peaks as described for 5a within 10 cm\(^{-1}\); \(\Delta\) NMR 5.43 (q, 1, H, CHCH\(_2\)), 1.5 (d, 3, H, CH\(_2\)). Other signals as described for 5a within 0.1 ppm. In contrast to 5a, 5b was stable.

L-Carbarylalanoyl-N(Im)-tosyl-L-histidine Methyl Ester (5e).\textsuperscript{10} This isocyanide was synthesized from 3.9 g (10.8 mmol) of 4c as described for 5a. Compound 5c was obtained as a crystalline white solid: yield 2.6 g (70%); TLC (CHCl\(_3\)-acetone, 4:1 v/v) R\(_f\) 5c 0.48, R\(_f\) 4c 0.10; mp 137-137.5 °C; [\(\alpha\)]\(_D\) +41.8°, (c 1, chloroform) (lit.\textsuperscript{10} mp 137.0-137.2 °C; [\(\alpha\)]\(_D\) +40.6° (c 2, chloroform).

n-Dodecyl isocyanide (6) was synthesized from n-dodecylamine as described in the literature.\textsuperscript{11}

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 \times 10\(^{-3}\) M of Nicl\(_2\)-H\(_2\)O 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: [\(\alpha\)]\(_D\) +205° (c 0.2, chloroform-methanol, 5:2 v/v); [\(\alpha\)]\(_D\) +206° (c 0.2, chloroform-methanol, 5:2 v/v); [\(\alpha\)]\(_D\) +206° (c 0.2, chloroform-methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), 1740 (OCOCH\(_3\)), 1660 cm\(^{-1}\) (NHCO).

Homopolymer 8p. 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: [\(\alpha\)]\(_D\) -33° (c 0.2, chloroform-methanol, 5:2 v/v); [\(\alpha\)]\(_D\) -31° (chloroform-methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), 1740 (OCOCH\(_3\)), 1660 cm\(^{-1}\) (NHCO).

Homopolymer 9p. The synthesis of this polymer was performed as described before.\textsuperscript{10}

Copolymer 10p. This polymer was obtained by mixing 2 mL of stock solution A and 1 mL of stock solution C in 1 mL of stock solution E. The reaction was completed within 0.5 h. Isolation of the product was achieved as described for 7p: yield 340 mg (76%) of 10p as a light-yellow powder: [\(\alpha\)]\(_D\) +134° (c 0.2, chloroform-methanol, 5:2 v/v); [\(\alpha\)]\(_D\) -12.0° (c, 1, chloroform); IR (neat) 3.1 dL/g (chloroform-methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3270 (NH), 1740 (COCH\(_3\), COOCH\(_3\)), 1660 (NHCO), 1600, 1375 and 1180 cm\(^{-1}\) (tosyl).

Copolymer 11p. This polymer was synthesized as described for 7p and 10p by mixing the following stock solutions: 1.5 mL of stock solution A, 1 mL of stock solution C, 3 mL of stock solution E. The reaction was completed within 0.5 h and yielded 349 mg (72%) of 11p as a white solid: [\(\alpha\)]\(_D\) +174° (c 0.2, chloroform-methanol, 5:2 v/v); [\(\alpha\)]\(_D\) +175° (c 0.2, chloroform-methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3270 (NH), 1740 (COCH\(_3\), COOCH\(_3\)), 1660 (NHCO), 1600, 1375 and 1180 cm\(^{-1}\) (tosyl).

Copolymer 12p. This polymer was synthesized as described for 7p and 10p by using 1 mL of stock solution A, 2 mL of C, and 0.5 mL of E. The reaction was completed within 0.5 h and yielded 340 mg (65%) of 12p as a white solid: [\(\alpha\)]\(_D\) +115° (c 0.2, chloroform-methanol, 5:2 v/v); [\(\alpha\)]\(_D\) -116° (chloroform-methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), (OCOCH\(_3\), COOCH\(_3\)), 1660 (NHCO), 1600, 1375 and 1180 cm\(^{-1}\) (tosyl).

Copolymer 13p. This polymer was synthesized as described for 7p and 10p by using 2 mL of solution A, 2 mL of C, 1 mL of D, and 1.2 mL of E. The polymerization took 1.5 h and yielded 380 mg (53%) of 13p as a white solid: [\(\alpha\)]\(_D\) +59° (c 0.2, chloroform-methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), 1740 (OCOCH\(_3\), COOCH\(_3\)), 1660 (NHCO), 1500, 1375 and 1180 cm\(^{-1}\) (tosyl).

Copolymer 14p. This polymer was synthesized as described for 7p and 10p by using 1.5 mL of stock solution B, 1.5 mL of C, and 0.7 mL of E. The polymerization took 3 h and yielded 340 mg (90%) of 14p: [\(\alpha\)]\(_D\) +28° (c 0.2, chloroform-methanol, 5:2 v/v); [\(\alpha\)]\(_D\) -94° (chloroform-methanol, 5:2 v/v, 30.00 °C); IR (KBr) 3260 (NH), 1740 (OCOCH\(_3\), COOCH\(_3\)), 1660 (NHCO),...
Manganese(III) γ-Lactone Annulation with Substituted Acids

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Manganese(III) acetate oxidation of several HOOCC=CHX, 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-Chloropropanoic acid led to the α-methylene γ-lactone after base induced elimination of HCl. Cyanoacetic acid produced α-cyano γ-lactones which could be hydrolytically decarboxylated or converted to the α-methylene γ-lactones in two steps. Potassium methyl malonate was oxidized and annulated onto alkenes to give α-carbomethoxy γ-lactones in reasonable yields. The method demonstrates a general route to several useful types of substituted γ-lactones.

The annulation of a γ-lactone ring onto an alkene by manganese(III) acetate, [MnO(OAc)₂(OAc)(HOAc)]:SH₂O = [MnO], according to eq 1 has been examined by us² and others.³ In addition, limited studies of substituted acetic acid, XCHO₂COOH, X = Me,³²CN,³⁶ have been reported

\[ RCH=CHO₂COOH \rightarrow RCH₂C(OH)CO₂H \]

including the use of malonic acid to generate spiro di-lactones.⁸ Our interest in furthering the use of Mn(III) in organic synthesis, and the desirability of a simple, one-step route to α-substituted γ-lactones led us to investigate the Mn(III) oxidation of a number of acids. This paper outlines our results with chloroacetic, 3-chloro-propanoic, cyanoacetic, and monomethyl malonic acid.