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Optically Active Polyampholytes Derived from L- and D-Carbarylalanyl-L-histidine

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ABSTRACT: Two optically active polymers with the general structure \( [\text{C}=\text{NCH}(\text{CH}_2\text{COOH})\text{C(O)}\text{NHCH}^\text{CH}_2\text{Im}])_n \), were prepared by the polymerization of L- and D-carbarylalanyl-L-histidine with catalytic amounts of nickel(II) chloride. The monomers were synthesized from the dipeptides L- and D-alanyl-L-histidine by converting the amino group of these compounds into an isocyano function. The polymer from D-alanyl-L-histidine has a \( \text{pK}_{\text{a}}(\text{ImH}^+) \) of 9.4. It shows a polyelectrolyte viscosity behavior. Its molar rotation is \( [\alpha]_2^\oplus c = +102^\circ \). The CD spectrum contains a single positive band, which does not provide information about the screw sense.

Enzymes combine high catalytic activity with high selectivity. Certain polymeric model systems, called synthazymes, have equal or even greater activity. Striking examples are the ethylenimine-based systems developed by Klots et al. and very recently by Kunitake et al. The success in this field contrasts sharply with the little progress that has been made in imitating the enantioselectivity of enzymes. In our opinion there is a lack of appropriate chiral polymers which can be tested as enantioselective catalysts. We are currently investigating whether poly(isocyanides), more properly called poly(iminomethylenes), \( [\text{RN}=\text{C}<]_n \), are useful as such polymers. These compounds are attractive for two reasons. First, they are readily obtainable from the monomeric isocyanides, \( \text{RN}=\text{C} \), with nickel chloride or a nickel(II) complex as catalyst. These monomers in turn can be prepared in great variety from the corresponding amines. Second, poly(iminomethylenes) have a stable helical structure. Left-handed and right-handed helices of poly(tert-butyliminomethylene) have been separated by resolution. Preferential formation of one screw occurs in the polymerization of one enantiomer of a chiral monomer.

In previous papers, we reported on the synthesis and catalytic activity of imidazole-containing poly(iminomethylenes) such as poly(carbarylhistidine), 1, which could be models for hydrolytic enzymes. We were unable to get 1 in optically active form because its carboxyl- and imidazole-protected monomer suffered from a rapid racemization. This was due to the presence of both a basic imidazole function in the molecule and two electron-withdrawing substituents at the chiral center, viz., the imidocarbonyl and carboxyl ester function.

We have now found that racemization problems can be avoided if one starts from isocyanides of dipeptides of histidine and other amino acids. The synthesis and physical properties of two polymers derived from such isocyanides, viz., poly(L-carbarylalanyl-L-histidine) and poly(D-carbarylalanyl-L-histidine), are described in this paper. Their catalytic activity in the hydrolysis of chiral esters will be described elsewhere.

Results and Discussion

Synthesis. As far as we are aware, isocyanides derived from dipeptides containing histidine have not been described in the literature. We have synthesized protected L- and D-carbarylalanyl-L-histidine, compounds 6a and 6b, according to Scheme I.

Prior to the coupling of the amino acids, the carboxyl group of histidine and the amino group of alanine were protected as the methyl ester and the formamide group, respectively. The latter protecting group was chosen because it can be transformed directly into an isocyano function. Dicyclohexylcarbodiimide in acetonitrile/N,N-dimethylformamide was used as coupling agent.

From the synthesis of 1 we learned that it is necessary to protect the imidazole nucleus before converting the N-formyl function into an isocyano group. We chose the \( p \)-toluenesulfonyl (Tos) group as an imidazole protecting group in 4. This group is easily introduced and can be removed under mild conditions, as we found recently. Moreover, a \( p \)-toluenesulfonyl group lowers the basicity of the imidazole nucleus, which reduces the chance of

(31) Mann, F. G.; Porter, J. W. G.
(37) Reference 35, p 316.
(38) Poindexter, G. S.; Meyers, A. I.
racemization during step 5 \(\rightarrow\) 6.

Isocyanides 6 were obtained by dehydration of formamides 5 with diphosgene and N-methylmorpholine. We used this combination of dehydrating agent and base because it is effective even at low temperature. This latter condition is a prerequisite for preventing racemization. To a small extent the formation of isocyanide was accompanied by detosylation of the imidazole moiety. This side reaction is probably subsequent to acylation of the imidazole ring by diphosgene. Nevertheless, the yields were satisfactory. After purification, 6a and 6b were obtained in 75\% yield as odorless, white solids. The monomers were soluble in halogenated hydrocarbons, sparingly soluble in alcohols, and insoluble in diethyl ether, water, benzene, and the lower straight-chain hydrocarbons. Their infrared absorption spectra showed characteristic isocyanide stretching vibrations at 2147 ± 1 cm\(^{-1}\) and 2149 ± 1 cm\(^{-1}\) (6b). The structures were further established by \(^1\text{H}\) NMR and mass spectrometry.

We checked separately whether racemization had occurred at the chiral centers during step 5 \(\rightarrow\) 6. If racemization had occurred each of the compounds 6a and 6b would have been contaminated to a certain extent by the other diastereomer. In the \(^1\text{H}\) NMR spectra of 6a and 6b the signals of the various corresponding protons differ sufficiently to make this check possible, even without the help of a shift reagent. It appeared that within the limits of detection of the NMR technique no racemization had occurred. This result is in line with the melting behavior of the two diastereomers. Compound 6a melted sharply at 137.0 ± 0.2 °C and compound 6b at 134.5 ± 0.2 °C, whereas a 1:1 mixture of 6a and 6b had a melting range from 116 to 118 °C. Moreover, we observed that methyl 2-isocyanoalaninate, a compound which is even more sensitive to racemization than 6a and 6b, is obtained as an optically pure product under the same reaction conditions.

Monomers 6a and 6b were polymerized by treatment with 0.2 mol \% of nickel(II) chloride in 1:1 chloroform-methanol (v/v). Under these conditions reaction was complete within a few hours at room temperature. This rate of polymerization is rapid compared to that of the monomer leading to polymer 1. In the latter case we had indications that imidazole residues block coordination sites on nickel, which are required for polymerization. Apparently this does not occur with compounds 6.

Poly(iminomethylene)s 7 were isolated in good yields as light yellow solids. The \(N^m\)-tosyl group in 7a was removed by acetic anhydride and pyridine to give polymer 8a. The latter polymer was insoluble in most common solvents. It was treated with 0.5 mol/L aqueous NaOH for 2 days at room temperature to give a light reddish brown solid. After ultrafiltration and freeze-drying of the acidified solution the purified product was analyzed and found to be the HCl salt of polymer 9a, containing 0.5 molecule of HCl and two molecules of crystal water per repeating unit. Acetic anhydride and pyridine were ineffective in the removal of the \(N^m\)-tosyl group of 7b, due to incomplete solubility of the latter compound in this solvent mixture. We succeeded in removing the \(N^m\)-tosyl and ester methyl group at the same time by treating this compound with 0.5 mol/L aqueous NaOH at 40 °C for 2 days. Ultrafiltration and freeze-drying of the dark red acidified solution afforded 9b as a dark reddish brown solid, containing 0.5 molecule of HCl and two molecules of crystal water per polymer repeating unit.

Physical Properties. The protected polymers 7a and 7b were insoluble in water, ethers, benzene, and the lower straight-chain hydrocarbons. Compound 7a was slightly soluble in methanol and soluble in chloroform. Compound 7b was very sparingly soluble in chloroform only. Polymers 7a and 7b showed high optical rotations of opposite sign (Table I).

The intrinsic viscosity of 7a was found to be [\(\eta\)] = 1.04 dL/g (chloroform, 30.00 °C). The intrinsic viscosity of 7b could not be measured due to its low solubility. Applying the Mark–Houwink equation as determined for poly[(1-methylheptyl)iminomethylene], [\(\eta\)] = 1.4 × 10\(^{-6}\)\(M_w^{1.76}\), a
molecular weight of 120,000 can be estimated for 7a.

The deprotected polymers 9a and 9b were insoluble in common organic solvents but soluble in water with a pH lower than 5 and higher than 7. In the pH range 5–7 the polymers precipitated since they have their isoelectric points in this region. These isoelectric points, as determined by the isoelectric focusing technique, were found to be 6.1 and 6.3 for 9a and 9b, respectively.

The ionization state of the imidazole and carboxylic acid functions in polymers 9 as a function of pH was determined by potentiometric titration. In accordance with the modified Henderson–Hasselbach equation

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

where \( \alpha \) stands for the fraction of unprotonated imidazole or carboxylate ions, plots of log \( \left( \frac{1 - \alpha}{\alpha} \right) \) vs. pH were linear. In Table II the values calculated for n and for \( pK_a(\text{ImH}^+) \) and \( pK_a(\text{COOH}) \) are presented as well as the \( pK_a's \) of model compounds. The \( pK_a \) of the carboxylic acid group in 9a and in 9b lies in the range which can be expected for a peptide, but its value is lower than the value of the corresponding group in 1. However, in polymer 1 the \( pK_a(\text{COOH}) \) is relatively high due to the fact that the carboxylic functions are situated close to the polymer main chain. The latter situation results in short distances between the carboxylic anions and strong interaction between them.

The \( pK_a \) value of the imidazole function in polymers 9 has increased considerably compared to the \( pK_a \) values of the model compounds in Table II. This increase suggests that the imidazole residues in 9 are strongly affected by the negative charge of the carboxylate ions. The increase is larger for 9a than for 9b. One can imagine that such a difference occurs if the distance between the imidazole rings and the carboxylate ions is larger in 9b than in 9a.

Molecular models of the two polymers show that such a difference in conformation is not unlikely.

The viscosity behavior of 9a and 9b is illustrated in Figure 1. Compound 9b behaves like a normal polyelectrolyte; that is, with increasing concentration of polymer the reduced viscosity decreases, due to the effect of counterions. The curve follows the relationship of Fuoss and Strauss for polyelectrolytes:

\[
 \eta_v = C \left( \frac{1}{Y} + \frac{1}{Y + 1} \right)
\]

where \( C \) is a constant and \( Y \) equals the intrinsic viscosity, [\( \eta \)], of the polyelectrolyte. For 9b the latter quantity was calculated to be 0.15 ± 0.01 dL/g.

A plot of reduced viscosity vs. concentration is linear for 9a. From the intercept and slope the intrinsic viscosity and Huggins constant were calculated to be \( \eta = 1.72 \) dL/g and \( k' = 0.57 \), respectively. Addition of increasing amounts of KCl to 9a lowered the reduced viscosity to about 70% of the value in the salt-free solution (Figure 1).

The difference in the hydrodynamic behavior of 9a and 9b is probably related to the width of the double layers surrounding these molecules. This width is determined by the net charge (ImH\(^+\) + COO\(^-\)) and by the distribution of these charges over the molecules. At the pH of the viscosity measurement (pH ≈ 3) both ampholytes have an approximately equal net positive charge. In 9b the positive charges are further away from the negative ones than they are in 9a (see above). Consequently, in 9b the positive charges will be located more at the outer side of the chain and the Cl\(^-\) ions will be pulled closer to the chain, giving rise to real polyelectrolyte behavior. Molecules of 9a have their surrounding Cl\(^-\) ions at a larger distance from the chain and their behavior is hardly affected by an increase in this Cl\(^-\) concentration. A polyelectrolyte effect is noted at polymer concentrations above 2 g/dL, whereas 9b shows a decrease in the viscosity at concentrations above 0.3 g/dL. The reduced viscosity of 9a is lower compared to 9b at a pH of 3.3. 

The potentiometric and viscometric data obtained for 9a and 9b are listed in Tables I and II. The data obtained for the model compounds serve to support these findings. The concentrations of KCl for these measurements were fixed at 10⁻² M (9a), 10⁻³ M (9b) and 10⁻⁴ M (9a).

Table I

<table>
<thead>
<tr>
<th>compd</th>
<th>([M]^o_{750,0} ) deg</th>
<th>compd</th>
<th>([M]^o_{750,0} ) deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>+164</td>
<td>7b</td>
<td>-700(^b)</td>
</tr>
<tr>
<td>6b</td>
<td>+75</td>
<td>9a</td>
<td>+1025</td>
</tr>
<tr>
<td>7a</td>
<td>+580</td>
<td>9b</td>
<td>0(^c)</td>
</tr>
</tbody>
</table>

\(^{a}\) Solvent (concentration in g/dL): 6a, CHCl\(_3\) (2); 6b, CHCl\(_2\) (1); 7a, CHCl\(_3\) (0.35); 7b, CHCl\(_3\) (0.05); 9a, H\(_2\)O (0.05); 9b, H\(_2\)O (0.005). The molar optical rotation of the polymers is expressed per polymer unit. \(^b\) Solutions of this compound in water are darkly colored. At the highest measurable concentration no optical rotation was observed. Estimated error ±45°. \(^c\) This compound is sparingly soluble in chloroform only. Estimated error ±10%.

Table II

<table>
<thead>
<tr>
<th>compd</th>
<th>( pK_a(\text{COOH}) )</th>
<th>( n_{\text{COOH}} )</th>
<th>( pK_a(\text{ImH}^+) )</th>
<th>( n_{\text{ImH}^+} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>2.85 ± 0.1</td>
<td>1.25 ± 0.1</td>
<td>9.4 ± 0.1</td>
<td>2.4 ± 0.05</td>
</tr>
<tr>
<td>9b</td>
<td>2.3 ± 0.2</td>
<td>3.0 ± 0.1</td>
<td>8.4 ± 0.2</td>
<td>2.2 ± 0.1</td>
</tr>
<tr>
<td>1(^b)</td>
<td>5.85</td>
<td>1.4</td>
<td>9.3</td>
<td>1.5</td>
</tr>
<tr>
<td>poly(\text{His})(^c)</td>
<td>5.9</td>
<td></td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>copoly(\text{His}–\text{Asp})(^c)</td>
<td>2.64</td>
<td></td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>( \beta )-\text{Ala}-\text{His}(^d)</td>
<td>1.82</td>
<td></td>
<td>6.0</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) In water at 25.0 °C. \(^{b}\) In 29% v/v EtOH/H\(_2\)O (see ref 14). \(^c\) See ref 28. \(^{d}\) See ref 29.
Figure 2. CD spectra of protected (solid line) and deprotected (broken line) poly(L-carbylalanyl-L-histidine), compounds 7a and 9a (compound (solvent, concentration in mol/L): 7a (CHCl₃, 2.2 × 10⁻³); 9a (water, 3.6 × 10⁻⁴)).

Figure 3. CD spectra of protected (solid line) and deprotected (broken line) poly(D-carbylalanyl-L-histidine), compounds 7b and 9b (compound (solvent, concentration in mol/L): 7b (CHCl₃, 8.5 × 10⁻⁴); 9b (water, 3.7 × 10⁻³)).

only when the much higher KCl concentration is present.

Although prepared under the same reaction conditions, polymers 9a and 9b show a striking difference in the magnitude of their intrinsic viscosities (θₛₐ/θₜₜₗₘ = 11.5) and, therefore, their molecular weights may differ. This difference may well be connected with a difference in the propagation rate of the two diastereomeric monomers 6. If so, the side chain of 6a would fit better into the growing helix than the side chain of 6b.

The UV spectra of the protected polymers 7a and 7b in chloroform 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 to the n−π* transition of the N=C chromophore of the polymer main chain. In poly(alkyliminomethylene) this transition has been found at the same wavelength position. The n−π* transition is also responsible for the CD spectra of 7a and 7b in the region from 250–400 nm (Figures 2 and 3). In this region polymer 7a shows a relatively strong positive Cotton effect, whereas polymer 7b exhibits the typical “couplet” of a helical polymer. The latter couplet is negative indicating that polymer 7b is predominantly in the right-handed P-helical configuration. This configuration should make a negative contribution to the molar optical rotation in the high-wavelength region. The optical rotation data of Table I are in line with this result: going from monomer 6b to polymer 7b, [M]₀°ₗₜₜₗ changes from +75 to −700°. In the CD spectrum of 7a no couplet is visible, either because the polymer consists of equal amounts of left- and right-handed helices or because its helical configuration does not give rise to a couplet pattern. For the moment we are not able to decide which of these two reasons is the correct one. However, it is worth mentioning here the behavior of a similar polymer derived from D-carbylalanyl-L-histidinol. Its CD spectrum shows no couplet when the polymer is protected but does show one when the polymer is deprotected, although the deprotection procedure has no effect on the number of left- and right-handed helices.

We ascribe the strong positive band in the CD spectrum of 7a primarily to the side-chain induction in the N=C chromophore. It is remarkable that this side-chain induction is almost absent in the CD spectrum of 7b. Apparently, in 7a the CD contributions of the two chiral centers in the side chain reinforce each other, whereas in 7b they compensate each other.

The UV spectra of the deprotected polymers 9a and 9b in water are presented in Figures 4 and 5. The n−π* transition of the N=C chromophore at 310 nm is not clearly visible in these spectra. An additional band is present at about 370 nm, which was not visible in the spectra of the protected polymers. The intensity of this band reversibly decreases with decreasing pH. Simultaneously, the intensity increases at higher wavelengths. In the case of 9a this behavior gives rise to an isosbestic point at 470 nm. We ascribe these absorptions to conjugation between neighboring N=C units in the polymers. This conjugation can occur if the angle between these units deviates to some extent from 90° due to electrostatic interactions of the charged imidazolyl and carboxylate groups in the side chain.

The CD spectra of the deprotected polymers 9 in water are similar to those of the protected ones in chloroform (Figures 2 and 3). These spectra reveal that the UV and visible absorptions at higher wavelengths are not CD active. In addition to the band at 310 nm the CD spectrum of 9a shows two weak bands, at 250 and 270 nm, which probably arise from the other chromophores in the polymer. The intensity of the couplet in the spectrum of 9a is lower than in the spectrum of 7b by a factor of about 5. Moreover, it was found that the intensity of 9b varies...
with pH. At pHs of 0.2, 7.0, and 12.9, $\Delta \epsilon$ at 350 nm is 0.12, 0.09, and 0.065, respectively. The origin of the intensity differences is not yet clear. Racemization of the helical main chain during the deprotection procedure might be an explanation. However, this is not likely, as the helix of poly(iminomethylenes) is stable under various conditions.

Experimental Section

Melting points were determined on a Mettler FP5/FPS1 photoelectric melting point apparatus. Rotations were measured on a Perkin-Elmer 241 polarimeter. Infrared (IR) spectra were recorded on a Perkin-Elmer 297 and 283 spectrophotometers. CD spectra were recorded on a home-built apparatus. The sensitivity of this instrument is better than $1 \times 10^{-4}$ in absorbance units. Ultraviolet (UV) spectra were recorded on a Cary 15 spectrophotometer. $^1$H NMR spectra were obtained on a Varian EM390 instrument. Chemical shifts (δ) are given in parts per million downfield from internal tetramethylsilane. Abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, dist d = distorted doublet, br = broad. Mass spectra (MS) were recorded on an AEI MS-902 mass spectrometer. Elemental analyses were carried out by the Element Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under the supervision of W. J. Buis. Solution viscosity data were obtained with a Cannon-Ubbelohde viscometer. TLC was performed on silica (Schleicher and Schüll TLC Ready Plastic Foil FR-1500) and detection was effected by UV and/or iodine. Column chromatography was performed on silica (Merck Kieselgel 60/230–400 mesh).

Starting Materials. L-Histidine monohydrochloride ([α]$_D^{19}$ +9.3° (c 5, 5 mol/L HCl)), L-alanine ([α]$_D^{19}$ +17.1 ± 1° (c 5, 5 mol/L HCl)), and d-alanine ([α]$_D^{19}$ -17.5 ± 3° (c 5, 5 mol/L HCl)) were purchased from Fluka.

L-Histidine Methyl Ester Dihydrochloride (2). This compound was obtained from L-histidine monohydrochloride through esterification with hydrogen chloride in methanol. It was used without further purification for the synthesis of 4: mp 197–199 °C (lit.29 mp 200–201 °C; [α]$_D^{19}$ +15.1° (c 1, methanol) [lit.30 +16.0° (c 1, methanol)].

N-Formyl-L-alanine (3a) and N-Formyl-D-alanine (3b). These compounds were prepared by formylation of the starting materials with acetic anhydride in formic acid. Recrystallization from acetone gave pure white crystals. 3a: mp 131 °C; [α]$_D^{19}$ -65° (c 2, 1 mol/L NaOH) [lit.32 mp 132 °C; [α]$_D^{19}$ +57° (c 2, 1 mol/L NaOH) (in our opinion the sign of the optical rotation is incorrect)]. 3b: mp 131 °C; [α]$_D^{19}$ +63° (c 2, 1 mol/L NaOH) [lit.32 mp 130 °C; [α]$_D^{19}$ -56° (c 2, 1 mol/L NaOH) (in our opinion the sign of the optical rotation is incorrect)].

N-Formyl-L-alanyl-L-histidine Methyl Ester (4a). A suspension of 14.3 g (69 mmol) of finely powdered 2 in 150 mL of 9:1 chloroform/methanol (v/v) was treated at 0 °C with dry ammonia gas for 30 min. The reaction mixture was filtered and concentrated in vacuo at 30 °C. Chloroform was added and the solution was once again concentrated in order to remove traces of ammonia. The resulting oil was dissolved in 300 mL of 3:1 acetonitrile/dimethylformamide (v/v), and 6.9 g (59 mmol) of 3a was added. The solution was cooled in ice, 12.4 g (60 mmol) of dicyclohexycarbodiimide was added, and the reaction mixture was stirred for 2 h at 0 °C. After the mixture was allowed to stand overnight at room temperature, the urea was filtered off and the solution was concentrated under an oil pump vacuum at a temperature lower than 40 °C. Acetonitrile (300 mL) was added to the obtained light brown semisolid, whereafter 4a solidified. The white solid was filtered off and dried in vacuo over P$_2$O$_5$ to give 8.5 g of 4a.

The mother liquid was concentrated and the residue dissolved in 100 mL of water in order to get another crop of 4a. The latter solution was extracted three times with 100-mL portions of dichloromethane. The pH of the water layer was adjusted to pH 8 with sodium hydroxide and sodium carbonate. After the addition of sodium sulfate the solution was extracted with 50-mL portions of 1-butanol until TLC (64 CHCl$_3$/EtOH (v/v), R$_f$(4a) 0.35) showed only traces of 4a persisting in the water layer. The combined 1-butanol fractions were concentrated to yield 5 g of 4a. The product was used without further purification for the synthesis of 5a: yield 13.5 g (51 mmol, 85%); mp 127–128 °C; IR (KBr) 3310 (NH), 1740 (COOH$_2$), 1650 (NHCO) cm$^{-1}$; $^1$H NMR (CD$_3$OD) 6 8.05 (s, 1 H, CHO), 7.65 and 6.90 (2 x s, 2 H, imidazole), 4.55 (2 x m, 2}

in exciton theory, there is also some conjugative interaction between these groups. Evidence for such conjugation in 9b comes from the UV–vis spectrum of this polymer, as outlined above (compare Pino et al.27).
H, CH3), 3.70 (s, 3 H, OCH3), 3.05 (dist d, 2 H, CH2), 1.30 (d, 3 H, CH3).

N-Formyl-d-alanyl-L-histidine Methyl Ester (4b). Synthesis was performed as described for 4a. A white precipitate was obtained after the semisolid had been stirred with 400 mL of 3:1 acetone/ethyl acetate (v/v). An additional small amount of impure 4b was obtained after the semisolid had been stirred with 400 mL of 85:15 chloroform/methanol (v/v) were added 5 g of anhydrous sodium sulfate and the chloroform was evaporated in vacuo at 40 °C. Subsequently crystallization occurred. The crystals were filtered off and from the resulting clear solution the optical ro-

tation of 4b was treated with 100 mL of 0.5 mol/L aqueous NaOH and subjected to ultrafiltration (Diaflo Ultra-Filter, UM-2). Freeze-drying of the resulting slightly moist precipitate was performed. Recrystallization from 85:15 chloroform/methanol (v/v) gave an additional amount of 1.6 g (4.0 mmol) of 6a: total yield 6.9 g (75%); white needles from methanol; mp 137.0–137.2 °C; [a]20 = +40.6 ° (2, chloroform); MS m/e 404 (M+), 350 (M' + CH2NCNH), 345 (M' + COOCH3), 249 (M' – tosyl), 235 (M' – CH3COOCH3NHC(O)(CH2NCNH)NC(OH), IR (KBr) 3300 (NH), 2147 ± 1 (NC, internal calibration), 1735 (COOCH3), 1665 (NHCO), 1600, 1375, and 1170 (tosyl) cm–1; 1H NMR (CDCl3) δ 0.0 (2 × 2, 2 H, imidazole), 7.80 and 7.35 (2 × 4, 4 H, tosyl), 7.30 (d, 1 H, NH), 4.95 (s of t, Jd = 7 Hz, Je = 5 Hz, 1 H, CH2Cl), 4.25 (s, 1 H, CH3), 3.65 (3 H, OCH3), 2.95 (s, 3 H, tosyl), 1.35 (d, 3 H, CH3). Finely powdered mixture of 15 mg of 6a and 15 mg of 6b had a melting range from 116 to 118 °C.

Poly-(1-carboxylalanyl-N-tosyl-L-histidine Methyl Ester) (7a). An amount of 5.7 mg (0.024 mmol) of NiCl2 .6H2O was added to a solution of 5 g (12.2 mmol) of 6a in 30 mL of 1:1 chloroform/methanol (v/v). After a short time the reaction mixture became cloudy and a paste was obtained after the mixture had been left for 24 h under a nitrogen atmosphere. The solu-
tion was removed in vacuo to give the polymer in quantitative yield as a light brown film. This film was used directly for the synthesis of the deprotected polymer. A sample was dissolved in a small volume of warm chloroform and this solution was added dropwise to a 30-fold excess of 3:1 methanol/water (v/v). The precipitate was filtered off, washed with 1:1 methanol/water (v/v) and ether, and dried in vacuo to yield pale yellow 7a: [α]20 = +144 ° (c 0.35, chloroform); g = 1.044 dL/g (chloroform, 30.0 °C); IR (KBr) 3260 (NH), 1740 (COOCH3), 1670 (NHCO), 1600, 1375, and 1180 (tosyl) cm–1. Anal. CaC6H10N3O3C6: C, 53.46; H, 4.95; N, 13.85; S, 7.92; O, 19.80. Found: C, 53.2; H, 5.1; N, 13.8; S, 7.7; O, 20.2.

Poly-(d-carboxylalanyl-N-tosyl-L-histidine Methyl Ester) (7b). Isocyanide 6b was polymerized quantitatively as described for 6a. After removal of the solvent a light brown solid was isolated in quantitative yield, which was used directly in the preparation of 9b. A sample of 7b was purified by stirring it in ethanol for 1 h, whereupon the polymer was filtered off and dried in vacuo. For optical rotation measurement a sample of the purified polymer was treated with 100 mL of 0.5 mol/L aqueous HC1 and subjected to ultrafiltration (Diaflo Ultra-Filter, UM-2). Freeze-drying of the resulting slightly moist precipitate was performed. Recrystallization from 85:15 chloroform/methanol (v/v) gave an additional amount of 1.6 g (4.0 mmol) of 9a: total yield 6.9 g (75%); white needles from methanol; mp 137.0–137.2 °C; [α]20 = +40.6 ° (2, chloroform); MS m/e 404 (M+), 350 (M' + CH2NCNH), 345 (M' + COOCH3), 249 (M' – tosyl), 235 (M' – CH3COOCH3NHC(O)(CH2NCNH)NC(OH), IR (KBr) 3300 (NH), 2147 ± 1 (NC, internal calibration), 1735 (COOCH3), 1665 (NHCO), 1600, 1375, and 1170 (tosyl) cm–1; 1H NMR (CDCl3) δ 0.0 (2 × 2, 2 H, imidazole), 7.80 and 7.35 (2 × 4, 4 H, tosyl), 7.30 (d, 1 H, NH), 4.95 (s of t, Jd = 7 Hz, Je = 5 Hz, 1 H, CH2Cl), 4.25 (s, 1 H, CH3), 3.65 (3 H, OCH3), 2.95 (s, 3 H, tosyl), 1.35 (d, 3 H, CH3). A finely powdered mixture of 15 mg of 6a and 15 mg of 6b had a melting range from 116 to 118 °C.
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(2) According to IUPAC nomenclature rules, the monomers are named (S)-2-[[5- and (R)-2-isocyano propionyl]amino]-3-(4-imidazolyl)propionic acid, respectively.

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