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Introduction

Anchoring of homogeneous catalysts to polymers is receiving much attention. The advantages are an easier recovery and sometimes an activity and selectivity higher than of the original species. To some extent the system approaches an enzyme in which the active site is also attached to a polymer. Therefore, the anchored catalyst systems have been used as enzyme models, e.g. imidazole anchored to vinyl and ethylenimine polymers as catalysts for the hydrolysis of activated esters. However, these systems did not show enantioselectivity in the hydrolysis of asymmetric esters. The reason might be that the structural characteristics of the supports so far studied, are too much different from those of enzymes. We are investigating the use of polyisocyanides, (R—N=C(—CH₃)), as supports for homogeneous catalysts. In earlier papers, we showed that these polymers probably have the configuration of a tightly coiled helix. Helices are chiral molecules. Poly(tert-butyl isocyanide) could even be resolved partly into its enantiomers and its screw sense derived from steric considerations as well as from CD spectra.

Polyisocyanides are obtained from the corresponding isocyanides, which in turn are synthesized from the amines. By starting from naturally occurring amino acids it might be possible to prepare polymers and copolymers of iso- cyanides which have a highly chiral structure and contain substituents which are catalytically active in enzymes. These polymers could be attractive model systems for the enantiospecific action of enzymes.

We decided to start from histidine; its imidazole group is a basicity and to prevent temperatures higher than ambient. Polymerization occurred with 1 mol % nickel chloride and a small amount of trifluoroacetic acid in methanol. The poly(carbylhistidine) showed no optical activity. The apparent pK₅ of the imidazole function in poly(carbylhistidine) has decreased to 5.2 ± 0.1 compared with free imidazole (7.2), whereas it rises to 9.4 ± 0.2 in poly(carbylhistidine).

Our first results as to the activity of these systems in the hydrolysis of esters are reported elsewhere.

Results and discussion

Masked carbylhistidine (7a) and carbylhistamine (7b) were synthesized from L-histidine and histamine, respectively. In order to obtain the former isocyanide in optically active form, it was necessary to work at low basicity and to prevent temperatures higher than ambient. Polymerization occurred with 1 mol % nickel chloride and a small amount of trifluoroacetic acid in methanol. The poly(carbylhistidine) showed no optical activity. The apparent pK₅ of the imidazole function in poly(carbylhistidine) has decreased to 5.2 ± 0.1 compared with free imidazole (7.2), whereas it rises to 9.4 ± 0.2 in poly(carbylhistidine).

Our first results as to the activity of these systems in the hydrolysis of esters are reported elsewhere.

Abstract. Polymer anchored imidazole functions were obtained by polymerization of carbylhistidine and carbylhistamine. These isocyanides were synthesized from L-histidine and histamine, respectively. In order to obtain the former isocyanide in optically active form, it was necessary to work at low basicity and to prevent temperatures higher than ambient. Polymerization occurred with 1 mol % nickel chloride and a small amount of trifluoroacetic acid in methanol. The poly(carbylhistidine) showed no optical activity. The apparent pK₅ of the imidazole function in poly(carbylhistidine) has decreased to 5.2 ± 0.1 compared with free imidazole (7.2), whereas it rises to 9.4 ± 0.2 in poly(carbylhistidine).

Polyisocyanides 1. Synthesis and polymerization of carbylhistidine and carbylhistamine

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Addition of a small amount of acid started the polymerization. Without acid, imidazole residues block free coordination sites on nickel, which are necessary for polymerization. Probably, without acid, imidazole residues block free coordination sites on nickel, which are necessary for polymerization. The highest optical rotation, measured on solutions of clear and colourless racemic carbylhistidine and of carbylhistamine was at -4.8°. Polymerization of racemic carbylhistidine and of carbylhistamine was attempted by 1 mol % of nickel chloride in methanol. Under these conditions no polymerization was observed. However, addition of a small amount of acid started the polymerization. Probably, without acid, imidazole residues block free coordination sites on nickel, which are necessary for polymerization. By protonation of imidazole this coordination is prevented.

Optically active carbylhistidine is expected to give on polymerization a polymer with predominantly one screw sense. However, so far no optical activity of the polymer could be detected, because of either a low value of its specific rotation or the low enantiomeric stability of the monomer. The optical activity of poly(carbylhistidine) as well as the synthesis of other optically active imidazole-containing polyisocyanides, like poly(carbylhistidinol) and poly(z-methylcarbylhistamine) are currently under investigation.

Polymers were isolated as creamish brown solids. They were soluble in chlorinated hydrocarbons, acetone, methanol and acidiﬁed water. Their spectroscopic data are in agreement with the structures given. Removal of the protecting groups in gave light-brown solids. After ultraﬁltration and freeze-drying the purified products were analyzed as the monohydrochlorides of polymers 9, containing a varying amount of water of crystallization. The polymers 9 were soluble in the lower alcohols and in water.

In most reactions catalyzed by imidazole, its unprotonated form appeared to be the catalytically active species. Therefore, it was of interest to determine the state of ionization of our polyisocyanide anchored imidazole. The relation between pH and degree of dissociation of imidazolium residues in 9, ω, was measured by ultraviolet and potentiometric titrations. In accordance with the modified Henderson–Hasselbach equation

\[
\text{pH} = \text{pK}_\text{im} - n \log \left[ \frac{(1 - \omega)/\omega} {1 - \omega} \right]
\]  

Scheme 1

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plots of log \((1 - x)/x\) versus pH were linear. In Table I the values calculated for \(pK_{\text{ba}}\) and \(n\) are presented as well as the \(pK_a\)'s of model compounds. The \(n\) values calculated from ultraviolet titration plots at different wavelengths, showed a wavelength dependency and are omitted from Table I.

<table>
<thead>
<tr>
<th>Table I</th>
<th>pK values of polyisocyanide anchored imidazoles and of model compounds.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td>(pK_{\text{ba}})</td>
</tr>
<tr>
<td>9c</td>
<td>9.4 ± 0.2a</td>
</tr>
<tr>
<td>9d</td>
<td>9.3 ± 0.15a</td>
</tr>
<tr>
<td>7p</td>
<td>5.2 ± 0.1a</td>
</tr>
<tr>
<td>1-Histidine (a)</td>
<td>6.0</td>
</tr>
<tr>
<td>Histamine (a)</td>
<td>6.0</td>
</tr>
<tr>
<td>Imidazole (a)</td>
<td>7.2</td>
</tr>
<tr>
<td>Poly(t-His) (a)</td>
<td>5.9</td>
</tr>
<tr>
<td>Copoly(t-His, t-Asp) (a)</td>
<td>7.0</td>
</tr>
</tbody>
</table>

\* In 29% \(v/v\) EtOH/H\(_2\)O at 25°; for the polymers the \(pK_{\text{ba}}\) is the apparent \(pK\) of the imidazole in the polymer.

\(a\) Ultraviolet titration.

\(b\) Potentiometric titration.

\(c\) In water; ref. 26.

\(d\) Ref. 27.

This wavelength dependency of \(n\) is probably caused by interferences with absorption bands of the polymer \(\text{C} = \text{N} - \text{N}\) backbone.

The potentiometrically determined \(n\) values of both polymers 9 are equal within experimental error. Their magnitude suggests that more than one imidazole group participates in the reversible binding of a proton. Apparently, our \(n\) value is independent of the presence of a carboxylic group in 9. It is remarked that in polyvinylpyridine the \(n\) value of the imidazole residues is affected by the introduction of a carboxylic function. Table I shows that the carboxylic plots of log \([\text{1} - a]/a\) were recorded under supervision of Dr. W. J. Buis.

Experimental part

Chemical shifts (\(\delta\)) in the \(1^H\)-NMR spectra are given in ppm downfield from internal tetramethylsilane or sodium 2,2,3,3-tetradeutero-\(\text{H}_2\)PO\(_4\) as reference. Abbreviations used are: s = singlet, d = doublet, t = triplet, br = broad, dist = distorted. Elemental analyses were carried out by the Elemental Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under supervision of W. J. Buiss. NMR spectra were recorded under supervision of Dr. M. J. A. de Bie.

Starting materials

1-Histidine monohydrochloride, [\(\delta\) \(H\) 3.00 + 9.30 (c, 5, 5 mol/l HCl), and histamine dihydrochloride were purchased from Fluka and Aldrich, respectively.

N(Im)-Benzyl-L-histidine (2)

This compound was synthesized by the method of Vignaud\(^{20}\) from 1 and benzyl chloride in liquid ammonia. M.p. 241–242\(^\circ\), [\(\alpha\) \(D\)]\text{oo} + 10.0\(^\circ\) (c, 2, water, 1 eq. HCl); lit.\(^{19}\) m.p. 248–249\(^\circ\), [\(\alpha\) \(D\)]\text{oo} + 20.5\(^\circ\) (c, 2, water, 1 eq. HCl). Lit.\(^{21}\) [\(\alpha\) \(D\)] + 10.1 ± 0.7\(^\circ\) (c, 2, water, 1 eq. HCl); the latter is more reliable.

N(Im)-Benzyl-L-histidine methyl ester hydrochloride (3)

This compound was obtained as an oil from 2 through esterification with hydrogen chloride\(^{22}\) or thionyl chloride\(^{23}\) in methanol. It was used without further purification for the synthesis of 6a; [\(\alpha\) \(D\)]\text{oo} + 9.90\(^\circ\) (c 2.5, methanol).

\(N(\text{Im})\)-Benzyl-N(\(z\))-formyl-L-histidine methyl ester (6a)

A suspension of 10 g (34 mmol) of 3 in 50 ml chloroform/methanol (9 : 1 \(v/v\)) was treated at \(0^\circ\) with dry ammonia gas for 30 min. After evaporation of the ammonia at \(0^\circ\) the precipitated ammonium chloride was removed by filtration and the resulting clear solution concentrated in vacuo at \(30^\circ\). The oily residue was dissolved in 100 ml formic acid and treated with 35 ml acetic anhydride while cooling in an ice-salt mixture. After stirring for 2 h at room temperature and removal of the excess of reagents by prolonged evacuation at 50\(^\circ\)/0.1 mm, compound 6a was obtained in quantitative yield.

1-Histidine monohydrochloride was purchased from Fluka and Aldrich, L-Histidine monohydrochloride, \([\alpha]\) \(D\) 5.2 ± 0.2. Table 1 shows that the carboxylic constant of an imidazole residue in 9 but not in 1. This suggests that more than one imidazole group participates in this compound. This compound was obtained as an oil from 2 through esterification with hydrogen chloride\(^{22}\) or thionyl chloride\(^{23}\) in methanol. It was used without further purification for the synthesis of 6a; [\(\alpha\) \(D\)]\text{oo} + 9.90\(^\circ\) (c 2.5, methanol).
purified sample. IR (KBr): 1740 (COOCH3), 1650 (C=O), br, cm^-1; 1H-NMR (CD2OD): δ 7.2 (7H, br, imidazolyl and benzyl), 4.9 (3H, br, CH and benzyl), 3.5 (3H, br, CH2 and OCH3).

Poly(carblyhistidine) (9c)

An amount of 1.0 g (3.72 mmol) of finely powdered 8a was suspended in 125 ml of dry liquid nitrogen. Finely divided metallic sodium was added over a period of 5 h until a blue colour persisted. The excess of sodium was then discharged with ammonia chloride and the ammonia was allowed to evaporate spontaneously. The residue was extracted with ether, dissolved in 60 ml of 1 mol/l HCl and subjected to ultrafiltration (Diaflo Ultra-Filter, UM-2). Freeze-drying of the resulting solution afforded a light-brown powder, which was dried over P2O5 at 40/12 mm. Yield 0.66 g (24.3 mmol, 65%) of 9c; [C,H,N,O,HCl; 1221 at pH 2.20). In the region from 300 to 350 nm both polymers 9 showed a shoulder on the onset of a strong absorbance band in the far ultraviolet. This shoulder shifted to longer wavelength on increasing the pH. The pKw value of the imidazole unit in 9c was determined by using its absorbance difference at 340 nm: ε 2170 at pH > 11.00 and 1311 at pH ≤ 5.0; for 9d the adsorbance difference at 300 nm was used: ε 1838 at pH > 12.00 and 1221 at pH ≤ 2.20.

Potentiometric titrations

Polymers 9 were dissolved in 29% v/v ethanol/water to a concentration of 3.4 × 10^{-3} mol/l. Samples of 20 ml were acidified (pH 2–3) by adding 1 mol/l HCl. An amount of KCl was added, such that at the end point of titration μ = 0.02 mol/l. The solutions were titrated with 0.10 mol/l NaOH in 29% v/v ethanol/water at 25°C under a nitrogen atmosphere while stirring. Blank titration curves were obtained by titrating 20 ml aliquots of 29% ethanol/water acidified to the same pH values and adjusted to the same ionic strength of 0.10 mol/l. Solutions (3.5 × 10^{-3} mol/l) of polymers 9 in 29% v/v ethanol/water, acidified (pH 2) by adding a small amount of 1 mol/l hydrochloric acid and adjusted to an ionic strength of 0.02 mol/l by adding KCl, were titrated with 0.1 mol/l of sodium hydroxide. After each addition of hydroxide the pH of the solution was measured and the ultraviolet spectrum recorded at 25°C. In the region from 300 to 350 nm both polymers showed a shoulder on the onset of a strong absorbance band in the far ultraviolet. The pKw value of the imidazole unit in 9c was determined by using its absorbance difference at 340 nm: ε 2170 at pH > 11.00 and 1311 at pH ≤ 5.0; for 9d the absorbance difference at 300 nm was used: ε 1838 at pH > 12.00 and 1221 at pH ≤ 2.20.

Acknowledgement

This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO). The authors are indebted to Charles F. Gudorf for experimental assistance.

Poly(carblyhistamine) (9d)

The above polymer (8b) was suspended in 50 ml of 96% ethanol, containing 1.5 g of KOH, and refluxed for 8 h. After evaporating the mixture to dryness in vacuo, 50 ml of water was added and a precipitate removed by filtration. The resulting solution was made slightly acidic with hydrochloric acid, submitted to ultrafiltration (Diaflo Ultra-Filter, UM 2) and freeze-dried. Yield 0.8 g (36 mmol, 52%) of 9d. As indicated by elemental analysis 9d still contained 4% of tosylated imidazole residues and some water of crystallization or N-oxide groups:

\[
\begin{align*}
\text{[C}_2\text{H}_6\text{N}_2\text{O}_2\text{HCl]_o}_\text{H}_2\text{O}_\text{So}_a\text{So}_a,} & \quad \text{(164.8)} \text{a; calc. C} 46.5, \text{H} 5.8, \text{N} 26.0, \text{O} 8.4, \text{Cl} 21.6, \text{S} 0.8; \\
\text{[C}_2\text{H}_6\text{N}_2\text{O}_2\text{HCl]_o}_\text{H}_2\text{O}_\text{So}_a} & \quad \text{(166.8)}, \text{calc. C} 46.9, \text{H} 4.9, \text{N} 26.2; \text{O} 8.4, \text{Cl} 12.8, \text{S} 0.8; \text{IR (KBr): 46.5, H} 4.8, \text{N} 26.2, \text{O} 8.7, \text{Cl} 13.2, \text{S} 0.8; \\
\text{IR (KBr): 3600-2200 (NH}_2, \text{H}_2\text{O}),} & \quad \text{1615 ± 1 cm}^{-1}.
\end{align*}
\]

Ultraviolet titrations

Solutions (3.5 × 10^{-3} mol/l) of polymers 9 in 29% v/v ethanol/water, acidified (pH 2) by adding a small amount of 1 mol/l hydrochloric acid and adjusted to an ionic strength of 0.02 mol/l by adding KCl, were titrated with 0.1 mol/l of sodium hydroxide. After each addition of hydroxide the pH of the solution was measured and the ultraviolet spectrum recorded at 25°C. In the region from 300 to 350 nm both polymers showed a shoulder on the onset of a strong absorbance band in the far ultraviolet. This shoulder shifted to longer wavelength on increasing the pH. The pKw value of the imidazole unit in 9c was determined by using its absorbance difference at 340 nm: ε 2170 at pH > 11.00 and 1311 at pH ≤ 5.0; for 9d the absorbance difference at 300 nm was used: ε 1838 at pH > 12.00 and 1221 at pH ≤ 2.20.

Alkaline titrations

Polymers 9 were dissolved in 29% v/v ethanol/water to a concentration of 3.4 × 10^{-3} mol/l. Samples of 20 ml were acidified (pH 2–3) by adding 1 mol/l HCl. An amount of KCl was added, such that at the end point of titration μ = 0.02 mol/l. The solutions were titrated with 0.10 mol/l NaOH in 29% v/v ethanol/water at 25°C under a nitrogen atmosphere while stirring. Blank titration curves were obtained by titrating 20 ml aliquots of 29% ethanol/water acidified to the same pH values and adjusted to the same ionic strength. Differential titration curves were derived graphically,25 from which the degrees of dissociation were evaluated. In the titration curve of 9c the inflection point between the dissociation of the imidazolium ion and the carbonyl group was not clearly observed. Therefore, the pKw was calculated from the value of half-neutralization of the imidazolium group. The n value was evaluated by applying eq. [1] to the pH values for which pH > pKw.