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 that 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 studied are too different from those of enzymes. We are investigating the use of polyisocyanides, \( \text{R} - \text{N} = \text{C} \), as supports for homogeneous catalysts. In earlier papers, we showed that these polymers probably have the configuration of a tightly coiled helix. Hinges 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 isocyanides 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 'screw' sense derived from steric considerations as well as from CD spectra. Poly(carbylhistidine) was 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 pK\(_a\) of the imidazole function in poly(carbylhistamine) 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 accordance with Scheme 1. Initial experiments with compounds having unprotected imidazole groups gave very low yields in step 6 to 7. It appeared that for the synthesis of 7a the imidazole nucleus of l-histidine could effectively be protected by a benzyl group (Bn). The latter group was less suitable for protecting the imidazole of histamine because of problems in isolating the N(Im)-benzylimidazole after reaction. A tosyl group (Tos) gave better results; it was introduced after conversion of the amine to the formamide. The isocyanides 7 were obtained by dehydration of the N-substituted formamides 6 using thionyl chloride in

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**Polyisocyanides**

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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 pK\(_a\) of the imidazole function in poly(carbylhistamine) has decreased to 5.2 ± 0.1 compared with free imidazole (7.2), whereas it rises to 9.4 ± 0.2 in poly(carbylhistidine).

References

addition of a small amount of acid started the polymerization. In these conditions no polymerization was observed. However, probably without acid, imidazole residues block free coordination sites on nickel, which are necessary for polymerization\(^1\). By protonation of imidazole this coordination is prevented.

Optically active carbylhistidine is expected to give on polymerization a polymer with predominantly one screw sense\(^1\). 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(2-methylcarbylhistamine) are currently under investigation.

Polymers 8 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 8 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\(^1\). 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 was determined by modified Henderson–Hasselbach equation\(^1\):

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


\(^{15}\) L. M. Bender, Mechanisms of homogeneous catalysis from proton to proteins, Wiley, New York, 1971.

plots of log \((1 - a)/a\) versus pH were linear. In Table I the values calculated for \(pK_{im}\) and \(n\) are presented as well as the \(pK^*_m\)'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 polysocyanide anchored imidazoles and of model compounds.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td>(pK_{im})</td>
</tr>
<tr>
<td>9c</td>
<td>9.4 ± 0.2(^b)</td>
</tr>
<tr>
<td>9d</td>
<td>9.3 ± 0.1(^d)</td>
</tr>
<tr>
<td>1-Histidine(^e)</td>
<td>6.0</td>
</tr>
<tr>
<td>Histamine(^e)</td>
<td>6.0</td>
</tr>
<tr>
<td>Imidazole(^e)</td>
<td>7.2</td>
</tr>
<tr>
<td>Poly(t-His)(^f)</td>
<td>5.9</td>
</tr>
<tr>
<td>Copoly(t-His, l-Asp)(^f)</td>
<td>7.0</td>
</tr>
</tbody>
</table>

\(^a\) In 29\% v/v EtOH/H\(_2\)O at 25°; for the polymers the \(pK_{im}\) is the apparent \(pK\) of the imidazole in the polymer.  
\(^b\) Ultraviolet titration.  
\(^c\) Potentiometric titration.  
\(^d\) In water; ref. 26.  
\(^e\) Ref. 27.

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

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 polyvinylpyrrolidone the \(n\) value of the imidazole residues is affected by the introduction of a carboxylic function\(^17\). Table I shows that the carboxylic function appreciably increases the apparent dissociation constant of an imidazole residue in 9 but not in 1. This behaviour suggests the presence of a strong anionic field in polymer 9c\(^18\).

**Experimental part**\(^19\)

Chemical shifts (\(\delta\)) in the \(^{1}H\)-NMR spectra are given in ppm downfield from internal tetramethylsilane or sodium 2,2,3,3-tetradeutero-\(\text{CD}_{3}\)) as internal reference. Abbreviations used are: \(s\) = singlet, \(d\) = doublet, \(t\) = triplet, \(br\) = broad, \(dist\) = distorted.

\(N(\text{Im})-\text{Benzyl-L-histidine (2)}\)

This compound was synthesized by the method of \(Vignaud\)\(^20\) from 1 and benzyl chloride in liquid ammonia. M.p. 241–243\(^°c\), \([\alpha]_D^20 +10.00°\) (c 2, water, 1 eq. HCl); lit. \(^20\) m.p. 248–249\(^°c\), \([\alpha]_D^20 +20.50°\) (c 2, water, 1 eq. HCl); lit. \(^21\) \([\alpha]_D^20 +10.1 ± 0.7°\) (c 2, water, 1 eq. HCl); the latter is more reliable.

\(N(\text{Im})-\text{Benzyl-L-histidine methyl ester hydrochloride (3)}\)

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; \([\alpha]_2^20 +9.90°\) (c 2.5, methanol).

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

A suspension of 10 g (34 mmol) of 3 in 50 ml chloroform/methanol (9:1 v/v) was treated at 0° with dry ammonia gas for 30 min. After evaporation of the ammonia at 0° the precipitated ammonium chloride was removed by filtration and the resulting clear solution concentrated in vacuo at 30°. The oily residue was dissolved in 100 ml formic acid and treated with 35 ml acetic acid anhydride while cooling in an ice-salt mixture. After stirring for 1 h at room temperature and removal of the excess of reagents by prolonged evacuation at 50°/0.1 mm, compound 6a was obtained in quantitative yield as a yellow brown syrup, which was sufficiently pure for the synthesis of 7a. Upon repeated stirring with acetone the syrup partly solidified. Filtration of the solid and recrystallization from acetic acid afforded white crystals. M.p. 120° (dec.), \([\alpha]_2^20 +17.4°\) (c 4.8, methanol); IR (KBr): 3180 (NH), 1730 (COOCH\(_3\)), 1670 (CHO), 730 and 700 (benzyl) cm\(^{-1}\); \(1^H\)-NMR (CD\(_3\)OD): 6.8.00 and 7.35 (2H, \(x\), imidazole), 8.05 (1H, s, CHO), 7.40 (5H, s, benzyl), 5.55 (2H, s, benzyl), 4.80 (1H, t, CH), 3.70 (3H, s, OCH\(_3\)), 3.20 (2H, dist, d, CH\(_2\)).

\(\text{Benzyl-L-cyanhistidine methyl ester (7a)}\)

To a stirred solution of 5 g (17.4 mmol) of 6a in 150 ml of N,N-dimethylformamide (DMF) was added, under a nitrogen atmosphere, a solution of 7.5 ml (100 mmol) of thiophenol chloride dissolved in 30 ml of DMF, at such a rate that the temperature was kept at about −60°. After addition, the cooling bath was temporarily removed to allow the temperature to rise to −38°; then it was replaced and 23 g (210 mmol) of anhydrous sodium carbonate were slowly added, maintaining a temperature of −45°. The mixture was subsequently stirred at this temperature for 10 min. The cooling bath was then removed and the temperature allowed to rise to 0°. After addition of 50 ml of DMF, stirring was continued for 20 h while cooling in ice. To the reaction mixture 250 ml of methylene chloride were added followed by 450 ml of ice cold water. The aqueous layer was separated and rapidly extracted with three 100 ml portions of methylene chloride. The combined extracts were washed, dried over MgSO\(_4\) and concentrated in vacuo. Addition of ethyl acetate to the resulting yellow-red syrup gave 85% (70%) of light yellow crystals of 7a. Further purification by chromatography on a silica gel column (acetone as eluent) afforded transparant, colourless crystals. M.p. 77.5–78.5°; \([\alpha]_2^20 +4.8°\) (c 5, acetone); C\(_6\)H\(_5\)N\(_2\)O\(_2\) (269.1); calcd. C 66.4, H 5.7, N 15.4, O 12.4; MS: M\(^+\) 269, M\(^+\)-OCH\(_3\), 238, M\(^+\)-COOCH\(_3\), 210, M\(^+\)-CH(NC)COOCH\(_3\), 171, tryptophan ion; IR (KBr): 2920 (CH\(_2\)), 1700 (COOCH\(_3\)) cm\(^{-1}\); \(1^H\)-NMR (CD\(_3\)OD, 60 MHz); \(\delta\) 7.65 and 7.00 (2H, \(x\), imidazole), 7.35 (5H, s, benzyl), 5.25 (2H, s, benzyl), 4.85 (1H, t, CH), 3.75 (3H, s, OCH\(_3\)), 3.15 (2H, dist, d, CH\(_2\)).

Isocyanide 7a can be recognized on thin-layer plates as red-brown spots by spraying with a solution of nickel chloride in ethanol.

**Poly(benzyl carbyhistidine methyl ester (8a)**

A solution of 1.5 g (5.6 mmol) of 7a, 0.015 g (0.06 mmol) of nickel chloride hexahydrate and 5 drops of trifluoroacetic acid in 5 ml of methanol was stirred for 2 days at 25°. After evaporation of the solvent, 8a was isolated in quantitative yield and used without purification for the synthesis of 9c. Dropwise addition of a chloroform solution of 8a into a hundredfold excess of ether afforded a
purified sample. IR (KBr): 1740 (COOCH3), 1650 (C=N), br, cm−1; 1H-NMR (CD3OD): δ 7.2 (7H, br, imidazolyl and benzyl), 4.9 (3H, br, CH and benzyl), 3.5 (3H, br, CH2 and OCH3).

**Poly(carblylhistidine) (9c)**

An amount of 1.0 g (3.72 mmol) of finely powdered 8a was suspended in 125 ml of dry liquid ammonia. 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 ammonium 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 (2.43 mmol, 65%) of 9c: [C,H,N,O2(31HCl)([H2]O)]0, (246.5) g. calcd. C 34.0, H 5.8, N 26.0, O 8.4, Cl 12.6, S 0.8; found C 34.2, H 5.8, N 26.0, O 8.4, Cl 13.2, S 0.8; IR (KBr): 3600-2200 (COOH, NH2 +, H2O), 1675 cm⁻¹; 'H-NMR (CDCl3): δ 8.15 (Av* 15 Hz) and 7.5 (Av, 27 Hz) (2H, 2 x, imidazole), 7.9 (1H, s, CHO), 7.3-7.5 (4H, 2 x, CH), 6.7 (1H, br, NH), 3.50 and 2.70 (4H, 2 x, CH2CH3).

N(Im)-Tosyl-N(z)-formy histamine (5)

This compound was obtained as a syrup from histamine dihydrochloride as described for the synthesis of 6a. Yield 21.6%; 1H-NMR (D2O): δ 8.70 and 7.40 (2H, 2 x, imidazole), 8.20 (1H, s, CHO), 3.60 and 3.00 (4H, 2 x, CH2CH3).

N(Im)-Tosyl-N(z)-formy histamine (6b)

To a solution of 7.5 g (54 mmol) of 15 and 15 g of Na2CO3 in 100 ml of water was added 15 g (78 mmol) of p-toluene sulfonyl chloride and kept at room temperature, extracted with ethyl acetate, dried over MgSO4, and the excess of sodium was then discharged with ammonium chloride. The resulting solution was acidified to the same pH values and adjusted to the same ionic strength. Differential titration curves were derived graphically, 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 carboxyl group was not clearly observed. Therefore, the pKα value was evaluated by applying eq. [1] to the pH values for which pH > pKαn. The pKα value 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 > pKαn. The pKα value 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 > pKαn.

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