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Synthesis of imidazole-containing poly(iminomethylenes). Choice of N(Im)-protecting group

J. M. van der Eijk, V. E. M. Richters, R. J. M. Nolte and W. Drenth

Laboratory of Organic Chemistry of the University at Utrecht, Croesestraat 79, 3522 AD Utrecht, The Netherlands
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Abstract. Four imidazole-containing isocyanides having different N(Im)-protecting groups at the tele as well as at the pros position have been synthesized. These isocyanides include N'(Im)-tosyl-N-carbonylhistamine (4a), N'(Im) benzyl-N'-carbonylhistamine (4b), N'(Im) benzyl-N'-carbonylhistamine (4c) and N',N'(Im) dibenzyl-N'-carbonylhistamine bromide (4d). Compounds 4a and 4d polymerize in the presence of nickel(II) ions, whereas compounds 4b and 4c do not. This result is explained by the type of nickel complex that is formed, viz. a tetrahedral or square-planar complex with general formula Ni(CNR)42+ in the case of 4a and 4d, and an octahedral complex with general formula Ni(CNR)22+ in the case of 4b and 4c. In the latter complexes, not only the isocyanide groups but also the imidazole groups coordinate to the nickel. Thus, the imidazole groups block the coordination sites which are required for polymerization of the isocyanate functions.

Introduction

In previous papers we reported on imidazole-containing poly(iminomethylenes) as models for hydrolytic enzymes2,3,4. Poly(N'-carbonylhistamine), 1, and poly(N'-carbonylhistidine), 2, have been prepared by polymerization of the corresponding isocyanides with nickel chloride5.

\[
n R-N=C \xrightarrow{\text{NiCl}_2} (R-N=C')_n
\]

In general, polymerization of isocyanides by nickel(II) is rapid and yields are almost quantitative7. However, the monomers leading to polymers 1 and 2 react slowly and often incompletely. The reason for this behaviour may be that imidazole residues block coordination sites on the nickel which are required for polymerization. In order to test this hypothesis and to develop a better polymerization procedure, we synthesized imidazole-containing isocyanides whose imidazole functions have different coordinative properties. The polymerization behaviour of these isocyanides is described in this paper. The results from this study have been successfully applied in the synthesis of optically active poly[(R)-N'-carbonyl-2-methylhistamine], 3.

Results and discussion

The coordinating ability of the imidazole group towards a metal centre is related to its basicity. The latter property can be varied by using different N(Im) protecting groups. Electron-withdrawing groups, such as the tosyl (Tos) group9, lower the basicity of the imidazole nucleus, whereas electron-donating groups, such as the benzyl (Bn) group10, enhance this basicity. Apart from the nature of the protecting group, its position at the ring is also important. The nitrogen atoms of a 4(5)-substituted imidazole ring are not equivalent, and are known to behave differently in various reactions11.

We prepared isocyanides 4a-d, which contain a tosyl or benzyl group at either the tele (t) or pros (p) position12 of the imidazole ring, as well as an isocyanide with benzyl groups at both positions of the ring. The coordinating ability of the imidazole nucleus in these compounds can be expected to increase in the series 4d < 4a < 4b, 4c.

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15. E.g., in the formation of peptides, N'-substituted histidine is less sensitive to racemization than is N'-substituted histidine. Compare ref. 10.
16. In accordance with IUPAC-IUB rules, the imidazole nitrogen at position 3 is called the tele nitrogen (symbol t), whereas the nitrogen atom at position 1 is called the pros nitrogen (symbol p).
The synthesis of isocyanides 4 is outlined in Scheme 1. The starting material used is histamine which was formylated, tosylated and subsequently dehydrated to give 4a. A similar sequence of reactions was followed to prepare the benzylated derivative 4b. For the synthesis of 4c, the N'-(Im)-nitrogen of N-formylhistamine was first protected with a triphenylmethyl (Tr) group. Subsequently, the N'-(Im)-nitrogen was quaternized by reaction with benzyl bromide and the N'- (Im)-Bn derivative generated by treatment with acid. After dehydration isocyanide 4c was obtained. The double benzylated isocyanide 4d was prepared by treating 4c with benzyl bromide.

Polymerization of isocyanides 4 was attempted with 1 mol % of nickel chloride in methanol or methanol/ chloroform as solvent. The results of these experiments are given in Table I. Monomers 4a and 4d give polymers in 80–90% yield. The molecular weights of these polymers are in the range 20,000–30,000. In the case of 4a, it was sometimes necessary to add trifluoroacetic acid to initiate polymerization. Apparently, the imidazole ring of this compound has weak coordinative properties which can be eliminated by protonation. Polymerization of 4d is relatively slow. This can be attributed to steric hindrance by the two bulky benzyl groups on the imidazole ring. Monomers 4b and 4c did not polymerize under the conditions applied and addition of trifluoroacetic acid failed to initiate polymerization. This suggests that the imidazole groups of 4b and 4c are very good ligands for divalent nickel.

Polymerization of isocyanides is proposed to proceed via a series of consecutive insertion reactions around the nickel centre. Reaction starts from a nickel complex containing 4 isocyanide ligands in a square-planar or approximately square planar configuration. Failure to polymerize might be caused by a type of coordination different to that usually found. In order to test this hypothesis, we prepared complexes of ligands 4 and nickel perchlorate by mixing solutions of the reactants in ethanol/ether. Precipitates were formed which were isolated and characterized. Table II summarizes some of the physical properties of the complexes. For comparison, data for the square-planar complex Ni[II](CN-Im)(ClO₄)₂ are also included. This complex has been previously prepared by us.

Isocyanides 4a and 4d form complexes which contain 4 ligands per nickel. The infrared spectra of these complexes show one single NC stretching vibration at 2250–2260 cm⁻¹. As compared to the free isocyanides, this stretching vibration has shifted to a higher wavelength number. The observed value fits in with a square-planar or tetrahedral Ni(CNR)₄⁺ ion. The magnetic moments of the complexes suggest a tetrahedral or distorted tetrahedral arrangement, at least in the solid state. So far, we have not been able to ascertain whether the same is true for the structure in solution. The electronic spectra of the complexes are inconclusive at this point as they show strong ligand absorption bands which obscure the nickel bands. The nickel complexes of 4b and 4c contain 3 ligands per nickel. In these complexes, the NC stretching vibration is at about 2220 cm⁻¹. The nickel complex of 4c shows additional weaker NC vibrations at 2260 and 2150 cm⁻¹.

Table I Polyimerization of imidazole-containing isocyanides using nickel(II) chloride.

<table>
<thead>
<tr>
<th>Isocyanide</th>
<th>Reaction conditions</th>
<th>Reaction time</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>MeOH/CHCl₃ (1/1, v/v), 25°</td>
<td>12 h</td>
<td>80–90</td>
</tr>
<tr>
<td>4b</td>
<td>MeOH, 40</td>
<td>a</td>
<td>–</td>
</tr>
<tr>
<td>4c</td>
<td>MeOH, 40</td>
<td>a</td>
<td>–</td>
</tr>
<tr>
<td>4d</td>
<td>MeOH, 40</td>
<td>2 days</td>
<td>80</td>
</tr>
</tbody>
</table>

* 6 Mmol of isocyanide; 0.06 mmol of NiCl₂•6H₂O; 5 ml of solvent.  
* Solvent, reaction temperature/°C.  
* If polymerization did not start, 5–10 drops of trifluoroacetic acid were added.  
* No polymerization was observed after a week; addition of trifluoroacetic acid did not initiate polymerization.

Table II Nickel(II) perchlorate complexes of imidazole-containing isocyanides 4.

<table>
<thead>
<tr>
<th>Isocyanide</th>
<th>Colour</th>
<th>MP/°C</th>
<th>n°</th>
<th>ν(NC)/cm⁻¹</th>
<th>βₑff/BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>yellow</td>
<td>218–220 (dec.)</td>
<td>4.0 ± 0.2</td>
<td>2258 (110)</td>
<td>2.25 (12)</td>
</tr>
<tr>
<td>4b</td>
<td>dark red</td>
<td>184 (dec.)</td>
<td>3.0 ± 0.2</td>
<td>2222 (74)</td>
<td>2.57 (25)</td>
</tr>
<tr>
<td>4c</td>
<td>grey</td>
<td>&gt;260</td>
<td>3.1 ± 0.2</td>
<td>2220 (78)</td>
<td>3.15 (51)</td>
</tr>
<tr>
<td>4d</td>
<td>lilac</td>
<td>–</td>
<td>3.8 ± 0.3</td>
<td>2251 (102)</td>
<td>3.04 (30)</td>
</tr>
<tr>
<td>t-BuNC⁶</td>
<td>white</td>
<td>127 (dec.)</td>
<td>4</td>
<td>2251 (119)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

* Number of ligands in the complex Ni[II](CNR)₄(ClO₄)₂, calculated from elemental analyses.  
* Shift of ν(NC) with respect to uncomplexed isocyanide is given in parenthesis.  
* At 300 K. All samples showed Curie-Weiss behaviour. θ/K values are given in parenthesis.  
* Additional isocyanide vibrations are present at 2260 and 2150 cm⁻¹.  
* Taken from Ref. 13.
The lower value of the main NC band suggests that in the complexes of 4b and 4c the formal positive charge on nickel has decreased compared to the complexes of 4a and 4d. Such a decrease is feasible when the imidazole functions of 4b and 4c coordinate to nickel. We propose octahedral structures for the nickel complexes of 4b and 4c. Taking into account the positions of the benzyl groups at the imidazole ring of the two ligands, the most likely structures are a monomeric one (A) for the 4b complex and a polymeric one (B) for the 4c complex.

The latter structure probably has a low symmetry as can be concluded from the occurrence of more than one NC vibration in the infrared spectrum. The low solubility of the nickel complex of 4c in organic solvents, coupled with its high melting point, supports the assignment of a polymeric structure. The magnetic moments of the complexes of 4b and 4c are in line with an octahedral arrangement. The value \( \mu_{\text{eff}} = 2.57 \) of the former complex suggests that in this compound the octahedral arrangement is somewhat distorted. Unfortunately, no information about the structure of the complexes could be obtained from electronic spectra, due to interference of nickel bands with ligand absorption bands, and also because of solubility problems in the case of the 4c complex.

We have previously shown that for polymerization of isocyanides, 4 coordination sites around nickel are required, which are successively used for carbon-carbon bond formation. These 4 coordination sites are available in the complexes of 4a and 4d, but not in those of 4b and 4c. Thus, in accordance with experiment, polymerization will occur in the case of the former two monomers, but not in the case of the latter two.

In summary, the data presented in this paper indicate that polymerization of imidazole-containing isocyanides can be achieved if the imidazole functions in these monomers are prevented from coordinating to the nickel catalysts. The latter situation can be attained by choosing \( N(\text{Im}) \)-protecting groups, which lower the basicity of the imidazole nucleus.
Experimental

Melting points were determined on a Mettler FP5/FP51 photoelectric melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 297 and 283 spectrophotometers. Ultraviolet spectra were recorded on a Cary 15 spectrophotometer. 1H NMR spectra were obtained on a Varian EM 390 instrument. Chemical shifts (δ) are given in ppm downfield from internal tetramethylsilane or sodium 2,2,3,3-tetradetero-3-(trimethylsilyl)propionate. Assignations used are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra were recorded on an AEl MS-902 mass spectrometer. Magnetic susceptibilities were measured by means of the Faraday force method.\textsuperscript{16,17} Elemental analyses were carried out by the Elemental Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under the supervision of Mr. W. J. Buis. TLC was performed on silica (Sleicher and Schuill TLC Ready Plastic Cord) and detected on an AEl MS-902 mass spectrometer. Magnetic susceptibilities were measured by means of the Faraday force method.\textsuperscript{16,17} Elemental analyses were carried out by the Elemental Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under the supervision of Mr. W. J. Buis. TLC was performed on silica (Sleicher and Schuill TLC Ready Plastic Cord) and detected on an AEl MS-902 mass spectrometer. Magnetic susceptibilities were measured by means of the Faraday force method.\textsuperscript{16,17}

N\textsuperscript{3}-Formylhistamine

This compound was synthesized from histamine dihydrochloride as described previously.\textsuperscript{3} 1H NMR (D\textsubscript{2}O): δ 8.70 and 7.40 (2H, d, benzyl), 5.0 (2H, t, CH\textsubscript{2}N). M.p. 110° (dec.). MS: M\textsuperscript{+} 275, CH\textsubscript{2}=NC 155, tosyl 155, tropylium ion 91. IR (KBr): 3300 (NH), 2920 (CH\subscript{2}), 2850 (CH\subscript{3}), 1660 cm\textsuperscript{-1}. [H NMR (D\textsubscript{2}O): 5 8.1 (s, 1H, CHO), 7.80 and 7.35 (4H, 2 x d, tosyl), 3.65 and 2.80 (4H, 2 x t, CH\textsubscript{2}N)], 2.40 (3H, s, CH\textsubscript{3}).

N\textsuperscript{(Im)}-Benzyl-N\textsuperscript{3}-formylhistamine

To a solution of 15 g (0.11 mol) of N\textsuperscript{3}-formylhistamine in 150 ml of N,N-dimethylformamide (DMF) were added 18 ml (0.15 mol) of benzyl bromide and 24 ml (0.12 mol) of dicyclohexylamine. After stirring for 4 h, the reaction mixture was filtered and subsequently concentrated in an oil pump vacuum. A solution of the resulting residue in 100 ml of 0.1 mol/l aqueous HCl was extracted with chloroform, whereafter the pH of the water layer was adjusted to pH 8 using sodium carbonate. The water layer was extracted four times with 75 ml portions of chloroform. The combined organic fractions were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo to give the monobenzylated formamide as a white solid. Yield: 4.2 g (18.3 mmol, 70%). M.p. 137–138°C. IR (KBr): 3200 (NH), 1660 cm\textsuperscript{-1} (CHO). 1H NMR (CDCl\textsubscript{3}): δ 8.10 and 7.20 (2H, 2 x s, isomazole), 7.80 and 7.35 (4H, 2 x d, tosyl), 3.65 and 2.80 (4H, 2 x t, CH\textsubscript{2}N)], 2.40 (3H, s, CH\textsubscript{3}).

N\textsuperscript{(Im)}-Tosyl-N\textsuperscript{3}-formylhistamine

This compound was synthesized from the corresponding formamide as described previously.\textsuperscript{3} M.p. 110° (dec.). MS: M\textsuperscript{+} 275, M\textsuperscript{+} - CH\textsubscript{2}=NC 235, tosyl 155, tropylium ion 91. IR (KBr): 2149 (NC), 1380 and 1170 (SO\textsubscript{2}N) cm\textsuperscript{-1}. 1H NMR (CDCl\textsubscript{3}): δ 8.15 and 7.20 (2H, 2 x s, isomazole), 7.85 and 7.40 (4H, 2 x d, tosyl), 6.7 (1H, br, NH), 3.50 and 2.70 (4H, 2 x t, CH\textsubscript{2}N)], 2.45 (3H, s, CH\textsubscript{3}).

N\textsuperscript{(Im)}-Benzyl-N\textsuperscript{3}-formylhistamine

To a solution of 10 g (0.26 mmol) of the previous trityl compound in 100 ml of DMF were added 4 ml (33 mmol) of benzyl bromide. After stirring overnight at room temperature, the reaction mixture was filtered and subsequently concentrated in an oil pump vacuum. To the residue were added 50 ml of formic acid and subsequently the reaction mixture was stirred for 1 h. After evaporation of most of the formic acid, 100 ml of water was added to the residue and the resulting solution was extracted three times with chloroform. The pH of the water layer was adjusted to 9 using sodium carbonate whereafter the water layer was extracted four times with 75 ml portions of chloroform. The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo to yield the formamide as a white solid. Yield: 4.2 g (18.3 mmol, 70%). M.p. 137–138°C. IR (KBr): 3200 (NH), 1660 cm\textsuperscript{-1} (CHO). 1H NMR (CDCl\textsubscript{3}): δ 8.10 (1H, CHO), 7.80 (d, 1H, NH), 7.30 and 7.00 (2 x m, 5H, benzyl), 7.40 and 6.80 (2 x s, 2H, imidazole), 5.10 (2H, benzyl), 3.35 (q, 2H, CH\textsubscript{2}N)], 2.65 (t, 2H, CH\textsubscript{2}Im).
Preparation of the nickel complexes

Nickel(II) complexes of isocyanides were prepared at —30°C by rapid addition of a 0.02 mol/l solution of Ni(C10 of the appropriate isocyanide in the same solvent. The complexes were precipitated instantaneously and were collected by centrifugation, after which they were washed once with ethanol/ether (1/4 v/v) and three times with ether. They were dried in vacuo over P2O5 at 40°C. Relevant physical data are summarized in Table II.

Acknowledgement

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