Polymerization

Acid-Initiated Stereospecific Polymerization of Isocyanopeptides**

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The occurrence of only one type of chirality in biomolecules is a remarkable fact of life that has piqued the curiosity of numerous research groups in a wide range of scientific disciplines. Most theories concerning the origin of this phenomenon assume that after the initial induction of a chiral bias, a process of chiral amplification has occurred.[1–4] One possible route for chiral amplification is through a process of molecular recognition between diastereomeric oligopeptides, which enables one form to polymerize or aggregate into larger chiral structures while the other form cannot.[4] Herein, we report on the unique acid-initiated polymerization of chiral isocyanodipeptides which occurs with unprecedented stereospecificity.

In the past, we and others have studied in great detail the polymerization of isocyanides by metal complexes, in particular nickel(II) derivatives. It was shown that these monomers yield polymers with a stable approximately 4_1 helical conformation.[5] More recently, we demonstrated that the polymerization of peptide-derived isocyanides results in polymers with a new type of helix structure, that is, a β helix in which the peptide side arms attached to the central helical core form a β-sheet-like architecture.[6,7] During these studies, it was discovered that isocyano-L-alanyl-D-alanine methyl ester (L,D-IAA) rapidly polymerizes even without a nickel(II) catalyst present. The resulting polymer was found to have exactly the same composition and conformation as poly(isocyano-L-alanyl-D-alanine methyl ester) (L,D-PIAA) prepared by using nickel(II) catalysis.[8] Further studies revealed that this polymerization, which occurs in chloroform, is initiated by free protons in this solvent. In stark contrast, when identical polymerization conditions were applied to the diastereomeric L,L-IAA monomer, no polymerization was observed to take place.[9]

To obtain more insight into the stereospecificity of this acid-catalyzed polymerization, kinetic studies were performed with trifluoroacetic acid (TFA) in dichloromethane, and the polymerization reaction was monitored by IR spectroscopy. During polymerization, the isocyanide absorption at $\nu = 2136\ cm^{-1}$ disappeared and the amide I absorption

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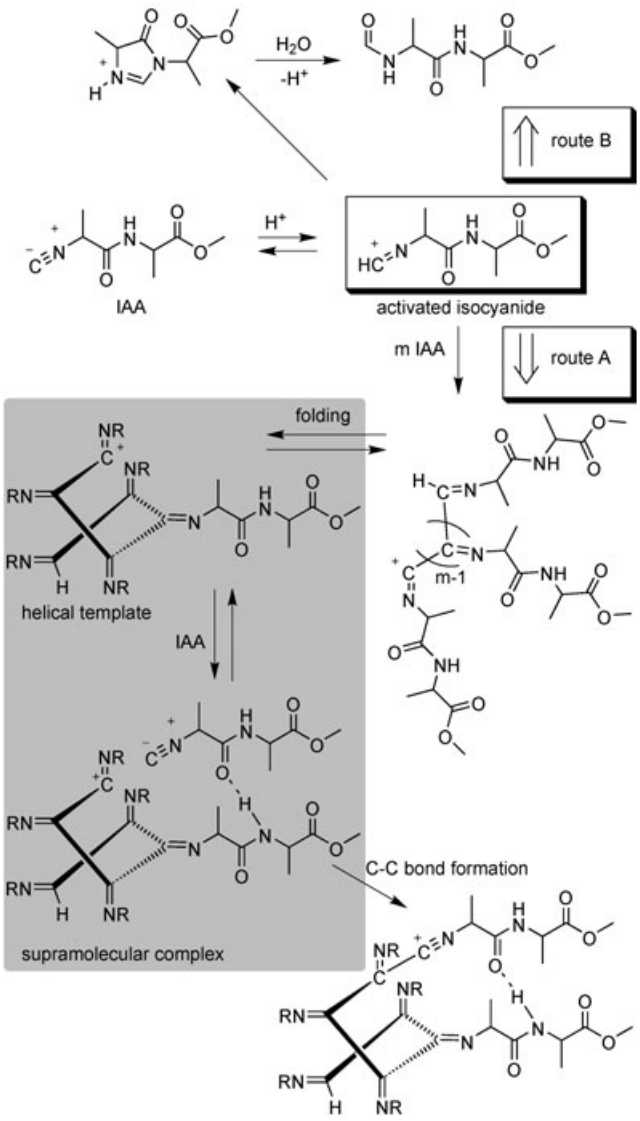
shifted from $\nu = 1686\ cm^{-1}$ to $\nu = 1656\ cm^{-1}$, thereby indicating the formation of the polymer and its simultaneous folding into a β-helical structure; this was also indicated by the arising Cotton effect at $\lambda = 306$ nm in the CD spectra. When 0.15 equivalents of TFA with respect to monomer were used, a slight induction period was clearly visible, after which the polymerization reaction (route A, Scheme 1) followed first-order kinetics with respect to the monomer. The reaction rate of L,D-IAA (16 mM) with TFA (1 mM) in dichloromethane was studied at different temperatures. Evaluation of the rate data in an Eyring plot revealed that the polymerization reaction displayed a large negative entropy of activation ($\Delta S^{\neq}$) of $-170\ J\,mol^{-1}\,K^{-1}$, which implies a very high degree of organization in the transition state,[10] and an activation enthalpy ($\Delta H^{\neq}$) of 42 kJ mol^{-1}; this gives an overall free energy of activation ($\Delta G^{\neq}_{293\,K}$) of 92 kJ mol^{-1}. At higher acid concentrations (that is, when > 0.15 equivalents of TFA with respect to monomer were used), IR, CD, and ^{1}H NMR spectroscopic studies indicated that a second reaction starts to compete with the polymerization reaction. This reaction is the hydration of the isocyanide through the formation of a cyclic imidazolone to form the corresponding formamide (FAA; route B, Scheme 1).[11] When the formation of polymer, calculated from the intensity of change in the molar circular dichroic absorption at $\lambda = 306$ nm ($\Delta\varepsilon_{306}$), was plotted as a function of the TFA concentration, a sigmoidal curve was obtained (Figure 1). As the polymer formation decreased, the formation of the formamide via the cyclic imidazolone increased concomitantly, as monitored by ^{1}H NMR spectroscopy. This indicates that at high acid concentrations the isocyanide monomers cannot be incorporated into the growing polymer chain and as a result cyclize to give the imidazolone (route B). Interestingly, the transition from polymerization to cyclization is a cooperative process, as highlighted by the S-shaped curve (Figure 1), and takes place in a rather narrow concentration range.



Scheme 1. Proposed initiation and propagation of the acid-initiated polymerization of isocyanopeptides (route A) and a side reaction forming the formamide via a cyclic imidazolone (route B).

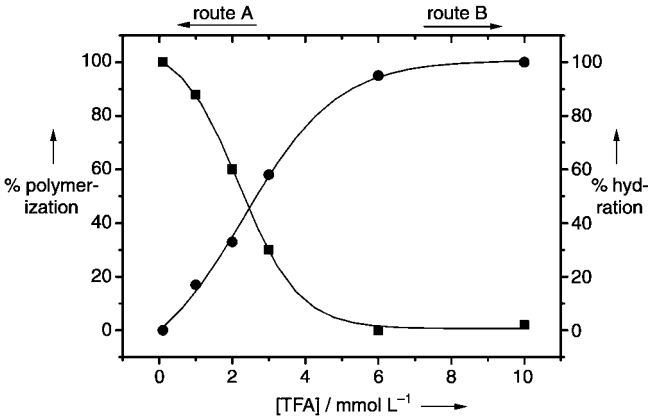


Figure 1. Polymerization (■) and hydration (●) of L,D-IAA as a function of the TFA concentration ([L,D-IAA] = 16 mmol L^{-1} in dichloromethane, $T = 25\,°C$).

The stereochemical nature of the polymerization was studied at a low acid concentration ([TFA]/[IAA] < 0.15) to negate the side reaction. The formation of both block and random copolymers of the different diastereomers (L,L-IAA, L,D-IAA, and D,L-IAA) was measured by CD spectroscopy ($\lambda = 306$ nm) as a function of time. An initial block of L,D-PIAA was grown by using TFA as an initiator. Once all of the L,D-IAA had been consumed, a second equivalent of this monomer was added and the reaction was found to proceed further (Figure 2, curve a). However, when the enantiomeric monomer D,L-IAA was added, no further polymerization took place and the added isocyanide was recovered (curve c). This remarkable observed inhibition is likely caused by the presence of trace residues of the enatiomeric L,D-IAA monomer, which poisons the poymerization reaction of D,L-IAA.[7,12] Remarkably, this stereospecificity was also observed when L,D-IAA and D,L-IAA were randomly copolymerized; the enantiomeric monomers inhibited each other and no

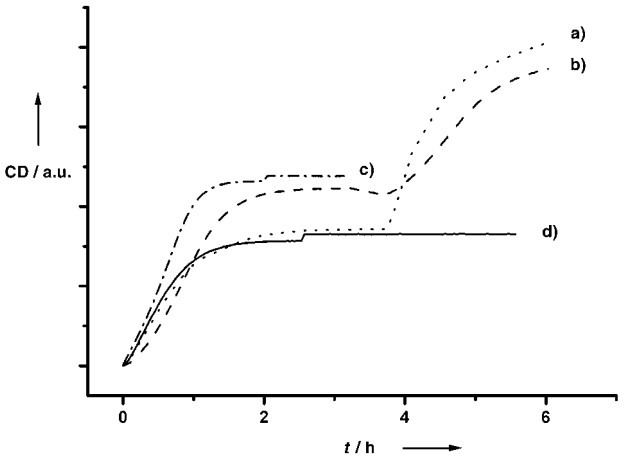


Figure 2. Acid-catalyzed block copolymerizations of L,D-IAA (16 mM) with a) L,D-IAA, b) L,L-IAA, c) D,L-IAA, and d) D,D-IAA, monitored by CD spectroscopy as a function of time at $\lambda = 306$ nm ([IAA] = 16 mmol L^{-1}, [TFA] = 1 mmol L^{-1}, CH_2Cl_2, $T = 25\,^{\circ}C$).

polymerization was observed, even when a monomer ratio of 99:1 was applied.[13] In contrast to the above observation, copolymerization of diastereomeric monomers was found to be possible. When L,L-IAA (which when polymerized with a Ni^{II} catalyst gives polymers with the same right-handed screw sense as L,D-IAA) was used as a second monomer in a block copolymerization with L,D-PIAA, the polymer continued to grow (curve b). However, addition of D,D-IAA, which is the enantiomer of L,L-IAA, did not result in any polymerization (curve d). The molecular weights for the two block copolymers L,D-PIAA/L,D-PIAA and L,D-PIAA/L,L-PIAA were obtained by AFM studies of the molecules deposited on a mica surface.[8] It was observed that the molecular weight for the block homopolymer L,D-PIAA/L,D-PIAA only slightly increased upon addition of the second monomer, a result indicating that mainly new L,D-PIAA polymers are formed. In contrast, for the block copolymer L,D-PIAA/L,L-PIAA, the observed molecular weight was found to almost double; this indicates that the second block grows almost exclusively on from the first. The energetic penalty caused by steric repulsion between the alanine methyl groups, which prevents the acid-initiated homopolymerization of L,L-IAA,[9] can evidently be overcome by the increased hydrogen bonding to the preformed helical L,D-PIAA macroinitiator. This increased hydrogen bonding is the result of polarization of the amides by the cooperative hydrogen-bonding network present in the helix architecture, an observation often observed in α helices.[14] The above results clearly demonstrate the critical effect of the configuration of the first chiral center of the dipeptide monomer on the polymerization reaction and show that the initiation step is crucial. The stereospecificity of the transition state of the acid-initiated polymerization is further highlighted by the fact that all of the above monomer combinations could readily be polymerized when a nickel(II) catalyst was used.[5]

Helix-sense-selective polymerizations, such as those of bulky methacrylates,[15] chloral,[16] and *N*-propargylamides,[17] are well documented, whereas for more dynamic helical polymers, for example, polyisocyanates,[18] polysilanes,[19] and polyacetylenes,[20] copolymerization with optically active monomers is required to obtain a lasting preferred helix sense. However, there are virtually no examples of monomers that are enantioselectively polymerized.[21] This unique stereoselectivity is remarkable in its efficiency, in that even when only 1% of the incorrect monomer is present the polymerization does not proceed. The exhibited stereoselectivity and also the switching of the reaction to a different product, that is, the cyclic imidazolone, can both be explained by the involvement in the reaction of a helical template, which is present at low acid concentrations and destroyed at high acid concentrations.

The formation of a helical template is not only a crucial step in the acid-initiated polymerization but was also found to play an important role in the Ni^{II}-catalyzed polymerization of isocyanopeptides. In a titration experiment in which L,L-IAA was added stepwise to tri(*tert*-pentyl isocyanide)[benzylamino(*tert*-pentylamino)carbene]nickel(II) perchlorate,[22] the formation of the helical polymer was monitored as a function of added monomer by recording the increasing Cotton effect coming from the n–π* transition at $\lambda = 308$ nm (Figure 3). The

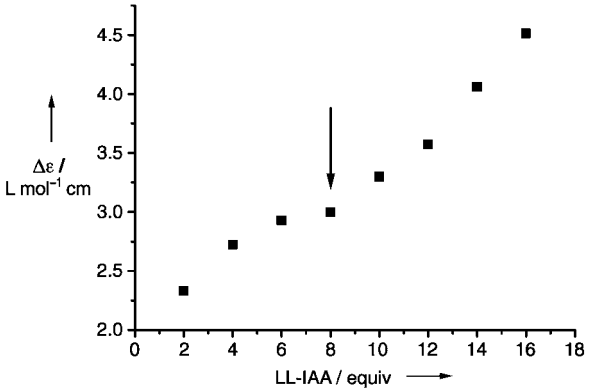


Figure 3. Titration of L,L-IAA to tri(*tert*-pentyl isocyanide)[benzylamino(*tert*-pentylamino)carbene]nickel(II) perchlorate, monitored by CD spectroscopy. The arrow indicates the start of the formation of the helical template. At this point, the signal of a hydrogen-bonded amide appears at $\delta = 9.4$ ppm in the ^{1}H NMR spectrum.

molar circular dichroic absorption ($\Delta\varepsilon_{308}$) increased in a nonlinear fashion with the number of added monomer equivalents. The steep increase after the addition of approximately eight equivalents of isocyanopeptide monomer results from a rearrangement of the secondary polyisocyanide structure from a random conformation when less than eight monomers are incorporated into the growing oligomer to a 4_1 helical conformation when more than eight monomers are built onto the growing polymer. These results were confirmed by monitoring the same titration experiment by ^{1}H NMR spectroscopy. Only when 8–10 molar equivalents of L,L-IAA had been added to a solution of the nickel(II) catalyst in deuterated chloroform, were signals at $\delta = 9.4$ ppm, corresponding to the hydrogen-bonded amide protons of the peptide side chains, observed.

In summary, for the acid-initiated polymerization of isocyanopeptides, we propose a polymerization mechanism in which an initial helical oligomer is formed, which acts as a template for the incorporation of subsequent monomer units through a supramolecular complex. The formation of this supramolecular complex is in line with the measured activation parameters, which point to a highly organized transition state. This result, in combination with the observed induction time of the polymerization suggests that for the polymerization reaction to occur, a helical template must first be formed (Scheme 1). When the acid concentration is increased, this helical template is destroyed in a cooperative fashion and the reaction switches from route A to route B in Scheme 1. Previous experiments have demonstrated the sensitivity of polyisocyanopeptides to an excess of TFA. In these experiments, the well-defined hydrogen-bonded network was disrupted in a cooperative fashion.[8b] The intermediate supramolecular complex also readily explains the high stereoselectivity observed, as the equilibrium for the complex formation will be predominantly shifted to the uncomplexed state in the case of configurationally incorrect monomers. Hence, no or very limited polymerization will occur. The combination of a peptide segment and a polymerizable isocyanide function give a unique type of monomer, which exhibits unprecedented polymerization properties when initiated with acid. The polymerization process is in competition with the formation of a reactive cyclic imidazolone, which depends on the acid concentration. The polymerization reaction stops in a rather narrow concentration range when the helical template is destroyed. Extreme stereospecificity is also found when diastereomeric isocyanopeptides are copolymerized. This observation is also explained by the formation of a highly organized supramolecular complex, which strongly retards the rate of polymerization when "nonfitting" monomers are present.

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[9] Earlier, molecular-modeling studies revealed that the L,L-PIAA polymer has a less favorable conformation than the L,D-PIAA polymer due to unfavorable steric interactions between the side chains n and $n+1$.[6] In the polymerization reaction, a similar unfavorable interaction is probably present, which prevents the polymerization reaction of L,L-IAA from taking place.
[10] The error in the activation enthalpy, $\Delta H^{\neq}$, is $\pm 10\,\%$ and in the entropy of activation, $\Delta S^{\neq}$, is $\pm 20\,\%$. For the nickel(II)-catalyzed polymerization of isocyanides, the activation parameters are $\Delta H^{\neq} = 61.4\,kJ\,mol^{-1}$, $\Delta S^{\neq} = -54\,J\,mol^{-1}\,K^{-1}$, and the free energy of activation, $\Delta G^{\neq}_{293\,K}$ is $77.2\,kJ\,mol^{-1}$ (R. J. M. Nolte, W. Drenth, *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 788). Note that for the acid-catalyzed polymerization $\Delta S^{\neq}$ is about three times more negative.
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