Use of Chiral Ruthenium and Iridium Amido−Sulfonamidate Complexes for Controlled, Enantioselective Polypeptide Synthesis

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Received November 18, 2002

Revised Manuscript Received January 3, 2003

Polypeptides are interesting polymers since their conformational order in solution can impart these materials with specific biological functions. One of the key variables that affects polypeptide chain conformation is stereochemical purity. Changing the chiral configuration of even a single amino acid residue can either greatly stabilize or disrupt the folded structures of peptides.[1] Likewise, incorporation of small amounts of optical impurities into homopolypeptides largely destabilizes their chain conformations.[2] For these reasons, we have been interested in developing methods for stereochemical control in polypeptide synthesis. Much work has been done in this area utilizing chiral initiators and catalysts; however, selectivities have always been low.[3] Recently, we found that nickel complexes containing optically active 2-pyridinyloxazoline ligands initiate the living polymerization of α-amino acid-*N*-carboxyanhydrides (NCAs) with modest enantiomeric selectivity (ca. 17% ee at low conversion).[4] While this system was promising, the use of the first-row metal nickel, with its highly fluxional coordination environment, prevented realization of higher selectivities with good efficiency.

An improved initiator might employ second- or third-row metals, as these possess stronger metal−ligand bonds and are less prone to ligand rearrangements, thus allowing formation of a rigid stereochemical environment around the active metal center.[5] This strategy has been hindered in that the crucial species required for controlled NCA polymerization, namely amido−amidate metallacycles,[6] have been difficult to isolate for non-first-row metals.[7] We sought to identify surrogates that would be functionally equivalent to these amido−amidate metallacycles, yet which could be readily prepared for second- and third-row metals. The Noyori complex, **1**),[8] seemed promising since the amido−sulfonamidate ruthenacycle appeared to possess the required key features for NCA polymerization initiation. The potential of **1** was suggested by the presence of both a nucleophilic amido group for NCA attack and a nonnucleophilic sulfonamidate group to act as a proton acceptor to release the growing chain from the metal center. Complex **1**, when mixed with suitable phosphine ligands, initiates the living polymerization of γ-benzyl glutamate NCA (Glu NCA) and polymerizes the enantiomers selectively. These initiators represent a new motif for controlled polymerization of NCAs and show good potential for improved stereocontrol in polypeptide formation.

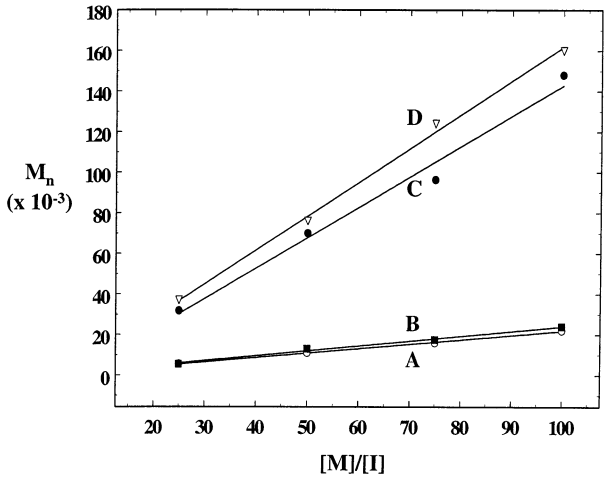
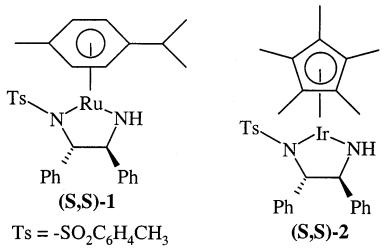


Figure 1. Molecular weights (M_n) of poly(γ-benzyl L-glutamate) vs monomer-to-initiator ratio ([M]/[I]) under different initiation conditions. (A) Theoretical molecular weight calculated from [M]/[I]. (B) Data for **(S,S)-1** + dmpe initiator in DMF. (C) Data for **(S,S)-1** + dmpe initiator in THF. (D) Data for **(S,S)-2** + dmpe initiator in THF. All polymerizations were carried out at 20 °C with [I] = concentration of initiator = 3.2 mM. [M] = concentration of L-Glu NCA. All polymers were isolated in >90% yield, and all M_w/M_n ranged between 1.05 and 1.30.



Complex **1** is readily prepared and well-characterized and catalyzes highly enantioselective ketone reductions.[8] As such, **1** appeared to be an attractive candidate as a second-row metal initiator for enantioselective NCA polymerizations provided the amido−sulfonamidate ligand could act as an efficient initiating group and also support controlled polymerization. The related, isoelectronic iridium complex, **2**,[9] also appeared to be a suitable chiral initiator. Polymerizations of L-Glu NCA in THF or DMF using **(S,S)-1** or **(S,S)-2** proceeded efficiently, yet these did not appear to be living polymerizations. Polymerization rates were erratic, and polypeptide chain lengths varied nonlinearly with monomer-to-initiator stoichiometry. However, upon addition of an aliphatic phosphine to monomer prior to initiator addition (2 P per Ru), the polymerizations exhibited features characteristic of living polymerizations, similar to results obtained with nickel, cobalt, and iron initiators.[6] The donors PMe_3 and dmpe (1,2-bis(dimethylphosphino)-ethane) gave initiators with comparable activities that were also the highest obtained for complex **(S,S)-1** (Table 1). The donor depe (1,2-bis(diethylphosphino)-ethane) gave much slower polymerizations, as might be expected due to its increased steric bulk. Weaker donor

10.1021/ma025844c CCC: $25.00
Published on Web 01/23/2003

Table 1. Kinetic Data for γ-Benzyl Glutamate NCA Polymerization Using Amido−Sulfonamide Initiators[a]

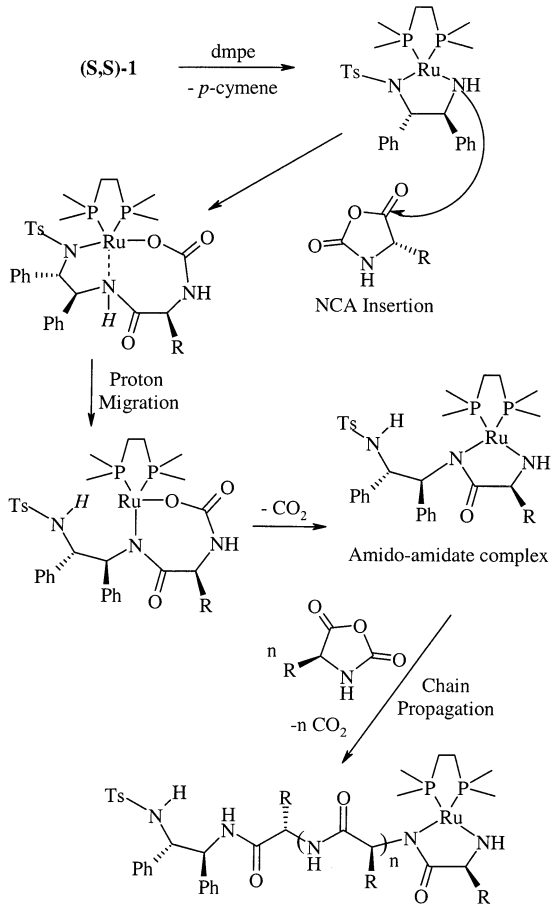
initiator	k_{obs} ($\times 10^4$ s^{-1}) D-Glu NCA	k_{obs} ($\times 10^4$ s^{-1}) L-Glu NCA
(S,S)-1 + 2PMe$_3$	8.4 ± 0.2	28 ± 6
(R,R)-1 + 2PMe$_3$	31 ± 5	9.8 ± 0.2
(S,S)-1 + dmpe	8.7 ± 0.5	70 ± 7
(R,R)-1 + dmpe	66 ± 5	12 ± 2
(S,S)-1 + depe	2.2 ± 0.1	8 ± 2
(R,R)-1 + depe	7.6 ± 0.5	2.5 ± 0.2
(R,R)-2 + depe[b]	6.4 ± 0.6	2.6 ± 0.3

[a] All ruthenium polymerizations were run in THF with [**1**] = 3.2 mM and [NCA] = 63 mM. All data were averages of two experiments. [b] [**2**] = 9.5 μM and [NCA] = 33 mM for the experiments with **2**.

aryl phosphines (PPh_3, DIPHOS) gave very sluggish polymerizations, and other ligand types (e.g., bpy, *t*-BuNC) were unable to support controlled NCA polymerizations. Attempts were made to isolate the active phosphine adducts of **(S,S)-1**. Studies of complex formation using ^{31}P NMR yielded spectra consistent with replacement of the *p*-cymene ligand by phosphines.[10] However, the resulting species were unstable in the absence of monomer and decomposed over time. These results seem reasonable considering that the proposed phosphine adducts of **(S,S)-1** contain only 14 valence electrons (or 16 electrons if the unpaired electrons on the amido ligand are donated to the metal) and thus might require coordinated monomers to be stable.

In the aliphatic phosphine-**(S,S)-1** systems, polypeptide chain lengths scaled linearly with monomer to initiator stoichiometry while molecular weight distributions were low (Figure 1). The polymerization rates were first-order in monomer concentration to 3.5 half-lives, which indicated the lack of significant chain termination events (vide infra). Molecular weights were greater than predicted in THF, which is similar to behavior observed for all other amido−metallacycle initiated polymerizations in this solvent.[6] As in these systems, low initiator efficiency was likely due to aggregation of the active metal centers through bridging amido and amidate ligands, where dimerized initiators are inactive and only the remaining fraction of unaggregated complexes are able to initiate polymerizations.[6d] This aggregation-based deactivation can be eliminated by conducting the polymerizations in DMF. In this better solvent, polymer chain lengths equaled the theoretical values within experimental error (Figure 1). To probe the stability of active chain ends, a chain extension experiment was undertaken. One equivalent of **(S,S)-1** was added to a mixture of 20 equiv of L-Glu NCA and 1 equiv of depe in THF, and the polymerization was allowed to go to completion. Analysis of an aliquot of this mixture gave M_n = 19 500 and M_w/M_n = 1.26 for the resulting poly(γ-benzyl L-glutamate). Eighty additional equivalents of L-Glu NCA were then added to the polymerization mixture, and the reaction was again allowed to proceed until all monomer was consumed. GPC analysis of the final polymer showed a unimodal distribution with M_n = 108 000 and M_w/M_n = 1.14. The apparent lack of unreacted short chains and good correlation of the chain lengths with stoichiometry suggests that nearly all of the chain ends remained active even after complete consumption of monomer. Experiments with other monomers (e.g., ε-carbobenzyloxylysine NCA) showed that **(S,S)-1** + phosphine was also able to initiate the controlled polymerization of a variety of NCAs.[10]

Scheme 1. Possible Mechanism for Controlled NCA Polymerization Using Initiator (S,S)-1



These results confirmed that the ruthenium amido−sulfonamidate unit was able to function equivalently to the amido−amidate metallacycles described earlier in initiating controlled NCA polymerizations. In similar studies, we have found that the related complexes of **(S,S)-2** + phosphine ligands were also efficient initiators for controlled NCA polymerizations (Figure 1). By analogy to the nickel, cobalt, and iron systems,[6] NCA polymerizations mediated by **(S,S)-1** + phosphine are thought to proceed as depicted in Scheme 1. The sulfonamidate group should behave like an amidate group in accepting a proton from the amide formed by monomer addition, thus releasing the chain end. This process also generates an amido−amidate propagating species, which is the ultimate resting state in all the metallacycle systems identified to date.[6] Initiators based on **(S,S)-2** + phosphine should act in a similar manner, with the exception that the cyclopentadienyl ligands will likely remain coordinated to the metal centers throughout the polymerization.

Since **(S,S)-1** contains a chiral initiating ligand, the polymerization of both D- and L-Glu NCA was explored to determine whether the initiator was selective for monomer stereochemistry. Since the chiral initiating ligand will be consumed upon first monomer addition, we originally thought that any selectivity on successive additions would arise via a "chain-end" control process, where the chirality of the peptide chain controls subsequent monomer additions. Initially, we chose to separately study the rates of D-NCA and L-NCA homopolymerizations, rather than the racemate polymerization, since the kinetics would be far less complicated.[11]

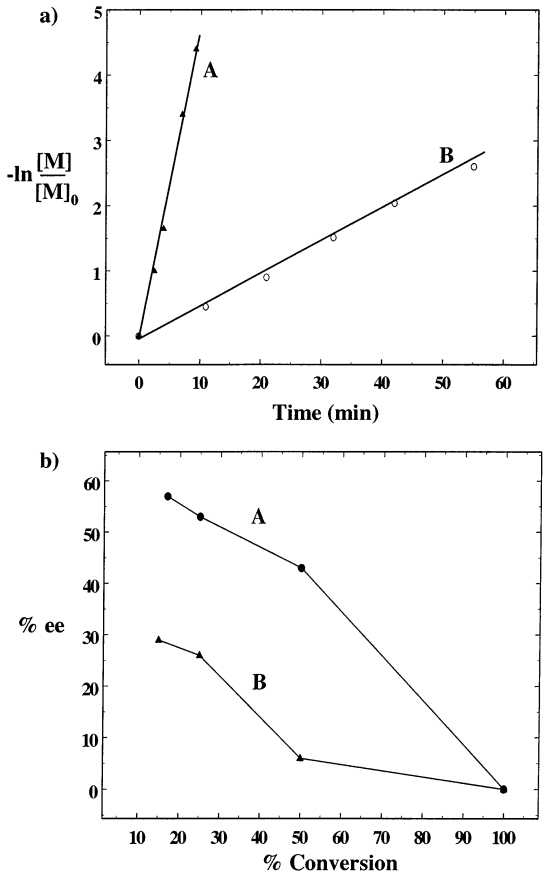


Figure 2. (a) Plots of kinetic data for polymerization of L- and D-Glu NCA Using **(S,S)-1** + dmpe initiator. Polymerizations were run at 25 °C in THF with [Ru] = [dmpe] = 3.2 mM and $[NCA]_0 = [M]_0 = 63$ mM. (A) Data for L-Glu NCA. (B) Data for D-Glu NCA. (b) Plots of enantiomeric excess (% ee) of L-glutamic acid found in poly(γ-benzyl glutamate) formed as functions of total monomer conversion (% conversion). Polymerizations were run at 25 °C in THF using racemic-Glu NCA monomer and **(S,S)-1** + phosphine initiator. [Ru] = [phosphine] = 13 mM and $[NCA]_0 = 260$ mM. (A) Data for **(S,S)-1** + dmpe initiator. (B) Data for **(S,S)-1** + depe initiator.

Figure 2a shows the monomer consumption over time for D- and L-Glu NCA polymerized separately using **(S,S)-1** + dmpe. With all three alkylphosphine complexes of **1**, the enantiomers of Glu NCA were polymerized at significantly different rates (Table 1). The dmpe adduct was highly selective, giving rate differences of greater than 5 to 1, which exceed the values for any other known system.[3,4] These selectivities were obtained at monomer conversion rates that were comparable to or greater than those of the fast, but unselective, nickel and cobalt systems.[6] In our previous studies on enantioselective nickel initiators for NCA polymerization, differences in enantiomer polymerization rates for Glu NCA of 5:1 were only obtained at the expense of a 5-fold decrease in overall polymerization rate compared to the nonselective polymerization.[4]

The results obtained with **(S,S)-1** showed good promise for obtaining high selectivity at high activity. The dominant role of the initiating ligand in rate of enantiomer consumption was verified by use of the opposite initiator enantiomer, **(R,R)-1**, for polymerizations and observation of reversed monomer selectivities (Table 1). The analogous iridium complex, **(R,R)-2**, also showed enantiomer selectivity. All these data suggested that the observed enantioselectivities were not due to chain-end control since, in this model, the chiral initiating ligand should only have an effect on rate during the first monomer additions, where one chiral monomer would react faster than its enantiomer due to diastereomeric interactions with the initiating ligand. Once all initiators had begun growing chains (either D or L), both enantiomers should polymerize at identical rates, as the growing active sites would be enantiomers of each other (D-monomer/D-chain vs L-monomer/L-chain). Rate differences would only occur during initiation, where the "wrong" enantiomer would initiate slowly over time while the "correct" enantiomer would initiate rapidly, leading to an apparent faster rate of monomer consumption. This can be tested by kinetic analysis, where the slow enantiomer should display non-first-order kinetics, where the rate increases over time. Since this was not observed, the selectivities of the chiral initiators must be due to some form of chirality at the metal centers (catalyst site control). This was an unexpected result since the initial source of chirality at the metal, the amido−sulfonamide ligand, was presumably being removed from the metal center upon monomer addition.

To test this model, we needed to verify that the chiral ligand was indeed acting as an initiator and not remaining on the metal as a spectator ligand. Analysis of a purified oligo-L-leucine sample prepared using **(S,S)-1** + dmpe by ^{1}H NMR revealed resonances assignable to the initiating ligand in good agreement with the predicted ratio to leucine resonances.[10] The poor solubility of this oligomer in most organic solvents allowed extensive washing to ensure removal of any free ligand that might have been present. This result, in combination with the well-controlled nature of NCA polymerizations observed using **(S,S)-1** + phosphine, led us to believe that the chiral ligand is initiating the polymerizations and thus ends up on the C-terminus of the resulting polypeptides, as illustrated in Scheme 1. The observed chirality at the propagating metal centers, therefore, must be due to a rigid, chiral coordination geometry at the metal center, which was set from the chirality of the initiating ligand in combination with the donor phosphine ligands. Fixed chirality at the active metal center would explain an initiator's ability to maintain enantiomeric selectivity even after multiple monomer additions. While the exact geometries of the active sites of these initiators are not known at this time, it is resonable to imagine that the chelate nature of the asymmetric propagating amido−amidate group as well as the presence of chelating phosphine ligands can help stabilize such a rigid, chiral coordination environment. In this respect, use of chelating dmpe vs similar size but nonchelating PMe_3 ligands gave rise to much greater enantioselectivities.

To further probe the selectivities of these initiators, we performed polymerization studies using optically pure initiators and racemic monomers. These experiments were also valuable since the enantioselective polymerizations of racemates is much more desirable in a practical sense than the ability to polymerize opposite enantiomers at different rates.[12] Polymerizations were conducted as before, using **(S,S)-1** + dmpe and **(S,S)-1** + depe as initiators and racemic Glu NCA as the monomer. The reactions were run in parallel, and samples were quenched at different degrees of monomer conversion so that the enantiomeric excess in the

resulting polymers could be measured using polarimetry (Figure 2b). In line with our initial kinetic studies, the results were very promising, with the dmpe complex especially showing selectivity much higher than has been observed in any other NCA system.[3,4] These results also confirm the presence of catalyst site control in this system as the presence of the opposite antipode monomer in the reaction mixture was not able to remove the enantiomeric preference of the initiators, even after significant monomer consumption. This selectivity, combined with the high activity of these ruthenium-based initiators, provides a solid base for realizing the kinetic resolution of racemic monomers and formation of tapered stereoblock copolymers.

These ruthenium-based amido−sulfonamidate complexes provide a means to obtain stereocontrol in NCA polymerizations that has been difficult to realize in other metallacycle-based systems. These results also allow a better understanding of NCA polymerizations through identification of new, effective initiator structures that can be correlated with reactivity. Full investigations into the mechanisms of these polymerizations are currently underway.

Acknowledgment. This work was supported by a National Science Foundation Award CHE-0099334 and partially supported by the MRSEC program of the National Science Foundation under Award DMR-0080034. T.J.D. is grateful for a Camille Dreyfus Teacher-Scholar Award.

Supporting Information Available: Details of all reactions and polymerizations. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Voet, D.; Voet, J. G. *Biochemistry*, 2nd ed.; Wiley: New York, 1995.
(2) Fasman, G. *Poly α-Amino Acids*; Dekker: New York, 1967.
(3) (a) Bührer, H. G.; Elias, H. G. *Makromol. Chem.* **1973**, *169*, 145−162. (b) Oguni, N.; Kuboyama, H.; Nakamura, A. *J. Polym. Sci., Chem. Ed.* **1983**, *21*, 1559−1565. (c) Tsuruta, T.; Inoue, S.; Matsuura, K. *Makromol. Chem.* **1963**, *63*, 219−221. (d) Matsuura, K.; Inoue, S.; Tsuruta, T. *Makromol. Chem.* **1964**, *80*, 149−157. (e) Makino, T.; Inoue, S.; Tsuruta, T. *Makromol. Chem.* **1971**, *150*, 137−162. (f) Yamashita, S.; Yamawaki, N.; Tani, H. *Macromolecules* **1974**, *7*, 724−727.
(4) Cheng, J.; Deming, T. J. *Macromolecules* **1999**, *32*, 4745−4747.
(5) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; Wiley: New York, 1988.
(6) (a) Deming, T. J. *Nature (London)* **1997**, *390*, 386−389. (b) Deming, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4240−4241. (c) Deming, T. J. *Macromolecules* **1999**, *32*, 4500−4502. (d) Deming, T. J.; Curtin, S. A. *J. Am. Chem. Soc.* **2000**, *122*, 5710−5717.
(7) (a) Goodwin, A. A.; Bu, X.; Deming, T. J. *J. Organomet. Chem.* **1999**, *589*, 111−114. (b) Deming, T. J. *J. Polym. Sci., Polym. Chem. Ed.* **2000**, *38*, 3011−3018.
(8) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285−288.
(9) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1201−1202.
(10) See Supporting Information.
(11) Sigwalt, P. *Pure Appl. Chem.* **1976**, *48*, 257−266.
(12) Okamoto, Y.; Nakano, T. *Chem. Rev.* **1994**, *94*, 349−372.

MA025844C