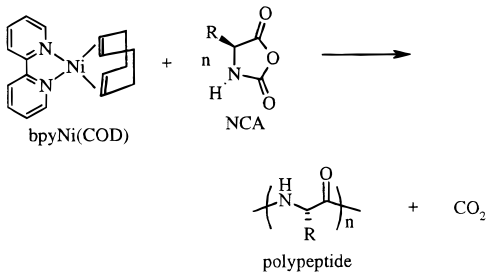
Cobalt and Iron Initiators for the Controlled Polymerization of α-Amino Acid-*N*-Carboxyanhydrides

Timothy J. Deming

Departments of Materials and Chemistry, University of California, Santa Barbara, Santa Barbara, California 93106

Received February 25, 1999

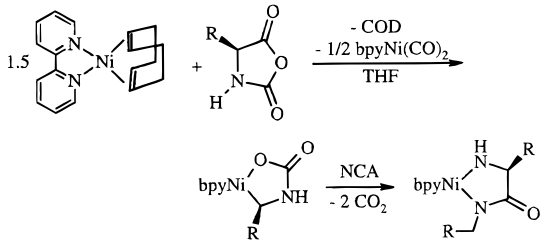
Polypeptides are interesting polymers because their structural complexity imparts these materials with specific biological functions. Although methods for preparation of high-molecular-weight polypeptides have existed for over 100 years, this chemistry, the polymerization of α-amino acid-*N*-carboxyanhydrides (NCAs), has been plagued by side reactions.[1] Chain transfer and termination reactions have limited this methodology to the preparation of polypeptides that lack the complexity of natural proteins. Recently, we discovered that the zerovalent nickel complex, bpyNi(COD), initiates the polymerization of NCAs and supports polymerization while greatly eliminating side reactions (eq 1).[2] After



(1)

identifying the mechanism by which this initiator operates, we sought to develop initiators based on other transition metals to see if they might provide advantages for polymerization. It was found that the reaction chemistry of NCAs with zerovalent metals is general for the metals iron, cobalt, and nickel, which all form products resulting from oxidative addition of the monomer to the metal across the O−C_5 anhydride bond. Due to the high reactivity of zerovalent cobalt, the complex $(PMe_3)_4Co$ was found to initiate NCA polymerizations more rapidly than did bpyNi(COD), allowing the preparation of well-defined short sequences of amino acids in block copolypeptides.

In our initial studies on nickel initiators, the zerovalent metal precursors were found to add NCAs across the O−C_5 anhydride bond to form metallacycles (eq 2)



(2)

that subsequently added additional NCA monomers to form polypeptides.[3] From these studies, the key requirements for formation of efficient initiators were determined to be (i) a low-valent metal, capable of undergoing a 2-electron oxidative-addition reaction, (ii) strong electron-donating ligand(s) to promote oxidative addition, and (iii) stability of the metal complex toward the functionalities found in polypeptides (i.e., ester, amide, thioether, etc.). We initially sought to extend the nickel chemistry to the related metals palladium and platinum. It was discovered that both of these metals react with NCAs at the N−H bond and thus do not form the correct propagating species for controlled polymerization.[4] It became evident that subtle features of individual metals and their complexes, such as nucleophilicity and basicity, were also important in determining their effectiveness in NCA polymerizations.

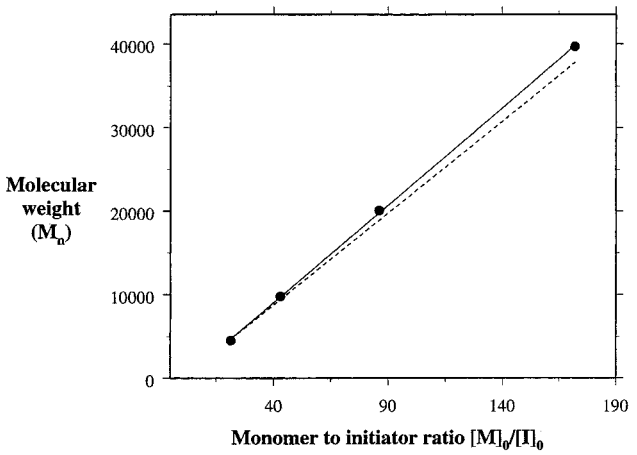


Figure 1. Plot of molecular weight of polypeptide obtained as a function of γ-benzyl-L-glutamate NCA monomer, **M**, and $Co(PMe_3)_4$ initiator, **I**. The dotted line represents the expected molecular weight. Polymerizations were run in DMF solvent at 23 °C for 16 h.

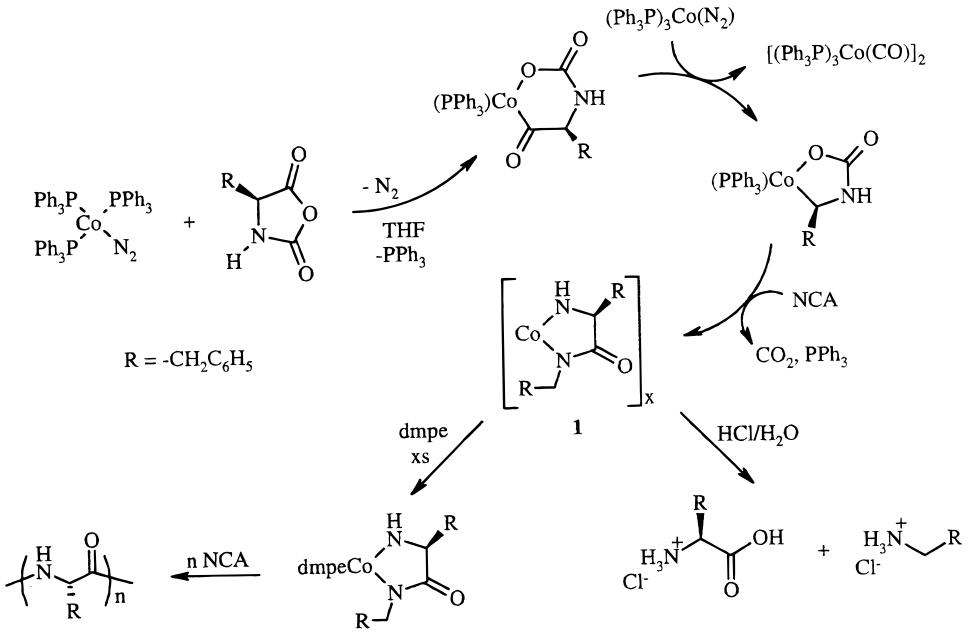
Since most first-row transition metals are stable in the divalent oxidation state and can also exist in the zerovalent oxidation state, we decided to investigate some of these metals for polymerization activity. Aside from nickel, the other first-row metals that would likely fit our requirements were cobalt and iron, since both are easily obtained in low oxidation states.[5] The most common zerovalent forms of these metals are the carbonyl compounds, $Co_2(CO)_8$ and $Fe(CO)_5$; however, the electron deficiency of these species, due to the π-acidity of CO, precludes their use as initiators. Carbonyl complexes of iron, cobalt, or nickel, even in the presence of strong donor ligands (e.g., PMe_3), react extremely slowly with NCAs at ambient temperature.

To circumvent this problem, we prepared the more reactive homoleptic phosphine complexes $(PMe_3)_4M$, M = Fe, Co.[6] These species were chosen since they are well-characterized complexes that are readily prepared and stable. In contrast to $Ni(COD)_2$,[7] which is versatile for making different initiators through facile ligand substitutions, pure olefin complexes of iron and cobalt are not very stable and were not used.[8] When the $(PMe_3)_4M$ complexes were mixed with NCAs, rapid reactions were observed for both metals. With cobalt, rapid polymerization of the NCA was observed, while with iron only small molecule products were formed.

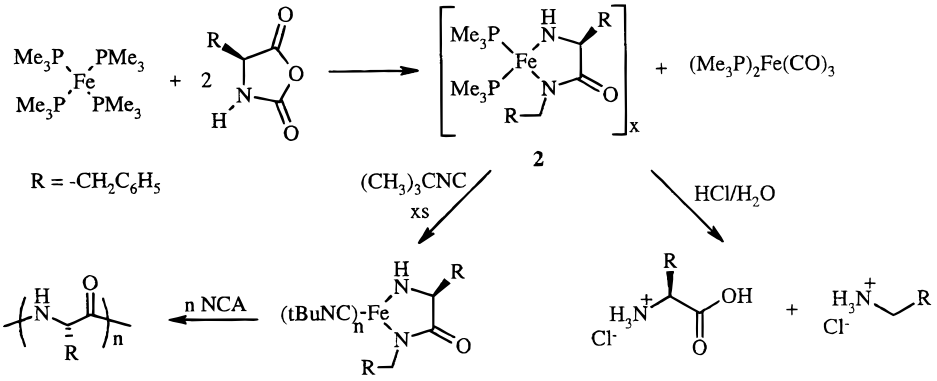
Similar to bpyNi(COD), $(PMe_3)_4Co$ promoted the controlled polymerization of NCAs. Polypeptides were prepared with molecular weights defined by monomer-

10.1021/ma9902899 CCC: $18.00
Published on Web 06/03/1999

Scheme 1. Formation and Reactivity of 1

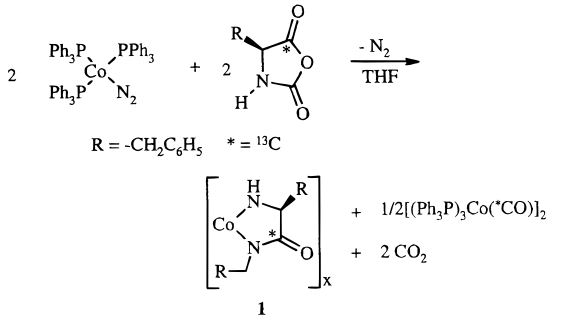


Scheme 2. Formation and Reactivity of 2



to-initiator stoichiometry and with low polydispersities (M_w/M_n < 1.15) (Figure 1). Furthermore, block copolypeptides could be prepared by sequential additions of different NCA monomers to the initiator.[9] An interesting feature of this cobalt system was that chain initiation was much faster than it was with nickel. In THF, at low monomer-to-initiator stoichiometries (e.g., [M]:[I] = 3:1), the cobalt system was able to produce short peptide oligomers with low polydispersity (M_n = 1100, M_w/M_n = 1.18), while bpyNi(COD) was only able to produce higher molecular weight oligomers (M_n = 12 100, M_w/M_n = 1.13) with most of the bpyNi(COD) left unreacted. The cobalt system has a clear advantage over bpyNi(COD) for the preparation of short peptide oligomer sequences in block copolymers.

To identify the propagating species in the cobalt-initiated polymerizations, we utilized the ability of the PPh_3 ligand to reduce polymerization activity. As with PPh_3 complexes of nickel(0),[3] when $(PPh_3)_3Co(N_2)$[10] was reacted with NCAs, metallacyclic products were formed that were incapable of further reactions with NCAs. Stoichiometric reactions of unlabeled and $^{13}C_5$-labeled L-phenylalanine NCA (Phe NCA) with $(PPh_3)_3Co(N_2)$ thus allowed the identification of this product. The reaction with unlabeled NCA in THF gave the byproduct $[Co(CO)(PPh_3)_3]_2$ [FTIR(THF): 1909, 1875 cm^{-1}, νCO] as well as an ether-insoluble tan powder, **1** [FTIR(THF): 1600 cm^{-1}, νCO]. When the reaction was run with the labeled monomer, the IR absorptions of both products were found to shift, indicative of isotopic labeling: $[Co(^{13}CO)(PPh_3)_3]_2$ [FTIR(THF): 1869, 1831 cm^{-1}, ν^{13}CO] and **1**-^{13}C [FTIR(THF): 1575 cm^{-1}, ν^{13}CO] (eq 3). These



(3)

results were entirely consistent with our previous observations from nickel-mediated polymerizations[3] and can be explained by the reaction sequence shown in Scheme 1.

The loss of CO from the C_5 position (trapped as $[Co(CO)(PPh_3)_3]_2$) conclusively indicated that initial oxidative addition of the NCA was occurring at the O−C_5 anhydride bond. Incorporation of the C_5 label into **1** also indicated that a second NCA addition to cobalt had

occurred. Additional evidence for the formation of this metallacycle was the similarity of this material to that formed with nickel and the isolation of L-phenylalanine and 2-phenethylamine from hydrolysis of **1** (Scheme 1). The amide bond of the metallacycle was presumably cleaved during hydrolysis by aqueous acid in the presence of Co^{2+} to yield the observed products. The lack of PPh_3 in the product was confirmed by elemental analysis. Confirmation that this metallacyclic product was also formed in $(PMe_3)_4Co$-initiated polymerizations was obtained by complexation of the ligand-free **1** with dmpe (Scheme 1). The resulting complex was found to efficiently initiate NCA polymerizations and provide molecular weight control similar to that found with $(PMe_3)_4Co$. All of these experiments were consistent with the cobalt initiators operating by a mechanism identical to that of the nickel system.

Investigation of the $(PMe_3)_4Fe$ reaction with NCAs revealed that similar chemistry was also occurring with iron. The reaction of $(PMe_3)_4Fe$ with 2 Phe NCA in THF gave a white powder, **2** [FTIR(THF): 1604 cm^{-1}, νCO], as well as a small amount of $(PMe_3)_2Fe(CO)_3$ [FTIR(THF): 1842 cm^{-1}, νCO] (Scheme 2). Use of $^{13}C_5$-labeled Phe NCA shifted both of these absorptions, as with cobalt and nickel: **2**-^{13}C [FTIR(THF): 1570 cm^{-1}, ν^{13}CO] and $(PMe_3)_2Fe(^{13}CO)_3$ [FTIR(THF): 1802 cm^{-1}, ν^{13}CO]. Polymerizations initiated with **2** in DMF were sluggish and gave low yields of polypeptide. It was believed that the inactivity of this complex was due to aggregation in solution. We have reported that nickel analogue of **1** aggregates in THF[3] and have found that **1** aggregates as well. Aggregation of **2** was expected to be quite strong since iron is more Lewis acidic than either cobalt or nickel and can bind tightly to the Lewis basic amido ligand. Osmotic molecular weight measurement of **2** in THF (ca. 3.0 mg/mL) revealed that the complex aggregates as a dimer. To disrupt aggregation, we reacted **2** with 6 equiv of *tert*-butyl isocyanide (Scheme 2). The bulky, strong donor isocyanide ligands formed a stable complex which was monomeric in THF. This unaggregated complex was also able to efficiently polymerize NCAs with good molecular weight control. With the proper ligands, iron initiators behaved similarly to both cobalt and nickel.

Overall, we have found that the reaction chemistry of NCAs with zerovalent metals is general for nickel, cobalt, and iron. Individual metals do require different ligand environments to realize controlled NCA polymerization, primarily to avoid aggregation of the amido propagating species. While bpyNi(COD) may be the most easily utilized initiator for preparation of block copolypeptides, since it can be prepared in situ from commercially available reagents, cobalt initiators have the advantage of providing fast initiation that allows the preparation of well-defined, oligomeric sequences of amino acids.

Acknowledgment. This work was supported by a National Science Foundation CAREER Award No. CHE-9701969, and partially supported by the MRSEC program of the National Science Foundation under Award No. DMR-9632716 and the U.S. Army Research Office Multidisciplinary University Research Initiative under Award No. DAAH04-96-1-0443. T. J. D. is grateful for Alfred P. Sloan and a Beckman Young Investigator Fellowships.

Supporting Information Available: Details of all reactions and polymerizations (9 pages). Ordering and Internet access instructions are available on any current masthead page.

References and Notes

(1) (a) Kricheldorf, H. R. *α-Amino Acid-N-Carboxyanhydrides and Related Materials*; Springer-Verlag: New York, 1987. (b) Kricheldorf, H. R. In *Models of Biopolymers by Ring-Opening Polymerization*; Penczek, S., Ed.; CRC Press: Boca Raton, 1990.

(2) Deming, T. J. *Nature* **1997**, *390*, 386−389.

(3) Deming, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4240−4241.

(4) Goodwin, A. A.; Bu, X.; Deming, T. J. *J. Organomet. Chem.*, in press.

(5) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; Wiley: New York, 1988.

(6) (a) Klein, H.-F.; Karsh, H. H. *Chem. Ber.* **1975**, *108*, 944−955. (b) Karsh, H. H.; Aresta, M. *Inorg. Synth.* **1980**, *20*, 69−76.

(7) Schunn, R. A. *Inorg. Synth.* **1975**, *15*, 5−9.

(8) Mackenzie, R.; Timms, P. L. *J. Chem. Soc., Chem. Commun.* **1974**, 650−651.

(9) See Supporting Information.

(10) Speier, G.; Markó, L. *Inorg. Chim. Acta* **1969**, *3*, 126−128.

MA9902899