Chain Initiation Efficiency in Cobalt- and Nickel-Mediated Polypeptide Synthesis

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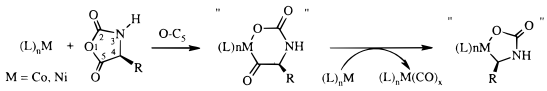
Abstract: In the presence of certain ligands and solvents, nickel- and cobalt-mediated living polymerizations of α-amino acid-*N*-carboxyanhydrides (NCAs) produce polymers with molecular weights several times greater than predicted by initial molar ratios of monomer to initiator. Such molecular weight inflation could result either from competitive formation of catalytic intermediates of reduced activity or from incomplete formation of a single catalytically active species. Evidence is presented here supporting the latter possibility. Specifically, evidence is given that the concentration of the key amido−amidate metallacyclic active species is reduced in situ by (1) complexation of metal(0) preinitiator by CO liberated upon addition of an NCA monomer to another molecule of preinitiator, (2) incomplete ring contraction of a six-membered amido−alkylmetallacyclic intermediate due to inefficient proton migration, and (3) dimerization of the amido−amidate active species to give catalytically inactive complexes.

α-Amino acid-*N*-carboxyanhydrides (NCAs) are attractive monomers for polypeptide synthesis since they are readily prepared from amino acids and since their polymerization is probably the most economical and expedient process to synthesize high molecular weight polypeptides.[1] Extensive utilization of NCAs, however, has been limited because of their complicated reactivity and tendency to uncontrollably polymerize.[2] We have recently reported the living polymerization of NCAs and synthesis of block copolypeptides using zerovalent nickel and cobalt initiators (i.e., bpyNi(COD) and $(PMe_3)_4Co$).[3,4] When polymerizations were carried out in DMF solvent, these initiators converted NCA monomers into polypeptides with narrow molecular weight distributions and molecular weights defined by monomer-to-initiator stoichiometry. We have since discovered that when these polymerizations are conducted in less polar solvents (e.g., THF), or with different ligands on the nickel complex (e.g., dmpe), polymers were obtained with molecular weights much greater than predicted by monomer-to-initiator ratios. Such molecular weight inflation could result either from competitive formation of catalytic intermediates of reduced activity or from incomplete formation of a single catalytically active species. Evidence is presented here supporting the latter possibility. Specifically, experiments showed that the concentration of the key amido−amidate metallacyclic active species was reduced in situ by (1) complexation of metal(0) preinitiator by CO liberated upon addition of an NCA monomer to another molecule of preinitiator, (2) incomplete ring contraction of a six-membered amido−alkylmetallacyclic intermediate due to inefficient proton migration, and (3) dimerization of the amido−amidate active species to give catalytically inactive complexes.

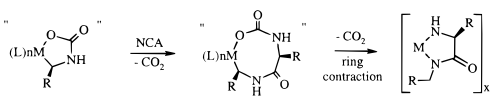
Background

In our initial reports on zerovalent nickel and cobalt NCA polymerization initiators, experiments were described that showed that both metals react identically with NCA monomers to form metallacyclic complexes by oxidative addition across the anhydride bond of NCAs.[4,5] These experiments took advantage of the diminished reactivity of triphenylphosphine complexes of cobalt(0) and nickel(0), which react with NCAs but are then unable to react with additional NCA monomers to form polypeptides. NCA monomers labeled with ^{13}C in either the C_2 or C_5 position were reacted with $(PPh_3)_2Ni(COD)$[5] or $(PPh_3)_3Co(N_2)$[4] to yield metallacyclic intermediates and byproducts that were identified by isotopic shifts in IR stretches, ^{13}C NMR, and identification of the organic components after hydrolysis of the metallacycles. Use of isotopic labeling allowed conclusive determination of the regioselectivity of the initial oxidative addition reactions, which were found to be completely selective for the $O-C_5$ bond (eq 1). These oxidative−addition



(1)

reactions were followed by addition of a second NCA monomer to yield complexes identified as five-membered amido−amidate metallacycles (eq 2). This transformation required the ring



(2)

contraction of a six-membered metallacycle intermediate, which

(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, FL, 1990.

(2) (a) Sekiguchi, H. *Pure Appl. Chem.* **1981**, *53*, 1689−1714. (b) Sekiguchi, H.; Froyer, G. *J. Polym. Sci. Symp.* **1975**, *52*, 157−171.

(3) Deming, T. J. *Nature* **1997**, *390*, 386-389.

(4) Deming, T. J. *Macromolecules* **1999**, *32*, 4500−4502.

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

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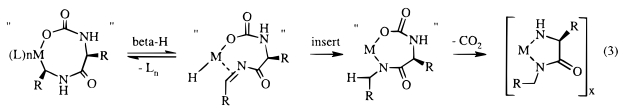
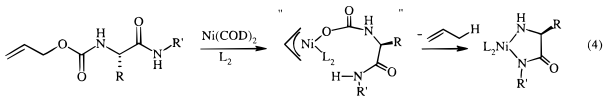
was thought to occur via a β-H elimination−reinsertion process (eq 3). There was considerable precedent for this reaction,[6]

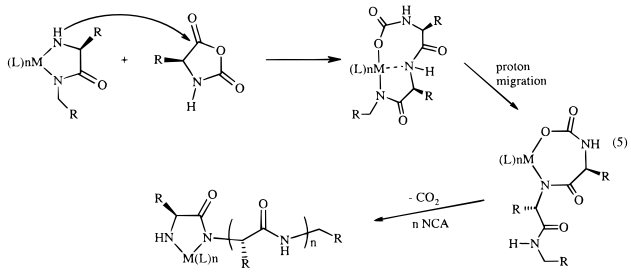


which, in our case, gave amido−amidate complexes that were attractive as active polymerization intermediates.

These metallacycles were believed to be the active species in NCA polymerizations since (i) addition of appropriate donor ligands (i.e., bpy for nickel and dmpe for cobalt) to these ligand-free metallacycles gave complexes with polymerization activities similar to the corresponding zerovalent complexes, and (ii) oxidative−addition chemistry identical to that found with the PPh_3 complexes was also observed for the active initiators bpyNi(COD) and $(PMe_3)_4Co$.[4,5] The validity of these five-membered amido−amidate metallacycles as polymerization intermediates was also substantiated by their synthesis via independent methods (eq 4) and finding similar polymerization



activity.[7] Propagation through the amido−amidate metallacycle was envisioned to occur by initial attack of the nucleophilic amido group on the electrophilic C_5 carbonyl of an NCA monomer (eq 5).This reaction would result in a large metalla-



cycle that could readily contract by elimination of CO_2. Proton transfer from the free amide to the tethered amidate group would further contract the ring back to the amido−amidate propagating species, while in turn liberating the end of the polymer chain. In this manner, the metal would be able to migrate along the growing polymer chain, while being held by a robust chelate at the active end.

On the basis of these studies, it was concluded that both zerovalent cobalt and nickel initiators reacted with NCAs via the same mechanism. The only practical differences between these two systems were (i) the greater reactivity of cobalt(0) relative to nickel(0) in the oxidative−addition step and (ii) a greater variety of potential initiators in the nickel system due to the stability of nickel(0) in a wide variety of ligand environments.[8] The first difference provides an advantage in that the cobalt initiator can be used to prepare short peptide oligomers at low monomer-to-initiator stoichiometries since all chains are activated well before all the monomer is consumed. These oligomers have been used to assist our mechanistic studies (vide infra) by allowing the identification of polymer end groups. The second difference also gave insight into the polymerization mechanism since use of initiators with different ligands, prepared by ligand substitution reactions with $Ni(COD)_2$, could be used to probe the steric and electronic environment around the active propagating species.

Table 1. Molecular Weight (M_n), Polydispersity (M_w/M_n), and Yield of PBLG When Polymerized Using Metal(0) Complexes with Different Ligands and in Different Solvents[a]

	THF			DMF		
initiator	M_n	M_w/M_n	yield (%)	M_n	M_w/M_n	yield (%)
$Ni(COD)_2$			0	na	na	na
bpyNi(COD)	109 000	1.05	96	19 500	1.14	97
phenNi(COD)	151 000	1.15	94	41 200	1.21	98
dmpeNi(COD)	192 000	1.04	90	60 300	1.33	96
tmedaNi(COD)	305 000	1.09	96	87 400	1.36	96
$(PPh_3)_2Ni(COD)$			0	na	na	na
$(PMe_3)_4Co$	77 100	1.15	98	20 300	1.17	97

[a] A total of 90 equiv of Glu NCA was added per mole of metal complex in all cases. All polymerizations were run at 20 °C with [Glu NCA] = 170 mM. Phen = 1,10-phenanthroline, dmpe = 1,2-bis(dimethylphosphino)ethane, tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. na, experiment not performed. Polymerizations conducted with the ligands in the absence of the metal gave either no polymer during the time span of the experiment (phosphines, bpy, and phen) or polymer with high polydispersity (tmeda, M_n = 124 000, M_w/M_n = 1.67).

The effects of varying both solvent and ligands in cobalt- and nickel-mediated NCA polymerizations are given in Table 1. The use of solvents less polar than DMF such as THF gave polymers with inflated molecular weights (similar molecular weight inflation was observed for polymerizations conducted in toluene, dioxane, DME, and ethyl acetate). Variation of the ligands bound to nickel(0) complexes had a similar effect, regardless of the solvent used. In all cases, polymers were obtained in high yield, with narrow molecular weight distributions, and with molecular weights that were linearly dependent on monomer-to-initiator stoichiometry. It appeared that variation of solvent or ligands did not adversely affect chain propagation by introduction of side reactions, but rather hindered the chain-initiation process in that diminished amounts of active species were formed in some circumstances. Since degree of polymerization is determined by monomer-to-initiator ratio in this system, decreasing the amount of active species would result in higher molecular weight chains. To identify the factors that influence the amount of active species that is formed in situ, the initiation and propagation steps of these polymerizations were investigated in more detail.

Experimental Section

General Information. Infrared spectra were recorded on a Perkin-Elmer RX1 FTIR spectrophotometer calibrated using polystyrene film. Tandem gel permeation chromatography/light scattering (GPC/LS) was performed on a SSI series III liquid chromatograph pump equipped with a Wyatt DAWN DSP light-scattering detector and Wyatt Optilab DSP. Separations were effected by 10^5-, 10^3-, and 500-Å Phenomenex 5-μm columns using 0.1 M LiBr in DMF eluent at 60 °C. NMR spectra were measured on a Bruker Avance 200-MHz spectrometer. MALDI mass spectra were collected using a Thermo BioAnalysis Dynamo mass spectrometer running in positive ion mode with samples prepared by mixing solutions of analyte in THF with solutions of 6-aza-2-thiothymine in THF and allowing the mixtures to air-dry. C, H, and N elemental analyses and electrospray mass spectroscopy (ESI-MS) were performed by the Microanalytical Laboratory and Mass Spectroscopy Facilities of the University of California, Santa Barbara. Chemicals were obtained from commercial suppliers and used without purification unless

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

otherwise stated. [$^{13}C_4$]-L-Leucine was obtained from Cambridge Isotope Labs. bpyNi(COD),[5] $(PPh_3)_2$Ni(COD),[5] $(PMe_3)_4$Co,[9] (*S*)-[CoNHC(H)RC(O)NHCHR]$_x$, R = $CH_2C_6H_6$,[4] dmpeNiNHCH(CH(CH$_3$)$_2$)C(O)NCH$_2$CH$_2$CH$_3$,[7] γ-benzyl-L-glutamate NCA (Glu NCA), ϵ-benzyloxycarbonyl-L-lysine NCA (Lys NCA), L-proline NCA (Pro NCA), L-leucine NCA (Leu NCA), L-phenylglycine NCA (Phg NCA), sarcosine NCA (Sar NCA), and L-phenylalanine NCA (Phe NCA) were prepared according to literature procedures.[1] Hexanes, THF, and THF-d_8 were purified by first purging with dry nitrogen, followed by passage through columns of activated alumina.[10] DMF and DMF-d_7 were purified by drying over 4-Å molecular sieves followed by vacuum distillation.

Sample Polymerization of Glu NCA in DMF Using a Metal(0) Initiator. In the drybox, Glu NCA (50 mg, 0.2 mmol) was dissolved in DMF (0.5 mL) and placed in a 15-mL reaction tube which could be sealed with a Teflon stopper. An aliquot of $(PMe_3)_4$Co (50 μL of a 40 mM solution in DMF−THF (1:1)) was then added via syringe to the flask. A stir bar was added and the flask was sealed, removed from the drybox, and stirred in a thermostated 25 °C bath for 16 h. Polymer was isolated by addition of the reaction mixture to methanol containing HCl (1 mM) causing precipitation of the polymer. The polymer was then dissolved in THF and reprecipitated by addition to methanol. The polymer was dried in vacuo to give a white solid, poly(γ-benzyl-L-glutamate) (PBLG; 42 mg, 99% yield). ^{13}C {^{1}H} NMR, ^{1}H NMR, and FTIR spectra of this material were identical to data found for authentic samples of PBLG.[11] GPC of the polymer in 0.1 M LiBr in DMF at 60 °C: M_n = 21 600; M_w/M_n = 1.11.

Sample Polymerization of Glu NCA in THF Using a Metal(0) Initiator. This polymerization was conducted exactly as described above except for substitution of THF for DMF. The resulting polymer was dried in vacuo to give PBLG (41 mg, 98% yield). GPC of the polymer in 0.1 M LiBr in DMF at 60 °C: M_n = 86 200; M_w/M_n = 1.13.

Sample Polymerization of Glu NCA in THF Using Various (Ligand)Ni(0) Initiators. This polymerization was conducted exactly as described above except for substitution of (dmpe)Ni(COD) (50 μL of a 40 mM solution in THF) for the cobalt initiator. The resulting polymer was dried in vacuo to give PBLG (40 mg, 98% yield). GPC of the polymer in 0.1 M LiBr in DMF at 60 °C: M_n = 216 000; M_w/M_n = 1.04.

Poly(ϵ-benzyloxycarbonyl-L-lysine-*block*-γ-benzyl-L-glutamate) (PZLL-*b*-PBLG) Sample Diblock Copolymer Prepared in THF. In the drybox, Glu NCA (25 mg, 0.01 mmol) was dissolved in THF (0.5 mL) and placed in a 15-mL reaction tube which could be sealed with a Teflon stopper. An aliquot of $(PMe_3)_4$Co (50 μL of a 40 mM solution in THF) was then added via syringe to the flask. A stir bar was added, and the flask was sealed and then stirred for 16 h. An aliquot (50 μL) was removed from the polymerization for GPC analysis (M_n = 44 300; M_w/M_n = 1.15). Lys NCA, (50 mg, 0.16 mmol) dissolved in THF (0.5 mL) was then added to the reaction mixture. After stirring for an additional 16 h, the polymer was isolated as before to give a white solid, PZLL-*b*-PBLG (62 mg, 97% yield). ^{13}C {^{1}H} NMR, ^{1}H NMR, and FTIR spectra of this material were identical to a combination of data found for authentic individual samples of PBLG and PZLL.[11,12] GPC of the block copolymer in 0.1 M LiBr in DMF at 60 °C: M_n = 124,600; M_w/M_n = 1.16.

Sample Polymerization of Glu NCA in THF in the Presence of $(PPh_3)_3$RhCl. In the drybox, Glu NCA (50 mg, 0.2 mmol) was dissolved in a THF solution of $(PPh_3)_3$RhCl (0.5 mL containing 8.0 μmol of Rh) and placed in a 15-mL reaction tube which could be sealed with a Teflon stopper. An aliquot of bpyNi(COD) (100 μL of a 40 mM solution in THF) was then added via syringe to the flask. This polymerization was then conducted exactly as described above to give PBLG (41 mg, 97% yield). GPC of the polymer in 0.1 M LiBr in DMF at 60 °C: M_n = 35 500; M_w/M_n = 1.16.

Sample Polymerization of Glu NCA Using (Ligand)NiNHCH(CH(CH$_3$)$_2$)C(O)NCH$_2$CH$_2$CH$_3$ Initiators. This polymerization was conducted exactly as described above except for substitution of dmpeNiNHCH(CH(CH$_3$)$_2$)C(O)NCH$_2$CH$_2$CH$_3$ (50 μL of a 40 mM solution in THF) for the cobalt initiator. The resulting polymer was dried in vacuo to give PBLG (38 mg, 91% yield). GPC of the polymer in 0.1 M LiBr in DMF at 60 °C: M_n = 107 000; M_w/M_n = 1.16.

Isolation of $(PPh_3)_2$Rh(CO)Cl from an Oligomerization Conducted in the Presence of $(PPh_3)_3$RhCl. In the drybox, Leu NCA (20 mg, 0.13 mmol) was dissolved in a THF solution of $(PPh_3)_3$RhCl (1.0 mL containing 0.05 mmol of Rh) and placed in a 15-mL reaction tube which could be sealed with a Teflon stopper. bpyNi(COD) (8.5 mg, 0.025 mmol) in THF (0.5 mL) was then added to the flask. A stir bar was added and the flask was stirred in the drybox for 16 h, whereupon L-leucine oligomers were observed to precipitate from solution. The red-orange supernatant was isolated by centrifugation, and hexanes (5 mL) was added to precipitate the Rh complex. The precipitate was extracted with THF (0.5 mL) and layered with hexanes to give a mixture of $(PPh_3)_3$RhCl and $(PPh_3)_2$Rh(CO)Cl as orange-red crystals (26 mg). FTIR spectra of this material gave data identical to that found for authentic samples of $(PPh_3)_2$Rh(CO)Cl.[13] IR (THF): 1978 cm^{-1} (νCO, vs).

(*S*)-[NiNHC(H)RC(O)NHCHR]$_x$, R = $CH_2C_6H_6$. In the drybox, Phe NCA (110 mg, 0.58 mmol) was dissolved in THF (1.0 mL) and added to a stirred homogeneous mixture of PPh_3 (310 mg, 1.2 mmol) and $(COD)_2$Ni (160 mg, 0.58 mmol) in THF−Et_2O (1.5 mL:10 mL). The red-brown solution was let stand for 24 h, after which a yellow precipitate was observed to form. This powder was washed with Et_2O (3 × 5 mL) and then dried to give the product as a yellow powder (80 mg, 85% yield). An ^{1}H NMR spectrum could not be obtained in THF-d_8, most likely because of paramagnetism of the complex (only broad lines for the phenyl rings were observed). IR (THF): 3310 (νNH, s br), 1580 cm^{-1} (νCO, amidate, vs). Anal. Calcd for $NiC_{17}H_{18}N_2O$: C, 62.81; H, 5.59; N, 8.61. Found: C, 62.40; H, 5.80; N, 8.25.

Isolation of L-Phenylalanine-1-deutero-2-phenylethylamide from (*S*)-[NiNHC(H)RC(O)NHCHR]$_x$, R = $CH_2C_6H_6$. In the drybox, [NiNHC(H)RC(O)NHCHR]$_x$, R = $CH_2C_6H_6$ (10 mg, 0.03 mmol), was dissolved in THF (5 mL) in a round-bottom Schlenk flask. The flask was placed under N_2 atmosphere on a Schlenk line and DCl (90 μL of a 1.0 M solution in D_2O) was then added. The light brown solution immediately changed color to green. The solvent was then removed in vacuo to leave a green gummy solid. This solid was extracted with D_2O to isolate the amino acid fragments. The isolated material (5 mg, 63% yield) was found to exclusively contain l-phenylalanine-1-deutero-2-phenylethylamide as determined by analysis and comparison to l-phenylalanine-2-phenylethylamide obtained by HCl quenching. ^{1}H NMR (D_2O): δ 7.20 (m, Ar-*H*, 5H + 5H), 4.05 (t, $NH_3CH(CH_2C_6H_5)C(O)$, 1H), 3.46, 3.25 (t, NHC*H*DCH$_2$C$_6$H$_5$, 1H), 2.98 (d, $NH_3CH(CH_2C_6H_5)C(O)$, 2H), 2.63 (d, NHCHDC*H*$_2$C$_6$H$_5$, 1H). ^{13}C {^{1}H} NMR (D_2O): δ 164.12 (s, amide *C*O), 133.24, 128.45, 126.10, 126.05, 122.35, 122.29, 121.23, 119.98 (aryl-*C*), 49.40 (s, $NH_3CH(CH_2C_6H_5)C(O)$), 38.34 (t, NH*C*HDCH$_2$C$_6$H$_5$, J_{C-D} = 25 Hz), 32.61 (s, $NH_3CH(CH_2C_6H_5)C(O)$), 27.93 (s, NHCHDC*H*$_2$C$_6$H$_5$). ESI-MS(D_2O): MD_5^+: 274.4 calcd, 274.1 found (4 protons of the amine and amide groups were replaced with deuterium from D_2O). For the compound quenched with HCl instead of DCl: ESI-MS(D_2O): MD_4^+: 273.4 calcd, 273.2 found.

Isolation of L-Phenylalanine and 1-Deutero-2-phenethylamine from (*S*)-[CoNHC(H)RC(O)NHCHR]$_x$, R = $CH_2C_6H_6$. In the drybox, (*S*)-[CoNHC(H)RC(O)NHCHR]$_x$, R = −$CH_2C_6H_6$ (10 mg, 0.031 mmol), was dissolved in THF (5 mL) in a round-bottom Schlenk flask. The flask was placed under N_2 atmosphere on a Schlenk line and DCl

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(10) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520.
(11) Block, H. *Poly(γ-benzyl-L-glutamate) and Other Glutamic Acid Containing Polymers*; Gordon and Breach: New York, 1983.
(12) Bamford, C. H.; Elliot, A.; Hanby, W. E. *Synthetic Polypeptides*; Academic Press: New York, 1956.
(13) McCleverty, J. A.; Wilkinson, G. *Inorg. Synth.* **1966**, *8*, 214−217.

(90 μL of a 1.0 M solution in H_2O) was then added. The light brown solution immediately turned pink and later changed to a deep blue. After 2 h, the solvent was removed in vacuo to leave a blue gummy solid. This solid was extracted with D_2O to isolate the amino acid fragments. The isolated products (4 mg) were found to be composed of a mixture of l-phenylalanine and 1-deutero-2-phenethylamine as determined by analysis, comparison to authentic samples, and comparison to the products obtained by HCl quenching.[4] ^{1}H NMR (D_2O): δ 7.10 (m, Ar-*H*, 5H + 5H), 4.01 (t, $NH_3CH(CH_2C_6H_5)C(O)OH$, 1H, J = 7.5 Hz), 3.12 (dd, $NH_3CH(CH_2C_6H_5)C(O)OH$, 2H, J_{gem} = 17.9 Hz, J_{H-H} = 7.9 Hz), 2.90 (m, $NH_3CHDCH_2C_6H_5$, 3H). ^{13}C {^{1}H} NMR (D_2O): δ 174.56 (s, *C*OOH), 137.34, 136.83, 132.15, 132.09, 129.40, 127.68, 127.60, 126.52 (aryl-*C*), 57.92 (s, $NH_3CH(CH_2C_6H_5)C(O)OH$), 40.86 (t, $NH_3CHDCH_2C_6H_5$, J_{C-D} = 23 Hz), 37.49 (s, $NH_3CH(CH_2C_6H_5)C(O)OH$), 32.33 (s, $NH_3CHDCH_2C_6H_5$,).

(*S*)-[NiNCH(CH$_2$CH$_2$CH$_2$)C(O)NCH(CH$_2$CH$_2$CH$_2$)]$_x$. In the drybox, Pro NCA (82 mg, 0.58 mmol) was dissolved in THF (1.0 mL) and added to a stirred homogeneous mixture of PPh_3 (310 mg, 1.2 mmol) and $(COD)_2Ni$ (160 mg, 0.58 mmol) in THF−Et_2O (1.5 mL:10 mL). The red-brown solution was let stand for 24 h, after which a yellow precipitate was observed to form. This powder was washed with Et_2O (3 × 5 mL) and then dried to give the product as a yellow powder (53 mg, 82% yield). An ^{1}H NMR spectrum could not be obtained in THF-d_8, most likely because of paramagnetism of the complex (only broad lines for the methylene groups were observed). IR (THF): 1576 cm^{-1} (νCO, amidate, vs). Anal. Calcd for $NiC_9H_{13}N_2O$: C, 48.27; H, 5.86; N, 12.51. Found: C, 47.90; H, 6.01; N, 12.76.

Isolation of L-Proline-α-deutero-pyrrolidinylamide from (*S*)-[NiNCH(CH$_2$CH$_2$CH$_2$)C(O)NCH(CH$_2$CH$_2$CH$_2$)]$_x$. In the drybox, (*S*)-[NiNCH(CH$_2$CH$_2$CH$_2$)C(O)NCH(CH$_2$CH$_2$CH$_2$)]$_x$ (10 mg, 0.04 mmol) was dissolved in THF (5 mL) in a round-bottom Schlenk flask. The flask was placed under N_2 atmosphere on a Schlenk line and DCl (90 μL of a 1.0 M solution in D_2O) was then added. The light brown solution immediately changed color to green. The solvent was then removed in vacuo to leave a green gummy solid. This solid was extracted with D_2O to isolate the amino acid fragments. The isolated material (4 mg, 53% yield) was found to exclusively contain L-proline-α-deutero-pyrrolidinylamide as determined by analysis and comparison to L-proline−pyrrolidinylamide obtained by HCl quenching. ^{1}H NMR (D_2O): δ 4.44 (dd, $NH_2CH(CH_2CH_2CH_2)C(O)$, 1H), 3.48 (m, $NH_2CH(CH_2CH_2CH_2)C(O)$, 2H), 3.32 (m, $C(O)NCHD(CH_2CH_2CH_2)$, 3H), 2.20 (dm, $NH_2CH(CH_2CH_2CH_2)C(O)$, 2H), 1.80 (m, $NH_2CH(CH_2CH_2CH_2)C(O)NCHD(CH_2CH_2CH_2)$, 6H). ^{13}C {^{1}H} NMR (D_2O): δ 174.2 (s, $NH_2CH(CH_2CH_2CH_2)C(O)$), 59.5 (s, $NH_2CH(CH_2CH_2CH_2)C(O)$), 47.1 (s, $NH_2CH(CH_2CH_2CH_2)C(O)$), 44.2 (s, $C(O)NCHD(CH_2CH_2CH_2)$), 42.7 (t, $C(O)NCHD(CH_2CH_2CH_2)$, J_{C-D} = 24 Hz), 28.7 (s, $NH_2CH(CH_2CH_2CH_2)C(O)$), 25.7 (s, $NH_2CH(CH_2CH_2CH_2)C(O)$), 24.3 (s, $C(O)NCHD(CH_2CH_2CH_2)$), 23.8 (s, $C(O)NCHD(CH_2CH_2CH_2)$). ESI-MS(D_2O): MD_3^+: 172.3 calcd, 172.0 found (2 protons of the amine group were replaced with deuterium from D_2O). For the compound quenched with HCl instead of DCl: ESI-MS(D_2O): MD_2^+: 171.3 calcd, 171.0 found.

(*S*)-(bpy)NiNCH(CH$_2$CH$_2$CH$_2$)C(O)NCH(CH$_2$CH$_2$CH$_2$). In the drybox, a golden brown solution of [NiNCH(CH$_2$CH$_2$CH$_2$)C(O)NCH(CH$_2$CH$_2$CH$_2$)]$_x$ (15 mg, 0.067 mmol) in DMF (0.5 mL) was added to a solution of bpy (42 mg, 0.27 mmol) in DMF (0.5 mL). The homogeneous mixture was stirred for 2 days at 50 °C, during which the color changed from yellow to red. THF (1 mL) and toluene (5 mL) were layered onto this solution, resulting in separation of a red oil. This oil was precipitated from DMF−THF−toluene (1:2:10) two additional times to give the product (19 mg, 74% yield). An ^{1}H NMR spectrum could not be obtained in THF-d_8, most likely because of paramagnetism of the complex. IR (THF): 1596 cm^{-1} (νCO, amidate, vs). Anal. Calcd for $NiC_{19}H_{21}N_4O$: C, 60.03; H, 5.58; N, 14.73. Found: C, 59.60; H, 5.65; N, 14.66.

Attempted Polymerization of Glu NCA Using (*S*)-(bpy)NiNCH(CH$_2$CH$_2$CH$_2$)-C(O)NCH(CH$_2$CH$_2$CH$_2$). This polymerization was conducted exactly as described above except for substitution of (*S*)-(bpy)NiNCH(CH$_2$CH$_2$CH$_2$)C(O)NCH(CH$_2$CH$_2$CH$_2$) (50 μL of a 40 mM solution in DMF) in place of the cobalt initiator. The reaction was worked up as above to give only a small amount of PBLG (1 mg, 2% yield). GPC of this material in 0.1 M LiBr in DMF at 60 °C: M_n = 8,900; M_w/M_n = 1.47.

Sample Polymerization of Phg NCA in DMF Using a Metal(0) Initiator. This polymerization was conducted exactly as described above except for substitution of Phg NCA (35 mg, 0.2 mmol) for Glu NCA. The resulting insoluble polymer was isolated by filtration, washed with methanol containing HCl (1 mM), and dried to give a white solid, poly(L-phenylglycine) (26 mg, 96% yield). This polymer was insoluble in most solvents; however, MALDI-MS analysis obtained from a TFA solution confirmed the identity of the polymer.[7]

Attempted Polymerization of Pro NCA in DMF Using $(PMe_3)_4Co$. This polymerization was conducted exactly as described above except for substitution of Pro NCA (50 mg, 0.35 mmol) for Glu NCA. An attempt was made to isolate polymer by addition of the reaction mixture to Et_2O containing HCl (1 mM) resulting in only a small amount of precipitate being formed. This precipitate was dried in vacuo to give a white solid (2 mg, 6% yield). GPC of this material in 0.1 M LiBr in DMF at 60 °C: M_n = 5200; M_w/M_n = 1.56.

Attempted Polymerization of Sar NCA in DMF Using $(PMe_3)_4Co$. This polymerization was conducted exactly as described above except for substitution of Sar NCA (50 mg, 0.43 mmol) for Glu NCA. An attempt was made to isolate polymer by addition of the reaction mixture to Et_2O containing HCl (1 mM) resulting in only a small amount of precipitate being formed. This precipitate was dried in vacuo to give a white solid (2 mg, 6% yield). GPC of this material in 0.1 M LiBr in DMF at 60 °C: M_n = 4900; M_w/M_n = 1.63.

Oligomerization of [$^{13}C_4$]-L-Leucine NCA using $(PMe_3)_4Co$ and Quenching with HCl−DCl. In the drybox, [$^{13}C_4$]-L-leucine NCA (40 mg, 0.25 mmol) was dissolved in THF (0.5 mL) and placed in a 15-mL reaction tube which could be sealed with a Teflon stopper. A solution of $(PMe_3)_4Co$ (18 mg, 0.05 mmol) in THF (0.5 mL) was then added to the flask. A stir bar was added and the flask was sealed, removed from the drybox, and stirred in a thermostated 25 °C bath for 16 h. The oligomerization was quenched by addition of either HCl or DCl (90 μL of a 1.0 M solution in H_2O or D_2O) resulting in an immediate color change from brown to light pink. Et_2O was added to precipitate the oligomers, which were washed with excess Et_2O (3 × 5 mL) and then dried (25 mg, 88% yield). The samples were analyzed by ^{13}C {^{1}H} NMR and MALDI MS. The ^{13}C {^{1}H} NMR spectra were found to be identical for both HCl and DCl quenched samples: ^{13}C {^{1}H} NMR (THF-d_8): δ 54.7 (m, $NHCH(CH_2CH(CH_3)_2)C(O)$), 48.2 (s, $NHCH_2CH_2CH(CH_3)_2$).

Results and Discussion

Our prior studies on the reactions of NCAs with nickel(0) and cobalt(0) were conclusive in identifying the first step in chain initiation. The major concern in reexamination of this system was comparison of the efficiency of these steps under different polymerization conditions. In determining the amount of metal(0) that was converted to active propagating species, there were a number of factors to be considered. These issues included quenching of the metal complexes to form inactive species, alternate reaction pathways to form inactive species, or simply poor conversion in the steps leading to active complexes. We searched for any evidence of these phenomena in all the stages of initiation.

First NCA Addition. In the first step of an NCA reacting with either cobalt(0) or nickel(0), our studies have shown that this reaction is selective for addition of the metal across the O−C_5 bond of the anhydride (eq 1).[4,5] This oxidative−addition

Table 2. Molecular Weight (M_n), Polydispersity (M_w/M_n), and Yield of PBLG When Polymerized Using Metal(0) Complexes in the Presence and Absence of 2 Equiv of $(PPh_3)_3RhCl$ Per Metal(0) Complex[a]

		no $(PPh_3)_3RhCl$			with $(PPh_3)_3RhCl$			
initiator	[M]/[I]	M_n	M_w/M_n	yield (%)	M_n	M_w/M_n	yield (%)	% recovery[b]
bpyNi(COD)	25	33 000	1.20	97	16 600	1.22	94	16.4
bpyNi(COD)	50	61 100	1.13	98	35 500	1.16	97	13.0
dmpeNi(COD)	45	96 400	1.21	94	43 200	1.16	98	12.6
depeNi(COD)	45	110 000	1.19	96	50 300	1.18	99	10.6
$(PMe_3)_4Co$	45	33 200	1.09	96	34 500	1.11	95	0.00
dmpeNi(COD)[c]	72	30 700	1.22	97	19 000	1.09	96	31.7

[a] [M]/[I] = moles of glu nca per mole of metal(0) complex. Polymerizations were run at 20 °C with [Glu NCA] = 170 mM in THF solvent. [b] % recovery, increased amount of metal(0) precursor that was able to form active initiator in the presence of $(PPh_3)_3RhCl$, as determined from polymer molecular weights. [c] This polymerization was run in DMF solvent, Otherwise under the same conditions as above.

product had not been isolated, since it rapidly reacts with an additional NCA to form the amido−amidate metallacycle, yet its formation was inferred by isolation of CO eliminated from the C_5-carbonyl of the complex.[14] Under polymerization conditions and with the PPh_3−metal(0) complexes, the initially formed six-membered metallacycles were observed to eliminate CO to form more stable five-membered rings before addition of the next NCA monomer (eq 1). In stoichiometric reactions, this CO was efficiently trapped by unreacted metal(0) complexes to give stable carbonyl compounds.[14] We had found that the resulting electron-poor carbonyl complexes of both nickel(0) and cobalt(0) only react with NCAs very slowly at ambient temperature.[4] It was conceivable that reaction of some metal(0) initiator with CO liberated from other NCA additions was fast enough to quench a fraction of the initiator through formation of these inert carbonyl complexes.

To see whether CO trapping was occurring in these polymerizations, a means to eliminate this reaction from polymerizations was sought. Wilkinson's catalyst, $(PPh_3)_3RhCl$, is known to be an extremely effective CO scavenger in solution and has been reported to remove CO from a variety of metal carbonyl complexes.[16] We have found that Wilkinson's catalyst does not react with NCAs at room temperature and therefore was potentially useful as a CO scavenger that might trap CO more efficiently than the metal(0) complexes, thus freeing additional metal centers for polymerization. Polymerizations were conducted with and without 2 equiv of Wilkinson's catalyst per metal(0) complex, and the results are given in Table 2. For polymerizations using bpyNi(COD) in THF, polypeptides were obtained with molecular weights ~6 times greater than predicted by monomer-to-initiator stoichiometry. When Wilkinson's catalyst was added to otherwise identical polymerizations, the resulting polymer molecular weights were found to decrease ~50% (i.e., to 3 times the predicted values), with no change in yield, polydispersity, or ability to control molecular weight. Similar results were obtained when other nickel initiators were used, and when the polymerizations were run in DMF solvent. When these reactions were conducted at very low monomer-to-initiator ratios (~5:1), $(PPh_3)_2Rh(CO)Cl$ could be isolated from the reaction mixture.

From these experiments, it appeared that Wilkinson's catalyst was effectively scavenging some CO from the reaction medium in the nickel-initiated polymerizations and thus allowed a greater fraction of the nickel(0) complexes to form active polymerization initiators. With cobalt(0), Wilkinson's catalyst had no effect, presumably since the reactive, electron-rich $(PMe_3)_4Co$ is a better CO scavenger than the rhodium complex. With the bpyNi(COD) initiator, the amount of Wilkinson's catalyst was varied to quantify the amount of CO poisoning. From the molecular weight data in Figure 1, it was determined that up to ~16% of the nickel polymerization activity was recovered as the amount of Rh was increased, presumably since trapping the CO with Rh prevented its complexation with Ni(0). Above ~0.5 equiv of Rh per Ni(0) center, no additional polymerization activity was observed, although ~45% of the initial amount of Ni(0) remained inactive in the polymerizations. Since this remaining inactivity was essentially unaffected by substantial increases in concentrations of Wilkinson's catalyst, it must be the result of other factors, and not CO complexation.

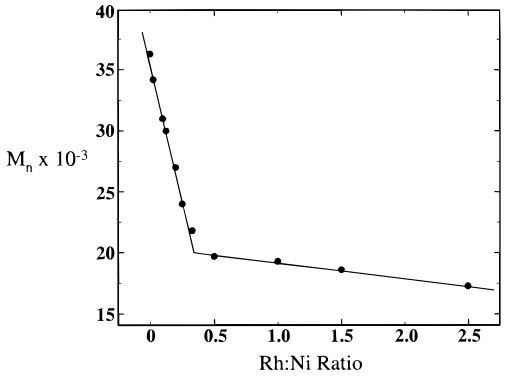
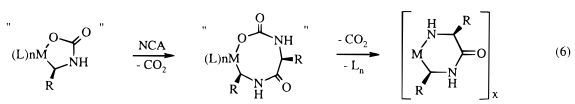


Figure 1. Molecular weights (M_n) of PBLG obtained from bpyNi(COD)-initated polymerizations of Glu NCA in THF at 20 °C as a function of the amount of $(PPh_3)_3RhCl$ added to the reactions. A total of 25 equiv of Glu NCA were added per mole of nickel complex in all cases. All polymers were obtained in >95% isolated yield and possessed M_w/M_n values of ~1.20.

Second NCA Addition. The search for additional loss of active initiator led to reinvestigation of the second step in active species formation (eq 2). This step involved insertion of an NCA into the carbamate metallacycle, followed by ring contraction to the five-membered amido−amidate active species. The main concern in this step was the efficiency of the ring contraction (eq 3). Upon reinvestigation of this reaction, we found that our previous studies had inaccurately identified the product of eq 2 as the five-membered metallacycle.[4,5] The products isolated from the reaction of PPh_3−Ni(0) and Co(0) complexes and NCAs were actually the noncontracted six-membered amido−alkyl complexes (eq 6). The inability to obtain informative NMR data



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on the metallacycles themselves due to their paramagnetism required the preparation of derivatives for the indirect charac-

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(15) Castaño, A. M.; Echavarren, A. M. *Organometallics* **1994**, *13*, 2262−2268.

(16) Dickson, R. S. *Organometallic Chemistry of Rhodium and Iridium*; Academic Press: London, 1983.

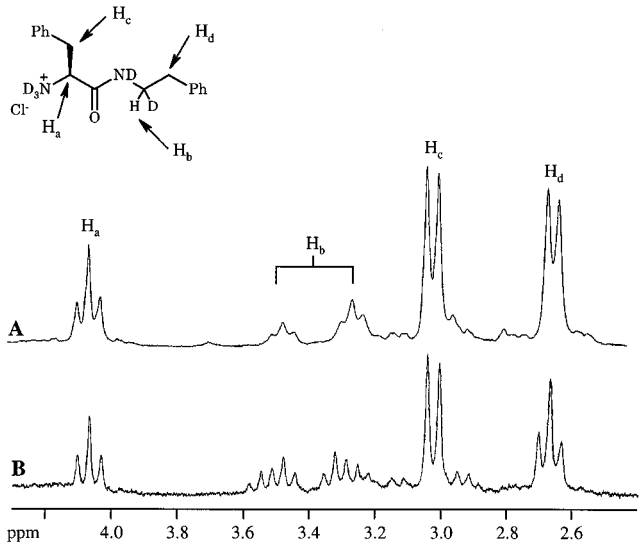
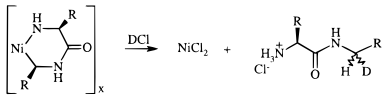


Figure 2. Partial ^{1}H NMR spectra in D_2O of the products from reactions of (*S*)-[NiNHCH(CH_2Ph)C(O)NHCH(CH_2Ph)]$_x$ with DCl (A) and HCl (B). The collapse of H_d from a triplet to a doublet, and H_b from two doublets of triplets to two triplets, when DCl was used confirmed the formation of the C−D bond. The presence of two triplets for H_b in (A) revealed that this carbon had undergone some racemization.

terization of their structures. Acidolysis of the metallacycles with HCl gave organic products that were assumed to be bound to the metal centers through nitrogen ligands. The metallacycles were correctly identified by acidolysis of the complexes with DCl, instead of HCl, followed by characterization of the organic byproducts (eq 7). ^{1}H NMR, ^{13}C {^{1}H} NMR, and MS analysis



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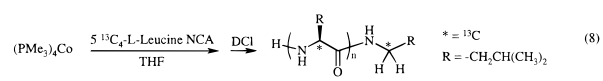
of the nickelacycle-derived compound revealed that the aminoamide byproduct was quantitatively deuterated at the carbon adjacent to the amide nitrogen, identifying this carbon as the point of attachment to nickel (Figure 2). Likewise, although the aminoamide product derived from the corresponding cobaltacycle was found to hydrolyze to amino acid and amine under the acidolysis conditions, the amine fragment was also found to be quantitatively deuterated at the carbon adjacent to the amino nitrogen. Therefore, with the PPh_3-derived complexes, no ring contraction to amido−amidate propagating species was found to occur. This result raised the question of whether the ring contraction occurs at all, and if so, under what conditions.

To determine whether the metal−carbon bond of the intermediate metallacycle is cleaved during the course of a polymerization, short peptide oligomers were prepared and analyzed using MALDI mass spectroscopy and ^{13}C {^{1}H} NMR. Five equivalents of [$^{13}C_4$]-L-leucine NCA were reacted with $(PMe_3)_4$Co in THF and the completed oligomerization was then quenched with either HCl or DCl (eq 8). If the cobalt−carbon



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bond remained intact throughout the polymerization, a resonance with ^{13}C−D coupling should be present in the ^{13}C {^{1}H} NMR spectrum when the bond is cleaved with DCl and should be a singlet with HCl quenching. Only singlet resonances and

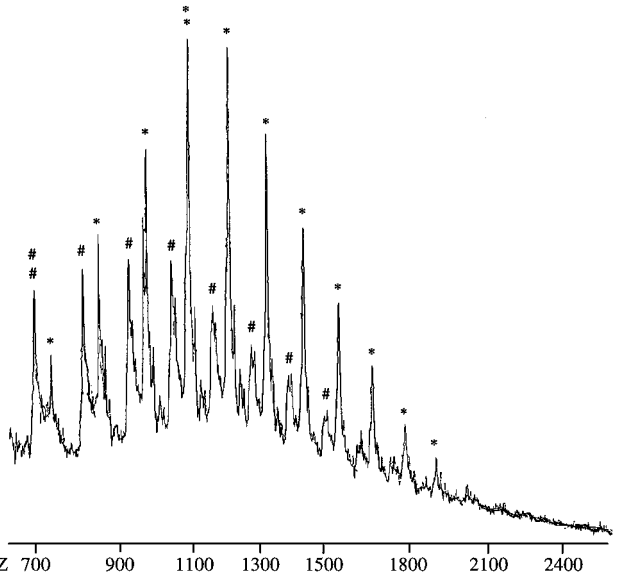


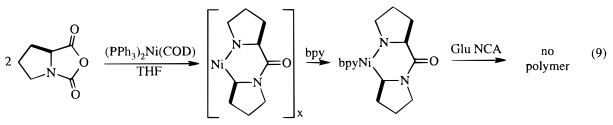
Figure 3. MALDI mass spectrum of [$^{13}C_4$]-L-leucine oligomers prepared using $(PMe_3)_4$Co in THF. The sample was prepared by mixing a solution of oligomer in TFA (2.0 mg/mL) with a solution of 6-aza-2-thiothymine in TFA (10 mg/mL) and allowing the sample to dry in air. Key: (#) series corresponds to H[NH^{13}CH($CH_2CH(CH_3)_2$)C(O)]$_n$OH oligomers; (*) series corresponds to H[NH^{13}CH($CH_2CH(CH_3)_2$)C(O)]$_n$NH^{13}CH$_2$CH$_2$CH(CH_3)$_2$ oligomers; (##) hexamer: calcd, 703.93 (MH^+); found, 702.7 (MH^+); (**) nonamer: calcd, 1116.54 (MH^+); found, 1116.1 (MH^+).

identical spectra were observed for both cases, indicating that the cobalt−carbon bond was being cleaved during the polymerization and prior to acidolysis. Similar results were obtained when bpyNi(COD) in DMF was used in place of cobalt.

Confirmation that the six-membered metallacycles were precursors to the active species in these polymerizations was also obtained by MALDI mass spectroscopy. Analysis of the oligomers from above showed well-defined masses corresponding to leucine repeats containing the isoamylamide C-terminus derived from the metallacycle (Figure 3). Some lower mass oligomers without the amide end cap were also observed, which were formed by hydrolysis of the end groups in the TFA matrix that was used. The observation of increasing amounts of hydrolyzed peptide over time confirmed this hypothesis. Overall, the NMR and MALDI-MS experiments on these oligomers showed that the metallacycles are involved in polypeptide formation and that the metal−carbon bond in these complexes is cleaved at some point during the polymerization. Since independently prepared five-membered amido−amidate nickelacycles are also able to prepare well-defined polypeptides,[7] we believe that the amido−amidate metallacycle is the true active species in the polymerization and is likely formed in situ from the six-membered metallacycle intermediates.

If this ring contraction does occur, it remained to be determined how, when, and to what extent this transformation was completed. We had proposed that this contraction might occur through a β-H elimination−reinsertion process (eq 3).[5] This now seemed unlikely, since the six-membered amido−alkylmetallacycles were thermally stable up to 80 °C, while related six-membered nickelacycles were found to contract at ambient temperature.[6] Another process, such as β-H elimination from the β-carbon of the amino acid, was also unlikely since L-phenylglycine NCA, which possesses no β-H, reacted with the metal(0) complexes and was able to form polypeptides. The obvious source of a proton to cleave the metal−carbon bond, and form the expected metal−amidate bond, would be from an

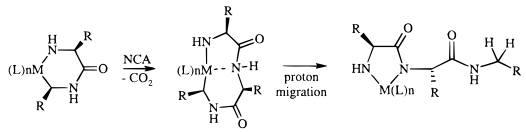
amide N−H. $(PPh_3)_2Ni(COD)$ was reacted with L-proline NCA, which lacks a proton on nitrogen, to study the need for an N−H group in initiator formation. This reaction formed the expected six-membered amido−alkylmetallacycle; however, after ligation of this product with bpy, a complex was formed that was a poor NCA polymerization initiator (eq 9). Likewise, when



(9)

excess L-proline NCA or sarcosine NCA were reacted with bpyNi(COD) or $(PMe_3)_4Co$ in THF or DMF, very little polypeptide was formed (∼2−5% yield).

The presence of a proton on the NCA nitrogen was found to be essential for effective initiator formation. Since the six-membered metallacycle was formed with L-proline NCA, the N−H group must be required only for subsequent initiation steps. Proton migration from an amide nitrogen to the metal−carbon bond would explain these phenomena. We have recently observed a similar reaction in the formation of amido−amidate nickelacycles by a different pathway. These metallacycles form by proton migration from a tethered amide group to an allyl−nickel bond to generate a nickel−amidate bond and propene (eq 4).[7] It is likely that a similar process is occurring in the metal(0)-initiated polymerizations to accomplish the ring contraction. Upon addition of an NCA monomer to the amido−alkylmetallacycle, the resulting complex may ring-contract by proton migration from the tethered amide to the metal−carbon bond, yielding the five-membered amido−amidate propagating species (eq 10).



(10)

If affected by solvent polarity and ligand environment, inefficiency in this ring contraction step could result in diminished formation of active polymerization centers. With the Alloc-aminoamide route to nickel initiators (eq 4), definite solvent effects on cyclization efficiency have been observed.[7] With ligands such as bpy and phen, ring closure to form the metallacycle occurs at ambient temperature in DMF, but requires heating to 80 °C in THF. This solvent sensitivity is also similar to that found for the related coupling of allylic halides using nickel where an allyl group is transferred to a nickel−allyl bond to generate biallyl and a nickel halide.[17] In this well-studied reaction, the coupling step has been found to be fast in polar solvents but sluggish in hydrocarbons.[18] Since this reaction has been found to involve complex equilibria and multiple nickel oxidation states, it is difficult to speculate on the exact role played by polar solvents in accelerating these reactions.[19]

However, on the basis of our observations and those on the allyl coupling reactions,[18] it is possible that highly polar solvents (i.e., DMF) accelerate ring contraction of the metallacycles by acting as coordinating ligands that disrupt stable aggregates of the amido−alkyl precursors. The ligand-free six-membered amido−alkylmetallacycles, prepared from PPh_3−metal(0) complexes, had in fact been found to exist as dimers in THF solution, but were monomeric in DMF.[5] This behavior was not unexpected since amido ligands are known to bridge between metals via strong dative bonds using the free lone pair on nitrogen.[20] It is likely that only monomeric six-membered metallacycles are able to react with additional NCA monomers (vide infra) and then undergo ring contraction (eq 10). This hypothesis is supported by the reactivity of the ligand-free six-membered metallacycles, which are able to polymerize NCA monomers in DMF but not in THF. Thus, spontaneous aggregation of the initial six-membered metallacycles in less coordinating solvents or with weaker ligands (i.e., PPh_3) may be contributing to loss of active species.

Table 3. Molecular Weight (M_n), Polydispersity (M_w/M_n), and Yield of PBLG When Polymerized Using (Ligand)NiNHCH(CH(CH$_3$)$_2$)C(O)NCH$_2$CH$_2$CH$_3$ Initiators with Different Ligands and in Different Solvents[a]

	THF			DMF		
ligand	M_n	M_w/M_n	yield (%)	M_n	M_w/M_n	yield (%)
bpy	160 000	1.17	92	29 500	1.24	93
phen	126 000	1.21	93	28 200	1.23	94
dmpe	107 000	1.16	91	29 300	1.25	94
depe	43 000	1.11	95	30 400	1.19	91

[a] A total of 100 equiv of Glu NCA was added per mole of metal complex in all cases. All polymerizations were run at 20 °C with [Glu NCA] = 170 mM. depe = 1,2-bis(diethylphosphino)ethane.

Aggregation of Amido−Amidate Metallacycles. In addition to inhibiting ring contraction to form the active amido−amidate species, aggregation was also suspected of decreasing the amount of reactive, monomeric amido−amidate complexes as well. In the course of working with Alloc-aminoamide-derived amido−amidate nickelacycles, it was found that these complexes, once isolated in high concentrations in an NCA-free environment, aggregate very strongly.[7] We had found that preformed bpy- and phen-ligated amido−amidate nickelacycles were inefficient initiators in THF, presumably since dimerization through the amido groups diminished their ability to react with NCA monomers. Dissociation of the complexes in DMF resulted in initiators with essentially quantitative efficiency. Results of polymerizations using different ligands with these preformed initiators in both THF and DMF are given in Table 3. It was seen that the nature of the ligand played a large role in initiation efficiency in THF, but had no effect in DMF. In THF, as ligand size increased, initiator efficiency also increased (as measured by a decrease in polymer molecular weight). These results could be rationalized by the existence of a monomer/dimer equilibrium for the metal complexes, where the monomer was active for polymerization, while the dimer was not. Bulky ligands, such as depe, disfavored the formation of dimer and more of the active monomer was present. Smaller ligands, such as planar bpy, allowed dimerization and very little active monomer was present. In DMF, which is a good donor solvent, all of the complexes existed in monometallic form and displayed identical initiation efficiencies.

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Table 4. Molecular Weight (M_n), Polydispersity (M_w/M_n), and Yield of PBLG When Polymerized Using Metal(0) Complexes at Different Concentrations in THF Solvent[a]

		$(PMe_3)_4Co$			bpyNi(COD)		
[I] (mM)	[M] (mM)	M_n	M_w/M_n	yield (%)	M_n	M_w/M_n	yield (%)
6.9	317	35 600	1.19	98	58 500	1.11	96
3.6	172	31 800	1.09	98	48 300	1.10	97
1.9	90	28 500	1.11	97	43 700	1.11	97
1.3	61	27 100	1.13	99	39 900	1.07	97

[a] A total of 45 equiv of Glu NCA was added per mole of metal complex in all cases. Polymerizations were run at 20 °C with [M] = [Glu NCA] and [I] = [metal(0) complex].

It was of interest to see whether similar aggregation equilibria existed in the metal(0)-initiated polymerizations and, thus, also contributed to loss of active species. Aggregation was not expected to be as dominant under these conditions since the amido−amidate species are typically generated in very low concentrations and in the presence of excess NCA monomer. Polymerizations were thus conducted over a range of initiator concentrations, at constant monomer-to-initiator ratios, to probe for any aggregation effects in THF. The results, shown in Table 4, show that polymer molecular weights were affected by overall initiator concentration, with more active species present at higher dilution. These data strongly suggest that the propagating species, or the amido−alkylmetallacycle precursors, in these polymerizations exist in a monomer(active)/dimer(inactive) equilibrium, similar to the preformed complexes.

Conclusions

Molecular weights of polymers obtained from cobalt(0)- and nickel(0)-mediated NCA polymerizations have been found to depend strongly on experimental reaction conditions. Using bpyNi(COD) or $(PMe_3)_4Co$ in DMF solvent, polypeptides can be prepared with molecular weights that are equal to the values predicted by monomer-to-initiator ratios. With different ligands on nickel, or in different solvents, polypeptides were obtained with molecular weights that were much greater than the predicted values. We have found that this molecular weight inflation was not due to diminished control of polymer formation, but rather was due to a decrease in the amount of active chain-propagating species that was formed. Loss of active initiator was found to be due to a combination of trapping of metal(0) complexes with CO, inefficient ring contraction of amido−alkyl intermediates, and aggregation of the propagating species in less polar solvents.

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