Transition Metal−Amine Initiators for Preparation of Well-Defined Poly(γ-benzyl L-glutamate)

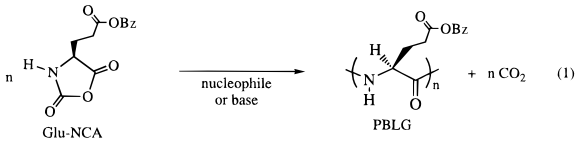
Timothy J. Deming

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

Received July 29, 1996

The α-helix is one of the key structural elements found in natural proteins. The discovery that this structure is adopted by select simple homopolypeptides has led to considerable progress in the understanding of this structural motif and its utility in materials science. Helical polypeptides, most notably poly(γ-benzyl L-glutamate) (PBLG), form ordered solutions because of their rodlike character and high aspect ratio of rod length to diameter.[1] PBLG was one of the first polymers found to display liquid crystalline behavior and can also be processed into ordered monolayer films. Research conducted with helical polypeptides has led to fundamental developments in areas relating to polyelectrolytes, liquid crystals, and the electric and magnetic alignment of polymers.[2] The synthesis of monodispersed PBLG of controlled chain length is necessary for future development of this material and its utilization in complex assemblies and devices.[3] We report herein the use of primary amine−transition metal initiators for the preparation of PBLG with very narrow molecular weight distribution ($M_w/M_n < 1.1$) and controllable chain length.

The best technique for synthesis of high molecular weight PBLG involves ring-opening polymerization of γ-benzyl L-glutamate *N*-carboxyanhydride (Glu-NCA) (eq 1).[4] Polymer



(1)

is readily obtained in high yield and without racemization at the α-carbon. However, PBLG prepared using this method is generally polydisperse ($M_w/M_n > 2$), and it has been difficult to control chain length in these polymerizations: polymers typically must be fractionated to isolate samples of different molecular weights.[5] Furthermore, crude polymerization products usually contain a substantial low molecular weight fraction in addition to the high molecular weight polymer.[4] The reason for this heterogeneity is the complex chemistry and side reactions inherent in NCA polymerizations (i.e., chain termination and chain transfer). For instance, NCAs can be deprotonated at nitrogen to yield anions which can act as nucleophiles toward other NCAs, or rearrange to α-isocyanato carboxylates which will react with free amine end groups.[4] These and other side reactions illustrate why controlled (i.e., living) polymerizations of NCAs are difficult to accomplish.

We want to eliminate these side reactions by using transition metal initiators to control the reactivity of polymer chain ends toward addition of NCA monomers. A transition metal based initiator system for polymerization of Glu-NCA employing $P(Bu)_3/M(OAc)_x$ heterogeneous mixtures (M = Ni, Co, Cr, Cd, Mg; $x = 1-3$; $P(Bu)_3$:M = 40:1) has been reported.[6] The identities of the active initiators were not determined, yet the polymer yield and molecular weight varied with each metal, with nickel being the most effective at preparing high molecular weight materials. These results indicate that transition metal complexes can influence NCA polymerizations and are potentially useful for controlling these polymerizations under appropriate conditions. The limitations of this system are the low efficiency (only a small fraction of metal centers are active initiators) and the heterogeneity, both of which preclude the possibility of obtaining living polymerizations.[7]

Our approach for developing initiators for the "living" polymerization of Glu-NCA utilized the formation of primary amine−metal complexes where both the metal and other ancillary ligands could easily be modified to fine tune catalytic activity.[8] The metals used in this study (Ni, Cu, Pd, Co, Zn) were chosen for their high affinities for nitrogen donors.[9] Formation of an amine coordination complex will diminish the reactivity of the amine to an extent controlled by the Lewis acidity of the metal, thus providing a source of reactivity control. Coordination of an NCA monomer to the metal center should then result in monomer addition to the chain within the coordination sphere of the metal. If the amine end group remains coordinated to the metal throughout the polymerization, we should be able to control monomer addition to the chains and obtain living polymerizations.

In polymerization experiments we evaluated amine−metal initiators in terms of activity, polymer yield, molecular weight, and molecular weight distribution. Initially, it was important to determine if primary amines, once coordinated to transition metals, were still able to initiate NCA polymerizations. Since we were utilizing metals which bind amines strongly, it was conceivable that the complexed amines might not be nucleophilic enough to act as good initiators. We began our investigations by preparing primary amine complexes of the anhydrous acetate salts of Co, Ni, Pd, and Cu. These amine−metal complexes were then screened for their ability to polymerize Glu-NCA in dioxane at 40 °C (Table 1).[10]

Phenethylamine, which was used as a control initiator, was found to rapidly produce PBLG, but with broad molecular weight distribution ($M_w/M_n > 2.8$) and a substantial oligomer fraction (*ca.* 25%, $M_n \approx 2000$). The amine−metal acetates produced much slower polymerizations and gave lower yields of polymer attributable to diminished reactivity of the primary amine once bound to a transition metal. The cobalt and palladium complexes with phenethylamine were found to be essentially unreactive toward Glu-NCA. The nickel and copper complexes showed moderate polymerization activities yet, with the exception of altering the molecular weights of the resulting polymers, provided little or no control over the polymerization process as evidenced by broad molecular weight distributions.

These results showed that metal−amine complexes can act as NCA polymerization initiators, but that simple coordination adducts cannot provide the chain growth control necessary to

(1) Block, H. *Poly(γ-benzyl-L-glutamate) and other Glutamic Acid Containing Polymers*; Gordon and Breach: New York, 1983.
(2) (a) Doty, P. *J. Polym. Sci.* **1957**, *23*, 851. (b) Horton, J. C.; Donald, A. M.; Hill, A. *Nature* **1990**, *346*, 44. (c) McMaster, T. C.; Carr, H. J.; Miles, M. J.; Cairns, P.; Morris, V. J. *Macromolecules* **1991**, *24*, 1428. (d) Poland, D; Scheraga, H. A. *Theory of Helix-Coil Transitions in Biopolymers*; Academic Press: New York, 1970.
(3) (a) Zhang, G.; Fournier, M. J.; Mason, T. L.; Tirrell, D. A. *Macromolecules* **1992**, *25*, 3601−3603. (b) National Research Council Solid State Sciences Committee on Biomolecular Materials. *Biomolecular Self-Assembling Materials: Scientific and Technological Frontiers*; National Academy Press: Washington, DC, 1996.
(4) (a) Kricheldorf, H. R. α-*Aminoacid-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.
(5) (a) Blout, E. R.; Karlson, R. H. *J. Am. Chem Soc.* **1956**, *78*, 941−950. (b) Doty, P.; Bradbury, J. H.; Holtzer, A. M. *J. Am. Chem Soc.* **1956**, *78*, 947−954. (c) Idelson, M.; Blout, E. R. *J. Am. Chem Soc.* **1957**, *79*, 3948−3957.
(6) Yamashita, S.; Tani, H. *Macromolecules* **1974**, *7*, 406−409.
(7) (a) Fetters, L. J. Monodisperse Polymers. In *Encyclopedia of Polymer Science and Engineering*, 2nd ed.; Wiley-Interscience: New York, 1987; Vol. 10, pp 19−25. (b) Szwarc, M. *Nature* **1956**, *178*, 1168−1169. (c) Quirk, R. P.; Lee, B. *Polym. Int.* **1992**, *27*, 359−357 and references contained therein.
(8) Deming, T. J. *Polym. Prepr.* **1996**, *37* (1), 435−436.
(9) Irving, H.; Mellor, D. H. *J. Chem Soc. A* **1962**, 5222−5245.
(10) We analyzed our polymer samples using tandem GPC/LS in 0.1 M LiBr in DMF at 60 °C ($dn/dc = 0.104$ mL/g) since PBLG does not aggregate in this solvent.[5b]

S0002-7863(96)02625-X CCC: $14.00

Table 1. Polymerizations of Glu-NCA in 1,4-Dioxane at 40 °C Using Amine−Metal Acetate Initiators[a]

initiator	time (d)	yield (%)	M_n	PDI
$PhEtNH_2$ (N)	1	78	17 200	2.8
$[NCo(OAc)_2]_x$	3	0		
$[N_2Ni(OAc)_2]_x$	3	51	6 300	3.1
$[N_2Pd(OAc)_2]_x$	3	3		
$[NCu(OAc)_2]_x$	3	52	12 100	2.1

[a] Monomer (M) to initiator (I) ratio 250:1. M_n was determined by GPC/LS in 0.1 M LiBr in DMF at 60 °C.[10]

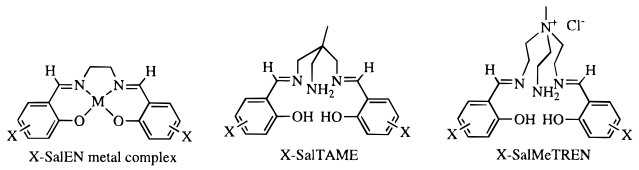


Figure 1. SalEN complexes and macrodentate ligands for initiator formation. M = metal. X = substituent(s) on aromatic ring.

Table 2. Polymerizations of Glu-NCA at 40 °C for 2 d Using SalTAME− and SalMeTREN−Metal Initiators[a]

initiator	yield (%)	M_n	PDI
3,5-di-*tert*-butyl-SalTAME + $Cu(OAc)_2$ (THF)	0		
3,5-di-*tert*-butyl-SalTAME + $Cu(OAc)_2$	100	19 500	1.35
3,5-di-Cl-SalTAME + $Cu(OAc)_2$	100	21 400	1.26
3,5-di-NO_2-SalTAME + $Cu(OAc)_2$	0		
3,5-di-*tert*-butyl-SalTAME + $Ni(OAc)_2$	94	24 600	1.68
3,5-di-NO_2-SalTAME + $Ni(OAc)_2$	0		
3,5-di-*tert*-butyl-SalTAME + $Co(OAc)_2$ (THF)	0		
3,5-di-*tert*-butyl-SalTAME + $Co(OAc)_2$	100	25 200	1.61
3,5-di-Cl-SalMeTREN + $Cu(OAc)_2$	100	26 400	1.42
3,5-di-NO_2-SalMeTREN + $Cu(OAc)_2$	0		
3,5-di-Cl-SalMeTREN + $Ni(OAc)_2$	92	14 000	1.51
5-NO_2-SalMeTREN + $Ni(OAc)_2$	95	20 200	1.46
3,5-di-NO_2-SalMeTREN + $Ni(OAc)_2$	98	12 800	1.08
3,5-di-NO_2-SalMeTREN + $Pd(OAc)_2$	100	17 800	1.31
3,5-di-NO_2-SalMeTREN + $Co(OAc)_2$	100	19 700	1.37
3,5-di-NO_2-SalMeTREN + $Zn(OAc)_2$	96	16 900	1.25

[a] Solvent is DMSO unless noted. Monomer (M) to initiator (I) ratio 75:1. M_n was determined by GPC/LS in 0.1 M LiBr in DMF at 60 °C.[10]

realize living NCA polymerizations. To enhance control over the propagation process, we replaced these simple adducts with macrodentate complexes containing structurally defining chelate ligands in addition to an amine initiator. These complexes were expected to be superior initiators since all the components are tethered and will form a stable rigid coordination environment around the metal center. The ligands were based on the well-known Schiff base ligands[11] with the added feature of a primary amine arm for initiation (Figure 1). The salicimine groups allowed adjustment of steric and electronic properties by variation of substituents on the aromatic rings. Since salicimines are very good ligands, we were also able to evaluate the catalysis potential of many different transition metals.

Our initial studies focused on ligands constructed from substituted salicylaldehydes and the triamines 1,1,1-tris(aminomethyl)ethane[12] (TAME) and methyltris(2-aminoethyl)ammonium chloride (MeTREN) (Figure 1). Polymerization activities of initiators prepared from different salicimine ligands and metals are given in Table 2. Solvent effects can be examined using the 3,5-di-*tert*-butyl-SalTAME + $Cu(OAc)_2$ system: in THF the initiator is completely inactive toward Glu-NCA, whereas in DMSO the initiator is very active. The greater polarity and ionizing ability of DMSO likely enhances the lability of the primary amine−copper bond, thus increasing the amine's ability to initiate polymerization. The related tetradentate copper complex prepared from *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)ethylenediamine and $Cu(OAc)_2$ was found to be an inactive initiator in DMSO, indicating that polymerization with our initiators is occurring *via* the primary amine ligand.

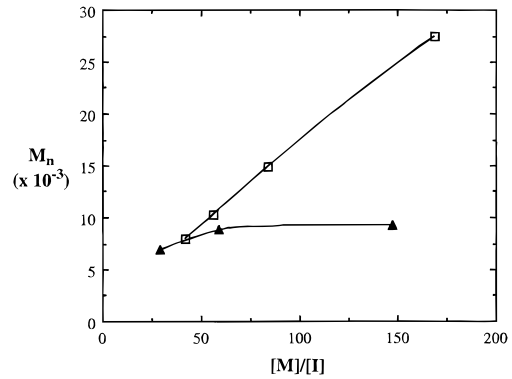


Figure 2. Molecular weights (M_n; GPC/LS in 0.1 M LiBr in DMF at 60 °C)[10] of PBLG samples prepared in DMSO at 40 °C using 3,5-di-NO_2-SalMeTREN + $Ni(OAc)_2$ (white squares) and phenethylamine (black triangles) at different monomer (M) to initiator (I) ratios.

A correlation was also observed between the electron-donating ability of salicylimine substituents and the activity of the initiators. When strong donors were used (*tert*-butyl groups), the metal center was electron rich and bound the amine ligand only weakly. Conversely, when strong electron-withdrawing groups were used (nitro groups), the metal center was electron deficient and held onto the amine ligand tightly, resulting in diminished polymerization activity. The trends observed for the different ligands and solvents were qualitatively similar when different metals were used as initiators. Overall, it was found that the use of MeTREN in place of TAME resulted in metal initiators with greater reactivity (e.g., compare reactivities of the 3,5-di-NO_2-Sal + $Ni(OAc)_2$ initiators in Table 2). The increased reactivity was reflected in the breadth of the polymer molecular weight distributions which were greater for most of the MeTREN initiators relative to TAME initiators.

An optimal combination of ligand and metal was found with the 3,5-di-NO_2-SalMeTREN + $Ni(OAc)_2$ initiator which produced PBLG in quantitative yield and with narrow molecular weight distribution. The high yield was significant since a low molecular weight, methanol soluble oligomer fraction was not formed in this polymerization. It appears that this nickel initiator possesses a near optimal balance of steric and electronic forces so that it is just reactive enough to initiate polymerization of Glu-NCA, but binds the amine end group tightly so that a controlled polymerization results. In the next level of analysis, Glu-NCA was polymerized at different ratios of NCA to nickel initiator to determine the extent of molecular weight control in this system. For comparison, similar experiments were conducted using phenethylamine as a control, and the results for both initiators are given in Figure 2. The data illustrate that this nickel initiator is able to control the chain length of PBLG very effectively whereas the conventional initiator is not.

Acknowledgment. This work was supported by a University of California Regents Junior Faculty Fellowship (awarded to T. J. D.), the donors of The Petroleum Research Fund administered by the American Chemical Society, University of California Santa Barbara Materials Department start up funds, and partially supported by the MRL program of the National Science Foundation under award No. DMR-9123048.

Supporting Information Available: Details of initiator preparations and polymerization methods (4 pages). See any current masthead page for ordering and Internet access instructions.

JA962625W

(11) (a) Mockler, G. M.; Chaffey, G. W.; Sinn, E.; Wong, H. *Inorg. Chem.* **1972**, *11*, 1308−1314. (b) Sacconi, L.; Bertini, I. *J. Am. Chem Soc.* **1966**, *88*, 5180−5185. (c) Ellis, J.; Mockler, G. M.; Sinn, E. *Inorg. Chem.* **1981**, *20*, 1206−1213. (d) Boge, E. M.; Mockler, G. M.; Sinn, E. *Inorg. Chem.* **1977**, *16*, 467−477. (e) Atkins, R.; Brewer, G.; Kokot, E.; Mockler, G. M.; Sinn, E. *Inorg. Chem.* **1985**, *24*, 127−134.

(12) Fleischer, E. B.; Gebala, A. E.; Levey, A.; Tasker, P. A. *J. Org. Chem.* **1971**, *36*, 3042−3044.