Controlled Polymerization of β-Lactams Using Metal−Amido Complexes: Synthesis of Block Copoly(β-peptides)

Jianjun Cheng and Timothy J. Deming*

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

The synthesis and characterization of β-peptides, oligomers of β-amino acids, have received considerable interest in recent years due to the ability of these peptides to resist proteases and mimic α-peptides and to potential as biomedical materials.[1−4] We have been interested in polymers of β-amino acids as analogues of poly(α-peptides).[5] Poly(β-peptides) have been prepared via condensation of short peptides,[6−9] polymerization of β-amino acid-*N*-carboxyanhydrides,[5,10−12] and polymerization of β-lactams.[13−17] However, the ring-opening of β-lactams has been the only method shown to yield high-molecular weight polymers.[13−17] These polymerization reactions are not optimized, in that chain length is difficult to control and side reactions such as imide formation, racemization of chiral centers, and branching lead to heterogeneous products and low yields.[14,17] We now report the discovery that certain metal−amido complexes can initiate the living polymerization of β-lactams to give poly(β-peptides) and block copoly(β-peptides) with controllable chain lengths and narrow molecular weight distributions.

(1) (a) Appella, D. H.; Christianson, L. A.; Klein, D. A.; Powell, D. R.; Huang, X.; Barchi, J. J.; Gellman, S. H. *Nature* **1997**, *387,* 381. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (c) Porter, E. A.; Wang, X.; Lee, H.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565.
(2) (a) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79,* 913−941. (b) Abele, S.; Guichard, G.; Seebach, D. *Helv. Chim. Acta* **1998**, *81,* 2141−2156. (c) Gademann, K.; Ernst, M.; Hoyer, D.; Seebach, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1223−1226.
(3) Gung, B. W.; Zou, D.; Stalcup, A. M.; Cottrell, C. E. *J. Org. Chem.* **1999**, *64*, 2176−2177.
(4) Hamuro, Y.; Schneider, J. P.; DeGrado, W. F. *J. Am. Chem. Soc.* **1999**, *121*, 12200−12201.
(5) (a) Cheng, J.; Ziller, J. W.; Deming, T. J. *Org. Lett.* **1999**, *2*, 1943−1946. (b) Cheng, J.; Deming, T. J. *Macromolecules* **2001**, *34*, 5169−5174.
(6) Kovacs, J.; Ballina. R.; Rodin, R.; Balasubramanian, D.; Applequist, J. *J. Am. Chem. Soc.* **1965**, *87*, 119−120.
(7) Hardy, P. M.; Haylock, J.; Rydon, H. *J Chem. Soc., Perkin Trans. 1* **1972**, 605.
(8) Yuki, H.; Okamoto, Y.; Taketani, Y.; Tsubota, T.; Marubayashi, Y. *J. Polym. Sci., Polym. Chem. Ed.* **1978**, *16*, 2237−2251.
(9) (a) Fernández-Santin, J. M.; Aymami, J.; Rodríguez-Galán, A.; Muñoz-Guerra, S.; Subirana, J. A. *Nature (London)* **1984**, *311*, 53−54. (b) Fernández-Santín, J. M.; Muñoz-Guerra, S.; Rodríguez-Galán, A.; Aymami, J.; Lloveras; J.; Subirana, J. A.; Giralt, E.; Ptak, M. *Macromolecules* **1987**, *20*, 62−68.
(10) (a) Birkofer, L.; Modic, R. *Liebigs Ann. Chem.* **1957**, *604*, 56. (b) Birkofer, L.; Modic, R. *Liebigs Ann. Chem.* **1959**, *628*, 162−172.
(11) Zilkha, A.; Burstein, Y. *Biopolymers* **1964**, *2*, 147−161.
(12) Kricheldorf, H. α-*Aminoacid-N-carboxyanhydrides and Related Heterocycles*; Springer-Verlag: Berlin, New York, 1987.
(13) (a) Graf, R.; Lohaus, G.; Börner, K.; Schmidt, E.; Bestian, H. *Angew. Chem.* **1962**, *74*. 523. (b) Bestian, H. *Angew. Chem.* **1968**, *80*, 304. (c) Schmidt, E. *Angew. Makromol. Chem.* **1970**, *14*, 185−202.
(14) (a) Rodríguez-Galán, A.; Muñoz-Guerra, S.; Subirana, J. A.; Chuong, B.; Sekiguchi, H. *Makromol. Chem., Macromol. Symp.* **1986**, *6*, 277−284 (b) Muñoz-Guerra, S.; López-Carrasquero, F.; Fernández-Santín, J. M.; Subirana, J. A. In *Encyclopedia of Polymeric Materials*; Salamone, J. C., Ed.; CRC Press: Boca Raton, FL, 1996; pp 4694−4700. (c) Ilarduya, A. M.; Alaman, C.; Garcia-Alvarez, M.; López-Carrasquero, F.; Muñoz-Guerra, S. *Macromolecules* **1999**, *32*, 3257−3263.
(15) (a) Eisenbach, C. D.; Lenz, R. W. *Macromolecules* **1976**, *9*, 227−230 (b) Eisenbach, C. D.; Lenz, R. W. *Makromol. Chem.* **1979**, *180*, 429−440.
(16) (a) Hashimoto, K.; Okata, M.; Nagata, S. *J. Polym. Sci., Part A.: Polym. Chem.* **1995**, *33*, 1995−1999. (b) Hashimoto, K.; Oi, T.; Yasuda, J.; Hotta, K.; Okata, M. *J. Polym. Sci., Part A.: Polym. Chem.* **1997**, *35*, 1831−1838. (c) Hashimoto, K.; Yasuda, J.; Kobayashi, M. *J. Polym. Sci., Part A.: Polym. Chem.* **1999**, *37*, 909−915.
(17) Šebenda, J.; Hauer, J. *Polym. Bull.* **1981**, *5*, 529.

Table 1. Polymerization of **1** Using Transition Metal Initiators

initiator	solvent	[M]/[I][a]	[M][b]	time (h)	yield (%)[c]
sodium 2-pyrrolidone	CH$_2$Cl$_2$	100	0.02	0.1	64
DepeNiAA[d]	CH$_2$Cl$_2$	100	0.02	24	99
DepeNiAA	DMF	100	0.02	24	0
DepeNiAA	THF	100	0.02	24	47
Co(N(TMS)$_2$)$_2$	CH$_2$Cl$_2$	50	0.02	24	98
Mg(N(TMS)$_2$)$_2$	CH$_2$Cl$_2$	100	0.02	0.2	100
BDIMgN(TMS)$_2$[e]	CH$_2$Cl$_2$	100	0.02	0.3	100
Sc(N(TMS)$_2$)$_3$ (**2**)	CH$_2$Cl$_2$	100	0.02	12	98
Cu(N(TMS)$_2$)$_2$	CH$_2$Cl$_2$	100	0.01	12	99
Zn(N(TMS)$_2$)$_2$	CH$_2$Cl$_2$	100	0.1	72	65
BDIZnN(TMS)$_2$[e]	CH$_2$Cl$_2$	100	0.1	72	24
Fe(N(TMS)$_2$)$_3$	CH$_2$Cl$_2$	100	0.02	24	87
Cr(N(TMS)$_2$)$_3$	CH$_2$Cl$_2$	100	0.02	48	8
Cp$_2$TiClNMe$_2$	CH$_2$Cl$_2$	25	0.02	48	0

[a] [M]/[I] = [**1**]/[initiator]. [b] [M] = initial concentration of **1**. [c] Total isolated yield of poly(**1**). [d] DepeNiAA = (1,2-bis(diethylphosphino)-ethane)Ni(NHCH(CH(CH$_3$)$_2$)C(O)NC(CH$_3$)$_3$). [e] BDI = 2-((2,6-diisopropylphenyl)amino)-4-((2,6-diisopropylphenyl)imino)-2-pentene.

The polymerization of β-lactams was first reported by Bestian,[13a] who prepared poly(β-peptides) from racemic monomers bearing small alkyl side chains. Functional side chains, similar to those of natural amino acids, are more desirable since they can impart biological activity to β-peptides. In this area, Muñoz-Guerra and co-workers have studied poly(α-alkyl-β-aspartates),[14] utilizing the anionic polymerization of readily available β-lactams of L-aspartic acid (eq 1). Under certain conditions, racemization and the

$$(1)$$
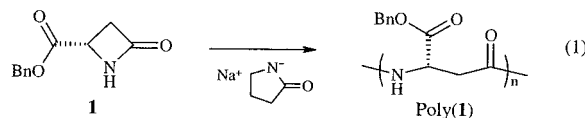
formation of imide linkages could be minimized; however chain lengths could not be controlled, and monomer conversions were seldom greater than 80%.[14] The best reported control in β-lactam polymerizations was obtained by Šebenda and Hashimoto who prepared narrow molecular weight distribution, low-molecular weight poly(β-peptides) anionically using *N*-acyl lactam activators.[16,17] In addition to requiring α,α-dialkyl substituted monomers, these were not living polymerizations since proton transfer from backbone amide groups was found to deactivate the growing chains.[17]

On the basis of our success using amido-containing metallacycles as initiators for poly(α-peptide) synthesis,[18] we explored the use of metal−amido complexes to control β-lactam polymerizations. The readily available β-lactam of α-benzyl-L-aspartic acid (**1**)[19] was chosen to evaluate different initiators. We screened a number of metal−amido complexes and sodium pyrrolidone for their ability to initiate and control polymerization of **1** (Table 1). From these studies, it appeared that most complexes were efficient initiators, although polymerization activity varied widely. Complexes of Ni, Co, Cu, Fe, Sc, and Mg were promising as they gave near quantitative yields of polymer with no detectable imide content or racemization, as seen in anionic polymerizations.[14,17] The most important parameter for identifying a suitable initiator was control over polymer chain length.[20] While some metal complexes (e.g., those of Mg) were extremely active, they

(18) (a) Deming, T. J. *J. Polym. Sci., Polym. Chem. Ed.* **2000**, *38*, 3011−3018. (b) Yu, M.; Nowak, A. P.; Pochan, D. P.; Deming, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 12210−12211. (c) Cha, J. N.; Stucky, G. D.; Morse, D. E.; Deming, T. J. *Nature* **2000**, *403*, 289−292.
(19) Salzmann, T. N.; Ratcliffe, R. W.; Christense, B. G., Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6163−6164.

Table 2. Synthesis of Poly(β-peptides) and Block Copoly(β-peptides) Using **2** at 20 °C

| solvent | first segment | | | diblock copolymer | | | yield (%)[d] |
	4[a]	$\bar{M}_n$[b]	$\bar{M}_w/\bar{M}_n$[b]	second monomer[a]	$\bar{M}_n$[c]	$\bar{M}_w/\bar{M}_n$[c]	
CH₂Cl₂	10	19 820	1.19	–	–	–	97
CH₂Cl₂	25	25 910	1.19	–	–	–	98
CH₂Cl₂	50	49 980	1.23	–	–	–	96
CH₂Cl₂	75	62 870	1.07	–	–	–	95
CH₂Cl₂	150	100 500	1.21	–	–	–	94
THF	25	49 580	1.15	–	–	–	99
THF	75	96 470	1.07	–	–	–	97
CH₂Cl₂	50	49 980	1.23	5 **1**	54 790	1.26	95
CH₂Cl₂	25	32 000	1.07	50 **3**	70 550	1.09	94
CH₂Cl₂	20	20 010	1.20	50 **4**	72 590	1.09	93
CH₂Cl₂	50	49 980	1.23	10 **5**	61 220	1.25	95

[a] Equivalents of monomer per initiator added to prepare the first and second polymer segments. [b] Molecular weight (g/mol) and polydispersity index after polymerization of the first monomer. [c] Molecular weight (g/mol) and polydispersity index after polymerization of the second monomer. [d] Total isolated yields of poly(**4**) and block copoly(β-peptides).

also gave molecular weights, estimated by viscosity measurements,[21] that were far greater than predicted by theory. These results indicated that only a fraction of the metal complexes were active during polymerization. Better results were obtained with Sc(N(TMS)₂)₃ (**2**) as chain lengths were lower, correlating with the low monomer-to-initiator ratios, and indicating that a greater portion of the scandium centers were active.[22]

To obtain accurate molecular weight data, we synthesized monomers that would give poly(β-peptide)s with greater solubility than poly(**1**). Transesterification of **1**[23] with tri- and tetraethyleneglycol monomethyl ethers gave monomers **3** and **4** (eq 2).
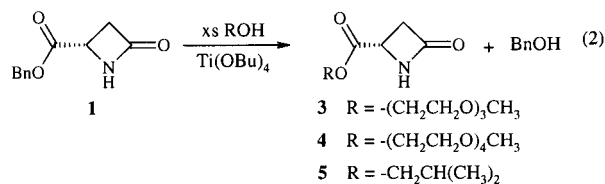
The polymer of **4** was found to be soluble in many solvents including H₂O and DMF such that molecular weight data could be obtained using tandem LS-GPC.[22] Polymerization of **4** with the initiator **2** at different monomer-to-initiator ratios and at different extents of reaction gave the data in Table 2 and Figure 1. Poly(β-peptide)s were obtained with narrow molecular weight distributions (MWD), and chain lengths could be controlled by both stoichiometry and monomer conversion, characteristic of a living polymerization system.[20] Kinetic analysis of polymerizations showed them to be first-order in monomer concentration with no deviation to 4 half-lives,[22] indicating no detectable chain termination. Since measured molecular weights were greater than predicted by theory, it is likely that not all of the metal centers were active in initiating chain growth. Preliminary mechanistic studies using ¹H NMR revealed that HN(TMS)₂ was liberated upon addition of β-lactam monomers to **2**.[22] These data suggest that the resulting metalated lactams are the true initiating species. It appears that the increased covalent nature of these metal−nitrogen bonds, relative to their alkali metal counterparts, serves to substantially eliminate side reactions.

Figure 1. Molecular weight of poly(**4**) versus monomer conversion. Polymerization was carried out at 20 °C in CH₂Cl₂ using initiator **2** with initial [**4**] = 0.02 M and [**4**]/[**2**] = 150. **A** = theoretical molecular weight calculated from monomer conversion. **B** = molecular weight of poly(**4**) determined by GPC/LS in 0.1 M LiBr in DMF at 60 °C (dn/dc^{25} = 0.105 mL/g).

Using initiator **2**, we were able to prepare the first examples of di- and triblock copoly(β-peptides) (Table 2).[24] LS-GPC chromatograms of the initial segments and complete block copoly-(β-peptides) were all unimodal with narrow MWD, indicating no deactivation of growing chain ends between monomer additions. No homopolymer contaminants could be detected by selective solvent extractions, and NMR measurements confirmed the expected comonomer compositions and lack of chain branching.[22] Using **2**, we were also able to synthesize a triblock copolymer, poly(**4**)₄₅-b-poly(**1**)₁₀-b-poly(**4**)₄₅, which gave a unimodal GPC peak with M_n^{25} = 58 350 g/mol and M_w/M_n^{25} = 1.17, indicating that sequences of greater complexity can be prepared.[22]

With the ability to readily transesterify **1**, a variety of different side-chain functionalized poly(β-aspartates) can be prepared to modify polymer properties (eq 2, Table 2). For example, block copolymerization of **4** with **5** gave surfactant-like hydrophilic-b-hydrophobic materials. These copolymers should also display interesting properties arising from the ability to adopt secondary structures. Using CD spectroscopy, Poly(**4**) was found to adopt an ordered conformation in H₂O,[22] similar to the 13₄-helix found for poly(**1**)[14] and the 3₁-helix of short β-peptide sequences.[2] Like β-peptide oligomers, these block copolymers can be thought of as mimics of their α-peptide analogues with the benefit of increased stability against enzymatic degradation. Thus, identification of these initiators for β-lactam polymerizations opens up many new areas of investigation for β-peptide materials.

Supporting Information Available: Details of all reactions and polymerizations; kinetic, LS-GPC, and CD data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0110022

(20) (a) Fetters, L. J. In *Encyclopedia of Polymer Science and Engineering*, 2nd ed.; Wiley-Interscience: New York, 1987; Vol. 10, pp 19−25. (b) Webster, O. *Science* **1991**, *251*, 887−893.

(21) Molecular weights of poly(**1**) were estimated using viscosity measurements in dichloroacetic acid. While not quantitative, this method is useful for identifying changes in molecular weight.[14,22]

(22) See Supporting Information.

(23) García-Alvarez, M.; López-Carrasquero, F.; Tort, E.; Rodríguez-Galán, A.; Muñoz-Guerra, S. *Synth. Commun.* **1994**, *24*, 745−753.
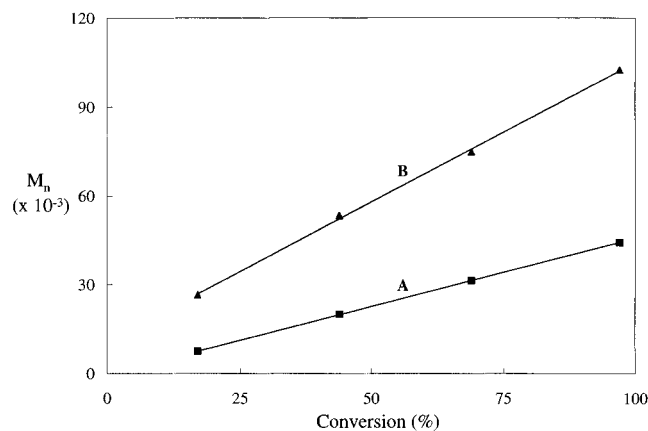
(24) The anionic synthesis of block copoly(β-peptides) was recently reported (Ramírez, R.; Morillo, M.; Arnal, M. L.; López-Carrasquero, F.; Martínez de Ilarduya, A.; Muñoz-Guerra, S. *Polymer* **2000**, *41*, 8475−8486). However, yields were low, and the polymers were not fully characterized to confirm the linear block architecture and to rule out the presence of imidization, racemization, and homopolymer byproducts typically observed in these polymerizations.

(25) Abbreviations: M_n = number-average molecular weight. M_w = weight-average molecular weight. η_{sp} = specific viscosity = $(t - t_0)/t_0$ at a specific polymer concentration. dn/dc = change in refractive index with concentration.