

Design of Catalytic Carbonylative Polymerizations of Heterocycles. Synthesis of Polyesters and Amphiphilic Poly(amide-*block*-ester)s

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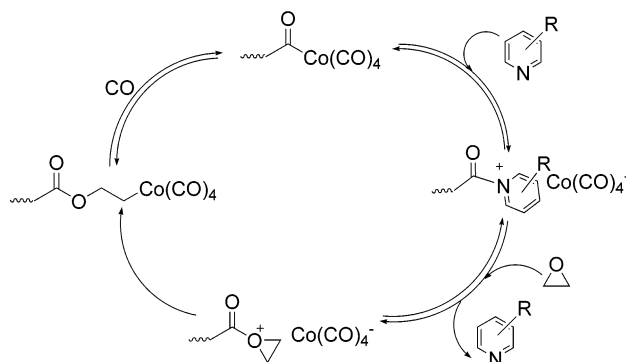
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Synthetic poly(β -peptide)s and the sister poly(β -hydroxy-alkanoate)s have received considerable recent attention due to their biomedical applications.^{1,2} We have reported the design and development of a catalytic process for the carbonylative polymerization of aziridines using the well-defined catalysts of the type acyl-Co(CO)₃L (L = phosphine or CO) for the synthesis of poly(β -alanine) and poly(β -alanoid)s.^{3,4} Metal-catalyzed carbonylative polymerization of epoxides was first reported in 1965 but has been neglected for decades.^{5,6} Recently, several research laboratories^{7–10} reported that the Co₂(CO)₈/pyridine system¹¹ converts CO and epoxides to polyesters as the major product and β -lactones as the minor product.^{8–11} The acyl-Co(CO)₄ species was recognized as the putative active species in these systems.^{7–9} While various roles were proposed for pyridine and its derivatives, either a proton or a Lewis acid (e.g., Co⁺ from reaction of Co₂(CO)₈ with pyridine) was invoked for the ring-opening of epoxides.^{7a,8a,9}

Parallel to our study on the carbonylative polymerization of aziridines,³ we have also been interested in developing the carbonylative polymerization of epoxides using the de novo design approach. The hypothetical catalytic cycle that we have envisioned for the polymerization is similar to that for the carbonylative polymerization of aziridines (Scheme 1). The key step of epoxide insertion again relies on the analogy between the Co(I)–acyl bond and the organic carboxylate ester bond, and the precedent of epoxide insertion into a carboxylate ester bond,¹² which likely involved the reactive acylpyridinium intermediate. Our attempts under this hypothesis using acyl-Co(CO)₃(PPh₃)/pyridine as the catalyst invariably afforded only trace amounts of poly(β -hydroxyalkanoate)s often containing ether linkages. Meanwhile, we have learned an important lesson from the mechanistic study on the carbonylative polymerization of aziridines carried out by Darensbourg's group, namely, that PPh₃ retards the polymerization, among other reasons, by competing against other nucleophiles (e.g., aziridines and pyridines) for the acyl site.¹³ Thus, we decided to revisit the carbonylative polymerization of epoxides with the isolated catalyst CH₃C(O)Co(CO)₃(P(*o*-tolyl)₃) (**1**), which upon exposure to CO, instantaneously loses the bulky P(*o*-tolyl)₃ that has little nucleophilicity.¹³ We report here that **1** in combination with a pyridine derivative catalyzes the selective carbonylative polymerization of epoxides to produce poly(β -hydroxyalkanoates). The same system catalyzes the living carbonylative polymerization of *N*-alkylaziridines to produce poly(β -alanoid)s. Further, poly(β -alanoid-*block*- β -hydroxypropionate)s, including an amphiphilic diblock copolymer, can be easily prepared in a truly one-step fashion from *N*-alkylaziridine and ethylene oxide.

The combination of catalyst **1** and a pyridine derivative as the cocatalyst (*tert*-butylpyridine **2**; *m*-methoxy pyridine, **3**) copolymerizes ethylene oxide with carbon monoxide to afford poly(β -hydroxypropionate) (PHP) highly selectively without producing any ether linkages or β -lactone (entries 1–3, Table 1). The PHP products possess the acrylate end group particularly with **2** as the cocatalyst besides the acetyl end group inherited from **1**. The acrylate end group likely arises from a well-known process of pyridine-assisted

Scheme 1. Hypothetical Catalytic Cycle for Cobalt/Pyridine-Catalyzed Carbonylative Polymerization of Epoxides



elimination, leading to chain scission and broadening of the polydispersity. The chain scission process can be suppressed to some extent by attenuation of the basicity/nucleophilicity of the cocatalyst. Cocatalyst **3** decreases the amount of acrylate end group relative to the acetyl end group and concomitantly narrows the polydispersity (entries 1 vs 2). Prolonged reaction time in an effort to achieve high conversions causes a high degree of chain scission and broadens the polydispersity (entry 3).¹⁴ While the reaction of EO proceeds smoothly in either THF or DME, the carbonylative polymerization of propylene oxide (PO) requires DME as the solvent (entry 4) and only gives a small amount of oily oligomers in THF. In all the above cases, the vinyl ester end group as the result of metal-centered β -hydrogen elimination is not observed.

An important advantage of the well-defined catalyst system used here in comparison to those generated in situ from Co₂(CO)₈ is that it also catalyzes the carbonylative polymerization of *N*-alkylaziridines, while the latter do not. Such versatility brings about the opportunity of synthesizing copolymers, particularly block copolymers since the epoxide reaction and especially the aziridine reaction possess living characters.^{3b,14} For the construction of the diblock copolymers (Table 2), we initially started with *N*-butylaziridine (**5**) as the comonomer for the poly(β -*n*-butylalanoid) (*p*- β -*n*BuA) block because it has been extensively used during our investigations on the synthesis of diblock poly(β -peptoid)s.¹⁵ We focused on EO as the other comonomer because it is more reactive than PO. In fact, the commonly practiced sequential addition of comonomers for block copolymer synthesis is entirely unnecessary because *N*-alkylaziridines are much more reactive than epoxides and appear to suppress the epoxide enchainment likely by competing for the electrophilic acyl-Co bond, i.e., the epoxide will not react until the aziridine is consumed.¹⁶ Addition of **5** and EO along with **3** altogether at the beginning of the polymerization produced a polymer composed of the *p*- β -*n*BuA and PHP chemical units (entry 2), virtually identical to the polymer produced by addition of EO and **3** after the consumption of **5** (entry 1).¹⁷ The molecular weights of the products obtained with the two methods are both definitely larger than that of *p*- β -*n*BuA prepared in a separate batch at the same ratio of **5** to **1**. That the products contain a copolymer as

Table 1. Carbonylative Polymerization of Epoxides with **1** as a Catalyst and Pyridine Derivatives as Cocatalysts^a

entry	monomer	cocatalyst	reaction time (h)	yield (g)	acryl/acyetyl ratio ^d	M_n^e (10 ³)	PDI ^e
1 ^b	EO	2	14	1.8	2.7	4.3	2.53
2 ^b	EO	3	14	1.5	0.8	8.4	1.18
3 ^b	EO	3	42	2.1	2.1	9.6	1.38
4 ^c	(S)-PO	3	20	1.2	0.6	4.3	1.17

^a Conditions: 0.2 mmol of **1**, 0.4 mmol of cocatalyst, 3 mL of epoxide, 1000 psi of CO, at 75 °C. ^b THF (40 mL) as solvent. ^c DME (40 mL) as solvent. ^d Estimated by ¹H NMR. ^e GPC with refractive index detector against polystyrene standards.

Table 2. Synthesis of Diblock Copolymers via Carbonylative Polymerization with **1** as a Catalyst and **3** as a Cocatalyst^a

entry	aziridine (g)	1 st block		overall polymer product		amide/ester ratio ^c	yield (g)
		M_n^b (10 ³)	PDI ^b	M_n^b (10 ³)	PDI ^b		
1 ^d	5 (0.8)	6.9 ^f (6.8) ^g	1.22 ^f (1.25) ^g	9.1	1.28	1:1.2	2.1
2 ^e	5 (0.8)	6.9 ^f (6.9) ^g	1.22 ^f (1.26) ^g	8.4	1.25	1:1.0	1.9
3 ^e	6 (0.4)	4.9 ^f (4.3) ^g	1.20 ^f (1.19) ^g	7.4 (6.8) ^h	1.40 (1.26) ^h	1:3.0 (1:1.0) ^h	2.0 (1.2) ^h

^a In 40 mL THF at 75 °C, 0.2 mmol of **1**, 1000 psi of CO, 3 mL of ethylene oxide. ^b GPC with a refractive index detector using polystyrene as the standards. ^c Estimated by ¹H NMR. ^d Ethylene oxide added after consumption of **5**. ^e Comonomers added all at once. ^f Polyamide prepared in a separate batch without addition of ethylene oxide. ^g Polyamide block after complete methanolysis of ester units. ^h Water-soluble diblock copolymer obtained by extraction with water.

opposed to a physical mixture of PHP and p-β-ⁿBuA is confirmed by the fact that they are completely soluble in refluxing THF, while p-β-ⁿBuA is completely insoluble once it precipitates out from the reaction medium. DSC study revealed two melting temperatures at 66 and 155 °C due to the PHP and p-β-ⁿBuA blocks, respectively, consistent with the block copolymer assessment. Methanolysis of the copolymers afforded p-β-ⁿBuA and methyl β-hydroxypropionate as the only products. The p-β-ⁿBuA obtained after methanolysis possess the same molecular weights as the p-β-ⁿBuA prepared separately. The results of methanolysis further support the presence of block copolymer in the product. Note that the acrylate end group exists in the products in both cases at the acetyl-to-acrylate molar ratio of 1:1, indicating that the products contain homo-PHP in addition to the diblock copolymer with about half of the ester units belonging to the homopolymer. Using *N*-(2-methoxyethyl)aziridine (**6**) and EO as the comonomers, amphiphilic diblock copolymer is prepared again by simple addition of both comonomers at the beginning of the polymerization (entry 3). The high solubility of the poly(β-(2-methoxyethyl)alanoid) (p-β-MOEA) block renders the overall solubility of the diblock copolymer in the aqueous phase. This allows the separation of the diblock copolymer from the hydrophobic PHP by simple extraction. The water-insoluble fraction mainly contains PHP caused by chain scission and a small amount of p-β-MOEA units probably belonging to the diblock chains with a very short p-β-MOEA block. The acrylate end group is absent in the water-soluble fraction. Note that methanolysis of the copolymer prepared by simultaneous addition of **6** and EO resulted in p-β-MOEA with slightly lower molecular weights than that of p-β-MOEA prepared in a separate batch, likely suggesting that there is a low degree of ester incorporation in the p-β-MOEA block.

In summary, we have demonstrated that the combinations of **1** and pyridines are versatile catalysts for the carbonylative polymerization of both epoxides and aziridines likely under closely resembling mechanisms. While less active for carbonylative epoxide polymerization than the catalysts generated in situ from Co₂(CO)₈,^{6–9} the well-defined acid-free catalyst allows the development of a very convenient synthetic method for diblock copolymers with a degradable block and a nondegradable block. The amphiphilic and degradable diblock copolymers are potentially useful for biomedical applications.

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Note Added after ASAP Publication: In the version published on the Web October 23, 2004, there was a production error in the data in Table 2. The version published October 26, 2004, and the print version are correct.

Supporting Information Available: Experimental procedures and polymer characterization information (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) Addition of aziridine after the formation of PHP resulted in a high degree of chain scission of PHP apparently due to the basicity and nucleophilicity of aziridine.
- (17) Slight reduction of yield and M_n when EO, **3**, and **5** are added together is likely a result of the competition of **3** against **5** for the acyl-Co site, which prolongs the time required for the complete consumption of **5**.

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