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Living Alternating Copolymerization of *N*-Alkylaziridines and Carbon Monoxide as a Route for Synthesis of Poly-β-peptoids

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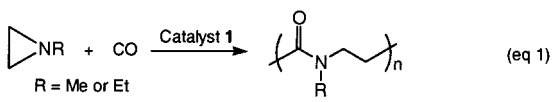
Synthetic analogues of natural polypeptides such as poly-β-peptides and polypeptoids have a wide range of potential biomimetic applications in areas including catalysis, materials, and pharmaceutics and have been intensively studied in the past decade.[1−4] Existing synthetic methods for β-peptide and peptoid oligomers and polymers,[5−7] including the recently elaborated living polymerization methods,[5,6] use organic carbonyl compounds as the starting materials. Alternative approaches capable of generating new structural types and complementing the existing methods are desirable. The possibility of direct copolymerization of aziridines and CO is therefore interesting.[8−12]

We have reported the copolymerization of unsubstituted aziridine and CO as a prototype of the synthetic route for poly-β-peptides.[12] The reaction has two notable drawbacks. First, the selectivity of CO−aziridine alternating enchainment is not satisfactory. Defective amine microstructures caused by repetitive aziridine insertions are present at low catalyst loadings. Second, the molecular weight distribution is broad. The poor selectivity is likely due to the competitive aziridine nucleophilic addition to the acylaziridium intermediate.[12] Proton abstraction by the cobaltate from the acylaziridinium intermediate likely is responsible for chain transfer and also opens up a chain combination pathway that further complicates the molecular weight distribution.[13] A priori, the copolymerization of *N*-alkylaziridines and CO should be more selective toward comonomer-alternating enchainment because *N*-alkylaziridines as tertiary amines are less nucleophilic than the unsubstituted aziridine. The molecular weight distribution can also be expected to change significantly because chain transfer and the subsequent chain combination will no longer be possible. We now report the living alternating copolymerization of *N*-alkylaziridines and carbon monoxide for the synthesis of poly-β-alkylalanoids.

The copolymerization of *N*-methylaziridine (**1**) and *N*-ethylaziridine (**2**) with CO is catalyzed by $BnCOCo(CO)_4$ (**3**) (eq 1). Catalyst



3 is generated by mixing $Na^+Co(CO)_4^-$ and phenylacetyl chloride in diethyl ether followed by extraction with hexane.[13,14] The hexane solution is used without further purification. The polymerization is carried out at 60 °C in dioxane under 1000 psi CO (Table 1).[13] Poly-β-methylalanoid (p-β-Ma) is insoluble in dioxane and is isolated by filtration. Poly-β-ethylalanoid (p-β-Ea) is partially soluble in dioxane and is isolated by removal of dioxane followed by washing with hexane. The polymerization proceeds at a moderate rate. For example, at the **2**-to-**3** initial molar ratio of 152:1, 64, 88, and 100% of **2** is converted in 2, 6, and 24 h, respectively (entries 7−9, Table 1). However, the copolymerization of **1** and CO substantially slows down as the reaction proceeds and practically stops after about 20 catalyst turnovers (entries 10 and 11, Table 1). Since the **1**−CO copolymerization and the **2**−CO copolymerization appear to significantly differ only in the solubility of the products in the reaction media, we suggest that the termination of the reaction is caused by precipitation of the nonswelling p-β-Ma that blocks the access to the catalyst, rather than the decomposition of the catalyst.

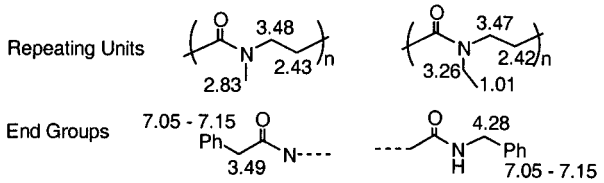


Figure 1. ^{1}H NMR chemical shifts (ppm) in $CDCl_2CDCl_2$ at 120 °C.

The structures of the polymers are characterized by NMR, IR, and MALDI MS techniques.[13] Both the ^{1}H and ^{13}C NMR spectra at the ambient temperature are affected by the hindered rotation about the amide bonds. The coalescence of the ^{13}C signals is not complete at the temperature as high as 120 °C. The ^{1}H NMR chemical shifts after coalescence are summarized in Figure 1. Excellent selectivity of comonomer-alternating enchainment is observed, especially for the copolymerization of **2** and CO. No amine defects are present in p-β-Ea produced at the **2**-to-**3** molar ratios up to 152:1, judged from the ^{1}H NMR spectra. A few barely discernible features around 2.6 ppm in ^{1}H NMR indicate that a minimal amount of the amine units may be present in p-β-Ma produced at the **1**-to-**3** molar ratio of 24:1 (entry 10, Table 1). At one end of the chain, the end group is the benzyl from **3**. The end group at the other end cannot be observed by NMR, but the masses of the polymer molecular ions detected by MALDI MS are consistent with a carboxylic acid end group, which likely arises from the oxidation or hydrolysis or both of an acyl−Co bond when the polymer is worked up in air. In support of this assumption, addition of benzylamine under CO after the complete conversion of **2** yields a benzyl amide end group. The presence of the benzyl amide end group is confirmed by NMR and MALDI MS. The benzyl amide bond apparently results from aminolysis of the acyl−Co bond (eq 2). The end groups suggest that the catalyst is, at least

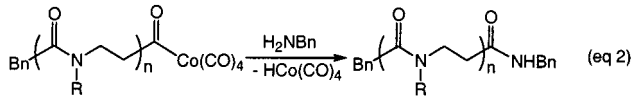


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Table 1. Copolymerization of *N*-Alkylaziridines and CO Catalyzed by **3**[a]

entry	aziridine	molar ratio (aziridine:catalyst)	catalyst concentration (mM)	reaction time (h)	yield (%)	M_n (10^3) (theoretical)[b]	M_n (10^3) (NMR)[c]	M_n (10^3) (GPC)[d]	M_w/M_n (GPC)[d]
1	**2**	19:1	5.8	48	100	2.02	2.12	3.22	1.26
2	**2**	38:1	2.9	48	100	3.90	3.80	5.91	1.13
3	**2**	57:1	1.45	48	100	5.78	5.98	10.7	1.11
4	**2**	76:1	1.16	48	100	7.66	7.66	11.4	1.12
5	**2**	95:1	0.97	48	100	9.54	11.0	19.6	1.27
6	**2**	152:1	0.73	72	100	15.2	14.1	25.0	1.63
7	**2**	152:1	0.73	24	100	15.2	15.1	27.5	1.64
8	**2**	152:1	0.73	6	88	13.4	11.7	24.2	1.45
9	**2**	152:1	0.73	2	64	9.72	8.64	13.1	1.21
10	**1**	24:1	5.8	48	83	1.74	2.44	3.05	1.39
11	**1**	48:1	2.9	48	45	1.86	2.78	3.11	1.33

[a] Reaction conditions: 60 °C, 1000 psi CO pressure, in dioxane (100 mL). [b] Calculated based on the aziridine-to-catalyst molar ratio and reaction yield. [c] End-group analysis. [d] Light scattering−viscometry−refractive index triple detectors. The refractive index increment d*n*/d*c* = 0.235.

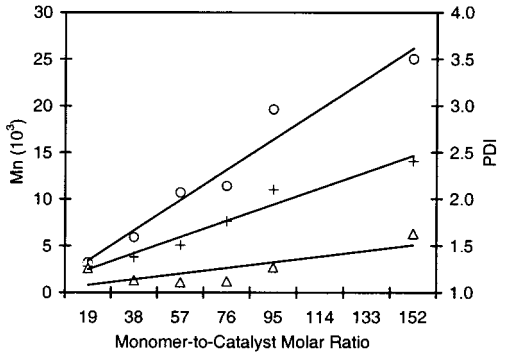

Figure 2. (○) M_n by GPC; (+) M_n by end-group analysis; (Δ) polydispersity index by GPC.

temporarily, attached to the chain end immediately after the consumption of the aziridine, providing the first indication that the copolymerization is living under the above conditions.

The molecular weights and polydispersity indices (PDI) of the poly-β-alanoids are determined by GPC equipped with a light-scattering detector, a viscometer, and a refractive-index detector. For p-β-Ea, narrow PDIs are found over a wide range of the **2**-to-**3** ratios (Table 1). The number average molecular weight (M_n) increases linearly with the increase of the **2**-to-**3** ratio (Figure 2). The M_n and PDI data thus further support the living nature of the copolymerization. Note that the absolute M_n values determined by GPC are larger than the corresponding theoretical M_n values calculated from the **2**-to-**3** molar ratios, assuming that the one catalyst only produces one chain (Figure 2). The discrepancy is not unexpected as the light-scattering detecting method intrinsically discriminates against small polymer chains and consequently often gives systematically overestimated molecular weights.[15] ^{1}H NMR end-group analysis is carried out to compare with the GPC results. The same linear increase of M_n with the increase of the **2**-to-**3** ratio is revealed by end-group analysis. The end-group analysis-determined M_n's are in excellent agreement with the theoretical M_n's (Figure 2),[16] supporting the assessment that the GPC-determined M_n's are higher than the actual values. Although the limited catalyst turnover number prevents the systematic study of the molecular weight of p-β-Ma, the PDIs of p-β-Ma are also very low. The values appear slightly higher than those of p-β-Ea produced at comparable monomer-to-catalyst ratios (entries 10 and 11 versus 1−3, Table 1), possibly reflecting the inhomogeneity of the copolymerization of **1** and CO.

In summary, the alternating copolymerization of *N*-alkylaziridines and carbon monoxide produces poly-β-alanoid with controlled molecular weights in high yields and selectivity. The copolymerization represents, to our knowledge, the first catalytic method for synthesis of poly-β-peptoids.

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Supporting Information Available: Polymerization procedure, NMR spectra, MALDI mass spectra, and IR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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