

Poly(β -alanoid-*block*- β -alanine)s: synthesis *via* cobalt-catalyzed carbonylative polymerization and self-assembly[†]

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The titled diblock copolymers are synthesized *via* cobalt-catalyzed living carbonylative polymerization of *N*-alkylaziridines under moderate pressures followed by a deprotection step. The poly(β -alanine) block is solubilized by the poly(β -alanoid) block in chloroform and remains fully hydrogen-bonded in the form of a sheet-like assembly.

β -Peptide oligomers and polymers have been explored in the past decade due to their structural analogy to peptides and, as such, their potential peptidomimetic applications.¹ Folding of such synthetic molecules into various helices has been well-studied both experimentally and theoretically. In comparison, investigations on sheet-like structures formed by β -peptides have not been prevalent.² Interestingly, the simplest member in the family, poly(β -alanine) or nylon 3, has been characterized by X-ray diffraction to exist as flat sheets in the solid state³ in contrast to the pleated β -sheets typically formed by peptides. It is therefore interesting to explore poly(β -alanine) as an element for construction of self-assembled supramolecular structures.

We have developed the synthesis of poly(β -alanine) and poly(β -alanoid)s or poly(*N*-alkyl- β -alanine)s *via* carbonylative polymerization of aziridines.⁴ By variation of the *N*-alkyl group, the poly(β -alanoid)s can be made soluble in water or organic solvents. The synthetic method therefore potentially provides a convenient route to block copolymers that may lead to interesting self-assemblies. We report here the synthesis of diblock poly(β -alanoid-*block*- β -alanine)s and our initial investigation of their self-assembling behaviors in an aprotic organic solution and in bulk.

The carbonylative polymerizations of *N*-substituted aziridines are living, but that of the unsubstituted aziridine is not.⁵ We hence chose to use a protective group strategy to produce poly(β -alanine) (β Ala) instead directly from the unsubstituted aziridine. The protected monomer to be used was *para*-(methoxybenzyl)aziridine (**1**). *N*-Butylaziridine (**2**) was adopted as the other co-monomer to give the solubilizing block, poly(*n*-butyl- β -alanoid) (ⁿBu β A), in the diblock copolymer. Catalyst CH₃COC(O)(CO)₃(*o*-tolyl)₃ (**3**) was used for the polymerization.[†]

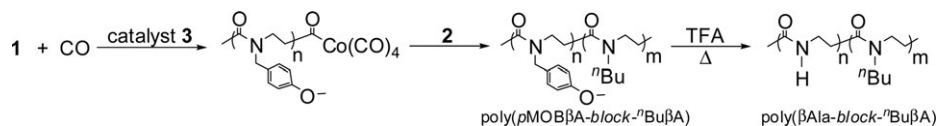
Numerous empirical trials were conducted to optimize the conditions for synthesis of the diblock copolymers by sequential addition of **1** and **2**. The results of the synthesis under the optimal conditions are summarized in Table 1. The solvent and pressure of the polymerization are key and deserve some elaboration. The choice of the polymerization solvents was between tetrahydrofuran (THF) and 1,4-dioxane ($\epsilon = 7.6$ and 2.2,⁵ respectively). Although the carbonylative polymerizations of **1** or **2** are living in either solvents, chain termination was difficult to avoid in THF after the consumption of the first aziridine monomer and when the second aziridine was added.⁶ Monoblock contaminations were observable by gel permeation chromatography (GPC) in the diblock copolymers synthesized in THF. The chain termination was also accompanied by ring-expanding carbonylation of the second aziridine co-monomer to give the corresponding β -lactam as the byproduct.⁶ When 1,4-dioxane was used as the polymerization solvent, chain termination could be avoided as long as the second monomer was added promptly after the consumption of the first. However, at 1000 psi of CO and 50 °C, which we had customarily adopted for the polymerization, a bimodal molecular weight distribution of the first block was observed by GPC (see ESI),[†] especially when the intended number average degree of polymerization (X_n , which theoretically equals the monomer-to-catalyst molar ratio) was low. The bimodality was more pronounced for poly(*para*-methoxybenzyl- β -alanoid) (*p*MOB β A) than for poly(ⁿBu β A). Although the mechanism that causes the bimodal distribution is still not clear, lowering the CO pressure unexpectedly alleviated the problem. At 150 psi and 50 °C, the bimodal distribution of the first block was no longer observable (Fig. 1). Even under such a low CO pressure, poly(*p*MOB β A-*block*-ⁿBu β A)s were produced in quantitative yields with no olefinic structures detectable by ¹H NMR, indicating the absence of chain termination by β -hydrogen elimination. The diblock copolymers displayed relatively low polydispersity without significant contamination of the monoblock dead chains regardless whether poly(*p*MOB β A) or poly(ⁿBu β A) was chosen as the first block (Fig. 1).

Refluxing poly(*p*MOB β A-*block*-ⁿBu β A)s in trifluoroacetic acid (TFA) selectively cleaved the *N*-methoxybenzyl group⁷ to give the corresponding poly(β Ala-*block*-ⁿBu β A)s. The completeness of deprotection is evidenced by the absence of *p*-methoxy and phenyl resonances in the ¹H NMR of the product (see ESI).[†] The poly(β Ala-*block*-ⁿBu β A)s with a relatively long β -Ala block (entries 3 and 4 in Table 1) are insoluble in common organic solvents. Those with a short β Ala block (entries 1 and 2 in Table 1) dissolve in chloroform

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[†] Electronic supplementary information (ESI) available: NMR, DSC, GPC traces, additional XRD data and unit cell sketch of poly(β Ala), and dynamic and static light scattering data. See DOI: 10.1039/c0cc00324g

Table 1 Synthesis of diblock polymers^a

Entry	Monomer ^b		1st block		Diblock		
	1st	2nd	M_n^c (10^3)	PDI ^c	M_n^c (10^3)	PDI ^c	PDI ^d after deprotection
1	1 (10)	2 (40)	1.50	1.44	9.87	1.21	1.20
2	1 (10)	2 (60)	1.50	1.44	11.8	1.24	1.27
3	1 (20)	2 (60)	2.55	1.26	13.2	1.35	—
4	2 (20)	1 (60)	2.25	1.26	13.0	1.33	1.23

^a 150 psi of CO, 50 °C, 79 mg of **3** in 200 mL of 1,4-dioxane (0.80 mM), quantitative yield. ^b Numbers in the parenthesis are the monomer-to-**3** ratio. ^c Relative to polystyrene standards by GPC with a refractometric detector using chloroform as the eluent. ^d GPC with a refractometric detector using HFIPA as the eluent. M_n values relative to poly(methyl methacrylate) standards are unrealistically high and not shown.

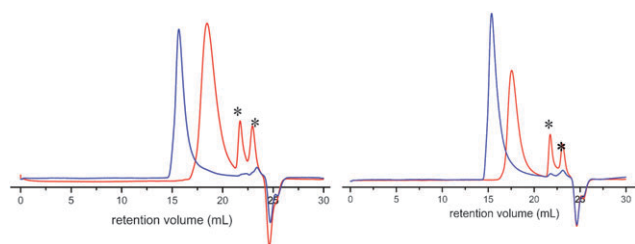


Fig. 1 GPC trace of polymers from entries 2 (left) and 4 (right) in Table 1. Red line: first block; blue line: diblock. The samples were collected directly after polymerization without any fractionation. The peaks labelled with asterisks are due to $\text{P}(o\text{-tolyl})_3$ and $\text{OP}(o\text{-tolyl})_3$ from the catalyst.

to form a visibly transparent solution, but the GPC traces were anomalous with chloroform as the eluent (see ESI),[†] signifying intermolecular association. Structural characterization by NMR also proved infeasible in common organic solvents. The ¹H NMR spectra in deuterated chloroform only revealed resonances attributable to the ⁿBuβA block (see ESI).[†] The absence of the signals from the βAla block confirms that it remains in a solid-like state. As the result, hexafluoroisopropyl alcohol (HFIPA) was used as the solvent for the NMR and GPC analyses. ¹H NMR spectroscopy confirmed the chemical compositions. GPC experiments confirmed that the PDI values remained low in the range of 1.2–1.3 (Table 1, see ESI for GPC traces),[†] indicating the absence of chain scission during deprotection. The inertness of the amide bond in the main chain during deprotection was further supported by the observation that the GPC traces of a monoblock poly(ⁿBuβA) sample before and after being subjected to the deprotection conditions exactly overlapped.

In the subsequent studies on the self-assembling property, we focused on the diblock copolymer **4** containing 10 βAla units and 40 ⁿBuβA units (from entry 1 of Table 1) as a representative example. Particularly, we are interested in answering the question whether the antiparallel sheet assembly of the βAla block is retained in solution.

The major evidence for the structure of the βAla block in chloroform came from Infrared (IR) spectroscopy, which has long been established by numerous studies of α-peptides and

nylons^{8,9} to be diagnostic for the conformation of secondary amides. In the present case, the amide A band of the βAla block of **4** in chloroform solution is located at 3293 cm⁻¹ (Fig. 2), where the hydrogen-bonded N–H stretching vibration is expected. The N–H absorption of free amide groups expected in the range of 3300–3500 cm⁻¹ is minimal if present at all. The amide I band apparently overlaps with the C=O stretching band of the tertiary amide in the ⁿBuβA block at 1643 cm⁻¹. The amide II band is located at 1545 cm⁻¹. As shown by the overlay, the amide A, I and II absorptions of the βAla block of **4** in chloroform are at the same positions as those of the pure poly(βAla) in the solid state where it is known to exist as antiparallel sheets.³ Comparison of the IR data thus suggests that the βAla block of **4** associates *via* intermolecular hydrogen bonding in chloroform to form the flat antiparallel sheets identical to what poly(βAla) adopts in the solid state. Unfortunately, the IR spectroscopy is incapable of giving information concerning the long-range order of or the degree of association between the solubilized sheets. Related to this, dynamic light scattering showed that the hydrodynamic diameters of the assemblies spread from a few tens to several hundred nanometres (see ESI).[†] The morphology of the assemblies of **4** in chloroform is evidently heterogeneous.

To augment the solution-phase characterization of the βAla block, we carried out wide angle X-ray diffraction (WAXD) studies of **4** in the bulk phases. Both blocks, βAla and ⁿBuβA are crystalline. Based on our DSC results, the βAla block melts

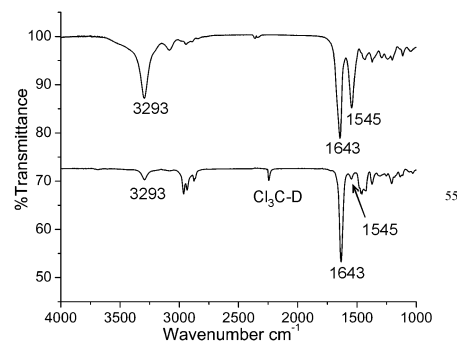


Fig. 2 IR spectra of **4** (bottom) in CDCl_3 solution (1 mg mL⁻¹) and poly(βAla) (top) in the solid state pressed into a pellet.

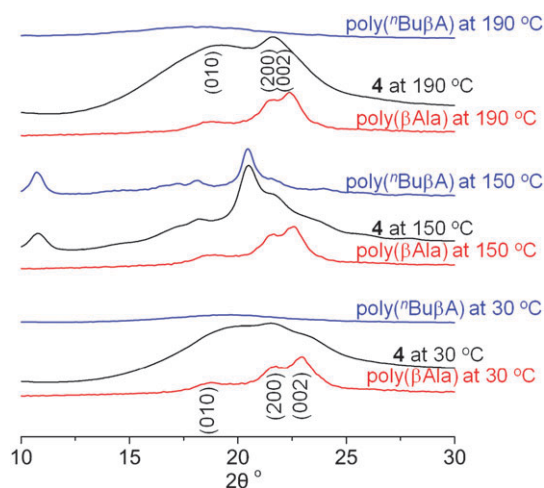


Fig. 3 WAXD patterns of poly(β Ala) (red), quenched **4** (black) and quenched poly(β ⁿBu β A) at representative temperatures. Assignments of the Bragg diffractions of poly(β Ala) are adopted from ref. 3.

or decomposes at >250 °C, while the ⁿBu β A block melts at $T_m = 163$ °C (see ESI).[†] The copolymer sample **4** for WAXD was prepared by heating it to 200 °C, that is far above the melting temperature of the ⁿBu β A block, and then quenching in liquid nitrogen. Fig. 3 illustrates the WAXD results. After quenching and when the WAXD experiment was carried out at 30 °C, the ⁿBu β A block is in an amorphous phase. Three broad diffraction halos are still discernible in the WAXD pattern taken at 30 °C. By comparison with the d -spacings of the WAXD pattern of pure poly(β Ala), which is also included in Fig. 3, the three halos are attributed to the (010), (200) and (002) diffractions ($d_{(010)} = 0.476$ nm, $d_{(200)} = 0.400$ nm, and $d_{(002)} = 0.377$ nm) of the antiparallel sheets stacked in a monoclinic unit cell³ formed by the β Ala block of **4**. The crystals in this sample possess very small crystallite sizes within several nanometres based on the Scherrer equation. The ⁿBu β A₄₀ block of **4** crystallizes during heating to exhibit Bragg diffractions as shown in the WAXD pattern taken at 150 °C in Fig. 3. By comparison with the WAXD pattern of the crystals of pure poly(ⁿBu β A), the diffractions of **4** with d -spacings of 0.82 nm, 0.49 nm, 0.43 nm and 0.41 nm are attributed to the crystals of the ⁿBu β A block (the crystal structure of pure poly(ⁿBu β A) is not available at this moment). Above the melting temperature of the crystals of ⁿBu β A block at 190 °C, two Bragg diffractions, which originate from the crystals of β Ala block, remain as shown in Fig. 3. One is assigned to the (010) diffraction, and the other is a merger of the (200) and (002) diffractions. This merge is previously known for poly(β Ala)³ and confirmed in our laboratory (see ESI)[†] and is due to the larger thermal expansion in the normal direction to the (002) planes than that in the normal direction to the (200) planes. The phenomenon can be easily understood since the interaction is van der Waals forces between the (002) planes, while hydrogen bonding between the (200) planes. The WAXD study therefore corroborates the propensity of the β Ala blocks in **4** to form the antiparallel sheet-like structure.

In summary, diblock poly(β -alanoid-*block*- β -alanine)s have been synthesized *via* the catalytic carbonylative polymerization

of aziridines followed by selective cleavage of the *N*-protective group. The diblock copolymers with a short β Ala block form soluble supramolecular aggregates in chloroform. IR spectroscopic evidences suggest that the β Ala block assembles into antiparallel sheets in the solution state *via* intermolecular hydrogen bonding. The WAXD studies support the notion that the antiparallel sheet conformation is highly favored by the β Ala block.

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Notes and references

[†] Monomer **1** was dried over CaH₂ and kept over *n*-Bu₂Mg, and **2** was dried and kept over Na/K alloy. They were freshly distilled before polymerization. The polymerization was carried out in a 300-mL stainless-steel reactor equipped with a mechanical stir and thermal couple (Autoclave Engineer). A stainless-steel tube was fitted to the top of the reactor *via* a ball-valve joint for monomer addition. The reactor was located in a ventilated hood, around which CO detectors were placed.

In a typical polymerization, a solution of **3** under CO (1 atm) and anhydrous 1,4-dioxane making the total volume 200 mL was charged into the reactor under a gentle CO flow. The reactor was then pressurized to 100 psi and heated to 50 °C. After the temperature stabilized, the first monomer was added through the addition tube pressurized to 150 psi. The polymerization was mechanically stirred at 500 rpm and monitored by ATR-IR *via* a SICOM probe (ReactIR IC, Mettler-Toledo) attached to the bottom of the reactor. When the polymerization of the first monomer reached completion (catalyst turnover frequency = ~ 10 and ~ 20 h⁻¹ for **1** and **2**, respectively), the second monomer was added into the reactor *via* the slightly overpressurized addition tube. The reaction was allowed to continue for an additional 5 h and stopped by releasing the pressure. Poly(*p*MOB β A-*block*-ⁿBu β A) was collected after removal of 1,4-dioxane under vacuum, washing with ether, and drying under vacuum at room temperature. The yields were essentially quantitative.

Deprotection of poly(*p*MOB β A-*block*-ⁿBu β A) was carried out in refluxing TFA for 4 h. After removal of TFA under vacuum, chloroform was added to the glassy residue to give either a solution or a slurry depending on the length of the β Ala block. Diethyl ether was added to precipitate the poly(β Ala-*block*-ⁿBu β A) product into a powder. The product was collected after filtration and drying in vacuum. The yields were $>80\%$.

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