Poly(Beta-Alanoid-Block-Beta-Alanine)s: Synthesis via Cobalt-Catalyzed Carbonylative Polymerization and Self-Assembly

Shaohui Lin, University of Akron Main Campus
Xinfei Yu, University of Akron Main Campus
Yinfeng Tu, University of Akron Main Campus
Hongyu Xu, Lehigh University
Stephen Z. D. Cheng, University of Akron, et al.
Poly(β-alanoid-block-β-alanine)s: synthesis via cobalt-catalyzed carbonylative polymerization and self-assembly†

Shaohui Lin, a Xinfu Yu, a Yingfeng Tu, a Hongyu Xu, b Stephen Z. D. Cheng a and Li Jia a

Received 11th March 2010, Accepted 14th April 2010
First published as an Advance Article on the web 19th May 2010
DOI: 10.1039/c0cc00324g

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) (βAla) 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) (BuβA), in the diblock copolymer. Catalyst CH3COCo(CO)3(P(OMe)3)(P(o-tolyl))2 (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 (ε = 7.6 and 2.2,6 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 (Xn, which theoretically equals the monomer-to-catalyst molar ratio) was low. The bimodality was more pronounced for poly(para-methoxybenzyl-β-alanoid) (pMOBβA) than for poly(′BuβA). 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(pMOBβA-block-′BuβA)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(pMOBβA) or poly(′BuβA) was chosen as the first block (Fig. 1).

Refluxing poly(pMOBβA-block-′BuβA)s in trifluoroacetic acid (TFA) selectively cleaved the N-methoxybenzyl group7 to give the corresponding poly(βAla-block-′BuβA)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(βAla-block-′BuβA)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.

† Electronic supplementary information (ESI) available: NMR, DSC, GPC traces, additional XRD data and unit cell sketch of poly(βAla), and dynamic and static light scattering data. See DOI: 10.1039/c0cc00324g
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 $^1$H NMR spectra in deuterated chloroform only revealed resonances attributable to the $^4$BuβA 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. $^1$H 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($^4$BuβA) 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 $^4$BuβA 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 nylon8,9 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 $^4$BuβA block at 1643 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 $^4$BuβA are crystalline. Based on our DSC results, the βAla block melts...
or decomposes at >250 °C, while the \( ^\text{8} \text{BuA} \) block melts at \( T_m = 163 \) °C (see ESI).\(^\dagger\) The copolymer sample \( 4 \) for WAXD was prepared by heating it to 200 °C, that is far above the melting temperature of the \( ^\text{8} \text{BuA} \) 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 \( ^\text{8} \text{BuA} \) 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(\( ^\text{8} \text{BuA} \)), 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 cell\(^3\) formed by the \( ^\text{8} \text{BuA} \) block of \( 4 \). The crystals in this sample possess very small crystallite sizes within several nanometres based on the Scherrer equation. The \( ^\text{8} \text{BuA} \) 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(\( ^\text{8} \text{BuA} \)), 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 \( ^\text{8} \text{BuA} \) block (the crystal structure of pure poly(\( ^\text{8} \text{BuA} \)) is not available at this moment). Above the melting temperature of the crystals of \( ^\text{8} \text{BuA} \) block at 190 °C, two Bragg diffractions, which originate from the crystals of \( ^\text{8} \text{BuA} \) 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(\( ^\text{8} \text{BuA} \))\(^3\) and confirmed in our laboratory (see ESI)\(^\dagger\) 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 \( ^\text{8} \text{Ala} \) block in \( 4 \) to form the antiparallel sheet-like structure.

In summary, diblock poly(\( ^\text{8} \text{alanoid-block-}\beta \text{alanine} \)) have been synthesized via the catalytic carbonylative polymerization of aziridines followed by selective cleavage of the \( \beta \text{Ala} \)-protective group. The diblock copolymers with a short \( ^\text{8} \text{Ala} \) block form soluble supramolecular aggregates in chloroform. IR spectroscopic evidences suggest that the \( ^\text{8} \text{Ala} \) 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 \( ^\text{8} \text{Ala} \) block.

We thank the NSF for supporting this research (CHE-0965060 and DMR-0906898) and funding University of Akron Magnetic Resonance Center to purchase the NMR instrument (CHE-9977144) used in this work. We are grateful to Tosoh Bioscience for running GPC analysis in HFIPA.

Notes and references

\( ^\dagger \) Monomer I was dried over CaH\(_2\) and kept over \( \text{n-BuMg} \) 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 stirrer and thermal couple (Autoclave Engineer). A stainless-steel tube was fitted to the top of the reactor via a ball-serve 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 reaction 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 = \( \sim 10 \) and \( \sim 20 \) h\(^{-1}\) for I and 2, respectively), the second monomer was added into the reactor via the slightly over-pressurized addition tube. The reaction was allowed to continue for an additional 5 h and stopped by releasing the pressure. Poly(\( ^\text{8} \text{MOB(}\beta\text{-block-}^\text{8} \text{BuA) \) 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(\( ^\text{8} \text{MOB(}\beta\text{-block-}^\text{8} \text{BuA) \) 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 \( ^\text{8} \text{Ala} \) block. Diethyl ether was added to precipitate the poly(\( ^\text{8} \text{MOB(}\beta\text{-block-}^\text{8} \text{BuA) \) product into a powdery. The powder was collected after filtration and drying in vacuum. The yields were >90%.

6 H. Xu, Carbonylation of Heterocyclic Compounds, Dissertation, Lehigh University, Bethlehem, PA, USA, 2005.