A tandem non-polymerizing strategy to higher order acrylamide oligomers; potential intermediates for conformational correlations of poly-*N*-acrylamides†

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This letter describes an efficient tandem non-polymerization strategy to deliver higher order *N*-acrylamide oligomers. These oligomers, accessible in an one-pot procedure, are potential intermediates for the correlation of stereochemistry (tacticity) with conformation and hydrogen bonding propensities in poly (oligo) *N*-acrylamides.

Poly-*N*-alkyl acrylamides are a class of functional polymers derived from acrylamide building blocks, connected together in various stereochemical arrangements. Recently, these functional polymers have attracted considerable attention mainly due to their enormous potential for high-technology applications in diverse fields; ranging from medical to nano-technology areas.[1] The interest in this class of polymers is further supplemented by the fact that the reversible thermo-precipitation displayed by some of them has close proximity, mechanistically, to protein denaturation.[2] Despite the significant advancement made in the understanding of poly-*N*-alkyl acrylamide tacticity (stereochemistry),[3,4] its exact correlation with conformational and hydrogen-bonding propensities largely remains to be clearly understood.[5,6]

Due to their sequence repetition, there exists a strong parallel between poly-*N*-acrylamides, sequential (repetitive/tandem) proteins[7] and a related class of synthetic oligomers called foldamers,[8,9] since all these three oligomer families are endowed with *repeating* structural units that are essential to their functional/conformational integrities. The conformation of macromolecules, whether synthetic or of biological origin, has a strong correlation to their bulk material properties. Just as the stereochemical arrangements of the individual amino acid residues strongly influence the conformation and biophysical properties of polypeptides,[10] so does the tacticity (backbone stereochemistry), on the bulk properties of poly-*N*-alkyl acrylamides.[5] A stark contrast of the conformation–material property relationship can be easily discerned by the comparison of the major fibrillar sequential (repetitive) proteins such as collagen and elastin. Where as the triple helical structure of collagen,[11] having the poly(Gly-Xaa-Yaa) repeat sequence (Xaa and Yaa positions contain a high content of proline and hydroxyproline, respectively) is responsible for its high tensile strength, the β-spiral conformation exhibited by elastin, a protein that also displays temperature-induced structural transitions as poly-*N*-alkyl acrylamides, has been attributed to this protein's high elasticity and resilience.[7] It is noteworthy that the conformation displayed by the shorter repeating sequences of sequential proteins is clearly replicated in the oligomer level as well,[12,13] a fact that has been overwhelmingly demonstrated in a related class of synthetic oligomers called foldamers.[8,9] Though it is easy to construct, through standard amino acid coupling, the shorter repeating sequences of sequential proteins for easy characterizations and conformational studies, the difficulty associated with the controlled oligomerization of *N*-alkyl acrylamides[14] to furnish shorter fragments of easily characterizable size has impeded such attempts to isolate and characterize them.

In order to provide insights into the exact relationship between poly-*N*-acrylamide tacticity, conformation and hydrogen-bonding propensities, we recently suggested a systematic *bottom-up* approach, by generating various lower *N*-alkyl acrylamide oligomers of well-defined size (length) and thus correlating their conformation and hydrogen-bonding propensities. Our preliminary findings based on single-crystal X-ray structure and solution-state NMR studies suggested that acrylamide oligomers having 1,3-*syn* stereochemistry (isotactic) have a strong propensity to adopt a protein β-sheet-like structure (Fig. 1), through robust intermolecular hydrogen-bonding interactions of the individual strands.[15]

In this letter, we present an efficient, one-pot non-polymerizing strategy[14] to deliver higher order acrylamide oligomers (octamers) of diverse stereochemistry, which would be potential intermediates for the conformational correlations of poly-*N*-acrylamides. The idea herein was to generate a library of *N*-alkyl acrylamide oligomers of different tacticities concurrently, and separating (for instance, by repetitive fractional crystallization) them to furnish oligomers of diverse tacticities, for correlating their tacticity with conformation and hydrogen-bonding propensities. An anticipated advantage of this approach would be that it may yield quick results, since enormous efforts need not be expended to synthesize each stereoisomer separately for conformational studies, as in the stereospecific strategy described earlier by us.[15]

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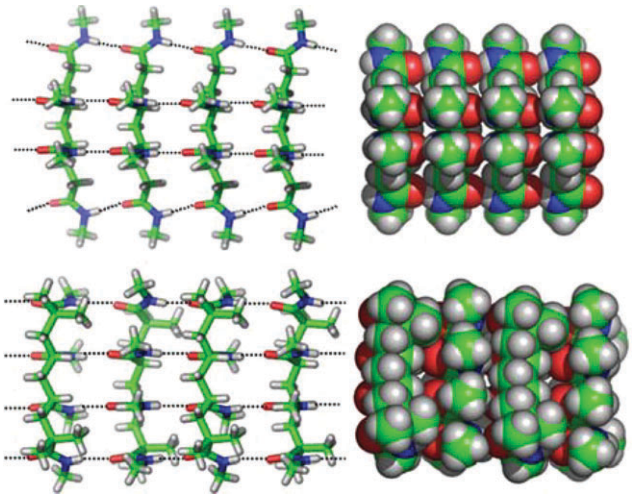


Fig. 1 Crystal structure of isotactic (1,3-*syn*) acrylamide oligomers showing self-assembled β-sheet-like structure.[15]

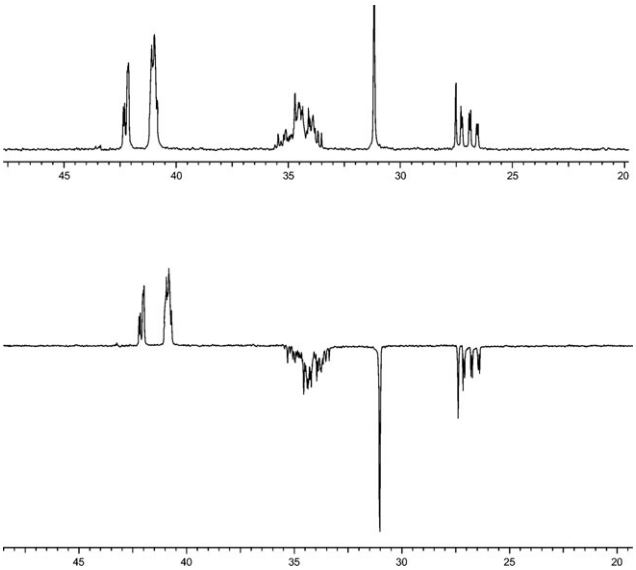
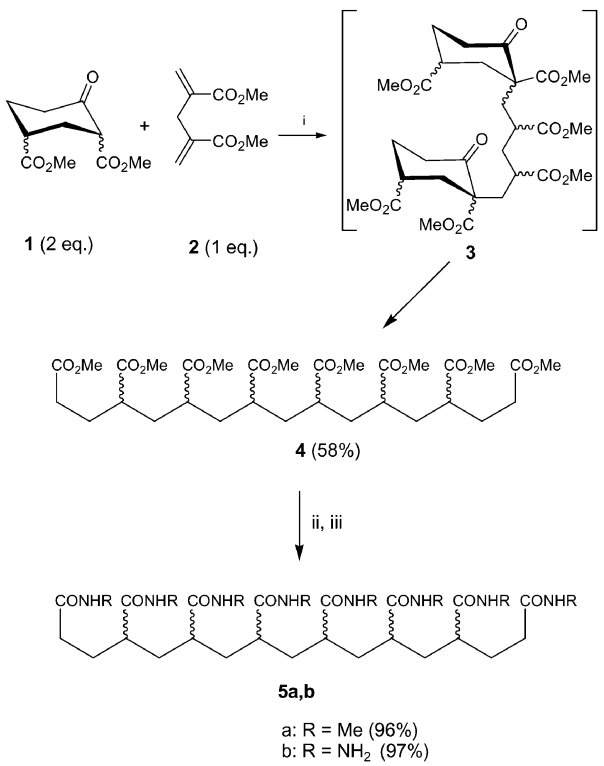


Fig. 2 ^{13}C (top) and ^{13}C DEPT-135 (bottom) NMR spectra of the octa ester **4** (125 MHz, $CDCl_3$).

It is noteworthy that considerable advancement has been made in the past in the controlled polymerization of acrylamides with uniform molecular weight distribution.[16] However, synthesis of short oligomers (telomers) of well-defined length/size by such strategies continues to be an overwhelming challenge. Several clever strategies have been attempted, mainly by Porter's group, to obtain telomers of pre-defined length by using radical reactions; but without significant advantages, since in most of the cases the dimers were the only isolable products.[14]



Scheme 1 Synthesis of **5**. *Reagents and conditions*: (i) (a) 1.5 equiv. DBU, MeOH, 45 °C, 48 h; (b) H^+; (ii) $MeNH_2$, MeOH, steel bomb, 75 °C, 4 days; (iii) NH_2NH_2, MeOH, steel bomb, 75 °C, 4 days.

In accordance with the aforementioned non-polymerizing strategy, we set out to synthesize acrylamide oligomers by a tandem protocol, as outlined in Scheme 1.

The starting material, cyclic β-ketoester **1**, was readily prepared by the base-mediated reaction of methyl acetate with methyl acrylate.[17] The bis-Michael acceptor **2** was obtained in three steps starting from methyl acrylate by a repetitive Baylis–Hillman protocol.[18,19] An excess of the β-keto ester **1** was reacted with the bis-Michael acceptor **2** in methanol containing DBU. It was anticipated that the bis-Michael adduct intermediate **3**, once formed will instantly undergo ring-opening reaction by methanol, induced by DBU. Indeed the reaction afforded the octa ester **4** straightaway in an one-pot procedure in moderate isolated yield (58%). The octa ester **4** was subjected to amidation, either by reacting with saturated methanolic methylamine to afford **5a** or by reacting with methanolic hydrazine to afford **5b**.

Proof of the formation of a library of stereoisomers, as anticipated, came from the inspection of the ^{13}C DEPT-135 (distortionless enhancement by polarization transfer)[20] NMR spectra of the octa ester **4** (Fig. 2). Comparison of the ^{13}C and ^{13}C DEPT 135 NMR spectra of **4** revealed that the de-phased ^{13}C methylene (CH_2) signals were considerably larger in number which can only account for the formation of a mixture of stereoisomers, as anticipated.

In summary, this letter describes a tandem one-pot non-polymerizing strategy to deliver a library of higher order acrylamide oligomers (octamers) of diverse stereochemistry, which would be potential intermediates for the conformational correlations of poly-*N*-acrylamides. Currently, efforts are underway to separate (by repetitive fractional crystallization) the stereoisomers to furnish oligomers of diverse tacticities for correlating their stereochemistry with conformation and hydrogen-bonding propensities. The results will be reported in due course.

Experimental

4,6,8,10,12,14-Hexakis(methoxycarbonyl)heptadecanedioic acid dimethyl ester (4)

To a flame-dried two-necked round-bottom flask containing 4-oxocyclohexane-1,3-dicarboxylic acid dimethyl ester **1** (2.9 g, 13.59 mmol) was added dry methanol (20 ml) followed by DBU (1,8-diazabicyclo(5.4.0)undec-7-ene) (1.24 g, 8.15 mmol) at 0 °C. The ice-bath was removed and the reaction mixture was stirred at room temperature for 45 min. Then, 2,4-dimethoxycabonylpenta-1,4-diene **2** (1 g, 5.43 mmol) dissolved in dry methanol (5 ml) was added. After the addition, the reaction mixture was stirred at 40–45 °C for 48 h. The volatiles were removed on a rotary evaporator under vacuum, and the reaction mixture was diluted with dichloromethane (200 ml) and the organic layer was washed successively with 2 M HCl, saturated bicarbonate and water. The organic layer was dried over anhydrous Na_2SO_4, concentrated and the product was purified by column chromatography (R_f = 0.25, 50% petroleum ether–EtOAc) to afford **4** (2.13 g, 58%) as a colorless thick oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 3.66 (s, 24H), 2.40–2.26 (m, 10H), 1.99–1.52 (m, 14H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 174.78, 174.74, 172.82, 51.65, 51.46, 51.36, 42.35, 42.29, 42.18, 42.15, 42.12, 41.09, 41.04, 40.96, 40.84, 35.45, 35.32, 35.21, 35.13, 35.10, 35.03, 34.95, 34.89, 34.83, 34.69, 34.63, 34.54, 34.51, 34.46, 34.40, 34.35, 34.16, 34.10, 34.03, 33.93, 33.90, 33.81, 33.68, 33.52, 31.16, 27.52; IR ($CHCl_3$) ν/cm^{-1}: 3024, 2952, 1735, 1448, 1379, 1217, 1166, 1049, 757, 667; LCMS: m/z 699.26 (M + Na), 715.27 (M + K), 1375.58 (2M + Na).

4,6,8,10,12,14-Hexakis(methylcarbamoyl)heptadecanedioic acid bismethylamide (5a)

A mixture of saturated solution of methylamine in methanol and **4** (0.5 g, 0.74 mmol) was taken in a steel bomb and heated at 75 °C for 4 days. The volatiles were removed on a rotary evaporator under vacuum and then dried which provided a pale yellow hygroscopic solid which was triturated with dry petroleum ether and decanted several times to furnish a soft hygroscopic solid **5a** (0.46 g, 96%). ^{1}H NMR (CD_3OD, 500 MHz): δ (ppm) 2.69–2.71 (m, 24H), 1.46–2.19 (br, 24H); ^{13}C NMR (CD_3OD, 50 MHz): δ (ppm) 177.55, 175.65, 45.61, 45.46, 45.36, 45.28, 45.07, 44.98, 44.65, 44.07, 43.83, 43.72, 43.47, 43.25, 43.13, 42.91, 42.83, 37.38, 37.15, 37.01, 36.69, 36.48, 36.40, 36.32, 36.27, 36.19, 35.84, 35.31, 35.18, 34.52, 30.70, 30.64, 30.31, 29.52, 29.22, 29.10, 26.53, 26.46, 25.74; IR (Nujol) ν/cm^{-1}: 3289, 3037, 2924, 2854, 1657, 1644, 1543, 1410, 1377, 1294, 1159, 1037, 759, 665; LCMS: m/z 669.46 (M + 1), 691.48 (M + Na).

Octa hydrazide (5b)

A mixture of octa ester **4** (0.20 g, 0.29 mmol), dry methanol (15 ml) and hydrazine monohydrate (0.39 g, 7.09 mmol) was taken in a steel bomb and heated at 75 °C for 4 days. The volatiles were removed and the residue was dried under vacuum, to afford **5b** as a colorless soft hygroscopic solid (0.194 g, 97%). ^{1}H NMR (D_2O, 500 MHz): δ (ppm) 2.18–1.55 (br, 24H); ^{13}C NMR (D_2O, 125 MHz): δ (ppm) 175.12, 174.86, 174.80, 174.71, 173.86, 41.77, 41.62, 41.52, 41.36, 40.52, 40.09, 39.95, 35.45, 35.34, 35.07, 35.02, 34.69, 34.58, 34.27, 34.14, 33.97, 33.42, 33.19, 30.85, 28.09, 28.03, 27.57, 27.37, 27.05; IR (Nujol) ν/cm^{-1}: 3285, 3186, 2924, 2854, 2725, 1651, 1612, 1461, 1377, 1021, 722; LCMS: m/z 677.39 (M + 1), 699.28 (M + Na), 1375.58 (2M + Na).

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