Isotactic *N*-alkyl acrylamide oligomers assume self-assembled sheet structure: first unequivocal evidence from crystal structures†

Amol Kendhale,[a] Rajesh Gonnade,[b] Pattuparampil R. Rajamohanan*[c] and Gangadhar J. Sanjayan*[a]

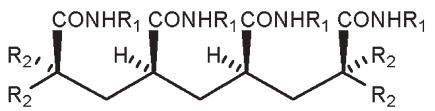
Received (in Cambridge, UK) 27th January 2006, Accepted 16th March 2006
First published as an Advance Article on the web 29th March 2006
DOI: 10.1039/b601317a

Herein we present the first unequivocal evidence of the ability of isotactic *N*-alkyl acrylamide oligomers to assume self-assembled sheet-like structures that are reminiscent of protein β-sheets.

Poly-*N*-acrylamides as a class of functional polymers have come into prominence primarily due to their enormous potential for high-technology applications in various fields.[1] Further interest in this class of polymers stems from the fact that the reversible thermo-precipitation displayed by some of the members in the class has close proximity, mechanistically, to protein denaturation.[2] Notwithstanding the considerable advancement made in the understanding of poly-*N*-alkyl acrylamide tacticity,[3] its exact correlation with conformational and hydrogen-bonding propensities largely remains to be clearly understood.[4]

In this communication, we present the first unequivocal evidence of the ability of isotactic *N*-alkyl acrylamide oligomers to assume self-assembled sheet-like structures that are reminiscent of protein β-sheets.[5] Remarkably, such a structural feature for isotactic *N*-alkyl acrylamide oligomers/polymers has never been considered before, even by computer modeling studies. The robust supramolecular self-assembly-driven sheet formation is clearly evident even under a non-propitious environment, as seen in the crystal structure of a sterically demanding isotactic *N*-methyl acrylamide oligomer **1e** (*vide infra*). The result described herein will have far reaching implications in the deeper understanding of the correlation between poly-*N*-alkyl acrylamide-tacticity, conformation and hydrogen bonding propensities. Furthermore, this finding also provides new insights that can be used to guide future attempts to engineer oligo-*N*-acrylamide-based novel protein secondary structural mimics that exclusively employ side chain amide groups for their secondary structure stabilization.[5]

In an effort to provide insights into the relationship between poly-*N*-acrylamide tacticity and conformation, we set out to generate a series of *N*-acrylamide oligomers of well-defined length and backbone stereochemistry by non-polymerizing synthetic strategies[6] and correlate unambiguously their conformational preferences and hydrogen bonding propensities with the backbone stereochemistry (tacticity). Herein we report the synthesis, and structural studies of a series of *N*-alkyl acrylamide tetramers **1a–e** (Fig. 1) having the side chain amide groups in a 1,3 *syn* configuration (isotactic) and show unambiguously by single crystal X-ray diffraction and NMR studies that such a stereochemical arrangement on the oligomer backbone can lead to the formation of self-assembled sheet-like structures.

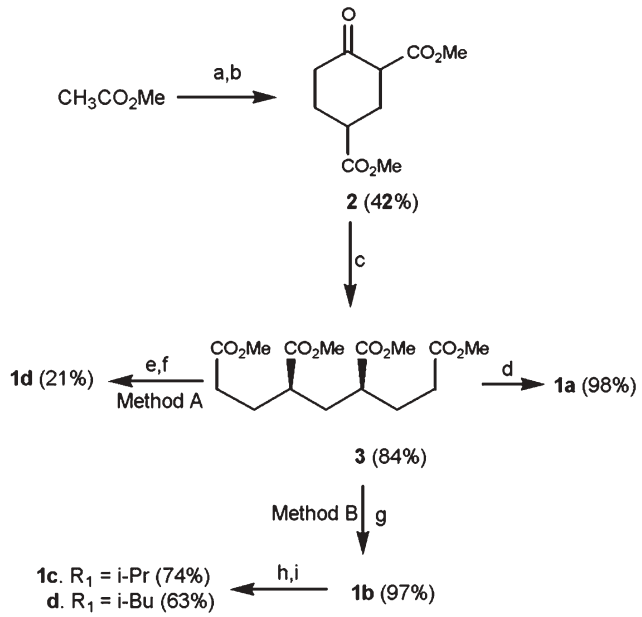


1a. R_1 = Me, R_2 = H
b. R_1 = NH_2, R_2 = H
c. R_1 = iPr, R_2 = H
d. R_1 = iBu, R_2 = H
e. R_1 = R_2 = Me

Fig. 1 Isotactic *N*-alkyl acrylamide tetramers **1a–e** synthesized by multi-step non-polymerising synthetic procedure.

N-Alkyl acrylamide tetramers **1a–e** were synthesized by multi-step non-polymerizing synthetic procedures, in moderate yields. It should be noted that synthesis of *N*-alkyl acrylamide oligomers (telomers) of well-defined length/size by polymerizing strategies continues to be an overwhelming challenge and diverse efforts made in the past to synthesize *N*-alkyl acrylamide oligomers, larger than dimers, by various polymerizing strategies have so far been unsuccessful.[6] 4,6-Bis-methoxycarbonyl-nonanedioic acid dimethyl ester **3**, a key intermediate in the synthesis of the *N*-acrylamide tetramers **1a–d**, was synthesized by a modified Robinson protocol as follows (Scheme 1, details in ESI†). The β-keto ester **2**,[7] obtained by the reaction of methyl acetate with methylacrylate in the presence of LDA at −78 °C, was subjected to a one-pot DBU-mediated Michael addition-ring opening reaction sequence by reacting it with methylacrylate in methanol to afford the tetra-ester **3** in good yield. The tetra-acrylamide **1a** could be readily obtained in excellent yield by the amidation of the ester **3** with saturated methylamine solution in methanol. Similarly, **1b** was obtained by reacting **3** with excess hydrazine in methanol. The tetra-acrylamide oligomers **1c** and **1d** were obtained by following the acyl azide procedure (method B), a strategy extensively used in solution-phase peptide coupling. The tetra-acrylamide oligomer **1d** could also be obtained by the reaction of tetra-ester **3** with $AlMe_3$-isobutyl amine complex (method A),[8] though the low yield of this strategy discouraged its further application in the synthesis of other oligomers.

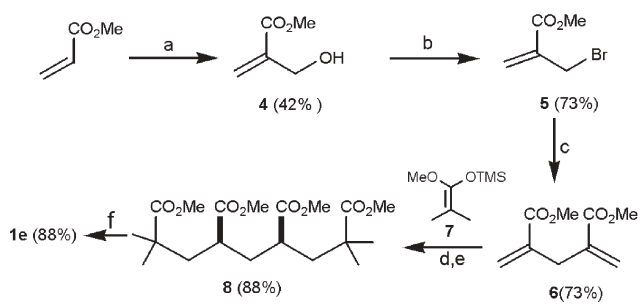
[a]*Division of Organic Synthesis, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411 008, India. E-mail: gj.sanjayan@ncl.res.in; Fax: (+91) 020-25893153; Tel: (+91) 020-25902082*
[b]*Central Material Characterization Division, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411 008, India*
[c]*Central NMR Facility, National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411 008, India. E-mail: pr.rajamohanan@ncl.res.in; Fax: (+91) 020-25893153; Tel: (+91) 020-25902075*
† Electronic supplementary information (ESI) available: Full experimental procedures, ^{1}H, ^{13}C, 2D NMR data (2D NOESY and HSQC), SEM images, ESI mass spectra. See DOI: 10.1039/b601317a



Scheme 1 Synthesis of **1a–d**. Reagents and conditions: (a) LDA, THF, −78 °C; (b) methyl acrylate, THF, −78 °C; (c) methyl acrylate, MeOH, DBU, 40 °C, 36 h; (d) MeOH, $MeNH_2$, RT, 24 h; (e) $AlMe_3$, isobutyl amine complex, toluene, 90 °C, 12 h; (f) H^+; (g) NH_2NH_2, MeOH, RT, 24 h; (h) $NaNO_2$, AcOH, 5N HCl, DCM; (i) R_1NH_2, Et_3N, DMAP, RT.

The tetra-acrylamide oligomer **1e** having terminal *gem*-disubstitution was obtained in high yield, following a different strategy using Mukaiyama–Michael addition[9] as a key reaction step (Scheme 2). Tetra-*n*-butylammonium bibenzoate (TBABB)-catalyzed[10] bis-conjugate addition of silyl ketene acetal **7** to the α,β-unsaturated bis-olefin **6**, obtained in three steps from methyl acrylate through a Baylis–Hillman protocol,[11] furnished cleanly the terminal *gem*-disubstituted tetra-ester **8** in 88% yield. Presumably due to high steric hindrance, the amidation of the terminal *gem*-disubstituted tetra-ester **8** could be carried out only under drastic conditions (steel bomb, 75 °C, 4 days).

The oligomers **1a–e** were highly resistant to yield to crystal formation under ordinary conditions used for crystallizing small organic compounds, as most of them formed gels in various organic solvents (SEM images in ESI†). However, **1a** and **1e** could be forced to yield crystals suitable for single crystal X-ray diffraction studies by slow evaporation of a mixture of water and ethylene glycol, a condition frequently used for crystallizing



Scheme 2 Synthesis of **1e**. Reagents and conditions: (a) CH_2O (37 wt.%), aq. Et_3N, 60 °C, 6 h; (b) 48% HBr, H_2SO_4, DCM, 12 h; (c) methyl acrylate, DABCO, RT, 7 days; (d) TBABB (3 mol%), THF, RT, 1 h; (e) 1 N HCl : THF (1:9); (f) MeOH, $MeNH_2$, steel bomb/75 °C, 4 days.

proteins.[12] **1a** crystallized in triclinic space group *P*-1. Analysis of the single crystal X-ray diffraction data revealed a fascinating self-assembled arrangement of the isotactic *N*-methyl acrylamide tetramer **1a** in the solid state (Fig. 2).

The self-complementary individual strands of **1a** undergo self-assembly through intermolecular N–H···O=C hydrogen bonding interactions forming 16-membered ring hydrogen-bonded networks. The hydrogen-bonding interactions are stronger with D–H···A distances [d(N–H···O)] in the range 1.95–1.99 Å and the D–H···A angle [∠(N–H···O)] in the range 173–179°. The *N*-methyl groups of the adjacent self-assembling modules are uniformly separated by the *a*-axis translation (4.897 Å). Further, we also note the fraying of the terminal amide groups, presumably due to the absence of further substitution at the terminal α-methylene carbons connecting them.[13] The isotactic *N*-methyl acrylamide oligomer **1e**, having *gem*-disubstitution at both the terminal methylene carbons, crystallized in orthorhombic space group $P2_12_12_1$. Analysis of the crystal data revealed a self-assembled arrangement of the self-complementary individual molecules through intermolecular N–H···O=C hydrogen-bonding interactions forming 16-membered ring hydrogen-bonded networks, as found in **1a**. However, unlike in **1a**, fraying of both the terminal amide groups is prevented in **1e**, apparently due to *gem*-disubstitution at the terminal methylene carbons (Thorpe–Ingold effect).[14]

Presumably due to supramolecular self-assembly,[15] the isotactic *N*-acrylamide oligomers **1a–e** were highly insoluble in non-polar solvents under ambient conditions, which impeded the solution-state NMR investigations of the self-assembling process in such solvents. However, the terminal *gem*-disubstituted isotactic oligomer **1e** readily dissolved in polar solvents such as water and

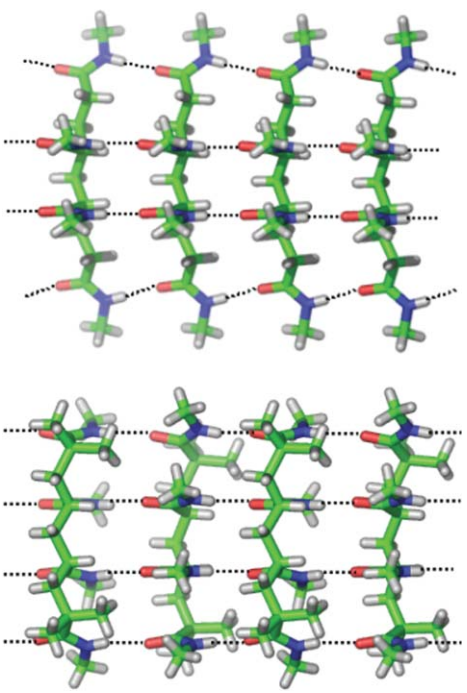


Fig. 2 Single crystal X-ray structures of **1a** (top) and **1e** (bottom) showing arrangement of the individual strands in the hydrogen-bonded self-assembled sheet-like supramolecular network. H-bonding is highlighted in black dots. Colour: C green, H grey, N blue, O red.

DMSO, under ambient conditions. The one-dimensional ^{1}H NMR (500 MHz) spectra of **1e**, in H_2O : D_2O, (90 : 10, v/v), and DMSO-d_6 were highly dispersed and showed a single set of well-resolved signals, suggesting the existence of a single conformer in these solvents. The observed nOe pattern in two-dimensional nuclear Overhauser spectroscopy (2D NOESY, Fig. 3) of **1e** (detailed data in ESI†) in both the solvents strongly suggested the prevalence of its solid-state extended conformation (of the individual molecule) in solution-state as well. Interestingly, the nOe patterns in both the solvents had a close resemblance to one another, implying that **1e** displays similar conformational features in both DMSO and H_2O.

In summary, the result reported herein constitutes the first unequivocal evidence of the ability of isotactic *N*-alkyl acrylamide oligomers to undergo hydrogen-bond-mediated supramolecular self-assembly, even under a non-propitious environment, forming robust sheet structures that are reminiscent of protein β-sheets.[5] The findings, supported unambiguously by single crystal X-ray diffraction (see crystal data‡) and 2D NOESY studies, would fuel intense research interests in delineating the exact correlation between poly-*N*-acrylamide tacticity, conformation, and hydrogen bonding propensities. In addition, this finding also provides new insights that can be used to guide future attempts to engineer oligo-*N*-acrylamide-based novel protein secondary structural mimics that exclusively employ side chain amide groups for their secondary structure stabilization.[5] Interestingly, a prominent question pops up eventually: what would have been the conformation and consequently the hydrogen-bonding arrangement if the oligo-*N*-alkyl acrylamide carbon backbone had the amide side chains in an 1–3 *anti* (syndiotactic) configuration? In order to answer such a question unambiguously, it is essential to generate *N*-alkyl acrylamide oligomers having the amide side chains in an 1,3 *anti* configuration; a work that we are rigorously pursuing at present.

AK thanks CSIR, New Delhi for a research fellowship.

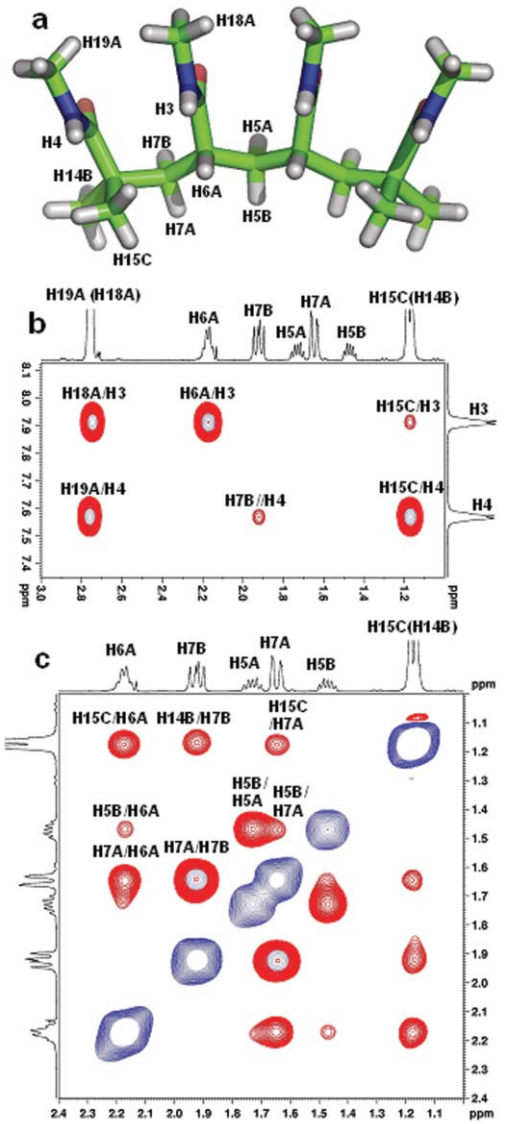


Fig. 3 Partial 2D NOESY spectra (500 MHz) of **1e** in H_2O : D_2O (90 : 10). For aiding spectral interpretation, the crystal structure of **1e** with selected labelled atoms is also shown. (a) Single crystal X-ray structure. (b) Partial spectrum showing nOe of NH *vs.* aliphatic region. (c) Partial spectrum showing nOe in aliphatic region (1.1–2.4 ppm).

Notes and references

‡ CCDC 273802 (**1a**) and 273803 (**1e**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b601317a

1 T. Miyata, N. Asami and T. Uragami, *Nature*, 1999, **399**, 766; I. L. Dale, R. P. Huber, M. A. Manginell, B. K. Samara and C. B. Bruce, *Science*, 2003, **301**, 352; R. Langer and D. A. Tirrell, *Nature*, 2004, **428**, 487; J. J. D. de Jong, P. R. Hania, A. Pugzlys, L. N. Lucas, M. de Loos, R. M. Kellog, B. L. Feringa, K. Duppen and J. H. van Esch, *Angew. Chem., Int. Ed.*, 2005, **44**, 2373.

2 W. Kauzmann, *Nature*, 1987, **325**, 763–764.

3 H. G. Schild, *Prog. Polym. Sci.*, 1992, **17**, 163; T. Nakano and Y. Okamoto, *Chem. Rev.*, 2001, **101**, 4013; J. F. Lutz, D. Neugebauer and K. Matyjaszewski, *J. Am. Chem. Soc.*, 2003, **125**, 6986.

4 Y. Zhang, S. Furyk, D. E. Bergbreiter and P. S. Cremer, *J. Am. Chem. Soc.*, 2005, **127**, 14505; M. V. Deshmukh, A. A. Vaidya, M. G. Kulkarni, P. R. Rajamohanan and S. Ganapathy, *Polymer*, 2000, **41**, 7951; M. V. Badiger, P. R. Rajamohanan, P. M. Suryavanshi, S. Ganapathy and R. A. Mashelkar, *Macromolecules*, 2002, **35**, 126.

5 R. P. Cheng, S. H. Gellman and W. F. DeGrado, *Chem. Rev.*, 2001, **101**, 3219; J. Venkatraman, S. C. Shankaramma and P. Balaram, *Chem. Rev.*, 2001, **101**, 3131.

6 Several clever strategies have been attempted, mainly by Porter's group, to obtain telomers of pre-defined length by using radical reactions; but without success, since in most of the cases, the dimers were the only isolable products. See: N. A. Porter, G. S. Miracle, S. M. Cannizzaro, R. L. Carter, A. T. McPhail and L. Liu, *J. Am. Chem. Soc.*, 1994, **116**, 10255; N. A. Porter, R. L. Carter, C. L. Mero, M. G. Roepel and D. P. Curran, *Tetrahedron*, 1996, **52**, 4181.

7 G. H. Posner and E. M. Shulman-Roskes, *J. Org. Chem.*, 1989, **54**, 3514.

8 D. R. Sidler, T. C. Lovelace, J. M. McNamara and P. J. Reider, *J. Org. Chem.*, 1994, **59**, 1231.

9 E. V. Gorobets, M. S. Miftakhov and F. A. Valeev, *Russ. Chem. Rev.*, 2000, **69**, 1001.

10 R. Gnaneshwar, P. P. Wadgaonkar and S. Sivaram, *Tetrahedron Lett.*, 2003, **44**, 6047.

11 D. Basavaiah, D. S. Sharada, N. K. Baran and R. M. Reddy, *J. Org. Chem.*, 2002, **67**, 7135.

12 Q. Huang, M. Teng and L. Niu, *Acta Crystallogr., Sect. D: Biol. Crystallogr.*, 1999, **55**, 1444.

13 M. E. Jung and G. Piizzi, *Chem. Rev.*, 2005, **105**, 1735.

14 C. Toniolo, M. Crisma, F. Formaggio and C. Peggion, *Biopolymers*, 2001, **60**, 396.

15 J. P. Mathias, E. E. Simanek and G. M. Whitesides, *J. Am. Chem. Soc.*, 1994, **116**, 4326; K. Damodaran, G. J. Sanjayan, P. R. Rajamohanan, S. Ganapathy and K. N. Ganesh, *Org. Lett.*, 2001, **3**, 1921.