Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7951–7955

Formation of a one-dimensional helical alignment of water molecules within a water-mediated supramolecular helix using molecular self-assembly of a water-soluble short pseudopeptide

Samit Guha,[a] Michael G. B. Drew[b] and Arindam Banerjee[a,*]

[a]*Department of Biological Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India*
[b]*School of Chemistry, The University of Reading, Whiteknights, Reading RG6 6AD, UK*

Received 23 June 2006; revised 23 August 2006; accepted 31 August 2006
Available online 26 September 2006

Abstract—The reported pseudopeptide **1** adopts a double turn molecular conformation consisting of an intramolecular 9-membered turn together with a water-mediated 11-atom turn and this pseudopeptide **1** self-assembles to form a water-mediated supramolecular helical structure with internal water molecules, which are aligned in a 1D helical array.

Helicity is an important property and it is ubiquitous in nature. It is present in many biological systems including the tobacco mosaic virus (TMV) coat protein assembly, α-helical structures in proteins, the collagen triple helix and the DNA double helical structure. Helicity can be induced in artificial chemical systems using suitable molecular building blocks. Significant efforts have been directed to construct supramolecular helices in non-natural systems using conformational restriction of macromolecules, hydrogen bonding functionalities, and metal ion chelation.[1] Water can also play a key role in forming and stabilizing the supramolecular helical architecture through hydrogen bonding.[2] Water is of great interest to chemists and biologists as it is the basis of life and it plays a crucial role in many biological and chemical processes.[3] Among different types of water clusters,[4] one-dimensional water chains[5] have attracted a great deal of attention because of their vital role in the biological transport of water, protons and ions.[3] The transport of water molecules across cell membranes in biological systems is significantly enhanced by the presence of aquaporins[6] through the arrangement of a single chain of water molecules. One-dimensional helical arrays of water molecules are rare in synthetic crystal hosts. There are a few examples of one-dimensional helical chains of water molecules inside a helical coordination polymer.[7] These examples include encapsulation of a hydrogen-bonded 1D helical chain of water molecules inside a staircase-like helical coordination polymeric architecture of a Ni^{2+} complex,[7a] a 1D helical chain of hydrogen-bonded water molecules with both handedness within a dicopper(II) containing supramolecular helical coordination polymer[7b] and a 1D water chain inside a supramolecular helix of a Zn^{2+} complex.[7c] However, a helical alignment of water molecules inside a water-mediated supramolecular helical architecture without any metal ion is barely reported in the literature. Parthasarathi and co-workers have examined a series of synthetic tripeptides[2] that form extended helical structures with intervening water molecules between two consecutive peptide molecules and they have demonstrated the hydrated helix pattern in crystals. However, water molecules are not entrapped within these water-mediated supramolecular helical channels. In this report, we present the formation of a one-dimensional helical alignment of water molecules within a water-mediated supramolecular helix using molecular self-assembly of a water-soluble pseudopeptide **1**.

Pseudopeptide **1** bis(*N*-α-amido-α-aminoisobutyric acid)-1,1-cyclopropane dicarboxylate was synthesized by conventional solution phase methodology,[8] purified, characterized and studied in detail. Colorless tetragonal

Keywords: Supramolecular chemistry; Pseudopeptide; Turn; Helix.
* Corresponding author. Tel.: +91 33 24734971; fax: +91 33 24732805; e-mail: bcab@mahendra.iacs.res.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.08.132

crystals of pseudopeptide **1** suitable for X-ray diffraction study (Fig. 1a and b)[9] were obtained from aqueous solution by slow evaporation. Pseudopeptide **1** crystallizes in space group I-4 with two water molecules in the asymmetric unit. We have used the conformationally constrained Aib residue to enhance crystallinity and to increase the helical nature of the pseudopeptide backbone. Dihedral angles around the C^{α} of Aib [$\phi 1 = -57.9$ (4)°, $\psi 1 = 150.6$ (3)°, $\phi 2 = 53.3$ (4)°, $\psi 2 = 34.5$ (4)°] fall within the helical region of the Ramachandran plot[10] except for the $\psi 1$ value of one of the Aib residues which deviates from the ideal helical ψ value (Table 1). Thus the overall molecular backbone of this pseudopeptide adopts a folded structure with the formation of an intramolecular hydrogen-bonded 9-membered ring conformation[11] (N3–H3···O91 angle 173°) which is one atom shorter than the usual 10-membered hydrogen-bonded β-turn conformation[12] and it also forms an 11-membered[13] water-mediated C6═O6···H22–O200–H21···O12═C1 hydrogen-bonded folded turn conformation (Fig. 2). The introduction of this hydrogen-bonded water molecule can perturb the helicity of one of the Aib residues and it is manifested by the adoption of the non-helical value of $\psi 1$. The hydrogen bonding parameters are listed in Table 2. The pseudopeptide **1**·$2H_2O$ is self-assembled to form a 1D helical array of water molecules within a water-mediated supramolecular helix along the crystallographic *a* axis (Fig. 3a and b). Between two water molecules in the asymmetric unit, H_2O(100) is involved in the outer supramolecular helix formation and H_2O(200) is involved in the inner one-dimensional helix formation. The outer supramolecular helix is formed through O100–H101(water)···O92═C9(carboxyl), O91–H91(carboxyl)···O100(water) and N7–H7···O4═C4(amide) hydrogen bonds and shows a hydrated helix pattern with a helical pitch length of 9.52 Å (Fig. 4). The interior of the water-mediated supramolecular helical channel is hydrophilic due to the presence of backbone –CONH moieties and –COOH groups with approximate dimensions of 6.36 × 5.44 Å. This water-mediated pseudopeptide based

Table 1. Selected torsional angles (deg) of pseudopeptide **1**

Torsion angle	Value (deg)
C4–N3–C2–C1 ($\phi 1$)	−57.9 (4)
N3–C2–C1–O11 ($\psi 1$)	150.6 (3)
C6–N7–C8–C9 ($\phi 2$)	53.3 (4)
N7–C8–C9–O91 ($\psi 2$)	34.5 (4)

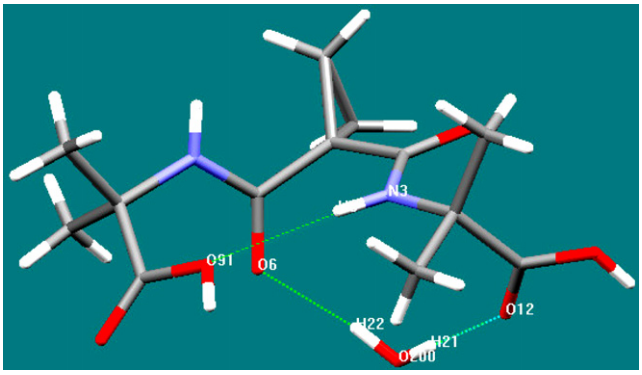

Figure 2. Molecular conformation of pseudopeptide **1** showing a 9-membered intramolecular hydrogen bond and an 11-membered water-mediated hydrogen bond. The other water molecule present in the asymmetric unit is omitted for clarity. Hydrogen bonds are shown as dotted lines.

Table 2. Intramolecular and intermolecular hydrogen bonding parameters of pseudopeptide **1** in the crystal state

D–H···A[a]	H···A (Å)	D···A (Å)	D–H···A (deg)
N3–H3···O91	2.40	3.256 (5)	173
N7–H7···O4 (a)	2.03	2.882 (5)	174
O11–H11···O200	1.77 (4)	2.597 (5)	171 (5)
O200–H21···O12 (b)	1.96 (6)	2.813 (6)	179 (7)
O200–H22···O6 (b)	1.95 (6)	2.795 (5)	162 (5)
O91–H91···O100 (c)	1.81 (4)	2.614 (5)	167 (4)
O100–H100···O6 (d)	2.34 (6)	3.194 (5)	165 (4)
O100–H101···O92	2.14 (6)	2.882 (5)	166 (6)

[a] Symmetry elements: (a) $-1/2 + y$, $1/2 - x$, $1/2 - z$; (b) $1/2 - x$, $3/2 - y$, $1/2 + z$; (c) y, $1 - x$, $1 - z$; (d) $1 - x$, $1 - y$, z.

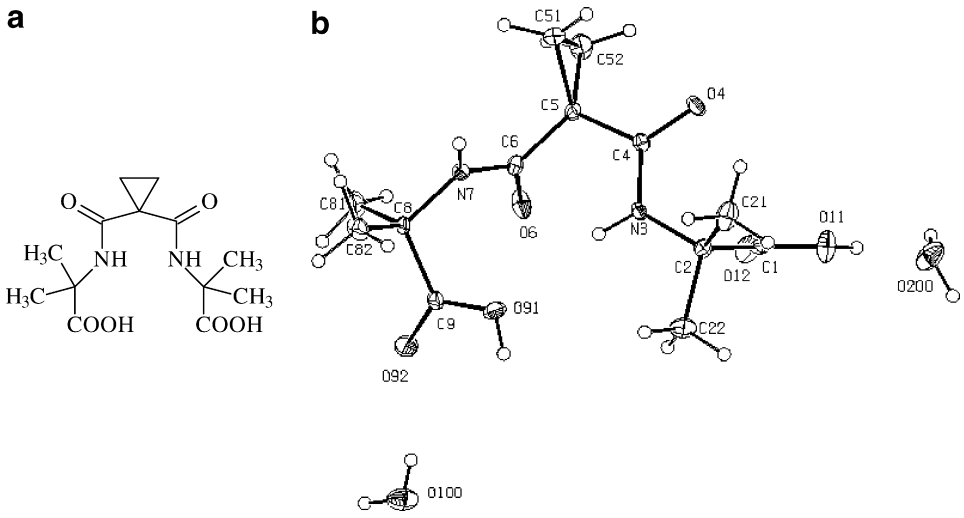

Figure 1. (a) Schematic representation of pseudopeptide **1**. (b) ORTEP diagram with atomic numbering scheme of pseudopeptide **1**. Thermal ellipsoids are shown at 30% probability level. Two water molecules are present in the asymmetric unit.

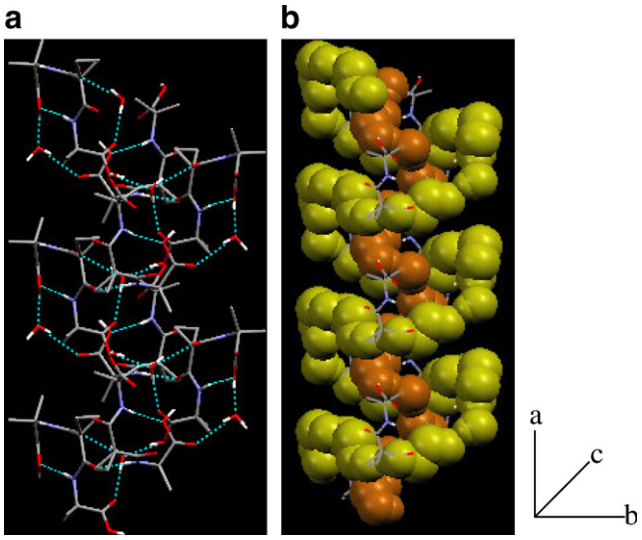

Figure 3. Capped-stick model (a) and space-filling model (b) of a 1D helical array of water molecules within a water-mediated supramolecular helix along the crystallographic *a* axis. Hydrogen bonds are shown as dotted lines. The side-chain hydrogen atoms of Aib and cyclopropyl groups are omitted for clarity.

supramolecular helical structure acts as a host to stabilize the one-dimensional helical array of water molecules. The exterior of the outer supramolecular helix is hydrophobic due to the presence of the side chains of Aib and cyclopropyl groups. The entrapped 1D helical array of water molecules within the water-mediated supramolecular helical channel is stabilized through C1═O12(carboxyl)···H21–O200(water), O11–H11(carboxyl)···O200(water) and C6═O6(carbonyl)···H22–O200(water) hydrogen bonds (Fig. 5). It is interesting to note that the oxygen atoms of the encapsulated water molecules [$H_2O(200)$] are in relatively close contact and are not bridged by a hydrogen atom. This structure differs from the aquaporin water channel, because both

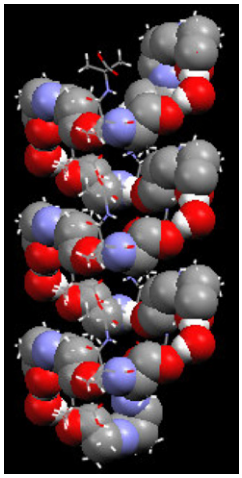

Figure 4. Space-filling representation of the water-mediated outer supramolecular helical assembly of pseudopeptide **1** using hydrogen bonding with a helical pitch length of 9.52 Å. Nitrogen atoms are blue, oxygen atoms are red and carton atoms are grey.

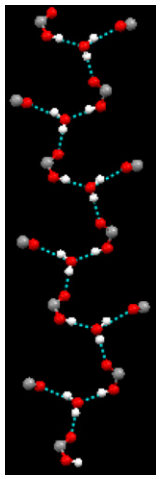

Figure 5. The entrapped 1D helical array of water molecules [$H_2O(200)$], which are stabilized through hydrogen bonding with the wall of the outer helical channel.

hydrogen atoms of $H_2O(200)$ point towards the wall of the outer helical channel, rather than to the neighboring water molecules, but each water molecule in the aquaporin water channel forms one hydrogen bond with the wall of the protein and one with an adjacent water molecule.[6] Antonijevic and his co-workers also reported a helical channel, occupied by water molecules, which forms a one-dimensional chain in which water molecules are not bridged via hydrogen bonds.[7c] This result is similar to that found in the present work with a non-hydrogen-bonded helical array of trapped water molecules. However, the outer helix in their study was not a water-mediated supramolecular helix as found here. Pseudopeptide **1** also forms a hydrophobic cleft using four pseudopeptide molecules through N7–H7···O4═C4 intermolecular hydrogen bonds around the crystallographic *c* axis with S_4 symmetry and approximate dimensions of 3.65×3.65 Å (see Supplementary data, Fig. 5). The crystal structure further revealed that this supramolecular architecture forms higher order supramolecular arrays of open framework-like architecture around the crystallographic *c* axes (see Supplementary data, Fig. 6) through hydrogen bonding and other non-covalent interactions.

We have studied the thermal stability of the water molecules in pseudopeptide **1**·$2H_2O$ by TGA–DTA (TGA: thermogravimetric analysis, DTA: differential thermal analysis) experiments (Fig. 6). The TGA experiment showed that two water molecules were removed in a single step with a weight loss of 10.96% in the temperature range 25–125 °C. The observed value compares well with the theoretical value of 10.71% for the loss of two water molecules, which is in good agreement with the X-ray crystal structure. Decomposition of the framework starts at ~230 °C and no chemical decomposition was observed between these temperatures. The DTA plot shows one endotherm centered at ~80 °C due to the loss of two water molecules. Elemental analysis also showed that two water molecules were present in the asymmetric unit.

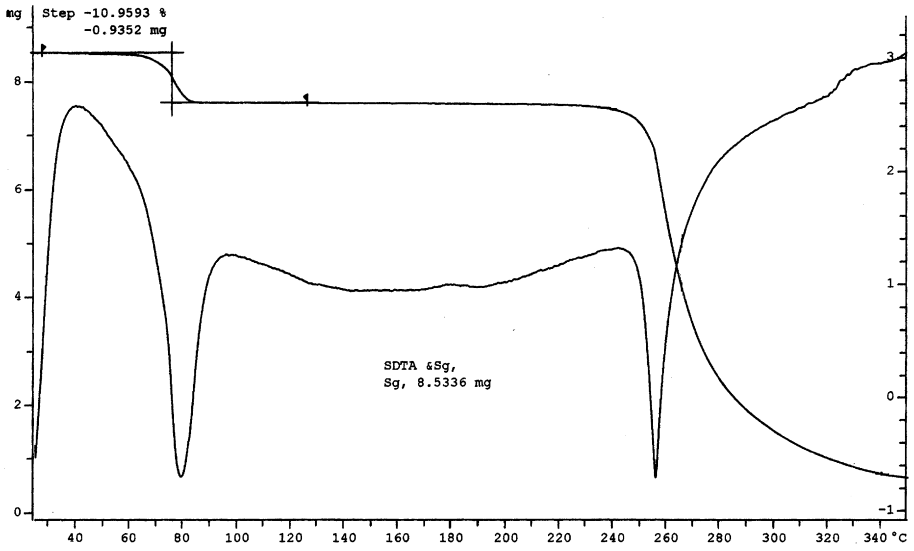

Figure 6. TGA–DTA plot showing the loss of two water molecules in a single step with a weight loss of 10.96%.

In conclusion, we have presented the formation of a 1D helical alignment of water molecules within a water-mediated supramolecular helix through molecular self-assembly of the water-soluble pseudopeptide **1** by way of various types of intra and intermolecular hydrogen bonds. A remarkable feature is that the reported water-soluble pseudopeptide **1** forms a water-mediated 11-membered hydrogen-bonded folded turn conformation which may allow deviation from the helical value of one of the Aib residues ($\psi 1$). Another noteworthy feature is that water molecules play a crucial role in forming and stabilizing both inner and outer helical frameworks. This water-mediated supramolecular outer helical structure forms a nanoscopic hole of dimensions 6.36×5.44 Å, which is occupied by a helical alignment of water molecules stabilized by hydrogen bonding interactions with the outer supramolecular helix. The loss of two water molecules at 80 °C indicates that the structure is quite stable and that the encapsulated water molecules are tightly held.

Acknowledgements

This work was supported by DST, New Delhi, India, Project No. (SR/S5/OC-29/2003). We thank the EPSRC and the University of Reading, UK, for funds for Marresearch Image Plate Systems. S.G. wishes to acknowledge the CSIR, New Delhi, India, for financial assistance.

Supplementary data

Syntheses, characterization and figures showing the hydrophobic cleft using four pseudopeptide molecules and the higher order supramolecular array of pseudopeptide **1** are included in the supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.132.

References and notes

1. (a) Lehn, J. M. *Supramolecular Chemistry*; VCH: Weinhein, 1995; pp 1–271; (b) Albrecht, M. *Chem. Rev.* **2001**, *101*, 3457–3497; (c) Brunsveld, L.; Folmer, B. J.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071–4097; (d) Piguet, C.; Bernardinelli, G.; Hopfgartner, G. *Chem. Rev.* **1997**, *97*, 2005–2062.
2. (a) Parthasarathy, R.; Chaturvedi, S.; Go, K. *Proc. Natl. Acad. Sci. U.S.A* **1990**, *87*, 871–875; (b) Ramasubbu, N.; Parthasarathy, R. *Biopolymers* **1989**, *28*, 1259–1269.
3. (a) Ludwig, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1808–1827; (b) Konozo, D.; Yasui, M.; King, L. S.; Agre, P. *J. Clin. Invest.* **2002**, *109*, 1395; (c) Roux, B.; MacKinnon, R. *Science* **1999**, *285*, 100–102.
4. (a) Pal, S.; Sankaran, N. B.; Samanta, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1741–1743; (b) Doedens, R. J.; Yohannes, E.; Khan, M. I. *Chem. Commun.* **2002**, 62–63; (c) Moorthy, J. N.; Natarajan, R.; Venugopalan, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3417–3420; (d) Atwood, J. L.; Barbour, L. J.; Ness, T. J.; Raston, C. L.; Rastoon, P. L. *J. Am. Chem. Soc.* **2001**, *123*, 7192–7193; (e) Barbour, L. J.; Orr, W. G.; Atwood, J. L. *Chem. Commun.* **2000**, 859–860; (f) Zuhayra, M.; Kampen, W. U.; Henze, E.; Soti, Z.; Zsolnai, L.; Huttner, G.; Oberdorfer, F. *J. Am. Chem. Soc.* **2006**, *128*, 424–425; (g) Oxtoby, N. S.; Blake, A. J.; Champness, N. R.; Wilson, C. *Chem. Eur. J.* **2005**, *11*, 4643–4654; (h) Lakshminarayanan, P. S.; Suresh, E.; Ghosh, P. *J. Am. Chem. Soc.* **2005**, *127*, 13132–13133.
5. (a) Sidhu, P. S.; Udachin, K. A.; Ripmeester, J. A. *Chem. Commun.* **2004**, 1358–1359; (b) Dong, Y. B.; Zhao, X.; Tang, B.; Wang, H. Y.; Huang, R. Q.; Smith, M. D.; Loye, H. C. *Chem. Commun.* **2004**, 220–221; (c) Cheruzel, L. E.; Pometun, M. S.; Cecil, M. R.; Mashuta, M. S.; Wittebort, R. J.; Buchanan, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5452–5455; (d) Birkedal, H.; Schwarzenbach, D.; Pattison, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 754–756; (e) Hummer, G.; Rasaiah, J. C.; Noworyta, J. P. *Nature* **2001**, *414*, 188–190.
6. (a) Mitsuoka, K.; Murata, K.; Walz, T.; Hirai, T.; Agre, P.; Heymann, J. B.; Engel, A.; Fujiyoshi, Y. *J. Struct. Biol.* **1999**, *128*, 34–43; (b) Agre, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4278–4290.
7. (a) Sreenivasulu, B.; Vittal, J. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5769–5772; (b) Mukherjee, A.; Saha, M. K.;

Nethaji, M.; Chakravarty, A. R. *Chem. Commun.* **2004**, 716–717; (c) Fei, Z.; Zhao, D.; Geldbach, T. J.; Scopelliti, R.; Dyson, P. J.; Antonijevic, S.; Bodenhausen, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2–7.

8. Pseudopeptide **1** was synthesized by conventional solution phase methodology (Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: New York, 1984; pp 1–282). Couplings were mediated by dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/HOBt). Methyl ester deprotection was performed via saponification. The final compound was fully characterized by 300 MHz ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, DEPT 135, mass spectrometry and IR spectroscopy. Yield = 2.7 g (9 mmol, 90%); Anal. Calcd for $C_{13}H_{20}N_2O_6{\cdot}2H_2O$ (336) C, 46.42; H, 7.19; N, 8.33. Found: C, 46.40; H, 7.23; N, 8.31. Mp 235 °C; IR (KBr): 3606, 3459, 3377, 3263, 1725, 1659, 1627, 1547 and 1536 cm^{-1}; δ_H (300 MHz; DMSO-d_6): 12.21 (–COOH, 2H, br); 8.21 (Aib NH, 2H, s); 1.34 (Aib C$^\beta$ Hs, 12H, s); 1.14 (cyclopropyl Hs, 4H, s); δ_C (300 MHz; DMSO-d_6): 176.4 (C of amide CO); 170.2 (C of acid CO); 56.2 (α-C of Aib); 29.9 (C-1 of cyclopropyl); 25.6 (β-C of Aib); 15.6 (C-2 of cyclopropyl); DEPT 135 (300 MHz; DMSO-d_6): δ_C 25.639 (positive), 15.634 (negative); mass spectral data HRMS (ESI) $(M+Na)^+ = 323.5077$, $(M+K)^+ = 339.4685$, $(2M+Na)^+ = 623.2576$, $M_{calcd} = 300.3080$.
9. Single crystal X-ray data for $C_{13}H_{20}N_2O_6{\cdot}2H_2O$ (pseudopeptide **1**), $M = 336.34$, tetragonal, space group I-4, $a = 18.75$ (2), $b = 18.75$ (2), $c = 9.518$ (9) Å, $V = 3347$ (6) Å^3, $Z = 8$, $\mu = 0.111$ mm^{-1}, $\rho_{calcd} = 1.335$ g cm^{-3}, $F(000) = 1440$. Diffraction data were measured for pseudopeptide **1**·2H$_2$O with MoKα ($\lambda = 0.71073$ Å) radiation at 293 K using a Marresearch Image Plate. The crystal was positioned at 70 mm from the image plate and 95 frames were measured at 2° intervals with a counting time of 2 min to give 8040 independent reflections. Data analysis was carried out with the XDS program.[14] The structure was solved by direct methods using the SHELXS-97[15] program. The water molecules were located from difference Fourier maps. Refinement was carried out with a full matrix least squares method against F^2 using SHELXL-97.[16] The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The structure was refined on F^2 using SHELXL. The final R values were $R1$ 0.0622 and $WR2$ 0.1311 for 2796 data with $I > 2\sigma(I)$. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre with reference number CCDC 607544.
10. Ramachandran, G. N.; Ramakrishnan, C.; Sasisekaran, V. *J. Mol. Biol.* **1963**, *7*, 95–99.
11. (a) Dado, G. P.; Desper, J. M.; Holmgren, S. K.; Rito, C. J.; Gellman, S. H. *J. Am. Chem. Soc.* **1992**, *114*, 4834–4843; (b) Dado, G. P.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 8630–8632; (c) Liang, G. B.; Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 3994–3995.
12. (a) Das, A. K.; Banerjee, A.; Drew, M. G. B.; Ray, S.; Haldar, D.; Banerjee, A. *Tetrahedron* **2005**, *61*, 5027–5036; (b) Maji, S. K.; Haldar, D.; Drew, M. G. B.; Banerjee, A.; Das, A. K.; Banerjee, A. *Tetrahedron* **2004**, *60*, 3251–3259; (c) Haldar, D.; Banerjee, A.; Drew, M. G. B.; Das, A. K.; Banerjee, A. *Chem. Commun.* **2003**, 1406–1407.
13. (a) Weber, K.; Ohnmacht, U.; Gmeiner, P. *J. Org. Chem.* **2000**, *65*, 7406–7416; (b) Gung, B. W.; Mackay, J. A.; Zou, D. *J. Org. Chem.* **1999**, *64*, 700–706; (c) Gardner, R. R.; Liang, G. B.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 1806–1816.
14. Kabsch, W. *J. Appl. Crystallogr.* **1988**, *21*, 916–932.
15. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.
16. Sheldrick, G. M. *SHELX97 Program for Crystallography Refinement*; University of Göttingen: Germany, 1997.