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Low Molecular Weight Organogelators from Self-assembling Synthetic Tripeptides With Coded Amino Acids: Morphological, Structural, Thermodynamic and Spectroscopic Investigations

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A series of self-assembling terminally blocked tripeptides (containing coded amino acids) form gels in various aromatic solvents including benzene, toluene, xylenes at low concentrations. However these tripeptides do not form gels in aliphatic hydrocarbons like *n*-hexane, cyclohexane, *n*-decane *etc*. Morphological studies of the dried gel indicate the presence of an entangled fibrous network, which is responsible for gelation. Differential scanning calorimetric (DSC) studies of the gels produced by peptide 1 clearly demonstrates thermoreversible nature of the gel and tripeptide–solvent complex may be produced during gel formation. FT-IR and ^{1}H NMR studies of the gels demonstrate that an intermolecular hydrogen-bonding network is formed during gelation. Single crystal X-ray diffraction studies for peptides 1, 2 and 3 have been performed to investigate the molecular arrangement that might be responsible for forming the fibrous network of these self-assembling peptide gelators. It has been found that the morph responsible for gelation of peptides 1, 2 and 3 in benzene is somewhat different from that of its xerogel.

Keywords: Gel; Self-assembly; Peptide; Fibrillar network

INTRODUCTION

Low molecular weight organogelators [1–4] belong to a distinct class of soft material in which three-dimensional networks are formed through molecular self-assembly of the gelator compounds and the gel network is able to encapsulate a large volume of organic solvents under suitable conditions. These gelator molecules are self-associated using various non-covalent interactions including hydrogen bonding interactions [5–25], π–π stacking [26–29], metal coordination [30–34], and van der Waals interactions [35–47] to form the network structure suitable for gelation. This is in contrast to the chemical gels where the three-dimensional network is formed through covalent linkage. Thermo-reversibility is a characteristic feature of low molecular mass organogels and this property is generally absent in chemical gels. Discovery and development of low molecular weight organogelators are particularly important due to their applications in structure directing agents [48–51], stabilization of organic photochromatic material [52], light-harvesting materials [53,54], drug delivery systems [2], dental composite carriers [55], and in preparing dye sensitized solar cells [56] among others [57–59]. Self-assembled gelators are classified into two categories based on their driving force;—hydrogen bond-based gelators [5–25] and non-hydrogen bond-based gelators [26–47]. DDOA (2,3-bis-n-decyloxyanthracene) [38,39], cholesterol derivatives [40–43], fluorinated hydrocarbons [44], alkynes [45] and other hydrocarbons [46,47], oligo(p-phylenevinylene) based molecules [27–29], trifluoromethyl-based cyanostilbene derivatives [26] are non-hydrogen bond-based gelators, whereas saccharides [5,6], amides [7–9], lysine based

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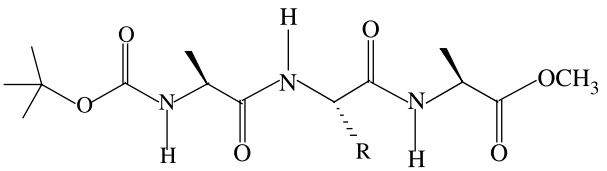
compounds [10–12], urea derivatives [13] carbamates [14,15], bile acid based gelators [16,17], organic salts of carboxylic acids [18,19], fatty acid derived amino acid based compounds [20–22], peptidomimetic cyclophanes [23,24], oligopeptides [60–63] and porphyrin derivatives [25] bearing suitable hydrogen bonding functionality are representatives of the hydrogen bond-based gelators.

It has been reported that many synthetic peptides form supramolecular structures such as β-sheet, ribbons, tapes and fibers through molecular self-assembly [64–68]. These types of three-dimensional structures may encapsulate the organic liquids under specific conditions and lead to the formation of gel-like phases [69,70]. Upon heating, the solubility of the low molecular weight compounds increased and the three-dimensional network disappeared in the liquid and re-gel on cooling below the gelation temperature (T_{gel}) [71]. There are some examples of oligopeptide based low molecular weight oganogelators [60–63].

In our previous study, we reported that low molecular weight synthetic peptides containing non-coded amino acids exhibit supramolecular double columnar sheet-like crystal structures and form thermoreversible gels in various organic solvents [61]. During the course of our investigations of the self-assembling tendency of short peptide-based molecules, we found that terminally protected synthetic peptides **1**, **2** and **3** Boc-A-X-A-OMe (where A = Alanine, X = Valine, Leucine, Isoleucine) containing natural amino acids (Fig. 1) form thermo-reversible gels in various aromatic organic solvents including benzene, toluene, 1,2-dichlorobenzene (*o*-DCB) and xylenes. Gelator peptides were studied by differential scanning calorimetry, ^{1}H NMR, FT-IR spectroscopy and transmission electron microscopic techniques. Single crystals of peptides **1**, **2** and **3** suitable for X-ray crystallography were obtained from methanol–water solution by slow evaporation and the crystal structures of these gelators are presented here to probe the types of molecular self-assembly that might be responsible for gelation.



Peptide **1**: R = $CH(CH_3)_2$
Peptide **2**: R = $CH((CH_3)(C_2H_5))$
Peptide **3**: R = $CH_2CH(CH_3)_2$

FIGURE 1 Chemical structures of peptides 1–3.

RESULTS AND DISCUSSION

Morphology and Characterization

The tripeptides **1**, **2** and **3** are readily soluble in different organic solvents with increasing temperature and when the solutions were allowed to cool at room temperature, gels are obtained within a few minutes. The gelating propensity of these reported tripeptides (Fig. 1) in a wide range of organic solvents including toluene, benzene, *ortho*-dichlorobenzene (*o*-DCB), *m*-xylene and *p*-xylene was studied by dissolving a small amount (1–10% w/v) of compounds in 1 mL of the desired solvent under heating. Upon cooling to room temperature (30°C), the complete volume of the respective solvent is immobilized and formed gel. The gelation was confirmed by the inverted test-tube method [60]. The results of gelation studies in various solvents are summarized in Table I. In *o*-DCB, peptides **1** and **3** produce gels at lower concentrations (~ or >2% w/v) and in solvents like *m*-xylene and *p*-xylene peptides **1**, **2** and **3** form gels at concentration ~ or >7% w/v. The gels reported in Table I are stable at room temperature.

Transmission electron microscopic (TEM) studies of the dried gels were performed to examine their morphologies. The TEM images of xerogel obtained from peptide **1** in benzene, peptide **2** in *o*-DCB and peptide **3** in *m*-xylene show an entangled fibrillar network (Fig. 2a–c respectively). The average fibrillar diameter varies from ~45 to 200 nm in all these nanofibrils that entrap these solvent molecules very effectively.

The thermal properties of the tripeptides gels in benzene (13% w/v) have been investigated by differential scanning calorimetry (DSC) (Fig. 3). For peptide **1**, the curves show one endothermic transition at $T \approx 91.9$°C on heating and one exothermic transition at $T \approx 30.1$°C on cooling (inset of Fig. 3). This thermogram indicates the

TABLE I Gelation properties of peptides **1–3** in organic solvents[a]

Solvent	**1**	**2**	**3**
(i) Ethyl acetate	S	S	S
(ii) Chloroform	S	S	S
(iii) Methanol	S	S	S
(iv) Ethanol	S	S	S
(v) 1-Butanol	S	S	S
(vi) Benzene	G (1.5)	G (7)	G (3.5)
(vii) *o*-DCB	G (2.5)	G (8.5)	G (2)
(viii) Toluene	G (5.5)	G (6.5)	G (4.5)
(ix) *m*-Xylene	G (7)	G (8)	G (8)
(x) *p*-Xylene	G (8)	G (10)	G (12)
(xi) DMF	S	S	S
(xii) Cyclohexane	I	I	I
(xiii) *n*-hexane	I	I	I
(xiv) *n*-decane	P	P	P

[a]G: stable gel formed at room temperature; in parenthesis: minimum gel concentration (% w/v); S: soluble; I: insoluble; P: precipitate.

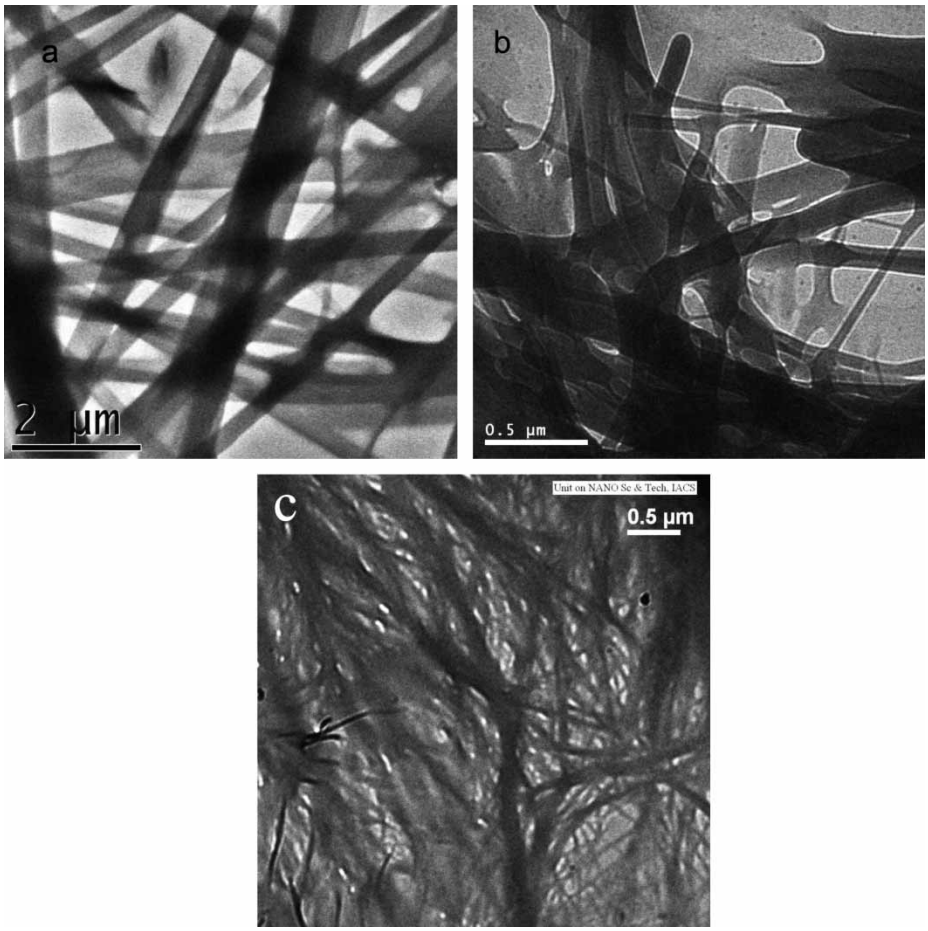


FIGURE 2 Transmission electron micrographs of the xerogels derived from (a) peptide 1 in benzene (1.5% w/v), (b) peptide 2 in *ortho*-dichlorobenzene (8.5% w/v) and (c) peptide 3 in *m*-xylene (8% w/v).

reversible first order phase transition, i.e., the peptide **1** produces a thermoreversible gel. Peptides **2** and **3** gels also show this first order phase transition. Thus the above three peptide–solvent system may be considered as thermo-reversible gels as both criteria e.g. fibrillar network structure and reversible first order phase transition have been attained [72, 73].

Thermodynamic Study

The thermodynamic characteristics of the gels have been ascertained using differential scanning calorimeter. This thermodynamic property of the gels is illustrated here with the peptide **1**/benzene system. The DSC thermogram (Fig. 3) of pure tripeptide shows two exotherms and two endotherms. The lower temperature exotherm corresponds to cold crystallization of tripeptide followed by an endotherm at 107°C where it melts (polymorph 1). This is followed by another exotherm indicating formation of another polymorph (polymorph 2) which melts at 178°C. It should be mentioned here that we did not observe any weight loss during the

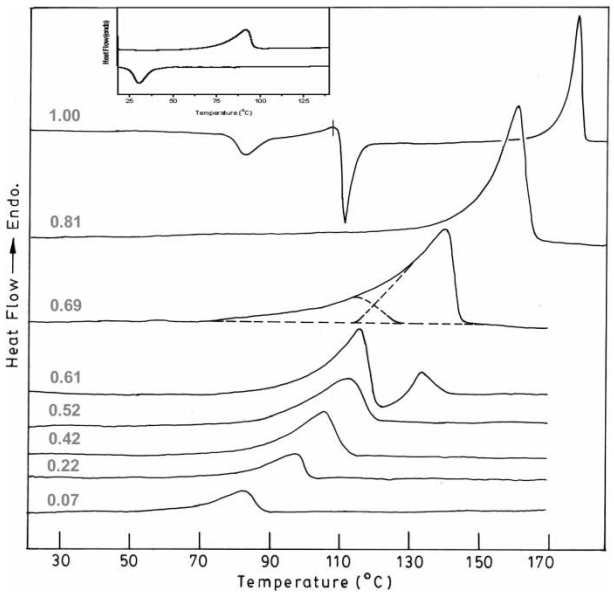


FIGURE 3 DSC thermograms of the peptide 1/benzene gel at the heating rate at 10°/min for indicated weight fraction of peptide. [Inset: Heating (10°/min) and cooling (5°/min) thermograms of 13% (w/v) peptide 1/benzene gel showing thermoreversibility].

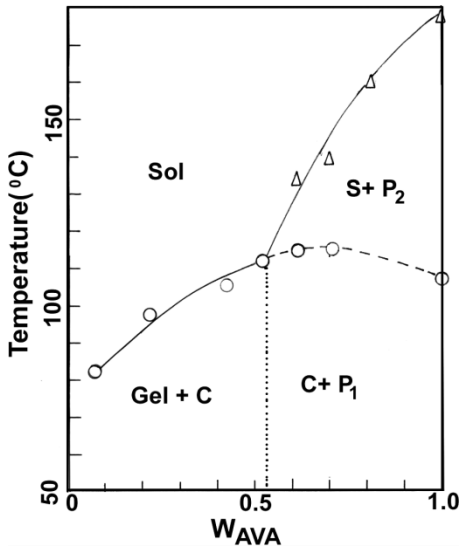


FIGURE 4 The phase diagram of peptide 1/benzene system (sol is the sol phase, gel is the gel phase, C is the complex, S is the solvent, P_1 is the crystalline polymorph 1 of peptide 1, P_2 is the crystalline polymorph 2 of peptide 1).

heating of the sample pan up to 180°C. This is because the LVC pan is sealed with O-ring which prevents any solvent loss at this high temperature.

For each composition the peak represents the melting temperature of the gel and these are plotted in Fig. 4 as part of the phase diagram. However this phase diagram is somewhat complicated because of the presence of a polymorphic transition of the peptide at 107°C from polymorph 1 (P_1) to polymorph 2 (P_2) that melts at 178°C. The total enthalpies of fusion of the samples are plotted against composition and are shown in Fig. 5. The plot is not linear, but rather shows positive deviation from linearity. The total enthalpy ΔH may be computed [60,74–77] as

$$\Delta H = \Delta H_S + \Delta H_P + \Delta H_C$$

where ΔH_S is the enthalpy of fusion of solvent, ΔH_P is that of peptide and includes all type of polymorphic transitions and ΔH_C is the enthalpy of complexation for any peptide complex that may be produced during gelation. At the temperature of interest ΔH_S is zero so

$$\Delta H = \Delta H_P + \Delta H_C$$

and the deviation ($\Delta H - \Delta H_P$) is the enthalpy of complexation. The positive deviation in Fig. 5 indicates that a tripeptide solvent interaction is occurring, forming some ordered structure (complex) during the gelation process. An approximate explanation of the phase diagram (Fig. 4) may be presented here. It has four boundaries separating the different phases as indicated in the phase diagram. An ordered tripeptide–solvent complex is present in the gel phase ($W_{AVA} \leq 0.53$) and also with the polymorph 1 (P_1) ($W_{AVA} \geq 0.53$). The former phase on heating produces the sol while the latter phase on heating converts into polymorph 2 (P_2) and free solvent (S). On further heating the polymorph P_2 melts and forms the sol phase.

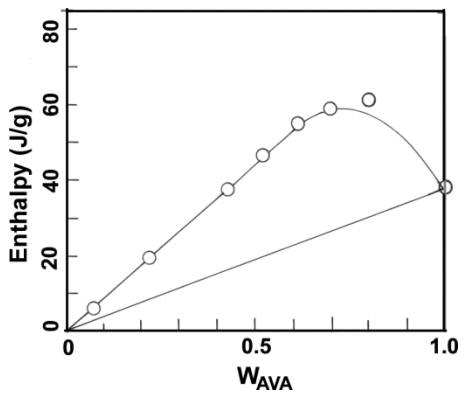


FIGURE 5 Enthalpy vs weight fraction of peptide 1 plot of peptide 1/benzene gel.

FT-IR Study

The FT-IR spectrum of peptide **1** in solid state (a), dried gel from *o*-DCB (b) and solvent subtracted spectrum in peptide **1**/*o*-DCB gel (c) are presented in Fig. 6. The FT-IR spectrum of peptide **1**/*o*-DCB gel shows absorption bands at 3311 cm^{-1} and 1634 cm^{-1} which can be assigned as N—H and C═O stretching vibrations. The 3318 cm^{-1} band is identified as a hydrogen-bonded NH stretching vibration indicating the intermolecular H-bonding in the dried gel. In solution (below the minimum gel concentration) of peptide **1** in *o*-DCB, no bands were observed around 3400 cm^{-1}. This result indicates that all NH groups are involved in intermolecular hydrogen bonding which also is responsible for the fibrillar network to form gel. The C═O stretching band at 1634–1639 cm^{-1} (amide I) suggests the β-sheet conformation [78] for peptide **1** in three different states indicating little change between these three states. For the entire reported tripeptide gelators, the FT-IR spectrum in the solid state as well as in the gel state has been recorded. Each of the reported peptides showed absorption bands at 3375–3270 cm^{-1} region (N—H stretching vibrations) and 1627–1650 cm^{-1} region (C═O stretching vibrations). From the solid state and gel state FT-IR data it has been suggested that all the reported peptides form intermolecularly hydrogen bonded sheet-like structures in the solid state as well as in the gel state. However, it is evident from the FT-IR data that there is close similarity between the solid state and dried gel state structure and but they are distinctly different from the wet gel state structure. There is a significant shift (29 cm^{-1}) from 3292 cm^{-1} to 3263 cm^{-1} of the N—H stretching

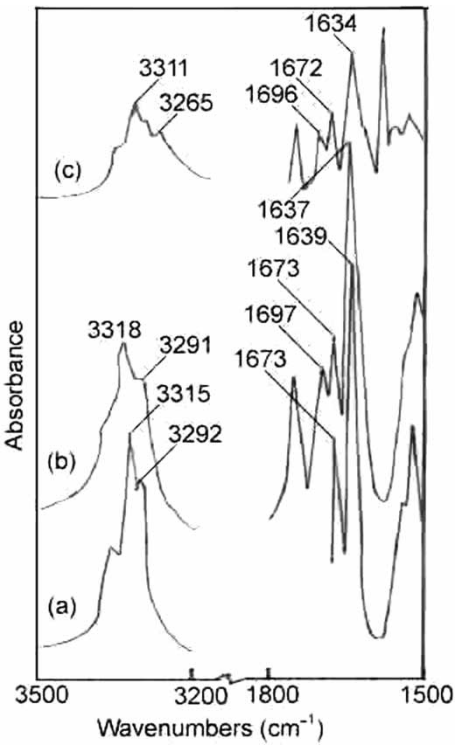


FIGURE 6 FT-IR spectra of peptide 1 in (a) solid state, (b) dried gel from *o*-DCB and (c) solvent subtracted gel in *o*-DCB.

vibration in the peptide **1**/benzene-gel (wet) state structure from that of the solid/xerogel state. This lower energy vibration might arise from the inclusion of solvent molecules in the β-sheet structure.

^{1}H NMR Study

^{1}H NMR studies have been performed to investigate the self-assembling behavior of the reported tripeptide gelators. The temperature dependence ^{1}H NMR chemical shifts of peptide **1** gel in C_6D_6 (2.2 wt%) have been recorded between the temperature range from 55°C (gel state) to 85°C (T_{gel} for peptide **1**) (Fig. 7). Figure 7 shows that there is a significant upfield chemical shift for all the NH groups of peptide **1** up to 85°C. These results indicate that all the NH groups of peptide **1** are intermolecularly hydrogen bonded to form the aggregated fibrils in the gel state. The addition of a small amount of highly polar hydrogen bonding solvent $(CD_3)_2SO$ in the C_6H_6 gels of tripeptides **1**, **2** and **3** disrupt the fibrillar network resulting a clear transition from gel state to solution state. Hence, these tripeptides aggregated through intermolecular hydrogen bonds to form gels. Figure 8 demonstrates that solvent perturbation experiments [79,80] on peptide **3** exhibit significant downfield shifts of all NH groups upon the addition of $(CD_3)_2SO$ (1% to 12.5%) into aggregated gel (5 wt%) of the peptide **3** in C_6D_6. The δ value changes of NH(1), NH(2) and NH(3) are 0.89, 0.57 and 0.76 respectively. This further supports the fact that all amide NHs of peptide **3** are involved in intermolecular hydrogen bonding in forming the aggregated gel state.

Single Crystal X-ray Diffraction Study

Single-crystal X-ray analyses have been performed to investigate useful information about the detail of the

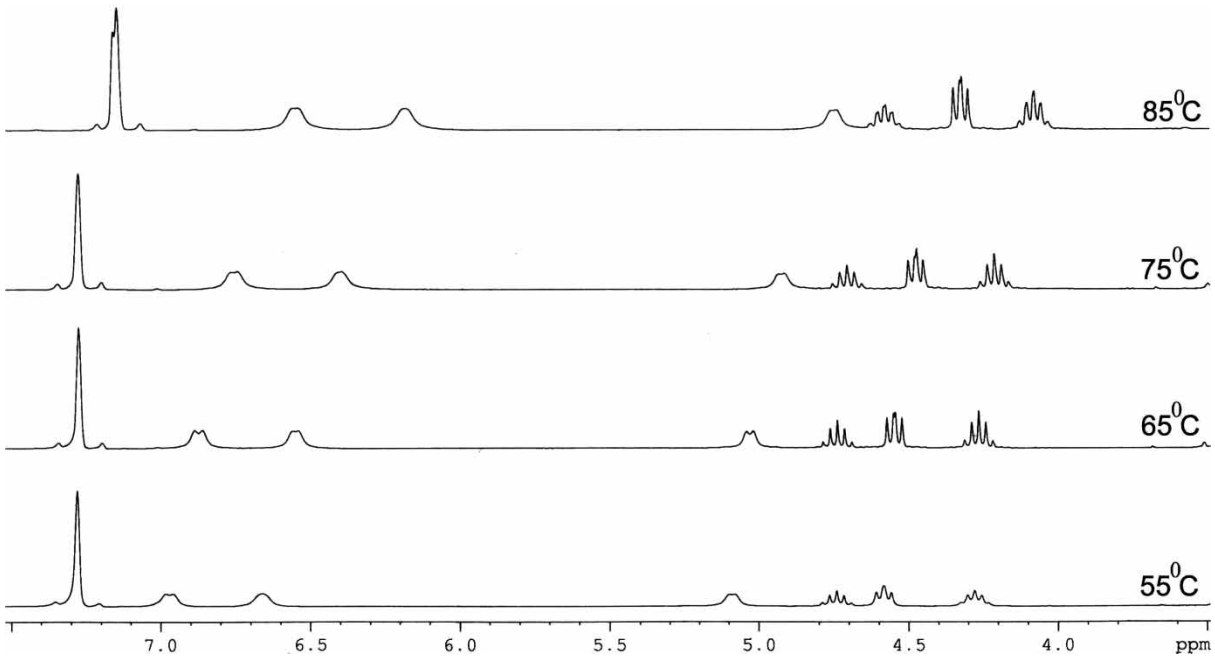


FIGURE 7 The temperature dependence ^{1}H NMR spectra of chemical shifts for the gelator peptide 1 in C_6D_6 (2.2% w/v) between the temperature range from 55°C (gel state) to 85°C (T_{gel} of peptide 1).

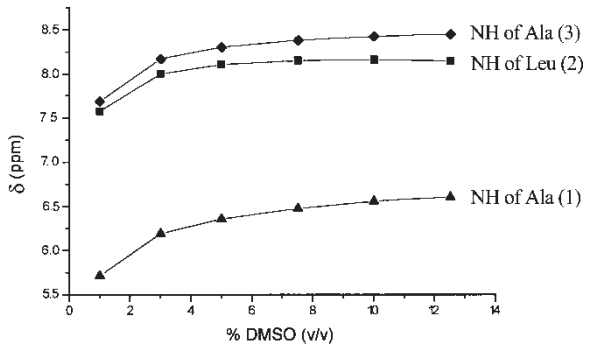


FIGURE 8 The plot of solvent dependence of NH chemical shifts of peptide 3 upon the addition of $(CD_3)_2SO$ into aggregated gel of the peptide 3 in C_6D_6.

intermolecular interactions and the molecular arrangement that might be responsible for the formation of fibrous network of these self-assembling gelator peptides. It is more difficult to crystallize a gelator molecule from its gelling solvents. We are able to get good quality single crystals for peptides **1**, **2** and **3** from hydrogen-bonding solvents (methanol–water solution) by slow evaporation, but, the gels only form in non-hydrogen bonding solvents. Single crystal X-ray diffraction studies of the peptide **3** revels that this peptide forms a hydrogen bonded molecular dimer in the asymmetric unit, which ultimately forms a supramolecular antiparallel β-sheet-like structure in higher order assembly [81]. In crystals, the tripeptides **1** and **2** Boc-Ala(1)-Val(2)-Ala(3)-OMe and Boc-Ala(1)-Ile(2)-Ala(3)-OMe adopt an overall extended backbone molecular structure in the asymmetric unit. There are two molecules (designated as A and B) in the asymmetric unit for both peptides **1** and **2**. The majority of the backbone torsional angles (except ψ3 of molecule A for peptide **1** and ψ3 of molecule B for peptide **2**) of both molecules A and B for tripeptides **1** and **2** fall within the extended β-sheet region of the Ramachandran diagram [82]. The backbone torsion angles for tripeptides **1** and **2** are listed in Table II. Each conformer (A and B) of peptides **1** and **2** self-assembles via intermolecular hydrogen bonds and other non-covalent interactions to form an infinite supramolecular antiparallel β-sheet assemblage in the crystal along the axis parallel to the crystallographic *a* direction. In tripeptide **1** there are six intermolecular hydrogen bonds (N3A–···H3A···O8B, N6A–H6A···O5B, N9A–H9A···O2B, N3B–H3B···O8A, N6B–H6B···O5A and N9B–H9B···O2A) that are responsible for connecting individual peptide molecules to form and stabilize the supramolecular monolayer β-sheet structures (Fig. 9a). Tripeptide **2** also has six intermolecular hydrogen bonds (N3A–H3A···O8B, N6A–H6A···O5B, N9A–H9A···O2B, N3B–H3B···O8A, N6B–H6B···O5A and N9B–H9B···O2A) which help to connect the individual peptide monomer to form and stabilize the antiparallel supramolecular monolayer β-sheet structures (Fig. 9b). Figure 9 exhibits all the hydrogen bonds are formed between the peptide functionalities. The hydrogen bonding parameters of peptides **1** and **2** are listed in Table III. In higher order self-assembly, both peptides **1** and **2** exhibit complex quaternary sheet structure by regular stacking of individual peptide molecules via van der Waals interactions and other noncovalent interactions along the screw axis parallel to the crystallographic *b* direction. Crystal data for peptides **1** and **2** are detailed in Table IV. From the single crystal X-ray structure analysis of the gelator peptides **1** and **2**, it is clear that a strong self-complementary and unidirectional intermolecular hydrogen-bonded one dimensional self-association exist in primary unit of the crystal of the gelator molecules. In a recent report, Shinkai and his coworkers suggest that 1D hydrogen-bonded network promotes gelation while 2D or 3D hydrogen-bonded network either does not promote gelation at all or form a weak gel [83,84]. So, in our system it may be concluded that the cause of gelation is due to unidirectional 1-D hydrogen bonding between the molecular strands.

From the present results a mechanism of gelation in these tripeptide systems may be worked out as follows. Both FT-IR and ^{1}H NMR spectra conclude

TABLE II Characteristics of peptides **1** and **2** in molecules A and B: Selected torsional angles (°) for peptide **1** and **2**

Peptide	Residue	Molecule	ϕ	ψ	ω
Peptide **1**	Ala(1)	A	−152.1(4)	147.3(4)	173.4(4)
		B	−140.4(4)	139.8(4)	−179.9(4)
	Val(2)	A	−143.1(4)	141.6(5)	174.6(4)
		B	−145.5(4)	136.6(4)	175.3(5)
	Ala(3)	A	−120.9(5)	177.1(4)	−176.1(5)
		B	−120.0(5)	24.2(7)	179.2(5)
Peptide **2**	Ala(1)	A	−137.0(4)	143.8(4)	−177.5(4)
		B	−148.8(4)	146.1(4)	171.9(4)
	Ile(2)	A	−150.9(4)	139.7(4)	172.7(4)
		B	−144.8(4)	136.0(4)	172.1(5)
	Ala(1)	A	−125.5(5)	35.7(7)	179.0(5)
		B	−104.0(6)	177.0(5)	179.2(6)

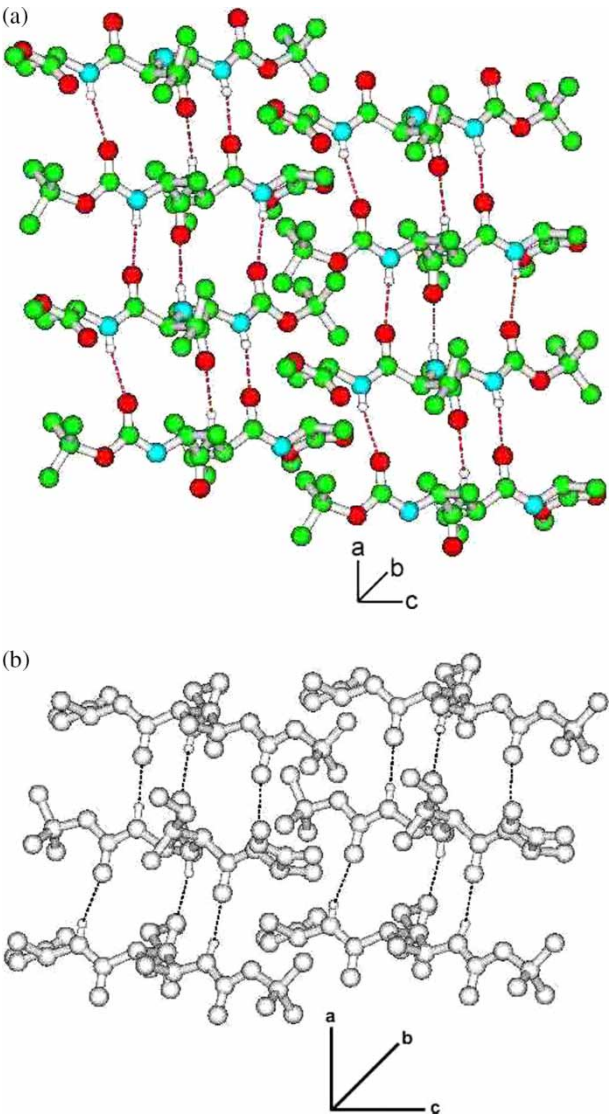


FIGURE 9 (a) Crystal packing diagram of peptide 1 showing the intermolecular hydrogen-bonded antiparallel β-sheet structure along crystallographic *a* direction. Nitrogen atoms are blue, oxygen atoms are red, carbon atoms are green and hydrogen atoms are grey. Hydrogen bonds are shown as dotted lines. (b) Packing diagram of peptide 2 showing intermolecular hydrogen-bonded antiparallel β-sheet structure along *a* axis. Hydrogen bonds are shown as dotted lines.

that intermolecular hydrogen bonds between the peptide molecules are present in the gels. As the hydrogen bonds are broken the gel structure is lost. The crystal structures of these tripeptides also indicate the presence of vacant spaces produced from intermolecular hydrogen bonds. These vacant spaces may be filled with solvent molecules having appropriate size and interaction with the peptide. From the structural study it is apparent that the vacant spaces are not big enough to encapsulate benzene without significant change in the structure, such as the breaking of the hydrogen-bonded network. The aromatic solvents in which gels are formed are easily polarizable having higher quadruple moment and therefore may be attracted by the $>C{=}O$ or $>NH$ groups.

CONCLUSIONS

We have successfully demonstrated that a series of tripeptides containing only proteinous amino acids self-assemble to form thermoreversible gels in various aromatic solvents including benzene, toluene, and xylenes. However, they do not produce gels in other aliphatic hydrocarbons such as hexane, cyclohexane, *n*-decane due to lack of sufficient solubility in these media. TEM study indicates presence of fibrillar network structure in the gel. DSC studies of gels indicate thermoreversible character and tripeptide–solvent complex may be produced. FT-IR and ^{1}H NMR studies of these gelator peptide indicates the formation of intermolecular hydrogen bonded β-sheet structure that is responsible for gelation. However, FT-IR data of wet gel of peptide **1** in benzene reveal that the gel structure is somewhat different from solid state and xerogel structures. Single crystal X-ray diffraction studies of the peptides **1** and **2** demonstrate that unidirectional intermolecular hydrogen bonded 1D self-assembly is present in the crystal structure, a feature that is responsible for gelation.

TABLE III Intermolecular hydrogen bonds for peptide **1** and **2**

Peptide	Symmetry element	Donor	Acceptor	H···O (A°)	N···O (A°)	N—H···O (°)
Peptide **1**	A	N3A	O8B	2.16	2.947	152
	B	N3B	O8A	2.10	2.947	169
	C	N6A	O5B	2.19	3.038	168
	D	N6B	O51A	2.18	3.022	167
	A	N9A	O2B	2.22	3.057	165
	B	N9B	O2A	2.21	3.064	171
Peptide **2**	E	N3A	O8B	2.09	2.940	171
	–	N3B	O8A	2.16	2.942	150
	–	N6A	O5B	2.16	3.001	165
	F	N6B	O5A	2.18	3.029	169
	E	N9A	O2B	2.18	3.036	172
	–	N9B	O2A	2.20	3.043	167

Symmetry equivalents [a]x − 1, y, z − 1; [b]x, y, z + 1; [c]x, y, z − 1; [d]x + 1, y, z + 1; [e]x − 1, y, z; [f]x + 1, y, z.

TABLE IV Crystallographic data for peptide **1** and peptide **2**

	Peptide **1**	Peptide **2**
Formula	$C_{17}H_{31}N_3O_6$	$C_{18}H_{33}N_3O_6$
Formula weight	373.45	387.47
Crystallizing solvent	Methanol–water	Methanol–water
Crystal system	Monoclinic	Monoclinic
Temperature [K]	293	293
Space Group	$P2_1$	$P2_1$
a [Å]	9.799(12)	9.759(12)
b [Å]	22.06(2)	22.47(2)
c [Å]	10.204(13)	10.272(12)
β [°]	106.71(1)	104.18(1)
U [Å^3]	2113	2184
Z	4	4
Dcalcd [g cm^{-3}]	1.174	1.179
λ [Å]	0.71073	0.71073
*R*1	0.0876	0.0843
*wR*2	0.1183	0.1747
max. and min. electron density e/Å^3	0.183, −0.191	0.391, −0.297

EXPERIMENTAL

Materials

The tripeptides were synthesized by conventional solution phase method [85] by using racemization-free fragment condensation strategy. The Boc group was used for N-terminal protection and the C-terminus was protected as a methyl ester. Couplings were mediated by dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/HOBt). All intermediates were characterized by ^{1}H NMR (300 MHz) and thin layer chromatography (TLC) on silica gel and used without further purification. The final products were purified by column chromatography using silica (100–200 mesh size) gel as stationary phase and chloroform–methanol (9:1) mixture as eluent. The purified final compounds have been fully characterized by 300 MHz ^{1}H-NMR spectroscopy.

Synthesis of Peptide 1

Synthesis of Boc-Ala(1)-OH **4**

See ref. [86].

Boc-Ala(1)-Val(2)-OMe **5**

A sample of Boc-Ala(1)-OH (1.89 g, 10 mmol) was dissolved in dichloromethane (DCM) (30 mL) in an ice-water bath. H-Val-OMe was isolated from the corresponding methyl ester hydrochloride (3.35 g, 20 mmol) by neutralization and subsequent extraction with ethyl acetate and the ethyl acetate extract was concentrated to 25 mL. This was added to the reaction mixture, followed immediately by dicyclohexylcarbodiimide (DCC) (2.06 g, 10 mmol). The reaction mixture was allowed to come to room temperature and stirred for 24 h. DCM was evaporated, and the residue was taken up in ethyl acetate (60 mL), and dicyclohexylurea (DCU) was filtered off. The organic layer was washed with 2 M HCl (3 × 50 mL), brine (2 × 50 mL), then 1 M sodium carbonate (3 × 50 mL) and brine (2 × 50 mL) and dried over anhydrous sodium sulfate, and evaporated in *vacuum* to yield **5** as white solid.

Yield = 2.5 g (8.3 mmol, 83(%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (1H, d, $J = 5$ Hz); 5.1 (1H, d, $J = 7.2$ Hz); 4.5 (1H, m); 4.2 (1H, m); 3.74 (3H, s); 2.1–2.23 (1H, m); 1.45 (9H, s); 1.36 (3H, d, $J = 7.1$ Hz); 0.89–0.94 (6H, m). Anal. Calcd. for $C_{14}H_{26}N_2O_5$ (302): C, 56.6; N, 9.27; H, 8.6. Found: C, 56.58; N, 9.28; H, 8.57. $[\alpha]_D^{20} = -25.3$ (*c* 0.54, CH_3OH).

Boc-Ala(1)-Val(2)-OH **6**

To a sample of **5** (2.42 g, 8 mmol), MeOH (50 mL) and 2 M NaOH (20 mL) were added and the progress of saponification was monitored by thin layer chromatography (TLC). The reaction mixture was stirred. After 10 h, methanol was removed under *vacuum*, the residue was taken up in 50 mL of water, washed with diethyl ether (2 × 20 mL). Then the pH of the aqueous layer was adjusted to 2 using 1 M HCl and it was extracted with ethyl acetate (3 × 30 mL). The extracts were pooled, dried over anhydrous sodium sulfate, and evaporated in *vacuum* to yield **6** as white solid.

Yield = 2.02 g (7 mmol, 87.5(). ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 12.64 (1H, b); 7.68 (1H, d, $J = 8.7$ Hz); 6.96 (1H, d, $J = 7.8$ Hz); 4.10–4.15 (1H, m); 3.97–4.07 (1H, m); 1.97–2.08 (1H, m); 1.35 (9H, s); 1.14 (3H, d, $J = 7.1$ Hz); 0.84–0.86 (6H, m). Anal. Calcd. for $C_{13}H_{24}N_2O_5$ (288): C, 54.17; N, 9.72; H, 8.33. Found: C, 54.21; N, 9.69; H, 8.36. $[\alpha]_D^{20} = -30.9$ (*c* 0.65, CH_3OH).

Boc-Ala(1)-Val(2)-Ala(3)-OMe **1**

1.90 g (6.6 mmol) of Boc-Ala(1)-Val(2)-OH in 15 mL of DMF was cooled in an ice-water bath and H-Ala-OMe was isolated from 1.84 g (13.2 mmol) of the corresponding methyl ester hydrochloride by neutralization and subsequent extraction with ethyl acetate and the ethyl acetate extract was concentrated to 8 mL. It was then added to the reaction mixture, followed immediately by 1.36 g (6.6 mmol) DCC and 0.89 g (6.6 mmol) of HOBt. The reaction mixture was stirred for three days. The residue was taken up in ethyl acetate (40 mL) and the DCU was filtered off. The organic layer was washed with 2 N HCl (3 × 40 mL), brine (2 × 50 mL), 1 M sodium carbonate (3 × 40 mL), brine (2 × 40 mL), dried over anhydrous sodium sulfate and evaporated in *vacuum* to yield **1** of white solid. Purification was done by silica gel column (100–200 mesh) using chloroform–methanol as eluent.

Yield = 1.98 g (5.3 mmol, 80(%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (1H, d, $J = 8.1$ Hz); 6.67 (1H, d, $J = 4.4$ Hz); 5.03 (1H, d, $J = 5.6$ Hz); 4.54–4.58

(1H, m); 4.26–4.31 (1H, m); 4.17–4.21 (1H, m); 3.75 (3H, s); 2.18–2.20 (1H, m); 1.45 (9H, s); 1.41 (3H, d, $J = 7.2$ Hz); 1.37 (3H, d, $J = 7.1$ Hz); 0.92–0.97 (6H, m). Anal. Calcd. for $C_{17}H_{31}N_3O_6$ (373): C, 54.69; N, 11.26; H, 8.31. Found: C, 54.71; N, 11.24; H, 8.35. $[\alpha]_D^{20} = -48.1$ (c 1.07, $CHCl_3$); MS (ESI) m/z 397.3 $(M + Na + H)^+$.

Synthesis of Peptide 2

Bol-Ala(1)-Ile(2)-OMe **7**

1.89 g (10 mmol) of Boc-Ala-OH was dissolved in a mixture of 30 mL dichloromethane (DCM) in an ice–water bath. H-Ile-OMe was isolated from 3.63 g (20 mM) of the corresponding methyl ester hydrochloride by neutralization and subsequent extraction with ethyl acetate and the ethyl acetate extract was concentrated to 10 mL. This was added to the reaction mixture, followed immediately by 2.06 g (10 mM) of di-cyclohexylcarbodiimide (DCC). The reaction mixture was allowed to come to room temperature and stirred for 24 h. DCM was evaporated, and the residue was taken up in ethyl acetate (60 mL), and dicyclohexylurea (DCU) was filtered off. The organic layer was washed with 2 M HCl (3 × 50 mL), brine (2 × 50 mL), then 1 M sodium carbonate (3 × 50 mL) and brine (2 × 50 mL) and dried over anhydrous sodium sulfate, and evaporated in *vacuum* to yield **7** as white solid.

Yield = 2.69 g (8.5 mmol, 85(%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (1H, d, $J = 6$ Hz); 5.00 (1H, d, $J = 6$ Hz); 4.47–4.51 (1H, m); 4.00–4.11 (1H, m); 3.66 (3H, s); 1.83–1.86 (1H, m); 1.37 (9H, s); 1.35 (3H, m); 1.27–1.29 (2H, m); 0.82–0.86 (6H, m). Anal. Calcd. for $C_{15}H_{28}N_2O_5$ (316): C, 56.96; N, 8.86; H, 8.86. Found: C, 56.99; N, 8.88; H, 8.84. $[\alpha]_D^{20} = -28$ (c 0.63, CH_3OH).

Boc-Ala(1)-Ile(2)-OH **8**

To 2.53 g (8 mmol) of **7**, 50 mL MeOH and 20 mL of 2 M NaOH were added and the progress of saponification was monitored by thin layer chromatography (TLC). The reaction mixture was stirred. After 10 h methanol was removed under *vacuum*, the residue was taken up in 50 mL of water, washed with diethyl ether (2 × 50 mL). Then the pH of the aqueous layer was adjusted to 2 using 1 M HCl and it was extracted with ethyl acetate (3 × 50 mL). The extracts were pooled, dried over anhydrous sodium sulfate, and evaporated in *vacuum* to yield **8** as white solid.

Yield = 2.05 g (6.8 mmol, 85(%). ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 12.59 (1H, b); 7.69 (1H, d, $J = 8.4$ Hz); 6.99 (1H, d, $J = 7.8$ Hz); 4.14–4.19 (1H, m); 3.96–4.04 (1H, m); 1.76 (1H, m); 1.36 (9H, s); 1.20 (3H, d, $J = 7.3$ Hz); 1.14 (3H, d, $J = 7.1$ Hz); 0.80–0.85 (6H, m). Anal. Calcd. for $C_{14}H_{26}N_2O_5$ (302): C, 55.63; N, 9.27; H, 8.61. Found: C, 55.61; N, 9.31; H, 8.63. $[\alpha]_D^{20} = -25.1$ (c 0.56, CH_3OH).

Boc-Ala(1)-Ile(2)-Ala(3)-OMe **2**

1.96 g (6.5 mmol) of Boc-Ala(1)-Ile(2)-OH in 15 mL of DMF was cooled in an ice-water bath and H-Ala-OMe was isolated from 2.36 g (13 mmol) of the corresponding methyl ester hydrochloride by neutralization and subsequent extraction with ethyl acetate and the ethyl acetate extract was concentrated to 8 mL. It was then added to the reaction mixture, followed immediately by 1.34 g (6.5 mmol) DCC and 0.88 g (6.5 mmol) of HOBt. The reaction mixture was stirred for three days. The residue was taken up in ethyl acetate (40 mL) and the DCU was filtered off. The organic layer was washed with 2 M HCl (3 × 40 mL), brine (2 × 50 mL), 1 M sodium carbonate (3 × 40 mL), brine (2 × 40 mL), dried over anhydrous sodium sulfate and evaporated in *vacuum* to yield **2** of white solid. Purification was done by silica gel column (100–200 mesh) using chloroform–methanol (9:1) as eluent.

Yield = 2.09 g (5.4 mmol, 83(%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (1H, d, $J = 8.4$ Hz); 6.60 (1H, d, $J = 5.7$ Hz); 5.02 (1H, d, $J = 9.1$ Hz); 4.53–4.58 (1H, m); 4.27–4.32 (1H, m); 4.14–4.18 (1H, m); 3.74 (3H, s); 1.93–1.96 (1H, m); 1.44 (9H, s); 1.40–1.42 (3H, d); 1.35–1.37 (3H, d, $J = 9$ Hz); 1.26–1.28 (3H, d, $J = 7.1$ Hz); 0.88–0.94 (6H, m). Anal. Calcd. for $C_{18}H_{33}N_3O_6$ (387): C, 55.81; N, 13.29; H, 8.53. Found: C, 55.79; N, 13.32; H, 8.51; $[\alpha]_D^{20} = -48.8$ (c 1.17, $CHCl_3$); MS (ESI) m/z 388.3 $(M + H)^+$, m/z 410.2 $(M + Na)^+$, m/z 797.5 $(2M + Na)^+$.

Synthesis of Peptide 3

Boc-Ala(1)-Leu(2)-OMe **9**

See ref. [87].

Boc-Ala(1)-Leu(2)-OH **10**

See ref. [87].

Boc-Ala(1)-Leu(2)-Ala(3)-OMe **3**

See ref. [81].

Transmission Electron Microscopic Studies

Transmission electron microscopy measurements were carried out to observe finer morphological details. A piece of gel of the corresponding compounds was added onto carbon-coated copper grids (200 mesh) and allowed to dry under vacuum at room temperature for 5 h without staining. Images were taken at an accelerating voltage of 200 kV. TEM was performed using a JEM 2010 Jeol electron microscope.

Differential Scanning Calorimetry (DSC)

For thermal studies of the gels were prepared in Perkin–Elmer LVC capsules by taking required amount of peptide and solvent and homogenizing at 170°C for 10 mins and then quenched to 10°C where the system was equilibrated for 15 mins. They were then heated in a differential scanning calorimeter (DSC-7, Perkin–Elmer) with heating at the rate of 10°C/min. The cooling runs were taken from the melt at 170°C at the rate of 5°C/min. The melting point and enthalpy of fusion were calculated from the thermograms using a computer attached to the instrument. The DSC was calibrated with indium before each set of experiment.

FT-IR Studies

The FT-IR spectra were obtained using Shimadzu (Japan) model FT-IR spectrophotometer. Solvent (DCB) spectra were obtained using a cuvette with 1 mm path length. A Nicolet FT-IR instrument (Magna IR-750 spectrometer (series II)) was used to obtain the solid state and gel state FT-IR spectra. The solvent spectrum was subtracted from the gel spectrum to obtain tripeptides spectra in the gel state. For the solid state measurements the KBr disk technique was used.

^{1}H NMR Studies

All ^{1}H NMR studies were carried out on a Brüker DPX 300 MHz spectrometer.

Mass Spectrometry

Mass spectra were recorded on a Hewlett Packard Series 1100MSD mass spectrometer by positive mode electrospray ionization.

Single Crystal X-ray Diffraction Studies

For peptides **1** and **2** single crystals were obtained from methanol–water solution by slow evaporation. Crystal data for peptides **1** and **2**, which are isomorphous, were collected on a Mar Research Image Plate with Mo Kα radiation. The crystals were positioned at 70 mm from the image plate. 100 frames were measured at 2 intervals with a counting time of 2 min. Data analysis was carried out with the XDS program [88]. The structures were solved using direct methods with the Shelx86 program [89]. Non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The structures were refined on F^2 using Shelxl [90]. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre reference CCDC 605303 for peptide **1** and CCDC 605302 for peptide **2**.

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