First snapshot of a nonpolymeric hydrogelator interacting with its gelling solvents†

D. Krishna Kumar, D. Amilan Jose, Amitava Das* and Parthasarathi Dastidar*

Received (in Cambridge, UK) 17th May 2005, Accepted 17th June 2005
First published as an Advance Article on the web 13th July 2005
DOI: 10.1039/b506941f

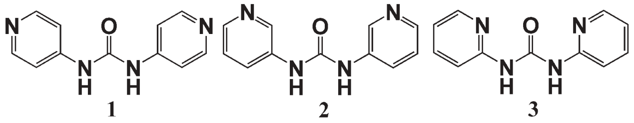
A pyridyl urea based low molecular weight supramolecular hydrogelator has been synthesized; crystallized from its gelling solvents, the single crystal structure of the gelator molecule interacting with its gelling solvents reported herein is the first example in the literature.

The majority of low molecular mass organic gelators (LMOGs) discovered to date display gelation ability with organic solvents.[1] LMOGs capable of gelling pure water or aqueous solvents are known as hydrogelators.[2] Hydrogels are an important class of materials that display many interesting applications.[3] The occurrence of LMOG derived hydrogelators in limited numbers compared to their organogelator counterparts is presumably due to the fact that a careful balance between hydrophobic interactions and hydrogen bonding in an aqueous solvent is essential to achieve the required three-dimensional elastic networks involving small gelator molecules within which the solvent molecules are immobilized. Therefore, designing a nonpolymeric LMOG based hydrogelator is a challenging and daunting task. To design a gelator molecule, it is important to understand the supramolecular architecture (crystal structure) of the meta-stable gel fiber in its native (gel) form. However, it is virtually impossible to determine the crystal structure of a gel fiber; only an indirect method using X-ray powder diffraction (XRPD) data may be applied.[4] However, recording good quality XRPD data of the gel fibers in their native form generally suffers from the scattering contribution of the solvent molecules and the less crystalline nature of the gel fibers and therefore, in most cases, attempts to record XRPD of gel fibers turn out to be a major disappointment. On the other hand, correlating the single crystal structure of a molecule in its thermodynamically more stable crystalline state with its gelling/nongelling behaviour seems to be more practical and our efforts in this regard have been quite useful in designing new LMOGs.[5] Thus, it is clear that single crystal structure information on a gelator molecule is as important. To the best of our knowledge, no such data are available for a supramolecular hydrogelator.

Our previous experience with a pyridyl amide based hydrogelator[5e] prompted us to investigate pyridyl urea based compounds as potential hydrogelators. Thus *N*,*N*′-bis(4-pyridyl) urea **1** and the corresponding 3- and 2-pyridyl derivatives (**2** and **3** respectively, Scheme 1) have been readily synthesized following a reported procedure.[6] While **1** shows remarkable gelation ability with pure water (Minimum Gelator Concentration, MGC = 0.8 wt %), the corresponding positional isomers **2** and **3** are nongelators. To the best of our knowledge, compound **1** reported herein represents the lowest molecular weight nonpolymeric urea based hydrogelator.

In a typical experiment, **1** is dissolved in pure water (1 wt %, w/v) by heating. An opaque thermo-reversible gel is formed after a few minutes upon cooling at rt under ambient conditions. However, due to its relatively poor solubility in pure water, gelation experiments on **1** cannot be performed beyond 1.4 wt % (w/v) concentration of the gelator. Therefore, gelation study of **1** is performed in water containing a co-solvent, namely ethylene glycol (EG). To estimate the thermal stability of the gel, the gel to sol melting temperature, T_{gel}†, is plotted against the gelator concentrations (wt % w/v) in 10% EG in water (v/v) and also against varying EG concentration in water (% v/v) at a fixed gelator concentration of 1 wt % as depicted in Fig. 1.

The increase of T_{gel} with the increase of gelator concentration and also the remarkably low minimum gel concentration for **1** indicate that self-assembly in the gel state is driven by strong intermolecular interactions. T_{gel} decreases with the increase of EG concentration, presumably due to the higher solubility of the gelator in excess EG. FT-IR experiments have been carried out to gain insights into the hydrogen bonding environment of the carbonyl group (C=O) of the urea moiety in **1** under various conditions. In the bulk solid, the C=O band appears at 1740 cm^{-1} whereas 1735 cm^{-1} is the band position in the gel (D_2O) state.



Scheme 1

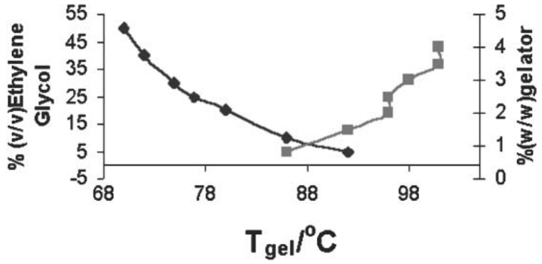


Fig. 1 Plot of T_{gel} at various conditions. (♦) T_{gel} *vs.* varying EG concentration in water (v/v) at a fixed concentration of 1 wt % gelator. (■) T_{gel} *vs.* gelator concentration; gel prepared in 10% EG/water (v/v).

Analytical Science Discipline, Central Salt & Marine Chemicals Research Institute, G. B. Marg, Bhavnagar, 364 002, Gujarat, India. E-mail: parthod123@rediffmail.com; dastidar@csmcri.org; amitava@csmcri.org; Fax: +91-278-2567562

† Electronic supplementary information (ESI) available: analytical data for **1** and **2**, T_{gel} measurement, crystallographic details including data collection, structure solution and refinement, hydrogen bonding parameters and ORTEP diagrams for **1·EG·H$_2$O**, **1·HCl·xH$_2$O**, **2** and **2·xH$_2$O**. See http://dx.doi.org/10.1039/b506941f

Thus a 5 cm^{-1} shift in the C=O band may be indicative of further hydrogen bonding of the carbonyl groups in the gel state.

The gelation behavior of **1** is quite pH sensitive. The pH of the aqueous solution of **1** is found to be 8.3 at MGC. When the pH is changed to 5.3 using 1% AcOH (v/v), it fails to form gel. On the other hand, when gelation experiments are performed at pH 9–10 using $NaHCO_3$, gels are formed. These results clearly indicate that the free pyridine nitrogen atoms might be contributing towards the required self-assembly of the gelator molecules through possible hydrogen bonding. To provide further support for this hypothesis, a monohydrochloride salt of the gelator **1** has been synthesized and it also turns out to be a nongelator. This indicates that both the ring nitrogen atoms of the gelator **1** must be free from protonation in order to form gel and also the relative arrangement of the ring nitrogen atoms in the molecule must be linear since the positional isomers, namely **2** and **3** fail to show any gelation property.

SEM pictures of xerogel of **1** in pure water (Fig. 2a) and in 10% EG/water (v/v) (Fig. 2b) display a typical fibrous network. The morphology of the several μm long slender fibers in pure water appears to be rod shaped with varying thickness, whereas highly intertwined tape type fibers are observed in the EG/water system. Understandably, the solvent molecules are immobilized in such a network of fibers resulting in gel formation.

Analysis of the single crystal structure of a gelator molecule provides useful information about the detail of the intermolecular interactions which might be responsible for gel fiber formation.[5,7] However, crystallizing a gelator molecule is a daunting task. Moreover, crystallizing a gelator molecule from its gelling solvents is even more difficult and to the best of our knowledge, no such example in supramolecular hydrogelators is known. Efforts to grow a single crystal of **1** from pure water have proved unsuccessful. However, **1** can be crystallized from its gelling solvent systems such as EG/water (1 : 9 and 1 : 1, v/v) when the gel is kept at rt under ambient conditions in an open test tube for about a month. The crystal structure of **1** thus obtained from its gelling solvents is found to contain both EG and water molecules! The crystal **1·EG·H_2O** belongs to a noncentrosymmetric space group (orthorhombic, $P2_12_12_1$) and the asymmetric unit contains one gelator molecule, one EG and one water.‡ The hydrogen bonding sites of the gelator molecule are fully satisfied through various hydrogen bonding interactions with the solvent molecules. The urea moiety does not display the usual propagating hydrogen bonding network involving the C=O group and NH hydrogen atoms;[8] instead the carbonyl group is involved in hydrogen bonding with a water molecule ($O\cdots O = 2.945$ Å, $\angle O–H\cdots O = 148.2°$) and the urea nitrogen atoms are interacting with oxygen atoms of the EG molecule ($N\cdots O = 2.805–2.864$ Å; $\angle N–H\cdots O = 160.0–173.8°$). Both the pyridine nitrogen atoms are also participating in hydrogen bonding interactions with water and the EG molecule ($N\cdots O_{H_2O} = 2.774$ Å, $\angle N\cdots H–O_{H_2O} = 177.1°$; $N\cdots O_{EG} = 2.718$ Å, $\angle N\cdots H–O_{EG} = 176.7°$) (Fig. 3).

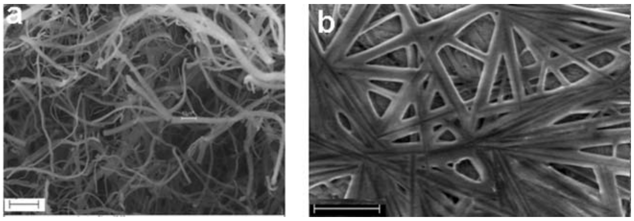


Fig. 2 SEM micrographs of xerogels of a) **1** in pure water at MGC (bar = 20 μ); b) **1** in 10% EG/water (v/v) at 1.2 wt % (bar = 100 μ).

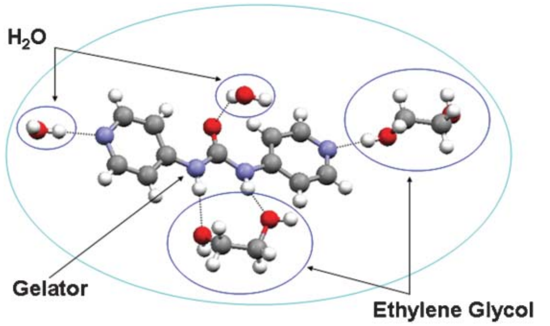


Fig. 3 Various hydrogen bonding interactions of the gelator with the gelling solvents as observed in the single crystal structure of **1·EG·H_2O**.

The supramolecular assembly of the gelator molecule and the interacting solvents in the crystal lattice displays microporous architecture. A continuous channel is formed along the crystallographic *a*-axis and the solvent molecules (both water and EG) are firmly held in the channel through hydrogen bonding interactions with the gelator molecules (Fig. 4).

To the best of our knowledge, the present crystal structure is the first example wherein the LMOG based hydrogelator molecule is shown to interact with its gelling solvents.

Attempts to record XRPD patterns of the gel fiber in its native state have proved unsuccessful due to a heavy scattering contribution arising from the solvent molecules. XRPD patterns of the xerogel (dried gel) prepared under various conditions are inconsistent presumably due to inhomogeneous solvent loss from the crystal lattice during xerogel formation. The XRPD pattern of the xerogel recorded after drying the sample at 120 °C for 6 h shows a high degree of noncrystallinity. Based on these results, it is reasonable to assume that the gelling solvent molecules might be included in the crystal lattice of the gel fibers (in the native state) and escape of the solvent molecules from the crystal structure of the gel fibers during xerogel formation results in the partial collapse of the crystal lattice and thus a high degree of noncrystallinity of the XRPD pattern of the xerogel (Figure S1).†

Since the gelation property of **1** is pH sensitive, it was considered worthwhile to examine the single crystal structure of the monoprotonated gelator molecule **1** in the form of its hydrochloride salt. Thus, a monohydrochloride salt of **1** was crystallized from a solution of **1** in 0.01 M HCl and its single crystal structure was investigated. It was observed that the crystal structure of **1·HCl·xH_2O** ($x = 1.66$) belongs to a centric triclinic space group

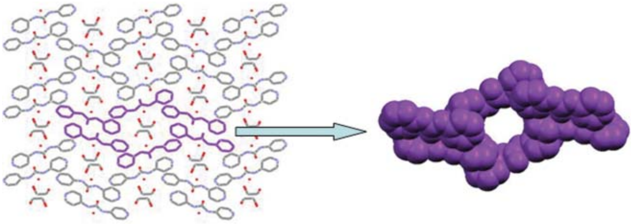


Fig. 4 Overall supramolecular assembly of the gelator molecule displaying microporous channel architecture. The space filling model on the right shows one such channel. Hydrogen atoms are omitted for clarity.

(*P*-1).‡ In the asymmetric unit, two monoprotonated urea, three water molecules and two Cl^- ions are located in general positions. The excess electron densities (two peaks) amounting to $\sim$1.2 e/Å^3 have been assigned as disordered oxygen atoms presumably arising from solvent water molecules.† The monoprotonated gelator molecules are held together by a N–H···N hydrogen bond (N···N = 2.737 Å; ∠N–H···N = 176.8°) resulting in 1-D hydrogen bonded chains which are further arranged in a parallel fashion held together by various hydrogen bonding interactions involving solvent water molecules and Cl^- ions (Figure S2).† Thus the single crystal structure of **1·HCl·*x*H$_2$O** clearly demonstrates that protonation of one of the ring nitrogens favours intermolecular hydrogen bonding through N–H···N interactions thereby preventing the molecule from forming hydrogen bonds with the solvent molecules involving ring nitrogen atoms.

It is remarkable that by going from 4-pyridyl to 3-pyridyl and 2-pyridyl derivatives (**2** and **3** respectively), the gelation ability disappears and therefore, it is important to study the molecular packing of the nongelators, if possible. Two different crystal structures of **2**, one devoid of any solvent molecule (crystallized from EtOH/water 1 : 1 v/v) and one with one water molecule included in the crystal lattice, **2·*x*H$_2$O** (x = 1.33) (crystallized from MeOH), have been obtained. The urea moiety in **2** is located on a 2-fold axis (orthorhombic, *Aba*2).‡ The molecules in **2** are held together by N–H···N hydrogen bonding involving pyridine ring nitrogen and urea nitrogen atoms (N···N = 3.056 Å; ∠N–H···N = 166.9°) resulting in 2-D nonplanar sheets which are further packed in a herringbone fashion in the crystal lattice (Figure S3).† On the other hand, the hydrated crystal of **2** displays a crystal structure belonging to a monoclinic centrosymmetric space group *C*2/*c*, the asymmetric unit of which contains one molecule of **2** and two molecules of water in general positions and half a molecule of **2** in a crystallographic 2-fold axis.‡ The overall assembly can best be described as a 3-D hydrogen bonded network involving the urea and water molecules (Figure S4).† The crystal structure of **3** (reported recently in a different context[9]) shows hydrogen bonded dimers which are packed in the crystal lattice further by van der Waals forces (Figure S5).† It is noteworthy that all the nongelator single crystal structures, namely **1·HCl·*x*H$_2$O**, **2**, **2·*x*H$_2$O** and **3** do not display any microporous architecture as observed in the solvated gelator structure **1·EG·H$_2$O**. It therefore appears that effective hydrogen bonding with the gelling solvent molecules is important in the present example for gelation.

In summary, we have reported the first crystal structure description of a supramolecular hydrogelator interacting with its gelling solvents. It is also the first report of a nonpolymeric hydrogelator crystallized from its gelling solvents. It may be reasonable to assume, based on the XRPD data of both gel and xerogel (see text), that the gel fibers in the native state might have a similar (may not be identical) microporous supramolecular environment wherein the gelling solvent molecules are embedded. While we recognize the importance of the identification of the crystal morph and crystal structure of the gel fiber in its native (gel) state, the single crystal structure information on the thermodynamically stable crystalline state of the gelator is as important if an alternative and more practical approach to correlating the crystal structure of a molecule with its gelling/nongelling property is to be probed. The results reported herein provide such attempts for the first time in a nonpolymeric hydrogelator.

The Department of Science & Technology, New Delhi and the Ministry of Environment and Forests, New Delhi are gratefully acknowledged for financial support. D.K.K. and D.A.J. acknowledge CSIR for an SRF fellowship.

Notes and references

‡ Crystal data for **1·EG·H$_2$O**: $C_{13}H_{18}N_4O_4$, FW = 294.31, Orthorhombic, $P2_12_12_1$, a = 8.1836(7), b = 10.6011(10), c = 16.4345(16) Å, V = 1425.8(2) Å^3, Z = 4, D_c = 1.371 g cm^{-3}, F(000) = 624, T = 100 K. Final residuals (for 258 parameters) were $R1$ = 0.0360 for 1807 reflections with $I > 2\sigma(I)$, and $R1$ = 0.0402, $wR2$ = 0.0894, GOF = 1.051 for all 1956 reflections. Crystal data for **1·HCl·*x*H$_2$O** (x = 1.66): $C_{22}H_{28}Cl_2N_8O_{5.32}$, FW = 560.54, Triclinic, *P*-1, a = 9.8236(12), b = 10.2628(12), c = 13.9993(17) Å, α = 101.696(2), β = 95.602(2), γ = 101.734(2)°, V = 1338.9(3) Å^3, Z = 2, D_c = 1.390 g cm^{-3}, F(000) = 585, T = 100 K. Final residuals (for 382 parameters) were $R1$ = 0.0493 for 4359 reflections with $I > 2\sigma(I)$, and $R1$ = 0.0718, $wR2$ = 0.1639, GOF = 1.113 for all 5734 reflections. Crystal data for **2**: $C_{11}H_{10}N_4O$, FW = 214.23, Orthorhombic, *Aba*2, a = 13.713(6), b = 6.977(3), c = 10.013(4) Å, V = 957.9(7) Å^3, Z = 4, D_c = 1.485 g cm^{-3}, F(000) = 448, T = 100 K. Final residuals (for 94 parameters) were $R1$ = 0.0348 for 583 reflections with $I > 2\sigma(I)$, and $R1$ = 0.0355, $wR2$ = 0.0868, GOF = 1.099 for all 592 reflections. Crystal data for **2·*x*H$_2$O** (x = 1.33): $C_{16.50}H_{19}N_6O_{3.50}$, FW = 357.38, Monoclinic, *C*2/*c*, a = 13.073(4), b = 11.793(7), c = 22.678(8) Å, β = 100.03(3)°, V = 3443(3) Å^3, Z = 8, D_c = 1.379 g cm^{-3}, F(000) = 1504, T = 298 K. Final residuals (for 276 parameters) were $R1$ = 0.0420 for 1494 reflections with $I > 2\sigma(I)$, and $R1$ = 0.0780, $wR2$ = 0.1039, GOF = 0.976 for all 2239 reflections. Details of data collection, structure solution and refinement for all the crystals are given in ESI. CCDC 267563–267566. See http://dx.doi.org/10.1039/b506941f for crystallographic data in CIF or other electronic format.

1 For excellent reviews on LMOGs see: (*a*) P. Terech and R. G. Weiss, *Chem. Rev.*, 1997, **97**, 3133; (*b*) D. J. Abdallah and R. G. Weiss, *Adv. Mater.*, 2000, **12**, 1237; (*c*) O. Grownwald and S. Shinkai, *Curr. Opin. Colloid Interface Sci.*, 2002, **7**, 148; (*d*) J. H. van Esch and B. L. Feringa, *Angew. Chem.*, 2000, **112**, 2351; (*e*) J. H. van Esch and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2000, **39**, 2263.

2 L. A. Estroff and A. D. Hamilton, *Chem. Rev.*, 2004, **104**, 1201 and references cited therein.

3 (*a*) F. Ilmain, T. Tanaka and E. Kokufuta, *Nature*, 1991, **349**, 400; (*b*) J. H. Holtz and S. A. Asher, *Nature*, 1997, **389**, 829; (*c*) L. Simonsen, L. Hovgaard, P. B. Mortensen and H. Brondsted, *Eur. J. Pharm. Sci.*, 1995, **3**, 329; (*d*) Y. Osada and J. P. Gong, *Adv. Mater.*, 1998, **10**, 827; (*e*) J. M. Weissman, H. B. Sunkara, A. S. Tse and S. A. Asher, *Science*, 1996, **274**, 959; (*f*) A. K. Andrianov, S. Cohen, K. B. Visscher, L. G. Payne, H. R. Allcock and R. J. Langer, *J. Controlled Release*, 1993, **27**, 69; (*g*) Y. Osada and A. R. Khokhlov, *Polymer Gels and Networks*; Marcel Dekker, New York, 2002; (*h*) Y. H. Chu, J. K. Chen and G. M. Whitesides, *Anal. Chem.*, 1993, **65**, 1314; (*i*) K. Lee and S. A. Asher, *J. Am. Chem. Soc.*, 2000, **122**, 9534; (*j*) J. C. Tiller, *Angew. Chem., Int. Ed.*, 2003, **42**, 3072.

4 E. Ostuni, P. Kamaras and R. G. Weiss, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1324; E. Ostuni, P. Kamaras and R. G. Weiss, *Angew. Chem.*, 1996, **108**, 1423.

5 (*a*) D. Krishna Kumar, D. A. Jose, P. Dastidar and A. Das, *Langmuir*, 2004, **20**, 10413; (*b*) D. R. Trivedi, A. Ballabh and P. Dastidar, *Chem. Mater.*, 2003, **15**, 3971; (*c*) A. Ballabh, D. R. Trivedi and P. Dastidar, *Chem. Mater.*, 2003, **15**, 2136; (*d*) D. R. Trivedi, A. Ballabh, P. Dastidar and B. Ganguly, *Chem.–Eur. J.*, 2004, **10**, 5311; (*e*) D. Krishna Kumar, D. A. Jose, P. Dastidar and A. Das, *Chem. Mater.*, 2004, **16**, 2332; (*f*) P. Dastidar, S. Okabe, K. Nakano, K. Iida, M. Miyata, N. Tohnai and M. Shibayama, *Chem. Mater.*, 2005, **17**, 741.

6 D. B. Grotjahn and C. Joubran, *Tetrahedron: Asymmetry*, 1995, **6**, 745.

7 (*a*) R. Luboradzki, O. Gronwald, M. Ikeda, S. Shinkai and D. N. Reinhoudt, *Tetrahedron*, 2000, **56**, 9595; (*b*) S.-I. Tamaru, R. Luboradzki and S. Shinkai, *Chem. Lett.*, 2001, 336.

8 M. D. Hollingsworth and K. D. M. Harris, in *Comprehensive Supramolecular Chemistry, Vol. 6*, ed. D. D. MacNicol, F. Toda and R. Bishop, Pergamon, Oxford, 1996, pp. 177.

9 P. S. Corbin and S. C. Zimmerman, *J. Am. Chem. Soc.*, 2000, **122**, 3779.