Probing Gelation at the Molecular Level: Head-to-Tail Hydrogen-Bonded Self-Assembly of an Inositol-Based Organogelator

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A simple cyclitol derivative has been found to gelate many low-polar solvents. A detailed molecular level investigation demonstrated that the intermolecular head-to-tail hydrogen bond plays a key role in the self-assembly of the monomers to generate supramolecular polymeric fibres. Such self-assembled oligomeric forms could be detected even in a competing protic solvent. Control experiments further established that optimally oriented hydroxy groups and chirality are the crucial factors for the gelation.

Introduction

There has been increased interest in low molecular weight gelators of organic solvents, due to their reversible natures and possible application in different fields.[1−9] Although this branch of supramolecular chemistry is continually developing, it is still in its infancy, as prediction of gelation ability on the basis of the chemical structure remains an unattained goal. A widely accepted mechanism of gelation is the spontaneous self-assembly of individual molecules into fibres and subsequent entanglement of these fibres into fibrous networks, including solvents in the interstices. Since the fibre formation step involves some sort of order or selectivity at the molecular level during the self-assembly, engineering of the fibre formation step by a suitable choice of supramolecular glues (noncovalent interactions) is the crucial step in designing an efficient gelator. The driving force for the self-assembly of molecules into fibres are noncovalent forces such as H-bonding, van der Waals interactions, π-π stacking, solvophobic interactions etc. The actual cause of gelation in a gelator displaying more than one such possible interaction could be a co-operative interplay between these different forces. Knowledge of the individual contributions of such non-covalent interactions would be desirable for the rational design of efficient gelators. Simple gelators with only one such possible non-covalent interaction are thus desirable for study of the contributions of such supramolecular glues towards gelation. Here we report an inositol-based gelator with only hydrogen bonding (other than van der Waals interactions) as the non-covalent interaction.

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Results and Discussion

During our ongoing program to synthesise various phosphoinositols, we serendipitously observed that 1D-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**1**)[10] gels with benzene. A systematic gelation experiment was carried out, and it was found that many low-polar solvents (mostly aromatic solvents) form gels with diol **1** at concentrations of 1−2 wt.-% (Table 1). While **1** dissolved in solvents such as chloroform, dichloromethane, methanol, ethanol, propanol, pyridine, DMSO, tetrahydrofuran, acetone and water (at 2 wt.-%), it was insoluble in diethyl ether and hexane, but very low concentrations of **1** in hexane resulted in a partial gel. In gelling solvents (Table 1), at concentrations lower than the CGC (critical gel concentration), the gel phase in some cases separated out of the solvent phase but in some other cases the gel dissolved to form a sol. The textures of these gels were examined by SEM pictures of their xerogels

Table 1. Physical data for gels of **1** with various solvents

Solvent	CGC in wt.-%	T_{Gel} in °C	Appearance
Benzene	0.7	80	transparent
Toluene	1.0	74	transparent
Chlorobenzene	1.0	60	transparent
o-Xylene	1.3	71	transparent
p-Xylene	1.2	74	transparent
m-Xylene	1.5	69	transparent
Ethylbenzene	2.0	57	transparent
CCl_4	2.0	77	cloudy

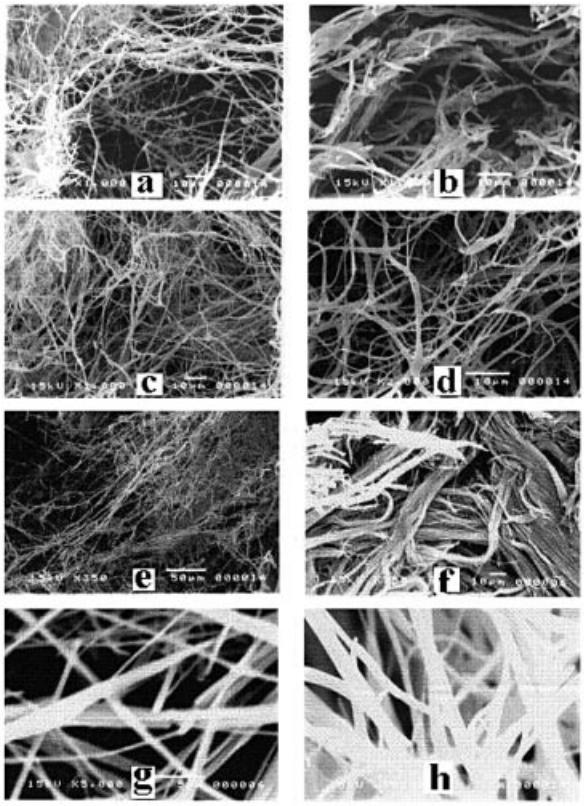
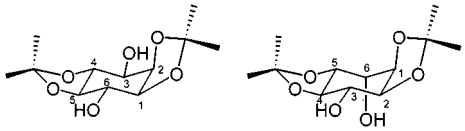


Figure 1. SEM pictures of: (a) benzene, (b) CCl_4, (c) toluene, (d) chlorobenzene, (e) *o*-xylene, (f) ethylbenzene, (g) *p*-xylene, and (h) *m*-xylene gels; scale bar corresponds to 10 μm

(Figure 1). As diol **1** is structurally simple, we set out to investigate the mechanism of gelation of diol **1** at the molecular level.



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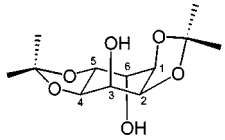

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Since **1** has two hydroxy groups arranged at the 1,4-positions of a cyclohexane ring, hydrogen bonding is believed to be responsible for the supramolecular polymerisation of monomers into fibres and subsequent entanglement. Shinkai et al. have carried out extensive investigations[11−23] into gelation of 4,6-benzylidene derivatives of various monosaccharides and have reported[24] that monosaccharide derivatives possessing two hydroxy groups, which form one-dimensional hydrogen-bonding arrays, are ideal candidates to be good gelators. Since inositols are structurally similar to carbohydrates (monosaccharides), such a generalisation can also be extended to inositols.

The FTIR spectrum of benzene gel (neat) showed a broad peak in the 3300−3500 cm^{-1} range, suggesting a hydrogen-bonded structure. A chloroform solution of diol **1** also showed peaks similar to those seen in the case of the benzene gel, suggesting that similar hydrogen bonding exists in chloroform solution, also even though no gel is formed. In addition, the IR spectra did not show any peak due to free OH groups, suggesting that both the hydroxy groups are involved in the hydrogen bonding. Since the hydroxy groups are disposed equatorially at 1,4-positions in a cyclohexane ring, intramolecular hydrogen bonding between them is ruled out, so it was inferred that intermolecular hydrogen bonding must exist in both benzene and chloroform solutions of diol **1**. The observed gelation can thus be explained in terms of this intermolecular H-bonding resulting in the supramolecular polymerisation of **1** into long fibres and subsequent entanglement.

To substantiate this line of thought, a concentration-dependence NMR experiment was put forward. Since **1** gels with benzene at low concentrations, a concentration-dependence NMR study in C_6D_6 appeared difficult. If self-assembly through hydrogen bonding were responsible for the gelation in benzene, though, it would also be reasonable to expect similar hydrogen bonding in other low-polar solvents. Since the IR spectra in benzene gel and in $CHCl_3$ solution were identical, we assumed similar intermolecular interactions in benzene and $CHCl_3$, and so a concentration-dependence NMR study in $CDCl_3$ was carried out.[25] Both the hydroxy groups shift downfield with concentration, suggesting that strong intermolecular hydrogen bonding exists even in chloroform (Figure 3). This could be either head-to-tail or head-to-head hydrogen bonding. To provide an insight into how the molecules are arranged, a NOESY experiment was carried out.

The NOESY spectrum (Figure 4) showed cross-peaks between 3-OH and 6-OH, which could be explained only on the basis of head-to-tail hydrogen bonding. In addition, C-3−OH showed minor cross-peaks with C-5−H and C-1−H as a result of head-to-tail arrangement. The fact that H-H COSY NMR (Figure 5) also showed such a cross-coupling between 3-OH and 6-OH suggests that the hydrogen-bonded system is very strong (like that in a covalent bond) and spatially rigid (on NMR time scales). Further important information obtained from the COSY spectrum is the coupling between C-6−OH and C-2-H. Such coupling is possible only between two adjacent molecules arranged in a head-to-tail fashion. These experiments unequivocally establish self-assembly through hydrogen bonding even in chloroform solution, although **1** does not form a gel with chloroform. This is not surprising as the gelation depends on various external factors such as concentration, temperature, solvent etc. even after self-assembly into supramolecular polymer (fibre) is achieved.[26−27]

The ^3J_H coupling constant of C-3−OH (10 Hz in C_6D_6 and 8.8 Hz in $CDCl_3$) in the ^1H NMR spectrum of **1** is

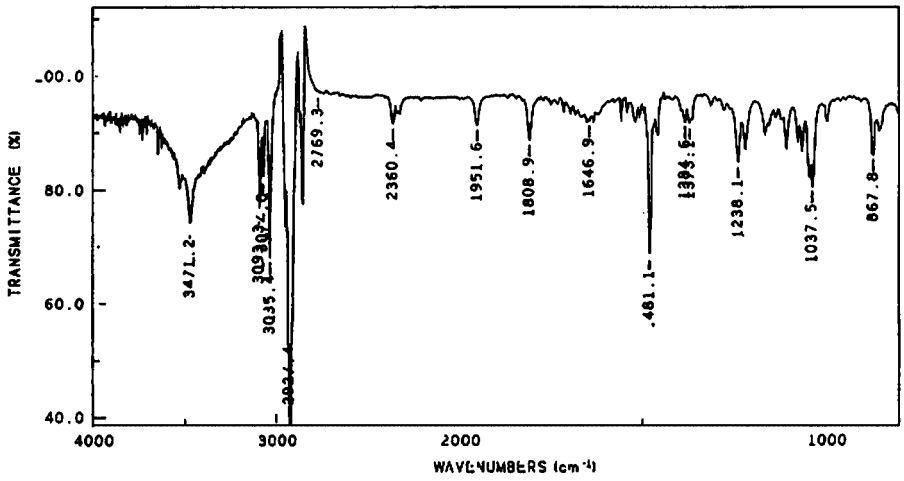


Figure 2. FTIR spectrum of benzene gel

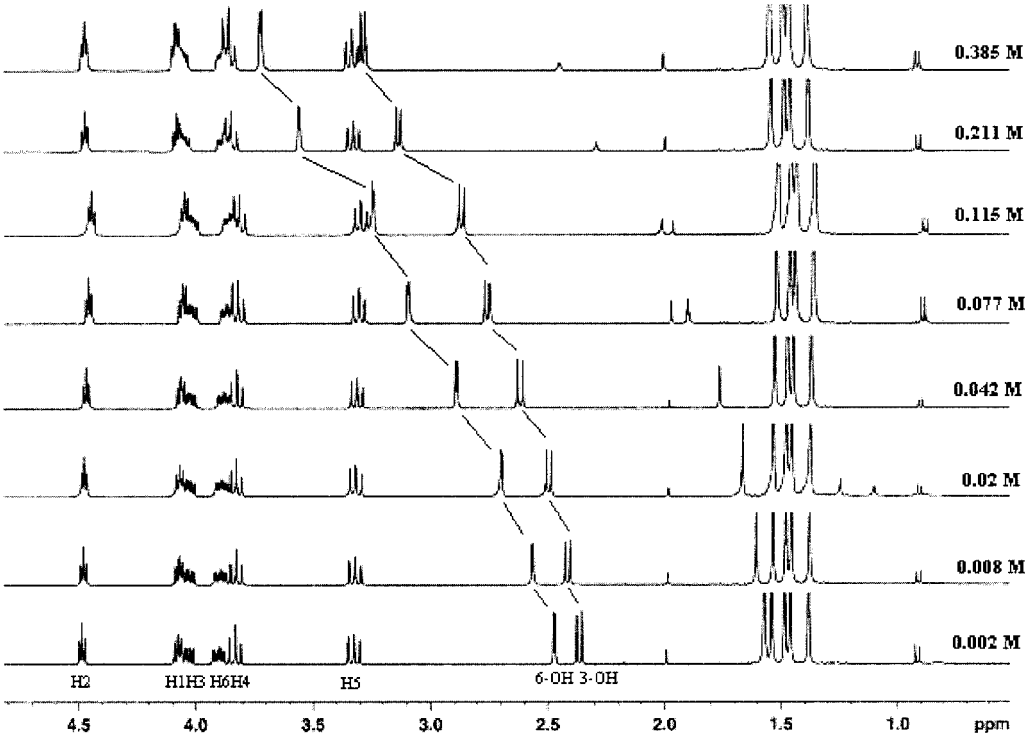


Figure 3. Concentration-dependent ^{1}H NMR of **1** in $CDCl_3$

found to be larger than that of C-6−OH (4 Hz in C_6D_6 and 2.9 Hz in $CDCl_3$). The larger coupling constant suggests that the dihedral angle between H-3 and 3-O−H is near to 180° (*anti*) or 0° (*syn*), while the cross-peaks of C-3−OH with H-6 and H-4 in the NOESY spectrum suggests that H-3 and 3-OH are *anti* (near to 180°). Although both the hydroxy groups show downfield shifts with concentration, the relative magnitude of the shift is larger for C-6−OH, suggesting that C-6−OH is more likely to be the hydrogen-bond donor. Moreover, both NOESY and COSY NMR suggests a head-to-tail arrangement of monomers. The cross-peak between C-6−OH and H-2 suggests that they are very near and that the assembly is tightly held as in a covalent bond. From these NMR results, a plausible arrangement and interaction at the molecular level could be as shown in Figure 6. Such an arrangement would explain all the NMR results reasonably well.

Cold spray ionisation mass spectroscopy (CSI MS) has emerged as an excellent means with which to detect supramolecular assemblies held together by non-covalent interactions.[28−34] Although we expected CSI MS to provide peaks due to higher polymeric forms, gelation and the instrumental limitations did not allow the CSI MS of benzene and chloroform solutions to be recorded, but diol **1** in a solvent mixture containing 90% MeOH and 10% benzene showed peaks due to a hexamer. More surprisingly, it was

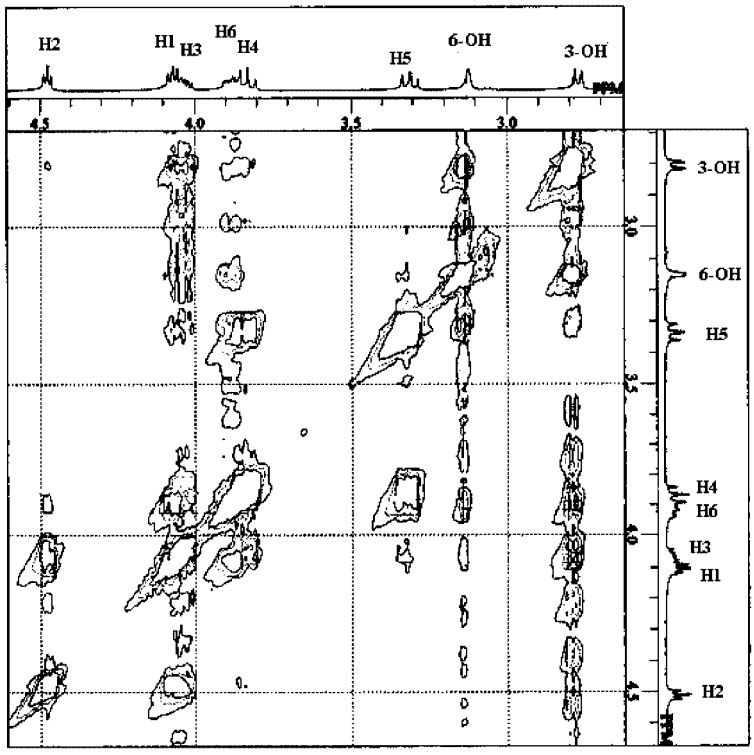


Figure 4. NOESY spectrum of **1** in $CDCl_3$

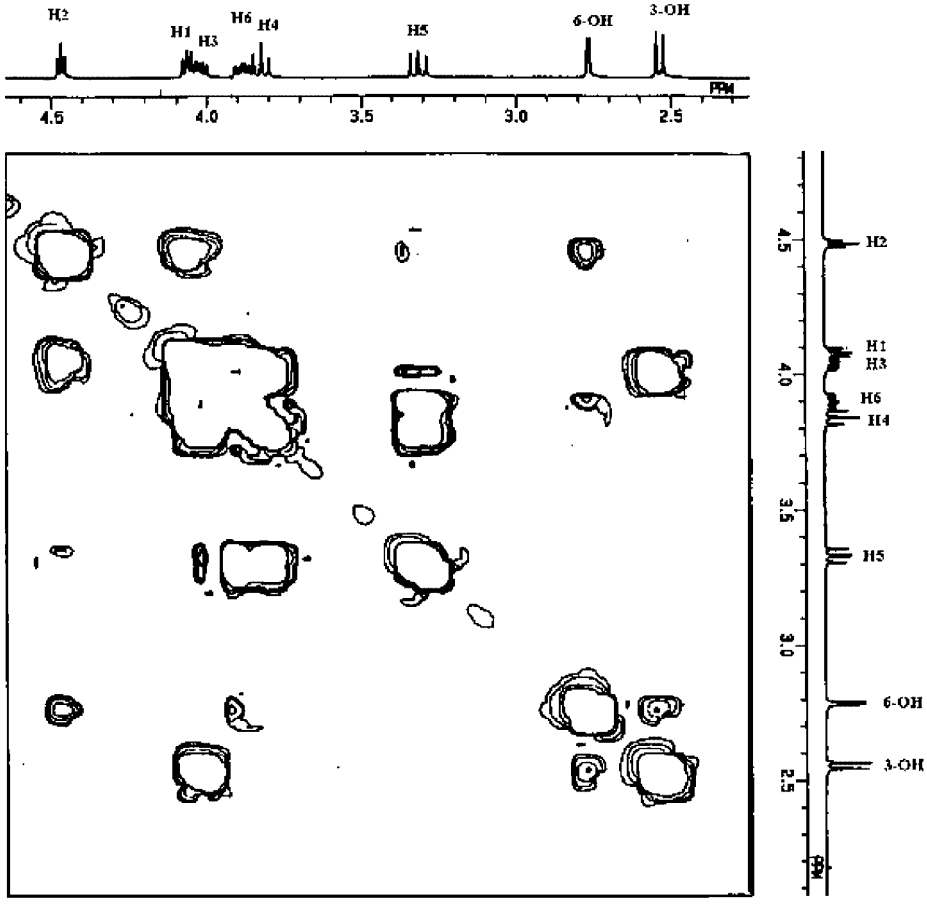
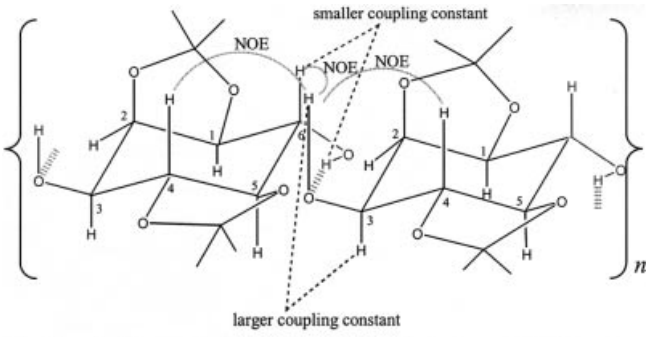


Figure 5. H-H COSY spectrum of **1** in $CDCl_3$



Plausible mode of aggregation of **1** showing explanation for the observed NMR interactions

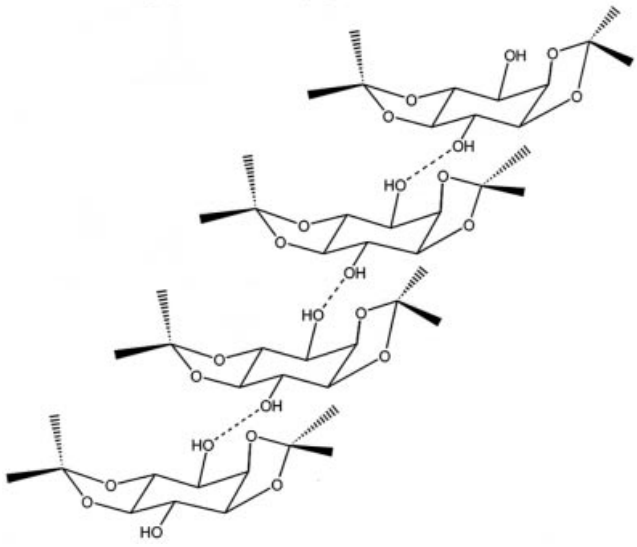


Figure 6. Mode of assembly of **1** in solution and gel

found that diol **1** in pure methanol (1 mM) also showed such oligomeric peaks up to a hexamer state (Figure 7). It is interesting to observe such a hydrogen-bonded assembly even in a protic solvent. It is noteworthy that the molar ratio of diol **1** to the competing MeOH in such a solution is 1:25000. This interesting observation demonstrates that the intermolecular hydrogen bonding is very much stronger and self-assembly (self-recognition) is predominant over solvation (hydrogen bonding with competing MeOH bulk).

The powder XRD of freeze-dried benzene gel (Figure 8) showed a low-angle sharp peak, demonstrating the supramolecular ordering in the gel state. The small-intensity sharp peaks at higher values of 2θ also suggest molecular ordering as in a crystal.

The effect of chirality on gelation is a topic of much controversy and until now it has not been possible to generalise. In some cases chirality is an essential factor for gelation, while in other cases it is not a prerequisite. There are also reported instances[35−36] in which racemic derivatives are better gelators than the homochiral ones. To address the effect of chirality in our case, gelation experiments with racemic **1** were carried out. The fact that the racemic diol (±)-**1** did not gelate any of the solvents suggests that chirality has an essential role[37] for the gelation of diol **1**. To address the effect of the relative orientations of hydroxy groups on gelation, the isomeric diols, 1L-1,2:4,5-di-*O*-isopropylidene-*chiro*-inositol (**2**) and 1L-1,2:4,5-di-*O*-isopropylidene-*allo*-inositol (**3**) with one or both hydroxy groups inverted (with respect to **1**), were synthesised. Surprisingly, neither the *chiro*-diol **2** nor the *allo*-diol **3** gelated any of the solvents tested. This fact led us to infer that the specific orientation or preorganisation of hydroxy groups in **1** is important for gelation. This is in agreement with Shinkai et al.'s observation that the gelation in monosaccharides depends on the orientation of hydroxy groups.[11−15]

Diol **1** is conformationally frozen with two ketal rings, and the contribution of such conformational locks towards gelation cannot be ignored. A perusal of the literature revealed that the majority of the organogelators so far re-

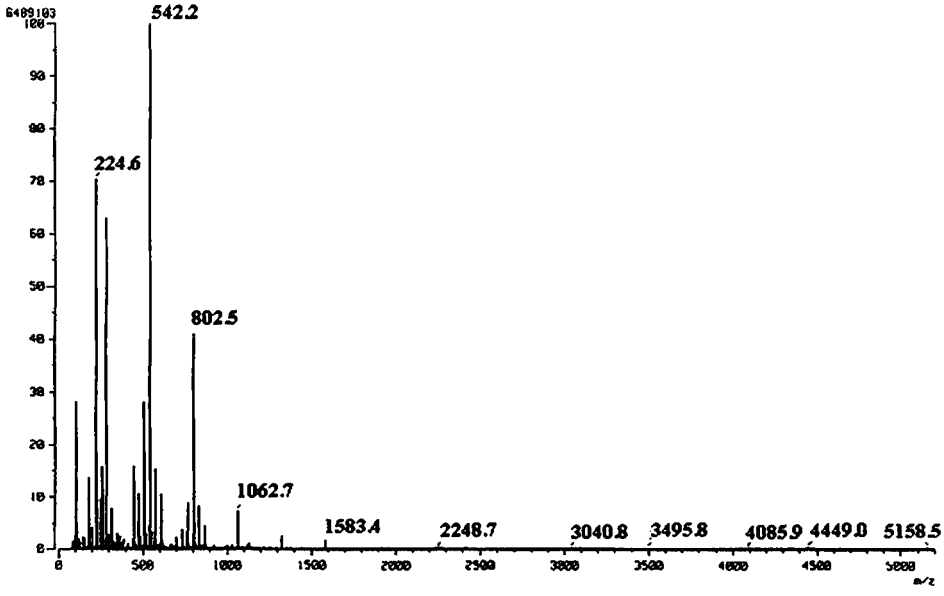


Figure 7. CSIMS of **1** in methanol at 1 mM concentration

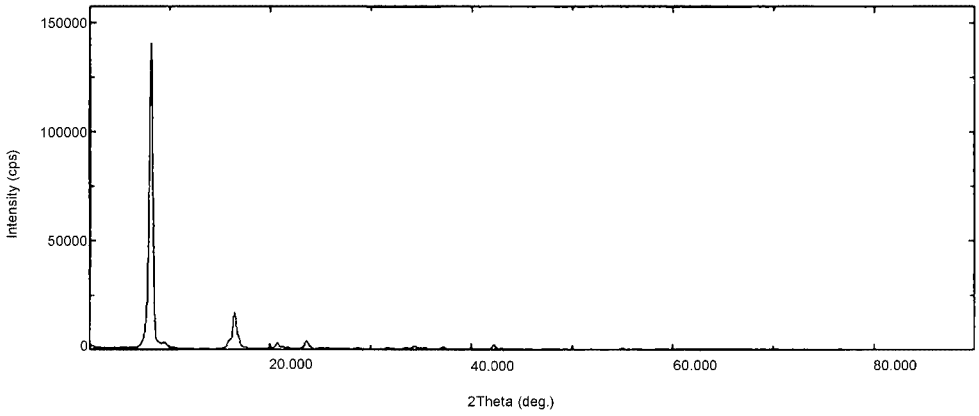


Figure 8. Powder XRD spectrum of benzene xerogel

ported contain conformational locks in the monomeric unit. All the sugar-based gelators, for instance, contain a benzylidene conformational lock, while cholesterol-based gelators and urea-based gelators[25] are inherently rigid. This conformational freezing of the monomer could aid in pre-organising and directing the non-covalent forces to self assemble.

Conclusion

In conclusion, the observed gelation of diol **1** has been investigated at the molecular level in order to identify how the molecules self-assemble and to elucidate the controlling factors for such gelation. Specifically oriented hydroxy groups and chirality are essential features in this gelator. These results demonstrate that highly directional hydrogen bonds can give rise to self-assembly even in methanol, a competing solvent. These observations may become the basis for the design of smart materials. As the gelator **1** displays only hydrogen bonding interactions and van der Waals interactions as its supramolecular glues, further reinforcement of gelation by suitable functionalisation may be possible. Since there are nine isomeric inositols and many different diol derivatives can be made from each isomer by application of known protection-deprotection strategies,[38] inositols offer a prospective library of molecules as potential supramolecular synthons. Inositol being a bio-molecule, and since these derivatives self-assemble even in protic solvents, there is much scope for development of inositol-based hydrogelators for use in biological applications: as drug carriers, for example. Structural variations and extensive screening in these systems are underway and will be reported in a full account elsewhere.

Experimental Section

General Remarks: Powder XRD was recorded with a Rigaku RINT 2100 X-ray diffractometer. ^{1}H NMR spectra were recorded with a Bruker DPX 400 instrument. NMR signal assignments were made by use of 2D NMR and vicinal H-H coupling constants. SEM pictures were taken in a JEOL JSM-5310 scanning electron microscope. IR spectra were recorded with a HORIBA FT-210 IR spectrometer. Racemic diol (±)-**1**[39] and the optically active diols **1**,[10] **2**[40] and **3**[40] were prepared as reported.

Gelation Experiment: The sample (about 10 mg) was heated in the solvent (1 mL) in a capped vial until it dissolved. The hot solution was allowed to cool slowly to room temperature and was classified as a gel if the cooled solution did not fall or move when turned upside down.

T_{gel} Determination: A small amount of gel in a test tube was heated slowly in an oil bath. The temperature at which the gel moved on tilting of the test tube was noted as the T_{gel}. T_{gel} increased with the concentration of the gelator as expected.

SEM Measurement: The gel was freeze-dried to a xerogel. The volume did not change from wet gel to xerogel. A small amount of xerogel was sputter-coated with gold, and the texture was observed under a JEOL JSM-5310 scanning electron microscope at an accelerating voltage of 15KV. Fibrous networks were observed in all cases (Figure 1). Xerogels obtained from CCl_4 (see b in Figure 1) and ethylbenzene (see f in Figure 1) showed bundles of fibres instead of fibrous networks. This explains the relatively higher CGCs for these solvents.

Acknowledgments

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