Solvent Effect on Organogel Formation by Low Molecular Weight Molecules

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Solvent−gelator interactions play a key role in mediating organogel formation and ultimately determine the properties of the gel. The effect of solvent on organogel formation was investigated in selected ester, ketone, and alcoholic solvents using unique symmetrical trehalose diesters as gelators. In solvents of the same class the gelation number (defined as the ratio of solvent molecules that gel per gelator molecule) decreased for trehalose 6,6′-diacetate and 6,6′-dibutyrate as the solvent Hildebrand solubility parameter increased. The opposite was observed for trehalose 6,6′-didecanoate and 6,6′-dimyristate. In general, the gelation numbers for all the gelators studied decreased in the order of esters > ketones > alcohols. Alcohols, which are capable of hydrogen bonding and can make substantial contribution to the total solvent−gelator interaction, significantly compromise gel formation. Optical microscopy and scanning electron microscopy revealed that for systems with high gelation numbers, such as trehalose 6,6′-diacetate and 6,6′-dibutyrate in ethyl acetate and trehalose 6,6′-didecanoate and 6,6′-dimyristate in acetonitrile, thin, flexible, and highly entangled nanofibers were formed. Conversely, thick, rigid, and often highly clustered fibers accompanied systems with poor gelation, such as gels formed from trehalose 6,6′-diacetate and 6,6′-dibutyrate in acetonitrile. Understanding the role of solvent in organogel formation is crucial in designing gels with desired structure and physicochemical properties. Such designed gels may provide controlled gelation by fine-tuning the solvent or the chemical environment of the gelator.

Introduction

Organogels have attracted increasing interest in recent years[1] due to their promising physical and morphological properties and potential use as templated materials,[2−5] drug delivery agents,[6−9] cosmetics,[10] enzyme immobilization matrixes,[11−13] and separation media.[14] While it is well-known that physical forces, including hydrogen bonding, hydrophobic interaction, and $\pi-\pi$ stacking, mediate thermoreversible organogel formation,[15] and that there are many known low molecular weight organogelators, very little is known about the mechanism of gel formation and the influence of gelator structure on gel behavior.[16,17] Gel network structure and molecular bonding information have been investigated using X-ray diffraction/scattering,[18−22] small-angle neutron scattering,[23] and ^{1}H NMR spectra[24] and FT-IR.[25] The mechanism of gelation has also been explored, and significant contributions of spinodal decomposition and nucleation−crystallization have been proposed.[26−29] However, the mech-

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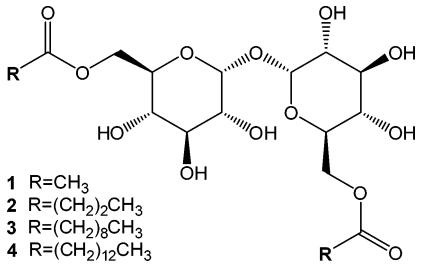

Figure 1. Trehalose-based gelator structures.

anism of molecular assembly in different solvents remains largely unknown. In particular, the heterogeneous nature of organogels consist of specific interactions of solvent and gelator molecules, and the critical interactions among these molecules govern the process of gelation and the physical behavior of the resulting gels. Therefore, key information on gel assembly is needed with respect to gelation in different solvents to reveal the relationship between solvent−gelator interactions during gelation.

Recently, we designed a family of enzymatically synthesized, highly symmetrical trehalose 6,6′-diesters (structures shown in Figure 1), which possessed excellent gelator properties over a broad spectrum of organic solvents.[30] The hydroxyl groups on trehalose, which can form intermolecular hydrogen bonds, were considered as the primary driving force for gel assembly. However, different gelation behavior was also observed in different solvents by varying the acyl chain length. Thus, H-bonding alone is insufficient to fully describe gelation in this sugar-based system. In the current work, we have used trehalose diester gelators to study the solvent effect on gel formation. We show that solvation power of the solvent and intergelator hydrophobic interactions are critical and compete with intergelator H-bonding interactions to govern gel assembly and resulting gel structure.

Experimental Section

Materials. Trehalose dihydrate, silica gel (grade 9385, 230−400 mesh), and all organic solvents were purchased from Sigma-Aldrich (St. Louis, MO). All solvents were dried over 3 Å molecular sieves at least 24 h prior to use to remove residual water. Novozym 435 (lipase B from *Candida antarctica*) was obtained from Biocatalytics Inc. (Pasadena, CA) and used without further treatment. Vinyl esters were obtained from TCI America (Portland, OR).

Trehalose Diester Synthesis. Trehalose 6,6′-diesters were synthesized as described previously.[30] Typically, 1.5 g of Novozym 435 was added to 100 mL of acetone containing 0.01 mol of trehalose dihydrate and 0.03 mol of a vinyl ester. The reaction mixtures were shaken at 200 rpm at 45 °C for 48 h. Product formation was monitored by thin layer chromatography (TLC) with the eluent ethyl acetate:methanol:water = 17:4:1 (v/v). The reactions were terminated by filtering off the solid enzyme and unreacted trehalose, and the solvents were removed by rotary evaporation. The crude products were purified by flash chromatography packed with silica gel using a mixture of ethyl acetate, methanol, and water (17:4:1, v/v) as the eluent. The isolated product yields ranged from 50 to 80% based on reacted trehalose dihydrate.

Gelation Number and Structure. The gelation number, which expresses the maximum number of solvent molecules gelled per gelator molecule, was determined by measuring the minimum amount of gelator required to gel the entire solvent at 25 °C. Gel microstructures were evaluated using a Nikon Eclipse TE 200 inverted microscope. A 4 mL glass vial containing 0.5 mL of gel was placed atop a glass slide and digital images were acquired by Spot software (version 4.1, Diagnostic Instruments Inc.). Field-emission scanning electron microscopy (FE-SEM) images were captured using a JEOL scanning electron microscope. Gel samples were placed on a silicon wafer and dried by slow evaporation of the solvent. The dried samples were coated with Au/Pd before imaging.

Critical Gelator Concentration. Trehalose 6,6′-dibutyrate was added to acetonitrile with weight percents ranging from 0.03 to 0.79. All samples were heated to dissolve completely the gelator and then cooled in a water bath (25 °C) for 5 h. The gelator concentration in the solution phase was determined by HPLC (Shimadzu SCL-10A *vp* with SPD-M10A detector, 95% acetonitrile and 5% water as mobile phase, column temperature at 35 °C). A similar procedure was applied to ethyl acetate using the same gelator.

Results and Discussion

In our previous work,[30] we discovered that trehalose diesters were capable of gelling a broad array of organic solvents ranging from highly hydrophilic acetonitrile to highly hydrophobic cyclohexane at low concentrations (as low as 0.04% (w/w) for trehalose 6,6′-diacetate in ethyl acetate and similarly as low in methyl methacrylate). In the current work, we enzymatically synthesized and subsequently purified four trehalose 6,6′-diesters spanning from diacetate (gelator **1**) to dimyristate (gelator **4**), as depicted in Figure 1. Selected solvents were used to study the solvent effect on gelation, including esters (methyl acetate, ethyl acetate, propyl acetate, and butyl acetate), ketones (acetone, 2-butanone, and 2-pentanone), alcohols (1-butanol, 1-pentanol, and 1-hexanol), and acetonitrile. With this diversity in acyl chain length and solvent spectrum, we proceeded to examine the influence of solvent−gelator interactions on organogel formation.

Influence of Solvent on Gelation. The gelation of low molecular weight molecules in organic solvents is a result of the gelator−gelator and solvent−gelator interactions, both of which involve specific and nonspecific intermolecular forces. The former refers to H-bonding, which can be further distinguished as H-bond donor (HBD or solvent acidity) or H-bond acceptor (HBA or solvent basicity) interactions. The latter include dipole−dipole, dipole-induced, and instantaneous dipole-induced forces (also called dispersion forces). The influence of these forces on gelation is critical for understanding the process of gel formation. In particularly, correlations of gelation number to solvent parameters can provide useful information on the specific interactions that dominate gel formation using the sugar ester gelators. Among various empirical solvent scales, the Hildebrand solubility parameter (denoted as δ) is derived from the cohesive energy density of the solvent and directly reflects the total forces that hold solvent molecules together.[31] The solvent polarity scale $E_T(30)$ is perhaps the most comprehensive and widely

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Table 1. Solvent Properties (Hildebrand Solubility Parameter δ, Polarity Parameter $E_T(30)$, Solvent Polarity−Polarizability SPP, Solvent Basicity SB, and Solvent Acidity SA) and Gelation Number (Maximum Number of Solvent Molecules Gelled per Gelator) of Gelators 1−4 in Different Solvents at 25 °C

	solvent properties					gelation number			
solvent	δ[a] ($cal^{1/2}\ cm^{-3/2}$)	$E_T(30)$[b] (kcal mol^{-1})	SPP[c]	SB	SA	1	2	3	4
methyl acetate	9.6	38.9	0.785	0.527	0.000	3490	1740	1250	970
ethyl acetate	9.1	38.1	0.795	0.542	0.000	12000	4370	1050	798
propyl acetate	8.8	37.5	0.782	0.548	0.000	12200	5180	840	573
butyl acetate	8.6	38.5	0.784	0.525	0.000	12500	6790	673	457
acetone	10	42.2	0.881	0.475	0.000	2130	809	845	959
2-butanone	9.3	41.3	0.881	0.520	0.000	2270	1180	660	573
2-pentanone	8.9	41.1	0.883	0.537	0.010	2480	1700	502	393
1-butanol	11.4	49.7	0.837	0.809	0.347	788	378	321	399
1-pentanol	10.9	49.1	0.817	0.860	0.319	878	531	232	336
1-hexanol	10.7	48.8	0.810	0.879	0.315	978	682	190	293
acetonitrile	11.6	45.6	0.895	0.286	0.044	2860	1690	8660	16700

[a] Data taken from ref 35. [b] Data taken from ref 32. [c] Data taken from ref 33.

used solvent scale and is based on the solvatochromic measurement of the pyridinium-*N*-phnoxide betaine dye, which is a good indicator of solvent polarity.[32] The Catalan solvent polarity−polarizability (SPP) scale is given by the difference between the solvatochromism of the probe 2-*N*,*N*-dimethyl-7-nitrofluorene and its homomorph 2-fluoro-7-nitrofluorene. SPP overcomes common drawbacks encountered by using a single probe.[33] These key solvent parameters may therefore be considered highly suitable for studying solvent−gelator interactions.

To that end, we chose Hildebrand solubility parameter δ to represent the total forces in a solvent, the polarity parameter $E_T(30)$ to represent the solvent−gelator interactions (the $E_T(30)$ measures the sum of nonspecific polarity/polarizability and specific solvent HBD/solute HBA interactions), and the Catalan polarity/ polarizability scale SPP, solvent acidity (SA scale), and solvent basicity (SB scale) to assess the influence of nonspecific and specific forces on gel formation.

Selected ester, ketone, and alcoholic solvents (Table 1), which are capable of supporting gelation, were chosen to study solvent−gelator interactions. The effect of Hildebrand solubility parameter δ on gelation is shown in Figures 2a−2c. Although δ does not reflect gelator−solvent molecular interactions, it does serve as a useful indicator of the solvation power of the solvent toward the gelators and, therefore, impacts gelation. Indeed, clear trends were obtained in all three types of solvents, with the gelation numbers decreasing for gelators **1** and **2**, while increasing for **3** and **4** at higher δ values.

Within each solvent class, δ increases as a result of reduced solvent molecular size and represents higher solvation of polar gelators. Therefore, solvents with high δ values would be expected to interact with the more polar gelators **1** and **2** to a greater extent than with the more nonpolar gelators **3** and **4**. This compromises the intergelator H-bonding interactions responsible for gelator assembly, leading to reduced gelation numbers. Conversely, the interaction of gelators **3** and **4** with solvents of higher δ values is expected to be weakened due to the long hydrophobic acyl chains, which facilitates gelator assembly and leads to higher gelation numbers.

The effect of the acyl chain length on gelation is shown in Figures 2d−2f. In general, the gelation number decreased as the acyl chain lengths on the gelator increased up to C10, although in acetone and alcohols further decrease in gelation number beyond C10 was not observed. This may be explained by the lateral hydrophobic interactions that are strengthened as acyl chain lengths increase, which weakens the directional H-bonding forces, thereby causing lower gelation numbers.

Interestingly, Figures 2d−2f indicate crossover points at which gelation number is independent of solvent. Specifically, gelators with C_8−C_9 acyl chains are insensitive to the property of the solvent within a given solvent series, e.g., esters, ketones, or alcohols. Furthermore, the effect of acyl chain length is substantially more significant for shorter acyl chains than for longer ones. At these crossover points, we hypothesize that the gelator molecule possesses a critical balance of sugar-dependent H-bonding and acyl chain-dependent hydrophobic interactions. Such hydrophilic/hydrophobic balance is well-known in the molecular assembly of biological membranes[34] and thus may be relevant in the assembly of sugar-based organogels.

The influence of solvent type on gelation number is shown in Figure 3 using $E_T(30)$ as the solvent property. Gelation numbers decreased in the order of esters > ketones > alcohols as $E_T(30)$ values increased. To assess the contribution of specific and nonspecific interactions, we took advantage of the correlation of $E_T(30)$ to other solvent properties, as provided in eq 1,[32] with the calculated values for each solvent given in Table 2.

$$E_T(30) = 20.1 \cdot \mathrm{SPP} + 24.9 \cdot \mathrm{SA} + 3.9 \cdot \mathrm{SB} + 20.7 \quad (1)$$

Unlike esters and ketones, in which nonspecific polarity/polarizability interactions are strongest, in alcohols H-

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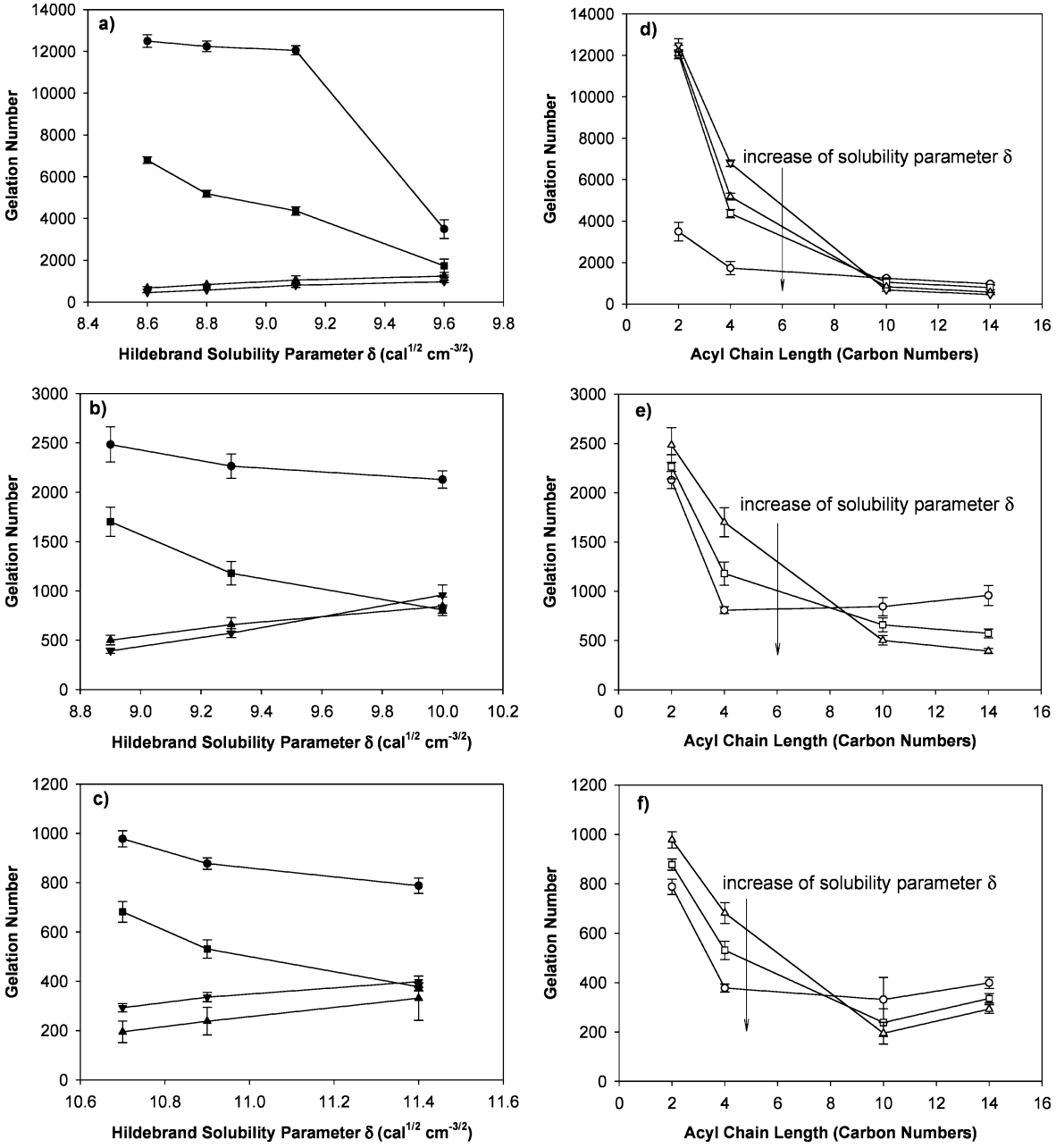

Figure 2. Effect of Hildebrand solubility parameter δ ($cal^{1/2}$ $cm^{-3/2}$) and gelator structure on gelation number. (a)−(c) Effect of solvent δ; (d)−(f) effect of gelator acyl chain length. (a) Esters; (b) ketones; (c) alcohols. In (a)−(c), (●) trehalose diacetate, (■) trehalose dibutyrate, (▲) trehalose didecanoate, and (▼) trehalose dimyristate. In (d), (○) methyl acetate, (□) ethyl acetate, (△) propyl acetate, and (▽) butyl acetate; in (e), (○) acetone, (□) 2-butanone, and (△) 2-pentanone; in (f), (○) 1-butanol, (□) 1-pentanol, and (△) 1-hexanol.

bonding substantially contributes to the overall solvent−gelator interaction (the ratio of H-bonding/nonspecific interactions is highest in alcohols among the solvent types studied). This compromises gelator−gelator H-bonding interactions, which lead to poor gelation. In esters and ketones, which are far less potent H-bonding solvents compared to alcohols, nonspecific forces dominate solvent−gelator interactions; therefore, gelation numbers are relatively high.

One notable exception to this solvent trend is acetonitrile, in which gelators **3** and **4** have much higher gelation numbers than in any other solvents despite the fact that this solvent has comparable specific and nonspecific interactions to that of the ketones. The cause of this behavior is unclear, yet it implies that more complicated gelator−solvent interactions may exist.

Gel Structure. To gain further insight into the solvent effect on gel structure, we examined the micro- and nanoscale structures of gels formed in ethyl acetate, a good gelation solvent for gelators **1** and **2**, and acetonitrile, a good gelation solvent for gelators **3** and **4**. Microscopic images of the gels are shown in Figure 4. Gelators **1** and **2** formed stable gels at high gelation numbers (12000 and 4370, respectively) in ethyl acetate and the corresponding microscopic images (Figures 4a and 4b, respectively) revealed finely entangled fibers. Conversely, gelators **3** and **4** formed weak gels in ethyl acetate, which were found to consist mainly of amorphous aggregates (Figures 4c and 4d, respectively).

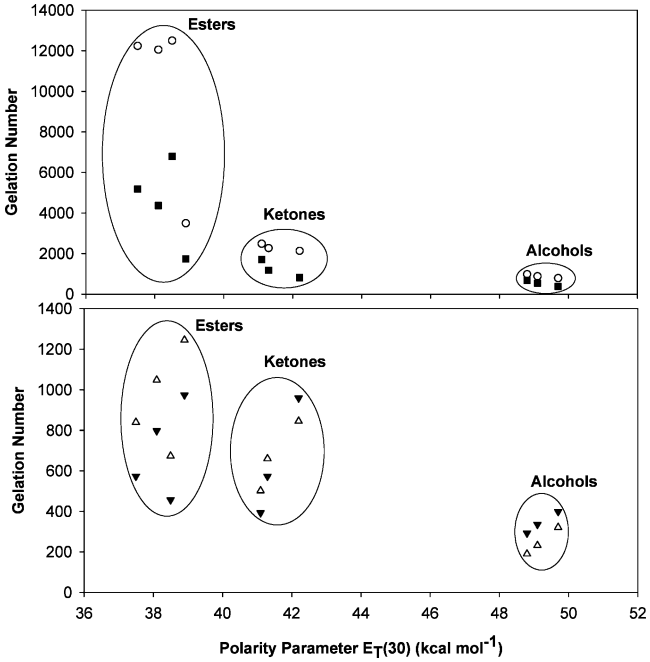

Figure 3. Effect of $E_T(30)$ on gelation number. (○) trehalose diacetate, (■) trehalose dibutyrate, (△) trehalose didecanoate, and (▼) trehalose dimyristate.

Table 2. Contribution of Nonspecific and Specific Forces to $E_T(30)$ According to $E_T(30) = 20.1 \cdot SPP + 24.9 \cdot SA + 3.9 \cdot SB + 20.7$[32]

	contribution from nonspecific and specific interactions				
solvent	20.1·SPP	3.9·SB	24.9·SA	HBA + HBD	H-bonding/ nonspecific
methyl acetate	15.779	2.055	0	2.055	0.130
ethyl acetate	15.980	2.114	0	2.114	0.132
propyl acetate	15.718	2.137	0	2.137	0.136
butyl acetate	15.758	2.048	0	2.048	0.130
acetone	17.708	1.853	0	1.853	0.105
2-butanone	17.708	2.028	0	2.028	0.115
2-pentanone	17.748	2.094	0.249	2.343	0.132
1-butanol	16.824	3.155	8.640	11.795	0.701
1-pentanol	16.422	3.354	7.943	11.297	0.688
1-hexanol	16.281	3.428	7.844	11.272	0.692
acetonitrile	17.990	1.115	1.096	2.211	0.123

These amorphous structures may reflect greater solvation of these gelators by solvent. Gels from **1** and **2** formed large clusters (wheat ear or star shaped) in acetonitrile (Figures 4e and 4f, respectively), which greatly reduced their gelation numbers, while **3** and **4** formed fine fibrous structures (Figures 4g and 4h, respectively), leading to high gelation numbers.

The structural differences of the gels were more apparent at the nanoscale, as evidenced by SEM (Figure 5). Long, thin, and highly entangled nanofibers were observed in gels formed by **2** in ethyl acetate (Figures 5a and 5b) and **3** in acetonitrile (Figures 5g and 5h); thick, rigid fibers were seen in gel formed by **2** in acetonitrile (Figures 5e and 5f). The gel formed from **4** in ethyl acetate completely lacked fibrous characteristics (Figures 5c and 5d). These structural features are determined by the extent of the solvent−gelator interactions. Gelator−gelator H-bonding is the strongest in a solvent that has minimum interaction with the gelator, which prefers the formation of fine nanofibers. With higher solvent−gelator interaction, the gelator molecules tend to aggregate to form

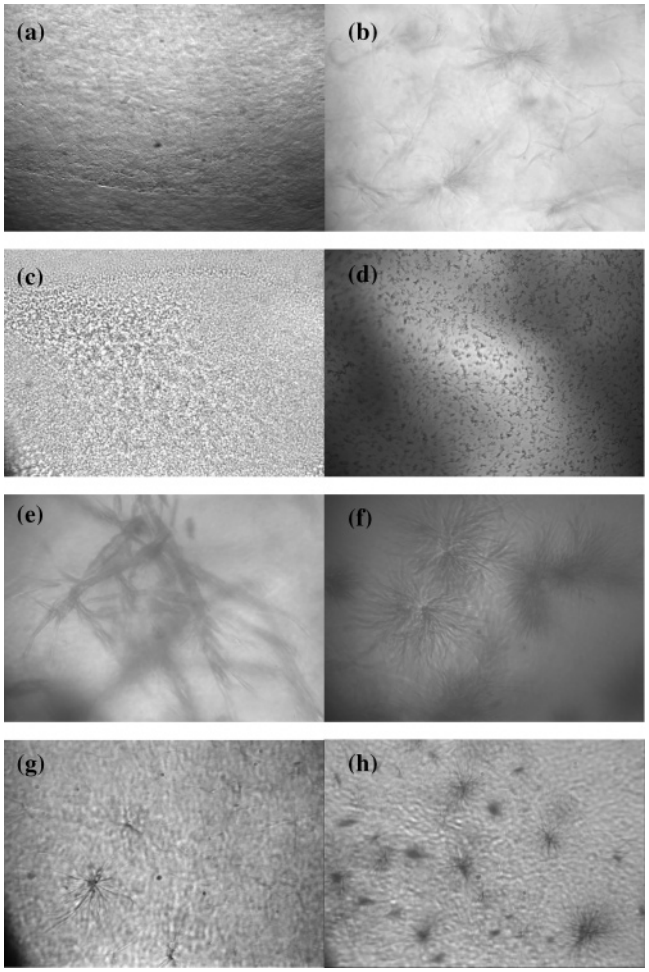

Figure 4. Bright field microscopic images of gels in ethyl acetate and acetonitrile (magnification: 400×). (a)−(d) Gels of **1**−**4** in ethyl acetate, respectively; (e)−(h) gels of **1**−**4** in acetonitrile, respectively.

bigger fibers. As the solvent−gelator interaction is too strong, isotropic gelator molecular aggregation may occur, resulting in complete loss of fibrous structure as seen in the gels formed by **4** in ethyl acetate (Figures 5c and 5d).

The time-dependent gelation processes of **2** in both ethyl acetate and acetonitrile were evaluated by real-time microscopy (see videos in the Supporting Information), which clearly revealed two distinct gel growth modes. In ethyl acetate, the nascent gelator assemblies (short fibers) were well-dispersed in the solvent and continued to grow. Inter-fiber clustering did not appear to take place. The resulting well-dispersed and entangled long fibers appeared to immobilize the solvent via entrapment. In acetonitrile, gelator molecules appeared to grow isotropically on the existing nucleus, resulting in large clusters. Gelation accompanies the interdigitation of these large clusters. As shown in Table 2, the major solvent−gelator interaction is from polarity/polarizability forces in both acetonitrile and ethyl acetate, but the force is stronger in acetonitrile (17.99 vs 15.98). Therefore, we hypothesize that, in acetonitrile, gelator molecules have more freedom of motion due to high solvent−gelator interactions and this favors addition onto the fiber nucleus, leading to the growth of large clusters. In ethyl acetate, however, relatively weak solvent−gelator interaction limits the branching and aggregation of gelator

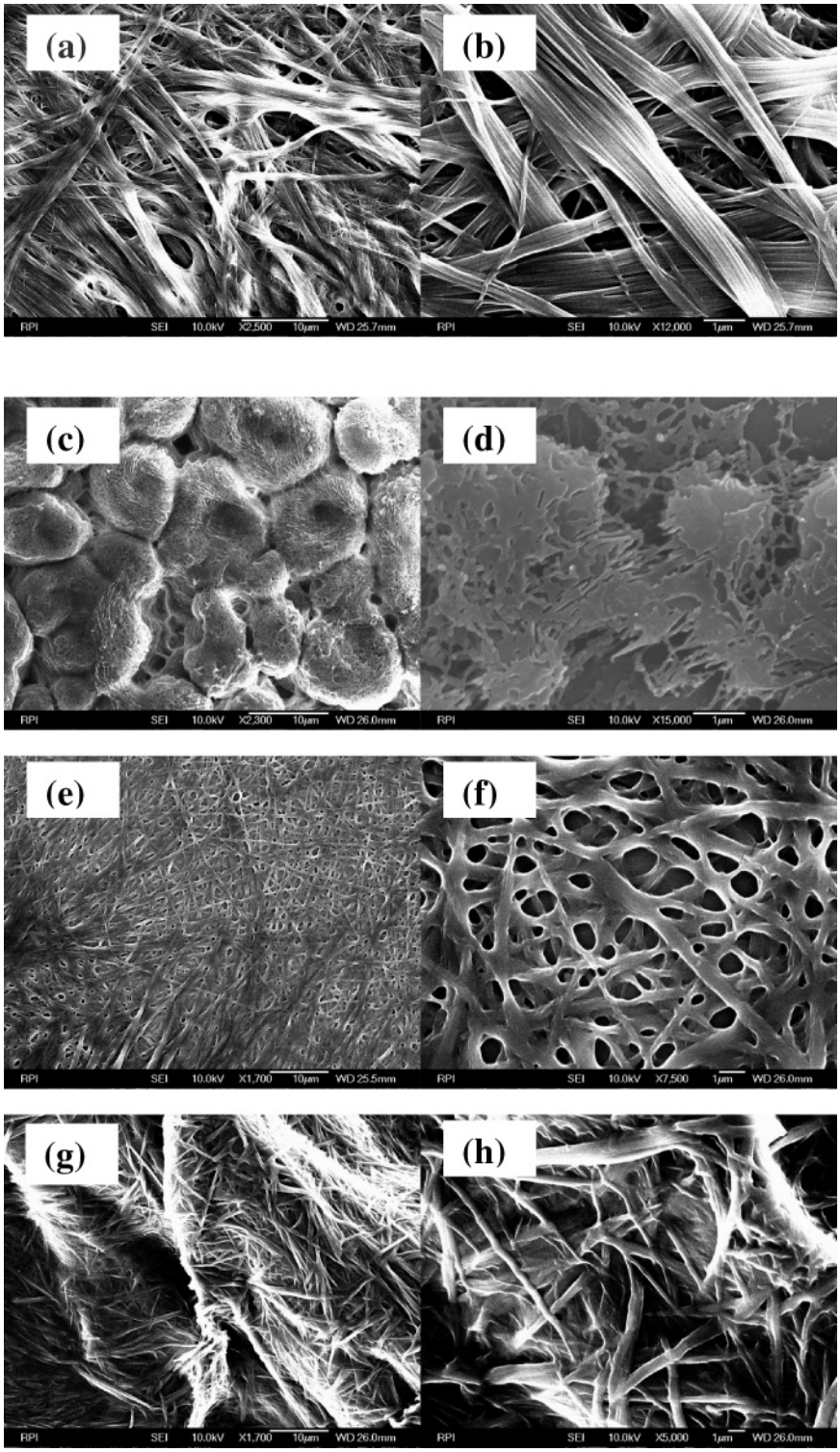

Figure 5. SEM images of gels in ethyl acetate and acetonitrile. (a) and (b): **2** in ethyl acetate, low and high magnification, respectively; (c) and (d): **4** in ethyl acetate, low and high magnification, respectively; (e) and (f): **2** in acetonitrile, low and high magnification, respectively; (g) and (h): **3** in acetonitrile, low and high magnification, respectively.

nanofibers by favoring the formation of well-dispersed and highly entangled fibers.

Critical Gelation Concentration. Molecular assembly of gelators occurs when a critical concentration of gelator is reached in a given solvent.[23] To ascertain this critical concentration, we evaluated the solubility of one of the gelators (**2**) in acetonitrile and ethyl acetate (Figure 6). As the concentration of **2** is increased, an increase of the solution-phase concentration of **2** is observed up to a concentration of 3.2 mM (0.19%, w/w) and 0.66 mM (0.036%, w/w) in acetonitrile and ethyl acetate, respectively. Further increase of **2** caused apparent gelator assembly, leading to a decrease of the solution-phase concentration. The corresponding photographs of the vials (Figure 6a) indicate that, at this point, a small amount of precipitate is observed. Above this concentration, the solution-phase concentration of **2** does not change, yet complete gelation of the solvent is observed. Qualitatively similar results were

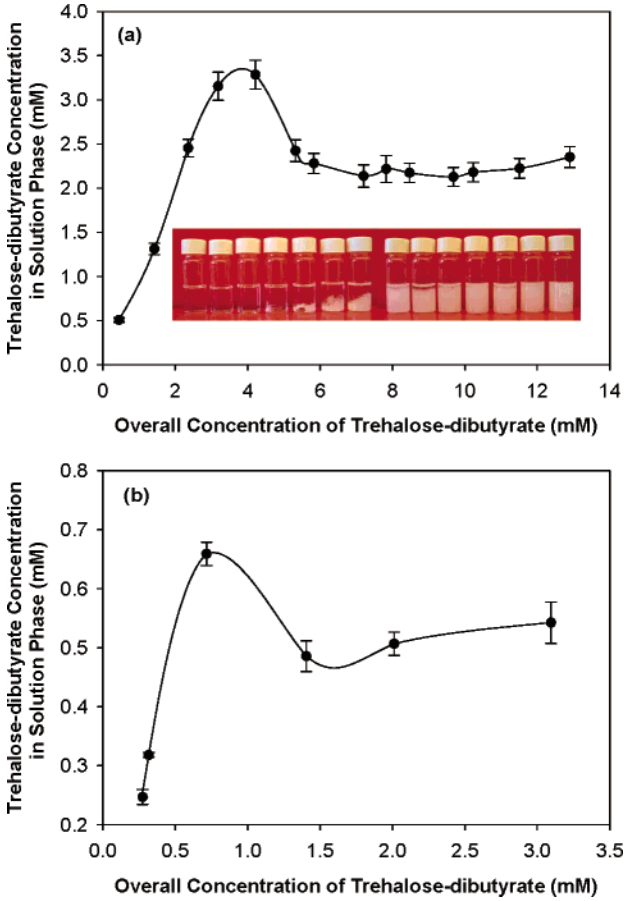

Figure 6. Gelation process of **2**: (a) in acetonitrile and (b) in ethyl acetate.

observed with the other gelators in acetonitrile and ethyl acetate (data not shown).

Based on these results, we may speculate that when the gelator concentration exceeds a critical point (i.e., the gelator's maximum solubility), molecular assembly commences, which continues until the entire solvent is immobilized. Because gelator solubility is strongly dependent on the nature of the solvent, we reasoned that minor changes in the physicochemical properties of solvent, for example, altering its polarity, would strongly affect critical gelator concentration, and hence the process of gelation. To that end, we examined the gelation of **2** at room temperature from its solution in water. As previously described, ethyl acetate is a good gelation solvent for **2** due to its relatively low polarity, while **2** is completely soluble in water, in which the critical gelation concentration can be considered to be infinite. Adding ethyl acetate to water will lower the polarity of the mixture, and therefore lower the critical gelation concentration that supports gelation. To demonstrate this, we performed a simple test by adding 2 mL of ethyl acetate to 15 μL of water containing 13.2 mg of **2** (45.8%, w/w) at room temperature. Gelation was instantaneous and the gel nanostructure was similar to that formed in pure ethyl acetate (Figure 7).

We expect that a similar gel preparation method can be applied to other gelator−solvent systems at room temperature by adding a good gelation solvent (low solubility of the gelator) to a solution of gelator (miscible with the good gelation solvent). Alternatively, the gelation ability of the gelators can be adjusted by using a solvent mixture. For example, our experimental results showed that the gelation numbers of gelators **1**−**4** in 1:1 and 1:4 (v/v) mixtures of methyl acetate and butyl acetate are approximately the same as those in pure ethyl acetate and propyl acetate, respectively. Interestingly, the solubility parameters of these solvent mixtures are equal to those of the pure ethyl acetate and propyl acetate, respectively. Compared to the conventional heat-triggered gelation process (the typical heating−cooling gelation process), solvent-mediated gelation may induce gelation at room temperature and offer more controllable gelation. This is important for processes involving incorporation of temperature- and solvent-sensitive components (such as biomolecules, e.g., proteins, DNA, polysaccharides, initially dissolved in an aqueous solution) into the gel network, which is not suitable through a conventional gelation process involving a heating step.

Conclusions

In conclusion, we have shown that the organogel formation process involves the close interaction between the solvent and gelator molecules, with the polarity of the solvent and the hydrophobic/hydrophilic characteristic of the gelator dominating gelation. In general, good gelation can be achieved by using a solvent that has limited interaction with the gelator molecules, such as the gelation of **1** and **2** in esters that are low in polarity and have no specific interaction with gelators. By more fully evaluating the gelation process and the resulting gel nanostructures, we showed that restricted solvent−gelator interaction boosts the growth of thin, flexible, and highly entangled fibers, leading to high gelation

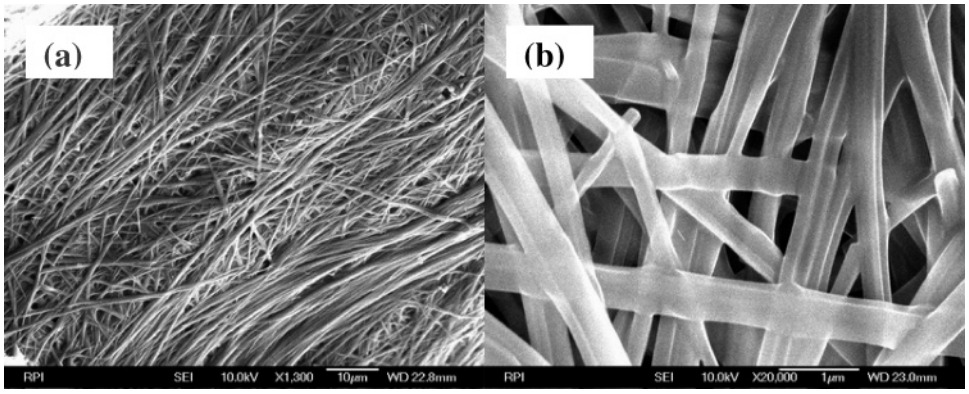

Figure 7. SEM images of gel formed by adding ethyl acetate to water solution of **2**: (a) low magnification and (b) high magnification.

numbers and stable gels. Conversely, strong solvent−gelator interactions favor the clustering of gelator assemblies, resulting in low gelation numbers and less stable gels. The gelation process can be tailored by simply adjusting the solvent polarity through addition of cosolvents to a gelator solution at room temperature. Such an approach may have potential applications that require the incorporation of biomolecules into organogel networks.

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Supporting Information Available: Videos showing the gelation of trehalose dibutyrate in ethyl acetate and acetonitrile. This material is available free of charge via the Internet at http://pubs.acs.org.

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