Gelation versus Crystallization

International Edition: DOI: 10.1002/anie.201506544
German Edition: DOI: 10.1002/ange.201506544

Stoichiometric Sensing to Opt between Gelation and Crystallization

*Adiyala Vidyasagar and Kana M. Sureshan**

Dedicated to Prof. Ganesh Pandey

Abstract: *A new class of organogelators having a cyclohexane-1a,3a-diol motif capable of congealing non-polar liquids was developed. These gelators underwent crystallization at low concentration and gelation above the critical gelation concentration (CGC) in the same solvent. The crystals and gel fibers were analyzed by single crystal XRD and PXRD respectively, which revealed their different modes of assembly. The XRD studies and thermogravimetric analysis (TGA) confirmed that the crystals contain a water of crystallization whereas the gel fibers do not. A systematic study revealed that when the concentration of the gelator exceeds that of adventitious water in the solvent, it congeals the solvent and when the concentration of the gelator is less than water, it undergoes crystallization. This unprecedented stoichiometric sensing behavior in deciding the mode of self-assembly offers a handle to opt between mutually competing gelation and crystallization. We have confirmed that the system can be biased to congeal or crystallize by varying the amount of water.*

Low molecular weight organogelators (LMOGs) continue to attract much scientific attention because of their ability to congeal organic liquids into thermoreversible organogels that find applications in many fields,[1] such as energy,[2] sensors,[3] sol–gel transcription,[4] medicine,[5] soft-optics,[6] and oil-spill recovery[7] to name a few. In most cases, the gelator molecules self-assemble through various non-covalent interactions to form fibrils and these fibrils aggregate to form high aspect ratio fibers that entangle into a 3D fibrous network. These sponge-like fibrous networks arrest the fluidity of the solvent through capillary force, resulting in the formation of a homogeneous gel.[8] Thus the crucial process for gelation is the self-assembly of solute (gelator) molecules to fibrils. The competing process of crystallization, which can lead to phase separation, also involves self-assembly of solute molecules. The subtle difference between the two is in the dimensionality of their growth. While gelation is favored when the assembly (growth) is promoted in one dimension leading to fibrils of high aspect ratio, crystallization is favored when the molecules self-assemble in all three dimensions at more or less comparable rates.[9] The study of the factors that control the fate of self-assembly viz-a-viz gelation vs crystallization is of utmost importance.[9,10] Herein we report, for the first time, a case wherein the relative amount of adventitious water present in the solvent dictates the fate of an organogelator to crystallize or to gel in the same solvent.

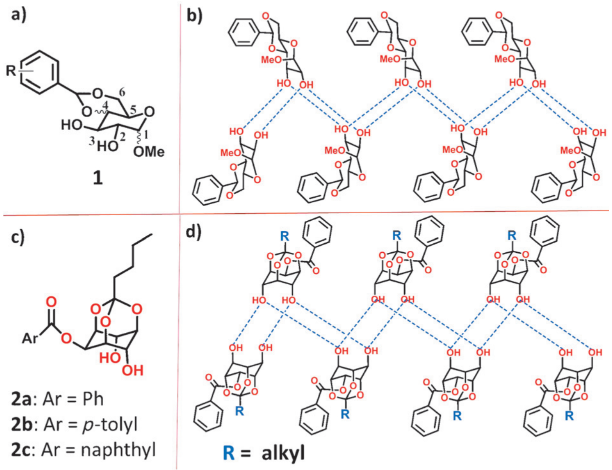

Figure 1. a) General structure of carbohydrate-based gelator. b) Consistent mode of 1D-hydrogen bonded arrangement in gels and crystals of carbohydrate-based gelators **1**. c) Proposed amphiphiles **2** having a cyclohexane-diaxial-1,3-diol motif. d) Proposed mode of assembly in 1,3-diols **2**.

Among all gelators known so far, hydrogen-bond based organogelators are the most common and carbohydrate-based organogelators constitute an important class in this category.[11] Shinkai et al. reported a variety of carbohydrate based amphiphiles having the general structure **1** (Figure 1 a) and correlated their gelation ability with crystal structure.[11a] This study revealed that a 4,6-*O*-arylidene unit, an alkyl group at anomeric oxygen, and a vicinal diol motif are the essential structural features of this class of gelators. The vicinal diol motif allows molecules to self-assemble through two parallel hydrogen bonds to one-dimensional zig-zag chain (Figure 1 b) and is implicated in the formation of gel fibers. Based on these structural features, many carbohydrate-based gelators have been synthesized.[12] Though 1,3-diaxial diols in a six-membered ring can also form such a 1D hydrogen-bonded assembly in principle (Figure 1 c and Figure 1 d), no such efforts have been made so far to investigate the gelation behavior of this group of molecules. Our interest in gels[4,5a,13] prompted us to investigate this possibility and thus to provide access to a novel class of gelators.

---

[*] A. Vidyasagar, Prof. Dr. K. M. Sureshan
School of Chemistry,
Indian Institute of Science Education and Research
Thiruvananthapuram, Kerala 695016 (India)
E-mail: kms@iisertvm.ac.in
Homepage: http://kms514.wix.com/kmsgroup

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201506544.

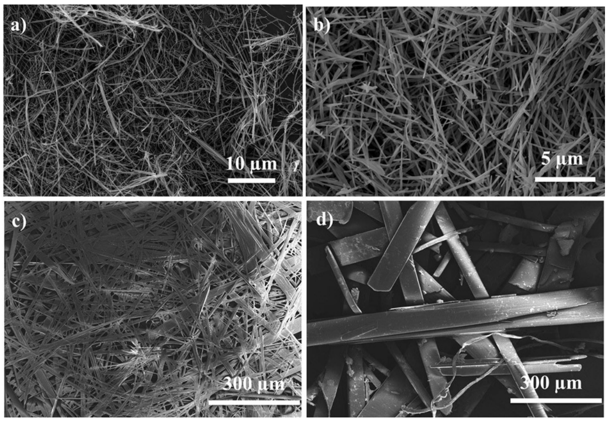

Figure 2. a) SEM images of xerogel made from cyclohexane-gel of **2a**. b) Xerogel made from cyclohexane-gel of **2c**. c) Dried petrol-gel of **2b**. d) Crystals of **2b** obtained from wet-petrol (made by addition of water drops to petrol).

We have synthesized several amphiphilic molecules possessing two diaxially oriented hydroxy groups at 1,3-positions by regioselective acylation of myo-inositol orthopentanoate (Supporting Information). As anticipated, aromatic esters, such as benzoate (**2a**), toluate (**2b**) and naphthoate (**2c**), showed gelation in non-polar solvents and oils. The critical gel concentration (CGC) and gel–sol transition temperature (Tgel) values are given in the Supporting Information (Table S1). Interestingly, these gelators showed low CGC values in many solvents and their gels showed high Tgel suggestive of their high stability (Supporting Information, Table S1). Additional evidence for their high strength was obtained from rheological studies (Supporting Information, Figures S1–S3). Scanning electron microscopy (SEM) of the xerogels obtained from these gelators showed spaghetti-like entangled fibrillar morphology (Figure 2 and Supporting Information).

As per our design, it is expected that intermolecular hydrogen bonding would be the major force for the self-assembly of these molecules. FTIR spectroscopy of the gelator at self-assembled state (xerogel) and dissociated state (solution in a non-gelling solvent; chloroform) revealed the role of intermolecular hydrogen bonding in the self-assembly and thus in gelation (Supporting Information). The appearance of O−H stretching frequency at relatively low wavenumber (3417, 3221, and 3350 cm^{-1} for **2a**, **2b**, and **2c** respectively) in their xerogel states, than in their chloroform solution (3479, 3477, and 3500 cm^{-1} for **2a**, **2b**, and **2c** respectively) supports the involvement of intermolecular hydrogen bonding in their self-assembly. Furthermore, concentration-dependent ^{1}H NMR titration of compounds **2a**, **2b** and **2c** in benzene-d6 showed downfield shift of OH signals with concentration confirming the involvement of intermolecular hydrogen bonding in their self-assembly (Supporting Information, Figures S7–S9).

Interestingly, compounds **2a** and **2b** formed thin crystals in petrol (gasoline)at low concentrations and translucent gels at high concentrations of the gelator. For instance, when two hot solutions of different concentrations of **2a** in the same batch of petrol (5 mg in 1 mL and 35 mg in 1 mL) was cooled, the less concentrated solution underwent exclusive crystallization and the more concentrated solution underwent gelation solely. However, solutions having intermediate concentrations of gelator (10–25 $\text{mg}\,\text{mL}^{-1}$) did not form gel or crystals but they formed cloudy viscous solutions. When the concentration was above 35 $\text{mg}\,\text{mL}^{-1}$, it formed a self-standing gel.

Single-crystal XRD analysis of the crystals of both **2a** and **2b** obtained from petrol at low concentrations revealed the presence of a molecule of water of crystallization. To see whether the presence or absence of water is the reason for different behavior, we have compared the thermogravimetric analysis (TGA) profiles of crystal and the xerogel of **2a**, both obtained from petrol (Figure 3b and Supporting Information). As suspected, the xerogel did not show any weight loss until 225 °C, suggesting the absence of water in gel fibers, whereas the crystals lost its water of crystallization at 90–95 °C. Gelator **2b** also behaved in a similar manner as **2a**, suggesting that this class of gelators behave in a consistently similar manner. This interesting observation throws light to a plausible reason for the puzzling effect of concentration of the gelator in deciding the fate of its solution between gelation and crystallization; At low concentration of the gelator, the adventitious water present in petrol may be sufficient enough to make crystals with a water of crystallization, and when the concentration of the gelator is more,

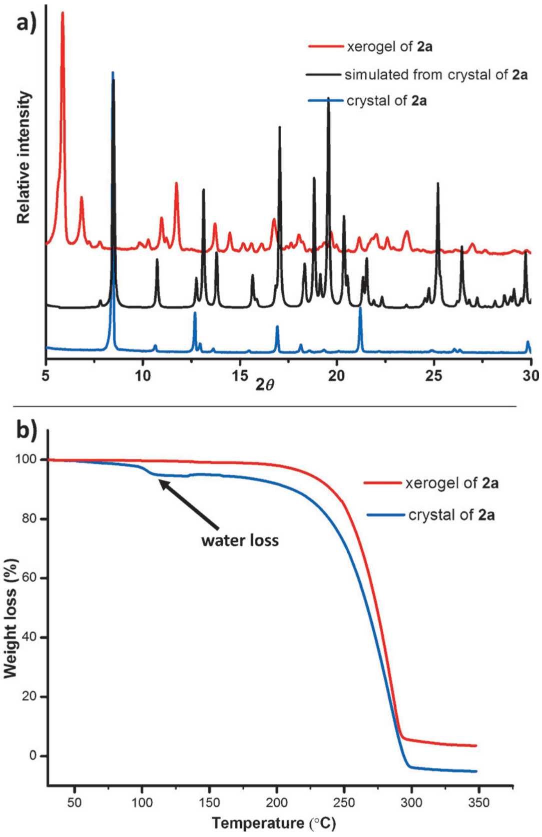

Figure 3. a) Powder XRD profiles of xerogels and crystals of **2a** obtained from petrol. b) TGA profiles of crystals and xerogels of **2a** showing the loss of water from crystals alone.

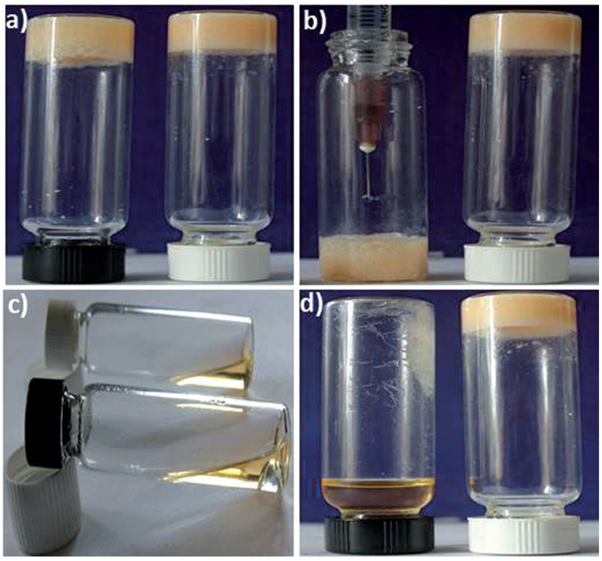

Figure 4. a) Two identical petrol-gels of **2a** having same concentration made in same batch of petrol. b) Water added to the gel in the black-capped vial. c) Both gels are heated to solution. d) The watered-solution formed crystals and the other one re-gelled.

the water may be insufficient to crystallize all the gelator molecules.

To probe this, we altered the water content in the petrol and the fate of gelator was observed. When the amount of water content was increased by adding drops of water to the petrol gel, and made a solution by heating and then cooled, it formed very fine crystals (Figure 2d and Supporting Information, Video S1). Also, when two hot solutions of gelator **2a** in petrol having same concentration but one with few drops of added water and other without were cooled simultaneously, the one with water crystallized and the other formed a free standing gel (Figure 4; Supporting Information, Video S2). These observations clearly support our argument that when sufficient amount of water is present, the gelator prefers to crystalize. However, when the water is insufficient, the gelator will congeal the solvent to a homogeneous gel.

The water content in the petrol was determined by Karl–Fischer titration and was found to be 0.03 % by volume. Thus, at a gelator concentration of 5 $\mathrm{mg\,mL^{-1}}$ of petrol, the water/gelator ratio is 1.1:1, which led to crystallization. In contrast, at a gelator concentration of 35 $\mathrm{mg\,mL^{-1}}$ of petrol, the water/gelator ratio is 0.17:1, which led to gelation. To probe the role of gelator: water ratio in deciding the fate of the solution (gelation vs crystallization), we made a systematic study with petrol samples containing different amount (%) of water. Exactly 35 mg of **2a** was dissolved in 1 mL of each of these petrol samples containing different amount of water, and we then studied their fate (Supporting Information, Table S2). It is very clear from Table S2 that, in a sufficiently concentrated solution, when the molar ratio of gelator to water is less than or equal to 1 crystallization occurs, and when this ratio is more than 1 gelation ensues. Though the effects of solvents[14] and other additives[15] on gel formation and stability have been investigated, the role of stoichiometry of an additive (water) in discriminating between gelation and crystallization is novel.

The absence of water in gel fibers was evident from its TGA profile. Also, a comparison of powder XRD of crystalline compound **2a** with powder XRD of its xerogels reveals that they have different arrangement of molecules (Figure 3a; Supporting Information, Figure S15). It is surprising that not even traces of crystal phase was found when the molecule congealed and no gel fiber was formed when the gelator underwent crystallization as was evident from a comparison of their bulk PXRD profiles. The molecules undergo one of the two competing modes of self-assembly depending on the amount of water present. Though many gels will transform into crystals if left unperturbed,[16] the gel formed by **2a–c** did not transform to crystal even after several months. From the foregoing discussions, it is evident that the fate of the gelator-solution is directly dependent upon the gelator concentration relative to the amount of water molecules present.

To get an idea about how the water molecules dictate the crystallization of an otherwise gelling molecule, we have analyzed the single crystal XRD structures of **2a** and **2b**. In both cases, along the *c* direction gelator molecules are arranged in a zig-zag manner, as anticipated from their 1D H-bonded assembly (Figure 5a,b). It is most likely that this is the direction of self-assembly in the case of gelation leading to

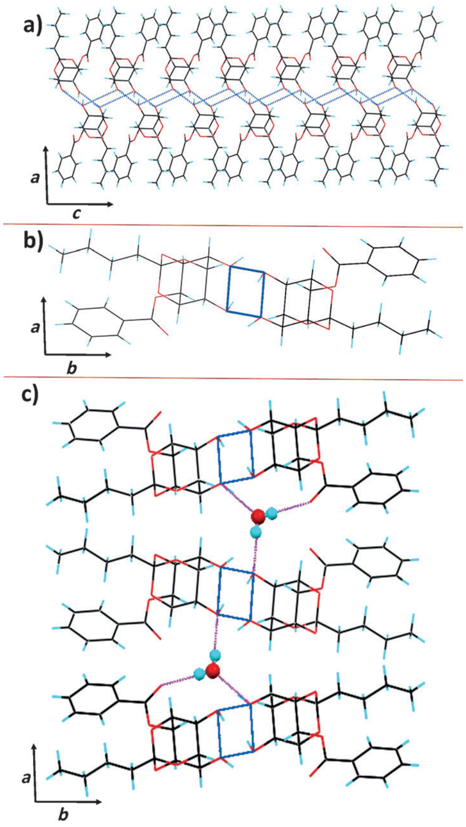

Figure 5. Zig-zag arrangement of molecules of **2a** forming a fibril: a) viewed along the *b* direction ; b) viewed along the *c* direction; and c) water molecules connecting adjacent fibrils along the *a* direction to form a 3D crystal.[19]

the formation of fibrils. However in the crystal, these fibrils are bridged in the *a* direction by the water molecules present, making the molecules assemble in 3D (Figure 5c). Clearly, water molecules connect several fibers in 3D transforming them to crystal.

In cases where organogelation is due to the assembly of gelator molecules through hydrogen bonding, water present in the solvent competes for hydrogen bonds with gelator molecules and thereby disrupts gelation.[17] There are a few cases wherein water molecules are known to enhance gelation by functioning as a connector between gelator molecules to form fibrils.[18] However, to the best of our knowledge, this is the first case wherein water molecules present in the solvent bias crystallization of an otherwise organogelator of the solvent by bridging molecules in 3D.

In conclusion, we have successfully designed a new class of organogelators based on cyclohexane-1,3-diols. Gelation and crystallization are the end results of two competing modes of self-assembly of solute molecules in a solution. Control over these mutually competing processes, though desirable, is one of the biggest challenges in the field of supramolecular chemistry. In this study we have established the role of water in opting between these two processes. When sufficient amount of water is present in the system, the gelator molecules undergo crystallization with a water of crystallization. When the amount of water is insufficient, the gelator molecules will instead congeal the solvent. This solute-dependent outcome, determined through some kind of molecular quorum sensing of the gelator-to-water ratio, is interesting and unprecedented. Studies exploiting such a switch between gelation and crystallization for applications might provide functional materials.

Acknowledgements

We thank Dr J. D. Sudha, NIIST Thiruvananthapuram, for her help in rheological studies, and K.M.S. thanks DST, India, for a Ramanujan Fellowship and Swarnajayanti Fellowship.

Keywords: crystals · gels · hydrogen bonding · self-assembly · supramolecular chemistry

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 12078–12082
Angew. Chem. **2015**, *127*, 12246–12250

---

[1] a) L. A. Estroff, A. D. Hamilton, *Chem. Rev.* **2004**, *104*, 1201; b) *Molecular Gels: Materials with Self-Assembled Fibrillar Networks* (Eds.: R. G. Weiss, P. Terech), Springer, Dordrecht, The Netherlands, **2005**; c) R. G. Weiss, *J. Am. Chem. Soc.* **2014**, *136*, 7519; d) D. González-Rodríguez, A. P. H. J. Schenning, *Chem. Mater.* **2011**, *23*, 310.

[2] a) K. Sugiyasu, N. Fujita, S. Shinkai, *Angew. Chem. Int. Ed.* **2004**, *43*, 1229; *Angew. Chem.* **2004**, *116*, 1249; b) A. Ajayaghosh, V. K. Praveen, C. Vijayakumar, S. J. George, *Angew. Chem. Int. Ed.* **2007**, *46*, 6260; *Angew. Chem.* **2007**, *119*, 6376; c) A. Ajayaghosh, S. J. George, V. K. Praveen, *Angew. Chem. Int. Ed.* **2003**, *42*, 332; *Angew. Chem.* **2003**, *115*, 346.

[3] a) P. Mukhopadhyay, Y. Iwashita, M. Shirakawa, S.-i. Kawano, N. Fujita, S. Shinkai, *Angew. Chem. Int. Ed.* **2006**, *45*, 1592; *Angew. Chem.* **2006**, *118*, 1622; b) T. H. Kim, M. S. Choi, B.-H. Sohn, S.-Y. Park, W. S. Lyood, T. S. Lee, *Chem. Commun.* **2008**, 2364; c) D.-C. Lee, K. K. McGrath, K. Jang, *Chem. Commun.* **2008**, 3636.

[4] a) M. Llusar, C. Sanchez, *Chem. Mater.* **2008**, *20*, 782; b) K. J. C. van Bommel, V. Bommel, A. Friggeri, S. Shinkai, *Angew. Chem. Int. Ed.* **2003**, *42*, 980; *Angew. Chem.* **2003**, *115*, 1010, references therein; c) J. H. Jung, Y. Ono, K. Hanabusa, S. Shinkai, *J. Am. Chem. Soc.* **2000**, *122*, 5008; d) K. Suzuki, S. Sato, M. Fujita, *Nat. Chem.* **2010**, *2*, 25.

[5] a) O. Wichterle, D. Lim, *Nature* **1960**, *185*, 117; b) A. Tanaka, Y. Fukuoka, Y. Morimoto, T. Honjo, D. Koda, M. Goto, T. Maruyama, *J. Am. Chem. Soc.* **2015**, *137*, 770; c) J. Li, C. Zheng, S. Cansiz, C. Wu, J. Xu, C. Cui, Y. Liu, W. Hou, Y. Wang, L. Zhang, I. Teng, H. Yang, W. Tan, *J. Am. Chem. Soc.* **2015**, *137*, 1412.

[6] a) A. Vidyasagar, K. Handore, K. M. Sureshan, *Angew. Chem. Int. Ed.* **2011**, *50*, 8021; *Angew. Chem.* **2011**, *123*, 8171; b) G. John, S. R. Jadhav, V. M. Menon, V. T. John, *Angew. Chem. Int. Ed.* **2012**, *51*, 1760; *Angew. Chem.* **2012**, *124*, 1794.

[7] a) A. Prathap, K. M. Sureshan, *Chem. Commun.* **2012**, *48*, 5250; b) S. R. Jadhav, P. K. Vemula, R. Kumar, S. R. Raghavan, G. John, *Angew. Chem. Int. Ed.* **2010**, *49*, 7695; *Angew. Chem.* **2010**, *122*, 7861; c) L. Yan, G. Li, Z. Ye, F. Tian, S. Zhang, *Chem. Commun.* **2014**, *50*, 14839; d) S. Bhattacharya, Y. Krishnan-Ghosh, *Chem. Commun.* **2001**, 185; e) G. Hayase, K. Kanamori, M. Fukuchi, H. Kaji, K. Nakanishi, *Angew. Chem. Int. Ed.* **2013**, *52*, 1986; *Angew. Chem.* **2013**, *125*, 2040.

[8] A. R. Hirst, D. K. Smith, J. P. Harrington, *Chem. Eur. J.* **2005**, *11*, 6552.

[9] a) D. J. Adams, K. Morris, L. Chen, L. C. Serpell, J. Basca, G. M. Day, *Soft Matter* **2010**, *6*, 4144; b) P. Dastidar, *Chem. Soc. Rev.* **2008**, *37*, 2699.

[10] N. N. Adarsh, P. Sahoo, P. Dastidar, *Cryst. Growth Des.* **2010**, *10*, 4976.

[11] a) O. Gronwald, S. Shinkai, *Chem. Eur. J.* **2001**, *7*, 4328; b) B. O. Okesola, V. M. P. Vieira, D. J. Cornwell, N. K. Whitelaw, D. K. Smith, *Soft Matter* **2015**, *11*, 4768.

[12] a) A. Friggeri, O. Gronwald, K. J. C. van Bommel, S. Shinkai, D. N. Reinhoudt, *J. Am. Chem. Soc.* **2002**, *124*, 10754; b) J. H. Jung, M. Amaike, S. Shinkai, *Chem. Commun.* **2000**, 2343; c) N. Amanokura, K. Yoza, H. Shinmori, S. Shinkai, D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans. 2* **1998**, 2585; d) P. Dastidar, S. Okabe, K. Nakano, K. Iida, M. Miyata, N. Tohnai, M. Shibayama, *Chem. Mater.* **2005**, *17*, 741; e) D. R. Trivedi, A. Ballabh, P. Dastidar, B. Ganguly, *Chem. Eur. J.* **2004**, *10*, 5311.

[13] a) K. M. Sureshan, K. Yamaguchi, Y. Sei, Y. Watanabe, *Eur. J. Org. Chem.* **2004**, 4703; b) B. P. Krishnan, S. Ramakrishnan, K. M. Sureshan, *Chem. Commun.* **2013**, *49*, 1494.

[14] a) K. K. Diehn, H. Oh, R. Hashemipour, R. G. Weiss, S. R. Raghavan, *Soft Matter* **2014**, *10*, 2632; b) Y. Lan, M. G. Corradini, X. Liu, T. E. May, F. Borondics, R. G. Weiss, M. A. Rogers, *Langmuir* **2014**, *30*, 14128; c) N. Yan, Z. Xu, K. K. Diehn, S. R. Raghavan, Y. Fang, R. G. Weiss, *J. Am. Chem. Soc.* **2013**, *135*, 8989.

[15] a) G. M. Peters, L. P. Skala, T. N. Plank, H. Oh, G. N. M. Reddy, A. Marsh, S. P. Brown, S. R. Raghavan, J. T. Davis, *J. Am. Chem. Soc.* **2015**, *137*, 5819; b) J. W. Steed, *Chem. Soc. Rev.* **2009**, *38*, 506; c) G. O. Lloyd, J. W. Steed, *Nat. Chem.* **2009**, *1*, 437.

[16] a) Y. Xu, C. Kang, Y. Chen, Z. Bian, X. Qiu, L. Gao, Q. Meng, *Chem. Eur. J.* **2012**, *18*, 16955; b) Y. B. He, Z. Bian, C.-Q. Kang, L.-X. Gao, *Chem. Commun.* **2011**, *47*, 1589; c) Y. B. He, Z. Bian, C.-Q. Kang, L.-X. Gao, *Chem. Commun.* **2010**, *46*, 5695; d) Y. J. Wang, L. M. Tang, J. Yu, *Cryst. Growth Des.* **2008**, *8*, 884; e) D. K. Kumar, D. A. Jose, A. Das, P. Dastidar, *Chem. Commun.* **2005**, 4059; f) N. M. Sangeetha, U. Maitra, *J. Phys. Chem. B* **2006**, *110*, 15224; g) J. R. Moffat, D. K. Smith, *Chem. Commun.* **2008**, 2248; h) D. Braga, S. d'Agostino, E. D'Amen, F.

Grepioni, *Chem. Commun.* **2011**, *47*, 5154; i) O. Lebel, M.-E. Perron, T. Maris, S. F. Zalzal, A. Nanci, J. D. Wuest, *Chem. Mater.* **2006**, *18*, 3616.

[17] a) E. L. Bonifazi, V. C. Edelsztein, G. O. Menendez, C. S. Lopez, C. C. Spagnuolo, P. H. Di Chenna, *ACS Appl. Mater. Interfaces* **2014**, *6*, 8933; b) N. Luisier, K. Schenk, K. Severin, *Chem. Commun.* **2014**, *50*, 10233.

[18] a) T. Zhang, Y. Wu, L. Gao, Z. Song, L. Zhao, Y. Zhang, J. Tao, *Soft Matter* **2013**, *9*, 638; b) M. Vatankhah-Varnoosfaderani, A. GhavamiNejad, S. Hashmi, F. J. Stadler, *Chem. Commun.* **2013**, *49*, 4685; c) S.-i. Tamaru, R. Luboradzki, S. Shinkai, *Chem. Lett.* **2001**, 336; d) A. Pal, J. Dey, *Langmuir* **2011**, *27*, 3401.

[19] CCDC 1053205 and 1053206 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Received: July 15, 2015