

External-stimuli responsiveness of self-assembled supramolecular architectures

Rakhi Majumdar

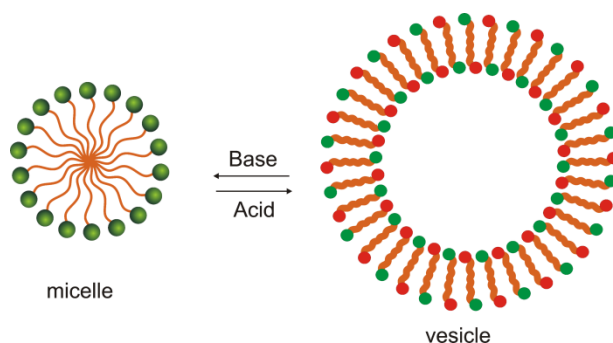
Department of Chemistry and Chemical Technology, Vidyasagar University, West Bengal

Email: majumdar10rakhi@gmail.com

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1. Abstract

Stimuli-responsive supramolecular materials are the materials of the future. Since these materials can change their shape and self-assembling behavior depending upon the external environments, these materials have a wide range of applications in diversified fields like drug delivery, nano-electronics, nano-devices etc. In this article we have discussed about the supramolecular assembly-disassembly of molecules depending upon the various external stimuli such as pH, light, redox, enzyme etc. which were developed in last one decade.



2. Introduction

Through thousands of years of evolution, nature has produced some basic set of molecules like amino acids, nucleotides, terpenes, lipid or sugar molecules. A vast range of fabrication units are created from these simple molecules in nature via natural process, which can further self-assemble into various complicated structures or materials. Inorganic minerals, inorganic/organic composite seashells, pearls, bone and teeth, wood, silk, horn, collagen, are the extraordinary examples of natural self-assembled materials. Interestingly, nature shows a strong preference for bottom-up strategy by building up molecular-assemblies over top-down material processing strategy. Inspired by the nature's bottom-up strategy for creating a diverse range of self-assembled materials¹, the material research community are involved in mimicking such natural materials with the aim of creating new and diverse structures with novel utilities beyond nature's gifts.

The bottom up strategy requires a deep understanding of the individual molecular

structures, their assemblies, and dynamic behaviors because it is a path from simplicity to complexity. Two key factors in molecular fabrications are chemical complementarity and structural compatibility both of which confer weak and non-covalent interactions that bind the building blocks together during self-assembly. Molecular self-assembly occurs via weak noncovalent interactions such as hydrogen bonding, electrostatic interactions, π - π stacking, donor-acceptor interactions, Van der Waals interactions and hydrophobic interactions which are individually quite insignificant. Collectively, however, these weak interactions play a crucial role to govern the structural conformations as well as to influence their interaction with other molecules.

Because of these non-covalent interactions, self-assembled supramolecular materials are dynamic by nature. In a supramolecular material, its components are bridged by reversible connections and can undergo spontaneous and continuous assembly/disassembly processes under specific conditions. Since these non-covalent interactions are

dynamic and reversible by nature, the supramolecular materials are stimuli-responsive and have the capability to adopt to their environment.

Depending on the external environments, molecular structures and shapes, and relative volume fraction of hydrophilic and hydrophobic parts, amphiphile molecules self-assemble into diverse supramolecular architectures, such as spherical or cylindrical micelles, vesicles, ribbons, and tubules. These supramolecular architectures are ideally suitable for the construction of the responsive materials since the dynamic and reversible conformational changes can be triggered by external environments. Normally, this change is completely reversible once the stimulus has been removed. Various possible applications in the fields of environmental sciences, biomedical sciences, and nano-devices have been described for stimulus-responsive materials.² During last few years, numerous dynamic supramolecular systems have been developed which can change their topologies and properties upon exposure to external triggers such as temperature, light, pH, redox potential, enzyme, etc.³

1. pH responsive self-assembly

The pH responsive supramolecular building blocks represent a special class of molecules containing ionizable functional groups which are capable of donating or accepting protons depending upon the external environment. For these molecules, electrostatic interactions between the charged functional groups play an important role during self-assembly/ disassembly process. During the last decade, this special class of molecules, particularly which have the pK_a value in the range of 5, has drawn a significant attention of the scientific community for drug-delivery purposes. The scientific community has exploited these molecules as drug delivery vehicle because of their pH responsiveness at physiological pH range and biocompatibility⁴.

Leroux *et al* has reported a pH sensitive molecular tweezer⁵ which can switch from U-shape to W-shape conformation at acidic pH. At neutral pH, the molecular tweezer posses U-

shape which can bind the anticancer drug mitoxantrone and quinizarin. But at acidic pH, due to the conformational change from U-shape to W-shape, they cannot bind the drug molecules and the drug molecules were released under acidic pH. This is a nice example of pH responsive supramolecular-assembly which can be used as potential drug-carrier.

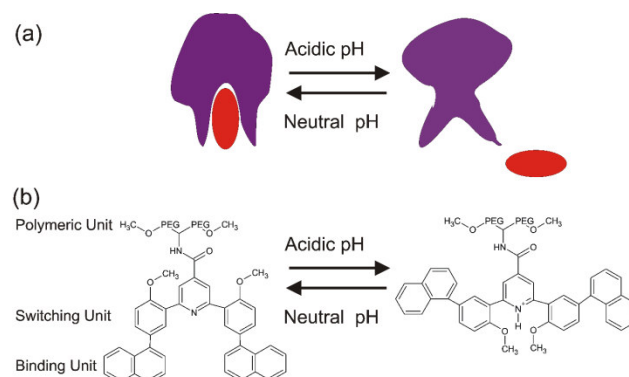


Figure 1: (a) Schematic representation of the pH sensitivity of the molecular tweezer; (c) pH responsive structural change of the molecular tweezer.

Banerjee *et al* has reported a nice example of pH responsive self-assembly of a short peptide which yielded hollow nanotubes at acidic pH (pH 4.3-6.0), both vesicles and nano tubes at pH 6.5 and exclusively vesicles at pH 7-9.2.⁶

Grzybowski *et al* has reported the pH sensitive self-assembly of oleic acid where pH can control the inter conversion of vesicles to micelles. The bilayer vesicles were formed when the pH range is very near to the acid's pK_a value (pH 7-8.3). In this condition, the solution contains both the protonated and deprotonated form of oleic acid. In the bilayer vesicles, the inner and outer hydrophilic surfaces are formed via the side by side arrangement of protonated and deprotonated carboxylic groups. But, when the pH was increased further to 9.4, then all the oleic acid molecules become deprotonated and

unilamellar micelles were formed with carboxylate head groups.⁷

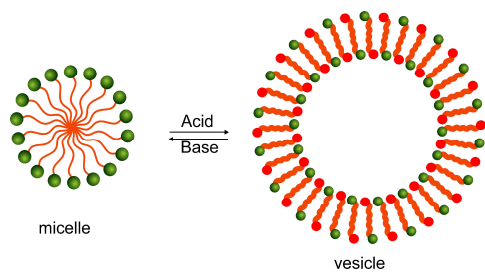


Figure 2: pH responsive inter-conversion from micelles to vesicles.

2. Photo responsive self-assembly

Photo responsive supramolecular building blocks are of great interest in recent years because their self-assemblies can be controlled by the external stimuli light. Generally, these types of supramolecular building blocks contain photo responsive chromophores like azobenzene, stilbene, diarylethene etc. The photo induced morphological changes occur for these systems due to trans-cis isomerization, 2 + 2 dimerization or photopolymerizations of the photo responsive chromophores containing supramolecular building blocks.

The photo induced trans-cis isomerisation of the azobenzene unit or stilbene unit strongly influence the self-assembly property of the corresponding supramolecular building block. Gelation ability or self-assembly abilities of both the azobenzene derivatives or stilbene derivatives decreased upon photo irradiation because of the steric hindrance in the cis isomers.

For example, *Tamaoki et al.* reported the photo responsive self-assembly of a series of azobenzene derivatives which exhibit gel-sol transitions upon photo-irradiation due to the trans-cis isomerisation of the azobenzene unit⁸.

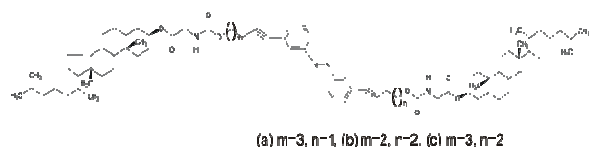


Figure 3: A photoresponsive azobenzene derivative

Eastoe et al have reported a stilbene based photo responsive organogel system. Upon photo irradiation, a gel to sol transformation has been demonstrated for this system⁹. Similarly, the following trans stilbene derivatives showed better gelation ability than that of cis isomers.¹⁰

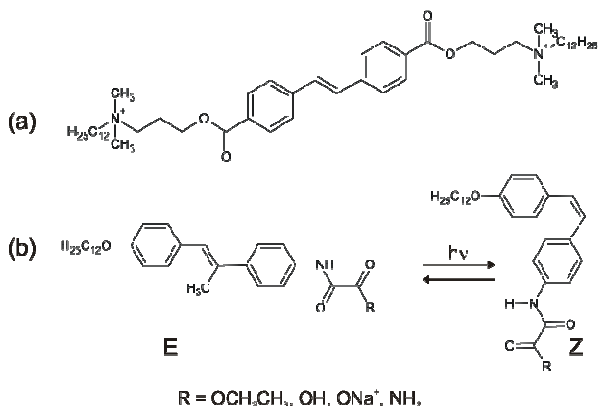


Figure4: (a) A photo responsive stilbene derivative; (b) photo responsive trans-cis isomerisation of a stilbene derivative.

Das et al. have reported the vesicular self-assembly of special class of butadiene based amphiphilic molecules. These amphiphilic molecules exist as their E forms and these E isomers gave excellent gels via vesicular self-assembly in polar solvent. However, upon photo irradiation the vesicular gel was destroyed and a gel to sol transition was observed due to the trans-cis isomerization of the butadiene unit.¹¹

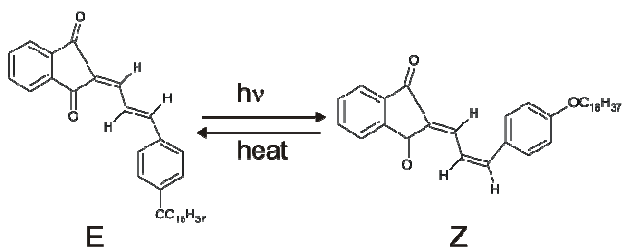


Figure 5: Photo responsive trans-cis isomerization of a butadiene based amphiphilic molecules which lead gel to sol transition.

3. Redox responsive self-assembly

The redox responsive supramolecular building blocks generally contain redox responsive moieties like ferrocene, conjugated

polymers, tetrathiafulvalene, transition metal ions and disulfide bonds etc¹².

For example, Harada *et al.* reported the redox responsive supramolecular assembly of poly(acrylic acid) modified cyclodextrin (Paa-CDs) and poly(acrylic acid) modified ferrocene (Paa-Fc) via host-guest interaction¹³. Due to the hydrophobic nature of the cyclodextrin group, it has a higher affinity for the reduced state ferrocene group where as it has very lower affinity for the oxidized state of the ferrocene group. So, for this system, the redox responsiveness of the ferrocene moiety played a crucial role during self-assembly via host-guest interaction. By using both chemical and electrochemical oxidation-reduction, the sol-gel transition can be induced in the system.

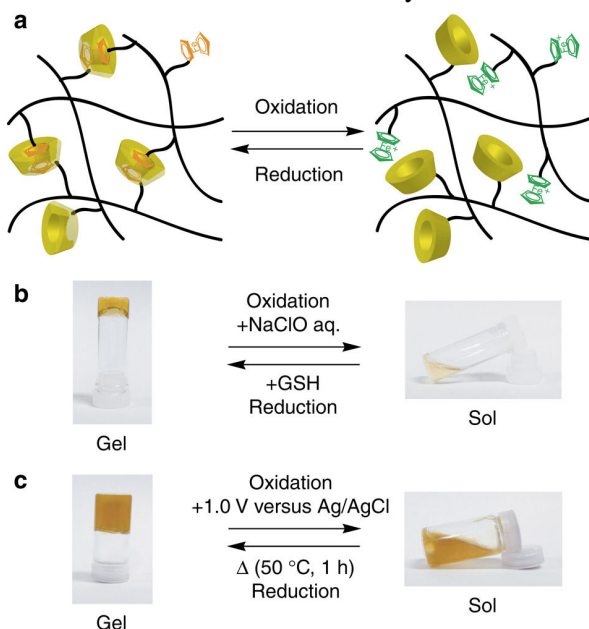


Figure 6: Sol-gel transition of the supramolecular system via host-guest interaction due to oxidation- reduction transition of the ferrocene group.(Copyright 2011, Nature publishing group)

Similarly, redox responsive sol-gel transition of a low molecular mass gelator containing ferrocenyl group was reported. For this system also the oxidation state of the ferrocenyl group play a crucial role during self-assembly by changing the hydrophobic environment of the system via oxidation-reduction. The oxidation of the ferrocenyl group

resulted the transformation of the supramolecular gel in to sol¹⁴.

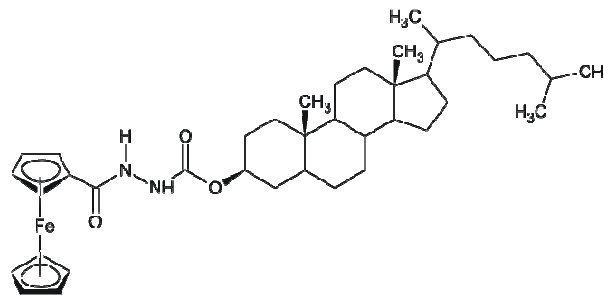


Figure 7: A redox responsive low molecular weight gelator.

Supramolecular building block containing Tetrathiafulvalene (TTF) moiety also give redox responsive gel. TTF can be reversibly transformed into corresponding radical cation or dication by chemical or electrochemical reaction. For example, the gelation via H-bonding of a Tetrathiafulvalene (TTF) derivative was reported¹⁵. Interestingly, on addition of Fe^{3+} ion or application of oxidation potential to the gel results gel to sol transition because of the H-bonding destruction due to the conversion of TTF into TTF^+ .

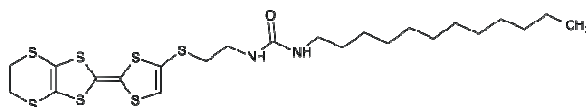


Figure 8: A redox responsive supramolecular building block containing Tetrathiafulvalene (TTF) moiety.

Many redox responsive supramolecular gels containing transition metal ions were also reported. The presence of transition metal ion makes the gel redox responsive due to their variable oxidation states depending upon external stimuli. For example, a redox reversible novel class of coordination gelator was reported by Shinkai *et al* which exhibited gel-sol transformation depending upon the oxidation state of Cu (Cu I/ Cu II).¹⁶ A 2,2'-bipyridine derivative bearing two cholesteryl groups gave bluish green gel in the presence of Cu (I) complex. In addition, when they took the 2,2'-bipyridine derivative /Cu(II) complex and added

ascorbic acid to this complex, the Cu(II) converted into Cu(I) and a greenish blue gel was formed. They observed the chemically reduced Cu(I) complex gel is basically same with the original Cu(I) complex gel. On the other hand,

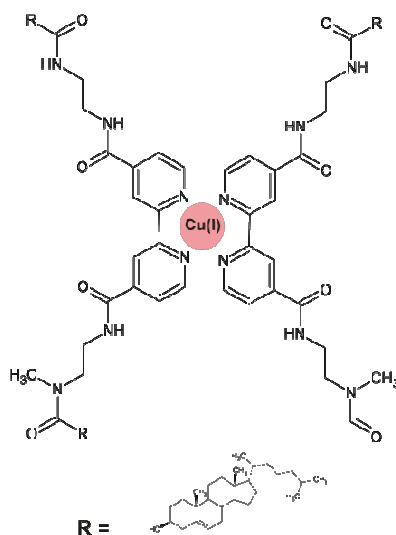


Figure 9: A novel redox responsive coordination gelator.

The gelation property of the following bischolesterol functionalized gelator was reported

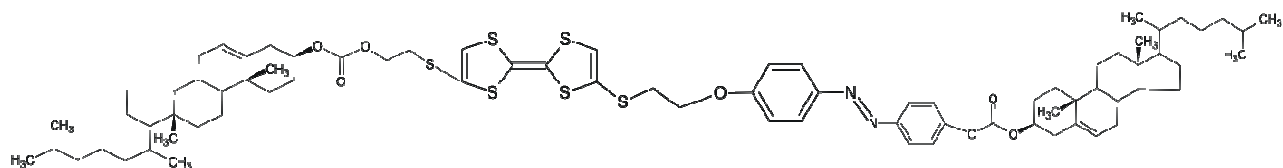


Figure 10: A photoresponsive as well as redox responsive gelator.

4. Enzyme responsive self- assembly

Over the last few years, the enzyme catalyzed reactions have been used as biological stimuli to trigger the self-assembly process. Developing of such materials which can change properties in response to enzyme catalysis is an emerging area in biomaterial research.¹⁸ This enzyme stimuli have many advantages over other stimuli because (a) they can work under mild

when the NOBF_4 was added to the 2,2'-bipyridine derivative/Cu(I) complex, the Cu(I) complex was transformed into Cu(II) complex. As a result the greenish blue gel transformed in to solution.

where the presence of both photo responsive azobenzene moiety and redox responsive TTF moiety make the gelator photo responsive as well as redox responsive¹⁷.

For example, T. Maruyama et al reported an enzyme triggered intracellular molecular self-assembly of a supramolecular gelator which causes critical damage to cancer cells while avoiding harm to normal cells.¹⁹ They designed a precursor peptide-lipid which could be hydrolyzed by an enzyme matrix

metalloproteinase-7 (MMP-7) which was produced and secreted by various cancer cells. After the hydrolysis, the precursor yielded a supramolecular gelator on enzymatic reaction which self-assembled inside the cancer cells caused inhibition of the cellular function as well as the death of the cancer cells.

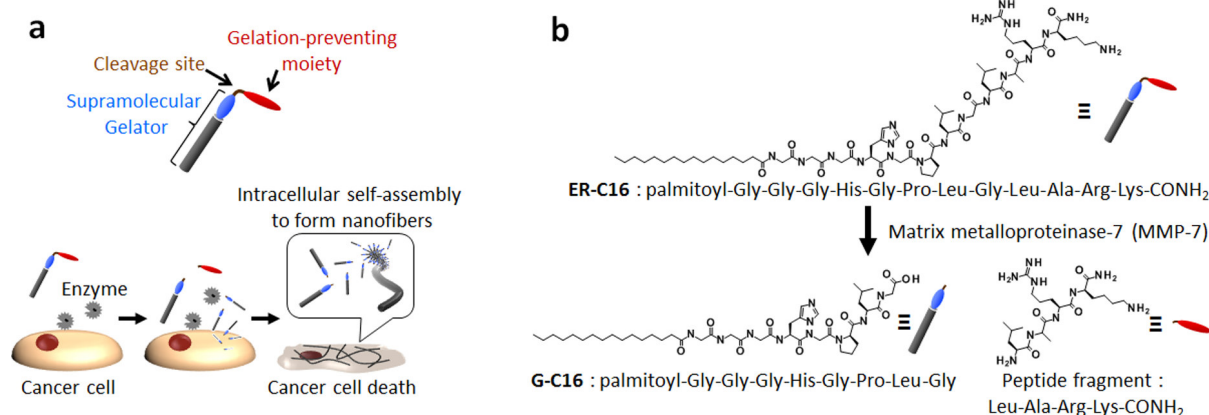


Figure 11: Schematic representation of the enzymatic cleavage of the peptide-lipid precursor yielded a supramolecular gelator and cancer cell death induced by the molecular assembly of this supramolecular gelator. copy right J. Am. Chem. Soc. 2015, 137, 770–775.

R. J. Amir et al reported an enzyme responsive disassembly of an amphiphilic hybrid composed of linear hydrophilic polyethyleneglycol (PEG) and an enzyme-responsive hydrophobic dendron.²⁰ These amphiphilic hybrids self-assembled in water into micelles with a hydrophilic PEG shell and a hydrophobic core which can be utilized as drug carriers for the hydrophobic drug molecules. In the presence of enzyme, due to the cleavage of the hydrophobic end groups from the dendron changed the amphiphilicity of the molecule. As a result, the disassembly of the molecules as well as the release of the entrapped drug molecules occurred.

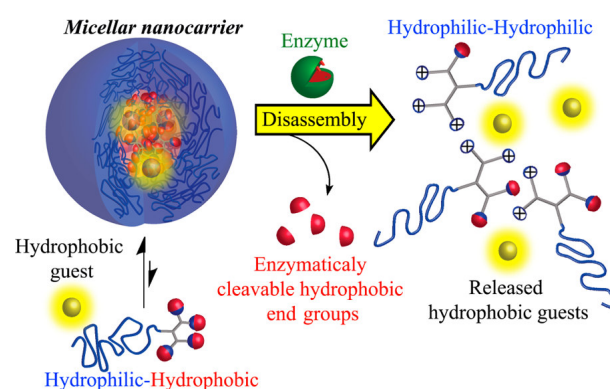


Figure 12: Schematic representation of the entrapment of hydrophobic drug molecule into the hydrophobic core of the micelle and after enzymatic cleavage of the hydrophobic ends the disassembly as well as the release of the drug molecules occurred. (reprint from J. Am. Chem. Soc. 2014, 136, 7531–7534.)

Enzymatic (de-) phosphorylation is another common method to control the molecular self-assembly-disassembly process by altering the structural features as well as the biological activity of the protein molecules. The addition or

removal of anionic phosphate groups can play a crucial role in the self-assembly process via electrostatic interactions. For example, Xu et al reported an enzyme responsive self-assembly via dephosphorylation.²¹ They demonstrated that the negatively charged phosphate groups inhibited electrostatic repulsion. But, after the (de-) phosphorylation, the resulting molecule self-assembled via π -stacking yielding gel.

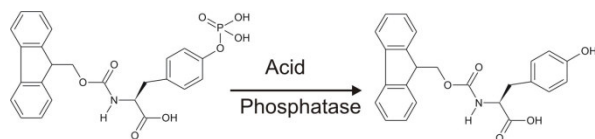


Figure 13: The transformation of phosphorylated fluorenylmethoxycarbonyl (Fmoc)-tyrosine into a hydrogelator after (de-) phosphophorylation by phosphatase.

4. Conclusions

Stimuli-responsive supramolecular materials are the materials of the future. Since these materials can change their shape and self-assembling behaviour depending upon the external environments, these materials have a wide range of applications in diversified fields like drug delivery, nanoelectronics, nanodevices etc. In this article we have discussed about the supramolecular assembly-disassembly of molecules depending upon the various external stimuli such as pH, light, redox, enzyme etc which were developed in last one decade.

5. References

- (a) J.M. Benyus, *Biomimicry: Innovation inspired by nature* (Quill-William Morrow, New York, 1997); (b) M. Gross, *Travels to the Nanoworld: Miniature machinery in Nature and Technology* (Plenum, New York, 1999)
- (a) Böhrner, H. G.; Kühnle, H.; Hentschel, J. Making “smart polymers” smarter: Modern concepts to regulate functions in polymer science. *J. Polym. Sci. Part A: Polym. Chem.* 2010, 48, 1–14. (b) R. Klajn, J. F. Stoddart, B. A. Grzybowski, *Chem. Soc. Rev.* 2010, 39, 2203–2237. (c) A. Ajayaghosh, V. K. Praveen, *Acc. Chem. Res.*, 2007, 40, 644–656. (d) C. de las Heras Alarco, n, S. Pennadam, C. Alexander, *Chem. Soc. Rev.* 2005, 34, 276–285.
- (a) P. M. Mendes, *Chem. Soc. Rev.* 2008, 37, 2512–2529. (b) S. Yagai, A. Kitamura, *Chem. Soc. Rev.* 2008, 37, 1520–1529. (c) S.-I. Kawano, N. Fujita, S. Shinkai, *J. Am. Chem. Soc.* 2004, 126, 8592–8593
- I. Drachuk, O. Shchepelina, M. Lisunova, S. Harbaugh, N. K. Loughnane, M. Stone, V. V. Tsukruk, *ACS Nano*, 2012, 6, 4266–4288
- J. Leblond, H. Gao, A. Petitjean, J.-C. Leroux, *J. Am. Chem. Soc.* **2010**, 132, 8544–8545.
- P.P. Bose, A.K. Das, R.P. Hegde, N. Shamala, A. Banerjee, *Chem. Mater.*, 2007, 6150–6157.
- I. Lagzi, D. Wang, B. Kowalczyk, B. A. Grzybowski, *Langmuir* 2010, 26(17), 13770–13772.
- Koumura, N.; Kudo, M.; Tamaoki, N. *Langmuir* 2004, 20, 9897.
- J. Eastoe, M. Sánchez-Dominguez, P. Wyatt, R. K. Heenan, *Chem. Commun.* 2004, 2608
- (a) S. Miljanić, L. Frkanec, Z. Meić, M. Žinić, *Langmuir* 2005, 21, 2754. (b) S. Miljanić, L. Frkanec, Z. Meić, M. Žinić, *Eur. J. Org. Chem.*, 2006, 1323.

- 11 N. S. S. Kumar, S. Varghese, G. Narayan, S. Das, *Angew. Chem. Int. Ed.* 2006, 45, 6317–6321
- 12 X. Sui, X. Feng, M. A. Hempenius, G.J. Vancso, *J. Mater. Chem. B*, 2013, 1, 1658
- 13 M. Nakahata, Y. Takashima, H. Yamaguchi, A. Harada, *Nat. Commun.*, 2011, 2, 511.
- 14 (a) J. Liu, J. L. Yan, X. W. Yuan, K. Q. Liu, J. X. Peng and Y. Fang, *J. Colloid Interface Sci.*, 2008, 318, 397; (b) J. Liu, P. L. He, J. L. Yan, X. H. Fang, J. X. Peng, K. Q. Liu, Y. Fang, *Adv. Mater.*, 2008, 20, 2508.
- 15 X. Yang, G. Zahng, D. Zhang, *J. Mat. Chem.* 2012, 22, 38.
- 16 S. Kawano, N. Fujita and S. Shinkai, *J. Am. Chem. Soc.*, 2004, 126, 8592.
- 17 C. Wang, Q. Chen, F. Sun, D. Zhang, G. Zhang, Y. Huang, R. Zhao, D. Zhu, *J. Am. Chem. Soc.* 2010, 132, 3092.
- 18 Rein V. Ulijn, *J. Mater. Chem.*, 2006, 16, 2217–2225.
- 19 A. Tanaka, Y. Fukuoka, Y. Morimoto, T. Honjo, D. Koda, M. Goto, T. Maruyama, *J. Am. Chem. Soc.* 2015, 137, 770–775.
- 20 A. J. Harnoy, I. Rosenbaum, E. Tirosh, Y. Ebenstein, R. Shaharabani, R. Beck, R. J. Amir, *J. Am. Chem. Soc.* 2014, 136, 7531–7534
- 21 (a) Z. Yang and B. Xu, *Chem. Commun.*, 2004, 21, 2424–2425; (b) Z. Yang, H. Gu, D. Fu, P. Gao, J. K. Lam and B. Xu, *Adv. Mater.*, 2004, 16, 1440–1444.