Hydrogen Bonded Supramolecular Polymers in Both Apolar and Aqueous Media: Self-Assembly and Reversible Conversion of Vesicles and Gels†

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In a preliminary letter (*Tetrahedron Lett.* **2010**, *51*, 188), we reported two new hydrazide-based quadruple hydrogen-bonding motifs, this is, two monopodal (**1a** and **1b**) and five dipodal (**2a**, **2b** and **3a**—**3c**) aromatic hydrazide derivatives, and the formation of supramolecular polymers and vesicles from the dipodal motifs in hydrocarbons. In this paper, we present a full picture on the properties of these hydrogen-bonding motifs with an emphasis on their self-assembling behaviors in aqueous media. SEM, AFM, TEM and fluorescent micrographs indicate that all the dipodal compounds also form vesicles in polar methanol and water-methanol (up to 50% of water) mixtures. Control experiments show that **1b** does not form vesicles in same media. Addition of **1b** to the solution of the dipodal compounds inhibits the latter's capacity of forming vesicles. At high concentrations, **3b** and **3c** also gelate discrete solvents, including hydrocarbons, esters, methanol, and methanol-water mixture. Concentration-dependent SEM investigations reveal that the vesicles of **3b** and **3c** fuse to form gels and the gel of **3c** can de-aggregate to form the vesicles reversibly.

Keywords supramolecular polymer, vesicle, organogel, self-assembly, hydrogen bond

Introduction

The cooperative interaction of discrete non-covalent forces plays a pivotal role in the generation of complicated three-dimensional structures and functions of biomacromolecules such as DNA and proteins. Inspired by this ubiquitous assembling feature of nature, in the past two decades chemists have been actively engaged in designing synthetic systems to construct supramolecular entities of defined structures and functions.[1] Among others,[2,3] hydrogen bonded supramolecular polymers have received considerable attention due to their reversible, tunable or "responsive" features.[4,5] To date, a number of triple and quadruple hydrogen bonding motifs, with association constants ranging from 10^2 to 10^8 $L \cdot mol^{-1}$ in chloroform, have been developed for this purpose.[6-8] To avoid the interference of the solvent, most of these hydrogen bonded supramolecular polymers are restricted in media of low-polarity. Nature has evolved smart strategies to maintain various hydrogen bonding motifs in water by burying them in hydrophobic microenvironments, as exemplified in the double helix of DNA and in the interior of proteins. Although several hydrogen bonded dimeric motifs have been reported to exist in artificial membranes,[9] secondary and higher-grade structures,[10] and ordered aggregates,[11] and to be used for studies in molecular recognition in aqueous media,[12] examples of hydrogen bonded supramolecular polymers in competitive media are quite limited.[13] Therefore, there is still a great demand for new hydrogen bonding motifs that are able to exist in polar media.

One family of structurally unique assembled architectures are vesicles, the membrane-enclosed sacs at the nano to micro scales, that have found wide applications in studies in biomimetics, nanomaterials and drug and gene delivery.[14] Inspired by the formation of biomembranes from amphiphilic phospholipids, chemists have created a large number of amphiphilic (co)polymers, dendrimers and surfactants that spontaneously form vesicles of varying sizes and functions.[15-17] Many examples of constructing vesicular structures from discrete amphiphilic rigid molecular systems have also been reported.[18] In contrast, non-amphiphilic structures that spontaneously form vesicles are rare.[19] Organogels are

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another family of assembled structures at the macro scale in which a gelator immobilizes the solvent through the formation of a three-dimensional entangled network.[20] Due to their potential usefulness in studies in various advanced materials, a variety of molecular and supramolecular gels have been developed.[21] Since the formation of both vesicles and gels is of bottom-to-top and reversible, these two assembled systems of different scales may convert into each other by modulating the assembling conditions such as concentration, temperature or pH value.[22,23] Efficient regulation of this conversion should be of fundamental and practical importance because entrapped species, if existing, may exhibit different physical, chemical or biological behavior. In a previous work, we found that dipodal molecules could form supramolecular polymers in apolar hydrocarbons, which further self-assembled into spherical vesicles.[24] Herein, we report that the supramolecular polymers can survive in polar solvents and further aggregate to form vesicles and gels. The new vesicles and gels can convert into each other reversibly through a fusion or de-aggregation process.

Results and discussion

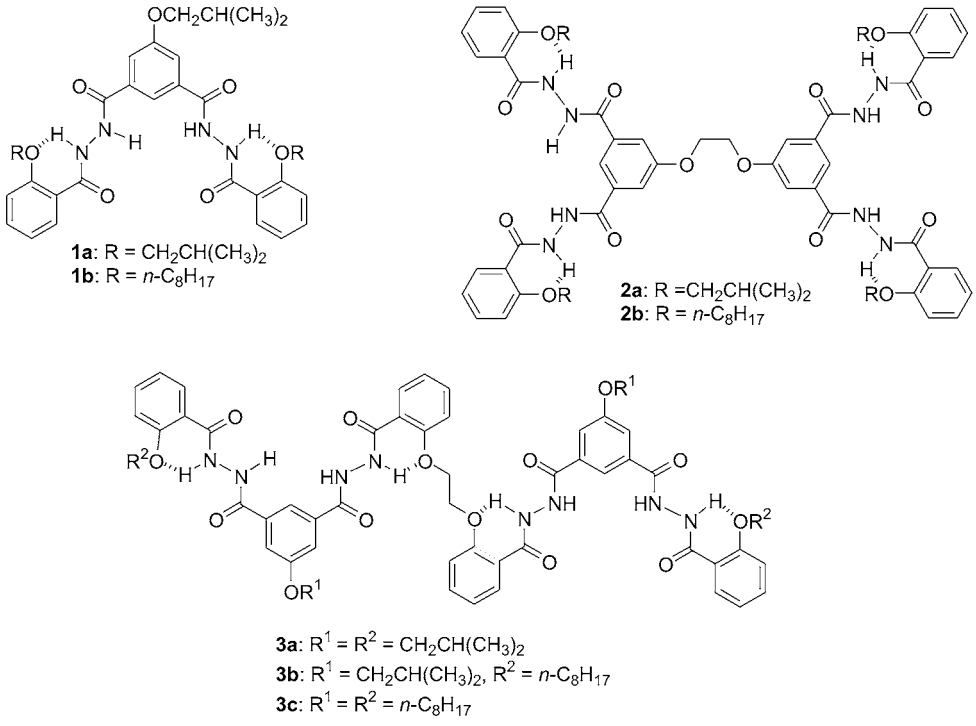
Design and synthesis

Different from their aryl amide analogues that usually form single C═O···H—N hydrogen bonding chain in the crystal structures, 1,2-dibenzoylhydrazine and their derivatives form stronger, double hydrogen bonding chains.[25,26] Their long extended derivatives also tend to aggregate in organic solvents through intermolecular stacking,[19c,27] leading to the formation of vesicles or organogels.[19c,26b] It was envisioned that rationally designed aryl hydrazide derivatives of this family might be used as monomeric segments to construct hydrogen bonded supramolecular polymers in polar media. The key for this purpose would be that the supramolecular polymers aggregate to create a hydrophobic microenvironment for the hydrogen bonding motifs to be shielded from polar solvents. To test this possibility, compounds **1**—**3** (Scheme 1) were designed and synthesized.[24] Compounds **1a** and **1b** were prepared as models, while **2a**, **2b** and **3a**—**3c** were synthesized for assembling the new hydrogen bonded supramolecular polymers. For all the compounds, the peripheral benzene rings were appended with alkoxyl groups at the *ortho* positions of the amide units. It was expected that these alkoxyl groups would not only increase the shielding effect, but also prevent the neighboring amide hydrogen atom from forming intermolecular hydrogen bonding and subsequently improve the assembling selectivity.[26c]

Formation of supramolecular polymers and vesicles in hydrocarbons

We previously reported that dipodal quadruple hydrogen-bonding motifs **2a**, **2b** and **3a**—**3c** self-assembled into supramolecular polymers in both solid state and in chloroform, as evidenced by the X-ray diffraction and ^{1}H NMR studies, and **2a**, **2b** and **3a** self-assembled into spherical vesicles in decalin.[24] The morphology of the vesicles was fully characterized by SEM, AFM, TEM, and fluorescence micrographs (reference 24 for details). The vesicular structures were proposed to be generated from the aggregation of the polymeric frameworks (Figure 2, vide infra), which was

Scheme 1



driven by the formation of intermolecular hydrogen bonds between the quadruple hydrogen-bonding motifs. Although the above examples were derived from low polar media in which the intermolecular hydrogen bonds should be strengthened, such supramolecular polymer might also exist in hydrogen-bond competitive solvents. Because the binding segments consist of three benzene units, they may stack to stabilize the inter-molecular hydrogen bonding in polar media. Therefore, the self-assembling property of these hydrogen-bonding motifs was further investigated in polar solvents.

Vesicle assembly in methanol and water-methanol mixtures

Compounds **2a**, **2b** and **3a**—**3c** were insoluble in pure water. We therefore chose methanol and water-methanol mixtures as the solvents to investigate their self-assembling property in polar media. SEM images showed that all the five compounds self-assembled to form vesicular structures in methanol or water-methanol mixtures. The representative SEM images are provided in Figure 1. The maximum water percentage that allowed the formation of vesicles for **2a**, **2b** and **3a**—**3c** was *ca*. 40%, 8%, 50%, 0.2%, and 0.2% (without the formation of fibrils, vide infra), respectively, which mainly depended on their solubility in the binary solvent. Compounds **2b**, **3b** and **3c** bear long hydrophobic octyl chains and therefore their values were remarkably lower. In the solvents of high water percentage, the vesicles of **2a** tended to aggregate to form vesicle clusters, but rarely gave partially fused structures. In contrast, for **3a**, few vesicles formed clusters of limited vesicles and more vesicles preferred to fuse to generate twins or triplets. This may be rationalized by considering that, compared to the centrally connected **2a**, the end-connected **3a** had an increased tendency of forming cross-linked supramolecular polymers, facilitating the fusion process. The vesicular structures formed in the polar media were further characterized by AFM images. For all the investigated vesicles, the ratios of their diameter and height were 5 to 10, indicating that, upon being transferred from solution to the mica surface, the vesicles became flattened. The result evidenced that the vesicles were hollow and entrapped the solvent, which evaporated on the surface, leaving the vesicles like flat balls. The hollow feature of the vesicles was further evidenced by the fluorescence micrographs, with **2b** as a representative, which showed that all the light spots exhibited an obvious luminance difference between their outer rings and inner areas. The luminance difference does not accurately reflect the size and shape of the vesicles,[18d,19c] but clearly shows that the vesicles are centrally hollow and filled with the solvent in solution. As observed by AFM, the entrapped solvent should also evaporate on surface, leading to a thickness and luminance difference between the outer and inner areas.

SEM control experiments by **1b** revealed that the monopodal molecule did not form vesicular structures in methanol or water-methanol mixtures. Therefore, the formation of the vesicles by **2a**, **2b** and **3a**—**3c** in the polar media should also be attributed to their capacity of generating supramolecular polymers. Adding **1b** to the solution of **2b** or **3b** also reduced or inhibited the formation of the vesicles, Similar to that revealed before in decalin. Because these molecules possess the identical aromatic segments, the stability of their hydrogen bonding motifs should be close. Therefore, the addition of **1b** would remarkably weaken the supramolecular

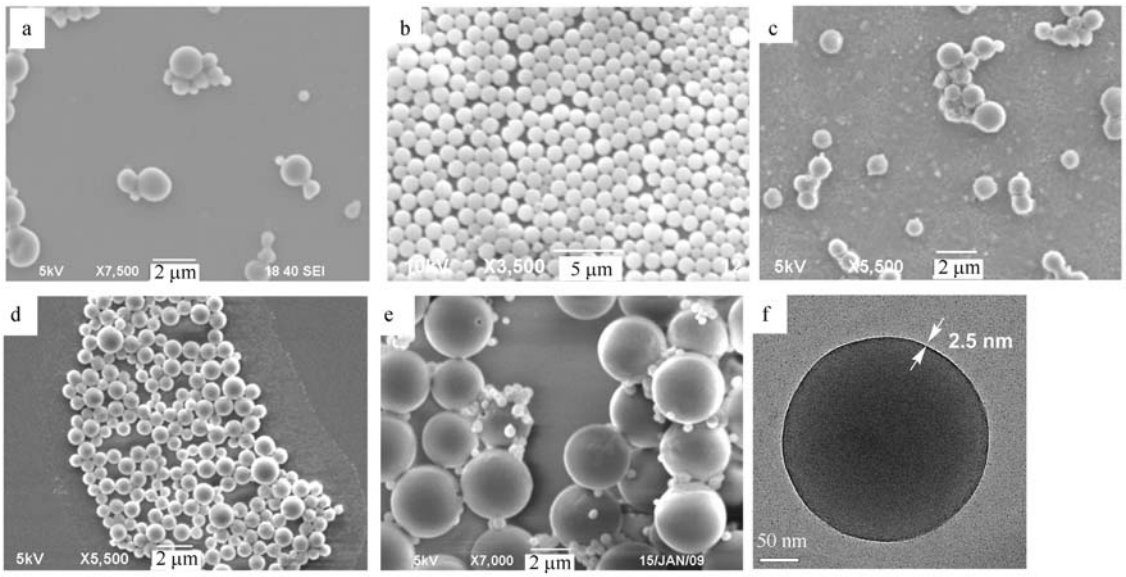


Figure 1 SEM images of the dried samples (1 mmol/L) of (a) **2a** and (b) **2b** in MeOH, (c) **3a** in water and methanol (2∶3, *V*∶*V*), (d) **2a** in water and methanol (2∶3), (e) **2b** in water and methanol (1∶10), and (f) TEM image of the sample of **2b** in methanol (0.4 mmol/L).

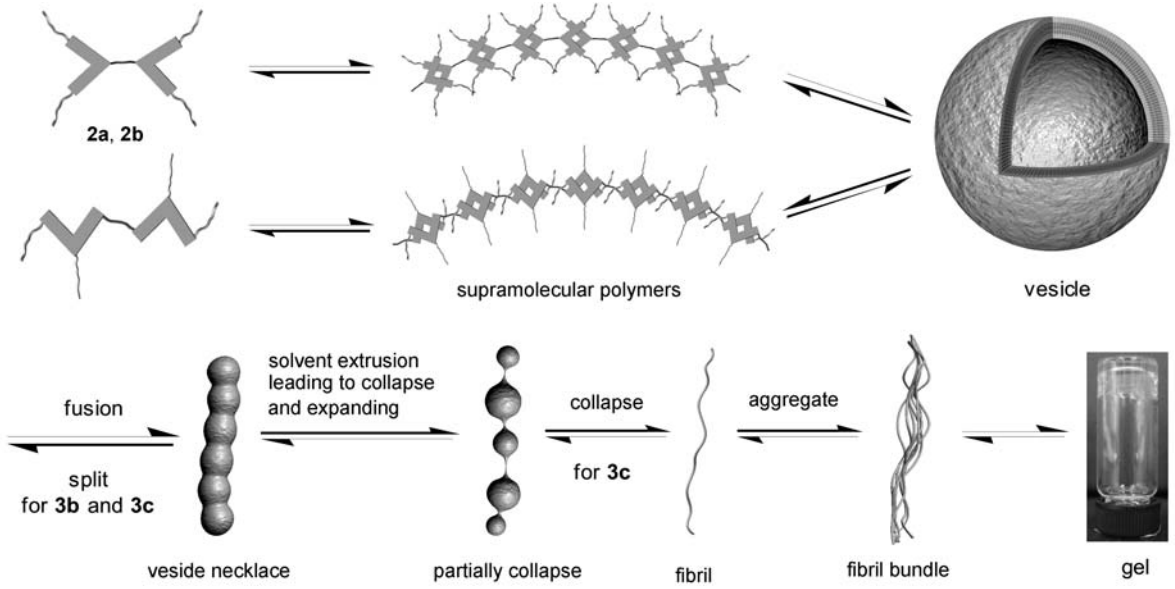


Figure 2 Tentative model for the formation of vesicles and gels from the quadruply hydrogen bonded supramolecular polymers in apolar and polar media. The conversion from vesicles to gels occurred for **3b** and **3c**, and the conversion from gels to vesicles occurred for **3c**.

polymers of **2b** or **3b**. This observation supported that the dipodal compounds formed hydrogen bonding-mediated supramolecular polymers, again indicating that the supramolecular polymeric structures of the dipodal molecules played a key role in the formation of the vesicles, which further aggregated to form the vesicles in the polar media. SEM also showed that adding chloroform, which is a "good" solvent for both aromatic and aliphatic derivatives,[28] to the methanol solution inhibited the formation of vesicles. When the percentage was increased to 40%—50%, no vesicles could be observed on the SEM images. Because the polarity of the medium was decreased with the addition of chloroform, this result supported that the quadruple hydrogen bonding motifs in the polar media should "live" in a hydrophobic microenvironment. Such a microenvironment could not be formed by a single supramolecular polymer, but should be generated through the aggregation of the supramolecular polymers. As revealed in the crystal structures of **2a** and **2b**, the stacking of the aromatic units and the aggregation of the long octyl chains could form the microenvironment to host the two different hydrogen bonding motifs.[24]

TEM showed that the vesicles formed in the polar media had a wall thickness of *ca*. 2.2 (**2a**), 2.5 (**2b**), 2.4 (**3a**), 2.7 (**3b**) and 2.8 nm (**3c**), respectively. As an example, the TEM image of a vesicle formed by **2b** in methanol is shown in Figure 1f. These results suggested that the vesicles were also generated through the monolayered stacking of the supramolecular polymers (Figure 2), as revealed for those formed in apolar decalin.

Gelation property

Previously we found **2b** could gelate the mixture of decalin and tetralin when the content of tetralin was 20%—40%, while **3b** and **3c** gelated both of them and their mixtures. The gelation capacity of all the compounds towards high polar solvents was then evaluated using the "inverse flow" method.[29] The results are listed in Table 1.[24] Compounds **1a**, **1b**, **2a** and **3a** were incapable of gelating any solvent, while **3b** and **3c** gelated all the tested solvents, ranging from apolar decalin to polar methanol or water-methanol mixtures. Their solubility was generally better than **2a**, **2b** and **3a**. Adding **1b** to the systems of **3c** in different solvents could prevent the formation of the gel, again supporting that the strong gelation capacity of the dipodal compounds was enabled by their formation of the supramoleclar polymeric structures. SEM images showed that fibrous structures were formed for all the gels. Figure 3 presents the images of **3b** as examples (vide infra).

Conversion between vesicles and gels

The formation of vesicles and gels by **3b** and **3c** in polar media raised the issue of interconversion between the two classes of aggregates of different scales. SEM investigations indicated that the conversion from vesicles to gels occurred for both **3b** and **3c**. That is, the gels were generated through the aggregation of the vesicles. Figure 3 shows the representative results of **3b** obtained in methanol. This compound exclusively formed vesicles when the concentration was <1.2 mmol/L (Figure 3a). The vesicles began to fuse to form peanut and necklace-like assemblies at 1.4 mmol/L (Figure 3b). With the increase of the concentration, fibrils of micrometer length and nanometer width were gradually generated, which should be produced from the long necklace-like assemblies through the extrusion of the entrapped solvent (Figures 3c—3e). The fibrils became increased

CHINESE JOURNAL OF CHEMISTRY

Table 1 Gelation results of the hydrazide derivatives in different solvents[a]

Solvent	**1a**	**1b**	**2a**	**2b**	**3a**	**3b**[b]	**3c**[b]
decalin	S	P	P[c]	P[c]	P[c]	G (0.40)	G (0.33)
tetralin	S	S	P	P	P	G (0.33)	G (0.33)
decalin-tetralin (10%)	S	P	P	P	P	G (0.40)	G (0.20)
decalin-tetralin (20%)	S	P	P	G (0.12)	P	G (0.46)	G (0.28)
decalin-tetralin (30%)	S	S	P	G (0.15)	P	G (0.47)	G (0.34)
decalin-tetralin (40%)	S	S	P	G (0.23)	P	G (0.40)	G (0.38)
decalin-tetralin (60%)	S	S	P	P	P	G (0.29)	G (0.33)
decalin-tetralin (80%)	S	S	P	P	P	G (0.18)	G (0.29)
butyl acetate	S	S	I	P	I	G (2.80)	G (1.60)
n-octanol	S	S	P	P	S	G (0.52)	G (0.11)
n-pentanol	S	S	P	P	P	G (1.00)	G (0.38)
n-butanol	S	S	P	P	SP	G (3.10)	G (0.34)
methanol	S	S	P	P[b]	P[b]	G (3.10)	G (0.52)
methanol-water (2%)	S	S	P	P	P	G (0.63)	G (1.18)
methanol-water (5%)	S	S	P	P	P	G (0.79)	G (3.35)
methanol-water (10%)	S	S	P	P	P	G (3.06)	P

[a] All the samples were tested at 20 mmol/L. P=precipitation; SP=self-supporting precipitate (gel-like solid which is unstable to inversion); S=soluble; I=insoluble. [b] In the parenthesis is the lowest gelation concentration (*w*/*w*). [c] Vesicles were generated in the solvent at low concentrations.

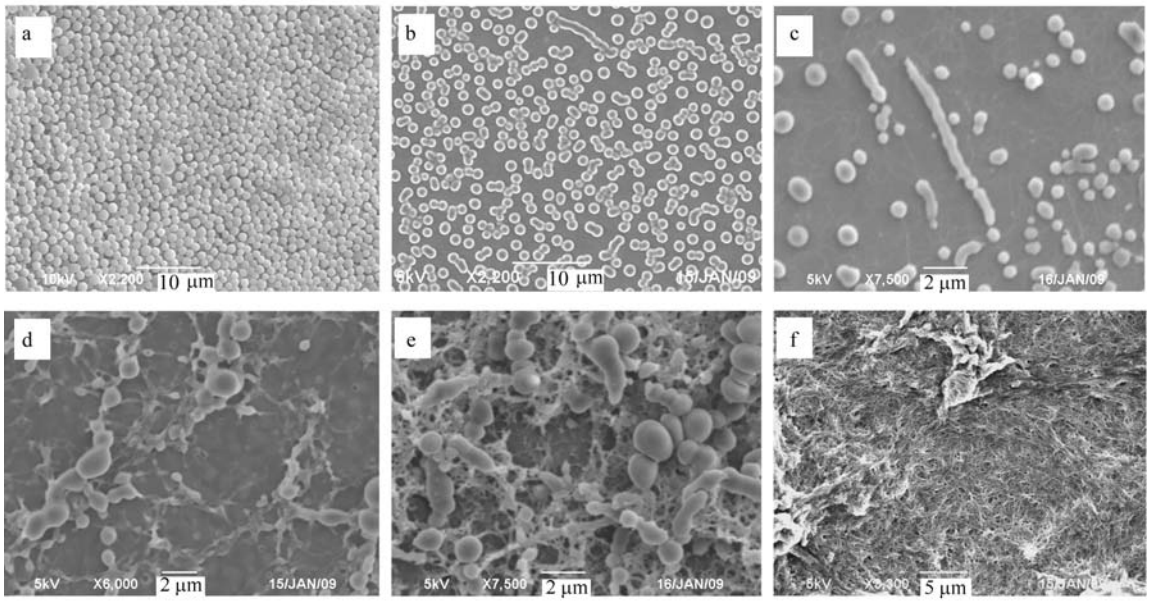


Figure 3 SEM images of the solution of **3b** in methanol: (a) 1.0, (b) 1.4, (c) 1.5, (d) 1.6, (e) 1.7, and (f) 5.0 mmol/L, highlighting the conversion of the vesicles to the fibrils.

with the decrease of the vesicles and finally were observed exclusively. Further increase of the concentration eventually resulted in the formation of a gel. Similar results were also observed for **3c** in methanol when the concentration was increased from 0.1 to 2.0 mmol/L. In addition, the conversion could occur inversely for **3c**. That is, the fibrils could de-aggregate to form vesicles by gradually diluting the solution. The gels of **3b** did not exhibit such an inverse conversion even after the samples were ultrasonicated for 12 h.[30]

The key for the above conversion of the vesicles to gels is that, upon increase of the concentration, the vesicles tended to fuse from their opposite sides. In this manner, one-dimensional fibrous structures could be generated and eventually led to the gelation of the solvent at high enough concentration. Since the linker of the dipodal compounds is flexible, the directionality of the intermolecular hydrogen bonding should not be increased at high concentrations. Thus, this directed fusion might be rationalized by considering that the end

part of the fused structures, starting from a twin, had a smaller curvature, a greater surface tension and thus an increased fusion tendency. The enhancement of the aromatic stacking at high concentrations might also contribute by promoting the formation of long, one-dimensional aggregates. The conversion of the wide necklaces to the thin fibrils could be explained by considering both the dynamic feature and the varying sizes of the beading vesicles (Figure 2). The smaller vesicles in the necklaces were expected to have larger surface tension. Therefore, the solvents entrapped in these beading vesicles would be extruded to flow into the larger ones. As a result, the smaller vesicles became even smaller and eventually collapsed to fibrils, while the larger ones were expanded (Figures 3d and 3e) and finally also collapsed to fibrils through the breaking of the membrane. The inverse conversion of the gels of **3c** to the vesicles well reflected the dynamic feature of the hydrogen bonded supramolecular polymers and the hollowness of the fibrils. An important step for this conversion should be the de-aggregation of the tangled bundles to separate hollow fibrils. Once these thin fibrils were formed, they soaked in the solvent and swelled to form the necklace-like structures, which split up into single vesicles at low enough concentration. The fact that this inverse conversion did not occur for **3b** might be attributed to the branching shape of its *iso*-butyl groups, which would be like anchors to fix the aggregated supramolecular polymers from each other in the fibrils. In contrast, the flexible octyl groups should prefer to adhere to the hydrophobic backbones of the supramolecular polymers to reduce the adhering force across the fibrils. As a result, the fibril bundles of **3c** could de-aggregate upon dilution. The kinetically irreversible behavior observed for **3b** is, to some extent, analogous to the denaturation of proteins, even though its molecular weight is much smaller.

Adding water to the solution of **3b** in methanol (1.0 mmol/L) also caused the conversion of the vesicles to the fibrils (Figure 4). The conversion was very sensitive to water and began in the presence of 0.2% of water and was completed when the water content was increased to approximately 5%. Since the hydrogen bonding could not be stabilized by water, it is reasonable to assume that the driving force for this conversion came from the aromatic stacking and the aggregation of the octyl groups, which were enhanced with the increase of the polarity of the medium. Similar conversion also occurred for **3c**. The mechanism should be similar to that revealed above for the conversion caused by changing the concentration. This process is different from the fusion mechanism of the vesicles formed by amphiphilic block copolymers in binary solvents,[31] which lead to the size increase of vesicles while keeping the spherical shape when the content of water is added.

Conclusions

We demonstrate that the new class of quadruply hydrogen bonded supramolecular polymers with an aromatic hydrazide-based binding pattern are able to self-assemble to two different entities, herein the vesicular structures and gels, in a wide range of solvents from apolar decalin to polar aqueous media. Whatever ultimate applications may be possible, the interesting and novel transitions between the vesicular and fibrous structures in aqueous media reflect the dynamic and reversible feature of hydrogen bonded supramolecular polymers. Since the dimeric hydrogen bonding pattern in these supramolecular polymers is not weakened with the increase of the polarity of the media, new supra-

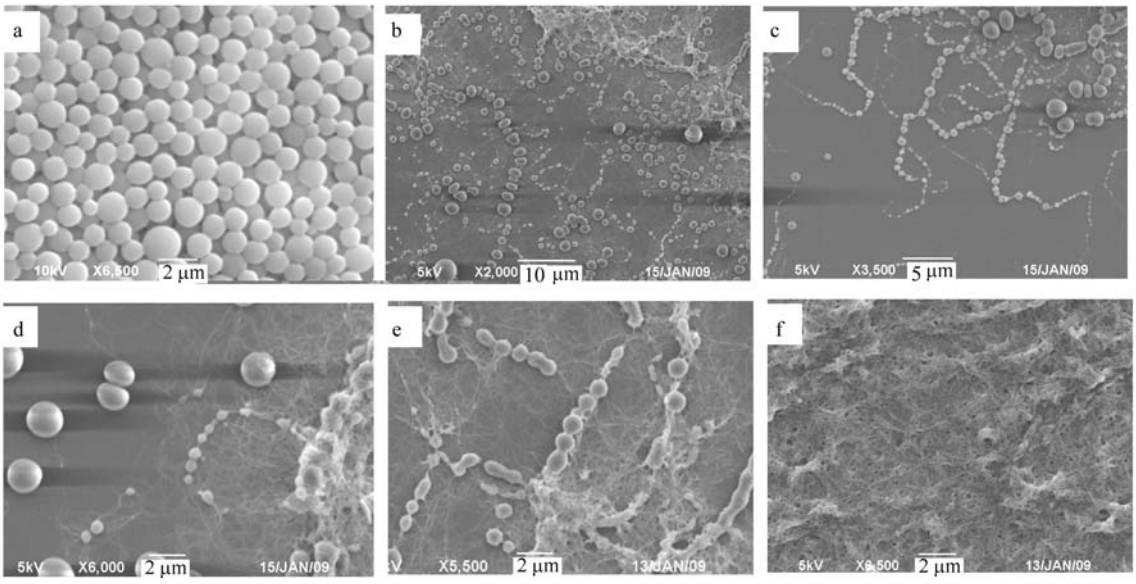


Figure 4 SEM images obtained from the solution of **3b** (1.0 mmol/L) in water and MeOH mixture. The content of water was (a) 0, (b) 0.2%, (c) 0.5%, (d) 1%, (e) 2%, and (f) 5%.

molecular polymers that survive in more polar solvents or even pure water may be expected if the corresponding monomers have enough solubility. This may be realized by replacing the aliphatic chains with ionic or neutral oligoglycol groups. In principle, photo- or electroactive aromatic units may be introduced to enable the formation of a similar hydrophobic cavity, which will lead to the assembly of new stimuli-responsible supramolecular polymers. Another interesting issue is the function of the linker. It is expected that replacement of the simple ethylene unit with long, or rigid or chiral units will remarkably affect the stacking interaction, leading to the formation of new assembling structures of varying properties.

Experimental

General methods

All reagents and chemicals were obtained from commercial sources and used without further purification unless otherwise noted. The solvents have been purified by standard procedures before use. The preparations of compounds **1a**, **1b**, **2a**, **2b** and **3a**, **3c** follow the procedures reported previously.[24] Transmission electron microscopy (TEM) images were recorded on a JEOL JEM-2010 microscope working at 200 kV; scanning electron microscopy (SEM) experiments were conducted on a JEOL JSM-6390-LV microscope; atomic force microscopy (AFM) measurements were performed on a Nano scope IIIa MultiMode microscope; a fluorescence microscope (Olympus IX51) was used for fluorescence microscopy study.

Preparation of samples for microscopic studies

The vesicles were prepared by heating the solutions of the compounds in selected solvents under reflux for several minutes and then the solutions being allowed to cool gradually to room temperature with stand, respectively. For TEM observations, the solutions of vesicles were dropped onto the carbon/Formvar coated copper grids and excess fluid was removed carefully with a filter paper, which had been left overnight in a vacuum oven at 25 ℃; for SEM studies, one drop of solution of the aggregates was pipetted onto freshly cleaved mica plates. After natural evaporation of the solvent at room temperature (*ca*. 25 ℃) under ambient atmosphere, the as-prepared samples were treated in a vacuum oven at 25 ℃ overnight; for AFM experiment, aliquot of solution of the aggregates was dropped onto freshly cleaved mica plates and spread by using a spin-coater operating at 1500 r/min, and then dried naturally under ambient atmosphere; for fluorescence microscopy studies, aliquots of solutions of the aggregates were pipetted onto microscope glass cover slip and then dried naturally under ambient atmosphere.

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