



Two novel quadruple hydrogen-bonding motifs: the formation of supramolecular polymers, vesicles, and organogels

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ABSTRACT

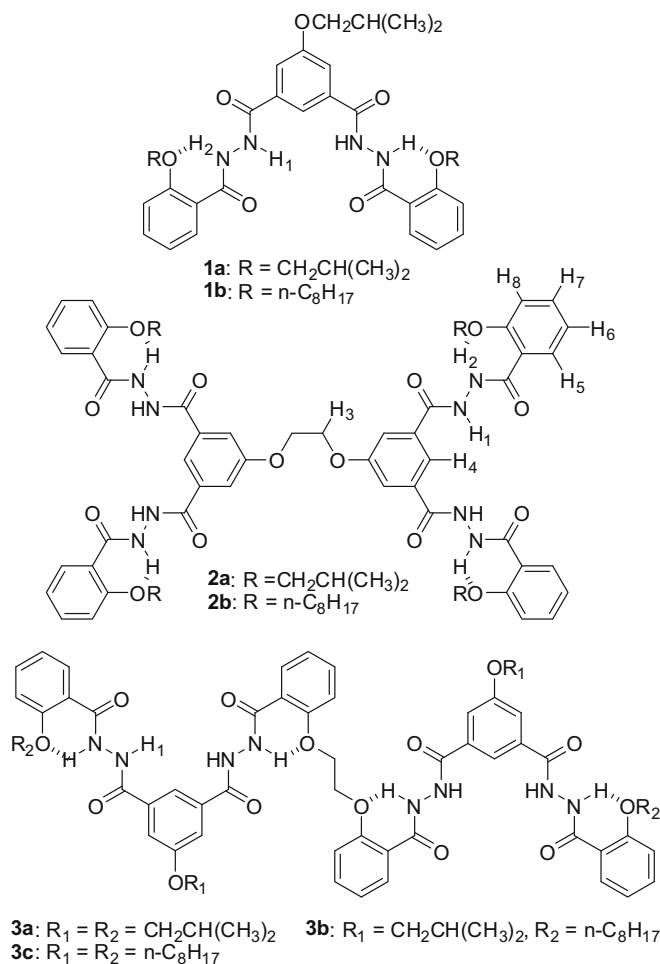
Two new hydrazone-based quadruple hydrogen-bonding motifs are described. Dipodals based on these two motifs are revealed to form supramolecular polymers, which can further aggregate to form vesicles and/or organogels in hydrocarbons. The quadruple hydrogen-bonding motifs are characterized by the X-ray diffraction and (2D) ^1H NMR experiments, while the vesicles and organogels are evidenced by SEM, AFM, TEM, and fluorescent microscopy.

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Hydrogen bonding is the most reversible noncovalent forces for forming well-defined supramolecular entities. In the past decades, the quadruple hydrogen-bonding motifs have received considerable attention due to their generally increased stability compared to the double or triple hydrogen-bonding motifs.¹ Moreover, this series of binding patterns has been widely utilized to construct dynamic supramolecular polymers.² We previously reported the self-assembly of a series of stable quadruple hydrogen-bonding pattern from complementary aromatic hydrazone-derived monomers.^{1h} More recently,³ we also constructed a variety of foldamers from aromatic hydrazone oligomers by using intramolecular hydrogen bonding as the driving force. We herein report two novel quadruple hydrogen-bonding motifs, whose monomers dimerize by adopting a twisted or perpendicular conformation. Notably, hydrogen-bonded supramolecular polymers constructed based on these motifs can self-assemble into both vesicles and organogels.⁴

Different from their aryl amide analogues, which usually form single $\text{C}=\text{O}\cdots\text{H}-\text{N}$ hydrogen-bonding chains, 1,2-dibenzoylhydrazines generate stronger double $\text{C}=\text{O}\cdots\text{H}-\text{N}$ hydrogen-bonding chains.^{5,6} We therefore synthesized compounds **1a**, **1b**, **2a**, **2b**, and **3a–c**. We envisioned that **1a** and **1b** would form a homodimer that is stabilized by four $\text{C}=\text{O}\cdots\text{H}-\text{N}$ hydrogen bonds, while the dipodals might form supramolecular polymers that are linked by this motif. The two outside NH units are locked by intramolecular six-membered $\text{O}\cdots\text{H}-\text{N}$ hydrogen bonds,⁷ which should suppress the formation of the intermolecular hydrogen bonding and thus improve their assembling selectivity.

The crystal structure of **1a** exhibited a dimeric motif that is stabilized by two pairs of $\text{C}=\text{O}\cdots\text{H}-\text{N}$ hydrogen bonds ($d = 2.03$ and 2.11 Å) (Fig. 1a). Notably, only one of the two *iso*-butoxy O atoms was engaged in the intramolecular hydrogen bonding, even though



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it is very stable and occurs even in aqueous media.^{7,8} The two central benzene rings of the dimer stacked in a face-to-face manner, which should also stabilize the hydrogen-bonding motif (Fig. 2a). The neighboring dimers were further connected with two strong C=O···H–N hydrogen bonds ($d = 2.05 \text{ \AA}$), while the peripheral benzene rings also stacked (not shown).

The crystal structure of **1b** revealed another quadruple hydrogen-bonding motif (Fig. 1b). The two monomers were arranged perpendicularly (Fig. 2b). The N–H···O distances were different slightly due to the unsymmetry of the arrangement. The octoxy O atoms were all engaged in intramolecular hydrogen bonding, while the octyl chains stacked with their counterparts of neighboring molecules (not shown). Different from that of **1a**, no aromatic stacking or other intermolecular hydrogen bonding was observed for **1b**. It seems that the larger peripheral aliphatic groups played a key role in promoting the formation of this motif. Compounds **1a** and **1b** are similar in shape to the V-styled N^1, N^3 -bis(6-acylamino-pyridin-2-yl)isophthalamides that can bind barbiturates via six hydrogen bonds.^{9,10} However, they form homodimers due to their self-complementary feature.

The crystal structure of **2a** (Fig. 3a) revealed the formation of a stair-styled supramolecular polymer that was mediated by a quadruple hydrogen-bonding motif very similar to that of **1a**. The central benzene rings stacked with each other, while the peripheral benzene rings stacked alternately with those of the neighboring polymeric chains. The crystal structure of **2b** exhibited another kind of supramolecular polymer (Fig. 1d) formed through a hydrogen-bonding motif similar to that of **1b** (Fig. 2b). No stacking or other intermolecular hydrogen bonds were observed in the packing structure. All the octyl chains were arranged along the polymeric framework and stabilized the packing structure through intermolecular van der Waals force.

¹H NMR experiments in CDCl₃ supported that the quadruple hydrogen-bonding motif also exists in solution. Diluting the solution of **1a** and **1b** in CDCl₃ from 64 or 100 mM to 0.25 mM caused the H-1 signal (see the structures) to shift upfield by 0.83 or

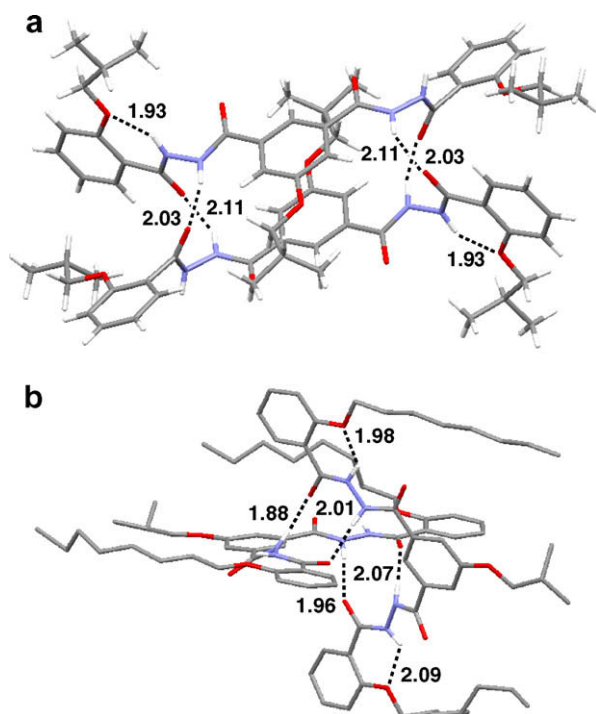


Figure 1. The crystal structures of (a) **1a** and (b) **1b** (only the amide hydrogen atoms are shown for clarity).

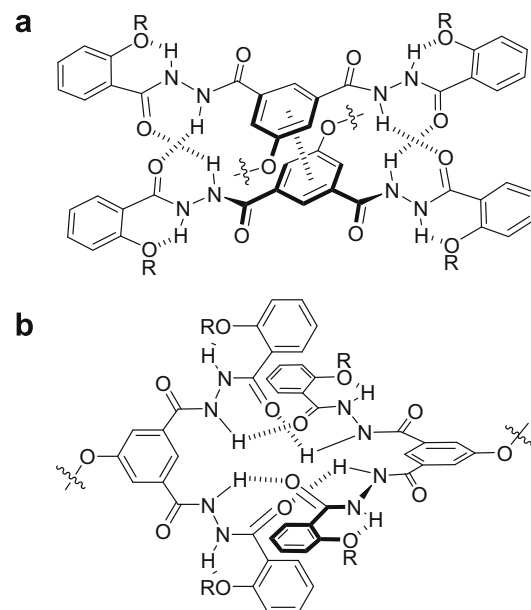


Figure 2. The two quadruple hydrogen-bonding motifs: (a) the central benzene rings stack with each other (for **1a** and **2a**); (b) the monomers are located perpendicularly (for **1b** and **2b**).

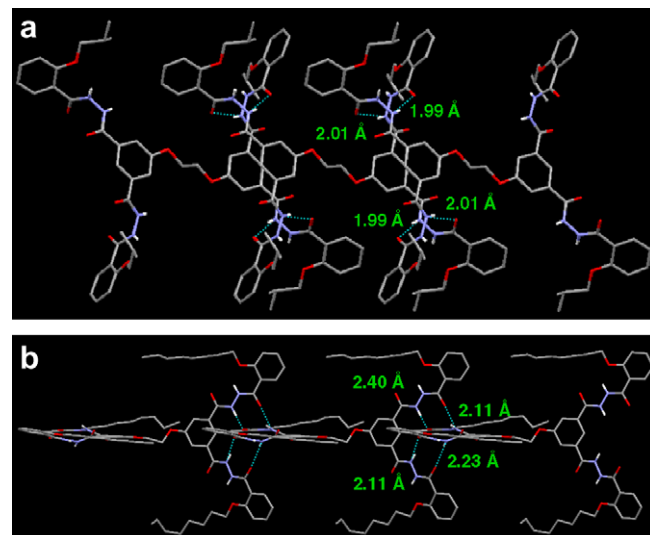


Figure 3. The quadruply hydrogen-bonded supramolecular polymers of (a) **2a** and (b) **2b** in the crystal structures (only the amide hydrogen atoms are shown for clarity). The single crystal of **2a** was grown by slow evaporation of its methanol solution and that of **2b** was grown by diffusing acetonitrile to its DMF solution.

1.05 ppm, indicating that it was strongly involved in intermolecular hydrogen bonding. In contrast, the H-2 signal was shifted downfield by only 0.24 or 0.26 ppm. The results were consistent with the above-mentioned X-ray results. By fitting the plots of $\Delta\delta$ versus the concentration to a nonlinear equation of the 1:1 binding model, association constants (K_{assoc}) of **1a–1a** and **1b–1b** were derived to be 600 and 480 M^{-1} .¹¹ The values are modest, possibly due to the twisting of the framework.

2D NOESY experiment for **2b** in CDCl₃ revealed NOEs between the central ethylene hydrogen (H-3) and the H-4, H-5, and H-6 atoms (see the structure), but not the H-2, H-7, or H-8 atom, indicating that the peripheral aromatic units were confined and did not rotate around the inner-located (Ar)C–C(=O) bond. Because the distances between H-3, H-4, H-5, and H-6 in the crystal

structure of **2a** are generally shorter than the corresponding ones in the crystal structure of **2b**, these results evidenced that in solution **2b** the first dimeric motif should also form. Diffusion-ordered 2D NMR (DOSY) experiments were further performed for **1b**, **2b**, and **3c** at two different concentrations,¹² giving the corresponding diffusion coefficients of 2.6×10^{-9} (**1b**, 10 mM), 2.5×10^{-9} (**1b**, 100 mM), 5.0×10^{-9} (**2b**, 10 mM), 6.0×10^{-10} (**2b**, 100 mM), 5.1×10^{-9} (**3c**, 10 mM), and 1.2×10^{-9} (**3c**, 30 mM) m^2/s . The values of **1b** are close, implying that it formed a simple dimer at both concentrations. In contrast, the values of **2b** and **3c** at higher concentration were remarkably smaller than those at lower concentration, clearly supporting that the dipodal compounds could form supramolecular polymers. At higher concentrations, they had a higher degree of polymerization, a larger size, and thus a smaller diffusion coefficient. The values of isomers **2b** and **3c** at 10 mM are comparable, indicating that their degree of polymerization was comparable as a result of forming the identical hydrogen bonding motif.

Since the new dimeric segments have a relatively large aromatic framework, we further investigated the potential of the supramolecular polymers to generate ordered structures in nonpolar hydrocarbons, including *n*-hexane, *n*-octane, *n*-dodecane, decalin, tetralin, benzene, and toluene, in which the hydrogen bonding and aromatic stacking should be enhanced. At room temperature, all the dipodals displayed low solubility in these solvents. Upon heating, the solubility of **2a**, **2b**, and **3a** in decalin was increased considerably (>1.0 mM). SEM images showed that all these compounds formed spherical vesicles with average diameters of ca. 0.6, 1.0, and 1.4 μm (Fig. 4a and b), respectively. SEM images also indicated that **2b** formed vesicles in *n*-dodecane (1 mM), but the vesicles were generally separate. In all the hydrocarbons, **1a** and **1b** did not form vesicles. Adding **1b** to the decalin solution of **2b** reduced the capacity of **2b** of forming vesicles, and 4 equiv of **1b** destroyed the vesicles completely. Adding chloroform to the decalin solution also suppressed the formation of the vesicles and when its content was 40%, no spherical structures were observed from the SEM images. Adding tetralin to the above-mentioned solutions in decalin also weakened, and at 25%, it prevented the

formation of vesicles. These results indicated that the formation of the supramolecular polymers and their aggregation were the keys for the generation of the vesicles: The addition of **1b** weakened the supramolecular polymers, while the addition of chloroform and tetralin, which might competitively stack with the aromatic units of the dipodals, reduced the aggregation of the supramolecular polymers.¹³

AFM also supported that **2a**, **2b**, and **3a** self-assembled into vesicles in decalin (see the Supplementary data). The diameter/height ratio of the vesicles was 5–15, evidencing their hollowness. Upon being transferred onto the surface, the vesicles were dried due to the evaporation of the entrapped solvent, leaving them like flat balls. The fluorescence micrographs also supported the hollowness. As shown for **2b** (Fig. 4c), the light spots all exhibit obvious luminance differences between the outer rings and inner areas,^{3b} suggesting that they were hollow and filled with the solvent in solution. When they were transferred onto the surface, the entrapped solvent was evaporated, leading to the difference in thickness and luminance.

TEM also evidenced the hollowness of the vesicles. Figure 4d shows the image of a vesicle of **2b**, which had an average wall thickness of ca. 2.6 nm. The crystal structures of **2a** and **2b** revealed that the width of their aromatic segments was ca. 2.0 nm. Due to their dynamic feature, the supramolecular polymers should exhibit a larger apparent thickness. Therefore, this result supports that the vesicles might have a monolayer structure that was generated by the aggregation of the polymeric frameworks' (Fig. 5). The molecules should also be movable in the membranes. Thus we propose that the two hydrogen-bonding motifs shown in Figure 2 should co-exist in the vesicles.

Compounds **1a**, **1b**, **2a**, and **3a** did not gelate any of the above-mentioned solvents. In contrast, **2b** gelated the mixtures of decalin and tetralin when the content of tetralin was 20–40%, while **3b** and **3c** gelated both of them and their mixtures (see the Supplementary data for details). The long octyl chains should contribute essentially by increasing the solubility and promoting the formation of the entangled networks.¹⁴ Adding **1b** to the above-mentioned organogels could cause the latter to turn to solution, again support-

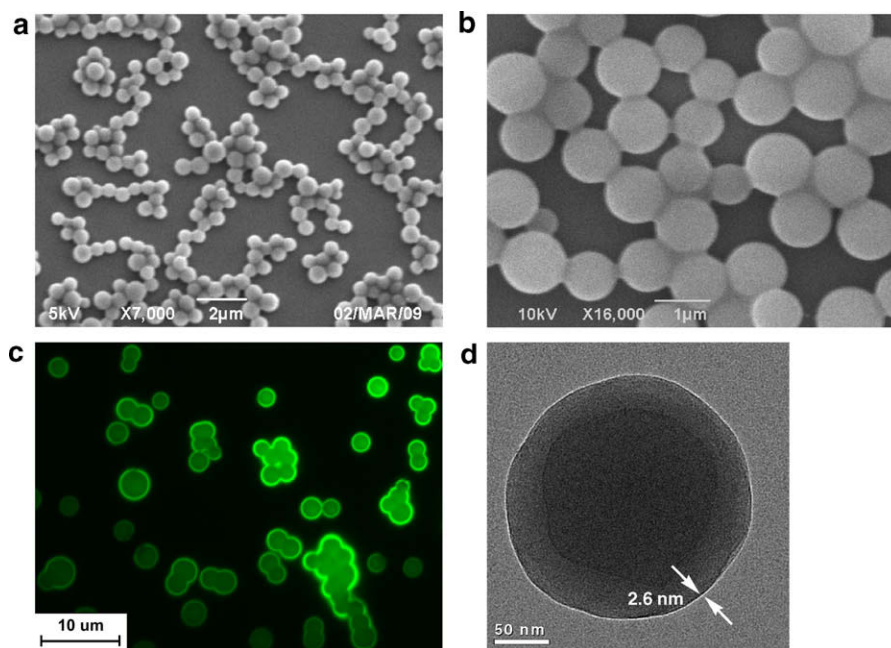


Figure 4. SEM images of the samples of (a) **2a** (1.0 mM) and (b) **2b** (1.0 mM), (c) the fluorescence micrograph of the sample of **2b** (20 mM), and (d) TEM image of the sample of **2b** (0.4 mM) in decalin.

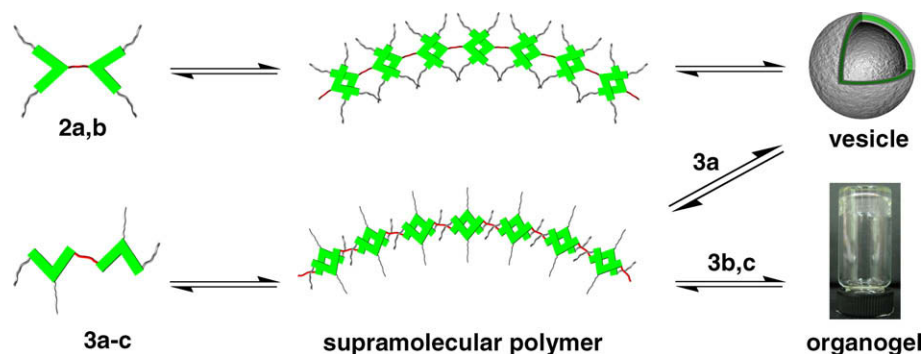


Figure 5. Tentative models for the formation of vesicles and organogels from the quadruply hydrogen-bonded supramolecular polymers in apolar media.

ing that the supramolecular polymers accounted for the gelation. SEM images showed that all the gels exhibited fibrous structures (see the [Supplementary data](#)), while concentration gradient experiments revealed that the fibrils could be formed by fusion of the smaller vesicles.

In conclusion, two novel quadruple hydrogen-bonding motifs have been developed from aromatic hydrazide-based monomers, which can be utilized to construct supramolecular polymers. Although the stability of the novel motifs is modest, the supramolecular polymers exhibit unique self-assembling property, that is, forming both vesicles and organogels in hydrocarbons. Because the binding segments consist of three benzene units, they may stack to stabilize the intermolecular hydrogen bonding in polar media,¹⁵ which will be exploited in the future.

Acknowledgments

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Supplementary data

Crystallographic data (excluding structure factors) for structures 1a, 1b, 2a, and 2b in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC 746809, 725875, 746808, and 725874, respectively. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: t44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Synthesis and characterizations, selected (2D) ¹H and ¹³C NMR spectra, additional AFM and SEM images, gelation results, typical procedure for the evaluation of association constants. Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.10.115](https://doi.org/10.1016/j.tetlet.2009.10.115).

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