

Vesicles and Organogels from Foldamers: A Solvent-Modulated Self-Assembling Process

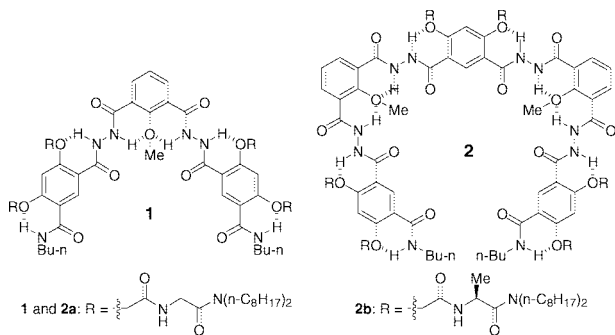
Wei Cai, Gui-Tao Wang, Yun-Xiang Xu, Xi-Kui Jiang, and Zhan-Ting Li*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Received March 4, 2008; E-mail: ztli@mail.sioc.ac.cn

Vesicles are important three-dimensional assemblies for studies in biomimetics, nanomaterials, and drug and gene delivery. Inspired by the formation of biomembranes from amphiphilic phospholipids, chemists have developed an ocean of amphiphilic polymers and surfactants that spontaneously form vesicles of various sizes and functions.^{1,2} Examples of vesicles that consist of amphiphilic dendrimers,³ calixarene,⁴ cucurbituril,⁵ fullerene,⁶ cyclodextrin,⁷ cyclophane,⁸ and sexithiophene or *p*-phenylene vinylene derivatives⁹ have also been reported. In contrast, design of nonamphiphilic structures that spontaneously form vesicles has been a great challenge.¹⁰ Herein we report an unprecedented self-assembly of foldamers,¹¹ which contain no hydrophilic segments but form vesicles in polar methanol and organogels in nonpolar aliphatic hydrocarbons.¹²

We previously reported a class of hydrazide-based foldamers,¹³ whose planar crescent conformations are stabilized by intramolecular three-center hydrogen bonding.^{11c-e} Since several aromatic foldamers had been revealed to aggregate via intermolecular π stacking,¹⁴ we envisioned that similar stacking would occur for foldamers **1** and **2a,b**, which might be modulated by intermolecular hydrogen bonding of the amide units and van der Waals interaction of the long peripheral aliphatic chains.



At room temperature, compounds **1** and **2a,b** all displayed low solubility in methanol. Upon heating, however, their solubility was increased considerably (>10 mg/mL). The resulting solution remained clear for weeks at room temperature, implying that some kind of assemblies was formed. Figure 1 shows their SEM images which were obtained on mica surface after the solvent was evaporated. It can be found that all the compounds self-assembled into spherical vesicles, the average diameter of which was estimated to be approximately 1.2 (**2a**), 3 (**1**), and 5 (**2b**) μm , respectively. It was also revealed that the vesicles could partially combine to generate twins, triplets, or even multiplets, suggesting that larger vesicles were formed by the fusion of the smaller ones.³⁻⁵ SEM images of **2a** from 2 mM solution were also obtained, which showed that smaller vesicles were formed, as observed for many of classical amphiphilic vesicles.⁷⁻⁹

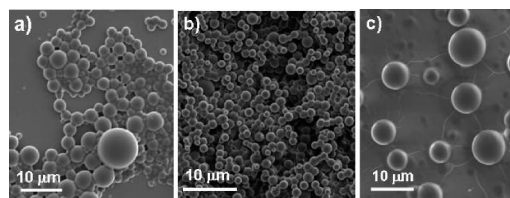


Figure 1. SEM images of the sample of (a) **1**, (b) **2a**, and (c) **2b** in methanol (4 mM) on mica surface after the solvent was evaporated.

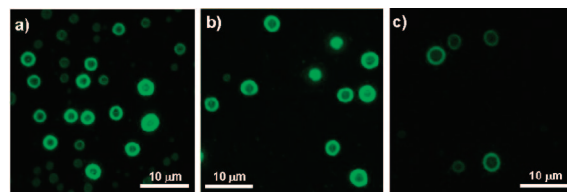


Figure 2. Fluorescence micrographs of the vesicles of (a) **1**, (b) **2a**, and (c) **2b** formed in methanol (1 mg/mL).

AFM also supported the formation of vesicular structures (see Supporting Information). Compounds **1** and **2a** formed isolated vesicles, whereas vesicles of **2b** preferred to further aggregate. The average diameter of the vesicles is ca. 0.7 μm for all three molecules, which was notably smaller than that revealed by SEM but was also revealed to be concentration-dependent.⁷⁻⁹ The ratio of the diameter and height of the vesicles formed by **1**, **2a**, and **2b** was estimated to be ca. 7, 16, and 36, indicating important flattening upon being transferred from solution to mica surface. This result may be attributed to the removal of solvent molecules from the hollow spheres and also the high local force applied by the AFM tip.^{3b,6}

The formation of vesicles in solution was also confirmed by dynamic light scattering study of the solution of **2a** in methanol (5 mM). The average hydrodynamic radius of the vesicles was observed to be 459 nm. Moreover, the vesicles also displayed a very narrow size distribution, indicating the formation of well-equilibrated structures. The hollow feature of the vesicles was evidenced by fluorescence microscopy images (Figure 2). Although the nanoscaled light spots could only roughly reflect the size and shape of the vesicles on the surface, the large difference of the luminance of the outer rings relative to that of the inner areas of the spots clearly showed that the vesicles were all centrally hollow and filled with fluorescence-silent solvent in solution.^{5,9b} The hollow feature of the vesicles was also confirmed by fluorescent dye (Rhodamine B) encapsulation experiments.⁵

TEM also evidenced the hollow feature of the vesicles. The wall thickness of vesicles of **2a** was estimated to be ca. 3 nm (Figure 3). Similar results were also observed for **1** and **2b**. Space-filling modeling revealed that the folded skeleton of **2** had a diameter of

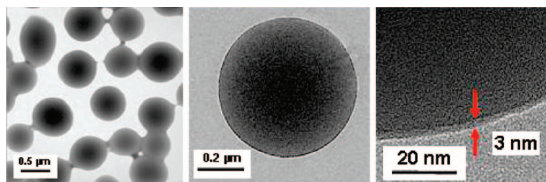


Figure 3. TEM images of the vesicles of **2a** (formed in 0.25 mM solution in methanol) on copper grid covered with Formvar film at different magnifications.

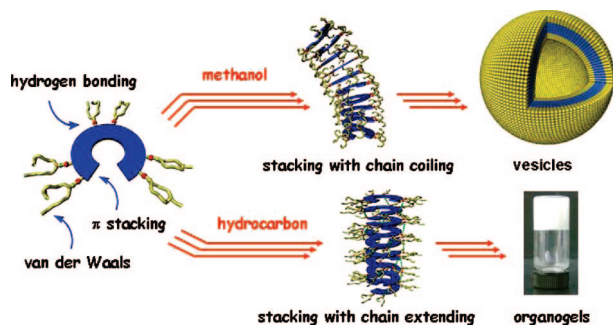


Figure 4. Tentative model for the self-assembly of vesicles and organogels from nonamphiphilic foldamers.

1.8 nm, whereas the peripheral chains at their extended state had a length of 1.6 nm. Thus, these results showed that the vesicles had a monolayer morphology and were generated by two-dimensional packing of cylindrical aggregates of the folded frameworks (Figure 4). The more polar aryl amide groups might be exposed to methanol, while the appended alkyl chains might be repelled by solvophobic effects to entangle each other along the cylinders. It has been reported that six-membered N–H···O H-bonding survives in aromatic amides in competitive media.¹⁵ The NH signal of model molecule *N,N'*-di(2-methoxybenzoyl)hydrazine and its 4-substituted isomer in ¹H NMR in DMSO-*d*₆ (4 mM) appeared at 10.75 and 10.20 ppm,^{13a} respectively. This large difference suggested that similar H-bonding also formed in hydrazide derivatives, which could induce the formation of folded conformations for **1** and **2** in polar solvents. Similar one-layered structures have been revealed for several linear amphiphilic conjugated systems.⁹

Interestingly, compounds **1** and **2b** were also found to gelate nonpolar aliphatic hydrocarbons including *n*-hexane, cyclohexane, *n*-heptane, *n*-octane, and *n*-decane. The solubility of **2a** was low in these liquids possibly due to stronger intermolecular H-bonding of its appended amides. However, both SEM and AFM studies showed that all three molecules formed entangled fibers when cast from these liquids. In contrast, only small particles and/or short fibers were formed when cast from chloroform. In nonpolar liquids, π stacking should exist for all these molecules. IR spectra of **1**, **2b**, and several intermediates in *n*-hexane exhibited NH stretching vibrations only at <3390 cm⁻¹, indicating that NH units in their side chains also formed intermolecular H-bonding. However, the peripheral aliphatic chains would be flexible. Therefore, we proposed that it was these flexible chains that entwined with each other, leading to the formation of three-dimensional networks which immobilized the liquid (Figure 4). Compared to those recorded in good solvent chloroform, UV spectra of the oligomers in both methanol and alkanes also exhibited hypochromicity, which increased with temperature decrease. In addition, chiral **2b** displayed circular dichroism in methanol or alkanes, which was temperature-

dependent, but not in chloroform. These results further supported π stacking of the oligomers.

In summary, we have shown that nonamphiphilic foldamers self-assembled to form monolayered vesicles in methanol owing to cooperative π stacking, hydrogen bonding, and van der Waals interactions. The fact that **1** and **2b** gelated nonpolar hydrocarbons illustrates that the self-assembly of foldamers can be modulated through appending additional groups. It is expected that both the folded segments and peripheral chains can be readily modified. Thus, the work may open the way for the design of a new generation of vesicles from nonamphiphilic architectures.

Acknowledgment. We thank the NBRP (2007CB808000), CAS (KJJCX2-YW-H13), and NSFC (Nos. 20732007, 20621062, 20425208, 20572126, 20672137) for financial support.

Supporting Information Available: Experimental details, spectra and microscopy images. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA801618P