

# Dynamic Control of Self-Assembly of Amphiphilic Conjugated Alkenes in Water by Reactions

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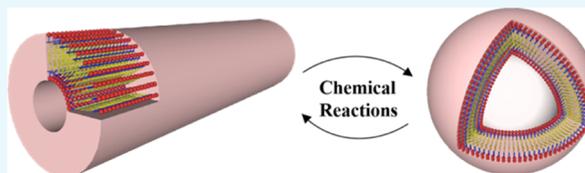


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**ABSTRACT:** Nature sets a great example of how to precisely control self-assembly to obtain distinct structures upon external stimuli and perform specific functions to sustain important biological tasks. In the present study, we report the design and control of self-assembly of an amphiphilic conjugated alkene in water. The morphologies of the self-assembled structures are highly dependent on the anions. The hydrophilic tosylate group can trigger the formation of nanotubes, while the less-hydrophilic inorganic bromide generates vesicles. The interchange of the two different structures can be controlled by employing different anions combined with a couple of reactions that act as signals. The result shown here provides an important tool for manipulating self-assembled behaviors in water and paves the way toward more complex systems.



## 1. INTRODUCTION

Self-assembly is crucial for life as many biological processes in nature rely on the correct supramolecular assemblies of small molecules into large and dynamic structures. Besides the complex but well-defined supramolecular structures, it is of great importance that the system is able to perform specific function in a fully controlled manner.<sup>1–3</sup> The formed supramolecular aggregates can adapt their morphologies in response to a series of feedback signals such as chemical reactions. Inspired by the fascinating examples in nature, the development of supramolecular systems created by assemblies of functional molecules via noncovalent interactions to achieve distinct functions upon the input of external stimuli has become a longstanding goal for many research fields.<sup>4–7</sup> These artificial responsive systems not only help us better understand and mimic highly sophisticated natural systems but also serve as a basic toward novel smart materials.

Addressing supramolecular assemblies in a controlled manner is not a trivial task due to the highly dynamic nature of supramolecular interactions involved in the system. In addition, it is more challenging when the whole process is responsive to external stimuli and fully operates in water as what the natural systems have achieved. Successful attempts include the use of photoresponsive building blocks.<sup>8–13</sup> The change of the structural conformation of the light-responsive molecules triggers morphological changes of the self-assembled structures. By applying irradiation with different wavelengths or heat values, the process is fully reversible. Another important approach is to use the ion effect, which are widely found in biological systems.<sup>14</sup> Different cations or anions are reported to be able to mediate the formation process of micelles,<sup>15</sup> nanotubes,<sup>16</sup> nanoribbons,<sup>17</sup> nanosheets,<sup>18</sup> and copolymers.<sup>19</sup>

Here, we show that the morphologies of self-assembled amphiphilic highly conjugated alkenes in water can be controlled with different anions. More importantly, the addition of anions can be achieved by specific reactions that release the corresponding anions and therefore allow dynamic tuning of the supramolecular structures via a series of chemical reactions. As shown in Figure 1, the design system consists of a rigid overcrowded alkene moiety as a core structure. Two dodecyl aliphatic chains are installed in the lower half of the amphiphile as the hydrophobic parts. The parallel two dodecyl chains are known to interdigitate with one another to form a bilayer as the driving force of the self-assembly. The upper half of the amphiphile contains a hydrophilic oligoethylene glycol unit, which is terminated with a trimethyl ammonium positively charged head group to facilitate its solubility in water. The conjugated aromatic core provides additional stacking interactions for self-assembly.<sup>20,21</sup> The counterion of the head group can be varied, and in the present study, the hydrotropic anion tosylate and inorganic counterion bromide are employed to investigate the counterion effect on self-assembly.

## 2. RESULTS AND DISCUSSION

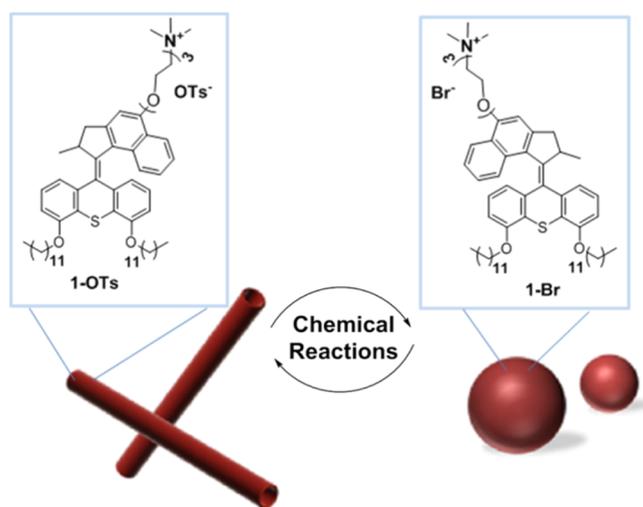
Amphiphilic overcrowded alkene **1-OTs** and **1-Br** were prepared according to the literature procedure, and synthetic details are reported in the Supporting Information. Self-

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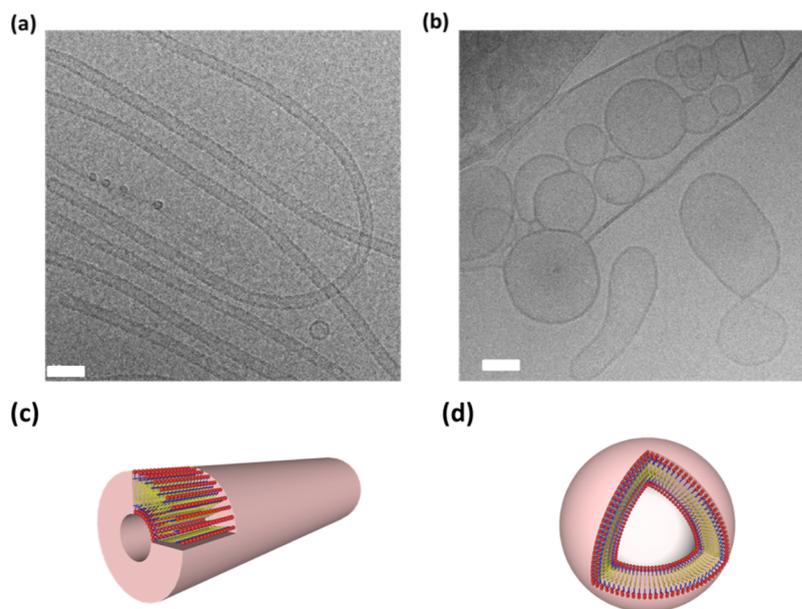


**Figure 1.** Schematic representation of interconverted self-assembled structures in water between nanotubes (1-OTs) and vesicles (1-Br) induced by chemical reactions.

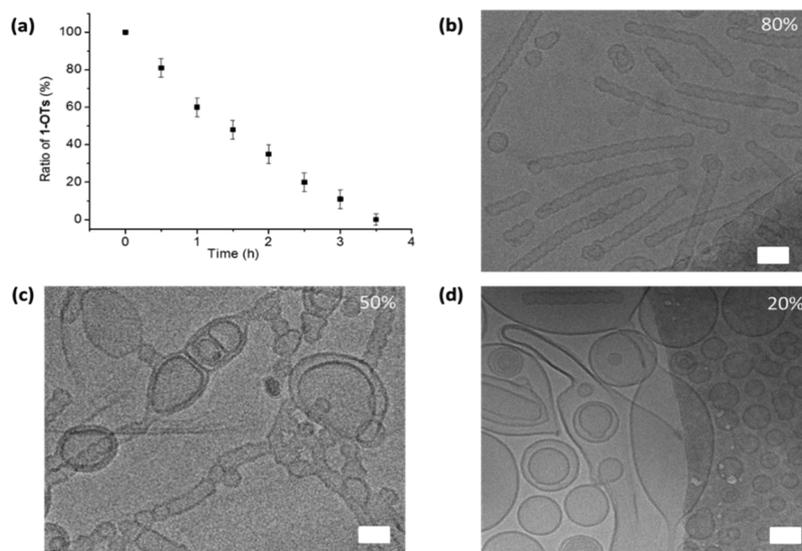
assembly of 1-OTs in water has been reported in the literature,<sup>21</sup> and identical conditions were employed in the present study. By addition of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) which is often used to help amphiphiles to form well-defined aggregated structures,<sup>21,22</sup> tubular structures were observed by cryo-transmission electron microscopy (cryo-TEM) when 2:1 ratio of 1-OTs and DOPC was used (Figure 2a). The obtained nanotubes are several micrometers long with diameters of ~20 nm. The wall of the nanotube is approximately 4 nm in thickness, which suggests a bilayer formation by interdigitation of the aliphatic chains of 1-OTs.<sup>21,22</sup> In addition, the bilayer walls are uneven and toroidal. However, when 1-Br was coassembled with DOPC (ratio 2:1) under the same conditions, only vesicles with diameters of 120 nm to micrometers were detected

(Figure 2b). Aggregation of pure 1-Br or DOPC in water resulted in either hardly any well-defined structures or vesicles with much smaller diameters (Figure S5). The above-mentioned controlled experiments indicate that the observed vesicles are formed by co-assembly of 1-Br and DOPC. The difference of the aggregated morphologies between 1-OTs and 1-Br is due to the different interactions of the anion with the polar positively charged head group in molecule 1.<sup>15</sup> The hydrophobic moiety of 1 is closely packed, while the hydrophilic part is left “standing” outside of the aggregates. The free space occupied by each charged head group plays an important role in the determination of the morphologies of the assembled structures. When adjacent head groups are held tight, the amphiphilic molecules tend to pack closely, and it usually results in tubular or sheet-like planar structures.<sup>23,24</sup> Alternatively, when a relatively large average interfacial area is occupied by each headgroup, amphiphilic molecules are prone to form aggregates like vesicles. In the present study, the tosylate anion of 1-OTs prefers to bind strongly with the organic positively charged trimethyl amine head group, and therefore, the adjacent hydrophilic parts are held in a close manner, which results in the formation of nanotubes (Figure 2c). In contrast, when the Br anion is used, it prefers to dissolve in aqueous solution, and as a result, the electronic repulsion between the adjacent head groups becomes more intense than that in the case of 1-OTs. Therefore, the interfacial area occupied by each head group is larger and bent interfaces are formed, affording the formation of vesicle structures (Figure 2d).

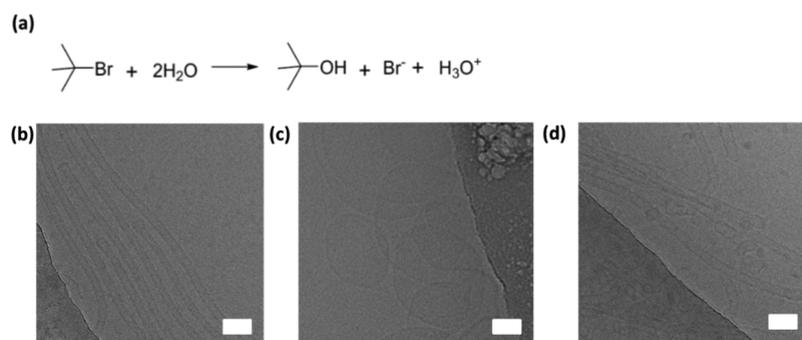
As the anion is crucial for the formation of specific structures of the aggregates, we envisioned that by exchange of anions it may be possible to dynamically control the morphologies of the assembled structures. Solutions containing the nanotubes formed by co-assembly of 1-OTs and DOPC were dialyzed against sodium bromide solution (2 equiv of 1-OTs). The percentage of 1-OTs in the mixture and morphologies of the aggregates were monitored by <sup>1</sup>H NMR and cryo-TEM,



**Figure 2.** Self-assembly of amphiphilic overcrowded alkene in water. (a) Cryo-TEM microscopy images of co-assemblies of 1-OTs and DOPC (total concentration of 3 mg/mL, ratio 2:1). (b) Cryo-TEM microscopy images of co-assemblies of 1-Br and DOPC (total concentration of 3 mg/mL, ratio 2:1). (c,d) Proposed explanation for the anion effect on self-assembled structures. Scale bar, 50 nm.



**Figure 3.** Conversion of nanotubes to vesicle self-assembled structures. (a) Proportion of 1-OTs upon dialysis against NaBr solution. Cryo-TEM images of (b) 80, (c) 50, and (d) 20%. Scale bar, 50 nm.



**Figure 4.** Controlling the self-assembled structures by a chemical reaction. (a) Scheme of hydrolysis of *tert*-butyl bromide. (b–d) Cryo-TEM image of co-assemblies 1-OTs and DOPC (total concentration of 3 mg/mL, ratio 2:1): (b) as-prepared; (c) after dialysis in the reaction solution of *tert*-butyl bromide (4 equiv of 1-OTs) in PBS buffer; and (d) after dialysis in solution of *tert*-butanol (4 equiv of 1-OTs) in PBS. Scale bar, 100 nm.

respectively. As shown in Figure S6, the singlet at 2.30 ppm and doublets at 7.05 and 7.35 ppm are characteristic peaks of the tosylate group. The singlet at 2.18 ppm corresponds to the absorption of the trimethyl ammonium head group. The ratio between the singlet at 2.30 ppm and a singlet at 2.18 ppm can be considered as the percentage of the tosylate anion in the mixture, and it started to decrease upon dialysis against sodium bromide solution. The completion of exchange of anions was within 4 h (Figure 3a), as evidenced by the disappearance of signals at 2.30, 7.05, and 7.35 ppm. In addition, cryo-TEM analysis revealed the morphological changes of the aggregates during the exchange of anions. When 80% of 1-OTs was present, tubular structures began to disassemble into shorter nanotubes (Figure 3b), while in the case of 50%, intermediates with no well-defined structures were observed (Figure 3c). As 1-Br became the majority of the mixture, vesicles were found (Figure 3d). The anion-exchange process can be reversed as well. Starting from a solution containing the vesicles formed by 1-Br and DOPC, dialysis against sodium *p*-toluenesulfonate (2 equiv of 1-Br) gave rise to tubular structures after 4 h. Furthermore, we examined the possibility of performing the anion exchange for cycles. To our delight, the system was able to conduct three cycles of dialysis with NaBr and NaOTs

alternatively accompanied by the interconversion of tubular and vesicle structures.

As the morphologies of the aggregates can be tuned dynamically with different anions, we envisioned that the exchange of anions can be coupled with reactions that generate bromide or tosylate anions as well. Tertiary bromide was employed as it can hydrolyze in water, allowing the slow release of bromide (Figure 4a). A solution of nanotubes of 1-OTs (Figure 4b) was dialyzed against tertiary bromide solution (4 equiv of 1-OTs)<sup>25</sup> in phosphate-buffered saline (PBS). After 12 h, the cryo-TEM measurement revealed the disappearance of tubular structures and vesicles were observed instead (Figure 4c). A control experiment was performed by use of tertiary alcohol, which does not hydrolyze to generate bromide anions. Under identical conditions, nanotubes remain intact after 12 h of dialysis (Figure 4d), which suggests that the release of bromide from tertiary bromide induced the morphological changes of the self-assembled structures.

Besides, 2-bromo-4'-hydroxyacetophenone has been reported to undergo photodegradation via UV irradiation, giving rise to 4-hydroxybenzoic acid and bromide.<sup>26–28</sup> Therefore, we next examined the possibility to tune the morphology of the aggregates photochemically. A solution of 1-OTs was then dialyzed against 2-bromo-4'-hydroxyacetophenone in PBS (2



## 4. MATERIALS AND METHODS

Chemicals and reagents were used as obtained from Sigma-Aldrich or Acros without further purification.  $^1\text{H}$  NMR spectra were recorded on a Varian MR400 (at 400 MHz) at ambient temperature. The splitting patterns are designated as follows: s (singlet); d (doublet); dd (double doublet); t (triplet); q (quartet); m (multiplet), and br (broad).  $^{13}\text{C}$  NMR spectra were recorded on a Varian MR400 (100.6 MHz) at ambient temperature. Chemical shifts are denoted in  $\delta$  (ppm), referenced to the residual protic solvent peak. Coupling constants  $J$  are denoted in Hz. Masses were recorded with a Thermo scientific LTQ Orbitrap XL mass spectrometer. Silicycle Siliacflash P60, 40–63 m, (230–400 mesh) was used for column chromatography. Irradiations were performed with Spectroline ENB-280C/FE UV lamps (8 W). For analysis by cryo-transmission electron microscopy (cryo-TEM), the turbid solution (2.5  $\mu\text{L}$ ) was placed on a glow-discharge holey carbon-coated grid (Quantifoil 3.5/1, QUANTIFOIL Micro Tools GmbH, Großlobichau, Germany). After blotting, the grid was rapidly frozen in liquid ethane (Vitrobot, FEI, Eindhoven, The Netherlands) and stored in liquid nitrogen until measurements. Grids were observed in a Gatan model 626 cryo-stage in a Philips CM120 or Tecnai T20 cryo-electron microscope operating at 120 or 200 KeV. Images were recorded under low-dose conditions on a slow-scan CCD camera.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c07026>.

Synthetic scheme of 1-Br,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of 1-Br, and kinetic studies of exchange experiment of 1-OTs and 1-Br (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. Molecular Self-Assembly and Nanochemistry: a Chemical Strategy for the Synthesis of Nanostructures. *Science* **1991**, *254*, 1312–1319.
- (2) Service, R. F. How Far Can We Push Chemical Self-Assembly? *Science* **2005**, *309*, 95.
- (3) Berg, J. M.; Tymoczko, J. L.; Stryer, L. *Biochemistry*; W.H. Freeman & Co: New York, USA, 2011.
- (4) Aida, T.; Meijer, E. W.; Stupp, S. I. Functional Supramolecular Polymers. *Science* **2012**, *335*, 813.
- (5) Stupp, S. I.; Palmer, L. C. Supramolecular Chemistry and Self-Assembly in Organic Materials Design. *Chem. Mater.* **2014**, *26*, 507.
- (6) Zhang, M.; Yan, X.; Huang, F.; Niu, Z.; Gibson, H. W. Stimuli-Responsive Host-Guest Systems Based on the Recognition of Cryptands by Organic Guests. *Acc. Chem. Res.* **2014**, *47*, 1995.
- (7) Isaacs, L. Stimuli Responsive Systems Constructed Using Cucurbit[n]uril-Type Molecular Containers. *Acc. Chem. Res.* **2014**, *47*, 2052.
- (8) Willerich, I.; Gröhn, F. Photoswitchable Nanoassemblies by Electrostatic Self-Assembly. *Angew. Chem., Int. Ed.* **2010**, *49*, 8104.
- (9) Hamada, T.; Sugimoto, R.; Vestergaard, M. C.; Nagasaki, T.; Takagi, M. Membrane Disk and Sphere: Controllable Mesoscopic Structures for the Capture and Release of a Targeted Object. *J. Am. Chem. Soc.* **2010**, *132*, 10528.
- (10) Higashiguchi, K.; Taira, G.; Kitai, J.-i.; Hirose, T.; Matsuda, K. Photoinduced Macroscopic Morphological Transformation of an Amphiphilic Diarylethene Assembly: Reversible Dynamic Motion. *J. Am. Chem. Soc.* **2015**, *137*, 2722.
- (11) Klajn, R. Spiropyran-based dynamic materials. *Chem. Soc. Rev.* **2014**, *43*, 148.
- (12) Zhang, J.; Jin, J.; Zou, L.; Tian, H. Reversible photo-controllable gels based on bisthiénylene-doped lecithin micelles. *Chem. Commun.* **2013**, *49*, 9926.
- (13) Chen, J.; Leung, F. K.-C.; Stuart, M. C. A.; Kajitani, T.; Fukushima, T.; van der Giessen, E.; Feringa, B. L. Artificial muscle-like function from hierarchical supramolecular assembly of photo-responsive molecular motors. *Nat. Chem.* **2018**, *10*, 132.
- (14) Dougherty, D. A. The Cation- $\pi$  Interaction. *Acc. Chem. Res.* **2013**, *46*, 885–893.
- (15) Bijma, K.; Engberts, J. B. F. N. Effect of Counterions on Properties of Micelles Formed by Alkylpyridinium Surfactants. 1. Conductometry and  $^1\text{H}$ -NMR Chemical Shifts. *Langmuir* **1997**, *13*, 4843.
- (16) Shi, D.; Schwall, C.; Sfintes, G.; Thyraug, E.; Hammershøj, P.; Cárdenas, M.; Simonsen, J. B.; Laursen, B. W. Counterions Control Whether Self-Assembly Leads to Formation of Stable and Well-Defined Unilamellar Nanotubes or Nanoribbons and Nanorods. *Chem.—Eur. J.* **2014**, *20*, 6853.
- (17) Leira-Iglesias, J.; Sorrenti, A.; Sato, A.; Dunne, P. A.; Hermans, T. M. Supramolecular pathway selection of perylene-dimides mediated by chemical fuels. *Chem. Commun.* **2016**, *52*, 9009.
- (18) Wu, G.; Verwilt, P.; Liu, K.; Smet, M.; Faul, C. F. J.; Zhang, X. Controlling the self-assembly of cationic bolaamphiphiles: counterion-directed transitions from 0D/1D to exclusively 2D planar structures. *Chem. Sci.* **2013**, *4*, 4486.
- (19) Ji, X.; Wang, H.; Li, Y.; Xia, D.; Li, H.; Tang, G.; Sessler, J. L.; Huang, F. Controlling amphiphilic copolymer self-assembly morphologies based on macrocycle/anion recognition and nucleotide-induced payload release. *Chem. Sci.* **2016**, *7*, 6006.

(20) Coleman, A. C.; Beierle, J. M.; Stuart, M. C. A.; Maciá, B.; Caroli, G.; Mika, J. T.; van Dijken, D. J.; Chen, J.; Browne, W. R.; Feringa, B. L. Light-induced disassembly of self-assembled vesicle-capped nanotubes observed in real time. *Nat. Nanotechnol.* **2011**, *6*, 547–552.

(21) van Dijken, D. J.; Chen, J.; Stuart, M. C. A.; Hou, L.; Feringa, B. L. Amphiphilic Molecular Motors for Responsive Aggregation in Water. *J. Am. Chem. Soc.* **2016**, *138*, 660.

(22) van Dijken, D. J.; Stacko, P.; Stuart, M. C. A.; Browne, W. R.; Feringa, B. L. Chirality controlled responsive self-assembled nanotubes in water. *Chem. Sci.* **2017**, *8*, 1783.

(23) Johnsson, M.; Wagenaar, A.; Stuart, M. C. A.; Engberts, J. B. F. N. Sugar-Based Gemini Surfactants with pH-Dependent Aggregation Behavior: Vesicle-to-Micelle Transition, Critical Micelle Concentration, and Vesicle Surface Charge Reversal. *Langmuir* **2003**, *19*, 4609.

(24) Wu, G.; Thomas, J.; Smet, M.; Wang, Z.; Zhang, X. Controlling the self-assembly of cationic bolaamphiphiles: hydrotropic counteranions determine aggregated structures. *Chem. Sci.* **2014**, *5*, 3267.

(25) 4 equiv of *tert*-butyl bromide was used to ensure the complete exchange of anions.

(26) Park, C.-H.; Givens, R. S. New Photoactivated Protecting Groups. 6. *p*-Hydroxyphenacyl: A Phototrigger for Chemical and Biochemical Probes 1,2. *J. Am. Chem. Soc.* **1997**, *119*, 2453.

(27) Givens, R. S.; Park, C.-H. *p*-Hydroxyphenacyl ATP1: A new phototrigger. *Tetrahedron Lett.* **1996**, *37*, 6259.

(28) Klán, P.; Solomek, T.; Bochet, C. G.; Blanc, A.; Givens, R.; Rubina, M.; Popik, V.; Kostikov, A.; Wirz, J. Photoremovable Protecting Groups in Chemistry and Biology: Reaction Mechanisms and Efficacy. *Chem. Rev.* **2013**, *113*, 119.