Reversible Self-Assembly of Supramolecular Vesicles and Nanofibers Driven by Chalcogen-Bonding Interactions

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Supporting Information

ABSTRACT: Chalcogen-bonding interactions have been viewed as new non-covalent forces in supramolecular chemistry. However, harnessing chalcogen bonds to drive molecular self-assembly processes is still unexplored. Here we report for the first time a novel class of supramolecules formed by Te…O or Se…O chalcogen-bonding interactions, and their self-assembly into supramolecular vesicles and nanofibers. A quasi-calix[4]-chalcogenadiazole (C4Ch) as macrocyclic donor and a tailored pyridine N-oxide surfactant as molecular acceptor are designed to construct the donor–acceptor complex via chalcogen–chalcogen connection between the chalcogenadiazole moieties and oxide anion. The affinity of such chalcogen-bonding can dictate the geometry of supramolecules, driving diverse self-assembled nanostructures. Furthermore, the reversible disassembly of these structures can be promoted by introducing competing halide ions or by decreasing system pH.

Molecular self-assembly, as a powerful and elegant technique to fabricate nanoscale architectures, is an eternal theme in supramolecular chemistry.1 Besides the plethora of examples of assembly of covalent amphiphiles, there has been growing interest in non-covalent-bond-based supra-amphiphiles.2 The dynamic and reversible nature of non-covalent interplay endows the supra-amphiphilic self-assembly with ideal tunability, adaptivity, and responsivity. To date, chemists have exploited a variety of non-covalent driving forces, including H-bonding,3 coordination,4 π–π stacking,5 charge transfer,6 and host–guest interactions,7 to build supra-amphiphile systems. Inspired by these common interactions, our interest in unconventional supramolecular forces motivates us to explore whether new forms of non-covalent bonds could drive the creation of supra-amphiphiles and related superstructures.

Chalcogen-bonding, as an emerging non-covalent motif, stems from the σ-holes associated with the σ* orbitals of the electron-deficient group VI elements, such as sulfur, selenium, and tellurium.8 Such new interactions have been involved in catalytic, biological, and medicinal areas.9 Recent theoretical and experimental studies of close contacts between chalcogen centers and nucleophilic sites have lifted the veil on the existence of chalcogen-bonding interactions.10 A simple example is provided by the benzylselenocyanate crystal, whose neighboring selenocyanate groups have strong chalcogen-bonding between Se and N atoms (SeCN…Se).11 Quantum calculations further disclose the similarity of chalcogen-bonding to halogen-bonding, and show that chalcogens are more directional and tend to bind multivalently.12 However, as compared to the familiar halogen-bonding, which has been widely used to create supramolecular materials,13 the application of chalcogen-bonding in self-assembly science is relatively unexplored. Here we address this challenging issue and report an unprecedented supra-amphiphile system and its tunable self-assembly based on chalcogen–chalcogen interactions.

The design of a proper molecular donor that possesses a chalcogen-bonding center is key to constructing a chalcogen-bonding supra-amphiphile. Previously, 1,2,5-chalcogenadiazole (1, Scheme 1a) has been proven as a good chalcogen-bonding donor that can adduct with a Lewis basic acceptor (Y…ChN2, where Y is a nucleophilic group such as an anion and Ch is a Te or Se atom).10 However, our attempt to obtain supra-amphiphiles based on chalcogen-bonding interactions and their reversible self-assembly into vesicles and nanofibers.

Scheme 1. (a) Structures of Macroyclic Donors (C4Ch, Ch = Te or Se), Surfactant (DPN), and Control Compounds (1 and 2), and (b) Schematic of the Formation of C4Ch·DPN Supra-amphiphiles Based on Chalcogen-Bonding Interactions and Their Reversible Self-Assembly into Vesicles and Nanofibers.

Received: May 5, 2018
Published: May 29, 2018
amphiphile by directly mixing 1 and a classic anionic surfactant, 4-dodecyl-pyridine N-oxide (DPN), failed because the weak affinity of single-site association (O⋯ChN) is insufficient to sustain the complexation in solution (Figure S1). To overcome this difficulty, we designed and synthesized two macrocyclic donors containing different chalcogen elements, quasi-calix[4]-telluradiazole (C4Te) and quasi-calix[4]selenadiazole (C4Se), replacing 1 (see detailed synthesis and characterization in Supporting Information, Figures S12–S19). C4Ch (Ch = Te and Se) compounds possess four equivalent chalcogen centers sterically positioned on the rim of bucket-shaped hosts, which is conducive to enhancing their recognition by the DPN guest in aqueous media (Scheme 1b). We expected that the resulting chalcogen-bonding supra-amphiphiles would further self-assemble into various nanostructures, such as vesicles and nanofibers. Their large distinction in dimensionality and shape would derive from the difference in two chalcogen-bonding forces, which play decisive roles in dictating the geometry of supra-amphiphiles. Owing to the reversibility of chalcogen bonds, a controllable disassembly of these structures could be promoted by adding competitive anions or decreasing solution pH, as shown in Scheme 1.

We first studied whether mixing C4Ch with DPN could realize the proposed supramolecular complexation and self-assembly behavior. In principle, as a typical surfactant, DPN itself can form spherical micelles above its critical micelle concentration (CMC, 8.5 × 10⁻⁴ M) in water (Figure S2). Thus, we chose a concentration far below its CMC for the investigation, and in such conditions DPN was molecularly dissolved. For the case of C4Te, when we added it into DPN aqueous solution in an equal molar amount (2.0 × 10⁻⁴ M), an opalescent colloidal solution appeared, implying the formation of a new kind of aggregates. Their CMC was determined to be 3.4 × 10⁻⁶ M using conductivity experiments (Figure S3), which is 2 orders of magnitude smaller than that of individual DPN. Transmission electron microscopy (TEM) revealed that they can self-assemble into a large globular shape ranging from 40 to 130 nm (Figure 1a). Some nano-objects with open mouths (indicated as arrows) illustrated that these aggregates are hollow and vesicular. This membrane-bound structure was confirmed by atomic force microscopy (AFM), as indicated by the clear contrast between protruding edge and central sag in the height image of assemblies (Figure S4a). The bilayer nature was further analyzed by small-angle X-ray scattering (SAXS) (Figure 1c). The aggregates had a strong diffraction peak at 2θ ≈ 1.5°, corresponding to a wall thickness of 5.9 nm calculated by Bragg’s law. Interestingly, if we altered the central chalcogen atom from Te to Se, C4Se with DPN resulted in a significant structural transition. The TEM image showed that they can generate a one-dimensional fibrous architecture with a uniform radial diameter of 6.5 nm (Figure 1b). This accorded well with the SAXS result of 6.8 nm (Figure 1d). The AFM image also evidenced this cylindrical morphology (Figure S4b). In a control experiment, we designed a macrocyclic analogue 2 (Scheme 1a) in which the chalcogen centers were replaced by carbon atoms. However, 2 and DPN showed no regular aggregates under the same conditions (Figure S5). From these results, we inferred that the chalcogen-mediated non-covalent interactions play key roles in facilitating the supramolecular complexation, and the bonding chemistry of different chalcogen donors is likely to influence the molecular packing fashion.

To gain deeper insight into the complexation mechanism, we used UV–vis spectroscopy, chalcogen elemental nuclear magnetic resonance (NMR), and mass spectroscopy (MS) to survey the weak interactions between C4Ch and DPN. As shown in Figure 2a, addition of DPN guest in C4Te host solution caused a bathochromic effect of telluradiazole chromophore (red arrow, λmax = 427–438 nm), accompanied by an enhancement in a long-wavelength band at 461 nm (blue arrow). This result is similar to the reported telluradiazole–tetrabutylammonium bromide adduct,14 indicating that the four telluradiazole moieties in C4Te are the main supramolecular motifs to bind DPN. The binding stoichiometry was evaluated to be 1:1 from the UV–vis Job plot (Figure S6). ¹²⁵Te NMR titration further showed that, in the absence of DPN, C4Te had a single Te peak at δ = 1684 ppm, ascribed to the four identical Te atoms; however, when DPN was gradually

![Figure 1](image1.png)

Figure 1. Top: TEM images showing the self-assembly structures of (a) C4Te and DPN, and (b) C4Se and DPN. Bottom: SAXS results of (c) C4Te and DPN, and (d) C4Se and DPN.

![Figure 2](image2.png)

Figure 2. Top: UV–vis spectral monitoring of C4Ch in THF/H₂O solution (1/2, v/v): (a) C4Te upon addition of DPN, and (b) C4Se upon addition of DPN. Bottom: NMR titration of C4Ch with DPN in THF-d₈ (from bottom to top): (c) ¹²⁵Te NMR changes of C4Te, and (d) ⁷⁷Se NMR changes of C4Se. The final molar ratio of C4Ch and DPN is 1:1 in all the experiments.
injected, the initial Te resonance split into two signals and yielded large downfield shifts ($\Delta \delta = 12$ and 29 ppm, Figure 2c). These indicated that chalcogen-bonding occurs between the tellurium in C4Te macrocycle and the N-oxide headgroup in DPN, and suggested that the quadruple Te···O interactions could be divided into two categories. Similar results have recently been found in the molecular tetramer of tellurazole-N-oxide.15 The above discussion was supported by electrospray ionization MS data. After complexation, there is a peak with $m/z$ 1203.04, which corresponds to the 1:1 orthogonal complex C4Te-DPN (Figure S7).

C4Se is also capable of binding with DPN via analogous Se···O interactions (Figure 2b,d; Figures S8 and S9). By contrast, its spectral red-shift phenomenon (Figure 2b, $\Delta \delta_{\text{max}} = 420\rightarrow 425$ nm) and NMR chemical splitting (Figure 2d, $\Delta \delta = 3.8$ and 9.2 ppm) are both weaker than those of C4Te, probably meaning that the Te···O interactions are superior to the Se···O ones.

To know the strength of chalcogen-bonding interactions, isothermal titration calorimetry (ITC) experiments were carried out.16 The association constant of C4Te and DPN was found to be $K_a = 7.12 \times 10^8$ M$^{-1}$ (Figure 3a), 5-fold larger than that of C4Se and DPN ($K_a = 1.4 \times 10^7$ M$^{-1}$, Figure 3b), validating our conjecture. The stoichiometry of binding ($n$) approximates to 1.0 in both cases, consistent with the UV–vis Job plot results. Moreover, the Gibbs free energies ($\Delta G$) were calculated to be $-32.8$ and $-28.9$ kJ mol$^{-1}$ for C4Te-DPN and C4Se-DPN complexes, respectively. To eliminate other conceivable modes of supramolecular interactions (e.g., anion–π interactions), we carried out an extra ITC experiment using 2 and DPN, where only anion–arene interplay exists. However, the results showed its $\Delta G = -5.9$ kJ mol$^{-1}$, much weaker than that for the chalcogen-containing systems (Figure S10). This demonstrates that the major driving force forming the C4Ch-DPN supra-amphiphile is attributable to the chalcogen-bonding interactions.

We next aimed to figure out why different chalcogen bonds can dictate different assemblies. To this end, a density function theory (DFT) simulation was used to investigate the supra-amphiphiles.17 For C4Te, the four Te atoms are partitioned diagonally into two groups, inside and outside the ring plane, respectively (Figure 4a, front view). In the orthogonal complex, the distances from the oxygen to the two groups of Te are 2.74 and 3.42 Å (Figure 4b, side view), and the length of the C4Te-DPN supra-amphiphile is 3.1 nm. In comparison, the Se···O distances in C4Se-DPN are a little longer (3.15 and 3.61 Å), and its molecular length extends to 3.7 nm (Figure 4c,d). Such small distinctions not only decide the strength rule of chalcogen-bonding interactions ($K_{\text{Te–O}} > K_{\text{Se–O}}$) but also are a main factor resulting in the assembly of different structures. It is known that the geometry of amphiphiles can be predicted by a critical packing factor ($p = V/a_{\text{md}}l$),18 where $V$, $a_{\text{md}}$ and $l$ are respectively molecular volume, area of headgroup, and molecular length. Generally, spheres can form when $0 < p < 1/3$, cylinders when $1/3 < p < 1/2$, and lamellae for $1/2 < p < 1$. Since C4Te-DPN has a shorter molecular length than that of C4Se-DPN, whereas their macrocycle areas are nearly the same, the calculated $p$ values for the two supra-amphiphiles, 0.54 and 0.43, correspond to the bilayer and worm-like shapes, respectively (Figure S11). Overall, the good match between experimental and theoretical data validates our initial assumption that chalcogen-bonding can act as a new type of non-covalent interaction to manipulate the molecular self-assembly.

The reversibility and responsibility of chalcogen-bonding interactions are highly desired. To probe this, we introduced competing anions into the C4Te-DPN vesicle system and observed whether the assemblies could be disrupted. After encapsulation of a drug, doxorubicin (DOX, 100 μg), in the vesicles, the release of DOX can reflect the vesicular disassembly. In the absence of stimuli, the fluorescence of DOX-loaded vesicles remained invariant, thus indicating no release happened (Figure 5a, black line). In contrast, large fluorescent enhancement was seen when halide anions (Cl$^-$ or Br$^-$) that have far stronger interactions with C4Te were added, indicating a fast vesicle cracking (Figure 5a, blue and red lines). Alternatively, decreasing the solution pH from 7.6 to 3.5 can have the same effect (Figure 5b). A possible reason is that the increase of pH can lead to the formation of H-bonding, which competes strongly with chalcogen-bonding.

The quest for new non-covalent interactions offers an impetus for the development of self-assembly science. This work demonstrates the first chalcogen-bonding-based supra-amphiphiles, and further presents a new strategy that harnesses chalcogen-bonding interactions to drive and regulate molecular...
Figure S. DOX release curves from C4Te vesicles upon (a) competing halides (Cl⁻ and Br⁻) and (b) pH decrease.

self-assembly. The intrinsic nature and mechanism of chalcogen bonds will need to be uncovered in future studies; however, this study opens a promising direction of chalcogen-bonding-mediated self-assembly nanotechnology.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b04569.

Synthetic procedures, characterization data, AFM images, Job plot, and control experiments, including Scheme S1 and Figures S1–S19 (PDF)

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Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was financially supported by National Natural Science Foundation of China (21674022 and 51703034) and acknowledged the Natural Sciences and Engineering Research Council of Canada.

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