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Vesicles

Size-Regulable Vesicles Based on Anion–π Interactions

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Abstract: Taking tetraoxacalix[2]arene[2]triazine as a functionalization platform, a series of new amphiphilic molecules were synthesized in 18 to 53 % yields by using a fragment coupling protocol. These amphiphilic molecules self-assembled into stable vesicles in a mixture of THF and water, with the surface of the vesicles engineered by electron-deficient cavities. Various anions are able to selectively influence the size of self-assembled vesicles, following the order of $F^- < ClO_4^- < SCN^- < BF_4^- < Br^- < Cl^- < NO_3^-$, as revealed by DLS measurements. Such a sequence was independent with the hydration cost and in agreement with the binding strength of anions with tetraoxacalix[2]arene[2]triazine host molecule, indicating that the anion–π interaction most probably competed over other possible weak interactions and accounted for this interesting selectivity. In addition, the chloride permeation process across the membrane of the vesicles was also preliminarily studied by means of fluorescent experiments. This study, in addition to providing the potentiality of heteracalixaromatics as new models to construct functional vesicles, opens a new avenue to study the anion–π interactions in aqueous and also potentially in living systems.

Introduction

Anion–π interactions are new motifs in supramolecular chemistry. Since the first theoretical studies by Mascal, Deyà, and Alkorta, the past decade has witnessed an increasing interest in anion–π interactions.[1] Whereas experimental evidences obtained from several groups including ourselves have substantiated the existence, generality, binding strength, and structure of anion–π interactions,[2] exploration of the applications of anion–π interactions in the functional molecular and supramolecular systems is one of the biggest challenges in the field.[1k,3] In this respect, the groups of Matile[1k,4a–c] and Ballester[4b] have reported examples of ion channels and catalysis based on anion–π interactions. However, application of anion–π interactions to the regulation of supramolecular assemblies is lacking.

Owing to the host–guest recognition properties of macrocyclic hosts (including crown ethers,[5] cyclodextrins,[6] calixarenes and resorcinarenes,[7] cucurbiturils[8] and pillararenes),[9] amphiphilic molecules, consisting of such a macrocyclic core structure, have been used to fabricate vesicles. As a consequence, the resulting vesicles show unique characteristics, such as surface recognition[5d,6a,b,8b] and the sequential aggregation,[6e] and responsiveness to external stimuli.[6d,7d,i,8d] Heteracalixaromatics are an emerging generation of macrocyclic host molecules in supramolecular chemistry.[10–12] In contrast to conventional calixarenes, the introduced heteroatoms, instead of the methylene moieties on the bridges of the macrocycles, result in the formation of unique cavities of varied conformations.[11a] The electronic nature of the bridging heteroatoms also enables the macrocylic molecules to self-adjust their conformations to best fit the guests, leading to versatile molecular recognition properties towards various guests.[11,2c–e] As a representative member of heteracalixaromatics, tetraoxacalix[2]arene[2]triazine adopts a 1,3-alternate conformation with the two triazine rings forming an electron-deficient V-shaped cleft.[12] In addition, the cleft has been shown to serve as a pair of tweezers to interact with the included anions through cooperative anion–π and lone-pair electron–π interactions, depending on the nature and geometry of anions.[2c,e] Our interests in anion–π interactions and cell membrane mimicry led us to carry out the current study. We envisioned that the unique structure, functionalization, and anion-recognition properties of tetraoxacalix[2]arene[2]triazine would make it an ideal molecular architecture for the construction of vesicles. The vesicles, bearing only anion-π interaction motifs on the surface, provide a pure model to study the anion effects on the properties of vesicles based on anion–π interactions. Reported herein is an unprecedented example of the regulation of vesicles using the emerging, new-type of anion–π interaction.

Results and Discussion

The target amphiphilic macrocyclic molecules were readily obtainable by the introduction of long alkyl chains on the larger

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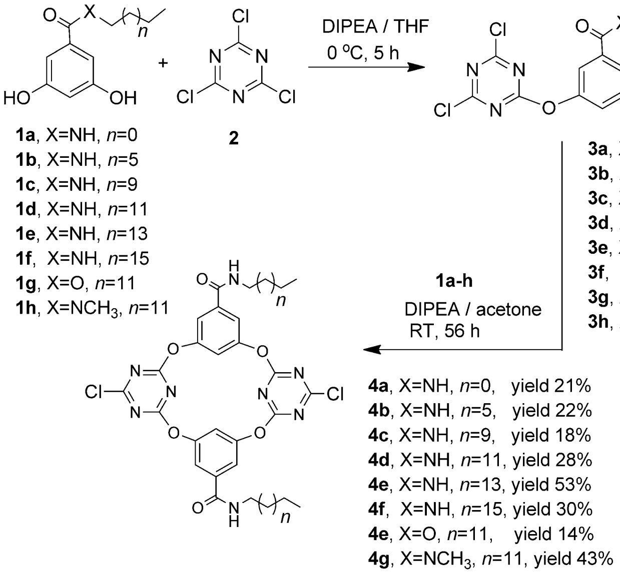
rims of tetraoxacalix[2]arene[2]triazine. We chose a secondary amido group as the linker between the polar macrocyclic head and the hydrophobic tail with the purpose of regulating the self-assembly through intermolecular hydrogen bonds. An efficient fragment coupling protocol was applied for the preparation of the molecules. We initiated the synthesis of the trimers **3a**–**f** from the treatment of **1a**–**f** (for synthesis of **1a**–**f**, see Scheme S2 in the Supporting Information) with cyanuric chloride **2**, as illustrated in Scheme 1. In the presence of diisopropylethylamine (DIPEA) as an acid scavenger, **1a**–**f** underwent nucleophilic aromatic substitution smoothly with two equivalents of cyanuric chloride **2** at 0 °C to afford the corresponding intermediates **3a**–**f** in yields ranging from 30 to 52 %. A 3+1 fragment coupling reaction was then performed by treating the trimers **3a**–**f** with the corresponding monomers **1a**–**f** at room temperature to give the desired compounds **4a**–**f** in 18 to 53 % yields. As a comparison, compounds **4g** and **4h** with tetradecyloxyl and *N*-methyl-*N*-tetradecyl formacyl groups attached on the larger rim of benzene rings of tetraoxacalix[2]arene[2]triazine were also synthesized under similar reaction conditions (Scheme 1 and Schemes S3 and S4, the Supporting Information).



Scheme 1. Synthesis of molecules **4a**–**h**.

With the amphiphilic molecules **4b**–**f** in hand, we investigated their self-assembly systematically. The compounds **4b**–**f** were firstly dissolved in tetrahydrofuran (THF; 0.3 mL), followed by the addition of water (0.7 mL). The final concentration of **4b**–**f** is 5.0×10^{-5} M. The mixtures were then placed in an ultrasonic bath for 30 min, yielding a slightly cloudy suspension that remained stable for at least four months at ambient temperature. DLS experiments revealed that the average hydrodynamic diameters of the aggregates are 569, 332, 239, 225, and 217 nm for **4b**–**f**, respectively (Figure 1 D and Figures S23–S27, the Supporting Information). The measured polydispersities (PDIs) are lower than 0.17, indicating a narrow size distribution of the aggregates formed with each compound. The exceedingly large diameters of the aggregates in comparison with the extended molecular length (1.61–2.85 nm, Figure S28, the Supporting Information) suggested that the amphiphilic molecules form vesicles rather than micelles. Spherical morphologies of the vesicles were confirmed with SEM (Figure 1 A and Figures S1–S5, the Supporting Information) and TEM (Figure 1 B and Figures S9–S14, the Supporting Information), and the observed diameters of the spheres are in agreement with the DLS results. In addition, as reflected by the images in Figure S14 (the Supporting Information), the sharp contrast between the periphery and center of the spheres verifies the hollow vesicular feature. In the case of **4f**, moreover, collapsed spheres were observed, which also support the hollow feature of the vesicles (Figures S5 and S13, the Supporting Information). Furthermore, laser scanning confocal microscopic experiments (LSCM) were performed by preparing the vesicles in a solution containing lucigenin followed by repeated dialysis to remove the fluorescent agent outside the vesicles. Blue spots were observed in Figure 1 C and Figures S18–S22 (in the Supporting Information), corresponding to the entrapped dye inside the vesicles. The above outcomes confirmed the formation of the vesicles. In addition, such vesicles are stable for over four months at ambient temperature with the vesicular morphology remained almost unchanged as

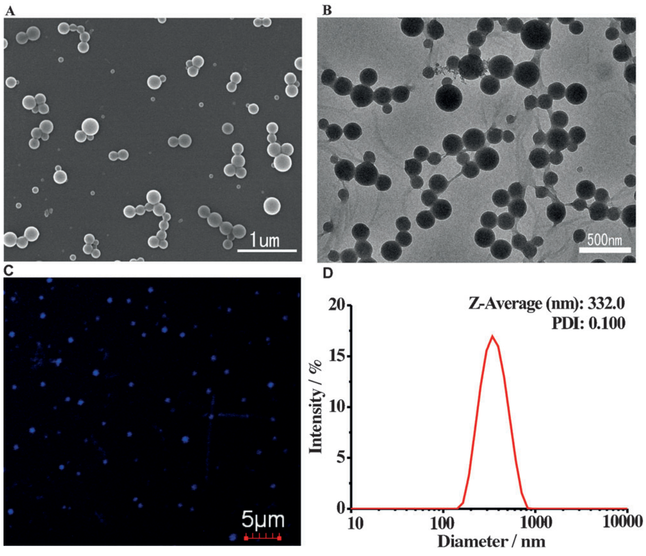


Figure 1. A) SEM, B) TEM, and C) LSCM images and D) DLS result of aggregates prepared from **4c** in a mixture of THF and H_2O (3:7, v/v).

revealed by SEM experiments (Figure S8, the Supporting Information).

To shed light on the mechanism of the self-assembly of amphiphilic molecules **4b**–**f** into vesicles, a series of studies were performed. As illustrated by the Corey–Pauling–Koltun space-filling (CPK) models in Figure S28 (the Supporting Information), the molecular mechanics calculation shows that the extended lengths of the molecules are 1.61, 2.11, 2.36, 2.61, and 2.85 nm for **4b**–**f**, respectively. On the basis of the small-angle X-ray scattering (SAXS) results illustrated in Figure S29 (the Supporting Information), the thicknesses of the vesicle membrane are 3.11, 3.35, 3.76, 3.85, and 4.26 nm for **4b**–**f**, respectively. The measured thicknesses of the membranes are nearly double that of the extended molecular length, indicating most likely the formation of a double layer. We then examined the effect of intermolecular hydrogen bonding on the regulation of the vesicles. Amphiphilic compounds **4g** and **4h** derived of ester or tertiary amido moieties, respectively, formed some irregular aggregates instead of well-assembled vesicles as observed by SEM (Figures S6 and S7, the Supporting Information) and TEM (Figures S16 and S17, the Supporting Information), suggesting that the secondary amido groups of **4b**–**f** played important roles on the formation of vesicles. To assist in understanding the hydrogen-bonding details of the secondary amido groups from molecular level, a single crystal of the model compound **4a** bearing 3-C alkyl chains on the larger rims of tetraoxacalix[2]arene[2]triazine was cultivated through slow evaporation of a methanol solution. As illustrated in Figure S30 (the Supporting Information), compound **4a** adopts a 1,3-alternate conformation with the two triazine rings forming a V-shaped electron-deficient cavity, similar to its parent molecule tetraoxacalix[2]arene[2]triazine.[12] The long distances between N–H atoms and carbonyl oxygen atoms of 4.619 Å (d_{O5-O8}) and 4.785 Å (d_{O6-N7}), respectively, exclude the formation of intramolecular hydrogen bonds between the secondary amido groups. Surprisingly, the secondary amido groups of one molecule of **4a** do not form intermolecular hydrogen bonds directly with another molecule, but through a solvent (water or methanol) molecule as a hydrogen bond bridge (Figure S30, the Supporting Information). The steric hindrance of the rigidity cavity of **4a** and the rotation hindrance of the secondary amido groups most probably leads to the formation of solvent-bridged hydrogen bonding. The observed intermolecular hydrogen bonds of **4a** suggest that the secondary amido groups of **4b**–**f** contributed to the formation of vesicles probably also through an intermolecular hydrogen-bond network among secondary amido moieties and water bridges. Together with the hydrophobic effect of long alkyl chains, intermolecular hydrogen bonds provide possible driving forces for the formation of vesicles. A postulated structure of the vesicle is illustrated in Figure 2.

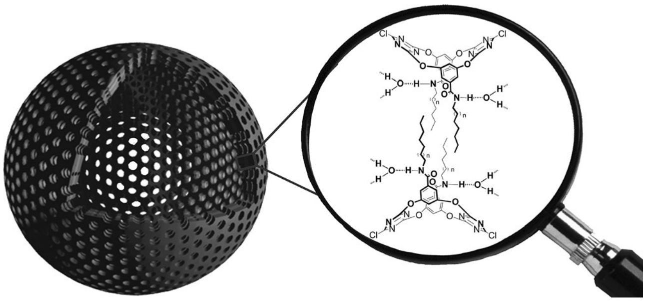


Figure 2. Schematic illustration of the vesicle.

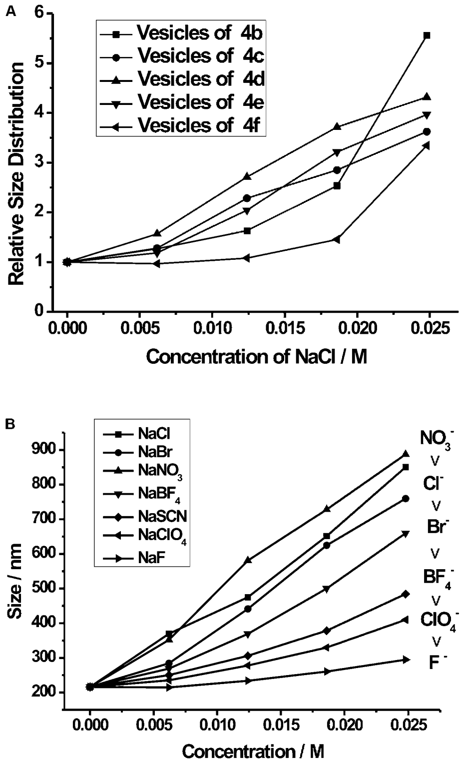


Figure 3. DLS measurements for: A) effect of NaCl on the vesicular size distribution of **4b**–**f**, and B) effect of various anions on the diameter of vesicles of **4d**.

As illustrated in Figure 2, one unique feature of the resulting vesicles is the location of V-shaped clefts or cavities of macrocyclic tetraoxacalix[2]arene[2]triazine on the surface.[7j] Encouraged by the anion-binding properties of the macrocyclic architecture,[2c–e] interactions of the vesicles and anions were then investigated. The relative size distribution (expressed as ratio of hydrodynamic diameter with and without the salt) of the aggregates corresponding to **4b**–**f**, respectively, increased with the increasing sodium chloride concentration, indicating the formation of larger aggregates, as depicted in Figure 3A. To investigate the selective interaction between vesicles and ions, compound **4d** was applied as a representative example and treated with various anions (as sodium salts). Figure 3B shows that different anions affect the aggregate sizes (expressed as hydrodynamic diameter) in a selective manner, with increments of the aggregates following the order of $F^- < ClO_4^- < SCN^- < BF_4^- < Br^- < Cl^- < NO_3^-$. Such a sequence is in contrast to anion effects on membranes containing positively charged or neutral (zwitterionic) phospholipids, in which Hofmeister series are mostly obeyed.[13] For example, the most hydrated

F^- only marginally affects the size of aggregates. The free hydration energy of NO_3^- ($-\Delta G_{hydr} = 306\ kJ\,mol^{-1}$) is lower than that of Cl^- ($-\Delta G_{hydr} = 347\ kJ\,mol^{-1}$) and Br^- ($-\Delta G_{hydr} = 321\ kJ\,mol^{-1}$),[14a] but NO_3^- most strongly affects the aggregate sizes. In another case, BF_4^-, an anion has smallest free hydration energy ($-\Delta G_{hydr} = 200\ kJ\,mol^{-1}$) in the investigated anion list,[14b] causes larger increments of the aggregate sizes over SCN^- and ClO_4^-. The outcomes indicated consequently that among the interactions between surface (macrocyclic cavities), anions and solvents, the interaction between anions and macrocyclic cavities most probably play more important roles. In our previous report, we have demonstrated that the V-shaped electron-deficient cavity of the parent tetraoxacalix[2]arene[2]triazine (**host**) served as a pair of tweezers to selectively interact with the included anions, giving the binding constants in the order of **host**$\cdot SCN^-$ ($239\ \text{M}^{-1}$) < **host**$\cdot PF_6^-$ ($291\ \text{M}^{-1}$) < **host**$\cdot BF_4^-$ ($673\ \text{M}^{-1}$) < **host**$\cdot F^-$ ($4036\ \text{M}^{-1}$) < **host**$\cdot Cl^-$ ($4246\ \text{M}^{-1}$) < **host**$\cdot NO_3^-$ ($16\,950\ \text{M}^{-1}$).[2c,e] The effect of anions on the size of aggregates, hence, is almost in agreement with the order of binding constants, with the exception of fluoride, in which the host–F^- interaction was extremely prohibited owing to its strong hydration in the aqueous system. The host–anion recognition study also provided an explanation of selective anion influence on the vesicles from molecular level.[2e] According to the crystal structure of the **host**$\cdot NO_3^-$ complex reported elsewhere,[2e] nitrate interacts with the triazine rings through strongest cooperative noncovalent and dual weak σ-type anion–π interactions, leading to its largest binding strength (up to $16\,950\ \text{M}^{-1}$) with the macrocyclic cavity. Host–anion crystal structures also revealed that though both BF_4^- and SCN^- formed dual noncovalent anion–π interactions with the host molecule, the former was in a more cooperative manner judging from the self-tuning of the cavity, and hence a larger binding constant. The above discussions indicated that anion–π interaction most probably competed over other possible weak interactions and account for this interesting selectivity. The affinity of anions on the surface of the vesicle was further confirmed by the Zeta (ζ) potential measurements. The measured negative ζ potentials listed in Table S1 (the Supporting Information) indicate indeed that the initially neutral surface of the vesicles become negatively charged in salt solutions. The procedure, however, is not fully clear currently for the formation of larger aggregates (Figure S15, the Supporting Information) upon the affinity of anions, the change of the surface ζ potential of the vesicles should be one of the contributions.

Encouraged by the observations of anion effect on vesicle sizes caused by affinity of anions on the surface, we then explored the sequential anion permeation through the membrane using a fluorescence protocol (Figure 4). Lucigenin, a selective fluorescent sensor for chloride, was incubated with **4d** during the preparation of vesicles. The fluorescent reagent outside the vesicles was removed through repeated dialysis. As illustrated in Figure 4A, after addition of NaCl (5 μL, 2.5 M) to the vesicle-containing solution (2 mL), the emission of inside lucigenin at 506 nm was quenched dramatically (line d). Further quenching (Figure 4A, line c) was observed with addition of another aliquot of NaCl (5 μL, 2.5 M), proving the permeation of chloride across the vesicle membrane from outside to inside, driven by the concentration gradient. Dialysis was then carried out to remove the salt outside the vesicles. Such procedure led to the reversed concentration gradient across the membrane. Consequently, the partially recovered intensity of lucigenin (line b) was observed from Figure 4A, which was probably due to the release of chloride from inside the vesicles. After dialysis, another treatment of the vesicles with NaCl (5 μL, 2.5 M) quenched the emission of lucigenin again (Figure 4A, line e). The repeated procedure is illustrated in the inset graph of Figure 4A. Figure 4B gives a schematic illustration of the transmembrane permeation of chloride.

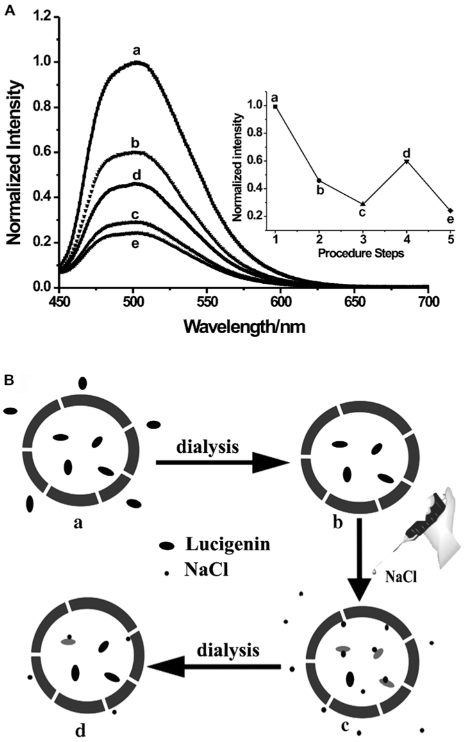


Figure 4. A) Normalized fluorescence intensity of lucigenin inside the vesicles of **4d** in response of transmembrane Cl^- permeation. Line a: initial normalized intensity of lucigenin included in the vesicles. Line d: normalized intensity of lucigenin after injection of NaCl (5 μL). Line c: normalized intensity of lucigenin after injection of NaCl (10 μL). Line b: normalized intensity of lucigenin after dialysis to remove NaCl outside the vesicle. Line e: re-injection of NaCl (5 μL) after dialysis. The inset shows the variations of the normalized fluorescence intensity at 506 nm with each step of the experimental procedures. B) Schematic illustration of anion permeation across the membrane.

Conclusion

Unique vesicles, with surfaces that are engineered by synthetic anion receptors, that is, tetraoxacalix[2]arene[2]triazines, have been successfully fabricated. Various anions were able to selectively influence the size of self-assembled vesicles through the noncovalent anion–π interactions. To the best of our knowledge, this is an unprecedented example of the regulation of vesicles by using anion–π interactions. In addition, anion permeation across the membrane of the vesicles was also preliminary exemplified by taking chloride as an example. Specific ion effects is an important issue in biological systems and its underlying principles remain unclear.[15] This study, in addition to providing one of the examples highlighting that anion–π interactions are highly useful in regulating supramolecular assemblies, opens a new avenue to study the anion–π interactions in aqueous and also potentially in living systems.

Experimental Section

General procedures for the synthesis of 4a–f

Both solutions of **3a** (0.84 g, 1.7 mmol) and **1a** (0.33 g, 1.7 mmol), **3b** (0.40 g, 1.5 mmol) and **1b** (0.85 g, 1.5 mmol), **3c** (0.69 g, 1.1 mmol) and **1c** (0.36 g, 1.1 mmol), **3d** (0.95 g, 1.5 mmol) and **1d** (0.37 g, 1.5 mmol), **3e** (0.68 g, 1.0 mmol) and **1e** (0.38 g, 1.0 mmol), **3f** (0.71 g, 1.0 mmol) and **1f** (0.41 g, 1.0 mmol), respectively, in acetone (100 mL) were added dropwise to a solution of diisopropyl(ethyl)amine (0.53 g, 4.1 mmol for **4a**, 0.50 g, 3.9 mmol for **4b**, 0.35 g, 2.7 mmol for **4c**, 0.50 g, 3.9 mmol for **4d**, 0.34 g, 2.6 mmol for **4e** and **4f**) in acetone (250 mL) within 8 h. The resulting mixtures were stirred at room temperature for another 48 h. After removal of the solvent under vacuum, the residue was chromatographed on a silica gel column (100–200 mesh) with a mixture of petroleum ether and ethyl acetate (10/1, v/v) as eluent to give pure **4a** (0.22 g, 21%), **4b** (0.26 g, 22%), **4c** (0.18 g, 18%), **4d** (0.38 g, 28%), **4e** (0.52 g, 53%), and **4f** (0.69 g, 30%) as white solids.

Preparation of vesicles

The compounds **4b–f**, respectively, were dissolved in tetrahydrofuran (THF, 0.3 mL), followed by the addition of water (0.7 mL). The final concentration of **4b–f** is 5.0×10^{-5} M. The mixtures were put under supersonic for about 30 min, yielding a slightly cloudy suspension. The resulting vesicle suspension was dried for SEM and TEM experiments.

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Keywords: anions · calixarenes · self-assembly · noncovalent interactions · vesicles

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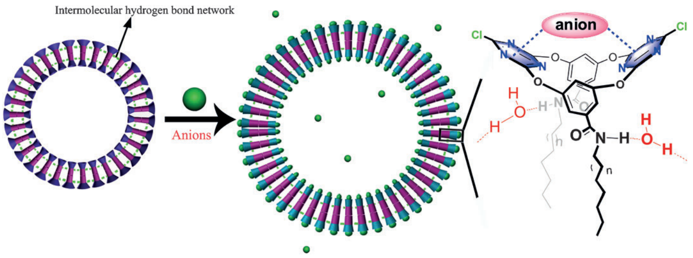

Accommodating hosts: Vesicles with surfaces engineered by tetraoxacalix[2]arene[2]triaizines were fabricated (see figure). The sizes of the vesicles are responsive to various anions, following the order $F^- < ClO_4^- < SCN^- < BF_4^- < Br^- < Cl^- < NO_3^-$. This study gives an unprecedented example of the regulation of vesicles by using the emerging, new-type anion–π noncovalent interactions.