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Formation and characterization of water-soluble hetero capsules derived from multiple ionic interactions

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ABSTRACT

We now report the formation and characterization of water-soluble hetero-capsules **1**·**2** resulting from the ionic interactions between positively charged flexible aniline hydrochloride **1** and negatively charged phosphonate **2** having rigid homooxacalix[3]arene units. The formation of the molecular capsules was studied by NOESY, DOSY NMR spectroscopy and ESI-Mass spectrometry. The water solubility of the capsules is improved by the introduction of mono- or triethylene glycol substituents in the homooxacalix[3]arene-based phosphonate units **2**.

1. Introduction

The synthesis of molecular capsules using noncovalent interactions is a very attractive area in host–guest chemistry.[1] The resulting molecular capsules have found applications in sensing,[2a] catalysis,[2b] selective recognition, and molecular storage.[1] One of the most challenging objectives of host–guest chemistry is the synthesis of water-soluble capsules for biological applications, such as drug encapsulation, transport through cell membranes, and drug delivery systems.[3] Recently, metal-coordination is mostly applied for the formation of water-soluble capsules, and many studies of the chemical reactions in these hydrophobic cavities have been reported by Fujita[4] and Raymond.[5] On the other hand, electrostatic interactions are also known as a useful attractive force for the formation of molecular capsules. Recently, Reinhoudt[6] and co-workers reported the formation of capsule-like structures based on electrostatic interactions in water as a heme-protein active site model (Fig. 1, type a). Reinhoudt,[7a–c] Schrader,[7d,e] and Verboom[7f] reported the formation of capsules based on electrostatic interactions in polar solvents (Fig. 1, type b). In these cases, to achieve the formation of capsules using electrostatic forces, rigid components, such as calix[4]arene, resorcin[4]arene and porphyrin units having C_{4v} (or D_{4h}) symmetry are essential to control the capsule formation. Due to this limitation, the water solubility of capsules becomes low, and consequently the formation of water-soluble capsules using electrostatic interactions is generally difficult. The most accessible building blocks, such as calixarene and resorcinarene have C_{4v} symmetry (i.e., calix[4]arene, resorcin[4]arene), and there is a big limitation on structure modification. Recently, Reek and co-workers reported the formation of a hetero capsule using a calix[4]arene tetraanion and bisphosphine tetraaminium units in MeOH solution.[8] On the other hand, the molecules having C_3 (C_{3v}) symmetry are easily accessible and a variety of structure

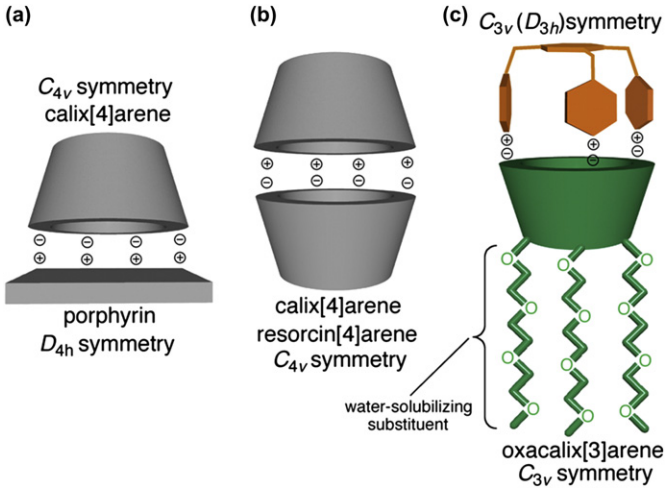

Fig. 1. Molecular capsules and capsule-like structures derived from (a) calix[4]arenes and porphyrins, (b) oppositely charged calix[4]arenes or resorcin[4]arenes, (c) oxacalix[3]arenes and a capping unit having C_{3v} (D_{3h}) symmetry.

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modifications are possible in contrast to a compound having C_4 (C_{4v}) symmetry.[9]

In this paper, we report the formation and characterization of new water-soluble capsules **1**·**2** having C_{3v} symmetry that consist of a cationic flexible aniline unit **1** and anionic lithium phosphonate unit **2**. The water solubility of the capsules is improved by the introduction of mono- or triethylene glycol substituents in the homooxacalix[3]arene-based phosphonate units **2** (Fig. 1, type c).

2. Results and discussion

2.1. Synthesis of anilinium unit 1

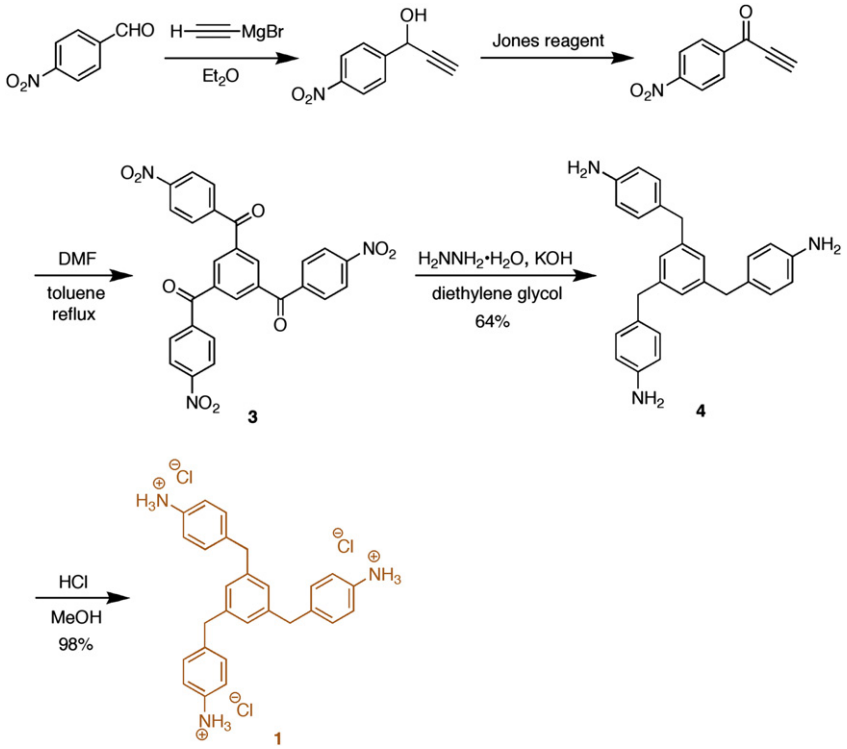
The anilinium unit (aniline hydrochloride) **1** was synthesized by the cyclotrimerization of aryl ethynyl ketone, followed by the Wolff–Kishner reduction (Scheme 1). The triaroyl benzene **3** was synthesized by the trimerization of 4-nitrophenyl ethynyl ketone in refluxing DMF.[10] The obtained triaroyl benzene **3** was converted to the corresponding aniline derivative **4** under the Wolff–Kishner condition ($KOH/H_2NNH_2 \cdot H_2O$). In this step, three carbonyl groups and three nitro groups were reduced, and 1,3,5-tris(4-aminobenzyl)benzene **4** was then obtained. The obtained aniline derivative **4** was treated with concd HCl in MeOH, and after evaporation of the solvent, the corresponding aniline hydrochloride **1** was obtained in quantitative yield. The obtained aniline hydrochloride **1** was readily soluble in methanol and water.

chromatography, the cone-isomers **6** were converted to the diethylphosphonate derivatives **8** by the Ni-catalyzed coupling reactions. The desired diethylphosphonate compounds **8** were treated with LiBr in 2-hexanone for the selective mono-lithiation; the lithium phosphonates **2** were precipitated and then collected by centrifugation. All these lithium phosphonates were readily soluble in water and methanol. The phosphonate **2c** having the triethylene glycol unit, which was introduced to improve its water solubility, had a higher hygroscopic property.

2.3. Formation of capsules 1·2

The formation of capsule **1**·**2a** (0.25 mM) was achieved by mixing equimolar solutions (0.5 mM) of **1** and **2a** in D_2O at room temperature (Scheme 3). The ^1H NMR spectrum of the desired solution shows the characteristic upfield and downfield shifts with respect to those of **1** and **2a** (Fig. 2). Interestingly, the characteristic upfield-shifts ($\Delta\delta_{CH2}$=0.37 ppm, $\Delta\delta_{CH3}$=0.47 ppm) for the protons of the phosphonate substituents (P-OEt) of **2a** were observed due to encapsulation of the substituents in the interior of the **1**·**2a** cavity (Scheme 4).

The molecular modeling study shows that the cavity size of **1**·**2a** is not big enough to encapsulate three ethyl phosphonate groups (P-OEt). One or two of the ethyl phosphonate groups (P-OEt) might be encapsulated in the cavity of **1**·**2a** (Fig. 3). A single set of proton resonances for the free and bonded building blocks was observed in

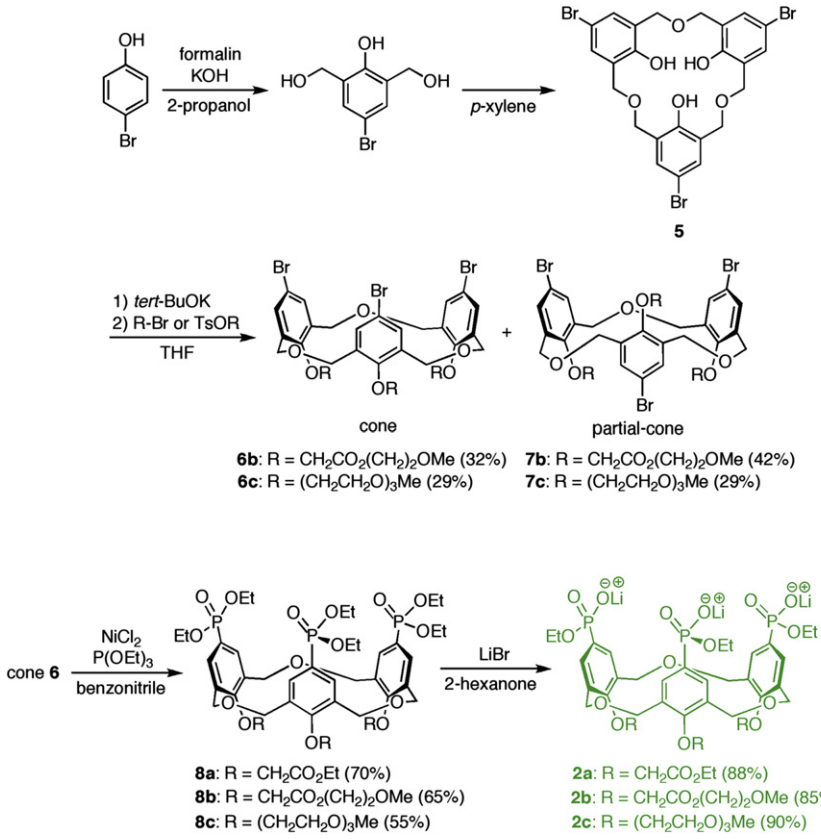


Scheme 1. Synthesis of anilinium unit **1**.

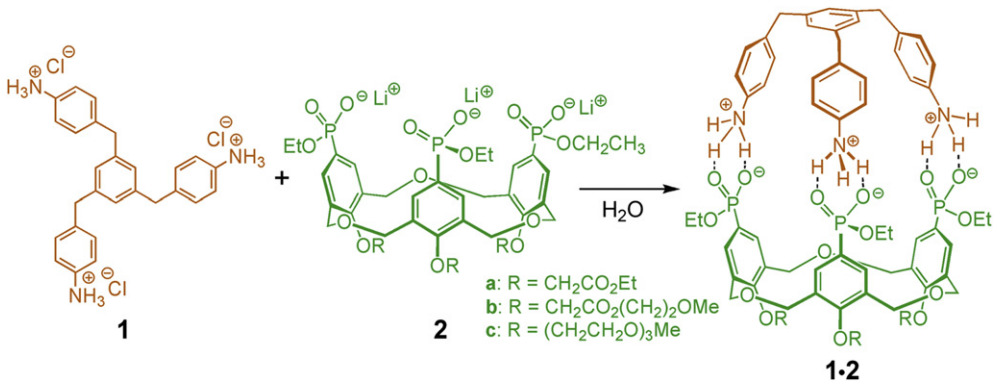
2.2. Synthesis of phosphonate units 2a–c

The phosphonate units **2a**–**c** were synthesized using a modified literature procedure for preparation of the calix[4]arene-based phosphonate compounds[7e] (Scheme 2). Tribromohexahomotrioxacalix[3]arene **5** was treated with *tert*-BuOK and the corresponding bromoacetate (R-Br) or tosylate (TsOR) in THF under reflux conditions to give the corresponding cone-isomers **6** and partial-cone isomers **7** in an almost 1:1 ratio. After separation by column

the temperature range of 5–25 °C, indicating a fast exchange process on the NMR time scale. The capsule **1**·**2a** was also prepared by mixing methanol solutions of **1** and **2a** in a 1:1 ratio. However, in the methanol solution, a smaller upfield shift of the ethyl phosphonate substituents (P-OEt) corresponding to the D_2O solution was observed in the ^1H NMR spectra ($\Delta\delta_{CH2}$=0.17 ppm, $\Delta\delta_{CH3}$=0.19 ppm for P-OEt, Fig. S1). This observation shows that the formation of capsule **1**·**2a** is driven by hydrophobic interactions due to encapsulation of the phosphonate substituents (P-OEt) into



Scheme 2. Synthesis of phosphonate units **2a**–**c**.



Scheme 3. Formation of capsules **1**·**2**.

the cavity of **1**·**2a**. For the formation of capsules **1**·**2b** and **1**·**2c** in D_2O, also shows a similar characteristic upfield-shifts ($\Delta\delta_{CH2}$=0.46 ppm, $\Delta\delta_{CH3}$=0.35 ppm for 0.25 mM **1**·**2b**, $\Delta\delta_{CH2}$=0.32 ppm, $\Delta\delta_{CH3}$=0.48 ppm for 0.25 mM **1**·**2c**) for the protons of the phosphonate substituents (P-OEt) of **2**, and smaller chemical shift change corresponding to the D_2O solution was observed in CD_3OD (Figs. S2–S5). However, big difference was not observed about ^1H NMR chemical shift change between the capsules **1**·**2a**, **1**·**2b** and **1**·**2c**, although the hydrophilic substituents were introduced in phosphonate unit **2b** and **2c**.

Further proof of the stoichiometry of the complexes was obtained from a Job's plot analysis of the titration experiments. For solubility reasons, the titrations were performed in CD_3OD instead of D_2O. A Job's plot analysis of **1**·**2a** definitely proved the 1:1 stoichiometry in the CD_3OD solution (Fig. 4). Additionally, a Job's plot analysis of **1**·**2b** and **1**·**2c** also showed a similar 1:1 stoichiometry (Figs. S6 and S7).

The binding constants for capsule formation were determined by ^1H NMR titrations in CD_3OD solution. The experimental data were fitted to a 1:1 binding model giving $K_{\mathbf{1}\cdot\mathbf{2a}}=3.0\pm0.7\times10^3$ M^{-1} for capsule **1**·**2a**, $K_{\mathbf{1}\cdot\mathbf{2b}}=2.5\pm0.6\times10^3$ M^{-1} for capsule **1**·**2b**, and $K_{\mathbf{1}\cdot\mathbf{2c}}=1.5\pm0.3\times10^3$ M^{-1} for capsule **1**·**2c** (Figs. S8–S10). According to the binding constants of the capsules **1**·**2** in CD_3OD ($K_{\mathbf{1}\cdot\mathbf{2}}=\sim10^3$ M^{-1}), these capsules may exist in equilibrium with free building blocks in CD_3OD solutions.

The NOESY spectrum of the capsule **1**·**2a** in CD_3OD–D_2O (1:9) at 283 K displays significant negative intermolecular NOE contacts between the aromatic protons of **1** and P(O*Et*) protons of **2a** (Fig. 5). For solubility reasons, a mixed solvent (CD_3OD–D_2O) was employed for the NOESY measurement of **1**·**2a**. The rather water-

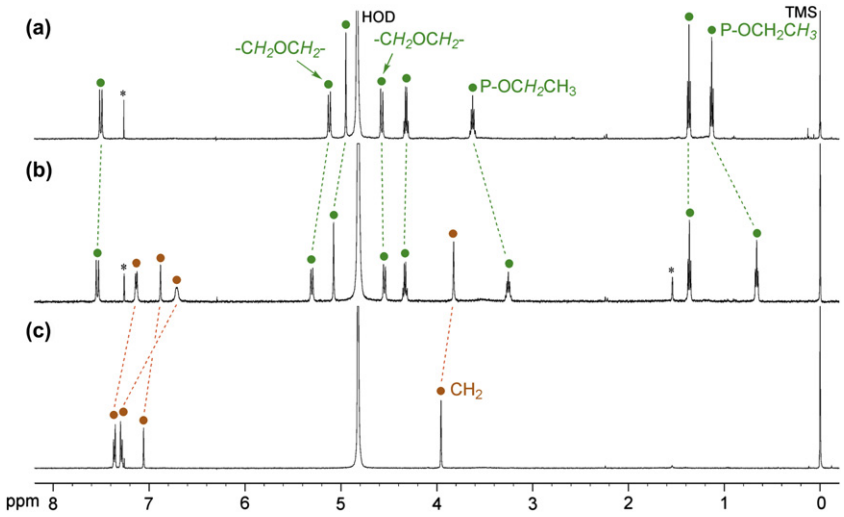
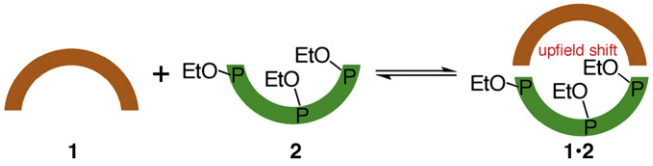


Fig. 2. ^{1}H NMR spectra (0.25 mM, D_2O, 298 K) of (a) **2a**, (b) capsule **1**·**2a** obtained by mixing equimolar solutions of **1** and **2a**, and (c) **1**. Asterisks indicate signals from the external standard (TMS/$CDCl_3$ in glass capillary).



Scheme 4. Schematic representation of the formation of capsule **1**·**2** and encapsulation of ethyl phosphonate substituents (P-OEt).

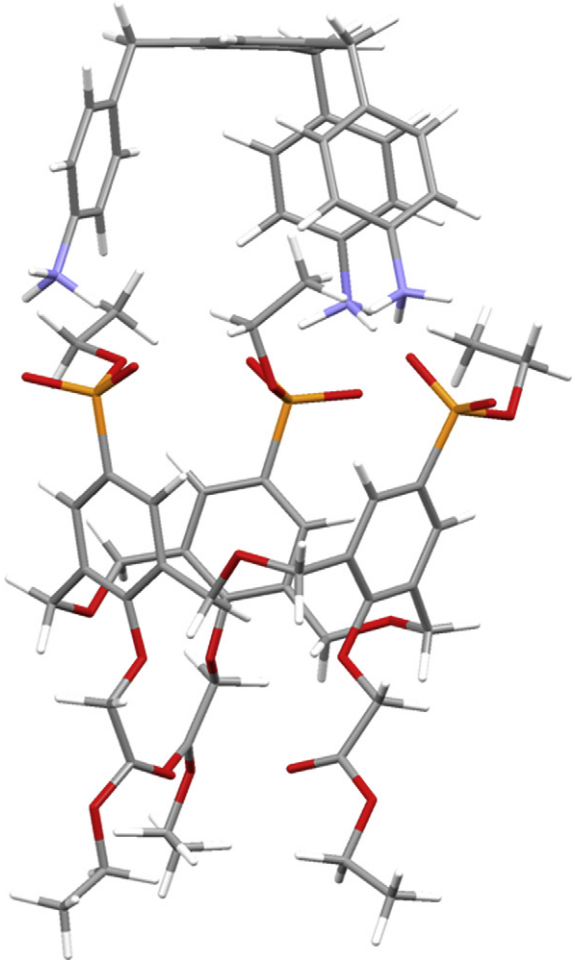


Fig. 3. Molecular structure of **1**·**2a** obtained by PM6 calculation in water.

soluble capsules **1**·**2b** and **1**·**2c** showed similar NOEs in D_2O at room temperature (Figs. S11–S13).

Additional evidence for the formation of capsule **1**·**2a** was obtained by electrospray ionization mass spectrometry (ESI-MS). The positive-mode ESI-MS spectrum of **1**·**2a** in H_2O–CH_3OH shows a prominent monoisotopic ion peak of the capsule at *m*/*z* 1384.5 corresponding to $[\mathbf{1}\cdot\mathbf{2a}+H]^+$. All the capsule's ion peaks correspond to 1:1 complexes, while no ion peaks for higher aggregates were detected (Fig. 6). The ESI-MS spectrum of capsules **1**·**2b** and **1**·**2c** also shows a similar spectroscopic character (Figs. S14 and S15).

Moreover, diffusion-ordered NMR spectroscopy (DOSY) was performed for the solutions of **1**, **2a**, and capsule **1**·**2a** in D_2O (Fig. 7). The DOSY spectra showed that the diffusion coefficient of capsule **1**·**2a** is lower than those of the corresponding free building blocks (**1**, **2a**), confirming the formation of the larger sized capsule **1**·**2a** (Fig. 7). The observed diffusion coefficients and calculated molecular volumes derived by the MM2 optimized structures (Fig. 8) for the capsules and building blocks are summarized in Table 1. The molecular volumes derived from the DOSY experiments are nearly consistent with the calculated molecular volumes derived from the optimized structures (Table 1). These findings suggest the formation of capsules **1**·**2a**–**1**·**2c** in water. However, in the DOSY spectrum of capsule **1**·**2c**, the diffusion signals derived from the anilinium unit **1** and the phosphonate unit **2c** were separately observed under the diffusion time (Δ) of 100–400 ms (Table 1, Figs. S17, S18). The separately observed DOSY signal for capsule **1**·**2c** shows that the capsules exist in equilibrium with free building blocks even in D_2O solution.

2.4. Water solubility of capsules 1·2a–1·2c

To compare the solubility of capsules **1**·**2a**–**1**·**2c**, we measured the ^{1}H NMR spectrum of the capsules (**1**·**2a**–**1**·**2c**) at different concentrations (0.125–3.0 mM) in D_2O. At a higher concentration, the capsules precipitated in the D_2O solutions after mixing the solutions of **1** and **2**. We estimated the concentration of the capsules in D_2O by comparison of the ^{1}H NMR integration of **1**·**2a**–**1**·**2c** with the internal standard (TMS/$CDCl_3$ in glass capillary) at different concentrations. The ^{1}H NMR integration of the clear solutions (0.125 mM for **1**·**2a** or 0.25 mM for **1**·**2b**,**1**·**2c**) were selected for the standard solutions, and the calculated changes in the NMR integration depended on the increasing concentration (Fig. 9). For capsule **1**·**2a**, a linear relationship of the prepared and estimated concentrations of the capsule was observed up to a 0.25 mM

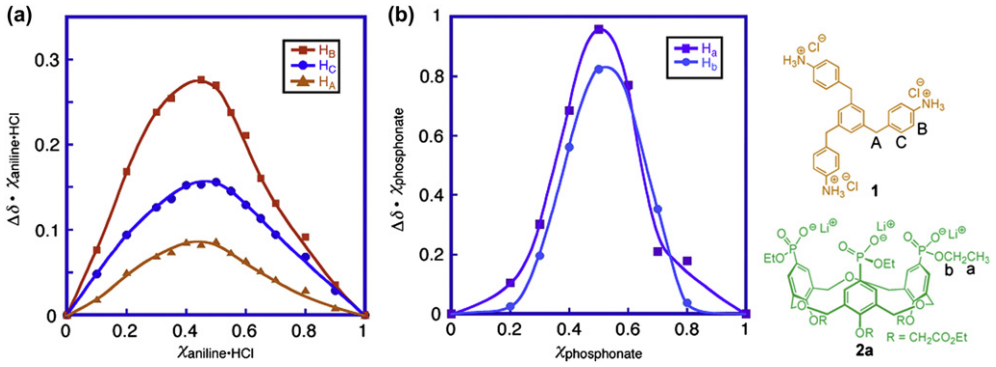


Fig. 4. Job's plot for the capsule formation between anilinium unit **1** and phosphonate unit **2a** at a total concentration of 4 mM in CD_3OD at 298 K, (a) for the anilinium protons (H_A, H_B, H_C), (b) for the phosphonate protons (H_a, H_b).

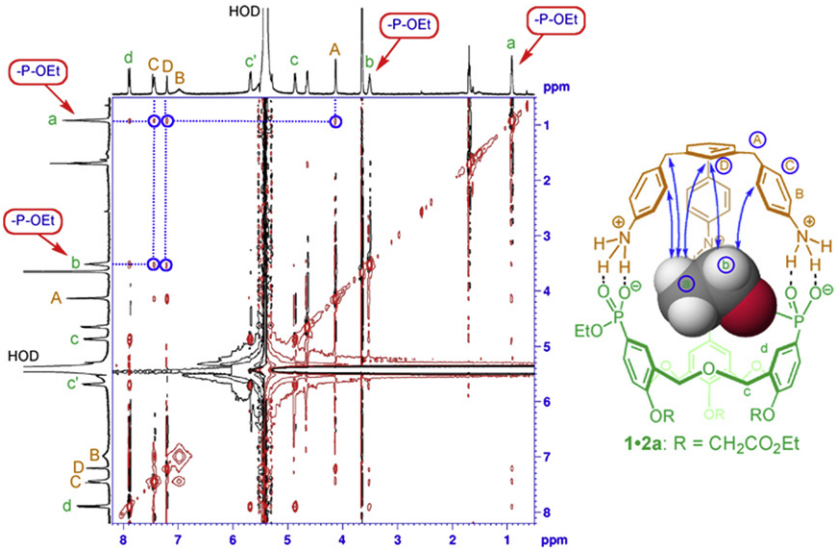


Fig. 5. NOESY spectrum of **1**·**2a** in CD_3OD–D_2O (1:9) at 283 K (mixing time: 0.5 s).

concentration. However, for the capsules **1**·**2b** and **1**·**2c** having ethylene glycol substituents, they had a linear relationship up to a 1 mM concentration. A remarkable increase in the water solubility was observed for capsules **1**·**2b** and **1**·**2c**. Although the water solubility was increased, we have to remember that the capsules exist in equilibrium with free building blocks.

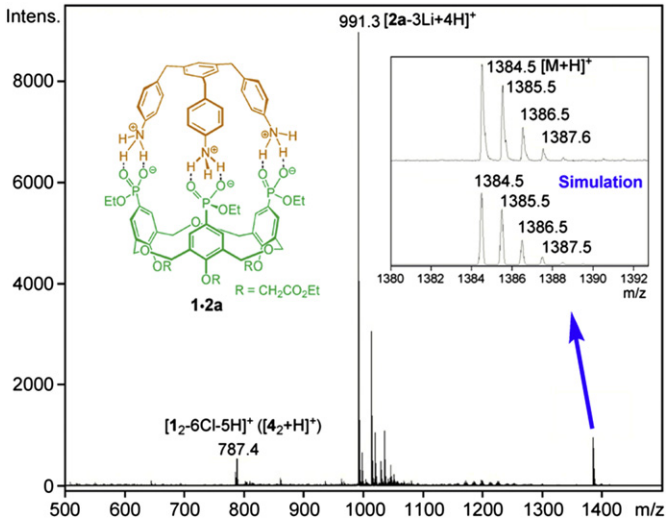


Fig. 6. ESI-MS spectrum of **1**·**2a** in H_2O/MeOH.

2.5. Guest binding study in 1·2a and 1·2c

To investigate the guest binding properties of capsules **1**·**2a** and **1**·**2c**, we carried out NMR measurements before and after the additions of the guest molecules. The ethoxy group (P-OEt) of the phosphonate unit **2** of capsule **1**·**2** was used as a probe to detect any guest encapsulation (Scheme 5).

The formation of capsule **1**·**2a** was achieved by mixing equimolar D_2O solutions of **1** and **2a**. The addition of an excess (0–50 equiv) of either 1-methylpyrazinium iodide **9** or 1,4-dimethylpyridinium iodide **10** to the capsule **1**·**2a** in D_2O (0.25 mM) causes a downfield shift of the proton signals of the ethyl phosphonate group P-OEt (Figs. S18 and S19). The guest resonance itself hardly shifts upon complexation, because it is an averaged signal for the free and complexed guest molecule. Additionally, similar guest binding properties are observed for the capsule **1**·**2c** with **9** (Fig. S20). The capsules **1**·**2** exist in equilibrium with free building blocks; the quantitative analysis of guest binding is difficult in this system. However, fitting of the ^{1}H NMR titration data for the 1-methylpyrazinium iodide **9** and 1,4-dimethylpyridinium iodide **10** to a 1:1 binding model gave $K_a = \sim 10^2$ M^{-1} in D_2O for capsule **1**·**2a** (Figs. S21 and S22).

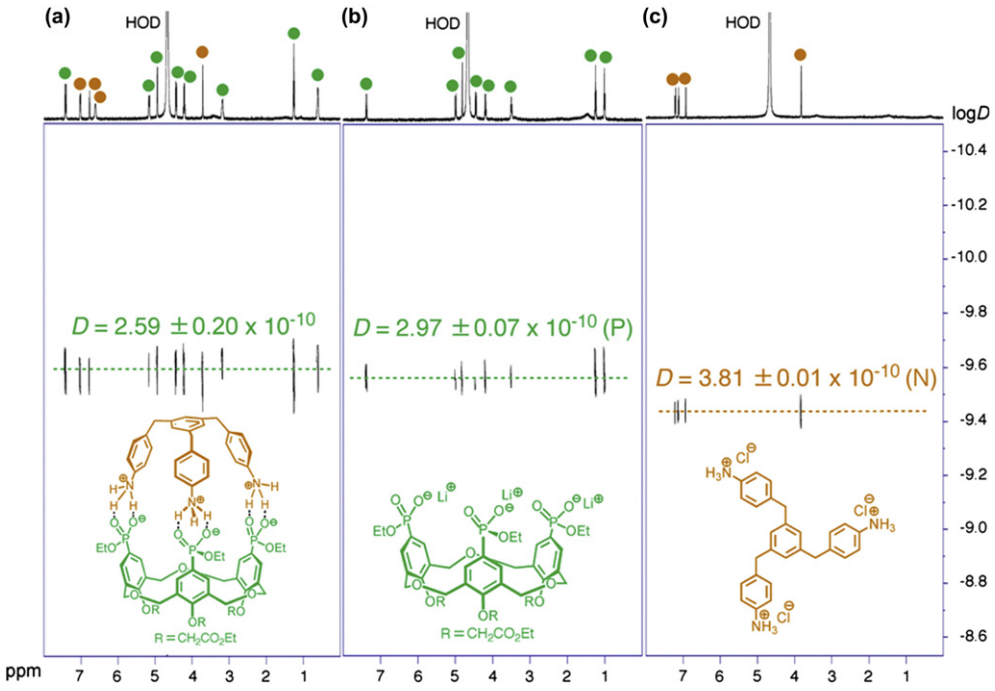


Fig. 7. DOSY spectra (0.25 mM in D_2O, 25 °C, Δ=100 ms) of (a) capsule **1**·**2a**, (b) phosphonate **2a**, and (c) aniline hydrochloride **1**.

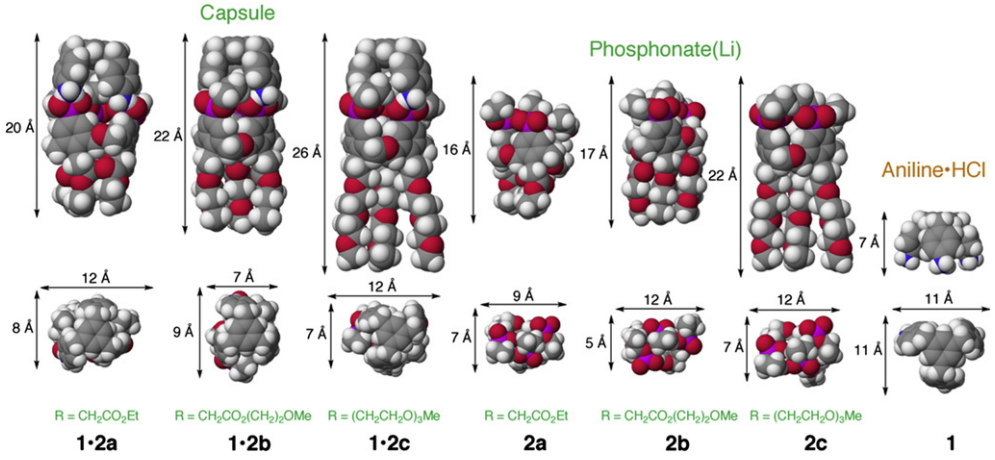


Fig. 8. Molecular model and measured dimensions of aniline hydrochloride **1**, phosphonates **2**, and capsules **1**·**2**.

Table 1
Comparison of diffusion coefficients, molecular radii, and volumes[a]

Compound	Concn (mM)	D (m^2 s^{-1})	r_H (Å)	V (Å^3)	V_{calcd}[c] (Å^3)
1	0.25	$3.81\pm0.01\times10^{-10}$	6.43	1114	1600
2a	0.25	$2.97\pm0.07\times10^{-10}$	8.26	2361	2800
2b	1.0	$2.62\pm0.02\times10^{-10}$	9.36	3435	3000
2c	1.0	$2.53\pm0.02\times10$	9.70	3823	3600
1·**2a**	0.25	$2.59\pm0.20\times10^{-10}$	9.47	3557	3700
1·**2b**	1.0	$2.52\pm0.07\times10^{-10}$	9.73	3859	4000
1·**2c**[b]	1.0	$2.54\pm0.02\times10^{-10}$ (N)	9.66	3776	4500
		$2.30\pm0.05\times10^{-10}$ (P)	10.7	5131	

[a] Diffusion coefficients were recorded at 25 °C (diffusion time Δ=100 ms), and molecular radii were calculated using the Stokes–Einstein equation.
[b] Diffusion time Δ=300 ms was employed.
[c] Calculations of molecular volumes were performed using HyperChem 7.52.

To investigate the ability of the water-soluble capsule **1**·**2** to include guest molecules, we carried out numerous preliminary experiments (such as with C_3 symmetry neutral guest molecules, neutral aromatic molecules). However, no binding was observed for the neutral guest molecules (toluene, benzene, and 1,3,5-trimethoxybenzene) in the ^{1}H NMR measurement. During the course of the investigations, a weak guest binding was observed for *iso*-propyl benzene (cumen) **11** ($\Delta\delta_{CH3}$=−0.01 ppm for cumene **11**, $\Delta\delta_{P\text{-}OCH2CH3}$=0.01 ppm for 0.25 mM **1**·**2a**) and dimethylphenylsilane (Me_2SiHPh) **12** ($\Delta\delta_{CH3}$=0.02 ppm for Me_2SiHPh **12**, $\Delta\delta_{P\text{-}OCH2CH3}$=0.01 ppm for 0.25 mM **1**·**2a**) in the D_2O solution of capsule **1**·**2a** (Figs. S23 and S24). The binding constant of neutral guest molecules could not determined due to the less water solubility of these guest molecules.

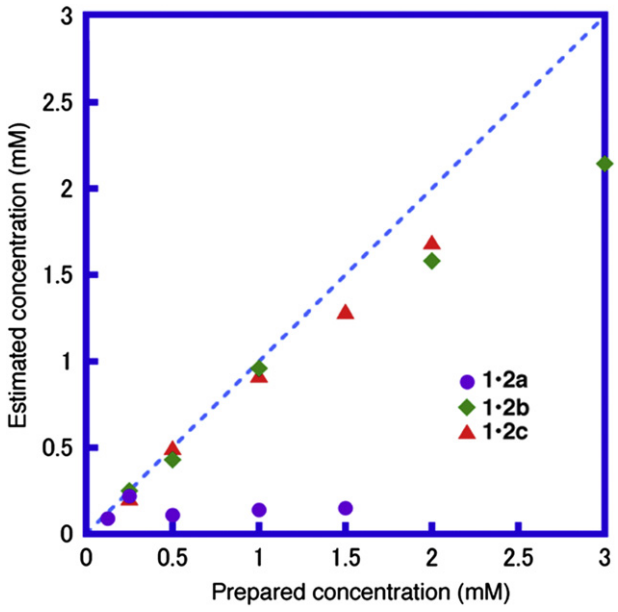
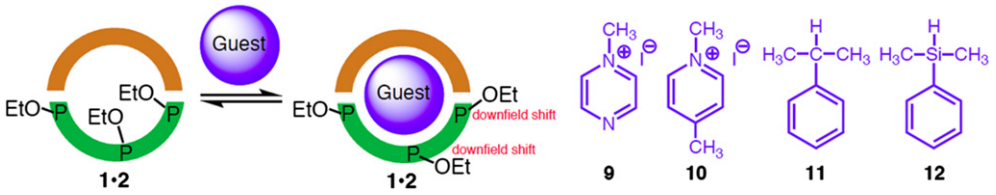


Fig. 9. Comparison of prepared and estimated concentrations of capsules **1**·**2a**–**1**·**2c** in D_2O.

calix[3]arene-25,26,27-triol (**5**),[11] 7,15,23-tribromo-25,26,27-tris[(ethoxycarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (**6a**),[11] 1,3,5-tris(4-nitrobenzoyl)benzene (**3**),[10] triethylene glycol monomethyl ether monotosylate,[12] and 2-methoxyethyl bromoacetate[13] were prepared by the published procedure.

*4.1.1. 7,15,23-Tribromo-25,26,27-tris[(3-oxabutoxycarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (**6b**, **7b**).* A mixture of 7,15,23-tribromo-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene-25,26,27-triol **5** (302 mg, 0.468 mmol) and *tert*-BuOK (941 mg, 4.78 mmol) in THF (45 mL) was stirred at 50 °C for 0.5 h under an argon atmosphere, and then 2-methoxyethyl bromoacetate (941 mg, 4.78 mmol) was added via a syringe during 15 min, and the mixture was stirred at reflux temperature for 3 h. After cooling, the reaction was stopped by the addition of ethanol (5 mL) and the solution was evaporated to dryness. After the addition of 1 N HCl (50 mL), the mixture was extracted with chloroform, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The products **6b** (cone-isomer, 151 mg, 32%) and **7b** (partial-cone isomer, 197 mg, 42%) were isolated after gel permeation chromatography ($CHCl_3$) followed by column chromatography (SiO_2, $CHCl_3$/AcOEt=3:1). Compound **6b** (cone-isomer): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.04 (s, 6H), 4.78 (d, J=13.0 Hz, 6H), 4.49 (s, 6H), 4.42 (d, J=13.0 Hz, 6H), 4.34 (m,



Scheme 5. Schematic representation of guest binding for the capsule **1**·**2** and structure of guest molecules.

3. Conclusions

We have synthesized a new family of water-soluble heterocapsules **1**·**2** having a homooxacalix[3]arene-based phosphonate unit and a flexible anilinium unit. The water solubility of the capsules was improved by the introduction of an ethylene glycol substituent in the phosphonate units. The formation of the molecular capsules was studied by NOESY, DOSY NMR spectroscopy and ESI-Mass spectrometry. This approach to building a water-soluble capsule by using C_{3v} symmetry building blocks opens up a new opportunity to synthesize a variety of water-soluble capsules by electrostatic interactions. The synthesis of larger water-soluble capsules is under investigation.

4. Experimental section

4.1. General

Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR were recorded on a Bruker DRX-500 (500, 125, and 202 MHz) spectrometer. FAB-mass spectra were recorded on a JEOL JMS-700 mass spectrometer. ESI-mass spectra were recorded on a Bruker micrOTOF mass spectrometer. Elemental analyses were obtained on a Yanaco MT-5 CHN recorder. Gel permeation chromatography (GPC) was performed on an LC 908 instrument (Japan Analytical Industry Co., Ltd.). All solvents and reagents were purified according to standard procedures. 7,15,23-Tribromo-2,3,10,11,18,19-hexahomo-3,11,19-trioxa-

6H), 3.63 (m, 6H), 3.39 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ=169.0 (C_q), 154.1 (C_q), 133.8 (C_q), 132.8 (CH), 117.3 (C_q), 71.0 (CH_2), 70.2 (CH_2), 68.7 (CH_2), 63.9 (CH_2), 58.8 (CH_3). HRMS (FAB, NBA+NaI) m/z=1017.0182 (calculated for $C_{39}H_{45}Br_3O_{15}Na$: 1017.0175). Compound **7b** (partial-cone isomer): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.46 (s, 2H), 7.39 (d, J=2.5 Hz, 2H), 7.35 (d, J=2.5 Hz, 2H), 4.97 (d, J=9.5 Hz, 2H), 4.93 (d, J=12.5 Hz, 2H), 4.73 (d, J=16.3 Hz, 2H), 4.56 (d, J=12.0 Hz, 2H), 4.28–4.11 (m, 12H), 4.07 (d, J=16.3 Hz, 2H), 3.55 (m, 6H), 3.40 (s, 3H), 3.38 (s, 2H), 3.35 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ=169.4 (C_q), 168.5 (C_q), 155.4 (C_q), 154.0 (C_q), 134.2 (CH), 133.9 (C_q), 133.6 (CH), 133.3 (C_q), 132.9 (CH), 132.3 (C_q), 116.9 (C_q), 116.2 (C_q), 70.7 (CH_2), 70.12 (CH_2), 70.06 (CH_2), 69.8 (CH_2), 68.7 (CH_2), 66.6 (CH_2), 64.4 (CH_2), 63.77 (CH_2), 63.75 (CH_2), 58.9 (CH_3), 58.7 (CH_3). HRMS (FAB, NBA+NaI) m/z=1017.0234 (calculated for $C_{39}H_{45}Br_3O_{15}Na$: 1017.0175).

*4.1.2. 7,15,23-Tribromo-25,26,27-tris(3,6,9-trioxadecyloxy)-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (**6c**, **7c**).* A mixture of 7,15,23-tribromo-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene-25,26,27-triol **5** (1.00 g, 1.56 mmol) and *tert*-BuOK (1.72 g, 15.4 mmol) in THF (150 mL) was refluxed for 0.5 h under argon atmosphere, and then triethylene glycol monomethyl ether monotosylate (4.78 g, 15.0 mmol) was added during 15 min and the mixture was stirred at reflux temperature for 22 h. The products **6c** (cone-isomer, 487 mg, 29%) and **7c** (partial-cone isomer, 494 mg, 29%) were isolated after gel permeation chromatography ($CHCl_3$) followed by column chromatography (SiO_2, AcOEt). Compound **6c** (cone-isomer): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.09 (s, 6H), 4.60 (d, J=13.5 Hz, 6H), 4.52 (d, J=13.5 Hz, 6H), 3.86 (m, 6H),

3.72 (m, 6H), 3.69 (s, 12H), 3.66 (m, 6H), 3.56 (m, 6H), 3.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ=153.3 (C_q), 133.8 (d, C_q), 131.9 (CH), 117.1 (C_q), 73.8 (CH_2), 71.9 (CH_2), 70.70 (CH_2), 70.66 (CH_2), 70.61 (CH_2), 70.2 (CH_2), 67.8 (CH_2) 59.0 (CH_3). HRMS (FAB, NBA+NaI) *m/z*=1107.1571 (calculated for $C_{45}H_{63}Br_3O_{15}Na$: 1107.1586). Compound **7c** (partial-cone isomer): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.44 (s, 2H), 7.38 (d, *J*=2.5 Hz, 2H), 7.29 (d, *J*=2.5 Hz, 2H), 4.75 (d, *J*=11.5 Hz, 2H), 4.63 (d, *J*=12.5 Hz, 2H), 4.48 (d, *J*=11.5 Hz, 2H), 4.37 (d, *J*=12.5 Hz, 2H), 4.21 (d, *J*=11.5 Hz, 2H), 4.19 (d, *J*=12.5 Hz, 2H), 3.81 (m, 2H), 3.68–3.47 (m, 32H), 3.38 (s, 3H), 3.37 (s, 6H), 3.08–3.01 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ=155.9 (C_q), 155.5 (C_q), 134.3 (C_q), 133.4 (C_q), 133.3 (CH), 133.1 (CH), 133.0 (CH), 132.9 (C_q), 116.3 (C_q), 116.1 (C_q), 74.0 (CH_2), 73.6 (CH_2), 71.9 (CH_2), 70.63 (CH_2), 70.53 (CH_2), 70.48 (CH_2), 70.36 (CH_2), 70.1 (CH_2), 69.7 (CH_2), 67.7 (CH_2), 64.9 (CH_2), 64.4 (CH_2), 59.0 (CH_3). HRMS (FAB, NBA+NaI) *m/z*=1107.1561 (calculated for $C_{45}H_{63}Br_3O_{15}Na$: 1107.1586).

*4.1.3. 25,26,27-Tris[(ethoxycarbonyl)methoxy]-7,15,23-tris(diethoxyphosphoryl)-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (**8a**).* To a solution of 7,15,23-tribromo-25,26,27-tris[(ethoxycarbonyl) methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene cone-**6a** (0.40 g, 0.44 mmol) and $NiCl_2$ (77 mg, 0.59 mmol) in benzonitrile (3 mL) was added dropwise $P(OEt)_3$ (0.56 mL, 3.2 mmol) during 15 min under argon at 160 °C and stirring was continued for 1 h. The reaction mixture was poured into toluene (50 mL), the organic layer was washed four times with 5% aqueous NH_3, dried over Na_2SO_4 and the solvent was evaporated. The remaining benzonitrile was removed under reduced pressure at 60 °C. The product **8a** (332 mg, 70% yield) was isolated after chromatography (SiO_2, $CHCl_3$/MeOH=20:1) as a colorless solid. Mp: 34–35 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ=7.40 (d, J_{P-H}=13.0 Hz, 6H), 5.03 (d, *J*=12.0 Hz, 6H), 4.70 (s, 6H), 4.45 (d, *J*=12.0 Hz, 6H), 4.25 (q, *J*=7.2 Hz, 6H), 4.0–3.8 (m, 12H), 1.32 (t, *J*=7.1 Hz, 9H), 1.27 (t, *J*=7.1 Hz, 18H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ=169.3 (C_q), 159.5 (d, J_{C-P}=3.5 Hz, C_q), 134.2 (d, J_{C-P}=10.7 Hz, CH), 132.1 (d, J_{C-P}=15.3 Hz, C_q), 124.0 (d, J_{C-P}=189.5 Hz, C_q), 70.9 (CH_2), 70.0 (CH_2), 62.1 (d, J_{C-P}=5.2 Hz, CH_2), 61.2 (CH_2), 16.3 (d, J_{C-P}=6.4 Hz, CH_3), 14.2 (CH_3). ^{31}P NMR (202 MHz, CD_2Cl_2, H_3PO_4 in D_2O as external standard) δ=17.6. MS (FAB, NBA+NaI) *m/z* 1098 ($M+Na^+$). Anal. Calcd for $C_{48}H_{69}O_{21}P_3\cdot 2H_2O$: C, 51.89; H, 6.62. Found: C, 51.51; H, 6.35.

*4.1.4. 7,15,23-Tris(diethoxyphosphoryl)-25,26,27-tris[(3-oxabutoxycarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (**8b**).* To a solution of 7,15,23-tribromo-25,26,27-tris[(3-oxabutoxycarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene cone-**6b** (132 mg, 0.133 mmol) and $NiCl_2$ (12.3 mg, 0.0949 mmol) in benzonitrile (1.5 mL) was added dropwise $P(OEt)_3$ (120 μL, 0.692 mmol) during 5 min under argon at 160 °C and stirring was continued for 2 h. The product **8b** (101 mg, 65%) was isolated after gel permeation chromatography (toluene) followed by column chromatography (SiO_2, AcOEt/MeOH=6:1) as a colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ=7.39 (d, J_{P-H}=13.0Hz, 6H), 5.02 (d, *J*=12.1 Hz, 6H), 4.73 (s, 6H), 4.44 (d, *J*=12.1 Hz, 6H), 4.32 (m, 6H), 4.0–3.8 (m, 12H), 3.62 (m, 6H), 3.36 (s, 9H), 1.27 (t, *J*=7.1 Hz, 18H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ=169.9 (C_q), 159.8 (d, J_{C-P}=3.9 Hz, C_q), 134.6 (d, J_{C-P}=10.8 Hz, CH), 132.6 (d, J_{C-P}=15.3 Hz, C_q), 124.3 (d, J_{C-P}=189.6 Hz, C_q), 71.3 (CH_2), 70.7 (CH_2), 70.4 (CH_2), 64.6 (CH_2), 62.6 (d, J_{C-P}=5.1 Hz, CH_2), 59.1 (CH_3), 16.7 (d, J_{C-P}=6.5 Hz, CH_3). ^{31}P NMR (202 MHz, CD_2Cl_2, H_3PO_4 in D_2O as external standard) δ=17.5. HRMS (FAB, NBA+NaI) *m/z*=1187.3751 (calculated for $C_{51}H_{75}O_{24}P_3Na$: 1187.3759).

*4.1.5. 7,15,23-Tris(diethoxyphosphoryl)-25,26,27-tris(3,6,9-trioxadecyloxy)-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (**8c**).* To a solution of 7,15,27-tribromo-25,26,27-tris(3,6,9-trioxadecyloxy)-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene **6c** (0.14 g, 0.11 mmol, cone-isomer) and $NiCl_2$ (9.7 mg, 0.075 mmol) in benzonitrile (1.5 mL) was added dropwise $P(OEt)_3$ (0.10 mL, 0.63 mmol) during 15 min under argon at 160 °C and stirring was continued for 4 h. The product **8c** (73 mg, 55% yield) was isolated after gel permeation chromatography (toluene) followed by column chromatography (SiO_2, AcOEt/MeOH=3:1). Compound **8c**: colorless oil; ^{1}H NMR (500 MHz, CD_2Cl_2) δ=7.38 (d, J_{P-H}=13.0 Hz, 6H), 4.82 (d, *J*=13.0 Hz, 6H), 4.56 (d, *J*=13.0 Hz, 6H), 3.98 (m, 6H), 3.89–3.80 (m, 12H), 3.79 (m, 6H), 3.69–3.64 (m, 12H), 3.60 (m, 6H), 3.50 (m, 6H), 3.31 (s, 9H), 1.26 (t, *J*=7.0 Hz, 18H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ=158.8 (d, J_{C-P}=3.8 Hz, C_q), 133.3 (d, J_{C-P}=11.3 Hz, C_q), 132.9 (d, J_{C-P}=15.1 Hz, CH), 123.7 (d, J_{C-P}=188.7 Hz, C_q), 74.2 (CH_2), 72.3 (CH_2), 70.9 (CH_2, 2C), 70.8 (CH_2), 70.6 (CH_2), 69.1 (CH_2), 62.3 (d, J_{C-P}=5.0 Hz, CH_2), 58.9 (CH_3), 16.5 (d, J_{C-P}=6.3 Hz, CH_3). ^{31}P NMR (202 MHz, CD_2Cl_2, H_3PO_4 in D_2O as external standard) δ=18.0. HRMS (FAB, NBA+NaI) *m/z*=1277.5184 (calculated for $C_{57}H_{93}O_{24}P_3Na$: 1277.5167).

*4.1.6. 25,26,27-Tris[(ethoxycarbonyl)methoxy]-7,15,23-tris(hydroxyethylphosphoryl)-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene, trilithium salt (**2a**).* 25,26,27-Tris[(ethoxycarbonyl)methoxy]-7,15,23-tris(diethoxyphosphoryl)-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene **8a** (100 mg, 0.093 mmol) and LiBr (26.7 mg, 0.31 mmol) were refluxed in 2-hexanone (10 mL) under an argon atmosphere. After 1.5 h, the white precipitate was collected by centrifugation and washed five times with Et_2O. The collected precipitate was dried over under vacuum to give trilithium salt **2a** as a white powder. Yield: 82.8 mg (88%); mp: >300 °C. ^{1}H NMR (500 MHz, D_2O, TMS in $CDCl_3$ as external standard) δ=7.50 (d, J_{P-H}=12.3 Hz, 6H), 5.12 (d, *J*=11.2 Hz, 6H), 4.95 (s, 6H), 4.58 (d, *J*=11.2 Hz, 6H), 4.32 (q, *J*=7.2 Hz, 6H), 3.63 (m, 6H), 1.37 (t, *J*=7.2 Hz, 9H), 1.13 (t, *J*=7.0 Hz, 9H). ^{13}C NMR (125 MHz, D_2O, TMS in $CDCl_3$ as external standard) δ=171.7(C_q), 158.2 (d, J_{C-P}=3.5 Hz, C_q), 134.3 (d, J_{C-P}=10.1 Hz, CH), 130.8 (d, J_{C-P}=14.4 Hz, C_q), 129.1 (d, J_{C-P}=178.5 Hz, C_q), 71.1 (CH_2), 69.6 (CH_2), 62.4 (CH_2), 61.2 (d, J_{C-P}=4.8 Hz, CH_2), 15.7 (d, J_{C-P}=6.8 Hz, CH_3), 13.4 (CH_3). ^{31}P NMR (202 MHz, D_2O, H_3PO_4 in D_2O as external standard) δ=14.3. MS (ESI negative, MeOH/H_2O) *m/z*=989 (M-3Li+2H)$^-$, 995 (M-2Li+H)$^-$, 1001 (M−Li)$^-$. Anal. Calcd for $C_{42}H_{54}Li_3O_{21}P_3\cdot 2H_2O$: C, 48.29; H, 5.60. Found: C, 47.92; H, 5.26.

*4.1.7. 7,15,23-Tris(hydroxyethylphosphoryl)-25,26,27-tris[(3-oxabutoxycarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene, trilithium salt (**2b**).* Yield 85%; mp: >300 °C. ^{1}H NMR (500 MHz, D_2O, TMS in $CDCl_3$ as external standard) δ=7.48 (d, J_{P-H}=12.0 Hz, 6H), 5.08 (d, *J*=11.0 Hz, 6H), 4.94 (s, 6H), 4.57 (d, *J*=11.0 Hz, 6H), 4.39 (t, *J*=4.3 Hz, 6H), 3.76 (t, *J*=4.3 Hz, 6H), 3.60 (m, 6H), 3.42 (s, 9H), 1.11 (t, *J*=7.0 Hz, 9H). ^{13}C NMR (125 MHz, D_2O, TMS in $CDCl_3$ as external standard) δ=171.5 (C_q), 158.2 (d, J_{C-P}=3.8 Hz, C_q), 134.3 (d, J_{C-P}=10.1 Hz, CH), 130.8 (d, J_{C-P}=15.1 Hz, C_q), 129.1 (d, J_{C-P}=179.8 Hz, C_q), 70.9 (CH_2), 69.9 (CH_2), 69.7 (CH_2), 64.3 (CH_2), 61.2 (d, J_{C-P}=5.0 Hz, CH_2), 58.2 (CH_3), 15.8 (d, J_{C-P}=6.3 Hz, CH_3). ^{31}P NMR (202 MHz, D_2O, H_3PO_4 in D_2O as external standard) δ=14.2. MS (ESI negative, MeOH/H_2O) *m/z*=1079 (M-3Li+2H)$^-$, 1085 (M-2Li+H)$^-$, 1091 (M−Li)$^-$. Anal. Calcd for $C_{45}H_{60}Li_3O_{24}P_3\cdot 5H_2O$: C, 45.47; H, 5.94. Found: C, 45.26; H, 5.43.

*4.1.8. 7,15,23-Tris(hydroxyethylphosphoryl)-25,26,27-tris(3,6,9-trioxadecyloxy)- 2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene, trilithium salt **2c**.* Yield 90%, mp: >300 °C. ^{1}H NMR (500 MHz, D_2O, TMS in $CDCl_3$ as external standard) δ=7.42 (d, J_{P-H}=12.0 Hz, 6H), 4.91 (d, *J*=12.0 Hz, 6H), 4.64 (d, *J*=12.0 Hz, 6H), 4.15 (br t, 6H), 3.91 (br t, 6H), 3.76–3.72 (m, 12H), 3.71 (m, 6H), 3.62 (m, 6H), 3.50 (m, 6H), 3.37 (s, 9H), 1.07 (t, *J*=7.0 Hz, 9H). ^{13}C NMR (125 MHz, D_2O, TMS in $CDCl_3$ as external standard) δ=157.8 (C_q), 133.3 (d, J_{C-P}=10.1 Hz, C_q), 131.1 (d, J_{C-P}=13.8 Hz, CH), 128.8 (d, J_{C-P}=178.6 Hz, C_q), 73.6 (CH_2), 71.2 (CH_2), 70.3 (CH_2), 69.9 (CH_2), 69.8 (CH_2), 69.7 (CH_2), 68.7

(CH_2), 61.1 (d, J_{C-P}=5.0 Hz, CH_2), 58.1 (CH_3), 15.8 (d, J_{C-P}=6.3 Hz, CH_3). ^{31}P NMR (202 MHz, D_2O, H_3PO_4 in D_2O as external standard) δ=14.4. MS (ESI negative, MeOH/H_2O) m/z 1169 (M-3Li+2H)$^-$, 1175 (M-2Li+H)$^-$, 1181 (M−Li)$^-$. Anal. Calcd for $C_{51}H_{78}Li_3O_{24}P_3\cdot 9H_2O$: C, 45.34; H, 7.16. Found: C, 45.40; H, 6.41.

*4.1.9. 1,3,5-Tris(4-aminobenzyl)benzene (**4**).* A mixture of 1,3,5-tris(4-nitrobenzoyl)benzene **3** (1.00 g, 1.64 mmol, including one molecule of CH_2Cl_2 in the crystal, see Ref. 10), hydrazine monohydrate (3.0 mL) and potassium hydroxide (1.0 g) in diethyleneglycol (30 mL) was heated at 180 °C for 40 h. The reaction mixture was poured onto ice and extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated in vacuo. The product **4** was isolated after chromatography (SiO_2, $CHCl_3$/MeOH=4:1) as a pale yellow solid. Yield 0.410 g (64%); mp: 117–118 °C. ^{1}H NMR (500 MHz, CD_2Cl_2): δ=6.92 (d, J=8.3 Hz, 6H), 6.83 (s, 3H), 6.59 (d, J=8.3 Hz, 6H), 3.75 (s, 6H), 3.6 (br s, 6H). ^{13}C NMR (125 MHz, CD_2Cl_2): δ=145.0 (C_q), 142.4 (C_q), 131.3 (C_q), 129.6 (CH), 127.0 (CH), 115.1 (CH), 41.1 (CH_2). MS (EI) m/z=393 M$^+$. Anal. Calcd for $C_{27}H_{27}N_3\cdot 0.7H_2O$: C, 79.85; H, 7.05; N, 10.35. Found: C, 79.75; H, 6.90; N, 10.06.

*4.1.10. 1,3,5-Tris(4-aminobenzyl)benzene trihydrochloride salt (**1**).* To a solution of 1,3,5-tris(4-aminobenzyl)benzene **4** (0.41 g, 1.04 mmol) in MeOH (10 mL), 1 mL of concd HCl was added. The solvent was evaporated in vacuo and the product **1** was obtained as a white solid. Yield 0.51 g (98%). Mp: >300 °C. ^{1}H NMR (500 MHz, D_2O, TMS in $CDCl_3$ as external standard) δ=7.36 (d, J=8.5 Hz, 6H), 7.31 (d, J=8.5 Hz, 6H), 7.03 (s, 3H), 3.92 (s, 6H). ^{13}C NMR (125 MHz, D_2O, TMS in $CDCl_3$ as external standard): δ=142.7 (C_q), 142.2 (C_q), 130.3 (CH), 127.9 (C_q), 127.2 (CH), 123.1 (CH), 40.4 (CH_2). MS (ESI positive, MeOH/H_2O) m/z=394 (M-3Cl$^-$−2H$^+$)$^+$. Anal. Calcd for $C_{27}H_{30}Cl_3N_3\cdot 0.5H_2O$: C, 63.35; H, 6.10; N, 8.21. Found: C, 62.97; H, 5.96; N, 8.28.

4.2. Formation of capsules 1·2a, 1·2b, and 1·2c

Capsules **1**·**2a**–**1**·**2c** were prepared in situ by mixing equimolar solutions of **1** and **2a**–**c** in D_2O. *Capsule* **1**·**2a** (0.25 mM in D_2O): ^{1}H NMR (500 MHz, D_2O, TMS in $CDCl_3$ as external standard): δ=7.54 (d, J=12.0 Hz, 6H), 7.14 (d, J=8.0 Hz, 6H), 6.88 (s, 3H), 6.72 (br s, 6H), 5.31 (d, J=10.0 Hz, 6H), 5.08 (s, 6H), 4.55 (d, J=10.0 Hz, 6H), 4.33 (d, J=7.0 Hz, 6H), 3.83 (s, 6H), 3.25 (m, 6H), 1.36 (t, J=7.0 Hz, 9H), 0.66 (t, J=7.0 Hz, 9H). ^{31}P NMR (202 MHz, D_2O, H_3PO_4 in D_2O as external standard): δ=13.5. *Capsule* **1**·**2a** (2 mM in CD_3OD): ^{1}H NMR (500 MHz, CD_3OD, TMS in $CDCl_3$ as external standard): δ=8.25 (d, J=12.2 Hz, 6H), 7.76 (d, J=8.0 Hz, 6H), 7.51 (s, 3H), 7.5 (br, 6H), 5.95 (d, J=10.9 Hz, 6H), 5.64 (s, 6H), 5.21 (d, J=10.9 Hz, 6H), 5.51 (q, J=7.2 Hz, 6H), 4.53 (s, 6H), 4.21 (m, 6H), 2.07 (t, J=7.2 Hz, 9H), 1.63 (t, J=7.0 Hz, 9H). *Capsule* **1**·**2b** (2 mM in D_2O): ^{1}H NMR (500 MHz, D_2O, TMS in $CDCl_3$ as external standard): δ=7.55 (d, J_{P-H}=12.0 Hz, 6H), 7.12 (d, J=8.0 Hz, 6H), 6.86 (s, 3H), 6.72 (br s, 6H), 5.32 (d, J=10.0 Hz, 6H), 5.13 (s, 6H), 4.54 (d, J=10.0 Hz, 6H), 4.42 (br s, 6H), 3.79 (s, 6H), 3.78 (br s, 6H), 3.43 (s, 9H), 3.20 (m, 6H), 0.58 (t, J=7.0 Hz, 9H). ^{13}C NMR (125 MHz, D_2O, TMS in $CDCl_3$ as external standard): δ=170.8 (C_q), 158.5 (C_q), 142.2 (C_q), 141.7 (C_q), 135.7 (d, J_{P-C}=10.0 Hz, CH), 130.19 (C_q), 130.18 (d, J_{P-C}=179.9 Hz, C_q), 130.05 (CH), 128.0 (C_q), 127.1 (CH), 122.3 (CH), 70.6 (CH, 2C), 69.8 (CH_2), 64.4 (CH_2), 60.9 (d, J_{P-C}=5.0 Hz, CH_2), 58.2 (CH_3), 40.4 (CH_2), 15.4 (d, J_{P-C}=6.3 Hz, CH_3). ^{31}P NMR (202 MHz, D_2O, H_3PO_4 in D_2O as external standard): δ=13.2. *Capsule* **1**·**2b** (2 mM in CD_3OD): ^{1}H NMR (500 MHz, CD_3OD, TMS in $CDCl_3$ as external standard): δ=8.26 (d, J=12.2 Hz, 6H), 7.76 (d, J=8.2 Hz, 6H), 7.51 (s, 3H), 7.48 (br, 6H), 5.97 (d, J=10.8 Hz, 6H), 5.68 (s, 6H), 5.20 (d, J=10.8 Hz, 6H), 5.11 (m, 6H), 4.40 (s, 6H), 4.19 (m, 6H), 4.13 (s, 9H), 1.62 (t, J=7.0 Hz, 9H). *Capsule* **1**·**2c** (3 mM in D_2O): ^{1}H NMR (500 MHz, D_2O, TMS in $CDCl_3$ as external standard): δ=7.54 (d, J=12.2 Hz, 6H), 7.08 (d, J=7.0 Hz, 6H), 6.81 (s, 3H), 6.68 (br s, 6H), 5.21 (d, J=9.6 Hz, 6H), 4.62 (br s, 6H), 4.51 (d, J=9.6 Hz, 6H), 3.95 (br s, 6H), 3.75 (s, 6H), 3.70–3.59 (m, 24H), 3.35 (s, 9H), 3.13 (m, 6H), 0.50 (t, J=7.0 Hz, 9H). ^{13}C NMR (125 MHz, D_2O, TMS in $CDCl_3$ as external standard): δ=158.7 (C_q), 142.3 (C_q), 141.7 (C_q), 135.6 (d, J_{P-C}=10.1 Hz, CH), 130.6 (d, J_{P-C}=13.8 Hz, C_q), 130.0 (CH), 129.7 (d, J_{P-C}=178.6 Hz, C_q), 127.7 (C_q), 127.0 (CH), 122.4 (CH), 73.1 (CH_2), 71.2 (CH_2), 70.8 (CH_2), 70.1 (CH_2), 69.9 (CH_2), 69.7 (CH_2), 69.6 (CH_2), 60.8 (d, J_{P-C}=5.0 Hz, CH_2), 58.1 (CH_3), 40.4 (CH_2), 15.3 (d, J_{P-C}=6.3 Hz, CH_3). ^{31}P NMR (202 MHz, D_2O, H_3PO_4 in D_2O as external standard): δ=13.2. *Capsule* **1**·**2c** (2 mM in CD_3OD): ^{1}H NMR (500 MHz, CD_3OD, TMS in $CDCl_3$ as external standard): δ=8.26 (d, J=12.3 Hz, 6H), 7.77 (br s, 6H), 7.50 (s, 3H), 7.5 (br, 6H), 5.89 (d, J=10.0 Hz, 6H), 5.22 (d, J=10.6 Hz, 6H), 5.22 (br s, 6H), 4.59 (m, 6H), 4.53 (br s, 6H), 4.44 (m, 12H), 4.39 (m, 6H), 4.29 (m, 6H), 4.17 (m, 6H), 4.05 (s, 9H), 1.58 (t, J=6.7 Hz, 9H).

4.3. ^{1}H NMR titrations

The ^{1}H NMR titrations of **1** with **2a**, **2b**, and **2c** were measured in CD_3OD at 298 K for solubility reasons in D_2O. The concentration of **1** was kept constant (2.0 mM) and the concentrations of **2a**, **2b**, and **2c** were varied from 0 to 10.0 mM. The chemical shifts of **1**·**2a**, **1**·**2b**, and **1**·**2c**, relative to the chemical shifts of **2a**–**c**, respectively, were calculated and fitted to a 1:1 binding model using a least-squares fitting procedure. The association constant found for capsule **1**·**2a** is $K_{\mathbf{1}\cdot\mathbf{2a}}$=3.0±0.7×10^3 M^{-1}, for **1**·**2b** is $K_{\mathbf{1}\cdot\mathbf{2b}}$=2.5±0.6×10^3 M^{-1}, and for **1**·**2c** is $K_{\mathbf{1}\cdot\mathbf{2c}}$=1.5±0.3×10^3 M^{-1}.

4.4. Jobs plot

Equimolar solutions (10 mM) of **1** and **2** in CD_3OD were prepared and mixed in various ratios. The total concentration of **1** and **2** was kept constant at 4 mM and only the **1**/**2** ratio was varied. ^{1}H NMR spectra of the mixture were recorded, and the chemical shifts of **1** and **2** were analyzed by Job's method.[14]

4.5. DOSY measurements

In the DOSY experiments with the free building blocks (**1**, **2a**–**c**) as well as the capsules (**1**·**2a**–**1**·**2c**), the concentrations of **1**, **2b**–**c**, and **1**·**2b**–**1**·**2c** were kept constant at 1.0 mM (the concentrations of **2a** and **1**·**2a** were kept at 0.25 mM due to lower solubility). ^{1}H DOSY experiments were carried out at 298 K on a Bruker DRX 500 spectrometer equipped with a GREAT 1/10 gradient generator and a 5-mm BBO probe with a z-axis gradient coil. Data were acquired and processed using the Bruker software XWINNMR 3.5. A series of diffusion-ordered spectra were collected on samples using the LEDbp pulse sequence.[15] Pulse-fields were incremented in 50 steps from 2% up to 95% of the maximum gradient strength in a linear ramp. Gradient length was selected between 2.0 and 3.0 ms, with a diffusion time of 100 ms, and an eddy current delay of 5 ms.

4.6. Computional methods

Optimization of **1**·**2a**: starting geometry was constructed via the CAChe WorkSystem Pro Version 5.02 and optimized using the PM6 Hamiltonian Ref. [16] in water (COSMO method) via the semi-empirical MOPAC2009 software (Stewart Computational Chemistry). Optimization for DOSY analysis: the structures of capsules (**1**·**2a**–**1**·**2c**) and free building blocks (**1**, **2a**–**c**) were optimized by the MM2 force field via the CAChe WorkSystem Pro Version 5.02 and the molecular volumes were estimated using HyperChem 7.52.

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Supplementary data

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