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Hinged Molecular Capsules: Synthesis and Conformational Control via Temperature, pH, or Solvent Composition

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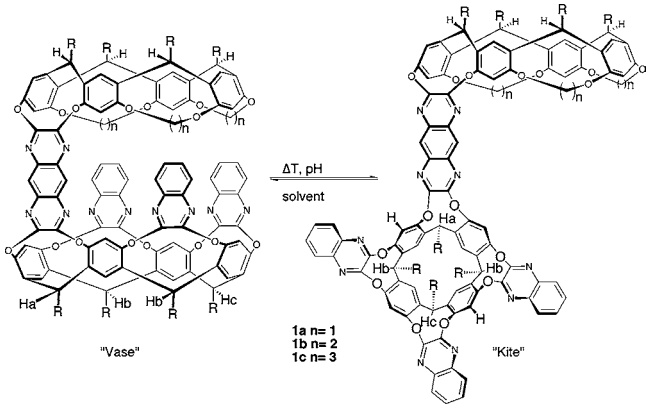

Three new covalently linked molecular capsules were synthesized from their resorcinarene cavitand precursors in good yields. The capsules undergo reversible conformational switching between the closed "vase" form and the open "kite" form upon temperature or pH variation. The kite conformation obtained via either method in $CDCl_3$ switches to vase conformation upon addition of polar solvents such as acetone-d_6 or THF-d_8.

Molecular capsules possessing enclosed cavities that can entrap smaller molecules are fascinating to chemists.[1,2] Potential applications for these and structurally related container molecules include use as molecular devices and microreaction vessels;[3] in separation technologies;[4] and as mimics of enzyme−substrate interactions.[5] Formation of capsules has been reported to involve reversible homo-dimerization of functionalized cavitands in nonpolar solvents, either through hydrogen bonds as in the elegant work of Rebek and others,[6] metal−ligand linkages,[7] or by using intermolecular linkers, such as 2-aminopyrimidine.[8] Few examples, however, exist of covalently assembled capsules that can be reversibly opened and closed under conditions that will not break bonds, including hydrogen bonds.[9]

In this paper, we present the syntheses and conformational studies of a series of "hinged" molecular capsules **1a**−**c**. Their structures are comprised of vaselike cavitands that are covalently "capped" by a second cavitand. The capsules vary in the bridge length within the cavitand "cap" from one to three carbons. This makes the cap progressively shallower, slightly reducing the depth of the capsule cavity as the bridge length increases from **1a** to **1c**[14a] providing overall cavity dimensions of approximately 15 × 8 Å to 14 × 8 Å, respectively. These compounds undergo

[†] Deceased December 29, 2004.

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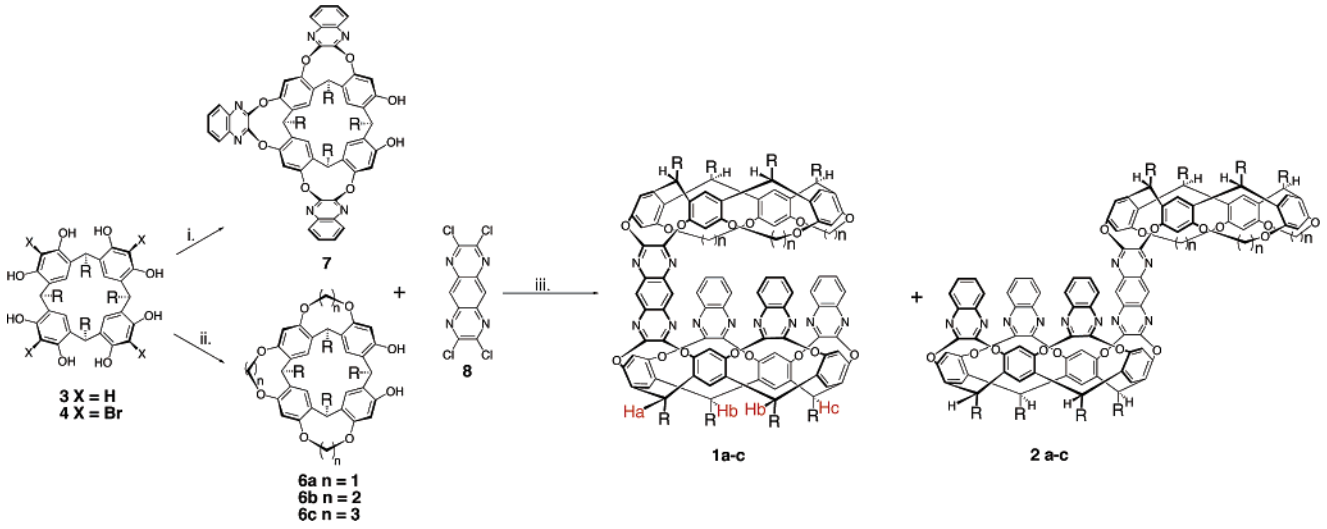
SCHEME 1. Synthesis of Capsules 1a−c and Isomers 2a−c[a]



[a] Key: (i) two steps, ref 15; (ii) **3** to **6a**, one step: K_2CO_3/$NaHCO_3$, $BrCH_2Cl$. **6b** or **6c**, three steps from **3**; (1) NBS/MEK; (2) $(CH_2)_2(OTs)_2$ or $(CH_2)_3(OTs)_2$; (3) *n*-BuLi/THF, then H_3O^+; (iii) CsF, DMF.

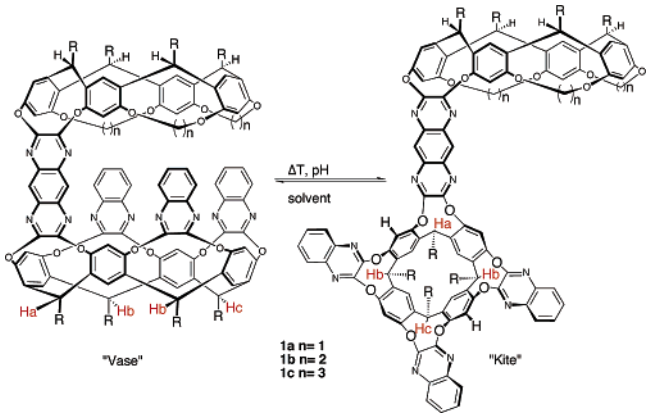


FIGURE 1. Capsule conformational switching. R = *n*-pentyl.

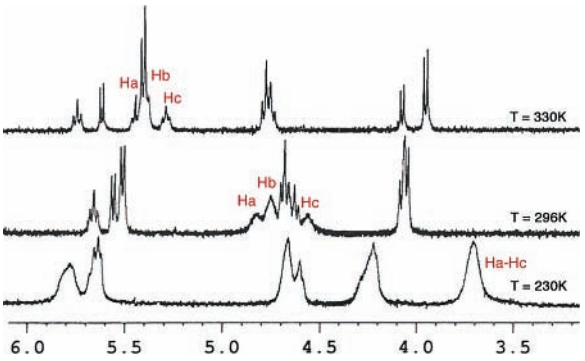


FIGURE 2. Capsule **1a** conformational switching via temperature in $CDCl_3$.

temperature- or acid-induced changes from enclosed capsules to opened conformers, Figure 1. The reverse process to reform the capsule occurs by increasing the temperature or by acid neutralization.[10a,11a] We have also recently observed capsule closure upon addition of polar cosolvents. To our knowledge, no other covalently linked capsules undergo such drastic, reversible opening that can be controlled by thermal, pH, or solvent manipulation.

Capsules **1a−c** and stereoisomers **2a−c** are prepared in yields of up to 30% each in ~1:1 *syn*/*anti* isomeric ratio by linking together the cavitand "cap" **6a−c** and the cavitand "vase" **7** with tetrachlorotetraazaanthracene **8**, Scheme 1.

Trimethylene-bridged cavitand "cap" **6a** and linker **8** were prepared according to literature procedures.[12,13] Direct bridging of resorcinarene **3** using ethylene or propylene ditosylate yielded <3% of either "cap" **6b** or **6c**, respectively. Brominated resorcinarene **4** provided better yields (~25%) of the trialkylidene-bridged **5b** or **5c** (not shown).[14] Debromination of **5b** or **5c** with *n*-butyllithium followed by quenching with H_3O^+ provided cavitand **6b** or **6c** in good yield. Triquinoxaline cavitand "vase" **7** was prepared in 60% yield by excision of a quinoxaline unit from the more readily available tetraquinoxaline cavitand.[10] This method was recently reported by our group[15] and provides cavitand **7** in 48% overall yield from resorcinarene **3**. Cesium fluoride[16] was employed as the base as use of K_2CO_3 resulted in longer reaction times and more side products. Characterization of the *syn* and *anti* isomers was carried out using ^1H and ^{13}C NMR, mass spectrometry, and elemental analysis. A preliminary crystal structure of "*anti*" isomer **2a** presents a vase-shaped quinoxaline cavitand lower half,[17] quite similar to the arrangement observed in crystal structures of tetraquinoxaline cavitands reported by Cram.[10a]

In 300 MHz ^1H NMR conformational studies of capsule **1** in $CDCl_3$, methine protons Ha, Hb, and Hc (see Figure 1 for labels) appeared as a set of three sharp triplets clustered between 5.28 and 5.44 ppm in a 1:2:1 ratio at 330 K, Figure 2. As the temperature was lowered to 230 K, the triplets broadened and shifted upfield with $\Delta\delta = 1.74$ ppm. These large shifts indicate a conformational switch in the capsule from "vase" to "kite", or closed to open, as the temperature was lowered. These results are similar to those reported for the conformational studies of tetraquinoxaline cavitands.[10a,11c] Other protons shifted as well,

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TABLE 1. pH-Induced Chemical Shifts of 1a Methine Protons at 293 K

entry	solvent	δH (ppm) TFA = 0	δH (ppm) TFA = 0.05−1.0 M[a]	Δδ (ppm)
1	$CDCl_3$	4.95 (Ha)	3.78 (Ha)	1.17 (Ha)
		4.83 (Hb)	3.78 (Hb)	1.05 (Hb)
		4.65 (Hc)	3.78 (Hc)	0.87 (Hc)
2	$C_6D_5CD_3$	6.10 (Ha)	3.99 (Ha)	2.11 (Ha)
		5.82 (Hc)	3.99 (Hc)	1.83 (Hc)
		5.81 (Hb)	3.99 (Hb)	1.82 (Hb)
3	C_6D_6	6.08 (Ha)	4.07 (Ha)	2.01 (Ha)
		5.89 (Hc)	3.99 (Hc)	1.90 (Hc)
		5.87 (Hb)	3.97 (Hb)	1.90 (Hb)
4	THF-d_8	5.83 (Ha)	5.83 (Ha)	0.00 (Ha)
		5.75 (Hb)	5.74 (Hb)	0.01 (Hb)
		5.73 (Hc)	5.73 (Hc)	0.00 (Hc)

[a] Shown in order of increasing [TFA]: entry 1, 0.05 M; 2, 0.68 M; 3, 1.0 M; 4, >1.0 M. See Figure 1 for proton labels.

but none as significantly (<0.30 ppm). The capsule did not appear to undergo the conformational switch in toluene-d_8 or THF-d_8 even when cooled below 213 K.[18] Only signal broadening was observed. Lack of solubility prevented low-temperature studies in acetone-d_6, DMSO-d_6, or dioxane-d_8. Benzene-d_6 has a melting point of 6.8 °C, precluding low-temperature studies.

We have also observed "vase" to "kite" switching of capsule **1a** under acidic conditions at 293 K in $CDCl_3$ (Table 1). Addition of trifluoroacetic acid (TFA), 0.05M, caused the methine protons Ha-Hc of **1a** to shift upfield as much as 2.0 ppm. Switching of capsule **1a** was also observed in toluene-d_8 and benzene-d_6, but not in THF-d_8. Higher concentrations of TFA were needed for the conformational switch to occur in the aromatic solvents: 0.68 M for toluene-d_8 and 1.0 M for benzene-d_6. Concentrations of TFA > 1.0 M in THF-d_8 did not induce the switch. This trend suggests better solvation of the interior surfaces of capsule **1a** vase conformation by benzene-d_6 compared to the other solvents. The conformational switch is reversible by addition of base (K_2CO_3 or triethylamine). A similar chemical shift trend is observed in titrations of capsule homologues **1b** and **1c**. These pH- and temperature-induced conformational trends for capsule **1a** parallel those for several uncapped quinoxaline cavitand derivatives reported in Diederich's thorough report.[11c]

Comparison of entry 1 with entries 2 and 3 at [TFA] = 0 in Table 1 suggests capsule **1a** is partially opened in $CDCl_3$ at 293 K compared to toluene-d_8 or benzene-d_6. Heating a solution of capsule **1a** in $CDCl_3$ from 293 to 330 K caused a 0.66 ppm downfield shift and sharpening of protons Ha−Hc from broad signals to triplets signifying further contraction of the quinoxaline bridged half of the capsule (Figure 2). A similar trend was observed by Cram for the chemical shift of the four identical methine protons of tetraquinoxaline cavitands in $CDCl_3/CS_2$.[10a] By comparison, in toluene-d_8 or benzene-d_6, the sharp triplets of Ha−Hc of **1a** shift downfield by less than 0.1 ppm upon heating from 293 to 373 K or 333 K, respectively. We attribute the $CDCl_3$ results to a lower density of this bulkier solvent molecule within the capsule cavity at higher temperatures.

Cram reported that tetraquinoxaline cavitands can be conformationally switched between vase and kite with changes in temperature,[10] while Diederich reported more comprehensively

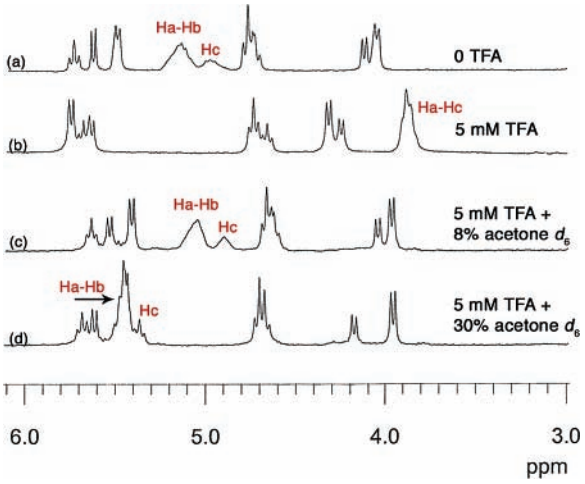

FIGURE 3. Kite-to-vase switch of capsule **1a** in $CDCl_3$ using acetone-d_6 at 293 K.

on the solvent-dependent temperature- and pH-conformational changes of a variety of quinoxaline cavitand based molecules.[11c] Zinc salts as switch effectors have been recently reported.[11d] We report here that addition of the polar solvents acetone-d_6 or THF-d_8 to the kite conformation of capsule **1a** achieved via acidic or low-temperature conditions resulted in the conformational switch to the vase. Thus, when capsule **1a** was opened at 293 K using TFA in $CDCl_3$, the methine protons Ha−Hc between 4.65 and 4.95 ppm shifted upfield to 3.78 ppm (Table 1). Titration with acetone-d_6 (30% v/v) reversed this process and closed the capsule as indicated by the methine protons downfield shift to 5.20−5.30 ppm (Figure 3). A similar trend was observed when the titration was carried out using THF-d_8 (33% v/v).

It appears that addition of polar solvents such as acetone-d_6 or THF-d_8 not only reversed the effects of the acid but also forced the capsule to close more tightly than in $CDCl_3$ alone (Figure 3a,d), similar to the effect of increasing the temperature from 296 to 330 K in $CDCl_3$, vide supra. At low temperatures in $CDCl_3$, the kite conformation of capsule **1a** likewise was switched to vase by the addition of either acetone-d_6 or THF-d_8.

The mechanism of acid-induced vase to kite switching has been described by Diederich as, in part, resulting from the repulsive charges of protonated quinoxaline nitrogens that force the quinoxalines apart.[11a,c] Addition of a polar solvent in the current work likely resulted in competition for coordination to these protons, diminishing the repulsive effect. More importantly, polar solvents do not solvate the aromatic surfaces of capsule **1a** well enough to maintain the kite conformation.[10,11c]

Capsules of molecular dimensions whose conformation is controlled by a variety of methods provide ample opportunity to study their intra- and intermolecular behavior. These studies are underway.

Experimental Section

Hosts 1a (*Syn*) and 2a (*Anti*): General Procedure. Two oven-dried 300 mL round-bottom flasks were used. Flask A was charged with trimethylenediol **6a** (102.6 mg, 0.127 mmol), CsF (367.1 mg, 2.42 mmol), and 100 mL of anhydrous DMF under N_2 atmosphere. The mixture was stirred at 23 °C for 15 min. In flask B, tetrachlorotetraazaanthracene **8** (N4) (43.0 mg, 0.134 mmol) was

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dissolved in 75 mL of anhydrous DMF. Using a cannula, the contents of flask A were added dropwise over 20 min to flask B. After the mixture was stirred at 23 °C for 10 min, the contents of flask B were transferred back to flask A. Triquinoxalinediol **7** in 5 mL of DMF was added in one portion to flask A. After 20 min at 23 °C, the reaction was quenched by pouring it into 500 mL of ice-cold brine. The resulting solid was collected in a Büchner funnel and washed with H_2O followed by methanol. Air-drying yielded 278 mg of crude material as a yellow solid. Separation by flash chromatography over silica gel (3.5 cm × 23 cm column) using a solvent gradient of 80/20 CH_2Cl_2/hexanes + 0−5% EtOAc afforded 94.3 mg (35%) of isomer **2a** ("*Z*") followed by 88.4 mg (33%) of isomer **1a** ("C"). Capsule **1a** was recovered as a yellow solid that was triturated with hot ethyl acetate to afford 77.5 mg (29%) of C-isomer as a white solid mp >360 °C.

Isomer 2a (*"Z"* or *anti*): 35% yield; mp >360 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 296 K) δ 8.41 (s, 2H), 8.17 (s, 2H), 8.14 (s, 2H), 7.97 (d, 2H, J = 8.3 Hz), 7.81 (m, 2H), 7.71 (d, 2H, J = 8.2 Hz), 7.53 (m, 4H), 7.47 (s, 2H), 7.39 (m, 2H), 7.25 (s, 2H), 7.21 (s, 2H), 7.20 (s, 2H), 7.14 (s, 2H), 6.40 (s, 2H), 5.76 (d, J = 7.2 Hz, 2H), 5.74 (t, J = 7.5 Hz, 1H), 5.62 (d, J = 7.2 Hz, 1H), 5.57 (t, J = 7.2 Hz, 3H), 5.51 (t, J = 7.2 Hz, 1H), 4.76 (t, J = 7.5 Hz, 2H), 4.69 (t, J = 7.5 Hz, 1H), 4.32 (d, J = 7.2 Hz, 2H), 4.24 (d, J = 7.2 Hz, 1H), 2.04−2.40 (m, 16H), 1.33−1.49 (m, 48H), 0.80−1.04 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 155.2, 154.9, 154.1, 152.9, 152.8, 152.7, 152.6, 152.5, 152.2, 151.5, 139.8, 139.74 139.71, 139.2, 138.8, 138.7, 137.9, 136.4, 136.0, 135.9, 135.8, 135.7, 129.6, 129.4, 128.0, 127.9, 127.8, 126.4, 123.6, 123.5, 122.7, 120.5, 119.0, 117.0, 116.7, 36.7, 36.5, 34.5, 32.6, 32.5, 32.2, 32.1, 30.3, 30.2, 29.9, 28.0, 27.9, 27.8, 27.7, 23.0, 22.9, 14.3; HRMS (MALDI) MH^+ $C_{133}H_{133}N_{10}O_{16}$, found 2125.9844, calcd 2125.9896 (error −2.4 ppm).

Isomer 1a ("C", capsule): 29% yield; mp >360 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 330 K) δ 8.45 (s, 2H), 8.00 (s, 2H), 7.98 (s, 2H), 7.81 (2H), 7.79 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 7.37 (s, 2H), 7.32 (s, 2H), 7.22 (s, 2H), 7.19 (s, 2H), 7.18 (s, 2H), 6.71 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 6.8 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 7.2 Hz, 1H), 6.36 (s, 2H), 5.74 (t, J = 8.0 Hz, 1H), 5.61 (d, J = 6.8 Hz, 1H), 5.43 (brt, 1H), 5.39 (m, 4H), 4.76 (t, J = 7.6 Hz, 2H), 4.74 (t, J = 8.0 Hz, 1H), 4.06 (d, J = 7.2 Hz, 1H), 3.94 (d, J = 7.2 Hz, 2H), 2.58−2.20 (m, 16H), 1.56−1.33 (m, 48H), 1.03−0.88 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 155.0, 154.9, 154.0, 152.9, 152.8, 152.7, 152.3, 152.0, 151.5, 151.1, 139.7, 139.6, 139.5, 139.4, 139.0, 138.9, 138.7, 138.0, 135.8, 134.9, 134.7, 134.5, 134.1, 129.5, 128.84, 128.8, 128.0, 126.1, 123.9, 123.8, 122.7, 120.6, 117.3, 116.8, 116.5, 99.6, 36.7, 36.4, 32.5, 32.2, 32.0, 30.4, 30.3, 30.1, 27.8, 27.7, 27.4, 23.0, 22.9, 22.8, 14.3, 14.2; HRMS (MALDI) MH^+ $C_{133}H_{133}N_{10}O_{16}$, found 2125.9791; calcd 2125.9896 (error: −4.9 ppm).

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Supporting Information Available: Experimental details for the syntheses of capsules **1a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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