

## Kinetics and Thermodynamics of Hexameric Capsule Formation

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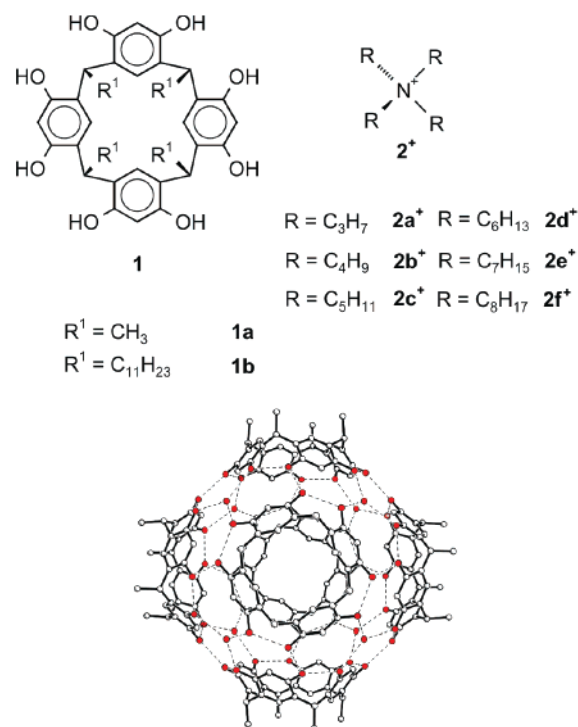
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**Abstract:** Resorcinarene **1b** forms a hexameric assembly in water-saturated CDCl<sub>3</sub> that encapsulates one tetraalkylammonium salt (**2<sup>+</sup>Br<sup>-</sup>**). The remaining space is occupied by coencapsulated solvent molecules. A maximum of three and minimum of one CHCl<sub>3</sub> molecule were found inside of capsules with tetrapropyl- and tetraheptylammonium bromide, respectively. The encapsulation of the salt is endothermic and entropically favored by the liberation of the solvent molecules. The stabilities of the encapsulation complexes and the rates of guest exchange decrease for larger cations. The higher activation barriers for in/out exchange of the larger guests suggest tight conformational restraints in the transition state. It is likely that complete dissociation of one resorcinarene molecule is necessary for the exchange of the alkylammonium salts.

### Introduction

Reversible encapsulation in solution creates complexes of molecular guests within supramolecular hosts.<sup>1</sup> The capsules are held together by multiple, weak intermolecular forces and form through the process of self-assembly. Those held together with hydrogen bonds are mostly dimeric, but a few tetrameric capsules are known.<sup>2</sup> The most complex and, improbably, the most accessible host capsule is derived from the commercially available resorcinarene (Figure 1). It assembles into a solvent-filled hexamer on mere dissolution of the monomer in wet organic solvents. The structure in solution was deduced by NMR methods<sup>3</sup> but owes much to the spectacular solid-state structure determined earlier by MacGillivray and Atwood.<sup>4</sup> The six resorcinarenes make up the sides of a notional cube, and water molecules are positioned at each of its eight corners. Solvent molecules within the capsule can be displaced by sizable quaternary ammonium salts,<sup>5</sup> and this research was undertaken to examine this substitution reaction. We report here progress on the dynamics and thermodynamics of guests exchange and propose mechanisms for the exchange processes.

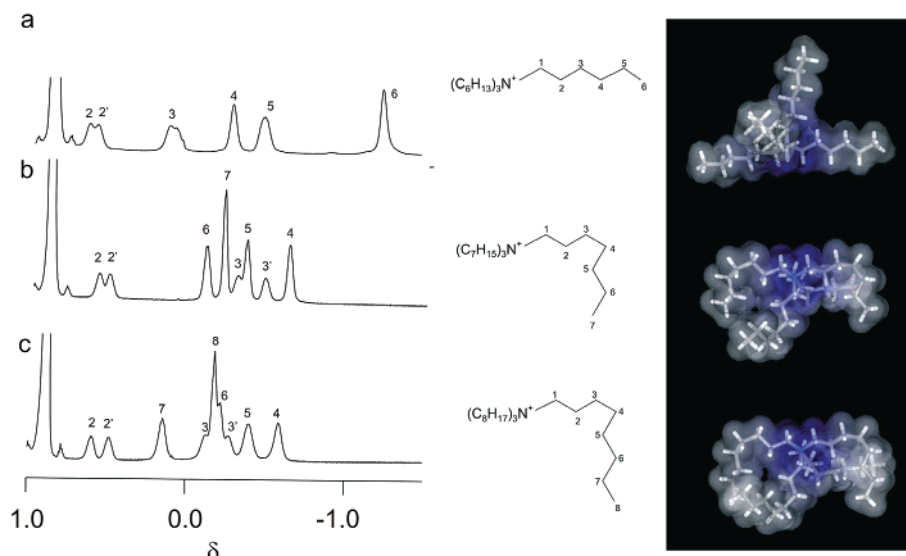
Capsules provide *mechanical barriers* between guests and the bulk solution; guest release requires rupture of multiple



**Figure 1.** Top: Resorcinarenes **1** and tetraalkylammonium cations **2<sup>+</sup>**. Bottom: Crystal structure of hexamer **1<sub>6</sub>·8H<sub>2</sub>O** in a ball and stick representation.<sup>4</sup>

hydrogen bonds to create a suitable opening. At ambient temperatures, this process is slow on the NMR time scale for most encapsulation complexes. Kinetic studies using EXSY spectroscopy have determined the guest exchange rates and provided a range of mechanisms. The release of benzene from the cavity of hydrogen-bonded calix[4]arene tetraurea dimer appears to require the complete dissociation of the capsule.<sup>6</sup>

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**Figure 2.** Left:  $^1\text{H}$  NMR spectra of the cations encapsulated in the resorcinarene hexamer ( $\text{CHCl}_3$ , 600 MHz,  $[\mathbf{1b}] = 12$  mM, 323 K). Middle: Numbering scheme of the cations. Right: Optimized structures of the cations encapsulated in the hexamer. Key: (a)  $\mathbf{1b} + 0.5 \mathbf{2d}^+\text{Br}^-$ ; (b)  $\mathbf{1b} + \mathbf{2e}^+\text{Br}^-$ ; (c)  $\mathbf{1b} + \mathbf{2f}^+\text{Br}^-$ .

For the dimeric tennis balls,<sup>7</sup> softballs,<sup>8</sup> and a cylindrical capsule,<sup>9</sup> guest exchange is *faster* than dissociation of the subunits and occurs through openings formed by partial disruption of the hydrogen-bonding seam. For a tetrameric glycoluril capsule, guest exchange involves partial dissociation of the assembly.<sup>10</sup> As we describe below, the size and shape of the guest determine the barriers to exchange through a similar partial dissociation of the hexamer at hand.

## Results and Discussion

**Solvent Molecules Coencapsulated with the Guest.** In water-saturated  $\text{CHCl}_3$ ,  $\mathbf{1b}$  forms a hexameric capsule, in which six solvent molecules occupy its enormous ( $1375 \text{ \AA}^3$ ) cavity. The addition of 0.5–1 equiv of tetraalkylammonium salts  $\mathbf{2}^+\text{Br}^- \cdot \mathbf{1b}_6$  in which both the cation and the anion<sup>5</sup> share the space with solvent molecules. The in/out exchange of both cation and  $\text{CHCl}_3$  molecules is slow on the NMR time scale at ambient temperatures. The signals of encapsulated  $\text{CHCl}_3$  molecules were assigned by 1D GOESY spectroscopy. The integration of the spectra revealed that the number of these solvent molecules depends on the size of the coencapsulated cation: Tetrapropyl- and tetrabutylammonium bromides share the cavity with three and tetrapentyl- and tetrahexylammonium bromides room with two, but tetraheptyl- and tetraoctylammonium bromides leave enough space for only one  $\text{CHCl}_3$  molecule. The induced chemical shift for the signal of  $\text{CHCl}_3$  ( $\Delta\delta$ ) is about  $-3.0$  ppm and does not depend very much on the size of the coencapsulated tetraalkylammonium cation. This indicates a longer average distance between solvent molecules and the shielding regions of the resorcinol rings when compared to the more tightly packed, dimeric cavitand capsules ( $\Delta\delta = -4.3$  ppm).<sup>11</sup>

**Table 1.** Induced Upfield Shifts for the Methyl Protons, Volumes of  $\mathbf{2}^+\text{Br}^-$ , and Linear Dimensions of  $\mathbf{2}^+$  in the All-Staggered Conformation

guests	$\Delta\delta$ (Me)	$V(\text{\AA}^3)$	PC
$6\text{CHCl}_3$		$6 \times 75 = 450$	0.33
$\mathbf{2a}^+\text{Br}^- + 3\text{CHCl}_3$	-1.36	$223 + 32 + 3 \times 75 = 480$	0.35
$\mathbf{2b}^+\text{Br}^- + 3\text{CHCl}_3$	-1.28	$286 + 32 + 3 \times 75 = 543$	0.39
$\mathbf{2c}^+\text{Br}^- + 2\text{CHCl}_3$	-1.92	$351 + 32 + 2 \times 75 = 533$	0.39
$\mathbf{2d}^+\text{Br}^- + 2\text{CHCl}_3$	-2.20	$416 + 32 + 2 \times 75 = 598$	0.43
$\mathbf{2e}^+\text{Br}^- + \text{CHCl}_3$	-1.12	$482 + 32 + 75 = 589$	0.42
$\mathbf{2f}^+\text{Br}^- + \text{CHCl}_3$	-1.07	$551 + 32 + 75 = 658$	0.48

**Alkyl Groups Adapt to Encapsulation by Changes in Shape.** The C–H resonances of the encapsulated cation experience the shielding effect of the resorcinol rings of the host such that the upfield shifts of their methyl protons steadily increase as the length of the aliphatic chains increase from propyl to hexyl (Table 1). Encapsulated cations  $\mathbf{2a}^+ - \mathbf{2d}^+$  adopt mostly staggered conformations (Figure 2a, middle and right) since the COSY spectra reveal a steady increase of induced chemical shift along the aliphatic chain (Figure 2a, left). In contrast, the most upfield shifted signals of tetraheptyl  $\mathbf{2e}^+$  and tetraoctylammonium  $\mathbf{2f}^+$  cations correspond to the resonances of the fourth methylene groups from the  $\text{N}^+$  (Figure 2b,c, left), while the methyl groups experience much less shielding. The protons of the third and fifth methylene groups become diastereotopic, indicating that buckling of the heptyl and octyl chains occurs. Molecular mechanics calculations also indicate that the alkyl chains of  $\mathbf{2e}^+$  and  $\mathbf{2f}^+$  bend at the fourth methylene group for the cation to fit into the cavity (Figure 2b,c, middle and right). Two gauche conformations along the 3–4 and 4–5 bonds are most probably responsible for the large difference in chemical shift of the diastereotopic hydrogens of the third methylene groups.<sup>12</sup> These gauche interactions represent the price of encapsulating larger ions.

**Larger Guests Form Less Stable Encapsulation Complexes.** Capsules  $\mathbf{2d}^+ - \mathbf{2f}^+\text{Br}^- \cdot \mathbf{b}_6$  coexist with the original  $\text{CHCl}_3$ -

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**Table 2.** Thermodynamics of Salt-Filled Hexameric Capsules: Apparent Equilibrium Constant between Salt-Filled and Solvent-Filled Capsules ( $K$ ,  $M^{-1}$ ) and Corresponding Values of Free Enthalpy ( $\Delta G_0$ , kcal/mol), Enthalpy ( $\Delta H_0$ , kcal/mol), and Entropy ( $\Delta S_0$ , cal/mol)

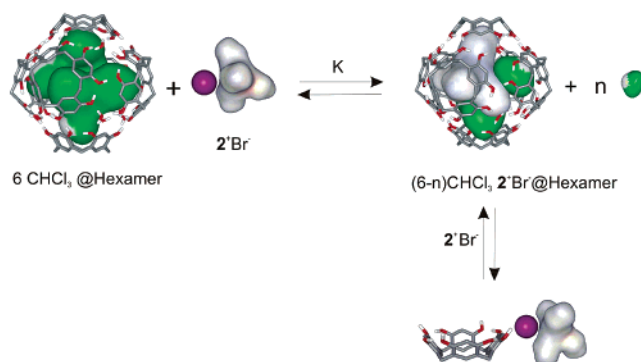
guest	$T$ (K)	$K^a$	$\Delta G_0^b$	$\Delta H_0^c$	$\Delta S_0^c$
$2d^+Br^-$	323	1237	-4.6	11.4	49.4
$2e^+Br^-$	323	452	-3.9	8.4	38.2
$2e^+Cl^-$	323	1687	-4.8	12.5	53.3
$2f^+Br^-$	323	157	-3.25	5.8	28.0

<sup>a</sup>  $K = [\text{hex-salt}]/[\text{hex-CHCl}_3][\text{salt}]$ . <sup>b</sup>  $\Delta G_0 = -RT \ln K$ . <sup>c</sup>  $\Delta G_0 = \Delta H_0 - T\Delta S_0$ .

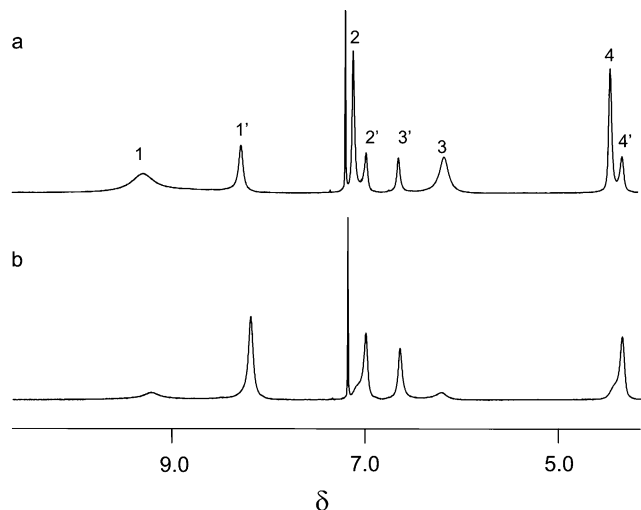
filled capsule and free salt at  $[\mathbf{1b}]/[2^+Br^-] = 6$ . Two sets of signals were observed at this ratio for the aromatic CH and OH protons of the resorcinarene. The new set of signals increased upon further addition of the salt at the expense of the original set of the  $CHCl_3$ -filled hexamer. The equilibrium constants of this exchange at 323 K are  $\sim 1200$ , 450, and  $150 M^{-1}$  for  $2d^+Br^-$ ,  $2e^+Br^-$ , and  $2f^+Br^-$ , respectively. Linear van't Hoff plots (see Supporting Information) reveal that encapsulation of these salts is *endothermic* (Table 2). The positive entropy apparently results from the liberation of bound solvent as was encountered with the “softball”.<sup>13</sup> The entropy gain decreases for larger cations, even though more solvent molecules are released. It is not obvious why this should be so. We propose that it results from the bending of the alkyl chains and reduced mobility of the cation in the cramped space of the capsule. The cost of this folding is expected to be 0.5–0.6 kcal/mol of each gauche interaction in the liquid state.<sup>14</sup> The endothermic effect may also reflect weaker host–guest interactions with the smaller ions that gradually increase with the larger cations. All attempts to investigate the encapsulation of alkylammonium salts by ITC failed to give reproducible results, most probably because of too slow exchange rates (see below).

**Anion-Dependent Stabilities of the Complexes.** For example,  $2e^+Cl^-$  binds about four times better than  $2e^+Br^-$ . This stabilization is entirely entropic (Table 2), but its source remains unclear. The equilibrium constant for  $2a^+Br^-$  and  $2b^+Br^-$  could not be determined since only the hexameric complex was detected at  $[\mathbf{1b}]/[\text{salt}] = 6$ . Competition experiments revealed that  $2a^+Br^-$  is at least 10 times better as a guest than  $2b^+Br^-$  whereas  $2b^+Br^-$  binds 4 times better than  $2c^+Br^-$ . Mixing of  $2d^+Br^-$  and  $2e^+Br^-$  in a 1:1 molar ratio gives the corresponding hexameric complexes in a 4:1 ratio, in good agreement with the ratio predicted by their stability constants (Table 2).

In solution, the optimal packing coefficient (PC) of neutral guests in capsules is 0.55,<sup>15</sup> which is a value typical for most nonassociated neat liquids. Much higher PC's have been found for encapsulation complexes of polar tetraalkylammonium and tropylium cations that are capable of C–H--- $\pi$  and charge-transfer interactions with aromatic rings of the capsule.<sup>16</sup> In contrast,  $CHCl_3$  included in the resorcinarene hexamer is more dilute than bulk  $CHCl_3$  (PC 0.33 and 0.5, respectively). Inclusion of  $2^+Br^-$  increases the PC up to 0.48 (Table 1) but with reduced



**Figure 3.** Equilibria of hexameric encapsulation complexes:  $n = 3$  for  $2a,bBr^-$ ;  $n = 4$  for  $2c,d^+Br^-$ ;  $n = 5$  for  $2e-f^+Br^-$ .



**Figure 4.**  $^1H$  NMR spectra of  $\mathbf{1b} + 4 \mathbf{2b}^+Br^-$  (600 MHz,  $[\mathbf{1b}] = 12$  mM,  $CDCl_3$ ): (a) at 303 K; (b) at 323 K. Signals of hexameric capsule: OH protons (1); protons of the resorcinol rings (2 and 3); methine protons of the bridges (4). Primed numbers indicate the corresponding protons of the monomeric resorcinarene.

stability. More space available for guests could result in entropic stabilization of the capsular assemblies harboring several species.

**Destruction of Capsules by Halide Ions.** The activation energies for the dissociation of hexameric salt capsules were evaluated through kinetic studies of their “melting” by an excess of the guest. The anion’s competition for hydroxyl groups of resorcinarenes is the likely cause.<sup>5</sup> In the presence of 4 equiv of  $2b^+Br^-$  for each 1 equiv of  $\mathbf{1b}$ , two sets of signals are observed at 303 K for the aromatic protons (Figure 4a): one of them corresponds to the hexameric capsule and the other to the open, monomeric complex (Figure 3, bottom right).<sup>17</sup> At 323 K, the equilibrium is shifted almost entirely to the monomer (Figure 4b) indicating a high  $\Delta S$  value for the dissociation of the hexamer. The complex nature of the equilibria did not allow determination of  $\Delta S$  and  $\Delta H$  values in this case.

The transfer of spin polarization from the hexameric complex of  $2b^+Br^-$  to its monomer occurs with overall rate of  $6.6 s^{-1}$  at 303 K and corresponds to  $\Delta G^\ddagger$  of 16.6 kcal/mol.<sup>18</sup> A similar experiment with encapsulated tetrahexylammonium bromide

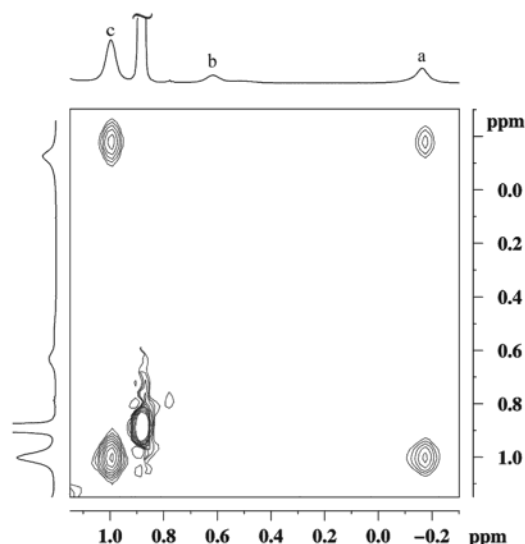
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(17) At  $[2b^+Br^-]/[\mathbf{1b}] = 8$  no signals for the encapsulation complex are found in the NMR spectrum at 303 K. The dynamic NOE studies of the open-ended complex reveal typical hydrodynamics of small molecules (see also ref 3c). The monomeric structure of the melting product was additionally proved by determination of diffusion coefficients through the DOSY NMR technique: Palmer, L.; Shivanyuk, A.; Rebek, J., Jr. Unpublished results.



**Figure 5.** Upfield region of the EXSY spectrum for **1b** + 0.5 **2a**<sup>+</sup>Br<sup>-</sup> (600 MHz, [**1b**] = 12 mM, CDCl<sub>3</sub>, mixing time 0.3 s). Methyl and methylene groups of the encapsulated cation are indicated by a and b, respectively; c is the signal for the methyl resonances of the free salt.

**Table 3.** Pseudo-First-Order Rate Constants for Release and Uptake of the Guest ( $k_{-1}$ ,  $k_1$ , s<sup>-1</sup>),<sup>24</sup> Second-Order Rate Constant of Guest Uptake ( $k_1^* = k_1/[\text{Guest}]$ , s<sup>-1</sup> M<sup>-1</sup>), and Free Activation Enthalpy of Guest Release ( $\Delta G_{-1}^\ddagger$ , kcal/mol) and Uptake ( $\Delta G_1^\ddagger$ , kcal/mol)<sup>a</sup>

guest	T (K)	$k_{-1}$	$k_1$	$k_1^*$	$\Delta G_{-1}^{\ddagger b}$	$\Delta G_1^{\ddagger c}$	[ <b>1b</b> ]/ [guest] <sub>total</sub>
<b>2a</b> <sup>+</sup> Br <sup>-</sup>	303	2.5	6.9	1725	17.2	13.3	2
<b>2a</b> <sup>+</sup> Br <sup>-</sup>	303	2.8	50.4	2191	17.1	13.1	0.5
<b>2a</b> <sup>+</sup> Br <sup>-</sup>	323	17.4	44.0	11000	17.0	13.0	2
<b>2b</b> <sup>+</sup> Br <sup>-</sup>	303	0.25	0.75	187	18.6	14.7	2
<b>2b</b> <sup>+</sup> Br <sup>-</sup>	323	1.7	2.9	727	18.7	14.8	2
<b>2b</b> <sup>+</sup> I <sup>-</sup>	303	0.49	2.7	270	18.2	14.4	1
<b>2b</b> <sup>+</sup> I <sup>-</sup>	303	0.58	8.6	390	18.1	14.2	0.5
<b>2c</b> <sup>+</sup> Br <sup>-</sup>	323	0.06	0.12	30	20.8	16.7	2
<b>2d</b> <sup>+</sup> Br <sup>-</sup>	323	0.08	0.2	50	20.6	16.5	2
<b>2e</b> <sup>+</sup> Br <sup>-</sup>	323	0.04	0.08	20	21.0	17.1	2
Bu <sub>4</sub> SbBr	323	0.02	0.05	2.5	21.6	17.3	2
Bu <sub>4</sub> SbBr	323	0.08	1.15	52	20.6	16.5	0.5

<sup>a</sup> Average values of kinetic parameters determined for different sets of protons are given. The errors did not exceed 10%. <sup>b</sup>  $\Delta G_{-1}^\ddagger = -RT \ln(hk_{-1}/k_B T)$ . <sup>c</sup>  $\Delta G_1^\ddagger = -RT \ln(hk_1^*/k_B T)$ .

gave comparable values of the rate constants and  $\Delta G^\ddagger$ s (10.8 s<sup>-1</sup> and 16.3 kcal/mol, respectively). From the tetrapropylammonium bromide complex, the rate was 36 s<sup>-1</sup> ( $\Delta G^\ddagger = 15.6$  kcal/mol). These values characterize the overall rate of hexamer disappearance, since there are six ways for the formation of the monomer from the hexamer.

**In/Out Exchange Rates Dependent on Guest Size.** The resonances of the encapsulated **2a**<sup>+</sup>Br<sup>-</sup> gave intense EXSY cross-peaks with the signals of the free guest at 303 K (Figure 5). The rate constant and  $\Delta G^\ddagger$  for the release of the encapsulated **2a**<sup>+</sup>Br<sup>-</sup> are 2.5 s<sup>-1</sup> and 17.2 kcal/mol, respectively (Table 3).<sup>19</sup> Decomplexation of **2b**<sup>+</sup>Br<sup>-</sup> is 10 times slower, and correspondingly, the activation barrier is 1.4 kcal/mol higher. Apparently, the larger volume and dimensions of **2b**<sup>+</sup> require more energy for its release from the capsule.

(18) This was determined by EXSY experiment (303 K, mixing time 0.3 s) for the signals of the aromatic protons of **1b** of the hexamer and monomeric complex.

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The exchange rates of **2b**<sup>+</sup> are nearly the same for Br<sup>-</sup> and I<sup>-</sup> salts (Table 3), but the covalent Bu<sub>4</sub>SbBr is released from the cavity 85 times more slowly than the approximately isosteric **2b**<sup>+</sup>Br<sup>-</sup>. The higher polarity of the ionic salt solution appears to make the hexameric capsule less kinetically stable.

The rate constants  $k_{-1}$  are nearly independent of the concentration of the salt, indicating that guest release is, not surprisingly, a unimolecular process. In contrast, the rate constants of guest uptake ( $k_1$ ) showed nearly linear dependence on the concentration of the free salt (Table 3), in keeping with the associative character for this process. To obtain a second-order constant  $k_1^*$  the value of  $k_1$  should be divided by concentration of free salt. The increase of salt concentration results in higher values of  $k_1^*$ . Hydrogen bonding of the external anion and hydroxy groups or extraction of the water molecules from the hexamer could be the cause.<sup>20</sup> Such associations would increase the local concentration of outer salt around the capsule and could facilitate the guest uptake.

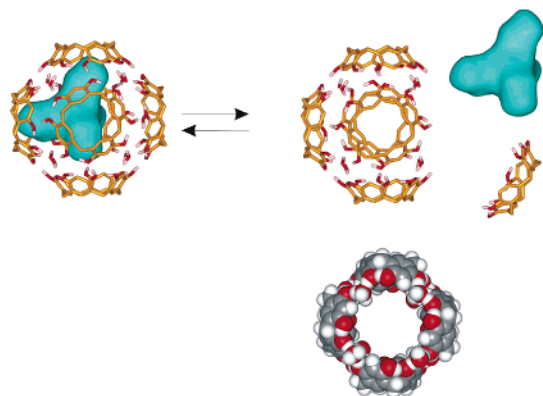
A sharp decrease of the guest exchange rates was observed for larger salts **2c**–**e**<sup>+</sup>Br<sup>-</sup>, and no exchange cross-peaks could be detected at ambient temperature and a mixing time of 0.3 s. At 323 K and a mixing time of 1.0 s, the rate constants of guest release  $k_{-1}$  vary between 0.08 and 0.04, corresponding to an activation barrier of about 21 kcal/mol (Table 3). The guest uptake is also considerably slower for **2c**–**e**<sup>+</sup>Br<sup>-</sup>, when compared to the smaller **2a**,**b**<sup>+</sup>Br<sup>-</sup>. The activation barrier for the entrance of the salt is about 4 kcal/mol higher than the barrier of the release. This value is an estimation for the energy of interaction between the salt and the interior of the capsule.

**Rate-Limiting Step of Guest Exchange Involving Rupture of the Capsule.** Many possibilities exist for the mechanism of guest exchange. Guest release (the rate-limiting step) must contain portals through which the cation can pass, either in its folded or unfolded state. It is unlikely that these portals can be formed without complete dissociation of at least one resorcinarene subunit. Hydrogen bonds can act as hinges, but the curvature of the resorcinarene subunit requires that most of the hydrogen bonds to a subunit must be broken as that unit is folded outward. The simplest mechanism would include dissociation of one resorcinarene to give a pentameric intermediate with one portal (Figure 6). This process should be favored both energetically (a minimum number of hydrogen bonds should be disrupted) and statistically (there are six possibilities for the formation of a pentamer). The activation barrier for the formation of the monomer from hexamer under the melting conditions—15.6–16.6 kcal/mol (see above)—gives a reasonable estimate for the energy cost of one portal formation. The difference between this value and the activation free enthalpy of guest release ( $\Delta G_{-1}^\ddagger$ ) is the estimation of activation barrier for passing the cation through the capsule opening. This increases from 1.6 kcal/mol for **2a**<sup>+</sup> to 4.3 kcal/mol for **2d**<sup>+</sup>, if cations of different size could pass through the same-sized opening.

## Conclusions

The encapsulation of large tetraalkylammonium salts by hexameric capsules is entropically driven by the release of

(20) Recently, Avram and Cohen showed that the diffusion coefficient of outer tetraethylammonium cation depends on the hexamer-to-salt ratio. The higher values at the higher ratio can be explained by the outer capsule salt interaction rather than by the formation of monomeric complex: Avram, L.; Cohen, Y. *Org. Lett.* **2003**, *5*, 1099–1102.



**Figure 6.** Top: Proposed mechanism for guest exchange. Anion and coencapsulated  $\text{CHCl}_3$  molecules are omitted for clarity. Bottom: CPK figure on the bottom showing the size of the portal in the pentameric transition state. Two resorcinarene molecules are omitted to show the size of the opening.

several solvent molecules. The number of coencapsulated molecules decreases with the increase of the cation size and permits control of the reversible encapsulation of the solvent. Dissociation of one resorcinarene molecule from the hexamer is required for guest exchange. The activation barrier becomes higher for larger cations, indicating some steric conflicts between host and guest exist in the exchange transition state. As is the case in most mechanistic studies, the investigations here raise more questions than the answers provided. The sheer complexity of the system and the number of molecules involved in each process provides a challenge that will keep us intrigued for some time. We hope that the ready availability of these capsules will encourage others to engage in the study of their behavior.

## Experimental Section

$^1\text{H}$ , 1D GOESY, 2D COSY, and EXSY NMR spectra were recorded on a Bruker DRX 600 (600 MHz) spectrometer using the solvent signals as internal reference. Mixing time of EXSY experiments varied between 0.3 and 1 s. Integrations of EXSY spectra were carried out by XWINNMR Buker software. The rate values were calculated for both methylene and methyl protons of the encapsulated cations. Compound **1** was prepared by a known procedure;<sup>21</sup> all guests were purchased from Aldrich and were used without further purification. The volumes of van der Waals surfaces of the guests were calculated using the Wab Lab Viewer program;<sup>22</sup> the volume of the cavity was calculated by the Swiss Pdb viewer program.<sup>23</sup>

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**Supporting Information Available:** Van't Hoff plots for equilibria of salt- and  $\text{CHCl}_3$ -filled hexamers. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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