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Hexameric Capsules of Lipophilic Pyrogallolarene and Resorcinarene in Solutions as Probed by Diffusion NMR: One Hydroxyl Makes the Difference

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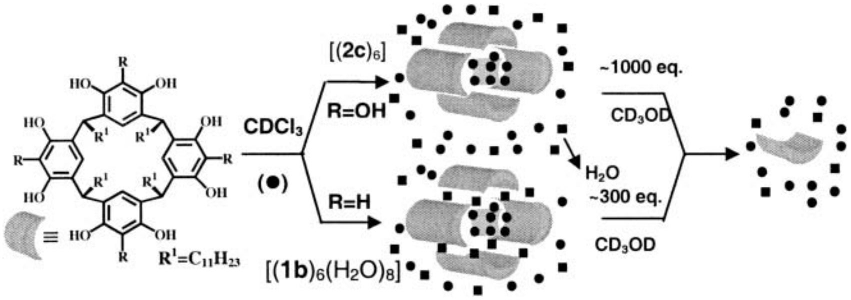
ABSTRACT



NMR diffusion measurements were used to characterize the self-assembled molecular capsule of pyrogallolarene 2c in $CDCl_3$ solutions. The results were compared with the characteristics of the hexameric capsule of 1b. Although both 2c and 1b self-assemble into hexameric capsules, the role of water in these capsules is rather different. It was also found that the capsule of 2c is more stable in polar media than that of 1b.

Hydrogen bonding is an important noncovalent interaction, which has been extensively used to construct supramolecular systems.[1] In recent years, this interaction has been utilized for the preparation of hydrogen-bonded molecular capsules through self-assembly processes.[2,3] Among those hydrogen-bound capsules, calixarene-based molecular capsules have attracted considerable interest.[2−4] Dimeric hydrogen-bonded molecular capsules were prepared first and probed in solution and in the solid state,[4] but it was the seminal paper by the Atwood group in 1997 that probed and launched the research of large-cavity hydrogen-bound molecular capsules based on calixarene scaffold.[5] Atwood and co-workers demonstrated that [*c*]-methyl resorcin[4]arene (**1a**) self-assembles in the solid-state to form a capsule of the $[(\mathbf{1a})_6(H_2O)_8]$-type. It was also argued, on the basis of vapor pressure osmometry, that **1b** maintains the structure of **1a** in a benzene solution.[5] In contrast, it was found that **1c** forms a dimeric capsule with triethylammoniun hydrate.[6a] Subsequently, Shivanyuk and Rebek demonstrated that **1b** forms 6 to 1 hexameric capsules

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[1] (a) Krische, M. J.; Lehn, J.-M. *Struct. Bonding* **2000**, *96*, 3−29. (b) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382−2426.

[2] For general reviews on encapsulation, see: (a) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. (b) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 1488−1508.

[3] For recent reviews concerning hydrogen-bond capsules, see: (a) Rebek, J., Jr. *Chem. Commun.* **2000**, 637−643. (b) Böhmer, V.; Vysotsky, M. O. *Aus. J. Chem.* **2001**, *54*, 671−677.

[4] For few early examples of dimeric hydrogen-bond capsules, see: (a) Shimizu, K. D.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12403−12407. (b) Hamann, B. C.; Shimizu, K. D.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326−1329. (c) Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. *Chem. Commun.* **1996**, 2533−2534. (d) Mogck, O.; Pons, M. Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, *119*, 5706−5712. For few recent examples of hydrogen-bond dimeric capsules, see: (e) Brody, M. S.; Schalley, C. A.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1999**, *38*, 1640−1644. (f) Vysotsky, M. O.; Böhmer, V. *Org. Lett.* **2000**, *2*, 3571−3573. (g) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Angew. Chem. Int. Ed.* **2000**, *39*, 1264−1267. (h) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Chem. Commun.* **2001**, 1890−1891.

[5] MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469−472.

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with specific guests such as tetrahexylammonium bromide and antimony(v) bromide in wet $CDCl_3$ solutions.[6b,c] First, Mattay's group and then Atwood and co-workers demonstrated that the macrocycle **2b** self-assembles in the solid state to form a hexameric capsule of the $[(\mathbf{2b})_6]$-type.[7] It was also stated that, due to these intermolecular interactions, this hexameric capsule, i.e., $[(\mathbf{2b})_6]$, is stable even in highly polar media.[7c]

Recently, we showed, using diffusion NMR,[8] that **1b** indeed self-assembles spontaneously into a hexameric capsule of the $[(\mathbf{1b})_6(H_2O)_8]$-type in water containing $CDCl_3$ solutions without the need for additional guests.[9a] We found, using diffusion NMR, that eight water molecules seem to participate in the construction of the hexameric capsule in solution.[9b] In addition, we showed that the role of water molecules is different in capsules of **1b** formed in the presence and in the absence of tetrahexylammonium bromide.[9c] Philips and Kaifer recently demonstrated that **1b** forms a hexameric capsule with a cobaltocenium cation but not with ferrocene.[10a] As these large molecular capsules are labile multicomponent molecular assemblies, their characterization in solution requires a combination of spectroscopic techniques. Here we present a NMR study, emphasizing diffusion NMR, of the self-assembled molecular capsule of **2c** in $CDCl_3$ solutions concentrating on the differences in structure and characteristics between the self-assembled capsules of the lipophilic resorcinarene **1b** and pyrogallolarene **2c**.

Pyrogallol[4]arene, **2c**, was prepared by the acid-catalyzed condensation of dodecanal with pyrogallol in 95% ethanol at room temperature over a period of 3 h.[11] The spectrum of **2c** in a $CDCl_3$ solution at 298 K is shown in Figure 1a. The diffusion coefficient extracted for **2c** in this solution was $0.26 \pm 0.01 \times 10^{-5}$ cm^2 s^{-1} (3 mM, 298 K). This value is very similar to the diffusion coefficient of **1b** in $CDCl_3$ ($0.28 \pm 0.02 \times 10^{-5}$ cm^2 s^{-1}) (3 mM, 298 K).[9a,b,12]

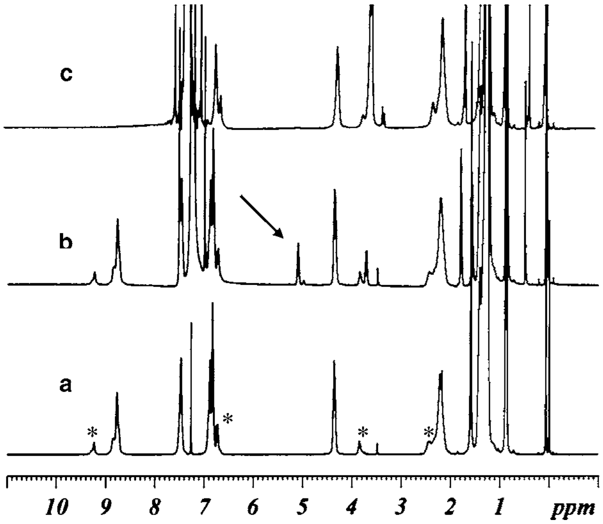
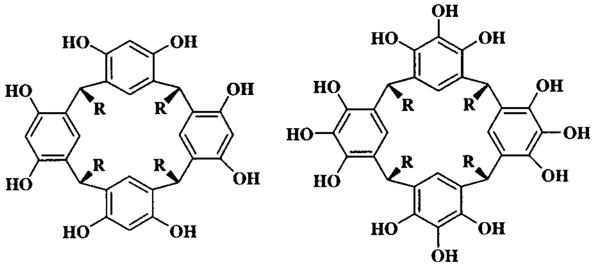


Figure 1. ^1H NMR spectra (400 MHz, 298 K) of (a) **2c** 24.8 mM in $CDCl_3$, (b) **2c** 27.3 mM in $CHCl_3$, and (c) same as b after the addition of ~200 equiv of CD_3OD. The arrow indicates the peak of the encapsulated chloroform molecules. An asterisk (*) indicates signals of the minor isomer of **2c**.

Compounds **1b** and **2c** have very similar structures (Scheme 1) and almost equal molecular weights (1104 and 1168 g/mol, respectively). Since **1b** self-assembles into a hexameric capsule and has the same diffusion coefficient as

Scheme 1



1a R=CH_3
1b R=$C_{11}H_{23}$
1c R=C_2H_5

2a R=CH_3
2b R=isobutyl
2c R= $C_{11}H_{23}$

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(6) (a) Shivanyuk, A.; Rissanen, K.; Kolehmainen, E. *Chem. Commun.* **2000**, 1107−1108. (b) Shivanyuk, A.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7662−7665. (c) Shivanyuk, A.; Rebek, J., Jr. *Chem. Commun.* **2001**, 2424−2425.

(7) (a) Gerkensmeier, T.; Iwanek, W.; Agena, C.; Fröhlich, R.; Kotila, S.; Näther, C.; Mattay, J. *Eur. J. Org. Chem.* **1999**, 2257−2262. (b) Atwood, J. L.; Barbour, L. J.; Jerga, A. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4837−4841. (c) Atwood, J. L.; Barbour, L. J.; Jerga, A. *Chem. Commun.* **2001**, 2376−2377.

(8) (a) Stejskal, E. O.; Tanner, J. E. *J. Chem. Phys.* **1965**, *42*, 288−292. (b) Tanner, J. E. *J. Chem. Phys.* **1970**, *52*, 2523−2526. For a review concerning the application of the PGSE NMR technique, see: Stilbs, P. *Prog. NMR Spectrosc.* **1987**, *19*, 1−45. For a few selected examples for the application of NMR diffusion measurements in supramolecular chemistry, see: (c) Rymdén, R.; Carlfors, J.; Stilbs, P. *J. Incl. Phenom.* **1983**, *1*, 159−167. (d) Mayzel, O.; Cohen, Y. *J. Chem. Soc. Chem. Commun.* **1994**, 1901−1902. (e) Pochapsky, S. S.; Mo, H.; Pochapsky, T. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2513−2514. (f) Gafni, A.; Cohen, Y. *J. Org. Chem.* **1997**, *62*, 121−126. (g) Frish, L.; Matthews, S. E.; Böhmer, V.; Cohen, Y. *J. Chem. Soc., Perkin Trans. 2* **1999**, 669−671. (h) Frish, L.; Sansone, F.; Casnati, A.; Ungaro, R.; Cohen, Y. *J. Org. Chem.* **2000**, *65*, 5026−5030. (i) Avram, L.; Cohen, Y. *J. Org. Chem.* **2002**, *67*, 2639−2644. (j) Otto, W. H.; Keefe, M. H.; Splan, K. E.; Hupp, J. T.; Larive, C. K. *Inorg. Chem.* **2002**, *41*, 6172−6174.

(9) (a) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15148−15149. Subsequently, such a conclusion was reached by the Rebek group; see for example: Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 3432−3433. (b) Avram, L.; Cohen, Y. *Org. Lett.* **2002**, *4*, 4365−4368. (c) Avram, L.; Cohen, Y. *Org. Lett.* **2003**, *5*, 1099−1102.

(10) (a) Philip, I. E.; Kaifer, A. E. *J. Am. Chem. Soc.* **2002**, *124*, 12678−12679. For more hydrogen bond molecular capsules containing charged guests, see for example: (b) Frish, L.; Vysotsky, M. O.; Matthews, S. E.; Böhmer, V.; Cohen, Y. *J. Chem. Soc., Perkin Trans. 2* **2002**, 88−93. (c) Frish, L. Vysotsky, M. O.; Böhmer, V.; Cohen, Y. *Org. Biomol. Chem.* **2003**, *1*, 2011−2014.

(11) Compound **2c** was prepared by a modification of the procedure given in: Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305−1312. The compound was crystallized several times from MeOH affording two stereoisomers in a ratio of about 1:20.

(12) NMR diffusion experiments were performed on a 400 MHz Avance NMR spectrometer (Bruker, Germany) equipped with a Great 1 gradient system using a conventional 5 mm inverse probe and using the stimulated echo sequence[8b] with the following parameters: relaxation delay 2.6 s, echo time 12 ms, diffusion time 62 ms, pulse gradient duration 2 ms. The diffusion gradients were increased incrementally from 0 to 40.2 G/cm in 10 equal steps.

that of **2c** in CDCl$_3$ solutions, it is reasonable to assume that **2c** also forms a similar hexameric capsule. To corroborate this assumption, the following experiments were performed. First, **2c** was dissolved in CHCl$_3$, and the same spectrum was obtained with an additional signal at 5.1 ppm. This peak, which is 2.2 ppm upfield from the "free" CHCl$_3$ and appeared in a chemical shift very similar to that of the CHCl$_3$ molecules encapsulated in the hexameric capsule of **1b**,[9a] was attributed to the encapsulated chloroform molecules (Figure 1b). Indeed, this new peak was found to have the same diffusion coefficient as that of **2c**, within experimental errors, and was found to be $0.23 \pm 0.01 \times 10^{-5}$ cm^2 s^{-1} for a 27 mM solution of **2c**. It should be noted that this is to be expected, as the encapsulated molecules and the molecular capsule diffuse as a single molecular entity.[8g,9a] By integration, we concluded that about 6−7 molecules of CHCl$_3$ fill the cavity of the hexameric capsule at different concentrations. When ~200 equiv of CD$_3$OD were added to the 27 mM chloroform solution of **2c**, the peak of the encapsulated chloroform molecules disappeared (Figure 1c). At this point where there is no increase in the diffusion coefficient of **2c**, the disappearance of the encapsulated CHCl$_3$ peak may originate from the loosened hydrogen bonds, which results in a faster exchange between the two CHCl$_3$ pools.

In addition, we titrated the CDCl$_3$ solution of **2c** with CD$_3$OD and, as a result of this titration, an increase in the diffusion coefficient of the peaks of **2c** was observed after the addition of more than 300 equiv of CD$_3$OD, as depicted in Figure 2. The diffusion coefficients of **2c** increased from $0.27 \pm 0.01 \times 10^{-5}$ cm^2 s^{-1} to $0.45 \pm 0.02 \times 10^{-5}$ cm^2 s^{-1} upon addition of 1000 or more equiv of CD$_3$OD (Figure 2). The numerical values of this titration are given in Table S1 of Supporting Information. This increase in the diffusion coefficient of the signals of **2c** indicates that **2c** forms aggregates in CDCl$_3$. The addition of a polar solvent disrupts the intermolecular hydrogen bonds, thus transforming the hexamer into its monomeric form. In the case of the hexameric capsule of **1b**, under similar experimental conditions, significantly less CD$_3$OD was needed to disrupt the hexamer as shown in Figure 2.

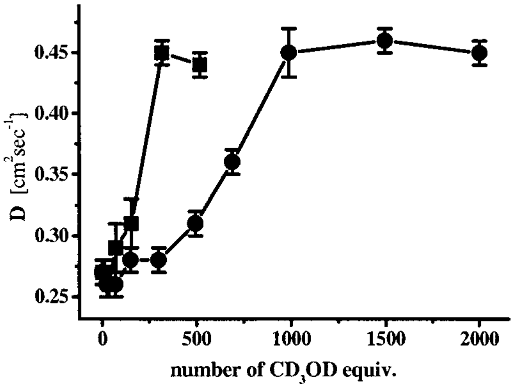

Figure 2. Changes in the diffusion coefficients of **1b** (■) and **2c** (●) (in 3 mM CDCl$_3$ solution, 298 K) as a function of the number of equivalents of CD$_3$OD added per 6 equiv of **1b** and **2c**.

Interestingly, we also found that the ^{13}C{^{1}H} NMR spectrum of **2c** is sensitive to its aggregation mode. Instead of the four signals expected, we found six different signals in the aromatic region of the ^{13}C NMR spectrum of the hexameric capsule of **2c**, indicating that in the hexamer of **2c**, all aromatic carbons in the phenyl ring are not chemically equivalent. Indeed, in a 70:30 CDCl$_3$/CD$_3$OD solution of **2c**, where the monomeric form of **2c** prevails, we found only four signals in the aromatic region of the ^{13}C{^{1}H} NMR spectrum, as expected. For **1b**, we found six signals in the aromatic region of its ^{13}C{^{1}H} NMR spectrum, which also collapsed into the four expected signals after addition of CD$_3$OD. The ^{13}C chemical shifts of the different species are detailed in Supporting Information.

It was stated that **2b** is stable in polar solutions due to a multiple of intermolecular hydrogen bonds that operate cooperatively.[7c] To examine this statement, we titrated the solution of **2c** with DMSO-d_6 and compared the results of this titration with those obtained for **1b**.[9a] Figure 3 shows the changes in the diffusion coefficients of **1b** and **2c** as a function of the addition of DMSO-d_6. It is clear that the two capsules behave differently in the presence of DMSO-d_6. Addition of the first 100 equiv of DMSO-d_6 had nearly no effect on the diffusion coefficient of **2c**, while they did increase the diffusion coefficient of **1b**. It seems that more DMSO-d_6 is needed to disrupt the hydrogen bonds in the case of **2c** than in the case of **1b**, indicating that the hexameric capsule of **2c** is more stable than that of **1b**.

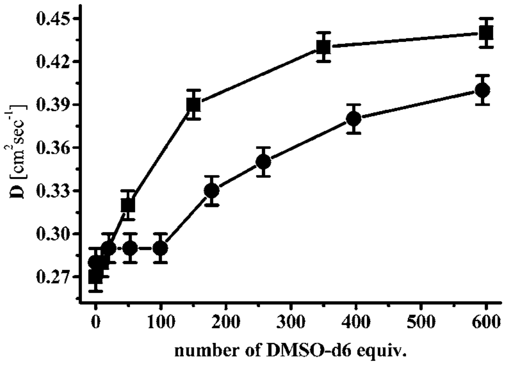

Figure 3. Changes in the diffusion coefficients for the CDCl$_3$ solutions of **1b** (■) and **2c** (●) as a function of the number of equivalents of DMSO-d_6 added per 6 equiv of **1b** or **2c**, respectively.

In addition, the role of the water molecules in the self-assembly of **2c** was examined using diffusion measurements. We prepared CDCl$_3$ solutions of **2c** with different **2c**/H$_2$O ratios. Only one peak of water was observed at all **2c**/H$_2$O ratios, and the chemical shift of the water peak was found at 1.5−1.6 ppm for all these CDCl$_3$ solutions. When we measured the diffusion coefficients of **2c** and water in these CDCl$_3$ solutions, we found nearly no effect of the **2c**/H$_2$O ratio on the diffusion coefficients of the water peak. The extracted diffusion coefficients are tabulated in Table S2 in Supporting Information, and the diffusion coefficients of the water peak and one of the peaks of **2c**, as a function of the **2c**/H_2O ratio, are graphed in Figure 4, superimposed on the same data for **1b**.

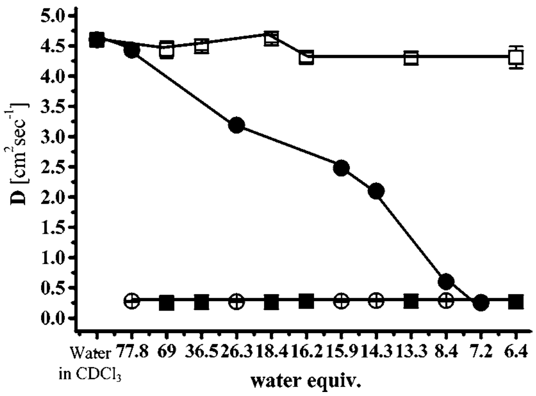

Figure 4. Diffusion coefficients of **1b** (○), **2c** (■), and water in the solution of **1b** (●) and **2c** (□) as a function of the number of water equivalents per 6 equiv of macrocycles.

The diffusion data clearly show that water molecules do not participate in the self-assembly of the hexameric capsule of **2c** in contrast to their role in the hexameric capsule of **1b**, where eight water molecules are needed to form the capsule in the water-saturated $CDCl_3$ solutions.[9b] There, eight water molecules were found to be part of the hydrogen bond network of the hexameric supramolecular systems. For this reason, when there were fewer than eight water molecules per six molecules of **1b**, the diffusion coefficient of the water peak was found to be equal to that of **1b**.[9b] However, for the capsule of **2c**, it seems that the water molecules are not part of the hexameric capsule, and even when the ratio between **2c** and water was 6:6.4, no decrease in the diffusion coefficient of the water peak was observed (Table S2). In fact, the diffusion coefficient of the water peak in the different solutions of **2c** remained the same as that of "free" water in $CDCl_3$, indicating that the water molecules have hardly any interaction with the supramolecular structure of **2c**. These results are in agreement with solid-state findings.[5,7b,c]

We also monitored the rate of exchange of different solvent molecules by monitoring the changes in the encapsulated peaks, as a function of time, for the capsules of **1b** and **2c**. This was achieved by measuring the appearance of the encapsulated peaks after the addition of protonated solvents to the deuterated solution of the capsules or by measuring the disappearance of the encapsulated peaks after dissolving the capsule isolated from the protonated solvents in the respective deuterated solvents. Such experiments were performed on the following pairs of solvents: $CDCl_3/CHCl_3$, C_6D_6/C_6H_6, and C_6D_{12}/C_6H_{12}. The exchange rates, which were found to be fast (on minutes scale) for chloroform and benzene and slow (on hours to days scale) for cylochexane, were found to be not very different for the hexameric capsules of **2c** and **1b**.[13] It was also found that cyclohexane has a higher affinity toward the cavity of **2c** than benzene, while an opposite trend is observed for the molecular capsule of **1b**.

In conclusion, we demonstrated, with the aid of diffusion NMR, that pyrogallolarene **2c** self-assembles spontaneously into a hexameric capsule in chloroform without the aid of water molecules. It was shown that, although **2c** and **1b** have very similar structures, they self-assemble into hexameric capsules that encapsulate several chloroform molecules but differ in several aspects. The hexameric capsule of **2c** is more stable in polar media than the capsule of **1b**. In the case of **2c**, more DMSO (or more CD_3OD) is needed to break the intermolecular hydrogen bonds and to convert the hexamer into a monomer than in the case of **1b**. In addition, for the hexameric capsule of **1b**, the major species in the $CDCl_3$ solution is the $[(\mathbf{1b})_6(H_2O)_8]$-type capsule, while in the hexameric capsule of **2c**, water molecules are not part of the supramolecular structure. We also found that the ^{13}C NMR spectra of these systems do report on their aggregation mode. All the results clearly indicate that the extra hydroxyl group has a dramatic effect on the structure and characteristics of the formed capsules, i.e., one hydroxy group, does make a difference.

Supporting Information Available: Tables S1 and S2, showing the numerical values presented in Figures 2 and 4, respectively, and detailed ^{13}C chemical shifts of **1b**, $(\mathbf{1b})_6(H_2O)_8$, **2c**, and $(\mathbf{2c})_6$. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] A similar trend of exchange rates was previously reported for the dimeric capsule of a tetraurea calix[4]arene derivative: Vysotsky, M. O.; Böhmer, V. *Org. Lett.* **2000**, 2, 3571−3574.