ORGANIC LETTERS

2010
Vol. 12, No. 21
4864−4867

Self-Assembly of a Hexameric Aggregate of a Lipophilic Calix[4]pyrrole−Resorcinarene Hybrid in Solution: A Diffusion NMR Study

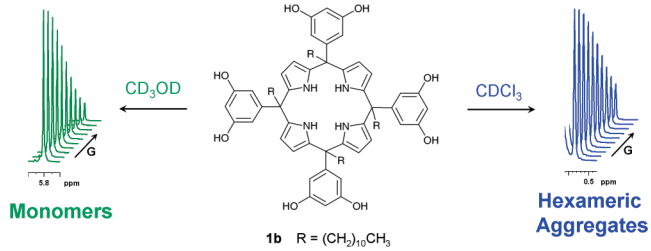
S. Slovak, T. Evan-Salem, and Y. Cohen*

School of Chemistry, The Sackler Faculty of Exact Sciences, Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel

ycohen@post.tau.ac.il

Received August 25, 2010

ABSTRACT



The lipophilic calix[4]pyrrole−resorcinarene hybrid 1b, the extended analogue of resorcin[4]arene 2b, was synthesized for the first time, and its self-assembly in solution was studied using ^{1}H and diffusion NMR. It was found that 1b self-assembles to hexameric aggregates in $CDCl_3$ solution. The interaction of trialkylamine guests with the hexameric aggregate of 1b was explored, and it appears that under the conditions used in the present study these guests interact with the external faces of the hexameric aggregate of 1b.

Hydrogen bond molecular capsules are of much interest in the field of supramolecular chemistry because of their potential to serve as nanoreactors where new chemistry and catalysis may occur.[1] The most extensively investigated molecular capsules based on hydrogen bond interactions are those based on substituted calix[4]arenes,[2] resorcin[4]arenes,[3] and pyrogallol[4]arenes.[4] Indeed, it was found that resorcinarenes form hexameric capsules in the solid state,[3a] in the solution,[3b,c] and even in the gas phase.[3d]

Resorcin[4]arene and pyrogallol[4]arene capsules are able to encapsulate various guests.[3b,4d,e,5] Another derivative of calix[4]arenes is calix[4]pyrrole.[6]

Calix[4]pyrroles are macrocyclic systems composed of four pyrrole rings linked through the meso-positions by carbon atoms. While their synthesis was pioneered by Baeyer

(1) (a) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50–52. (b) Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2004**, *126*, 11408–11409. (c) Giles, M. D.; Liu, S.; Emanuel, R. L.; Gibb, B. C.; Grayson, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 14430–14431.

(2) (a) Shimizu, K. D.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12403–12407. (b) Mogck, O.; Pons, M.; Böhmer, V.; Vogt, W. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *119*, 5706–5712. (c) Frish, L.; Matthews, S. E.; Böhmer, V.; Cohen, Y. *J. Chem. Soc., Perkin Trans. 2* **1999**, 669–671. (d) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 1264–1267. (e) Bogdan, A.; Rudzevich, Y.; Vysotsky, M. O.; Böhmer, V. *Chem. Commun.* **2006**, 2941–2952.

(3) (a) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469–472. (b) Shivanyuk, A.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7662–7665. (c) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15148–15149. (d) Beyeh, N. K.; Kogej, M.; Åhman, A.; Rissanen, K.; Schalley, C. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5214–5218.

(4) (a) Gerkensmeier, T.; Iwanek, W.; Agena, C.; Fröhlich, R.; Kotila, S.; Näther, C.; Mattay, J. *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) Avram, L.; Cohen, Y. *Org. Lett.* **2003**, *5*, 3329–3332. (d) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2003**, *125*, 16180–16181. (e) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2004**, *126*, 11556–11563.

(5) (a) Yamanaka, M.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 2939–2943. (b) Dalgarno, S. J.; Tucker, S. A.; Bassil, D. B.; Atwood, J. L. *Science* **2005**, *309*, 2037–2039. (c) Evan-Salem, T.; Baruch, I.; Avram, L.; Cohen, Y.; Palmer, L. C.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 12296–12300.

10.1021/ol1020114
Published on Web 10/08/2010

more than 100 years ago,[6a] they have attracted much attention in the past decade due to their ability to bind anions,[6b] neutral substrates,[6c] and metal ions.[6d] Very recently, it was demonstrated that tetraurea calix[4]pyrroles form dimeric capsules reminiscent of that of tetraurea calix[4]arenes.[7] The Ballester group recently reported the synthesis and the self-assembly in the solid state of a new α,α,α,α-isomer of the calix[4]-pyrrole−resorcinarene system **1a**.[8] It was found that this sparingly soluble macrocycle self-assembles in the solid state, in the presence of tetramethylammonium chloride guest, into a hexameric structure driven by hydrogen bonding and electrostatic interactions. This study and the resemblance of **1a** to resorcin[4]arene **2a**[3a] prompted us to synthesize compound **1b**, the lipophilic calix[4]pyrrole analogue of resorcin[4]arene **2b**[9] (see Figure 1).

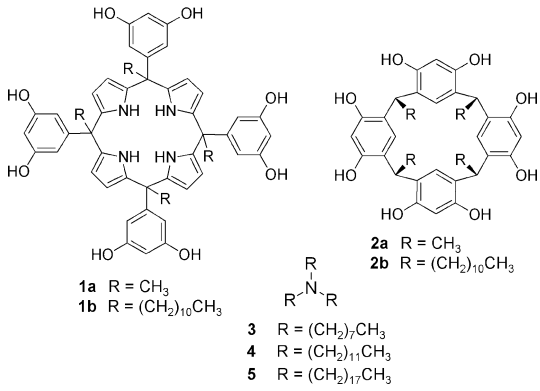


Figure 1. Structures of calix[4]pyrroles **1**, resorcin[4]arenes **2**, trioctylamine (**3**), tridodecylamine (**4**), and trioctadecylamine (**5**).

Compound **1b** was synthesized by the acid-catalyzed condensation of 1-(3,5-dimethoxyphenyl)dodecan-1-one with pyrrole and was isolated as the α,α,α,α-isomer after purification.[10] The ^{1}H NMR spectrum of 10 mM of **1b** in CD_3OD is shown in Figure 2a. The spectrum contains sharp and well-defined peaks of the α,α,α,α-isomer of **1b**. The presence of only three types of protons in the downfield part of the ^{1}H NMR spectrum (δ = 5.80, 6.15, 6.17 ppm) of **1b** suggests that **1b** is locked in the cone conformation or is in fast exchange between different conformations on the ^{1}H NMR time scale.

Compound **1b** was also found to be soluble in $CDCl_3$, and the ^{1}H NMR spectrum of 10 mM **1b** in $CDCl_3$ is shown in Figure 2b. Clearly, a different line shape is observed in $CDCl_3$ as compared to CD_3OD (compare Figure 2b to 2a).

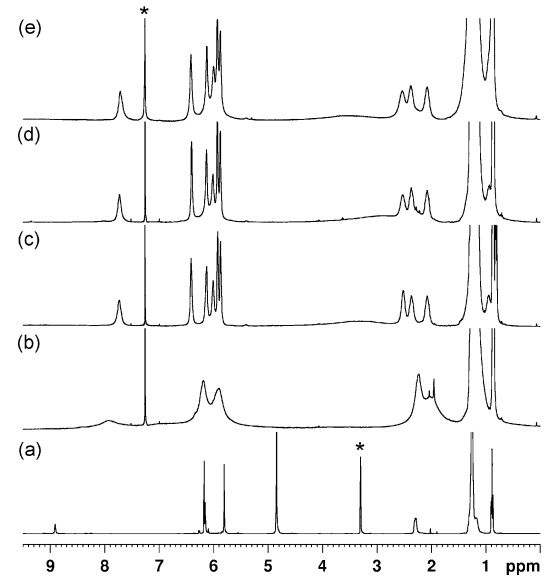


Figure 2. ^{1}H NMR spectra (400 MHz, 298 K) of 10 mM solution of **1b** (a) in CD_3OD, (b) in $CDCl_3$, in the presence of (c) 5 mM **3**, (d) 5 mM **4**, and (e) 5 mM **5** in $CDCl_3$. * indicates residual protonated solvents.

The difference in line shape can be attributed, inter alia, to different conformations that **1b** adopts in different solvents, a different dynamic, or even the formation of not very well-defined aggregates in the $CDCl_3$ solution. It is well-known that calix[4]pyrrole conformation, for example, depends on the polarity of the solvents used. For example, it was found that the 1,3-alternate conformation is the most populated conformation of calix[4]pyrroles in most of the solvents, but the population of the 1,3-alternate conformer was found to decrease as the polarity of the solvent increases.[11] In the presence of small anions, the cone form is the major conformation as a result of anion−π binding between the anion and NHs of calix[4]pyrrole.

To verify which of the options is responsible for the peculiar line shape of **1b** in $CDCl_3$ solution, we reverted to diffusion NMR[12] which has been used for characterization of supramolecular assemblies in solution and was found to be extremely useful in studying both dimeric[2c,13] and hexameric capsules.[3c,4c−e,14] Interestingly, the diffusion coefficient found for the peaks of **1b** in $CDCl_3$ (see Figure 2b) was $0.22 \pm 0.01 \times 10^{-5}$ cm^2 s^{-1}. This diffusion coefficient is somewhat smaller than that found for the

(6) (a) Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2184–2185. (b) Gale, P. A.; Sessler, J. L.; Kral, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141. (c) Gale, P. A.; Sessler, J. L.; Kral, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 12471–12472. (d) Floriani, C. *Chem. Commun.* **1996**, 1257–1263.

(7) Ballester, P.; Gil-Ramirez, G. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 10455–10459.

(8) Gil-Ramirez, G.; Benet-Buchholz, J.; Escudero-Adan, E. C.; Ballester, P. *J. Am. Chem. Soc.* **2007**, *129*, 380–382.

(9) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Wieser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305–1312.

(10) See Supporting Information for the synthesis of **1b**.

(11) (a) Wu, Y.-D.; Wang, D.-F.; Sessler, J. L. *J. Org. Chem.* **2001**, *66*, 3739–3746. (b) Blas, J. R.; López-Bes, J. M.; Márquez, M.; Sessler, J. L.; Luque, F. J.; Orozco, M. *Chem.—Eur. J.* **2007**, *13*, 1108–1116.

(12) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 520–554.

(13) (a) Frish, L.; Vysotsky, M. O.; Matthews, S. E.; Bohmer, V.; Cohen, Y. *J. Chem. Soc., Perkin Trans. 2* **2002**, 88–93. (b) Frish, L.; Vysotsky, M. O.; Bohmer, V.; Cohen, Y. *Org. Biomol. Chem.* **2003**, *1*, 2011–2014.

(14) (a) Avram, L.; Cohen, Y. *Org. Lett.* **2002**, *4*, 4365–4368. (b) Avram, L.; Cohen, Y. *Org. Lett.* **2006**, *8*, 219–212. (c) Avram, L.; Cohen, Y. *Org. Lett.* **2008**, *10*, 1505–1508. (d) Evan-Salem, T.; Cohen, Y. *Chem.—Eur. J.* **2007**, *13*, 7659–7663. (e) Wirtheim, E.; Avram, L.; Cohen, Y. *Tetrahedron.* **2009**, *65*, 7268–7276. (f) Slovak, S.; Avram, L.; Cohen, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 428–431.

hexameric capsule of **2b** at the same concentration in $CDCl_3$ solution ($0.25 \pm 0.01 \times 10^{-5}$ cm^2 s^{-1}). The ^{1}H NMR signal decay as a function of gradient strength (G) of **1b** and of **2b** is presented in Figure S4 (Supporting Information). This finding is to be expected as the molecular weight of **1b** is slightly higher than that of **2b** (molecular weights of 1365 g/mol and 1104 g/mol for the monomers of **1b** and **2b**, respectively). Since it is well-known that **2b** molecules self-assemble into hexameric capsules in $CDCl_3$ solution,[3c,4d] it is reasonable to conclude that **2b** also forms a hexameric assembly. To corroborate this conclusion further, we added increasing amounts of CD_3OD, a solvent which disrupts hydrogen bonding, to the solution of **1b** in $CDCl_3$. The addition of CD_3OD resulted in a significant increase in the diffusion coefficient of **1b** (Figure 3) as in the case of **2b**.[3c,4e]

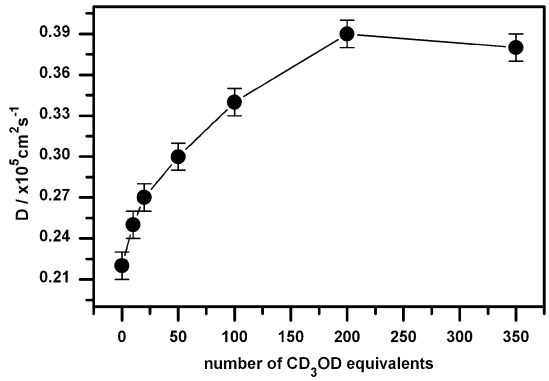


Figure 3. Effect of methanol titration on the diffusion coefficient (D) of **1b** (10 mM) in $CDCl_3$ at 298 K.

At 200 equiv of CD_3OD, a plateau was reached for the diffusion coefficient of **1b** which was found to be $0.39 \pm 0.01 \times 10^{-5}$ cm^2 s^{-1}. These observations are in accordance with the formation of hexameric aggregates of **1b** in chloroform solution which disaggregate upon addition of CD_3OD.

Since **1b** is an extended analogue of **2b**, we assumed that in the case of hexameric capsule formation the cavity of **1b** would be significantly larger than that found for **2b**. Our next step was to explore the relative affinity of **1b** to different long-chain trialkylamine guests such as trioctylamine (**3**), tridodecylamine (**4**), and trioctadecylamine (**5**) (Figure 1). Addition of **3** to the solution of **1b** in $CDCl_3$ resulted in a dramatic change in the ^{1}H NMR spectrum of **1b** (Figure 2c). We found much sharper peaks in the ^{1}H NMR spectrum of **1b** after the addition of **3**. Appearance of five singlets (in a 1:1:1:1:1 ratio) in the region of 5−7 ppm, which were assigned to the aromatic protons of **1b** ($\delta = 5.87$, 5.92, 6.01, 6.13, 6.41 ppm), indicates that a molecular species with a lower symmetry is formed following the addition of **3**. In addition, a small downfield shift was observed for the peaks of compound **3**. Similar spectra were obtained after the addition of **4** or **5** to **1b** (Figure 2d and 2e, respectively). The NOESY spectrum of **1b** in the presence of **3** in $CDCl_3$ solution shown in Figure S5 (Supporting Information) indicates that **1b** is locked in the cone conformation, a conformation needed for the formation of hexameric capsules.

Figure 4 presents the diffusion coefficients of **1b**, **5**, and mixtures of **1b** and **5** in $CDCl_3$ solutions. The diffusion

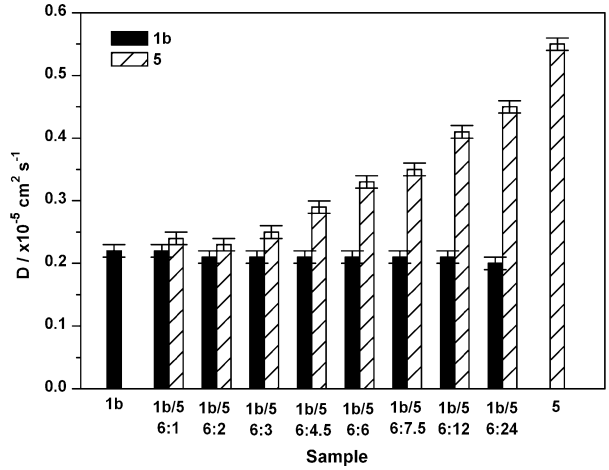


Figure 4. Diffusion coefficients (D) (298 K, $CDCl_3$) of **1b** and **5** in different samples and of mixtures of **1b** and **5** at the indicated ratios. The concentration of **1b** was 10 mM in all samples.

coefficients of **1b** and **5**, for the 6:1, 6:2, and 6:3 solutions of **1b/5**, were $0.22 \pm 0.01 \times 10^{-5}$ and $0.24 \pm 0.01 \times 10^{-5}$ cm^2 s^{-1}, respectively. Interestingly, the diffusion coefficient of **5** was much lower than that found for free **5** in the same $CDCl_3$ solution ($0.55 \pm 0.01 \times 10^{-5}$ cm^2 s^{-1}). These results indicate that **1b** and **5** in that solution diffuse as a single molecular entity. Further addition of **5** to the same solution resulted in an increase in the diffusion coefficient of **5**, which means that the "bound" **5** and "free" **5** molecules are in fast exchange on the NMR time scale. These results suggest that the hexameric structure of **1b** interacts with three molecules of **5**. For **1b** in the presence of **3** or **4**, similar results were observed (see Figure S6 and S7, Supporting Information).

The next step was to determine whether the formed hexameric aggregate of **1b** is indeed a hexameric capsule as in the case of **2b** with other trialkylamines.[4e] It should be noted that in the case of **2b** encapsulated guests are characterized by upfield chemical shifts, slow exchange, and low diffusion coefficient which is identical to that of the host. On one hand, since the guests **3**, **4**, and **5** show only one set of peaks, downfield chemical shifts, and diffusion coefficient which increases with the increase of the guest/host ratio, it is not clear that the formed hexameric aggregate of **1b** is a hexameric capsule as in the case of **2b**. On the other hand, however, **1b** forms hexameric aggregates in which all six monomers are equivalent as in the case of the hexameric capsule of **2b**, and Ballester showed that **1a** forms hexameric capsules in the solid states.[8] Therefore, it seems that the most plausible explanation for all the results presented here is that **1b** self-assembles into hexameric capsules, with relatively leaky faces, to which the trialkylamine guests (**3**, **4**, and **5**)

are attached to the external faces of the hexameric aggregate of **1b**. Such interactions have been documented very recently for the hexameric capsule of **2b** with trialkylamine guests.[15]

To explore the strength of the interaction between **1b** and **4**, for example, we titrated the 6:3 solution of **1b/4** with CD_3OD. The graph showing the changes in the diffusion coefficients of **1b** and of **4** upon the addition of CD_3OD is shown in Figure 5. For **4**, the initial addition of 10−20 equiv

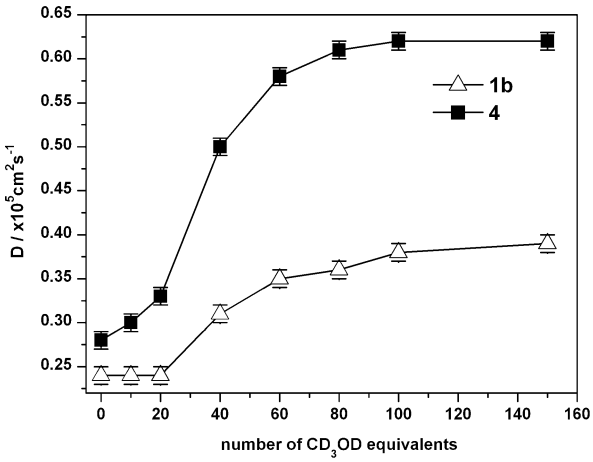


Figure 5. Effect of CD_3OD titration on the diffusion coefficient (D) of **1b** and of **4** in the 6:3 $CDCl_3$ solution of **1b** (10 mM) in the presence of **4** at 298 K.

of CD_3OD resulted in the increase in the diffusion coefficient. Further titration of the solution of **4** with CD_3OD resulted in an increase in the diffusion coefficient until a plateau was reached when 80−100 equiv of CD_3OD was added. For **1b**, the diffusion coefficient, however, remained constant upon the addition of the first 20 equiv of CD_3OD, and here again a plateau was reached after addition of 80−100 equiv of CD_3OD. These results show that the interactions between **4** and **1b** are easily disrupted even when a small amount of CD_3OD is added which does not disaggregate the aggregate of **1b**. These results are similar to the results obtained recently for the hexameric capsule of **2b**.[4e]

To conclude, we prepared, for the first time, a chloroform soluble derivative of a calix[4]pyrrole−resorcin[4]arene hybrid (**1b**), having a structure reminiscent to **2b**. ^{1}H NMR and more specifically diffusion NMR spectroscopy showed that **1b** self-assembles into hexameric aggregates both in the absence and in the presence of trialkylamine guests. These aggregates can be disrupted by addition of polar solvents such as methanol. Addition of trialkylamine (**3**−**5**) resulted in a complex for which the ^{1}H NMR spectrum has a lower symmetry. We found that the guest molecules are in fast exchange between their free and bound states on the NMR time scale. The absence of the high-field peaks of the guest in the ^{1}H NMR spectrum seems to suggest that no guest encapsulation occurred. Due to the recent findings that indicate that **1a** self-assembles into the hexameric capsules in the solid state[8] and the fact that **2b**, the resorcin[4]arene analogue of **1b**, forms hexameric capsules in solution,[3c,4e] we expected **1b** to form extended hexameric capsules in the solution capable of encapsulating extremely large guests. It seems that **1b** forms hexameric capsules and that **3**, **4**, and **5** interact inter alia with the external faces on this relatively leaky hexameric capsule. Further studies with various guests are currently in progress.

Acknowledgment. We gratefully acknowledge the financial support from the Israel Science Foundation (ISF, Grant No. 301/07), Jerusalem, Israel.

Supporting Information Available: Experimental procedure, characterization data, NMR spectra for all new compounds, and diffusion coefficients of **1b**, **3**, and **4** and mixtures thereof. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1020114

(15) Slovak, S.; Cohen, Y. *Supramol. Chem.* **2010**, DOI: 10.1080/10610278.2010.506549.