Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Published on 10 Mawuwani 2014. Downloaded by Fail Open on 2025-05-07 09:53:31.

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 6561

Received 19th May 2014,
Accepted 10th July 2014

DOI: 10.1039/c4ob01032a

www.rsc.org/obc

Folded alkyl chains in water-soluble capsules and cavitands†

Jesse V. Gavette,[b] Kang-Da Zhang,[b] Dariush Ajami[b] and Julius Rebek Jr.*[a,b]

A deep cavitand with ionic "feet" dimerizes around hydrophobic compounds in D_2O. Longer *n*-alkane guests, C14–C18, are encapsulated in contorted conformations and NMR is used to deduce their shapes. Competition experiments establish the driving forces involved and how they compensate for the steric clashes in the folded structures of the encapsulated alkanes. Bolaamphiphiles instead prefer to bind in the monomeric cavitand with conformations that bury the methylenes but expose the polar head groups to solvent.

We recently described a deep cavitand **1a** with a self-complementary array of hydrogen bond donors and acceptors on the "rim" (Fig. 1).[1] This motif was introduced by de Mendoza,[2] and dimerization to capsules occurs in organic solvents with cavitands **1b** and **1c** and suitable guests. The pyridinium "feet" of **1a** impart solubility in water (D_2O) and hydrophobic groups – short *n*-alkanes, the hydrocarbon end of ibuprofen and the octanoyl group of ghrelin – are readily bound in the open-ended cavitand.[3] Longer *n*-alkanes (C10–C14), stilbenes and benzanilides induce dimerization and are encapsulated in **1.1** in D_2O. We report here that even longer *n*-alkanes can be driven into the capsule **1.1**, while α,ω-amino acids (bolaamphiphiles) are taken up in the monomeric cavitand **1a**. In either container, the guests must assume folded shapes to be accommodated.

Extended (3 h) sonication of **1a** in D_2O overlayered with *n*-alkanes C14–C18 gave complexes that showed characteristically shifted NMR signals (Fig. 2). The magnetic shielding of the aromatic panels of the host structure induce upfield shifts of the guest signals. The guests show symmetrized spectra: only 7 peaks appear for C14, and 8 for C15 or C16, and the two ends of the capsule show the same magnetic environments.

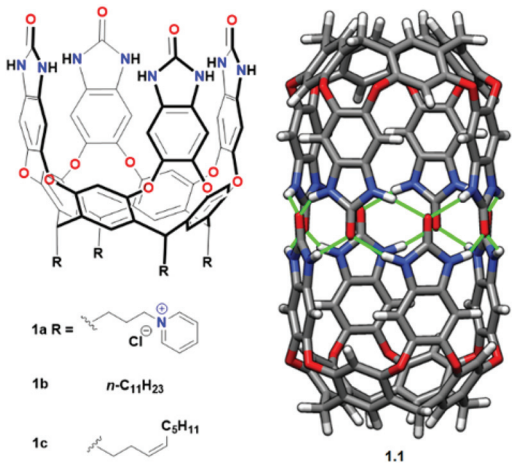

Fig. 1 Structures of water-soluble **1a** and de Mendoza's[2] organic soluble cavitands **1b** and **1c**. A model of the capsular dimer **1.1** is shown with highlighted hydrogen bonds (solubilizing R-groups have been removed from the model for clarity).

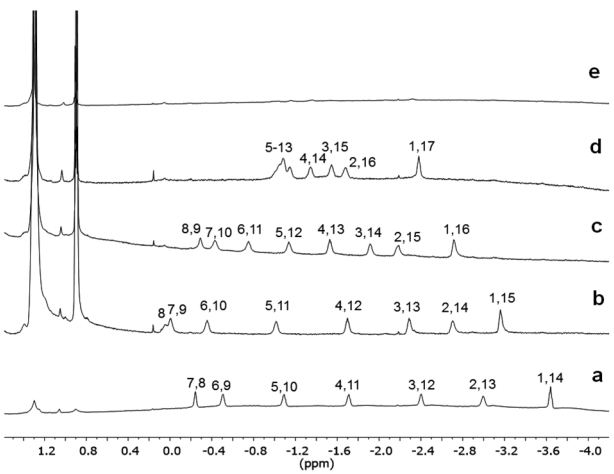

Fig. 2 Partial ^1H NMR (600 MHz, D_2O, 298 K) spectra of the complexes formed between host **1.1** (1.0 mM) and (a) *n*-C14; (b) *n*-C15; (c) *n*-C16; (d) *n*-C17; (e) *n*-C18.

[a]*Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China*
[b]*Skaggs Institute for Chemical Biology, and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA. E-mail: jrebek@scripps.edu; Fax: +1 858-784-2876*

†Electronic supplementary information (ESI) available: Details of NMR spectra and computations. See DOI: 10.1039/c4ob01032a

Published on 10 Mawuwani 2014. Downloaded by Fail Open on 2025-05-07 09:53:31.

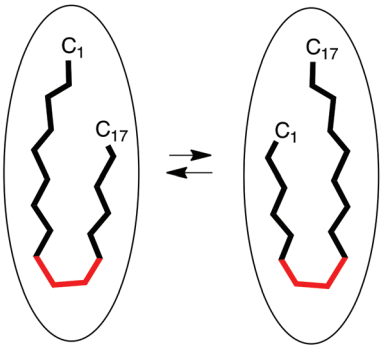

Fig. 3 Cartoon of proposed C17 shape in the capsule **1.1**; the bending is limited to a few C atoms with *gauche* conformations while the remainder of the chain is extended.

The space and guests are symmetrical – at least on the NMR timescale. For *n*-tetradecane almost identical NMR spectra have been observed in capsules in organic solvents,[4] The maximum shift in this space approaches a $\Delta\delta$ of −4.5 ppm which is observed for the methyl groups of *n*-tetradecane at the tapered end of the cavity. But the spectrum of *n*-pentadecane in **1.1** shows that its methyl has moved out of the end of the capsule: The signal shifts *downfield*, and the methyl signal continues moving downfield with C16 and C17. Only traces of C18 are encapsulated.

The NMR signals indicate a bending of the guest, which leads to a time averaged environment for the signals. Specifically, the methyl signals represent the average chemical shift of one methyl deep in the tapered end and the other away from the resorcinarene. Rapid exchange of the two methyl environments is proposed schematically for C17 in Fig. 3, in which a capsule widened at the midsection is implied. This is in accord with observations of alkyl folding in a wider capsule having thiourea hydrogen bonding seams.[5] Folded alkyl groups have been observed in naturally-occurring receptors such as proteins[6] and γ-cyclodextrins.[7] In synthetic receptors such as reversibly formed capsules, folding usually requires wider spaces than **1.1** presents.[5,8] The guest can be folded or coiled but there is not room enough for both. The longest extended alkane that is accommodated in a capsule of the same length is C11.[4]

Pairwise competition experiments were performed to determine relative affinities and to estimate the price paid for the alkane contortions. The baseline is C14, which is known to be coiled in a helix with up to 11 *gauche* interactions in capsules of this length.[9] The spectra are reported in the ESI† and indicate a decrease in affinity with alkane length. Apparently, a single fold (C15) is more energetically costly than 11 *gauche* interactions (C14) in this limited space. Each methylene added to the guests increases their volumes and exposed surfaces, but also effects the partitioning of the alkane into the aqueous (D_2O) phase. On the other hand, partitioning from the aqueous phase into the capsule is just the reverse of these effects, and to a first approximation, the interactions of the guest with the aqueous phase are cancelled.

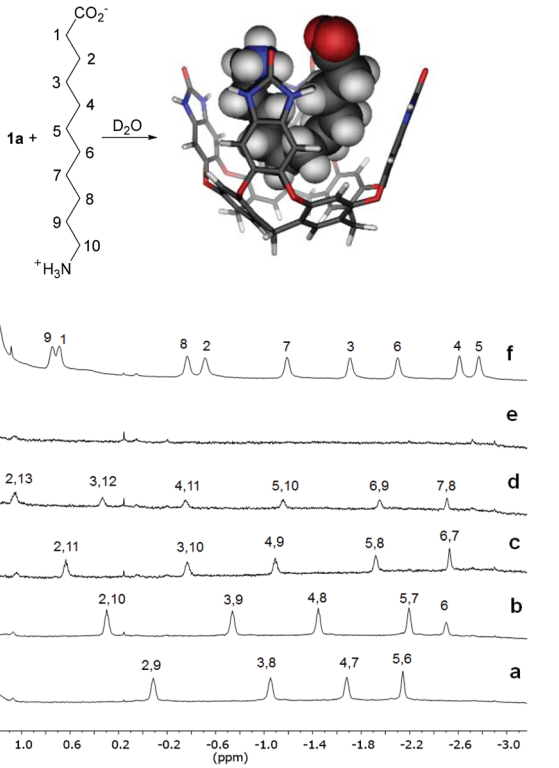

Fig. 4 Partial ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of the complexes formed between host **1a** (0.8 mM) and (a) 1,10-decanediol; (b) 1,11-undecanediol; (c) 1,12-dodecanediol; (d) 1,14-tetradecanediol; (e) 1,16-hexadecanediol; (f) 11-amino-undecanoic acid (assignments based on 2-D NMR, see ESI†). The cavitand "feet" were removed for clarity.

Several α,ω-diols (bolaamphiphiles) were also bound, but reside in the monomeric cavitand **1a** (Fig. 4a–e) rather than the dimeric capsule. The high symmetry of their signals is that expected for a neatly folded guest in the cavitand with the polar headgroups exposed to solvent. Similar binding motifs where observed in a related system[10] which highlights the favoured interaction of the polar headgroups with solvent molecules at the exposed rim of the cavitand (*versus* interaction with the pi-basic interior surfaces in the capsule binding motif) which is the likely driving force for this conformational preference for the bolaamphiphiles. The C16 diol proved to be too large be bound by **1a**. Typical α-amino acids did not give kinetically stable complexes with **1a**, but the zwitterionic 11-amino-undecanoic acid was an excellent guest. Again, the polar terminal groups promoted binding in a folded conformation within the monomeric cavitand (Fig. 4f).

The upfield signals in the NMR spectrum show that 9 out of 10 of its methylenes are surrounded by **1a**. In these spectra the furthest upfield signals appear at −2.75 ppm ($\Delta\delta$ = −3.8 ppm) and this chemical shift reflects the nearest approach a $-CH_2-C\boldsymbol{H}_2-CH_2-$ group can make to the resorcinarene at the tapered end of the cavitand. As mentioned above, a methyl group can make a closer approach ($\Delta\delta$ = −4.5 ppm).

How do the cavitand and capsule increase their width to accommodate folded alkanes? Such bending in cavitands, has

 This journal is © The Royal Society of Chemistry 2014

Published on 10 Mawuwani 2014. Downloaded by Fail Open on 2025-05-07 09:53:31.

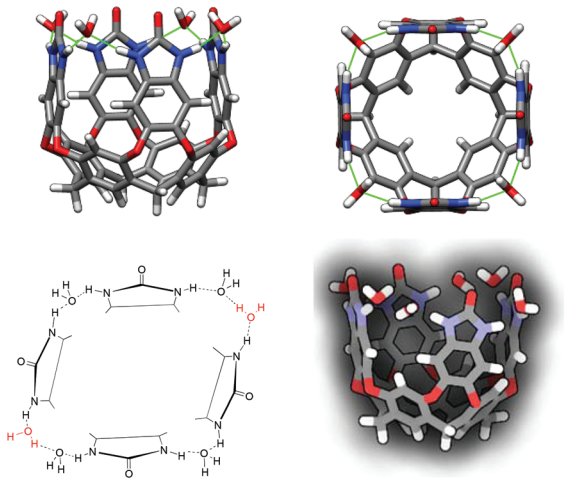

Fig. 5 (Top) Two views of **1a** stabilized with 4 bridging water molecules. (Bottom left) Addition of 2 waters on opposite corners widens the opening. (Bottom right) An energy-minimized structure of the widened cavitand. Cavitand "feet" were replaced with hydrogens for clarity and to reduced computational time.

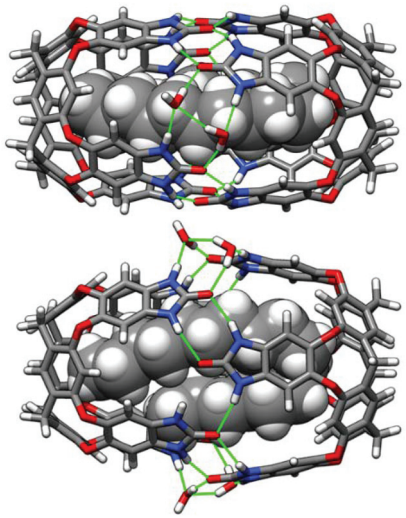

Fig. 6 Two views of encapsulated C17. Four water molecules were inserted on opposite sides of the capsule then energy minimized (HF/6-31G*). Hydrogens replaced "feet" to reduce computational time.

been observed only recently,[8f,10] and only in containers that do not involve hydrogen bonding for structure. For **1a**, it is likely that hydrogen bonds stabilize the vase form; these bonds are provided by water molecules which bridge adjacent cavitand walls. The hydrogen bonds resist changes in cavitand shape. A minimal arrangement is shown in Fig. 5 with one water at each corner.[3] Two more water molecules could be inserted at opposite corners to accommodate a folded alkane positioned diagonally in the space. This widens the opening at the top and creates a less symmetrical shape as proposed in the figure. Even more waters could lead to further widened openings.

In the capsule, the interaction of water with the seam of hydrogen bonds, particularly as the assembly undergoes "breathing" motions, is apt to widen the effective girth of the capsule but does not appear to affect the capsules length. A computational study of encapsulated C17 at *ab initio* (HF/6-31G*) level revealed that at least four water molecules are required to disrupt the polar seam in the middle (Fig. 6). This reduces the D_2d symmetry of capsule to C_2 and provides the desirable alignment of aromatic walls to accommodate the folded alkane. Although addition of more water molecules could result in even more space for motion of the alkane, the favourable CH/π interactions between host and the guest would be weakened.

Normal alkanes have proven useful probes of shape, capacity and chemical surface of synthetic containers. The alkanes are flexible and assume shapes complementary to the container. These shapes are often inaccessible for molecules in bulk solution, but the small spaces impose the contortions, however transiently. The bolaamphiphiles are especially intriguing in that they offer conformations conducive to cyclization reactions. We will report on these in the sequel.

We are grateful to the National Science Foundation (CH 1213415) and the Defense Threat Reduction Agency Joint Science and Technology Office for financial support.

Notes and references

1 K.-D. Zhang, D. Ajami and J. Rebek Jr., *J. Am. Chem. Soc.*, 2013, **135**, 18064–18066.
2 M. H. K. Ebbing, M. J. Villa, J. M. Valpuesta, P. Prados and J. de Mendoza, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 4962–4966.
3 K.-D. Zhang, D. Ajami, J. V. Gavette and J. Rebek Jr., *Chem. Commun.*, 2014, **50**, 4895–4897.
4 (*a*) A. Scarso, L. Trembleau and J. Rebek Jr., *Angew. Chem., Int. Ed.*, 2003, **115**, 5657–5660; (*b*) A. Scarso, L. Trembleau and J. Rebek Jr., *J. Am. Chem. Soc.*, 2004, **126**, 13512–13518.
5 A. Asadi, D. Ajami and J. Rebek Jr., *J. Am. Chem. Soc.*, 2011, **133**, 10682–10684.
6 G. Zanotti, G. Scapin, P. Spadon, J. Veerkamp and J. Sacchettini, *J. Biol. Chem.*, 1992, **267**, 18541–18550.
7 N. J. Turro, T. Okubo and C.-J. Chung, *J. Am. Chem. Soc.*, 1982, **104**, 1789–1794.
8 (*a*) D. Fiedler, R. G. Bergman and K. N. Raymond, *Angew. Chem., Int. Ed.*, 2004, **43**, 6748–6751; (*b*) H. Gan and B. C. Gibb, *Chem. Commun.*, 2013, **49**, 1395–1397; (*c*) M. Yamanaka, A. Shivanyuk and J. Rebek Jr., *J. Am. Chem. Soc.*, 2004, **126**, 2939–2943; (*d*) L. C. Palmer and J. Rebek Jr., *Org. Lett.*, 2005, **7**, 787–789; (*e*) S. M. Biros, R. G. Bergman and K. N. Raymond, *J. Am. Chem. Soc.*, 2007, **129**, 12094–12095; (*f*) S. Liu, D. H. Russell, N. F. Zinnel and B. C. Gibb, *J. Am. Chem. Soc.*, 2013, **135**, 4314–4324.
9 W. Jiang, D. Ajami and J. Rebek Jr., *J. Am. Chem. Soc.*, 2012, **134**, 8070–8073.
10 K.-D. Zhang, D. Ajami, J. V. Gavette and J. Rebek Jr., *J. Am. Chem. Soc.*, 2014, **136**, 5264–5266.