ChemComm
www.rsc.org/chemcomm

Coencapsulation of large and small hydrocarbons

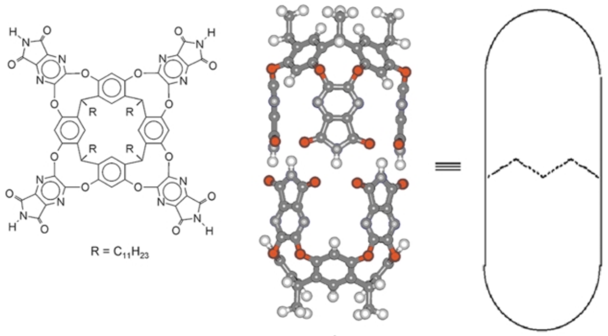
Alexander Shivanyuk, Alessandro Scarso and Julius Rebek, Jr.*
The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA. E-mail: jrebek@scripps.edu; Fax: +1 858 784 2876; Tel: +1 858 784 2250

Received (in Columbia, MO, USA) 27th January 2003, Accepted 1st April 2003
First published as an Advance Article on the web 2nd May 2003

Combinations of small, gaseous hydrocarbons and sizable aromatics, *e.g.* methane and anthracene, are directly observed in a cylindrical capsule by NMR.

Reversible encapsulation occurs when a self-assembled host structure temporarily surrounds a smaller guest molecule.[1] The assembly of the host capsule requires the presence of suitable guests, and is driven by molecular recognition: size, shape and chemical surface complementarity are involved. Size is both the most and least apparent factor. Guests larger than the host cavity obviously cannot be surrounded, but there are many ways that the space of a capsule can be filled. Single guests in solution that fill, typically, 55% of the capsule's space result in stable complexes.[2] A combination of two *different* guests may fit a capsule better than either guest alone.[3] This relatively rare event — coencapsulation — can define new forms of stereochemistry,[4] create chiral nanoenvironments[5] and even accelerate certain bimolecular reactions.[6] We report here the coencapsulation small gaseous hydrocarbons with sizable aromatic structures. These combinations greatly expand the range of guests that can be observed by NMR, and provide information on the spatial requirements of coencapsulated gases.

The capsule **1** (Fig. 1) binds a number of different structures in its roughly cylindrical cavity but shows subtle selectivity. For example, two toluene molecules[7] are encapsulated, but the slightly larger *p*-xylene is not accommodated: two molecules are too large to fit comfortably inside while one alone does not occupy enough space for a stable complex.



1

Fig. 1 Line drawing of the tetraimide subunit, ball and stick model of the cylindrical capsule and cartoon representation used elsewhere in this work.

We examined *p*-xylene as a partner for small, gaseous guests, and found a number of combinations that provide stable complexes. They are shown in Fig. 2, along with their chemical shifts in ppm. Isobutane, butenes and cyclopropane all formed stoichiometric complexes, and these small hydrocarbons had never before been encapsulated. Saturated solutions of these gases alone in mesitylene-d_{12} show only **1** with encapsulated impurities from the deuterated solvent. The relative binding affinities for the gases were too difficult to determine, as their concentrations could not be reliably controlled. The ethane complex was considerably less stable than the others: even with a large excess of the gas, less than 10% of the complex formed.[8]

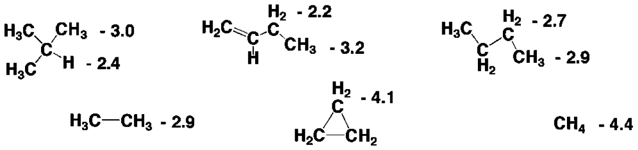


Fig. 2 ^{1}H NMR chemical shifts (ppm) of gases coencapsulated with *p*-xylene-d_{10}. For methane the coguest was anthracene.

Unexpectedly, the larger guest has the effect of slowing the in/out exchange of the smaller one, and the rates of these processes become slow on the NMR timescale. In addition, the two ends of the capsule remain distinct: the guests are too large to move past each other while inside the capsule. No evidence of methane coencapsulation was observed with *p*-xylene but this guest was observed in the capsule when the larger anthracene was present. Methane, ethane and their derivatives have been detained in the smallest of synthetic receptors — cryptophanes[9] and tennis balls[10] — while xenon, nitrogen and oxygen were bound in hemicarcerands.[11] In the solid state, recent work by Atwood[12] shows that methane and Freon can be stored.

With appropriately substituted large guests, coencapsulated gases can show social isomerism[13] (Fig. 3). Specifically, *p*-ethyltoluene and cyclopropane give two different complexes. This phenomenon is caused by the interaction of one guest with another and their limitations of motion inside the cylindrical capsule. The *p*-ethyltoluene is too long to tumble (at least on the NMR timescale) while in the capsule and presents either its methyl or ethyl to the cyclopropane.

Neither naphthalene nor azulene has been observed inside **1**, but coencapsulation with ethane or propene was successful. For the latter with azulene only the single social isomer shown in

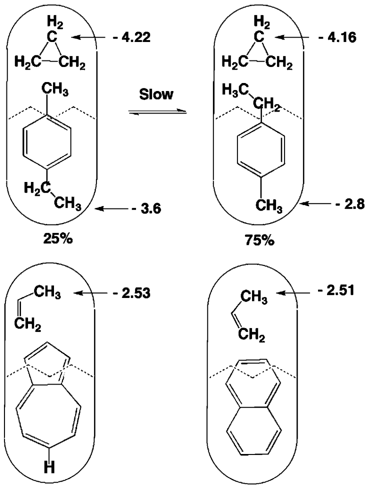


Fig. 3 Top: social isomerism caused by limited motions of two guests in the capsule. Bottom: coencapsulation of propene with azulene and naphthalene. The chemical shifts of the small guests are indicated.

DOI: 10.1039/b300996c

Fig. 3 was present. It was identified by the upfield chemical shift characteristic of the proton shown in the seven-membered ring at the end of the capsule.

The combinations provide a good fit, *i.e.* the space not occupied by the larger guest is appropriate for the smaller one. The fit may be thought of in terms of dimensions or volume, and these are by no means unrelated. The capsule's volume is ~410 Å^3 and the shape of this space is shown in Fig. 4. When one end of the capsule is occupied by the *p*-xylene, the accessible volume remaining for the small guest is ~170 Å^3.

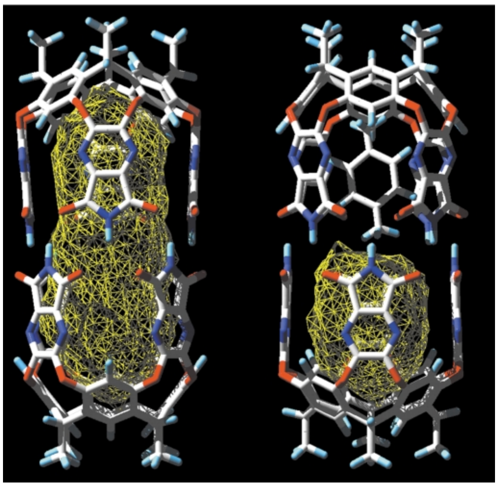


Fig. 4 The shape of the inner space of the empty capsule (410 Å^3, left) and the remaining space when one end is occupied by *p*-xylene (170 Å^3, right).

We calculated packing coefficients (PC's) of the various gases with *p*-xylene and other combinations (Table 1). The packing coefficients are consistently much lower than the 0.55 observed for encapsulation of single guests in solution, or the value for typical liquids.[2] The numbers raise questions about the experience of molecules in the cavity and the space that a gas molecule occupies in a capsule.

Table 1 (A) Coencapsulation of guests with *p*-xylene-*d*$_{10}$ in **1** at 295 K. (B) Coencapsulation of other combinations

(A)		(B)	
Smaller guest (Vol, Å^3)	PC[a]	Guests	PC[a]
CH_3–CH_3 (45)	0.37	$(CH_2)_3$ + *p*-ethyl toluene	0.42
$(CH_2)_3$ (52)	0.39	$H_2C{=}CH$–CH_3 + azulene	0.47
$H_2C{=}CH$–CH_3 (53)	0.39	$H_2C{=}CH$–CH_3 + naphthalene	0.40
$HC(CH_3)_3$ (75)	0.45	CH_4 + anthracene	0.44
$H_2C{=}CH$–CH_2CH_3 (67)	0.43	CH_3–CH_3 + anthracene	0.48
H_3C–CH_2–CH_2–CH_3 (76)	0.45	CH_3–CH_3 + naphthalene	0.38

[a] Packing Coefficients calculated from the cavity volume of the capsule (410 Å^3), using DeepView, Swiss PDB Viewer, Guex, N.;Peitsch, M.; Schwede, T.; Diemand, A. GlaxoSmithKline, and Web Lab Viewer Pro Version 5. 2000. Molecular Simulation Inc. The default probe (1.4 Å) was used to generate the surfaces.

The nature of the inner phase of covalently bound carceplexes was first considered by Cram.[14] The barriers to amide rotation in incarcerated DMF depended on cavity size, with activation energies that ranged between those observed in the gas and solution phases. The low values for the packing coefficients imply that gaseous guests provide stable coencapsulation complexes when slightly more than 40% of the space is occupied.[15] A somewhat smaller average value is calculated if only the space remaining for the gaseous guest is considered.

The stabilizing effects of a large guest on the encapsulation of a small one are not limited to gases. For example, no signals for encapsulated solvent appear in neat CH_2Cl_2 even though the NMR spectrum shows sharp signals for the capsule. The exchange of the guest with bulk solvent is probably fast on the NMR timescale. When deuterated *p*-xylene is present as a cosolvent, the spectrum shows that the capsule is formed, it is unsymmetrically filled, and the signal for encapsulated CH_2Cl_2 appears at 0.6 ppm.[16]

Competition experiments were arranged in which isobutane and cyclopropane were offered a choice of coencapsulation with *p*-xylene or *p*-ethyltoluene. Both gases preferred the smaller coguest, a result that also supports a lower PC for gas coencapsulation. However, isopropyl chloride and CH_2Cl_2 made the same choices: about twice as much *p*-xylene was coencapsulated as *p*-ethyl toluene in those cases, given equal volumes of each aromatic solvent.

In summary, the capsule **1** accommodates guests one, two or even three at a time, depending on their size.[4] Coencapsulation of guests with widely different sizes can fill the space properly when the combinations match the volume requirements of the host. That volume depends, in turn, on the phase of the guests. Gases need more space for molecular recognition and coencapsulation allows their direct observation by NMR, even in large capsules.

We are grateful to the Skaggs Institute for Research and the National Institutes of Health (GM 50174) for support. We thank Professor J. Dunitz for valuable advice and for reference 15. A. S. and A. S. are both Skaggs Postdoctoral Fellows.

Notes and references

1 M. M. Conn and J. Rebek, Jr., *Chem. Rev.*, 1997, **97**, 1647; J. C. Sherman, *Tetrahedron*, 1995, **51**, 3395; D. L. Caulder and K. N. Raymond, *Acc. Chem. Res.*, 1999, **32**, 975; M. Fujita, K. Umemoto, M. Yoshizawa, N. Fujita, T. Kusukawa and K. Birhada, *Chem. Commun.*, 2001, 509; V. Böhmer and M. O. Vysotsky, *Austral. J. Chem.*, 2001, **54**, 671; F. Hof, S. L. Craig, C. Nuckolls and J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 1488.

2 S. Mecozzi and J. Rebek, Jr., *Chem.-A Eur. J.*, 1998, **4**, 1016.

3 T. Heinz, D. Rudkevich and J. Rebek, Jr., *Nature*, 1998, **394**, 764; M. K. Ebbing, M.-J. Villa, J.-M. Malpuesta, P. Prados and J. de Mendoza, *Proc. Natl. Acad. Sci. U.S.A.*, 2002, **99**, 4962.

4 A. Shivanyuk and J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 684.

5 A. Scarso, A. Shivanyuk, O. Hayashida and J. Rebek, Jr., *J. Am. Chem. Soc.*, in press.

6 J. Chen and J. Rebek, Jr., *Org. Lett.*, 2002, **4**, 327.

7 S. K. Körner, F. C. Tucci, D. M. Rudkevich, T. Heinz and J. Rebek, Jr., *Chem.-A Eur. J.*, 1999, **6**, 187.

8 The protons of encapsulated ethane, propene and cyclopropane showed unusually slow spin-lattice relaxation. Accordingly, delays between 20 and 40 sec were used to insure complete relaxation.

9 J. Costante-Crassous, T. J. Marrone, J. M. Briggs, J. A. McCammon and A. Collet, *J. Am. Chem. Soc.*, 1997, **119**, 3818; J. Canceill, L. Lacombe and A. Collet, *J. Am. Chem. Soc.*, 1985, **107**, 6993.

10 N. Branda, R. Wyler and J. Rebek, Jr., *Science*, 1994, **263**, 1222; N. R. Branda, R. M. Grotzfeld, C. Valdés and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1995, **117**, 85.

11 D. J. Cram, M. E. Tanner and C. B. Knobler, *J. Am. Chem. Soc.*, 1991, **113**, 7717; T. A. Robbins, C. B. Knobler, D. R. Bellew and D. J. Cram, *J. Am. Chem. Soc.*, 1994, **16**, 111.

12 J. L. Atwood, L. J. Barbour and A. Jerga, *Science*, 2002, **296**, 2367.

13 A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 12074.

14 J. C. Sherman and D. J. Cram, *J. Am. Chem. Soc.*, 1989, **111**, 4527.

15 "Molecular Crystals and Molecules" by A. I. Kitaigorodsky, Academic Press, New York, 1973. pp. 18–19. "The packing coefficients for the overwhelming majority of crystals are between 0.65–0.77, *i.e.*, of the same order as the close-packing of spheres and ellipsoids… Experimental studies of benzene, naphthalene, and anthracene have shown that when the packing coefficient *k* is above 0.68 these substances are in the solid state. When changing from a solid phase to liquid phase, *k* instantly drops to 0.58. A further increase of the liquid temperature up to the boiling point causes a decrease of *k*, *e.g.*, for naphthalene, down to 0.51. At $k \leq 0.5$ these substances become gaseous".

16 A. Shivanyuk and J. Rebek, Jr., *Chem. Commun.*, 2002, 2326.