ChemComm
www.rsc.org/chemcomm

Coencapsulation of three different guests in a cylindrical host

Toru Amaya and Julius Rebek, Jr.*
The Skaggs Institute for Chemical Biology, Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA. E-mail: jrebek@scripps.edu; Tel: +1 858.784.2250; Fax: +1 858.784.2876

Received (in Columbia, MO, USA) 17th May 2004, Accepted 27th May 2004
First published as an Advance Article on the web 8th July 2004

Combinations of anions and organic solvent molecules were screened to give encapsulation complexes with three different guests inside.

For most of the last four decades, molecular recognition in chemistry was concerned with binding a single target with high affinity and selectivity.[1] Occasionally, bimolecular targets—model complexes of nucleic acid base pairs—arose and synthetic receptors were devised to recognize them.[2] In the last decade self-assembled capsules appeared.[3] They offer well-defined spaces capable of accommodating many types of guests, and pairwise recognition of smaller molecules as coencapsulation complexes has become more common.[4,5] The cylindrical capsule **1·1**[4] (Fig. 1a) shows recognition based on the proper filling of space: one large, two medium and three small molecules are accommodated. The limited motions of the guests within the confined space give rise to new types of stereochemistry such as social isomerism.[6] and constellational isomerism.[7] This research was undertaken to examine the behavior of the capsule when offered three different guests, and we report here some findings on the selectivity of the encapsulation process.

Three arrangements in space are available for three different guests inside the capsule (Fig. 1b), and we define selectivity as the formation of a single constellational isomer. Some preferences are expected since the capsule offers a gradient of polarity: the most polar environment is near the seam of hydrogen bond donors and acceptors that hold the capsule together at its center; the least polar is the π surface of the resorcinarenes at the tapered ends. Accordingly, anions gravitate to the polar center of the capsule and earlier we showed that one $CHCl_3$ occupies each end of the capsule when anions such as Cl^-, BF_4^-, PF_6^- or IO_4^- are detained in the middle.[8] We used this tendency to limit the isomeric possibilities by positioning PF_6^- as the anionic guest in the center of the capsule and used ^{19}F NMR spectroscopy to monitor the environment of the anion. The remaining spaces were presented to combinations of small solvent molecules (Fig. 2). The coencapsulated solvent guest species are easily identified by the strong upfield shifts ($\Delta\delta$ up to -5 ppm) in the ^1H NMR spectra. The intense anisotropy arises from the eight aromatic rings that line the ends of capsule. When two different guests are included at the ends, the two halves of the capsule are no longer equivalent and the NMR signals of the capsule are doubled.

We first examined the combination of dichloromethane, PF_6^- and benzene (entry I). In the presence of excess $n\mathrm{Bu}_4\mathrm{N}^+\mathrm{PF}_6^-$ in dichloromethane-d_2 the cylindrical capsule exists entirely as a PF_6^- bound species **2** (Fig. 3a). After addition of 50 μL benzene to this mixture, new sets of signals appeared in ^1H NMR and ^{19}F NMR (Fig. 3b, see arrows). These signals gradually grew with addition of benzene. After addition of 200 μL of benzene, approximately 90% of **2** had been converted to the new capsule (Fig. 3c). The singlet around 3.6 ppm was assigned to the encapsulated benzene by a 1D GOESY experiment (mixing time = 1.0 s). The large change in chemical shift ($\Delta\delta = -3.57$ ppm) shows the encapsulated benzene stays at the end of the capsule and its integral (6 H) indicates one benzene molecule is accommodated inside. The encapsulation of PF_6^- was separately confirmed by ^{19}F NMR spectroscopy, and the

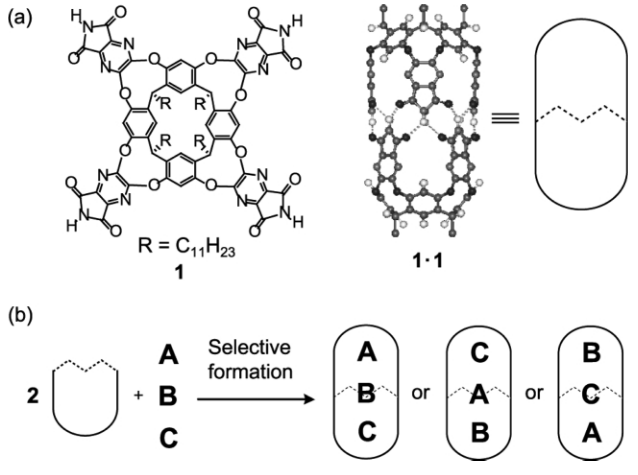
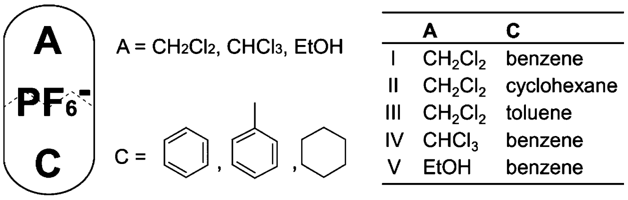


Fig. 1 (a) Line drawing of tetraimide subunit, ball and stick model of the cylindrical capsule and cartoon representation used elsewhere in this work. (b) Constellational isomers possible for the encapsulation of three different guests **A**, **B**, and **C**.



	A	C
I	CH_2Cl_2	benzene
II	CH_2Cl_2	cyclohexane
III	CH_2Cl_2	toluene
IV	$CHCl_3$	benzene
V	EtOH	benzene

Fig. 2 Combination of molecular guests.

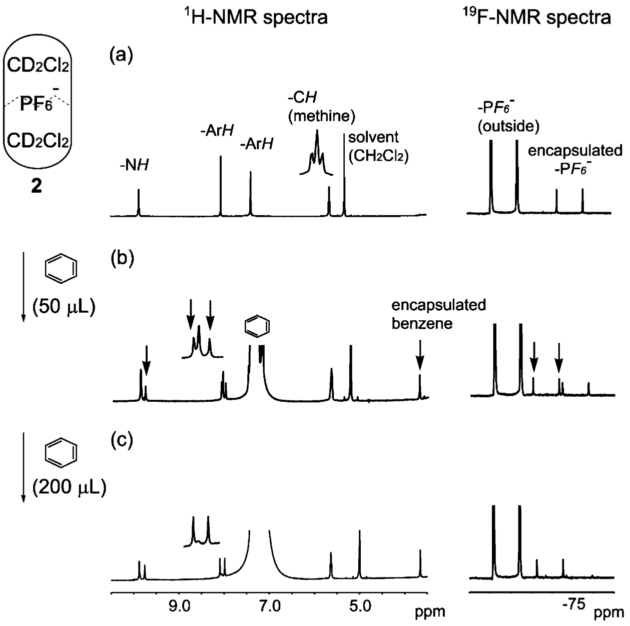


Fig. 3 Dilution experiment of **7** with benzene. *Conditions*: **1·1** (1 mM), $n\mathrm{Bu_4NPF_6}^-$ (20 mg), dichloromethane-d_2 (600 μL), 300 K, ^1H NMR (600 MHz), ^{19}F NMR (564.5 MHz), C_6F_6 was used as a external standard (-162.0 ppm) for ^{19}F NMR.

DOI: 10.1039/b406945e

splitting of N–H and Ar–H resonances of the capsule in ^{1}H-NMR spectrum revealed that two halves of the capsule are no longer equivalent. These results indicate that the capsule contains three different guests.[9] In the case of a 1 : 1 ratio of dichloromethane-d_2 and benzene-d_6, capsule **3** was formed in high conversion[10] and selectivity (> 99%, > 99%)[11] (Fig. 4). The observed selectivity is attributed to the guests of **3** filling the space of the cavity better than in **2** (packing coefficient: 46% for **3**, 41% for **2**).

The other entries II, III, IV, and V were also investigated. In the case of II and IV, we could detect ABC-type encapsulation, however those were not selective. For entry II, the excess addition of cyclohexane gave an ABC-type capsule and the capsule with two cyclohexanes; with less cyclohexane both the ABC-type capsule and the capsule with two dichloromethanes with the anion were present. Similar results were observed for entry IV. When toluene (case III) was used instead of benzene, the ABC-type capsule was not obtained but a broad, complicated spectrum was observed because toluene was too long to fit well. On the other hand, the combination of entry V formed the capsule **4** selectively in the presence of 40 μL of ethanol. In this case the dissociated capsule was also observed.[12] We could observe signals of the each of the encapsulated guests (Fig. 5). The large $\Delta\delta$ of the encapsulated ethanol (−4.28 for CH_3, −4.46 for CH_2, −3.85 for OH ppm) and benzene (−3.05 ppm) clearly shows these guests are positioned at the capsule's ends. The $\Delta\delta$ of PF_6^- (−3.1 ppm) in the ^{19}F spectrum was comparable to the encapsulated PF_6^- previously reported,[8] which confirmed that PF_6^- is in the middle of the capsule.

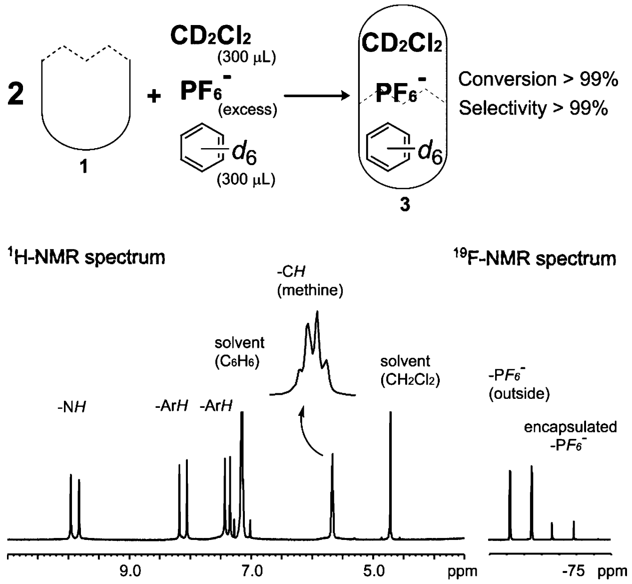
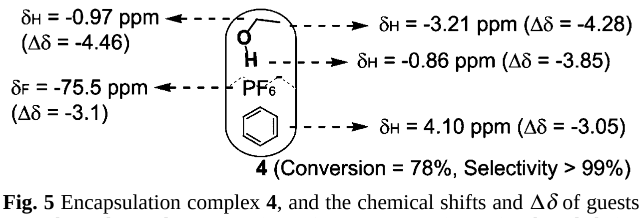


Fig. 4 Selective encapsulation of dichloromethane-d_2, PF_6^-, and benzene-d_6. ^{1}H NMR spectrum at 600 MHz and ^{19}F NMR spectrum at 564.5 MHz.



4 (Conversion = 78%, Selectivity > 99%)

Fig. 5 Encapsulation complex **4**, and the chemical shifts and $\Delta\delta$ of guests are indicated. *Conditions*: **1·1** (1 mM), nBu$_4$NPF$_6^-$ (10 mg), ethanol-d_6 (40 μL), benzene-d_6 (560 μL), 300 K, ^{1}H NMR (600 MHz), ^{19}F NMR (564.5 MHz), C_6F_6 was used as an external standard (−162.0 ppm) for ^{19}F NMR.

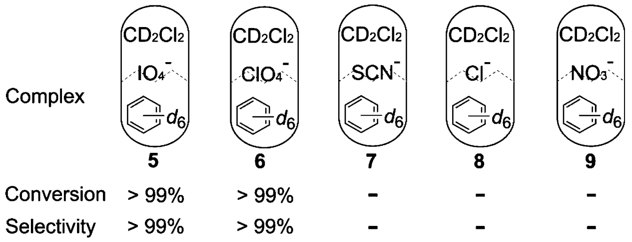


Fig. 6 Encapsulation complexes **5–9** of various anions.

A few other anions were examined for ABC-type encapsulation with dichloromethane and benzene (Fig. 6). In the case of IO_4^- and ClO_4^-, **5** and **6** formed in good conversion (> 99% for **5** and > 99% for **6**) and selectivity (> 99% for **5** and > 99% for **6**). In the other cases (SCN^-, Cl^-, and NO_3^-), broad and complicated spectra were obtained instead of ABC-type capsule **7**, **8**, and **9**. These results are likely to be caused by weak binding of the anions to the capsule.

In summary, we have demonstrated the coencapsulation of three different guests, with cases of surprising selectivities. The coencapsulation of three guests gives 18 combinations and, if these can be selected for, maintained and read out, information storage could be possible in this nano-scale capsule.

We are grateful to the Skaggs Institute for Research and the National Institutes of Health (GM 50174) for support, and to Drs Alexander Shivanyuk and Osamu Hayashida for preliminary experiments. T. A. is a Skaggs Postdoctoral Fellow.

Notes and references

1 *Comprehensive Supramolecular Chemistry*, **Vol. 1–3**, Eds. J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vögtle, Pergamon, Oxford, 1996.

2 (*a*) E. Mertz, S. Mattei and S. C. Zimmerman, *Org. Lett.*, 2000, **2**, 2931–2934; (*b*) S. C. Zimmerman and P. Schmitt, *J. Am. Chem. Soc.*, 1995, **117**, 10769–10770.

3 F. Hof, S. L. Craig, C. Nuckolls and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2002, **41**, 1488–1508.

4 T. Heinz, D. M. Rudkevich and J. Rebek, Jr., *Nature*, 1998, **394**, 764–766.

5 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.

6 A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 12074–12075.

7 (*a*) A. Shivanyuk and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2003, **42**, 684–686; (*b*) M. Yamanaka, A. Shivanyuk and J. Rebek, Jr., *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 2669–2672.

8 O. Hayashida, A. Shivanyuk and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2002, **41**, 3423–3426.

[9] An attempt was made to observe encapsulated CH_2Cl_2 by titrating this solvent into a solution of the salt in benzene-d_6. While the downfield region of the spectrum was as shown in Fig. 3c, no new signals in the upfield (0.5 to 1.5 ppm) were observed. This region is, unfortunately, dominated by the alkyl groups of the host and ammonium salt.

[10] Conversion represents the extent of capsule formation relative to monomer.

[11] These values were determined by ^{1}H NMR.

[12] In the absence of PF_6^-, no encapsulated signals of ethanol and benzene were observed, only monomer **1** was present.