Bis-Capsules: Cooperative Reversible Encapsulation of Two Molecules in Adjacent Separate Chambers**

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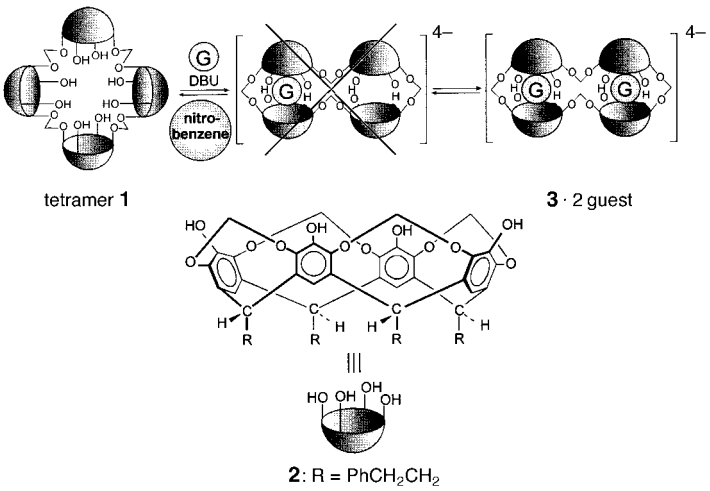
The study of discrete species that reversibly or irreversibly encapsulate small molecules in solution has captured the attention of numerous researchers in the past decade. The first such species were carceplexes, which permanently entrap guests within their confines.[1] Next were hemicarceplexes, which form kinetically stable complexes in solution, but can release guests without rupture of covalent bonds.[1b, c, 2] Most recently created were systems that reversibly encapsulate small molecules; these are often called capsules.[3] Current efforts are underway to create larger and higher order encapsulating species.[3, 4] We recently reported the first bis-carceplex, where two carceplexes are covalently linked such that one guest molecule is entrapped in each of two adjacent but physically separate chambers.[4] We report here the corresponding first bis-capsule[3c] and demonstrate that it forms cooperatively and that the guests can communicate with one another.

The bis-carceplex had been prepared from tetramer **1** by bridging the phenols using CH_2BrCl,[4] just as two molecules of tetrol **2** had been bridged to give the prototypical mono-carceplex.[5] In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), two tetrols were linked by charged hydrogen bonds to yield a reversible capsule.[6] Under similar conditions, tetramer **1** should be predisposed to form bis-capsule **3**·2 guest (Scheme 1). The ^{1}H NMR spectra of tetramer **1** and DBU are broad in [D_5]nitrobenzene at 373 K, but addition of pyrazine yields a new set of sharp host signals as well as a new signal at $\delta = 5.10$, which we assign to encapsulated pyrazine. Integration yields a ratio of one host (four bowls) to two guest molecules, and the symmetry of the spectrum is similar to that of the bis-carceplex[4] (Figure 1 shows the ^{1}H NMR spectrum of **3**·2$CDCl_3$; see below). Analogous results were obtained using methyl acetate (MeOAc) as guest.

The observation of a single set of signals for the host–guest complex in the presence of a single guest suggests the species corresponding to a 1:1 ratio of host to guest (middle structure in Scheme 1) is not formed in significant quantities at equilibrium. The proposed instability of such a species is



Scheme 1. In the presence of DBU, **1** changes configuration to encapsulate two guest molecules and form **3**·2 guest.

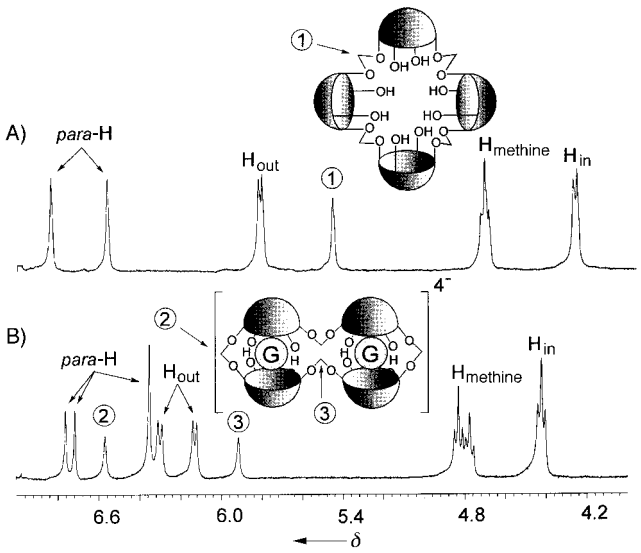


Figure 1. ^{1}H NMR spectra (400 MHz) of A) tetramer **1** (2.7 mM in $CD_3OD/CDCl_3$ (5/95)) and B) bis-capsule **3**·2$CDCl_3$ (2.7 mM tetramer **1**, 11.9 mM DBU in $CDCl_3$). H_{in} and H_{out} refer to the diastereotopic intra-bowl acetals; *para*-H refers to H *para* to OH, O^-, or inter-bowl acetal. The C_4 axis of symmetry in **1** is clearly lost in **3**·2$CDCl_3$.

supported by the following experiment: Recording the ^{1}H NMR spectra in the presence of mixtures of pyrazine and MeOAc yields a third set of host and guest signals that we assign to the mixed bis-capsule **3**·pyrazine·MeOAc. Integration of all host and guest signals indicates that all capsules are filled. The signals of the guest molecules are shifted by -0.9, $+0.19$, and $+0.16$ ppm[7] from their positions in the corresponding bis-capsules **3**·2 pyrazine and **3**·2 MeOAc (see the Supporting Information for full NMR data). Such large $\Delta\delta$ for hetero- versus homo-bis-capsules suggest that it is highly unlikely that all host and guest signals for 1:1 and 1:2 host–guest species would coincide (indeed, the asymmetry of the 1:1 complex alone would not likely yield such simple NMR spectra as those observed). We conclude that the 1:1 complex is not formed to an appreciable extent under any conditions, presumably because it is thermodynamically unfavored; thus formation of the bis-capsules is highly cooperative.[8] Exami-

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nation of Correy–Pauling–Koltun (CPK) models reveals that clamping down of two adjacent bowls of tetramer **1** about a guest forces the remaining two bowls to clamp down due to the short tether between the capsules. Because of the extreme rigidity of the bowls, the clamping would result in an empty cavity (nitrobenzene is too large to fit in such a cavity), which is clearly not going to be thermodynamically stable. Indeed, neither empty mono-capsules nor empty mono-carcerands have ever been observed in the tetrol system.[5, 6, 9] These results are also consistent with the broad NMR signals obtained in [D_5]nitrobenzene. In the absence of a suitable guest, no well-defined capsules can form, and only aggregates are observed. Similar results have been obtained for the tetrol system.[6]

Unlike nitrobenzene, chloroform can fit inside the tetrol-based capsules (Figure 1).[6] Addition of MeOAc to a ^{1}H NMR sample containing tetramer **1** and DBU in $CDCl_3$ gave rise to two sets of complexed MeOAc signals ($\delta = -0.57/-2.13$ and $\delta = -0.41/-1.97$). With excess MeOAc, exclusively the latter set of signals is observed, and integration yields 2 MeOAc:1 host; thus we assign this latter signal set to bis-capsule **3**·2 MeOAc and the former signal set to bis-capsule **3**·MeOAc·$CDCl_3$.[10]

We have determined the relative guest affinities (K_{rel}) for tetrol-based capsules by performing competition experiments.[6] Similarly, K_{rel} can be determined for **3**·2 guest. A ^{1}H NMR sample of tetramer **1** (1.61 mM), DBU (8 mM), and MeOAc (32.2 mM) in $CDCl_3$ at 298 K showed a mixture of the bis-capsule compounds **3**·2$CDCl_3$, **3**·$CDCl_3$·MeOAc, and **3**·2 MeOAc, in a ratio of 1:4.7:8.6 at equilibrium (Figure 1). From these data, K_{rel} was determined to be 1300.[11] The corresponding K_{rel} for MeOAc:$CDCl_3$ in the tetrol-based capsule is 72000 in [D_5]nitrobenzene at 298 K.[6b] The general trend in guest selectivity holds, as MeOAc is a far better guest in both systems. There is a discrepancy factor of 55 between these data, which may be in part a solvent effect, but such variation is common to non-C_4-symmetric capsules derived from tetrol **2**.[12] The inter-capsule tether in the bis-capsule may force a small separation between the bowls in each capsule, thus creating a slightly larger cavity, which would better accommodate the larger $CDCl_3$, and thus diminish the selectivity for MeOAc. The bis-capsule does appear to have a larger cavity than the tetrol system, as MeOAc has restricted motion in the tetrol system,[6b] but moves freely within the bis-capsules above ambient temperatures.

Communication between guests in adjacent capsules is evident by the difference in chemical shifts of the guests when their neighbor is changed. Table 1 lists the $\Delta\delta$ values for MeOAc in various hetero-bis-capsules. The overall range of these values is 0.31, which is large considering that the pairs of guests are physically separated by two molecular walls. The two sets of $\Delta\delta$ (one for each methyl group of MeOAc) parallel each other, suggesting that the communication is a global one and is not local to one bowl or part thereof. The communication is most likely transmitted through conformational fluctuations as follows: The bowls clamp down tightly on small guests, but are forced to open somewhat when surrounding larger guests.[5, 9, 13] Since the two capsules are linked by a short tether, the partial opening of one pair of bowls perturbs the clamping or opening of the other pair. This is consistent with the trend observed in Table 1: The better,[5, 9] smaller guests generally yield relative downfield shifts in the neighboring MeOAc, while the larger, poorer guests tend to impart upfield shifts. Thus, partial opening of one capsule may allow the other capsule to clamp down more tightly on MeOAc and cause a greater upfield shift. The same trend holds for the guest signals in other complexes: δ(**3**·MeOAc·pyrazine) $-$ δ(**3**·2 pyrazine) $= -0.9$ in [D_5]nitrobenzene and δ(**3**·MeOAc·$CHCl_3$) $-$ δ(**3**·2 $CHCl_3$) $= +0.32$ in $CDCl_3$/$CHCl_3$ (1/1), where the MeOAc neighbor allows stronger clamping on the better guest (pyrazine), but weaker clamping on the poorer guest ($CHCl_3$).

Table 1. Values of $\Delta\delta$ for MeOAc in bis-capsule **3**·guest·MeOAc in $CDCl_3$ at 298 K.[a]

Guest	$CH_3CO_2CH_3$	$CH_3CO_2CH_3$
DMS[b]	+0.15	+0.13
1,4-dioxane	+0.15	+0.12
pyrazine	+0.13	+0.11
[D_6]acetone	+0.05 (+0.09)	+0.03 (+0.07)
DMSO	+0.09	+0.06
MeOAc	0	0
[D_6]benzene	−0.06 (−0.03)	−0.06 (−0.03)
THF	−0.11	−0.11
$CDCl_3$	−0.16	−0.16

[a] $\Delta\delta = \delta$(**3**·MeOAc·guest) $-$ δ(**3**·2 MeOAc). Values corrected for solvent effects are given in parentheses, as large volumes of these guests were used (**3**·2 MeOAc was used as an internal reference). [b] DMS = dimethyl sulfide.

In summary, we have presented the first side-to-side bis-capsules, where guest molecules are reversibly encapsulated in adjacent, but physically separate, chambers. Formation of the bis-capsules is cooperative, as no 1:1 host:guest species was observed. Unprecedented communication between the guest molecules is evident by the neighbor-dependent chemical shifts of encapsulated guests. Such communication may find application in switching devices or as sensors.

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[7] The value −0.9 is δ(pyrazine in **3**·pyrazine·MeOAc) − δ(pyrazine in **3**·2pyrazine). The value +0.19 is $\delta(CH_3COCH_3$ in **3**·pyrazine·MeOAc) − $\delta(CH_3COCH_3$ in **3**·2MeOAc). The value +0.16 is $\delta(CH_3COCH_3$ in **3**·pyrazine·MeOAc) − $\delta(CH_3COCH_3$ in **3**·2MeOAc).

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[10] The ^{1}H NMR spectra of **1** and DBU in $CHCl_3/CDCl_3$ (1/1) at 298 K gave signals for encapsulated $CHCl_3$ ($\delta = 5.04$); thus the free species is **3**·2$CHCl_3$. Upon addition of MeOAc, a new signal for encapsulated $CHCl_3$ ($\delta = 5.36$) appears, in addition to the new signals of encapsulated MeOAc and host; integration yields **3**·MeOAc·$CHCl_3$. Cooperativity appears at first to be lost in $CDCl_3$, but this is because the second capsule is actually filled with $CDCl_3$, which is "invisible" in the ^{1}H NMR spectra. See the Supporting Information for plots of [**3**·2$CDCl_3$], [**3**·MeOAc·$CDCl_3$], and [**3**·2MeOAc] as a function of $[MeOAc]_{initial}$.

[11] The formation of all complexes reported here is reversible; equilibrium is reached in minutes in [D_5]nitrobenzene at 373 K and in 24 h in $CDCl_3$ at 298 K. For calculations of K_{rel}, $[\mathbf{1}]_{initial} = 1.61$ mM; $[MeOAc]_{initial} = 32.2$ mM; $[CDCl_3] = 12.5$ M; [**3**·$CDCl_3$·MeOAc] = 0.525 mM; [**3**·2MeOAc] = 0.972 mM; [**3**·2$CDCl_3$] = 0.113 mM; $[MeOAc]_{free} = 29.7$ mM. $K_{rel} = [cap \cdot MeOAc][CDCl_3]/[cap \cdot CDCl_3][MeOAc]$, where cap = any capsule; for example, [cap·MeOAc] = [**3**·$CDCl_3$·MeOAc] + 2[**3**·2MeOAc]. See the Supporting Information for the derivation of this equation.

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A Two-Step Spin Crossover in [(TPA)Fe^{III}(cat)]BPh$_4$**

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In our studies of mimics for intradiol catechol dioxygenase[1] we synthesized [(TPA)Fe(cat)]BPh$_4$ (**1**, TPA = tris(2-pyridylmethyl)amine, cat = catecholate dianion), a close analogue of [(TPA)Fe(DBC)]BPh$_4$ (**2**, DBC = 3,5-di-*tert*-butylcatecholate dianion) prepared first by Que et al.[2] The latter, in the presence of O_2, gives a nice example of intradiol dioxygenase activity with cleavage of the intradiol C–C bond.[2a] As a routine check of the spin state, we measured the magnetic susceptibility of **1** as a function of temperature and discovered that it exhibits a spin crossover,[3] and moreover one in two steps. We report here the preliminary study of this unusual phenomenon.

Elemental analysis confirmed that complex **1** is consistent with the formula [(TPA)Fe(cat)]BPh$_4$ and is unsolvated. The UV/Vis spectrum of **1** in acetonitrile/DMF (9/1) contains two broad ligand–metal charge transfer (LCMT) bands with maxima at 502 nm (2680 $M^{-1}cm^{-1}$) and 808 nm (3890 $M^{-1}cm^{-1}$), similar to those observed in other iron(III)-catecholato complexes.[2b] It may be inferred from this result that the cat ligand chelates the iron(III) ion in an analogous manner to DBC in **2**.[2a] The structure we propose for **1** is represented in Figure 1.

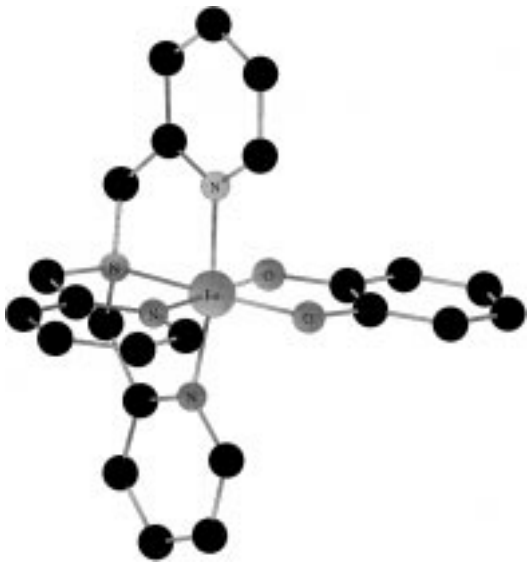

Figure 1. Proposed structure for the [(TPA)Fe(cat)]$^+$ ion.

The temperature dependence of $\chi_M T$ (χ_M = molar magnetic susceptibility) of a microcrystalline sample of **1** (Figure 2) provides evidence for a spin crossover between $S = ½$ (low spin) and $S = 5/2$ (high spin) states of the iron(III) ion.[4, 5] The expected value of $\chi_M T$ for the high-spin iron(III) ion is 4.375 $cm^3 mol^{-1} K$. As the room temperature value of $\chi_M T$ is 4.14 $cm^3 mol^{-1} K$, it is expected that most of the iron(III) ions are in the $S = 5/2$ state. From the data it can be estimated that about 3% of the molecules are in the low-spin state at room temperature. The value of $\chi_M T$ is 0.49 $cm^3 mol^{-1} K$ at 45 K and stays nearly independent of temperature down to 5 K. This value is characteristic of low-spin iron(III) ions and hence of a complete spin conversion at low temperature. These data recorded at decreasing and increasing temperatures did not show any hysteresis effect. Between 45 and 175 K, the $\chi_M T$ versus T curve reveals that the spin-crossover phenomenon takes place in two distinct steps centered at 79 and 106 K (Figure 2, inset). A rather abrupt transformation is observed between 45 and 94 K (80% of the conversion occur within

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