Supramolecular Chemistry

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Efficient Loading and Kinetic Trapping of Hexameric Pyrogallolarene Capsules in Solution**

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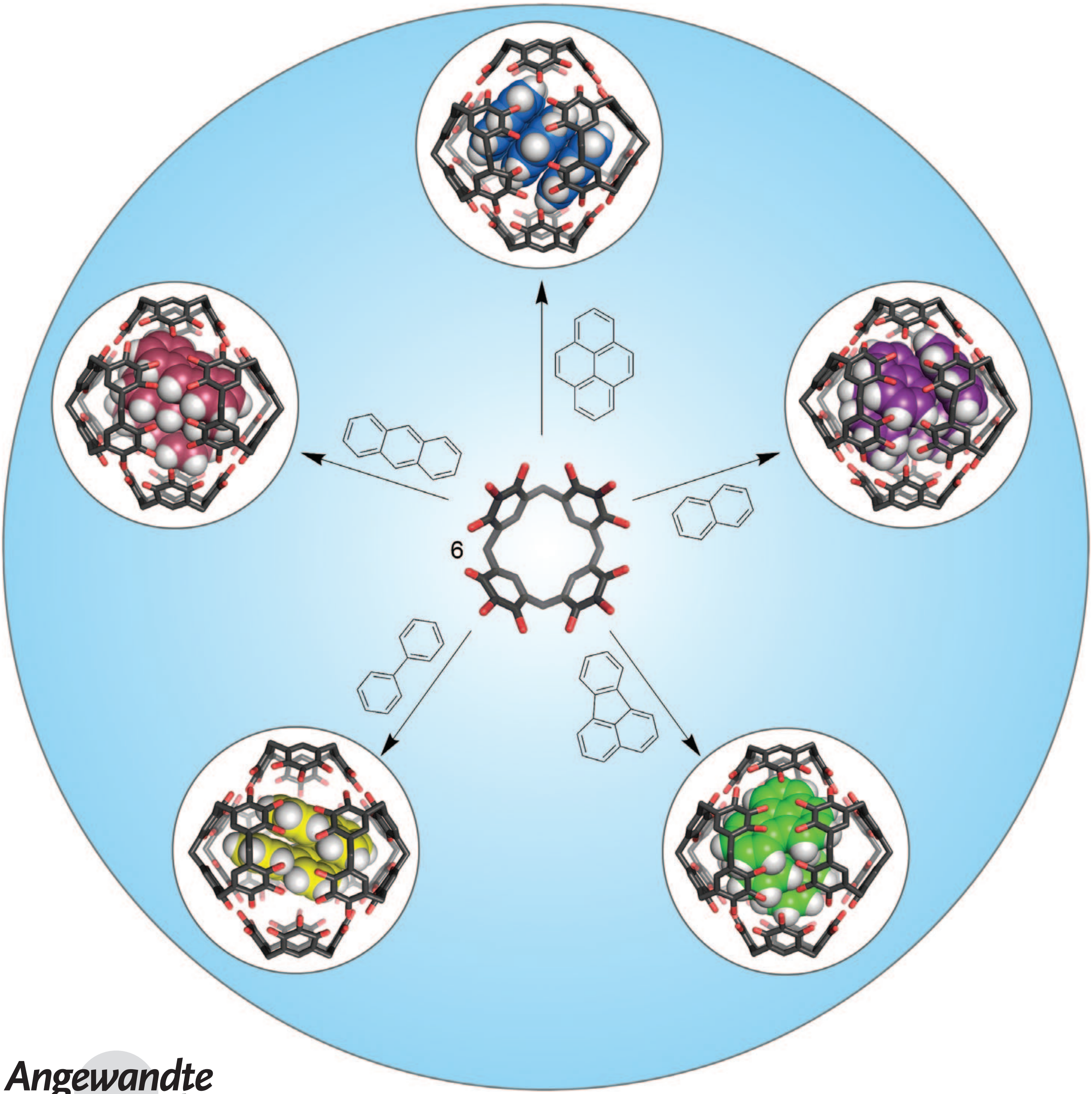

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Although they are among the easiest host molecules to synthesize, pyrogallolarenes and resorcinarenes exhibit some of the most remarkable properties and applications.[1] Both self-assemble by hydrogen bonding (the resorcinarene aided by eight water or alcohol molecules) to form hexameric capsules enclosing some 1300 Å^3 of space—stable in solution and in the solid state.[2] Dimeric capsules have also been observed, primarily in the gas phase and the solid state.[3] These two capsule components self-sort to form hexamers with 100% fidelity,[2c,4] and a requirement for multiple concomitant hydrogen-bond breakage causes the exchange of capsule components and guests to be unusually slow.[5] While guest binding by hexameric resorcinarenes in solution is the subject of numerous studies,[6] no NMR data has been reported for pyrogallolarene hexamers containing guests that are solids under ambient conditions: previously reported guests are solvent molecules[1b,6a] and a few tertiary amines.[6b] Here we present highly efficient solvent-free methods for hexamer assembly that probe the limits of guest binding and provide kinetically trapped guest complexes that cannot be prepared in the presence of solvent.

Previous reports have provided clear evidence for the encapsulation of tris(2,2′-bipyridyl)ruthenium(II) in the gas phase,[7] and the encapsulation of pyrenebutyric acid (PBA) has been resolved crystallographically.[8] The reported solution-phase characterization of PBA and other fluorescent molecules encapsulated in the pyrogallolarene hexamer has used only UV/Vis and fluorescence spectroscopy with no NMR spectra reported for the complexes,[9] and the reported data is in most cases consistent with a low-percent occupancy. We hypothesized that competition from solvent molecules was limiting the efficient loading of pyrogallolarene hexamers in solution, as solvent molecules can interfere with encapsulation either by disrupting the assembly or competing for the inner space. Therefore we set out to examine solvent-free conditions for hexamer assembly with the inclusion of a variety of guests. Our goal was to optimize conditions for guest loading in solution so that NMR spectroscopy can be used for detailed structural, kinetic, and thermodynamic characterization of the guest-dependent behavior of these assemblies. Accordingly, we chose pyrene as a prospective guest and tested three solvent-free methods for self-assembly of mixtures of pyrene and decylpyrogallolarene: dry grinding with mortar and pestle, melting of the mixture with a heat gun, and melting of the mixture plus paraffin wax as a "solvent".

The first method of dry grinding with mortar and pestle could not be made to yield encapsulated pyrene and was discarded. In contrast, melting of a 1:1 mixture (by weight) of decylpyrogallolarene and pyrene with a heat gun under N_2 and subsequent cooling proved to be very successful in allowing pyrene to be encapsulated during self-assembly of the capsule (Figures 1 and 2). The solid that resulted from the melting method was simply dissolved in $CDCl_3$ and characterized by NMR spectroscopy. Notably, there was no binding of pyrene in the capsule if the mixture had not been melted prior to dissolution. To control for the possibility of chemical changes during heating, we added CD_3OD, which disrupts the assemblies,[10] and saw only peaks for free pyrene and pyrogallolarene in the NMR spectrum. One limitation to the melting procedure is that the guest molecules must have a relatively low melting point (below 260 °C) and must not decompose while heating. In order to overcome this limitation, a third procedure was tested in which paraffin wax was used as a "solvent" when melting the mixture. Paraffin wax was shown, using the above melting procedure, not to be encapsulated in the hexamer (expectedly; it is too large). For this procedure, equal weights of decylpyrogallolarene and the guest molecule were combined with a tenfold excess of paraffin wax and heated to 100 °C, which is above the melting point of the wax. The liquid wax acts as a noncompetitive solvent, allowing the pyrene to be encapsulated within the hexamer.

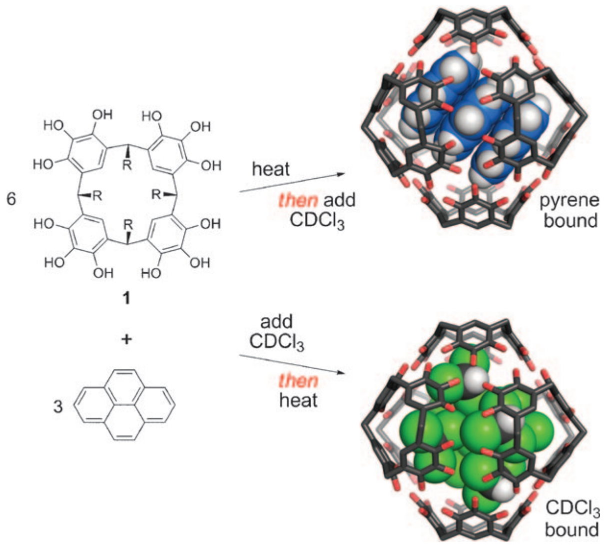

Figure 1. Pyrogallolarene **1** self-assembles to form a hexameric capsule enclosing three molecules of pyrene when heated first and then dissolved in solvent and forms a hexameric capsule containing $CDCl_3$ when dissolved first and then heated. Molecular models were energy-minimized using HyperChem and PM3. R = $C_{10}H_{21}$; R groups are truncated from the models for viewing clarity.

The ^{1}H NMR spectra of pyrene encapsulated within the pyrogallolarene hexamer showed upfield-shifted peaks in the $\delta = 5.3$–6.3 ppm region, assigned to three molecules of encapsulated pyrene (Figure 2). Remarkably, this configuration was not kinetically stable. A change in the NMR spectrum occurred at room temperature over the course of the next 6 h (Figure 2). The encapsulated pyrene peaks shifted slightly upfield and a spliting of the pyrogallolarene

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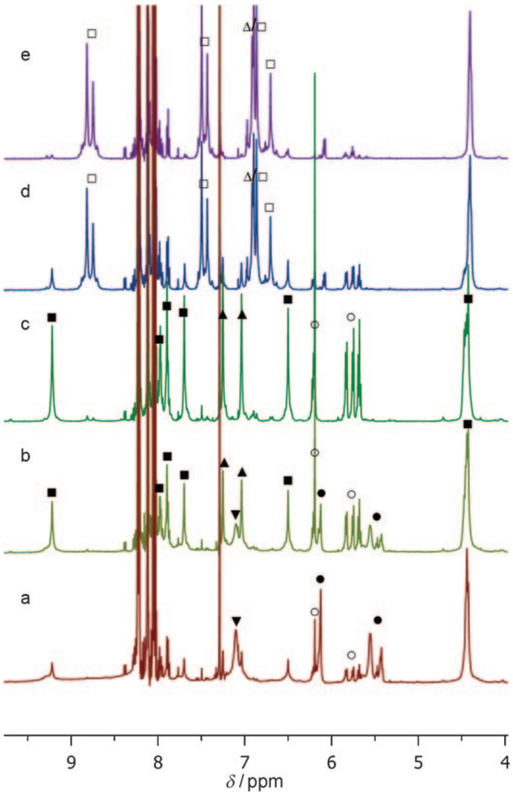

Figure 2. ^{1}H NMR spectra for the configuration change and substitution of solvent for pyrene as guest in hexameric pyrogallolarene ($CDCl_3$). a) 18 min at 25 °C; b) 70 min at 25 °C; c) 6 h at 25 °C; d) 19 h at 70 °C; e) 43 h at 70 °C; Peak assignments: ● initial bound pyrene; ○ bound pyrene after reconfiguration; ▼ initial **1** aromatic hydrogen; ▲ **1** aromatic hydrogen after reconfiguration; △ **1** aromatic hydrogen when solvent-encapsulated; ■ **1** hydroxy after reconfiguration; □ **1** hydroxy when solvent-encapsulated. H-D exchange (addition of D_2O) showed that the initial pyrogallolarene **1** hydroxy signals appear as a broad resonance centered at 8 ppm in (a) (not visible at this scale).

and pyrene peaks showed a loss of symmetry, yet integration shows that the number of pyrenes bound within the capsule did not change. A DOSY measurement gave diffusion coefficients of $(1.4 \pm 0.3) \times 10^{-6}\,cm^2\,s^{-1}$ for both the first and second configurations, while the free pyrene has a diffusion coefficient of $(9.5 \pm 4) \times 10^{-6}\,cm^2\,s^{-1}$, which indicates that the assemblies are of the same size (see DOSY spectrum in the Supporting Information).[11] Under our conditions, a pyrogallolarene dimer should have approximately a diffusion coefficient of $2.2 \times 10^{-6}\,cm^2\,s^{-1}$,[10,12] which, if present, would be clearly resolved in our measurement. The evidence supports an interpretation of two hexamer configurations. We hypothesize that this observed configuration change involves a reordering of the hydrogen bonding of the capsule[13] or a change in the guest packing or both, that is uncommonly slow on the NMR timescale. Once the reconfiguration has occurred, the capsule is very stable. There was no further change or release of guests as indicated by periodic NMR measurements over a period of 9 weeks (the NMR tubes were flame-sealed).

While the second hexamer configuration is kinetically stable it is not the thermodynamic minimum of the system. It was found that upon heating at 70 °C the encapsulated pyrene was released into solution and replaced with $CDCl_3$ as the guest (Figure 2 and 3). Moreover, a 1:1 mixture of decylpyrogallolarene and pyrene that was dissolved in $CDCl_3$ and *then* heated at 70 °C for 24 h in a sealed tube gave only the hexamer filled with $CDCl_3$. The thermodynamic minimum for the pyrene complex in $CDCl_3$ is the solvent-encapsulated state, yet the second configuration of encapsulated pyrene is kinetically trapped and appears to be indefinitely stable at room temperature. These observations support our interpretation of a change of hexamer configurations: the initially formed complex cannot dissociate completely or it would form the thermodynamically preferred $CDCl_3$ complex.

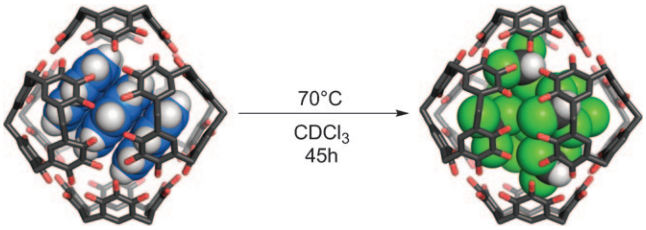

Figure 3. When heated at 70 °C in $CDCl_3$ for 45 h the pyrene is released into solution and replaced by solvent. For line drawings see Figure 1.

We tested the melting methods also for resorcinarene hexamers with a variety of guests, but have not observed the assembly of kinetically trapped encapsulation complexes. This result is likely due to the lower kinetic stability of resorcinarene hexamers and the requirement for water to participate in their assembly.[6d] Water is driven off during melting of the mixture of resorcinarene and guest.

Having obtained highly efficient loading of the pyrogallolarene hexamer with pyrene using the melting method, we tested the encapsulation of a series of prospective guest compounds using the same procedure with a final dissolution in $CDCl_3$ (Table 1 shows guest compounds that are solid at room temperature; liquid guests are tabulated in the Supporting Information). Like the hexameric resorcinarene, hexameric pyrogallolarene has a limited tolerance for polar functional groups on the interior. Ketones, esters, alcohols, amides and amines were tried with little success, unless only one of these functional groups was present on a large hydrocarbon framework. Aromatic and aliphatic hydrocarbons were generally very good guests for the hexamer. NMR measurements showed that encapsulated 2-ethylanthracene, 9-methylanthracene, acenaphthylene, anthracene, biphenyl, carbazole, cetyl alcohol, coumarin, *E*-stilbene, fluoranthene, fluorene, indole, naphthalene, and norbornene could be characterized by NMR resonances shifted upfield by 1–3 ppm. 2,3-benzanthracene, 2-methylanthracene, chrysene, ferrocene, pyrogallol, tetrabutylammonium bromide, tetrabutylammonium chloride, tetrabutylammonium iodide, and pentacene were also tested but were determined not to be encapsulated or they decomposed during heating. Although our screening has not identified a substance that is encapsulated only when using the molten wax method, the validity of the approach is clearly seen with a variety of compounds. The

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Table 1: Guest molecules tested for binding in hexameric pyrogallolarene.

Entry	Guest	Bound with melting	Bound in wax	Average number bound[a]
1	2,3-benzanthracene	no	no	–
2	2-ethylanthracene	yes[b]	no	nd
3	2-methylanthracene	d	no	–
4	9-methylanthracene	yes[b]	yes[b,c]	nd
5	acenaphthylene	yes	yes[b]	2 (0.22)[d]
6	acetanilide	–	no	–
7	anthracene	yes	yes	3 (0.39)
8	benzoic acid	–	no	–
9	biphenyl	yes	yes[b]	2 (0.23)
10	carbazole	yes[b]	no	nd
11	cetyl alcohol	yes	yes[b]	nd
12	chrysene	d	no	–
13	coumarin	yes[b]	no	nd
14	*E*-stilbene	yes[b]	no	nd
15	ferrocene	no	d	–
16	fluoranthene	yes	yes	3 (0.42)
17	fluorene	yes	yes	2 (0.24)[d]
18	indole	yes[b]	yes[b,c]	nd
19	naphthalene	yes	yes	6 (0.57)[d]
20	norbornene	yes	yes[c]	2 (0.15)
21	pentacene	d	no	–
22	pyrene	yes	yes	3 (0.42)
23	pyrogallol	no	no	–
24	NBu_4Br	no	no	–
25	NBu_4Cl	no	no	–
26	NBu_4I	no	no	–
27	triphenylmethane	no	no	–

[a] Apparent packing coefficients are given in parentheses. [b] Low guest loading. [c] High concentration of guest and pyrogallolarene needed for binding. [d] Average determination of bound molecules. d = decomposed, nd = not determined.

low solubility of some guest molecules in molten wax appears to be the primary limitation of the method.

For some compounds, the spectra were sharp and clearly indicate the presence of a single predominant hexameric species, for example, pyrene and fluoranthene (entries 7, 9, 16, 22; Table 1) (all ^{1}H NMR spectra of encapsulation complexes are shown in the Supporting Information). These spectra allowed for the determination of the number of molecules bound within the capsule. Some of the spectra showed a complex pattern of upfield-shifted peaks for the guests, indicative of a mixture of hexamers with different configurations or occupancy or both, for example, naphthalene (entries 5, 17, 19), and accordingly a quantitative determination of encapsulated molecules could be averaged at best. There are also cases of broad upfield-shifted guest peaks of low signal intensity, for example, coumarin and *E*-stilbene (entries 2, 4, 10, 11, 13, 14, 18). These likely also represent a mixture of hexamers with different configurations or occupancy or both with dynamics at an intermediate rate on the NMR timescale.

The apparent low occupancy of some hexamers is at odds with well-established observations that typical packing coefficients for cavity-containing molecules are around 0.55 for guests that are liquids and 0.55–0.70 for those that are solids under ambient conditions.[14] This is partly explained by crystallographic observations of the ability of these hexamers to change shape slightly in response to guests.[2b,8] Our packing coefficient determinations are based on an average cavity volume of 1300 Å^3, which does not account for this shape flexibility. Moreover, the observation of hexamer rearrangement that does not involve complete dissociation in our pyrene experiments suggests that solvent molecules could "leak in" to unstable hexamer configurations during the dissolution in deuterated solvents after melting. This would fill any remaining space, stabilizing the hexamers, but because of the deuterium, not be apparent in the NMR spectra.

The melting method of guest loading for pyrogallolarene has been proven to be simple and effective for the encapsulation of guest molecules that are solids under ambient conditions. Importantly, the hexameric capsules immediately generated are often densely packed with the guest, even if these complexes are not the most thermodynamically stable configurations in solution. The success of the method reveals complex packing arrangements that are kinetically stable and that place the same molecule within different environments inside the hexamer, with remarkably slow exchange. The complex pattern of the NMR spectra and the slow kinetics are a special feature of these capsules, which is revealed clearly in complexes produced by the melting method. Detailed structural, kinetic, and thermodynamic studies of these remarkable encapsulation complexes are underway in our laboratory and will be the subject of future reports.

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