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An NMR Study of the Rates of Single-Molecule Exchange in a Cylindrical Host Capsule

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The dynamic character of noncovalent, reversible molecular assemblies is directly responsible for their unique properties; the facile exchange of constituents results in host structure and guest selectivity which are thermodynamically, rather than kinetically, determined. Reversible encapsulation occurs when a self-assembled host more or less completely surrounds a molecular guest.[1] The capsules, whether held together by hydrogen bonds or by metal−ligand interactions, have become modern tools of physical organic chemistry. They offer features such as the stabilization of reactive intermediates,[2] molecular recognition,[3] and reversible polymerization.[4] In our work on encapsulation complexes, the exchange of guests residing in a self-assembled host superstructure contributes to the acceleration and catalysis of reactions,[5] enantioselective recognition through memory effects,[6] and a form of chemical amplification reminiscent of autocatalysis.[7] Central to these properties is the mechanism by which guests enter and exit their host capsules. We report here studies of guest exchange for the cylindrical capsule **1**[8,9] (Figure 1). These experiments reveal a mechanistic continuum for exchange that depends on the structure of the guest[10] but does not involve complete dissociation of the capsule or the creation of empty volumes.

To address the mechanism of supramolecular substitution, the exchange rates of guests within **1** with those outside the capsule were determined. The assembly containing one benzene with one *p*-xylene molecule in the capsule—a particularly favored arrangement[11]—was studied as a representative example of small guest exchange. The exchange of encapsulated and external benzene was observed by ^{1}H magnetization transfer NMR spectroscopy[12] at 335 K;[13] following the application of a 180° pulse to the resonance of external benzene, the exchange may be observed from the decrease in the intensity of the encapsulated benzene resonance as a function of mixing time. Capsule **1** (1.0 mM[14]) was placed in *p*-xylene-d_{10} containing four different concentrations of benzene (16−160 mM[15]). The rate of benzene exchange increases linearly with the total benzene concentration in solution (Figure 2).

The results in Figure 2 point to two parallel mechanisms for benzene exchange. One process, first-order in external benzene, gives rise to the concentration-dependent exchange rate. The second-order rate constant for this process (∼6.5 M^{-1} s^{-1}) is given by the slope of the line in Figure 2. The nonzero *y*-intercept (∼0.25 s^{-1}) is the rate constant for a second process that is independent of external benzene concentration.

The nature of these two processes is further revealed by monitoring exchange between the magnetically inequivalent capsule halves[8] and also exchange of the second guest, *p*-xylene. Quite surprisingly, no measurable magnetization transfer between capsule halves was observed. This suggests that **1** remains intact during

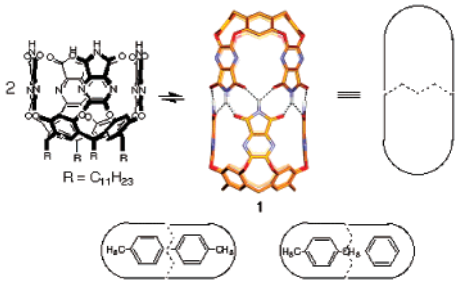

Figure 1. Cylindrical capsule **1** with guests 4,4-dimethylbiphenyl and benzene/*p*-xylene molecules.

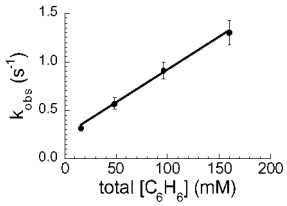

Figure 2. Rate of benzene exchange as a function of benzene concentration. [**1**] = 1.05 mM; T = 335 K. Error bars are estimated at ±10%.

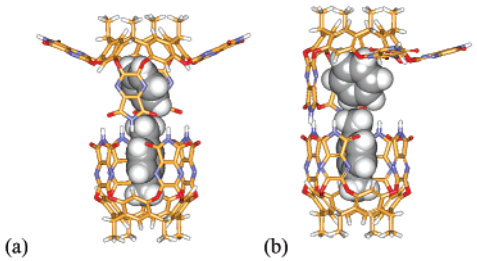

Figure 3. Proposed structures responsible for benzene guest exchange with (a) two opposite walls opened and (b) two adjacent walls opened.

the benzene-exchange process, and that *the incoming benzene must reside in the same half of the capsule vacated by the outgoing benzene*. Consistent with an intact capsule, we also observe that *p*-xylene exchange does not occur on this time scale.[16]

The pathways for benzene exchange can be elucidated from the experimental data as follows. An intact "half-empty" capsule with only the *p*-xylene as a guest is inconsistent with an entering benzene participating in the rate-determining step. Instead, we suggest that flaps in the capsule open to allow one benzene molecule to displace another without complete dissociation of the capsule. One possible structure, shown in Figure 3a, is still held together by six hydrogen bonds (two bifurcated, four linear). A related structure (Figure 3b), with two adjacent walls open, also exposes the resident benzene for displacement and leaves five hydrogen bonds intact (three bifurcated, two linear). The latter features one wall of the capsule

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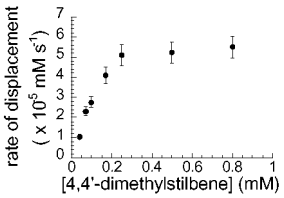

Figure 4. Rate of displacement of **2** by **3** as a function of incoming guest concentration. [**1**] = 0.1 mM; T = 295 K. Error bars are estimated at ±10%.

half containing the *p*-xylene unsecured and free to bend away from the hydrogen-bonding seam, an opening still too small for escape of the guest.[17]

The mechanism of the first-order process is less certain. Calculations by Houk[18] suggest that vacated capsules are viable intermediates, but the open walls of a vacated capsule would rapidly close, and it is unlikely that the two capsule halves of such a species would remain distinct. We therefore propose a mechanism similar to that of the second-order process, in which the nascent benzene is displaced instead by a solvent xylene molecule. The solvolysis prevents closure to the symmetric, single-xylene assembly until the capture of the eventual new benzene guest.[19]

The exchange of guests that are large enough to serve as lone occupants is typically slower than that of small molecules, enabling the rate of exchange to be followed by conventional 1D NMR.[20] We studied the supramolecular substitution of encapsulated 4,4′-dimethylbiphenyl (**2**) with incoming guest 4,4′-dimethylstilbene (**3**); **3** is favored in equilibration studies, and thus the reaction is practically irreversible. The initial rates as a function of concentration of 4,4′-dimethylstilbene are plotted in Figure 4. At low concentrations (0.1−0.2 mM) of the incoming **3**, the rate is proportional to [**3**]. At high concentrations (0.2−1 mM), a leveling off occurs. The break in the plot of Figure 4 indicates a change in the rate-determining step at higher concentrations of incoming guest and requires an intermediate.

A viable mechanism is analogous to that proposed for the spherical "softball"[6,21] capsules. Displacement of the first guest by solvent leaves an intermediate that can either reclaim **2** or bind **3**. At high concentrations of **3**, every intermediate leads to substitution, and the kinetics saturate. The mechanism is confirmed by the observation of an inverse dependence of exchange rate on the concentration of outgoing guest **2** in solution. The intermediacy of an "empty" capsule seems unlikely, given that smaller vaccums are not observed in the previous system. Capsule dissociation is also not required; direct displacement is observed for the pseudoself-exchange of 4,4′-di(perdeuteriomethyl)biphenyl (**2-*d*$_6$**) for **2**, which has a linear dependence on incoming guest concentration (see Supporting Information).

In conclusion, the direct displacement of one guest by another has been revealed by kinetic and dynamic NMR measurements. A picture emerges for molecular exchange in which one molecule is replaced smoothly by another. As the size and shape of the molecules increases, solvent-bridged intermediates determine the rates; empty volumes on the molecular scale need not be invoked.

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Supporting Information Available: Experimental details, plots of magnetization transfer data for exchange of small guests and exchange rates for large guests (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The resting state of the capsule in the deuterated mesitylene on commercial offer holds one molecule of deuterated benzene and one molecule of deuterated *p*-xylene. Both are minor impurities, as established by control experiments, but their concentrations are sufficiently low that they can be easily replaced by their protio counterparts
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(13) The cylindrical capsule is assembled at temperatures between 220 and 335 K.
(14) When higher concentrations of capsule **1** were employed, no benzene exchange was observed. We suspect that at high capsule concentrations, aggregation of the long alkyl chains on the lower rim of the resorcinarene occurs and prevents guest exchange. S. Lin and J. Rebek, Jr., unpublished results.
(15) Higher concentrations of guest were not used as there were complications in data collection with such a large excess of proteobenzene relative to that of capsule **1**.
(16) The absence of *p*-xylene exchange was determined by two-dimensional ROESY spectroscopy at 315 K and magnetization transfer spectroscopy at 335 K.
(17) We have observed under conditions of benzene exchange, the *p*-xylene molecule is rotating such that the methyl groups at the 1,4-positions are exchanging. This motion is likely possible only with a flexing of the capsule wall(s). S. Lin, J. Rebek, Jr., unpublished results.
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