Self-Assembled Molecular Capsule Catalyzes a Diels−Alder Reaction

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Earlier work established that the multiring structure **1** (Figure 1) exists as an hydrogen-bonded dimer (**1**−**1**) in organic solvents.[1] The 16 hydrogen bonds are like the stitches along the seam of a softball that hold its two pieces together, and because the dimer has a pseudo-spherical shell, we refer to **1**−**1** as a notional "hydroxy softball." The dynamic qualities of hydrogen bonds cause the hydroxy softball to form and dissipate on the time scale of milliseconds and provide a temporary receptacle for smaller, complementary molecules. Some unusual physical constraints[2] and chemical behaviors[3] are imposed on the molecules held inside; even the acceleration of a Diels−Alder reaction has been observed.[4] Here we report the use of the hydroxy softball as a true *catalyst* in this context.

The specific Diels−Alder reaction is that of *p*-benzoquinone (**2**) with the thiophene dioxide derivative **3** (Scheme 1) in *p*-xylene-d_{10}. When a large excess of the *p*-benzoquinone is present and high temperatures are used, the initial adduct **4** loses SO_2 and aromatizes to a naphthalene skeleton.[6] Further oxidation to the corresponding naphthoquinone can also be observed. We had hoped that the loss of SO_2 from the adduct—inside the softball—would result in a molecule whose dimensions could no longer be accommodated and would be released into the bulk solvent. This should force turnover in the same way that Hilvert's system forced turnover in his demonstration of Diels−Alder reaction catalysis by antibodies.[7] The hydroxy softball does indeed catalyze the reaction, but for quite different reasons.

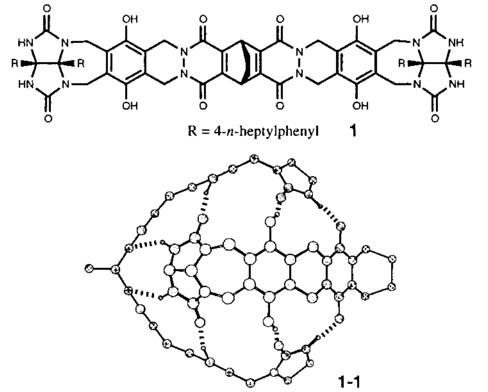
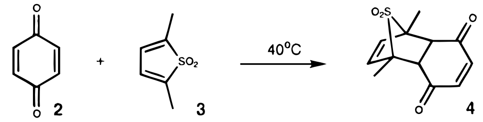
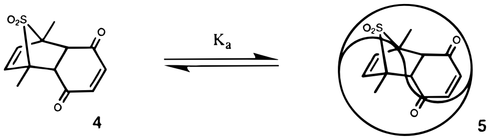


Figure 1. Self-complementary molecule **1** (top) and the hydrogen-bonding network of dimeric capsule **1**−**1** (bottom), the hydroxy softball, as calculated using MacroModel 5.5[5] with the AMBER force field. The dimer is presented in cross-section, and the peripheral atoms have been deleted for viewing clarity.

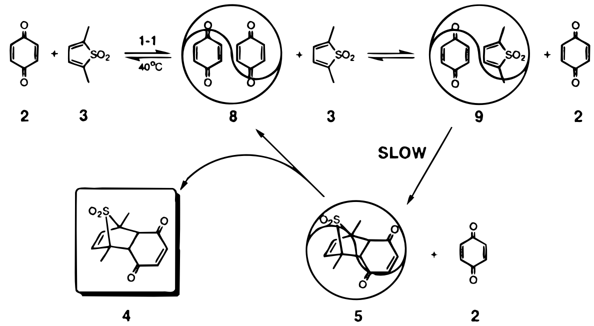
Scheme 1



Scheme 2



Scheme 3



At lower temperatures, the initial adduct **4** can be isolated and characterized and its affinity for the softball can be determined by NMR titration. Because the exchange of **4** in and out of the softball is slow on the NMR time scale in *p*-xylene-d_{10}, resonances for free and encapsulated adduct can be integrated and used to calculate the association constant, K_a, for the process of Scheme 2. The value is 155 M^{-1}, a number more than an order of magnitude lower than observed for adamantane or ferrocene derivatives under these conditions.[1] To the softball, the adduct is an unwelcome guest and it is driven out of the cavity by *p*-benzoquinone ($K_a = 1.9 \times 10^5$ M^{-2}).[4] This preference of the softball augurs well for catalysis of the Diels−Alder reaction. Binding studies with the thiophene dioxide were not successful; it showed a much-reduced affinity, and no encapsulated **3** could be observed even when solution concentrations up to 700 mM were employed.

In the experiment that indicates catalysis, solutions of diene **3** (10 mM) and *p*-benzoquinone (**2**, 10 mM) in *p*-xylene-d_{10} solvent at 40 °C were exposed to the softball (1 mM). The reaction was monitored by NMR and showed approximately 55% conversion after 2 days and 75% conversion after 4 days (Figure 2). Without the softball present, 10% and 17% conversions are obtained, after these times, respectively. An additional experiment was performed using the corresponding S-shaped isomer **6**. The S-shaped isomer **6** features all of the acidic functionalities of **1** but does not assemble into a capsule. Compound **7** does not catalyze the reaction under consideration. The structure of [2,2]paracyclophane (**7**) makes it an excellent guest,[8] and it is expected

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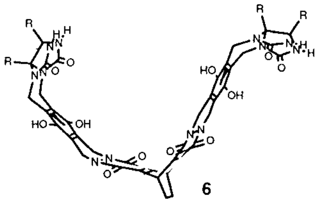

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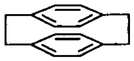

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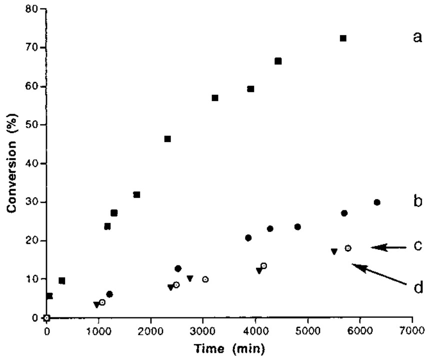

Figure 2. Comparative study of the formation of the Diels−Alder adduct along the time: (a) catalyzed reaction; (b) reaction inhibited with 1 equiv (with respect to the softball) of [2,2]paracyclophane (**7**); (c) background reaction; (d) use of S-shaped isomer **6** instead hydroxy softball.

to compete with the reaction components for encapsulation. When **7** is present in addition to the softball, inhibition of the reaction is indeed the result. Accordingly, the experimental evidence supports the conclusion that the reaction takes place within the capsule.[9] That true catalysis takes place is shown by turnover: over 7 times as much adduct as softball is obtained after 4 days under the conditions described above.

The catalytic cycle is proposed in Scheme 3. The resting state of the capsule contains two quinones **8**, one of which is occasionally displaced by the thiophene dioxide to give the fully loaded "Michaelis" complex **9**. A moderately enhanced cycloaddition ensues, followed by displacement of the adduct **4** by two molecules of *p*-benzoquinone (**2**). The exchange of the different encapsulated species in and out of the softball is fast compared to the chemical step, the formation of **5**.

Consistent with these approximations, the formation of the product **4** follows pseudo-first-order kinetics (Figure 3). The plot is linear over two half-life times (75% conversion), indicating that product inhibition is not a factor: true catalysis is observed. The rate enhancement, based on the ratio of half-life for the background reaction, at 10 mM each benzoquinone and thiophene, vs the reaction inside the softball is 10-fold.

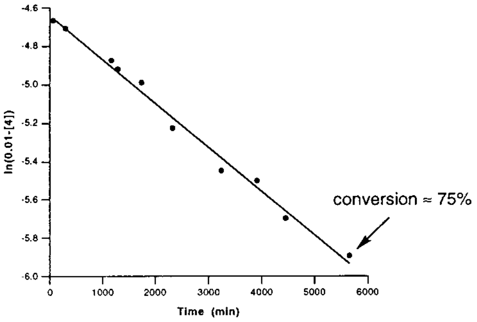

Figure 3. Logarithmic plot of the formation of the Diels−Alder adduct using hydroxy softball as catalyst. It shows linearity over 75% conversion. The experiment has been performed in *p*-xylene-d_{10} at 40 °C, with concentrations of 10 mM for the reactants and 1 mM for the capsule.

While the strategy based on the extrusion of the SO_2 failed to develop, the higher affinity of the *p*-benzoquinone reactant forced turnover. The displacement of a single molecule of adduct from the softball by two *p*-benzoquinones is disfavored on entropic grounds,[1] but turnover takes place due to the poorer affinity of the Diels−Alder product for the capsule. The catalysis is admittedly modest, and many other ways of catalyzing Diels−Alder reactions exist;[7,10−20] nevertheless, catalytic the present result offers further promise for the use of molecular capsules as catalytic reaction chambers.[21]

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