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Selectivity in an Encapsulated Cycloaddition Reaction

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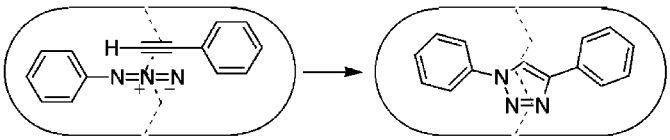
ABSTRACT



A 1,3-dipolar cycloaddition takes place within a reversibly formed, self-assembled capsule. The reaction proceeds through an unsymmetrically loaded encapsulation complex with absolute regioselectivity.

Synthetic receptors that apply molecular recognition to catalysis aim at elusive, moving targets—transition states. Cycloaddition reactions are popular in this context, perhaps because there are so few enzymatic examples or because their transition states resemble stationary targets—the products. The latter feature makes product inhibition inevitable, but cyclodextrins,[1] cucurbituril,[2] multimeric porphyrins,[3] and reversibly formed encapsulation complexes[4] have all shown promise in accelerating these reactions. We report here a synthetic chamber that accelerates a 1,3-dipolar cycloaddition. Although the system does not solve the turnover problem, it allows the direct observation of the "Michaelis complex".

Earlier we described a capsule with a roughly cylindrical cavity[5] in which two different aromatic guest molecules can be accommodated simultaneously. Their orientation is constrained to edge-to-edge approaches, and only their peripheral substituents make contact. Figure 1 uses the interaction of the methyl groups of two encapsulated toluene molecules to illustrate this point. The arrangement hints at reactions between such substituents, anchored in the capsule by their respective aromatic nuclei.

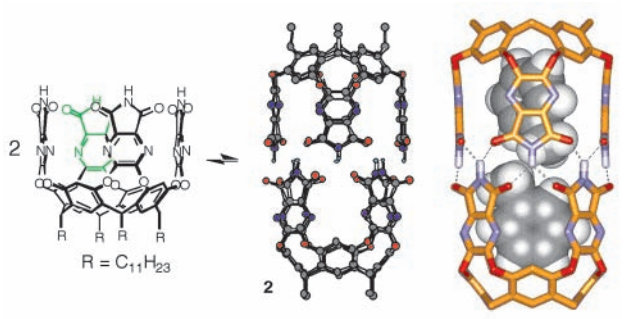


Figure 1. Line drawing of the resorcinarene subunit (left) and ball-and-stick model of the dimeric capsule (center). Two toluene molecules are encapsulated in the energy-minimized complex (right).

The cycloaddition involves phenylacetylene **3** and phenyl azide **4** (Figure 2). These compounds react very slowly to give roughly equal amounts of two regioisomeric triazoles **5** and **6**.[6] At ambient temperature in mesitylene solvent the rate constant is 4.3×10^{-9} M^{-1} s^{-1} and corresponds to a half-life (at 1 M each component) of several years. At the

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(3) Marty, M.; Clyde-Watson, Z.; Twyman, L. J.; Nakash, M.; Sanders, J. K. M. *Chem. Commun.* **1998**, 2265−2266.
(4) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50−52.
(5) Heinz, T.; Rudkevich, D. M.; Rebek, J., Jr. *Nature* **1998**, *394*, 764−766. Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 4928−4929. Körner, S. K.; Tucci, F. C.; Rudkevich, D. M.; Heinz, T.; Rebek, J., Jr. *Chem.—Eur. J.* **1999**, *6*, 187−195.

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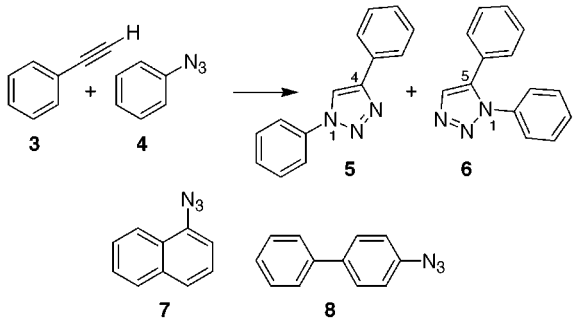

Figure 2. The reaction of the acetylene and azide gives comparable amounts of the two regioisomers.

millimolar concentrations used in the experiments below, the rate is negligible on the human time scale.

A solution of **3** (50 mM), **4** (25 mM), and **2** (5 mM) in deuterated mesitylene shows the encapsulated product within a few days (Figure 3A−D). The product triazole gives a

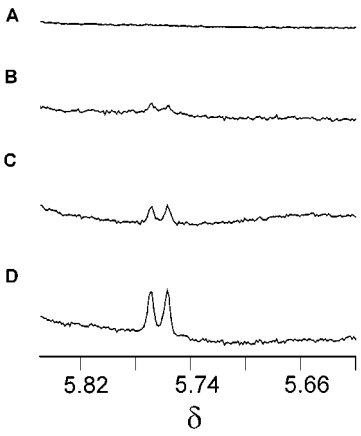

Figure 3. Formation of the 1,4-isomer inside the capsule from phenyl azide (25 mM) and phenylacetylene (50 mM) in the presence of the capsule (5 mM) in mesitylene-d_{12}. (A) $t = 0$; (B) $t = 1540$ min; (C) $t = 4320$ min; (D) $t = 8500$ min.

unique signal at 5.76 ppm as it is formed (Figure 3). The initial rate of product formation, determined over 6 days, is 1.3×10^{-9} M s^{-1}.

Only the 1,4-isomer is formed. Control experiments established that only the 1,4-isomer is encapsulated in mesitylene and this compound is liberated by the addition of DMF (Figure 4A). The product obtained from the capsule on treatment with DMF is shown in Figure 4B; the appropriate regions of the spectrum of the 1,5-isomer are shown for comparison in Figure 4C.

(6) Kirmse, W.; Horner, L. *Liebigs Ann.* **1958**, *614*, 1. For discussions, see the following: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1977; p 155. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.

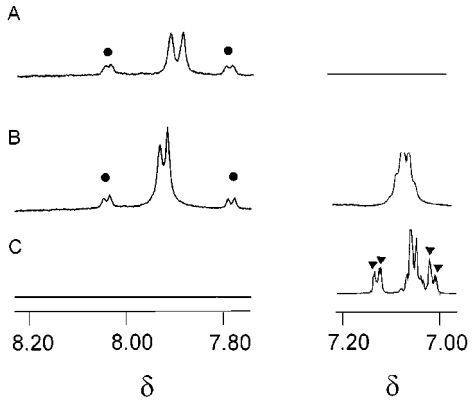

Figure 4. Selective formation of the 1,4-isomer. (A) Addition of DMF-d_7 to a solution of authentic encapsulated 1,4-isomer in mesitylene-d_{12}. (B) Addition of DMF-d_7 to the mesitylene-d_{12} solution obtained from phenyl azide (25 mM) and phenylacetylene (50 mM) in the presence of the capsule (5 mM). (C)Addition of DMF-d_7 to solution of authentic 1,5-isomer in mesitylene-d_{12}. (●) Released 1,4-isomer; (▽) 1,5 isomer.

Further evidence for an encapsulated transition state (rather than, say, regioselective catalysis by functional groups of the capsule) involves size and shape selectivity. Neither 1-naphthyl azide **7** nor 4-biphenyl azide **8** show rate accelerations in their cycloadditions with **3** when in the presence of the capsule. The naphthyl azide is not encapsulated, while the biphenyl azide is quickly displaced from the capsule by two phenyl acetylenes.

The various encapsulated species were identified as follows. The capsule in the presence of an excess of **4** alone gives a single symmetrical species. The aryl CH resonances are as shown in Figure 5 and were assigned from their

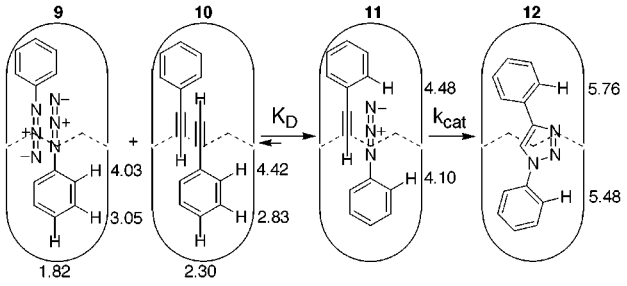

Figure 5. The disproportionation equilibria of encapsulated reactants. Selected chemical shifts are given in ppm.

relative shifts and multiplicities. The only orientation consistent with these shifts is that shown in **9**. The arrangement is consistent with the preference of polar groups to be near the seam of hydrogen bonds.

The assignments for encapsulated acetylene were complicated by a pesky impurity in the commercial material that could not be removed by distillation. Excess acetylene gave

not only the symmetrically loaded capsule **10** but also 20−40% (depending on the other components present) of an unsymmetrically filled capsule. This species was identified by the addition of excess dioxane as a capsule containing one acetylene and one dioxane molecule.

A new, unsymmetrical complex appeared when a mixture of azide and acetylene were present, and it was the most abundant species. Fortunately, its NH resonances were well separated from those of the other capsule species (Figure 6) and allowed clean integration and quantification of this "Michaelis complex."[7]

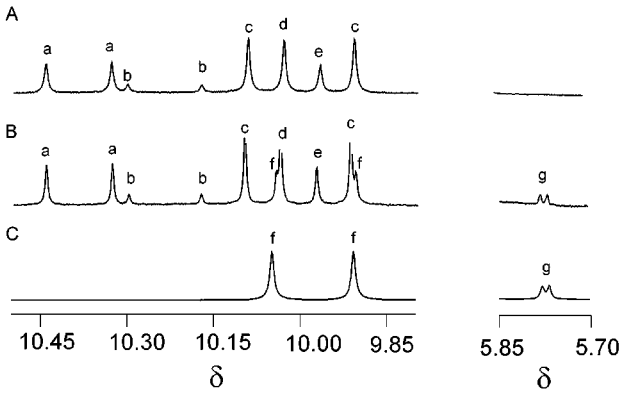

Figure 6. Encapsulated species in a solution of capsule **2**, phenyl azide, and phenylacetylene in mesitylene-d_{12}. (a) NH resonances of the capsule with acetylene and dioxane; (b) NH resonances of capsule with azide and dioxane; (c) NH resonances of "Michaelis" complex **11**; (d) NH resonance of capsule complex **9**; (e) NH resonance of capsule complex **10**; (f) NH resonances of product complex **12**; (g) *ortho*-protons of the phenyl rings of encapsulated 1,4-isomer **5** in complex **12** (see assignments in Figure 5). (A) At $t = 0$ incubating **3** (50 mM), **4** (25 mM), and capsule **2** (5 mM) in mesitylene-d_{12}. (B) $t = 8500$ min for the same system as in (A). (C) Encapsulation of authentic 1,4-isomer **5** with **2** in mesitylene-d_{12}.

We studied the disproportionation equilibrium of Figure 5. A purely statistical distribution of the two guests predicts twice as much heterocapsule **11** as either homocapsule, since there are two ways to fill the former and only one way to fill either of the latter (given the orientation preferences discussed above). The effect of dioxane, the spectator guest, was comparable on both homocapsules; i.e., no great preference for homocapsules exists. For the equilibrium $K_D = [\mathbf{11}]^2/[\mathbf{9}][\mathbf{10}]$, the statistical distribution would predict K_D to be 4. Six determinations with various mole fractions of the azide and acetylene showed $K_D = 9 \pm 3$. The exchange of these small guests is fast. They equilibrate on mixing; the system is at a steady state. Perhaps the space in **11** is better occupied or there is a weak attractive force between the occupants. In any case, the preference for **11** is only a few tenths of a kcal/mol.

At these concentrations, chosen for convenience of monitoring by NMR, the capsule is saturated. Increasing the external concentrations of the reactants does not increase the concentration of the heterocapsule, but it increases the rate of the cycloaddition reaction outside. The rate inside is fixed at saturation, and comparing the k_{cat} to the outside rate k_2 suffers all of the ambiguities that arise when a bimolecular rate is compared to a unimolecular one.

The calculated concentrations inside are a matter of volume: the capacity is ~450 Å^3, and the two reactants enjoy a 3.7 M engagement for a matter of seconds when they are encapsulated. The rate inside, assuming the appropriate orientation can be achieved, would then be $\sim 6 \times 10^{-8}$ M s^{-1}, a figure larger than the initial rate actually observed. One might well ask, why is the reaction not faster inside? Perhaps they are positioned in a way that is not ideal for the transition state; we have no reason to believe that the transition state is bound better than the reactants. At these concentrations the reaction outside the capsule is calculated to proceed at a rate of 5.4×10^{-12} M s^{-1}, some 240 times slower than inside the capsule.

The direct observation of the Michaelis complex is, to our knowledge, unique to the case at hand. While it simplifies the analysis, one thing is clear: the product is the best guest in the system, gradually the capsule is filled with it, and the reaction, slowed by product inhibition, grinds to a halt.

Overcoming the general problem of product inhibition remains a challenge for the future.[8] In the meantime, the exquisite selectivity for the extended regioisomer **5** augurs well for controlling reactions within reversibly formed capsules.[9]

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(7) Because both reactants form symmetrical complexes (e.g., **9** and **10**) the system shows substrate inhibition and does not obey Michaelis−Menten kinetics; for a discussion, see: Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; W. H. Freeman: New York, 1985; p 114.

(8) For a discussion, see: Nakash, M.; Clyde-Watson, Z.; Feeder, N.; Davies, J. E.; Teat, S. J.; Sanders, J. K. M. *J. Am. Chem. Soc.* **2000**, *122*, 5286−5293 and references therein.

(9) For examples with metal−ligand capsules, see: Zeigler, M.; Brumaghim, J. L.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4119−4121. Caulder, D. L.; Raymond, K. N. *J. Chem. Soc., Dalton Trans.* **1999**, 1185−1200. Umemoto, K.; Yamaguchi, K.; Fujita, J. *J. Am. Chem. Soc.* **2000**, *122*, 7150−7151. Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, N.; Kusukawa, T.; Biradha, K. *Chem. Commun.* **2001**, 509−518.