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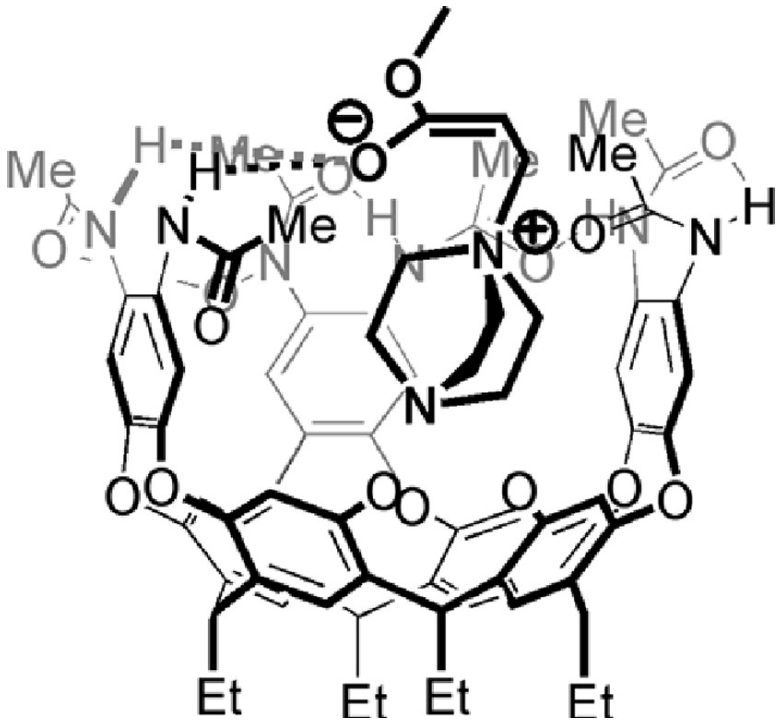

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Deep Cavitands Provide Organized Solvation of Reactions

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Cavitands **1** are deep, vase-like structures capable of binding suitably sized neutral and cationic guests.[1] The aromatic walls at the base of the cavity provide an extended π surface, while the upper rim is an environment rich in H-bond donors and acceptors. The latter features a ring of eight secondary amides organized in a head-to-tail manner. These regions are fixed in space through synthesis and presented to guests *independent of the nature of the external bulk solvent* and alter their reactivities. Quinuclidine, for example, shows much enhanced reactivity as a nucleophile when the base is detained in a cavitand bearing an inwardly directed methyl ester.[2] The amides of the rim stabilize the developing charge at the transition state near the reactive centers. Here, we report effects of organized solvation and catalysis in the α-deuteration of activated olefins.[3,4]

Methyl acrylate **2** was combined with stoichiometric amounts of diazabicyclo[2.2.2]nonane (DABCO) **3** and cavitand **1c** in acetone-d_6 at a concentration of 13.9 mM, and the reaction was monitored by ^{1}H NMR (600 MHz). Binding of DABCO is shown by ^{1}H peaks at 0.85 and −0.25 ppm. After 3 days reaction, all of the methyl acrylate was converted to α-D-methyl acrylate **6**. Kinetics measurements gave an initial rate of reaction of 0.021 mM/min. In the absence of cavitand, no deuteration was observed by NMR after 5 days at either 23 or 60 °C, nor was deuteration observed when performed in the presence of 8 equiv of acetanilide, a mimic for the generic H-bonding abilities of the cavitand. Assuming a detection limit of 5% for the ^{1}H NMR measurements, this translates to a rate acceleration of at least 200-fold.

Combination of methyl acrylate and DABCO in CD_3OD (a much stronger acid than acetone-d_6) in the absence of cavitand does result in α-deuteration, albeit slowly (the observed initial rate is 0.008 mM/min). The effect of the addition of cavitand (both stoichiometric and catalytic amounts) is shown in Figure 3. Even in the presence of only 2% cavitand **1b** (**1c** is insoluble in CD_3OD), a 40% increase in initial rate is observed. Use of a stoichiometric amount of **1b** provides a 2-fold rate acceleration. Performing the reaction in a more polar, protic medium reduces the effect of cavitand, but the organized solvation in the system is still more effective at charge stabilization than CD_3OD solvent.

The scope of deuteration effects was tested, using quinuclidine **4** as catalyst due to its higher reactivity and binding properties. The results are summarized in Table 1. The rate of deuteration is generally correlated with the electron-withdrawing abilities of the activating group; methyl vinyl ketone **7** and phenyl vinyl sulfone **8** both reacted very quickly, with quantitative deuteration in acetone-d_6 observed after only 30 and 120 min, respectively (entries 1 and 2). These more active olefins did show a very slow background rate (<15% conversion after 8 days), shown as $V_{0(uncat)}$ in Table 1. This allows a measurement of the relative acceleration $V_0/V_{0(uncat)}$ for the deuteration. The accelerations observed were 1400-fold for methyl vinyl ketone **7** and 800-fold for phenyl vinyl sulfone **8**, even higher than that estimated previously. Both acrylonitrile **9** and

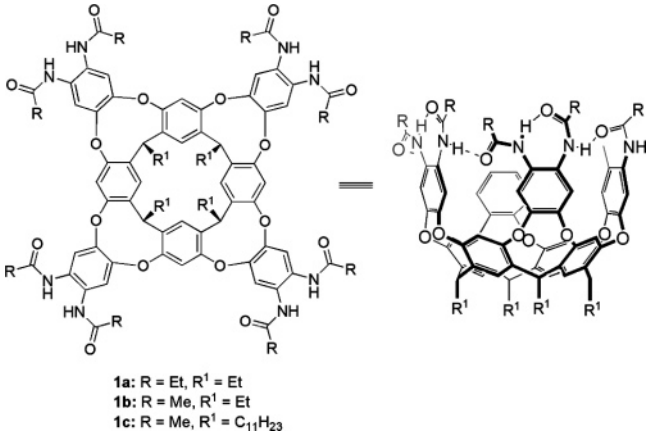

Figure 1. Deep cavitands used.

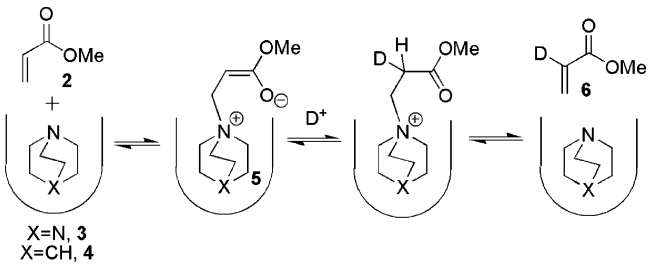

Figure 2. Proposed mechanism of deuteration.

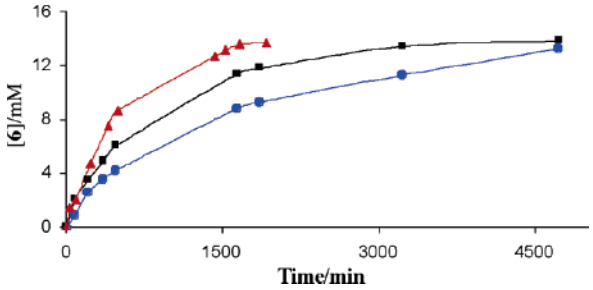

Figure 3. Rate dependence of formation of **6** on [**1b**] in CD_3OD. Initial [**2**] = 13.9 mM, [**3**] = 13.9 mM, (▲) = 13.9 mM **1b**; (■) = 0.3 mM **1b**; (●) = 0 mM **1b**.

methyl acrylate **2** were susceptible to deuteration; however, the reaction was much slower (entries 3 and 4), and no background reaction could be observed under the conditions. A similar assumption for the sensitivity of ^{1}H NMR as before can be used to give a lower limit on the acceleration. Acrolein was also tested and reacted quickly but gave a complex mixture of products. Acrylamide and *trans*-methyl crotonate were unreactive to deuteration, which is consistent with literature observations of their slow reaction rate in processes of this type.[5] Diethylvinylphosphonate was unreactive to deuteration under these conditions.

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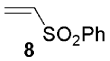
Table 1. Scope of the Reaction[a]

Entry	Substrate	V_0 (mM/min)	$V_{0\ (uncat)}$ (mM/min)	$V_0/V_{0\ (uncat)}$
1	 **7**	0.550	0.0004	1400
2	 **8**	0.165	0.0002	800
3	 **2**	0.066	<0.00005	>1000
4	 **9**	0.009	<0.00005	>200

[a] Substrate (13 mM) was combined with **1c** (6.5 mM) and **4** (6.5 mM) in acetone-d_6 at 23 °C.

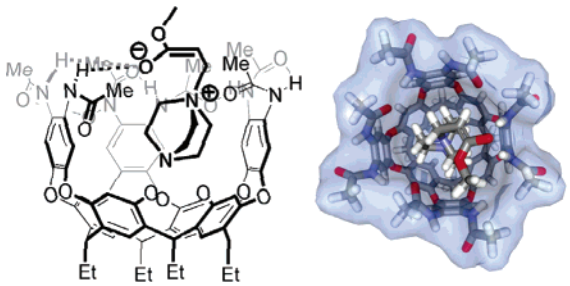


Figure 4. Representation of bound enolate intermediate (some groups removed for clarity) and molecular minimization of the same (plan view, AMBER force field).

During reaction in both acetone-d_6 and CD_3OD, the NH's of cavitand are rapidly exchanged with deuterium. However, the significantly different rates of deuterium exchange in acetone-d_6 and CD_3OD suggest that deuterium exchange occurs via direct abstraction from solvent and not via exchange through the cavitand walls. Even so, it is possible to effect deuteration of **7** directly from the cavitand itself. Cavitand **1c** can be easily converted to the octadeuterio equivalent **1c**-d_8 by treatment with CD_3OD/acetone-d_6. Combination of **1c**-d_8, **4**, and **7** in toluene-d_8 (an aprotic solvent which is a poor cavitand guest) effects deuterium exchange at an initial rate of 0.26 mM/min at [**7**] = 13 mM, approximately half the exchange rate in acetone.

Molecular modeling suggests reasons for the rate accelerations observed. Molecular mechanics minimization (using the AMBER force field) of the bound enolate formed after conjugate addition of DABCO shows a reorganization of the amide groups on the rim. They provide two hydrogen-bond donors to the oxyanion, as shown in Figure 4. The amide groups on the rim need only to rotate in order to accommodate this interaction and allow the flexible cavitand walls to fold inward. Hence, the cavitand provides active stabilization for the addition intermediate. The rate-determining step for this process is most likely the addition of encapsulated NR_3 to the activated olefin (especially in acidic CD_3OD). The stabilization of intermediate **5** accelerates this process.

Consistent with these calculations, addition of other electrophiles (where the rate-determining step will be *later* than the addition of DABCO to olefin) to the acceptors proved difficult.[6] No addition of a variety of aldehydes to **2** or **7** was observed in the presence of **1**.[7] However, use of **7** (the most reactive olefin tested) did allow

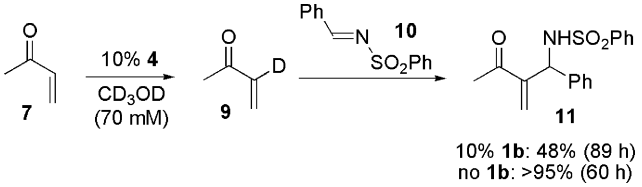


Figure 5. Addition of sulfonyl imine **10**.

the addition of (*E*)-*N*-benzylidene benzenesulfonamide **10**[8] in the presence of **1b** and quinuclidine **4** using CD_3OD as solvent. Methyl vinyl ketone **7** was quantitatively deuterated (as expected) in less than 5 min under the reaction conditions, and so the conversion of α-D-methyl vinyl ketone **9** to adduct **11** was monitored by NMR (Figure 5). In the absence of cavitand, **7** was completely converted to **11** in 60 h. However, in the presence of 10% **1b**, only 48% conversion was observed after 89 h, corroborating the hypothesis that the cavitand stabilizes the enolate intermediate and, in this case, slows a reaction with a later rate-determining step.

In summary, it is well-known that cavitands can form host−guest complexes; however, the new and fixed environs can also increase guest reactivity by providing a polar nanoenvironment around the reactive centers that stabilize charged intermediates. While hydrogen-bonding effects have long been recognized as vital to the organization of large biomolecules and synthetic receptors, the use of organized hydrogen-bonded networks for the acceleration of chemical transformations is just now emerging. The mechanical barriers of cavitands and capsules are not as passive as they might at first glance seem.

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Supporting Information Available: Experimental details and tabulated kinetics data. This material is available free of charge via the Internet at http://pubs.acs.org.

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