Communication

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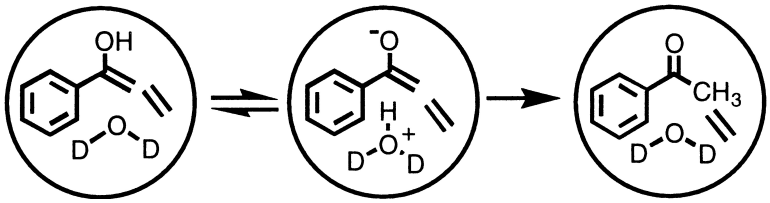

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Ketonization of Incarcerated Acetophenone Enol

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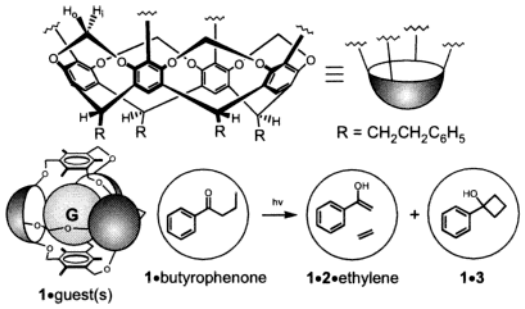
Carceplexes and hemicarceplexes render incarcerated species physically isolated from solution, which has allowed cyclobutadiene,[1] benzyne,[2] and phenyl carbene[3] to be kinetically stabilized. Enols are reactive species that have attracted the attention of physical organic chemists for decades because of the opportunities they provide to study fundamental mechanisms and because they are involved in countless biological transformations.[4] Simple enols (i.e., those that have no steric or electronic stabilizing groups) are unstable, as they quickly ketonize in solution.[5] Even in the absence of acid, base, or protic solvents, the enols themselves provide proton sources for ketonization. An incarcerated enol would remove all proton sources, save the single proton on the hydroxyl. Can ketonization take place under such circumstances? Okazaki created an endohedral cavitand in which a covalently linked enol precursor was held within the cavitand's cavity.[6] The enol was generated, and it ketonized in 3 days in $CDCl_3$ at room temperature in the presence of trifluoroacetic acid (TFA).[6] We report here the detailed analysis of the inner phase ketonization of a free-standing (noncovalently linked) simple enol incarcerated in trimer carceplex **1**·guest(s).

The synthesis of trimer carceplexes **1**·butyrophenone and **1**·hexanophenone were described recently.[7] **1**·Butyrophenone was photolyzed (λ = 300 nm, 5−6 h) in degassed C_6D_6 at ambient temperature to yield a mixture of the Norrish Type II cleavage product, **1**·acetophenone enol·ethylene (**1·2·**ethylene), and the Yang cyclization product **1·3** (Scheme 1, Figure 1). The product ratio was 5.6:1 for 2:3, which is close to that found in solution by us (6.3:1) and by others.[8] Characterization was by ^{1}H NMR (see Supporting Information for details and for characterization of **1·3**): in brief, in $CDCl_3$, the enol's vinyl proton cis to the hydroxyl ($H_{ca.}$) appears at 0.94 ppm, and the corresponding trans proton (H_{ta}) appears at 1.73 ppm (Figure 1b). These signals integrate to one proton each, show COSY and NOESY correlations, and they are geminal (^{1}H−^{13}C HMQC). The enol hydroxyl proton (5.31 ppm) shows nOes to H_{ta} and $H_{ca.}$; cis and trans were assigned on the basis of the intensity of these correlations and those between H_1' and H_{ca}/H_{ta}. The cohabiting ethylene yields a singlet (2.01 ppm) and has nOe correlations with host protons H_i and H_o, as well as a weak correlation to H_1'. No starting material or other ketone was observed after photolysis according to ^{1}H NMR and IR spectra (there are no carbonyl stretches).

Photolysis of **1**·hexanophenone resulted in no change in the ^{1}H NMR spectra, even after 7 h. According to MM2 calculations and the guest's chemical shifts,[7] the γ-hydrogens of the entrapped hexanophenone remain distal from the carbonyl oxygen, which precludes abstraction, the first step in either photocleavage or cyclization.

No ketonization of **1·2·**ethylene was observed under Okazaki's conditions (TFA, 3 days, $CDCl_3$). This is consistent with **1** having smaller pores than Okazaki's inverted cavitand; thioformaldehyde escaped his pocket,[6] whereas ethylene cannot escape ours. Thus, TFA can likely reach Okazaki's enol, but not **1·2·**ethylene. Water

Scheme 1



can also play a role, which we explore here with **1·2·**ethylene, but we cannot address the role of water in Okazaki's experiments because the amount of water in his solvent is not clear. We recently found that water can enter the cavity of **1**·guest(s), and this is the case for **1·2·**ethylene (see Supporting Information). Thus, to more rigorously pursue ketonization of **1·2·**ethylene, it was heated in water-saturated organic solvents at high temperatures for extended periods to give **1**·acetophenone·ethylene (Figure 1c).[9] Pseudo-first-order rate constants for ketonization were derived from linear plots. For ketonization at 100 °C in H_2O-saturated nitrobenzene, k_{obs}^{100} (H_2O) = 1.5 × 10^{-4} s^{-1} ($t_{1/2}$ = 78 min, $\Delta G^{\ddagger}$ = 29 kcal/mol).[10] At 25 °C, k_{obs}^{25} (H_2O) is estimated to be 7.4 × 10^{-9} s^{-1} ($t_{1/2}$ = 1.6 × 10^6 min = 3 years).[10] The rate constant (k_{uc}) for the "uncatalyzed" ketonization of **2** at 25 °C in aqueous media is 0.18 s^{-1}.[12] Thus, in H_2O-saturated nitrobenzene, incarceration in **1** retards ketonization of **2** by 2.4 × 10^7. No ketonization of **1·2·**ethylene was observed in nitrobenzene-d_5 containing crushed 4 Å molecular sieves over 26 days at 100 °C. Thus, ketonization is estimated to be at least 7.5 × 10^3 times faster in the presence of water.[12]

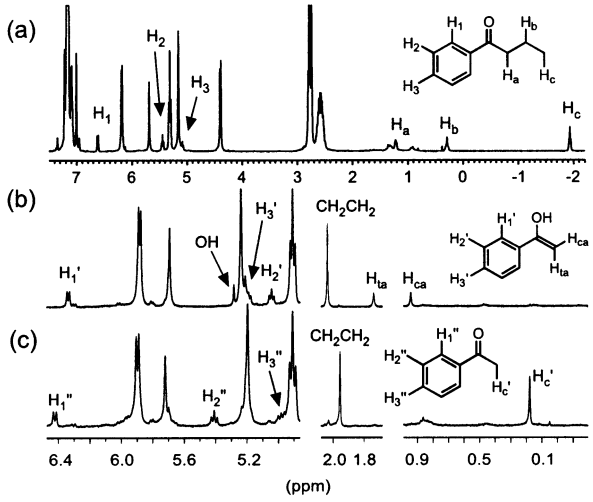


Figure 1. ^{1}H NMR (400 MHz, 300 K, over crushed 4 Å sieves) spectra of (a) **1**·butyrophenone in $CDCl_3$, (b) **1·2·**ethylene in C_6D_6, and (c) **1**·acetophenone·ethylene in C_6D_6.

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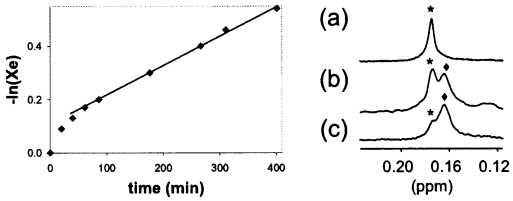
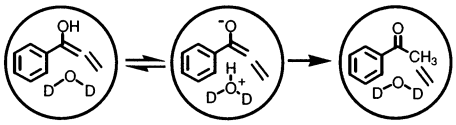


Figure 2. Left: plot ($-\ln(\chi_e)$ versus time) for the ketonization of **1·2·** ethylene in D_2O-saturated nitrobenzene at 100 °C, where χ_e = mole fraction of **2**. Right: ^1H NMR spectra (400 MHz, $CDCl_3$ over crushed 4 Å sieves) of **1·2·**ethylene after heating at 100 °C for (a) 32 h in H_2O-saturated nitrobenzene, and (b) 3 h and (c) 32 h in D_2O-saturated nitrobenzene-d_5. * = CH_3 protons of acetophenone. ♦ = CH_2D protons of acetophenone-*d*.

Scheme 2



The rate constant for H/D exchange of the enol OH was determined by heating **1·2·**ethylene in D_2O-saturated nitrobenzene at 100 °C and monitoring the disappearance of the enol OH by ^1H NMR. k_{obs}^{100} (H/D) is 1.8×10^{-4} s^{-1} ($t_{1/2}$ = 64 min, $\Delta G^{\ddagger}$ = 28 kcal/mol), which is nearly the same as the rate constant for ketonization in H_2O-saturated nitrobenzene. A plot ($-\ln(\chi_e)$ versus time, where χ_e = mole fraction of **2**) of ketonization in D_2O-saturated nitrobenzene at 100 °C (Figure 2, left) shows biphasic kinetics, which is a result of partial fast delivery of protons to the enol carbon, initially: protio acetophenone is initially observed to form along with acetophenone-*d* (Figure 2, right, b). After OH/D exchange is complete (hours), and all protons have been washed out of the cavity via rapid exchange of HOD with bulk D_2O (faster than seconds at 100 °C), only acetophenone-*d* is formed (Figure 2, right, c; the protio acetophenone observed at this point is from the initial production).[13] After 2 h, the plot (Figure 2, left) is linear, and the observed rate constant is k_{obs}^{100} (D_2O) = 2.3×10^{-5} s^{-1} ($t_{1/2}$ = 500 min, $\Delta G^{\ddagger}$ = 30 kcal/mol). The isotope effect for ketonization is 6.5 (k_{obs}^{100} (H_2O)/k_{obs}^{100} (D_2O)): C−D or O−D bonds are made or broken in the RDS.

The above results are largely consistent with Kresge's mechanism for the uncatalyzed ketonization of **2** (Scheme 2).[11] Neither a concerted mechanism nor a mechanism via a protonated enol is consistent with delivery of a proton to the carbon in D_2O-saturated nitrobenzene. This observation also rules out the escape of charged species ($D_3O^+/H_3O^+/D_2OH^+$) from the cavity. There is likely to be a large energy barrier for leaving a charged species (enolate) alone with no counterion in the nonpolar interior of carceplex **1·**guest(s).[14] Thus, the same molecule of water that deprotonates the enol OH delivers the H/D to the enol carbon.[15] Removal of the enol OH proton is comparable in rate to delivery of the proton to the carbon. If H/D exchange were fast, we would only observe incorporation of D onto the carbon. If H/D exchange were slow, we would observe H and D incorporated onto the carbon at a constant ratio. Kresge's mechanism (delivery of the proton to the carbon is the RDS) is perturbed inside **1** as the hydrophobic cavity decreases the rate of formation of charged species, thus bringing enolate formation equal in rate to enolate quenching at carbon.

In summary, an incarcerated free-standing enol ketonizes slowly via enolate formation by bound water. The same cation thus formed delivers a proton to the carbon at a rate equal to that of enolate formation.

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Supporting Information Available: Details of all experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Ketonization reactions were followed by a workup that includes water removal. ^1H NMR spectra shown contain molecular sieves.

(10) $\Delta G^{\ddagger} = -RT \ln(kh/k_BT)$.

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(12) The effect of acid and base on ketonization of **1·2·**ethylene was explored. Benzene was chosen as solvent for its stability to base, and trichloroacetic acid and tetrabutylammonium hydroxide were chose for their solubility in benzene, their high boiling points, and the small size of H^+/OH^- (greater potential for delivery through the pores). Rates were determined from single-point experiments. Acid and base actually inhibit ketonization, by factors of 5 and 1.5, respectively (see Supporting Information). This is likely a result of removal of water from the cavity to solvate the charged species in benzene, as has been observed for other guests in **1·**guest(s) (ref 7a). Neither H^+ nor OH^- appear to be able to enter the cavity in appreciable amounts. The rate of ketonization is ∼50 times slower in nitrobenzene than in benzene, in the presence of the same amount of water. The more polar nitrobenzene likely retains more water in solution (withdrawn from the carceplex) than benzene.

(13) Subjecting **1·**acetophenone**·**ethylene to D_2O-saturated nitrobenzene at 100 °C gave no **1·**acetophenone-*d***·**ethylene. Thus, all incorporation of deuterium is from ketonization, and no d_2- or d_3-acetophenone is formed during ketonization.

(14) The slow rate of H/D exchange for the enol OH further suggests the instability of charged species within a carceplex.

(15) This assumes that only one water molecule is involved in ketonization. We cannot determine how many waters are in the carceplex cavity nor what percentage of the carceplex cavities are hydrated. Moreover, there are several hydrated species, and it is not clear which one effects ketonization.

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