The Reversible Formation of the Enolate of Benzocyclobutenone under Aqueous Conditions

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Evidence for benzocyclobutenone (**1**),[2,3] in the presence of bases, reacting through an enolate intermediate has largely been circumstantial due to the reduced reactivity of **1**, relative to similar compounds, and the instability of the first formed products.[4] Presumably, the unusual reactivity of **1** can be explained on the basis of the antiaromatic 8π electron system and the strained cyclobutyl ring, which destabilizes the enolate upon formation. Herein, we report the second-order rate constants for the deuterioxide and general-base-catalyzed deprotonation of **1** by quinuclidine in D_2O at 25 °C, $I = 1.0$ (KCl).

Evidence for the generation of the enolate of benzocyclobutenone has come about through the generation of dimer **2** (Scheme 1) which was rationalized on the basis of initial enolate addition to another benzocyclobutenone molecule and subsequent rearrangement of the initially formed aldol product.[4b] Direct evidence for the formation of the enolate has been reported for the reaction of 2-methylbenzocyclobutenone, where the aldol product has been isolated,[5] and for the reaction of benzocyclobutenone, where the enolate was trapped with chlorotrimethylsilane.[6] In both cases, the carbanion was generated in THF at −78 °C, using lithium tetramethylpiperidide.

As with the studies described above, we found that the α-protons of **1** are considerably less labile than those of related carbonyl compounds. The source and a measure of the relative magnitude of the change in reactivity of the α-protons of **1** compared to structurally similar compounds such as 2-indanone,[7] 2-tetralone,[7d] 2-benzosuberone,[7d] and phenylacetone ($pK_a = \sim 16$)[7c,8] was of particular interest. In answering these questions we have shown that **1-E** can be generated under aqueous conditions and the reaction can be followed by observing the extent of deuterium incorporation into the starting material, by ^{1}H NMR (Figure 1).[8,9]

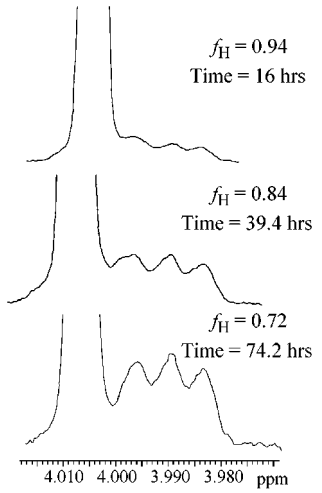
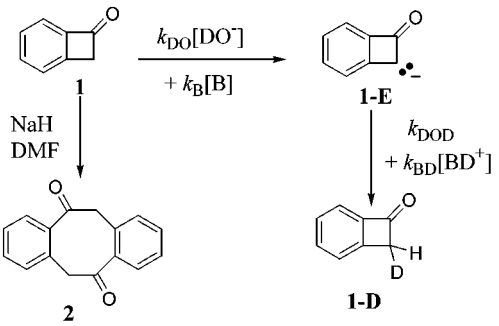


Figure 1. Representative change in the partial ^{1}H NMR spectra at 400 MHz (obtained in $CDCl_3$ at 25 °C) of benzocyclobutenone (**1**) for the reversible deprotonation in D_2O at 25 °C and pD = 12.5 catalyzed by 0.44 M quinuclidine ($I = 1.0$, KCl). A function of the protium remaining in **1** and **1-D** (f_H) and the time at which the sample was collected is indicated beside the appropriate spectrum.

Scheme 1



Proton transfer at the α-carbonyl methylene unit of **1** was catalyzed by quinuclidine ($pK_{BD} = 12.1$)[9b] in D_2O at 25 °C, $I = 1.0$ (KCl),[10] and was followed using 400 MHz ^{1}H NMR.[11] The exchange of the methylene protons for deuterium was followed

$$f_H = \frac{A_{CH_2}}{A_{CH_2} + A_{CHD}} \quad (1)$$

$$\ln f_H = \frac{-k_{obsd}t}{2} \quad (2)$$

$$k_{obsd} = k_{DO}[DO^-] + k_B[B] \quad (3)$$

by comparison of the area of the upfield shifted triplet for CHD,

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(10) (a) The reactions of **1** (4−5 mM) were initiated by dilution of a stock solution of **1** in CD_3CN (1 M) into a D_2O solution containing quinuclidine buffer. At timed intervals a 1.5 mL aliquot was removed and acidified with DCl. This was then extracted with $CDCl_3$, which was dried via passage over a $MgSO_4$ column in a Pasteur pipet. The $CDCl_3$ solutions obtained in this manner were stable indefinitely but the spectra were usually obtained with 36 h of the generation of the sample. (b) The pD was measured before the reaction was initiated and after the reaction was completed. The pD was obtained by adding 0.4 to the observed pH reading. (Glascoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 18−190.)

(11) ^{1}H NMR spectra were obtained using a Varian Mercury 400 MHz instrument with probe temperature maintained at 25 °C and the samples dissolved in $CDCl_3$. All chemical shifts are reported relative to $CHCl_3$ at 7.27 ppm.

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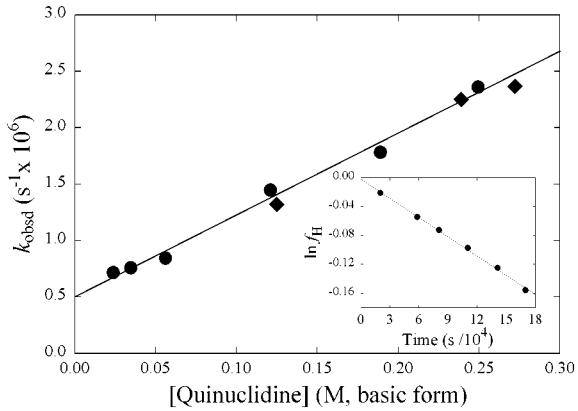

Figure 2. Dependence of the observed rate constant for deuterium exchange into benzocyclobutenone (**1**) (k_{obsd}) on the concentration of the basic form of quinuclidine in D_2O at 25 °C and $I = 1.0$ (KCl). (●) k_{obsd} for exchange for deuterium at pD = 12.5 ([B]/[BD^+] = 2.5). (◆) k_{obsd} for exchange for deuterium at pD = 12.0 ([B]/[BD^+] = 0.79) where k_{obsd} has been corrected for $k_{DO} = 1 \times 10^{-4}$ M^{-1} s^{-1}. Inset: Representative logarithmic plot of f_H vs time for the exchange of deuterium into **1**, as catalyzed by quinuclidine buffer ([B + BH^+] = 0.27 M, pD = 12.48) in D_2O at 25 °C and $I = 1.0$ (KCl).

at 3.989 ppm (Figure 1), to the area for the unreacted CH_2, at 4.005 ppm. These areas were then used to calculate f_H according to eq 1.[12] The observed rate constants for deuterium incorporation were obtained by plotting f_H according to eq 2 (see inset in Figure 2 for an example of such a plot).

The k_{obsd} values were then plotted versus the concentration of the basic form of the quinuclidine buffer as seen in Figure 2. The second-order rate constant for the deprotonation of benzocyclobutenone catalyzed by the basic form of quinuclidine was found to be $k_B = 7.2 \times 10^{-6}$ M^{-1} s^{-1}. Experiments performed at different buffer ratios[13] fall on the same correlation line (see Figure 2) leading to the conclusion that it is the basic form of the buffer that is catalyzing deprotonation. In addition, the nonzero *y*-intercept in Figure 2 indicates that k_{obsd} consists of both a buffer-catalyzed reaction and a deuterioxide-catalyzed reaction (see eq 3). For the experiments performed at pD = 12.5, $k_{DO}[DO^-] = 5.2 \times 10^{-7}$ s^{-1}, which gives a second-order rate constant for the deuterioxide-catalyzed reaction of $k_{DO} = 1 \times 10^{-4}$ M^{-1} s^{-1}.[13b]

As previously determined, we found that **1** was very susceptible to aldol addition and rearrangement upon extended exposure to the reaction conditions used herein.[4b] A related observation was that as the total buffer concentrations were lowered, the onset of observable amounts of **2** (by ^1H NMR) occurred earlier in deuterium incorporation experiments.[14] This observation is in accord with other studies of this type where deuterioxide and D_2O tend to fall below the Brønsted correlations for the buffers used to protonate and deprotonate the compounds of interest.[9b,d,15] This provides an explanation for why previous attempts[4d,e] to observe deuterium incorporation into **1** did not yield the deuterated product.

Table 1. The pK_a Values and Rate Constants for the Hydroxide-Catalyzed Deprotonation for a Variety of Carbonyl Compounds

	pK_a	k_{HO} (M^{-1} s^{-1})	k_{rel}[a]
1		7.1×10^{-5} [b]	1
acetone	19.3[c]	0.11[d,g]	1.6×10^3
2-indanone	12.2[e]	220[e]	3.1×10^6
2-tetralone	12.9[f]	376[f]	5.3×10^6
2-benzosuberone	14.9[f]	3.7[f]	5.2×10^4
ethyl acetate	25.6[g]	1.2×10^{-4} [g]	1.7

[a] k_{rel} values are relative to k_{HO} for **1**. [b] Calculated from k_{DO} for **1** and assuming $k_{DO}/k_{HO} = 1.4$ (ref 16). [c] Reference 17. [d] Statically corrected for one methyl group of acetone ($k_{HO} = 0.22$ M^{-1} s^{-1}, ref 18). [e] $I = 0.1$, at 25 °C; ref 7c,d. [f] $I = 0.1$, at 25 °C; ref 7d. [g] Rate uncorrected for the number of ionizable α-protons, $I = 1.0$, at 25 °C; ref 9b.

We have shown that the α-protons of **1** are considerably less reactive than the α-protons of compounds with similar structure (see k_{rel} in Table 1 for a comparison the relative rates of deprotonation by hydroxide). Comparison of the rate for hydroxide-catalyzed deprotonation of **1** vs 2-indanone suggests that there is approximately an 8−9 kcal/mol difference in the activation energy for the deprotonation. This large energy difference between superficially similar systems indicates that the transition state leading to **1-E** must be considerably less stable than the transition state for the formation of the enolate of 2-indanone. Two possible sources for this destabilization are ring strain and antiaromaticity.

We conclude that **1-E** can be reversibly formed in the presence of hydroxide and general-base catalysts. Ring strain upon formation of the carbanion undoubtedly plays a role in the relative instability of **1-E** but it has been shown for cyclobutanone (pK_a = 19.6)[19] that ring strain has a small effect on the pK_a of the α-protons as compared to acetone (pK_a = 19.3).[17] The similarity of the second-order rate constants for the hydroxide (see Table) and quinuclidine-catalyzed deprotonation of **1** ($k_B = 7.2 \times 10^{-6}$ $M^{-1}s^{-1}$) and ethyl acetate ($k_B = 2.4 \times 10^{-5}$ M^{-1} s^{-1}, pK_a = 25.6)[9b] suggests that reactivities of the α-hydrogens of **1** more closely resemble those of ethyl acetate than those of the structurally related compounds (see Table 1). Thus, antiaromaticity must play a large role in the destabilization of **1-E** relative to the enolate of 2-indanone or possibly inhibit enolate formation.

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(13) (a) The observed rates at differing pD values (other than pD = 12.5, see Figure 2) were adjusted for the deuterioxide reaction using $k_{DO} = 1 \times 10^{-4}$ M^{-1} s^{-1} and the [DO^-] determined by pD measurements (ref 13b). (b) The [DO^-] was determined from the following equation where $K_w = 10^{-14.87}$ for D_2O (Covington, A. K.; Robinson, R. A.; Bates, R. G. *J. Phys. Chem.* **1966**, *70*, 3820−3824.) and $\gamma_{OL} = 0.79$ (ref 9b): [DO^-] = $10^{pD-K_w}/\gamma_{OL}$.

(14) Due to this competing reaction, deuterium incorporation for experiments involving lower concentrations of quinuclidine ([total buffer] <0.1M) was followed for 20−25% loss of the first proton. At buffer concentrations greater than 0.1 M (basic form of the buffer), deuterium incorporation could be followed up to 40% loss of the first proton with no significant evidence for the formation of **2**.

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