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Determination of the pK_a of Cyclobutanone: Brønsted Correlation of the General Base-Catalyzed Enolization in Aqueous Solution and the Effect of Ring Strain

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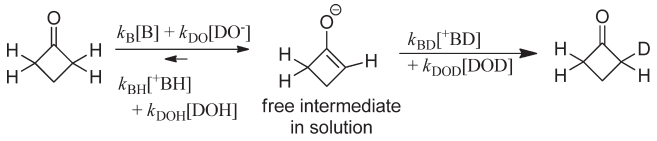

The induction of strain in carbocycles, thereby increasing the amount of s-character in the C−H bonds and the acidity of these protons, has been probed with regard to its effect on the rate constants for the enolization of cyclobutanone. The second-order rate constants for the general base-catalyzed enolization of cyclobutanone have been determined for a series of 3-substituted quinuclidine buffers in D_2O at 25 °C, I = 1.0 M (KCl). The rate constants for enolization were determined by following the extent of deuterium incorporation (up to ∼30% of the first α-proton) into the α-position, as a function of time. The observed pseudo-first-order rate constants correlated to the [basic form] of the buffer and yielded the second-order rate constants for the general base-catalyzed enolization of cyclobutanone for four tertiary amine buffers. A Brønsted β-value of 0.59 was determined from the second-order rate constants determined. Comparison of the results for cyclobutanone to those previously reported for acetone and a 1-phenylacetone derivative, under similar conditions, indicated that the ring strain of the carbocycle appeared to have only a small effect on the general base-catalyzed rate constants for enolization. The similarity of the rate constants for the general base-catalyzed enolization of cyclobutanone to those determined for acetone allowed for an estimation of the limits of the rate constant for protonation of the enolate intermediate of cyclobutanone by the conjugate acid of 3-quinuclidinone ($k_{BH} = 5 \times 10^8 - 2 \times 10^9\ M^{-1}\ s^{-1}$). Combining the rate constants for deprotonation of cyclobutanone (k_B) and protonation of the enolate of cyclobutanone (k_{BH}) by 3-quinuclidinone and its conjugate acid, the pK_a of the α-protons of cyclobutanone has been estimated to be pK_a = 19.7−20.2.

Introduction

The generation of enolates as intermediates in the formation of carbon−carbon bonds and other processes, is fundamentally important both biologically[1−10] and synthetically.[11−16] Chemists' attempts to understand the factors involved in their generation,

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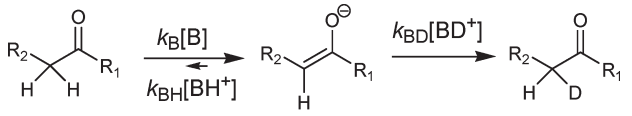
stabilization, and eventual reaction have led to extensive studies probing the nature of this reactive intermediate.[17−38] A primary theme of the work completed to date has been the determination of the effect of substituents in positions R_1 and R_2 (see Structure **1**) on the rate constants of enolate production, and these results have led to a general understanding of the substituent effects. One area that has proved more difficult to investigate has been the effect of ring strain on the generation and reactivity of enolates in cyclic ketones. Such a system is of fundamental interest as it incorporates structural features that are often invoked to help explain some of the catalysis achieved by enzymes.[39,40] Two factors that are often discussed as possible contributors in the observed efficiency of some enzymes are the induction of strain and restriction of mobility (both conformational and rotational).[39,40] For example, bond angle strain in a carbocycle is alleviated by an increase in the s-character of the carbon component of the C−H bonds leading to an increase in the acidity of these hydrogen.[41] Also, in carbocyclic compounds, the rotational degrees of freedom of the α-carbon are reduced, decreasing entropic considerations for alignment of orbitals during proton removal.[42−44] In fact, two prior studies have investigated a series of cyclic ketones, and both studies concluded that cyclobutanone was significantly more reactive than the other cyclic ketones.[45,46] In contrast to these earlier results, our studies showed that sensitivity of cyclobutanone to a general base catalyst was similar to that found for acetone and a phenylacetone derivative.[47] These results[47] pointed to a conclusion that ring strain did not have an apparent effect on the reactivity of cyclobutanone vs that of other ketones, contradicting the results of other studies.[45,46]

SCHEME 1. General Base-Catalyzed Enolization in D_2O



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The question of why cyclobutanone (**2**) has not been as thoroughly investigated as other ketones was not due to a lack of interest in the compound itself but rather to experimental limitations of the halogenation technique that was the primary method used to follow enolate generation in solution.[27] Problems, such as relative rates of enolate generation vs halogenation and enhanced reactivity of the halogenated product relative to that of starting material which led to byproducts that further consumed halogen, restricted the structural diversity of the carbonyl derivatives that could be studied.[27] However, the development of methods and procedures for the investigation of reactive intermediates has broadened the spectrum of compounds that can now be studied. One procedure, developed by Richard and co-workers, utilizing ^{1}H NMR as a means of following enolate generation for a variety of carbon acids, has proven to be quite versatile.[19−22,24,25,36,37,48−51] In general, these experiments were performed in deuterated solvents with the progress of the reaction being measured by the fraction of deuterium incorporation into the α-position of the starting material (or loss of deuterium). The method is predicated upon the idea that if the carbanion is stable enough to separate from the conjugate acid of the base that removed the proton (free intermediate in solution), then the proton removed from the carbon acid will mix with the bulk deuterated solvent. As a result, when the carbanion/enolate reacts with an acid source, a deuteron will be added (see Scheme 1). A major advantage to this method was that it did not lead to significant modification of the reactivity of the substrate, relative to that of its protonated state, making the method ideal for the investigation of compounds with more complex reactivity patterns. Also, by comparing the rate constants for deprotonation between structurally similar compounds whose pK_a's are well established, Richard and co-workers were able to estimate the rate constant for

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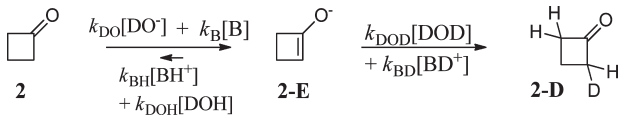
SCHEME 2. Base-Catalyzed Enolization of Cyclobutanone in D_2O



protonation of the enolate (k_{BH}) and, using eq 1, to predict the pK_a for a variety of compounds.[22,24,36,37,48]

$$pK_a = pK_{BH} + \log(k_{BH}/k_B) \quad (1)$$

This technique has proven to be well-suited for a wide range of carbonyl derivatives including strained-ring ketones where initial studies focusing on benzocyclobutenone found the hydroxide-catalyzed enolate formation to be $k_{HO} = 7.1 \times 10^{-5}$ M^{-1} s^{-1} as compared $k_{HO} = 0.22$ M^{-1} s^{-1} for acetone (**3**).[25,52] This was the first direct evidence that the enolate of benzocyclobutenone could be generated in aqueous solution as a free intermediate with no significant precautions. (The enolate had been previously generated and trapped with chlorotrimethylsilane and as the aldol product at −78 °C in THF.)[53,54] The large difference between the rate constants for the enolization of benzocyclobutenone vs acetone was attributed to two primary effects (a) antiaromaticity of the enolate generated upon deprotonation and (b) ring strain that occurs upon rehybridization of the α-methylene group to sp^2-hybridization, both of which would lead to a higher-energy transition state relative to that of acetone.[25]

Wanting to probe the effect of ring strain on the rate constant for enolate generation, the 3-quinuclidinone-catalyzed enolization of the cyclobutanone (**2**) was investigated ($k_B = 3.3 \times 10^{-4}$ M^{-1} s^{-1}, D_2O, 25 °C, $I = 1.0$ M (KCl)), and this rate constant was comparable to that determined for acetone ($k_B = 5.2 \times 10^{-4}$ M^{-1} s^{-1}), under the same conditions. The similarity of these rate constants indicated that the barriers to the formation of the enolates for both **2** and **3** were similar but differences in the structure of the two compounds precluded a direct estimate of the protonation rate constant (k_{BH}) for **2-E** (see Scheme 2). More information concerning the nature of the transition state leading to the formation of **2-E** was required before a value for k_{BH} could be proposed. Presented here are the results of the study of the general base-catalyzed deuterium incorporation of cyclobutanone using a structurally similar series of tertiary amine buffers whose pK_a's span ~4 pK_a units. The second-order rate constants for the general base-catalyzed reaction have been determined and correlated to the pK_a of the buffers in a Brønsted plot which led to an estimate of the pK_a of cyclobutanone.

Results

The general base-catalyzed deuterium incorporation studies were performed by injecting neat cyclobutanone (final concentration was ~10 mM) into a D_2O solution at 25 °C, $I = 1$ M (KCl). A series of 3-substituted quinuclidine buffers were used to both maintain the pD of the solution and act as general base catalysts. After initiation of the reaction, at timed intervals, an aliquot was removed, quenched and the organics extracted with $CDCl_3$. Deuterium exchange of the α-protons of cyclobutanone was followed by monitoring the disappearance of the α-CH_2 group and the appearance of the upfield shifted α-CHD peak using a 400 or 500 MHz ^{1}H NMR. Due to coupling of the α-protons (C_2 and C_4) to the C_3 methylene group, the protons on the C_3 position were subjected to inverse gated homonuclear decoupling during acquisition, resulting in the α-CH_2 signal simplifying to a singlet.[48,55] The course of deuterium incorporation was followed by measuring the decrease in the area of the peak for the α-CH_2 position at 3.11 ppm and the increase in the peak at 3.09 ppm ($J_{HD} = 2.2$ Hz) for the α-CHD. During the exchange studies no evidence, by ^{1}H NMR, for the buildup of enolate addition products was observed.

$$R_{CH_2} = \frac{A_{CH_2}}{A_{CH_2} + A_{CHD}} \quad (2)$$

$$\ln R_{CH_2} = \frac{-k_{obsd}t}{4} \quad (3)$$

The deuterium incorporation experiments were followed up to ~30% of the first proton of the α-CH_2 group with the progress of the reaction (R_{CH2}) calculated as shown in eq 2.[56,57] Incomplete resolution of the singlet of the α-CH_2 group and the upfield shifted α-CHD required that the A_{CHD} be calculated by multiplying the most upfield shifted peak of the α-CHD triplet by three. The A_{CH2} was then determined by measuring the area of the peaks for the α-CH_2 and the α-CHD groups and subtracting the calculated A_{CHD}. The observed pseudo-first-order rate constants for the exchange reaction were determined by plotting the natural log of the progress of the deuterium incorporation (R_{CH2}) vs time, according to eq 3.[56,57] The observed rate constants were corrected by a factor of 4 as k_{obsd}, in eq 3, is the observed rate constant for the loss of a single α-proton in the total population and the rate constant must be statistically corrected for the presence of two equivalent α-methylene units.[56,57] A representative plot of the natural log of R_{CH2} vs time at a series of [buffer] is shown in Figure 1. All the k_{obsd} values determined as a function of [buffer] can be found in Tables 1S−5S of the Supporting Information.

$$k_{obsd} = k_{DO}[DO^-] + (k_B)_{obsd}[Buffer] \quad (4)$$

$$k_{obsd} - k_{DO}[DO^-] = k_B[B] \quad (5)$$

For the studies discussed here, plots of k_{obsd} vs the total [Buffer] (see Figure 2) showed nonzero intercepts indicating, that at the pD at which the experiments were performed, there was a general base-catalyzed, as well as, a deuteroxide-catalyzed enolization ($k_{DO}[DO^-]$). Plots of k_{obsd} vs [Buffer] (total buffer concentration in solution) were linear, with the y-intercept being $k_{DO}[DO^-]$, and the slope being $(k_B)_{obsd}$, the

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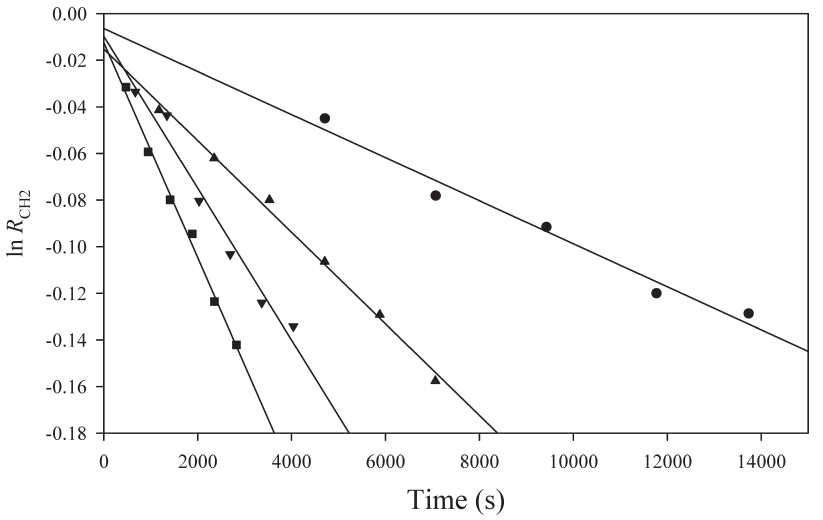

FIGURE 1. Representative natural logarithmic plots of R_{CH2} vs time (s) for the exchange of protium for deuterium at the α-position of cyclobutanone catalyzed by 3-chloroquinuclidine at pD = 9.84 in D_2O at 25 °C and I = 1.0 M (KCl). (●) 0.0090 M basic form of buffer, (▲) 0.0240 M basic form of buffer, (▼) 0.0367 M basic form of buffer, and (■) 0.0588 M basic form of the buffer.

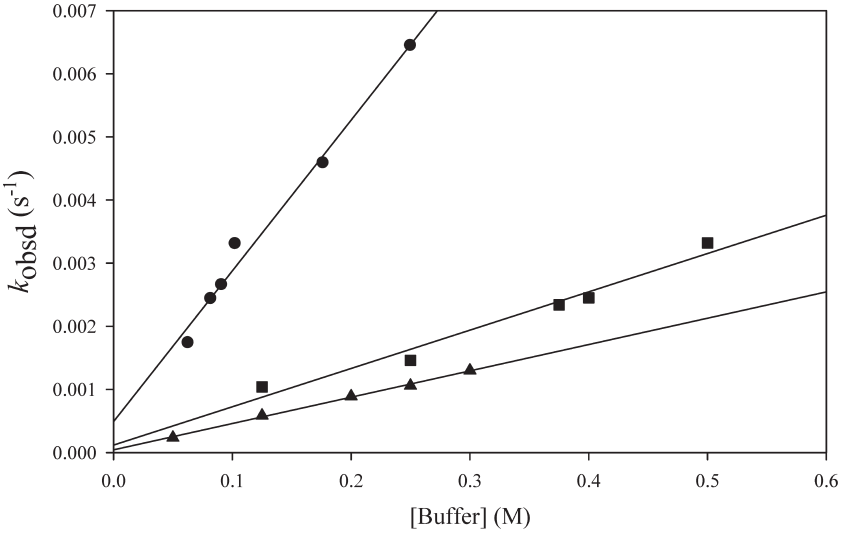

FIGURE 2. Representative plots of the observed rate constants (k_{obsd}) for buffer-catalyzed deuterium incorporation into the α-position of cyclobutanone vs total buffer concentration in D_2O, at 25 °C, I = 1.0 M (KCl). (●) Quinuclidine at pD = 11.98; (■) quinuclidine at pD = 11.16; (▲) 3-quinuclidinol at pD = 10.36.

second-order rate constant for the buffer-catalyzed exchange for the [Buffer] (see eq 4). (At the pD of the experiments performed, the k_{DOD} rate constant for the water reaction would be very slow compared to $k_{DO}[DO^-]$.) However, plots of k_{obsd} vs [Buffer] led to intercepts that varied significantly, which, in turn, led to greater error in the determined deuteroxide-catalyzed rate constant than was acceptable.

To determine the second-order rate constant for the general base-catalyzed reaction (k_B, see eq 5) plots of k_{obsd} vs the concentration of the basic form of the base catalyst ([B]) required a reliable k_{DO} rate constant to correct k_{obsd} for small variations in pD that occur upon dilution (see Tables in Supporting Information). As a result, competition experiments were performed wherein acetone and cyclobutanone were allowed to react in a phosphate buffered solution at the same time and the relative rate constants for enolization determined in D_2O, at 25 °C, I = 1.0 M (KCl) at the pD of solution. The observed rate constants for deuterium incorporation were linearly dependent upon [phosphate] with the second-order rate constant for the phosphate-catalyzed reaction for acetone being $k_{phos} = 4.1 \times 10^{-2}$ M^{-1} s^{-1} and for cyclobutanone $k_{phos} = 4.2 \times 10^{-2}$ M^{-1} s^{-1}. Figure 3 shows a plot of k_{obsd} vs [phosphate] (basic form) where k_{obsd} values for **2** were determined according to eqs 2 and 3 and those for **3** were determined using eqs 6 and 7.[56,57] The y-intercept yielded the background reaction ($k_{DO}[DO^-]$ for the ketones studied) at the pD at which the study was performed. In all cases **2** reacted more slowly than **3** over the [phosphate] studied with the second-order rate constants for the deuteroxide-catalyzed reactions determined by dividing y-intercept, from the phosphate experiments, by the $[DO^-]$ (determined from the pD of the solution[58] according to eq 8, using $K_w = 10^{-14.87}$

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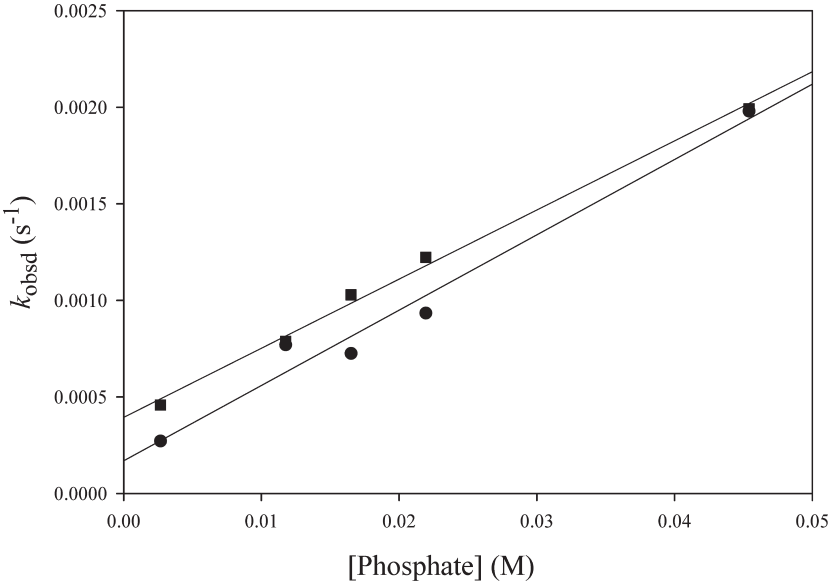


FIGURE 3. Plot of k_{obsd} vs [basic form of the phosphate buffer] for the phosphate-catalyzed deuterium incorporation into acetone (■) and cyclobutanone (●) at pD 12.5, in D_2O, at 25 °C, I = 1.0 M (KCl).

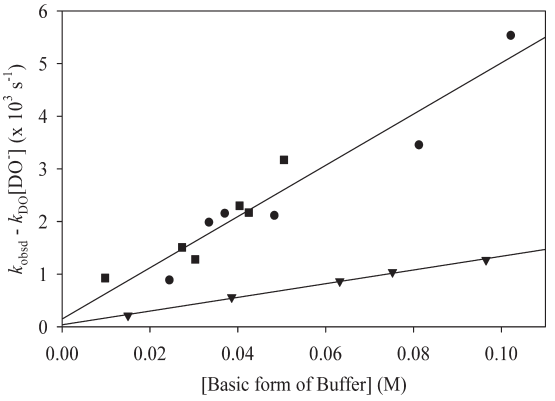


FIGURE 4. Plots of $k_{obsd} - k_{DO}[DO^-]$ for the deuterium incorporation of the first alpha-proton of cyclobutanone vs the concentration of the basic form of the 3-substituted quinuclidine buffer in D_2O, at 25 °C, I = 1.0 M (KCl); for (▼) 3-quinuclidinol, pD = 10.36; (■) quinuclidine, pD = 11.15; (●) quinuclidine, pD = 11.67.

and $\gamma_{OL} = 0.79$).[36] The second-order rate constants for the deuteroxide-catalyzed enolate formation established in this manner from three phosphate experiments were then averaged to yield $k_{DO} = 0.21 \pm 0.02\ M^{-1}\ s^{-1}$ and $k_{DO} = 0.051 \pm 0.005\ M^{-1}\ s^{-1}$ for acetone and cyclobutanone, respectively.

$$R_{CH_3} = \frac{A_{CH_3}}{A_{CH_3} + A_{CH_2D}/2} \quad (6)$$

$$\ln R_{CH_3} = \frac{-k_{obsd}t}{6} \quad (7)$$

$$[DO^-] = \frac{10^{pD - pK_w}}{\gamma_{OL}} \quad (8)$$

The second-order rate constants for the general base-catalyzed enolization of **2** were determined according to eq 5, using $k_{DO} = 0.051\ M^{-1}\ s^{-1}$ with the [DO^-] calculated on the basis of the measured pD of the reaction solution, vs the [basic form of 3-substituted quinuclidine buffer] (see Figure 4 for a representative plot). The concentration of the basic form of the 3-substituted quinuclidine buffer was calculated on the basis of the known total [buffer], the measured pD of the reaction solution, and the apparent pK_{BD}'s of the quinuclidine buffers in D_2O at 25 °C and I = 1.0 M (KCl) (see Table 1).[36] The plots were linear over the [3-substituted quinuclidine] studied and, after k_{obsd} had been corrected according to eq 5, the rate constants for the general base-catalyzed reactions performed at different buffer ratios fell on the same correlation line. This result indicated that it was the basic form of the 3-substituted quinuclidine (B) that was the primary catalyst in the reaction and the acidic form of the tertiary amine (BH^+) had no significant contribution (see Figure 4) at the pD that the studies were performed. The remainder of the plots for the other 3-substituted quinuclidine buffers ($k_{obsd} - k_{DO}[DO^-]$) vs [B] plots can be viewed in the Supporting Information. The second-order rate constants for the exchange studies at the pD of the study are listed in Table 1 as k_B^{obs} and the k_B values, in Table 1, are the average of the observed values in those cases where multiple pD values for the same general base-catalyst were investigated.

Discussion

Deuterium Incorporation and Mechanism of Exchange Studies. Deuterium exchange proceeded smoothly, with no evidence for the formation of aldol products over the time scale of the experiments. Studies that were allowed to proceed for extended periods of time did show the presence of new ^{1}H NMR peaks that were presumably due to enolate addition. The identity of these new peaks in the ^{1}H NMR spectrum were not investigated.

Another concern, early in these studies, was the degree of hydration of cyclobutanone in aqueous solution as formaldehyde and aliphatic aldehydes are well-known to be significantly hydrated in aqueous solution.[59] For example, formaldehyde,

(59) Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1–29.

TABLE 1. Second-Order Rate Constants for the General Base-Catalyzed Exchange of the First α-Proton with Deuterium for Cyclobutanone Using a Series of 3-Substituted Quinuclidine Buffers in D_2O, at 25 °C, I = 1.0 M (KCl) and Previously Determined Second-Order Rate Constants for the Enolization of 2-(2′-Oxopropyl)benzaldehyde by the Same Series of Buffers in H_2O, at 25 °C, I = 1.0 M (KCl)

buffer/base	pK_{BH}[a]	pK_{BD}[b]	pD	k_B^{obs} (M^{-1} s^{-1})[c]	k_B (M^{-1} s^{-1})[d]	k_B (M^{-1} s^{-1}) for **4**[e]
quinuclidine	11.5	12.1	11.15	5.3×10^{-2}	$(5.4 \pm 0.5) \times 10^{-2}$	9.3×10^{-2}
			11.60	5.5×10^{-2}		
3-quinuclidinol	10.0	10.7	10.36	1.3×10^{-2}	$(1.6 \pm 0.2) \times 10^{-2}$	2.1×10^{-2}
			11.01	1.9×10^{-2}		
3-chloroquinuclidine	9.0	9.7	9.84	3.1×10^{-3}	$(3.1 \pm 0.3) \times 10^{-3}$	5.7×10^{-3}
3-quinuclidinone[f]	7.5	8.3	8.33	3.3×10^{-4}	$(3.3 \pm 0.3) \times 10^{-4}$	5.8×10^{-4}

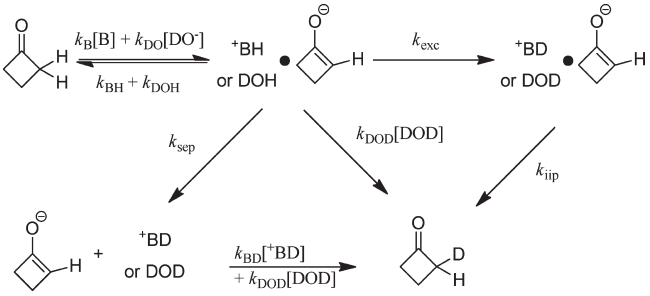
[a] pK_a's measured in H_2O, at 25 °C, I = 1.0 M (KCl), see Gresser, M.J.; Jencks, W.P. *J. Am. Chem. Soc.* **1977**, *99*, 6963−6970. [b] Apparent pK_a's in D_2O, at 25 °C, I = 1.0 M (KCl), see ref 36. [c] Second-order rate constants for the general base-catalyzed exchange of the α-proton of cyclobutanone observed at the pD that the experiment was performed. [d] Second-order rate constant for the general base-catalyzed exchange of the α-proton of cyclobutanone averaged where multiple experiments with the same buffer were performed but at differ pD's. [e] Second-order rate constant for general base-catalyzed deprotonation of 2-(2-oxopropyl)benzaldehyde (**4**) from ref 23, in H_2O, at 25 °C, I = 1.0 M (KCl). [f] Previously reported in ref 47.

acetaldehyde, and acetone are ~98%,[60] ~55%[61] and ~0.1%[59,62,63] hydrated in aqueous solution, respectively. The degree of hydration of the carbonyl compound diminishes the apparent reactivity of the carbonyl compound under investigation by reducing the concentration of the reactive form of the carbonyl precursor.[64] However, previous studies investigating rate constants for the enolization of acetone did not correct for this minor amount of acetone in the hydrate form.[37,65] Control experiments, performed by ^{1}H NMR, wherein **2** was dissolved in 1 M KCl in D_2O showed no evidence for the presence of significant amounts of hydrated cyclobutanone and this result was in accord with ^{1}H NMR studies performed by Wiberg et al. who found that **2** was ~0.2% hydrated in D_2O.[62] As with the previous studies investigating the enolization of acetone,[37] no correction for the small amount of **2** in the hydrated form was performed.

The exchange of an α-proton on cyclobutanone was followed by monitoring the disappearance of the α-CH_2 group and the appearance of the α-CHD group by ^{1}H NMR. This modest structural change to cyclobutanone could be followed due to the ^{2}H perturbation of the ^{1}H resonances that leads to an upfield shift of the signal for α-CHD (3.09 ppm) relative to α-CH_2 (3.11 ppm). The reaction was followed for approximately 7.5% of the total α-protons available in **2**, and no products due to enolate addition were observed by ^{1}H NMR over the time scale of the exchange studies.

Initial studies of deuterium incorporation into the α-position of cyclobutanone showed that coupling by the protons in the C-3 position to those in the C-2 and C-4 positions complicated the resonances for the α-protons. To simplify the observed spectrum, the protons in the C-3 position were subjected to inverse gated homonuclear decoupling.[55] This simplified the observed resonance for the α-protons and the progress of the reaction could be followed by comparing the singlet at 3.11 ppm for the α-CH_2 group to the upfield shifted triplet at 3.09 ppm for the α-CHD group having a coupling constant of 2.2 Hz. Reactions followed in this manner and treated according to eq 2 and eq 3, led to plots like that seen in Figure 1.

SCHEME 3. Potential Routes Leading to Deuterium Incorporation



The plots of k_{obsd} vs the [3-substituted quinuclidine] having nonzero intercepts indicated that, at the pD of the experiments, both deuteroxide and the tertiary amine were capable of leading to deuterium incorporation. Shown in Scheme 3 are the possible mechanisms by which exchange of an α-proton of **2** could occur. The observation that the rate constant for deuterium exchange into the α-position was dependent on [basic form of the 3-substituted quinuclidine] was good evidence that the enolate intermediate generated upon removal of the α-proton had a significant lifetime in solution. If the enolate that was generated upon deprotonation were highly unstable, the intimate ion pair complex (enolate/conjugate acid) would not exist long enough to diffuse apart. Thus, the principle of microscopic reversibility dictates that the same proton that was removed by the general base catalyst would be returned to the α-position (k_{BH} and k_{DOH} in Scheme 3). In such a case, catalysis of deuterium incorporation by deuteroxide may be observed through relaxation of the intimate ion pairs and delivery of a deuteron, but buffer catalysis of deuterium incorporation would not be observed. Alternatively, protium/deuterium exchange between the solvent and tertiary amine buffer could occur, thus leading to deuterium incorporation in the intimate ion pair (k_{iip} in Scheme 3). This mechanism seems unlikely as proton exchange between protonated quinuclidine buffers and solvent is slow ($k_{exc} < 10^3$ s^{-1})[66] when compared to diffusional separation of the ions from the ion-pair ($k_{sep} = \sim 1.6 \times 10^{10}$ s^{-1}).[67,68] Once the ions have separated (k_{sep} in Scheme 3), forming the solvent equilibrated enolate intermediate, ketonization occurs through reaction

(60) Lewis, C. A., Jr.; Wolfenden, R. *J. Am. Chem. Soc.* **1973**, *95*, 6685–6688.
(61) Kurz, J. L. *J. Am. Chem. Soc.* **1967**, *89*, 3524–3528.
(62) Wiberg, K. B.; Morgan, K. M.; Maltz, H. *J. Am. Chem. Soc.* **1994**, *116*, 11067–11077.
(63) Hine, J.; Redding, R. W. *J. Org. Chem.* **1970**, *35*, 2769–2772.
(64) Ankem, R. V.; Murphy, J. L.; Nagorski, R. W. *Tetrahedron Lett.* **2008**, *49*, 6547–6549.
(65) Chiang, Y.; Kresge, A. J.; Morimoto, H.; Williams, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 3981–3982.
(66) Berg, U.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 6997–7002.
(67) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373–1383.
(68) Finneman, J. I.; Fishbein, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 4228–4239.

with D_2O (k_{DOD}) or with a deuterated form of the tertiary amine acid (k_{BD}[BD]). (Previous studies investigating relative rate constants for the deprotonation and aldol condensation reactions showed that these acids are very effective at protonation of enolate intermediates.)[23,24]

For deprotonation by deuteroxide, reorganization within the solvent shell could be hypothesized as a reasonable mechanism for the incorporation of deuterium into **2**. Deprotonation of **2** by deuteroxide leads to DOH·**2-E** complex which, through relaxation within the solvent shell and reorganization, generates a DOD·**2-E** complex ($k_{exc} \approx 10^{11}$ s^{-1})[69−71] which could now lead to **2-D**. While this mechanism cannot be ruled out as a pathway for the incorporation of deuterium into **2**, k_{sep} ($k_{sep} = \sim 1.6 \times 10^{10}$ s^{-1})[67,68] is substantially faster than the reaction of **2-E** with D_2O (upper limit for $k_{DOD} = \sim 6 \times 10^4$ s^{-1} based upon estimated pK_a for **2**, see explanation below) suggesting that **2-E** separates from the conjugate acid of the base that removed the proton.

On the basis of these arguments, it was concluded that the intermediate **2-E**, generated upon deprotonation of **2**, is a free solvent-equilibrated intermediate with a significant lifetime in solution. Thus, the k_{DO} and k_B values reported are the rate constants for the deprotonation of **2** yielding intermediate **2-E**.

Determination of the Rate Constant for the Deuteroxide-Catalyzed Enolization of Cyclobutanone. Plots of k_{obsd} vs [Buffer] for experiments performed with quinuclidine, 3-chloroquinuclidine, and 3-quinuclidinol did not have zero-intercepts (see Figure 2), indicating that both the tertiary amines and deuteroxide were catalyzing the enolization of **2** (eq 4). Previous studies, investigating the reactivity of other carbonyl derivatives, were able to obtain a second-order rate constant for the deuteroxide-catalyzed enolization reaction by plotting the rate of the background reaction (y-intercepts of the tertiary amine-catalyzed incorporation studies) vs the [DO^-] at which the experiments were performed.[25,36,37] However, in the current study, plots of the type described above led to a second-order rate constant for the deuterium-catalyzed deprotonation of cyclobutanone with significant error (plot not shown). A more dependable value for the deuteroxide-catalyzed deprotonation of **2** became necessary when small variations in pD occurred, due to dilution of stock buffered solutions. These variations led to error in the k_{obsd} value for the buffer-catalyzed reaction (see eq 5).

To determine the deuteroxide-catalyzed enolization of cyclobutanone under the conditions of our studies, a series of competition experiments were performed where both acetone and cyclobutanone were reacted concurrently. The studies were performed in the same manner as described for the general base-catalyzed deuterium incorporation but using a series of phosphate concentrations, with experiments being performed at three different pD's. The observed rate constants for the phosphate-catalyzed enolization of acetone and cyclobutanone, at each of the pD's studied, are shown in Table 2 and the results show that the $k_{phos}^{acetone}/k_{phos}^{cyclobutanone}$ ratio was ~1. This could be compared to $k_{DO}^{acetone}/k_{DO}^{cyclobutanone}$ of ~4 (see below), and k_B for the 3-quinuclidinone-catalyzed reaction under similar conditions ($k_B^{acetone}/k_B^{cyclobutanone} = 1.6$)[37,47] As previously noted, these results illustrate the similarity in the reactivity of acetone and cyclobutanone over a wide range of general base catalyst.[47] The second-order rate constant for the deuteroxide-catalyzed enolate formation for acetone ($k_{DO} = 0.21$ M^{-1} s^{-1}, determined in D_2O, at 25 °C, $I = 1.0$ M (KCl)), was approximately the same as the value reported for the hydroxide-catalyzed enolization of acetone ($k_{HO} = 0.22$ M^{-1} s^{-1}) in H_2O, at 25 °C, $I = 0.1$ (NaCl).[52] This result was somewhat unexpected as a k_{DO} for acetone has been estimated to be $k_{DO} = 0.32$ M^{-1} s^{-1} based upon a solvent isotope effect of $k_{DO}/k_{HO} = 1.4$.[36] The origin of this apparent lack of solvent isotope effect was not investigated but the observation could be due to error in the rate constant determined by the method utilized and due to the limited pD over which the studies were investigated. Regardless of the potential error in the absolute value of the k_{DO} for both compounds, the differences in the k_{DO} values for acetone ($k_{DO} = 0.21$ M^{-1} s^{-1}) vs cyclobutanone ($k_{DO} = 0.051$ M^{-1} s^{-1}) and the differences in the k_{obsd} values for the phosphate-catalyzed reactions (see Figure 3) clearly indicate that cyclobutanone reacted more slowly than acetone under the same conditions.

TABLE 2. Second-Order Rate Constants for the Phosphate-Catalyzed Exchange of the First α-Proton with Deuterium for Cyclobutanone and Acetone in D_2O, at 25 °C, $I = 1.0$ M (KCl)

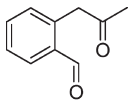
ketone	pD[a]	k_{Phos}^{obs} (M^{-1} s^{-1})[b]	k_{Phos} (M^{-1} s^{-1})[c]
acetone	12.3	3.6×10^{-2}	
	12.2	2.8×10^{-2}	$(4.1 \pm 0.5) \times 10^{-2}$
	12.5	6.0×10^{-2}	
cyclobutanone	12.3	2.3×10^{-2}	
	12.2	3.9×10^{-2}	$(4.2 \pm 0.5) \times 10^{-2}$
	12.5	6.4×10^{-2}	

[a]pD's determined by adding 0.4 to measured pH, see ref 58. [b]Second-order rate constants for the general base-catalyzed exchange of the α-proton of ketone observed at the pD that the experiment was performed. [c]Second-order rate constant for the phosphate-catalyzed exchange of the α-proton of the ketone for the three pD's studied.

The rate constant ratios presented above generate a confusing picture of the reactivity of cyclobutanone, especially when considered in the light of other base/general base-catalyzed enolization studies of cyclobutanone. For example, Dessy et al. studied the generation of the enolates for a series of ketones in DMF with 1 M triethylamine and 5 M D_2O at 40 °C.[45] In these studies, Dessy et al. reported that the relative reactivity for the series of ketones studied was $C_4 > C_5 > C_6 > C_7 >$ 4-heptanone (number indicates the size of the carbocycle), where the ratio of rate constants of cyclobutanone/4-heptanone was 290 and cyclobutanone/cyclohexanone was 25.[45] (As a reference point, the ratio for the hydroxide-catalyzed enolization (k_{HO}) of acetone/cyclohexanone is ~2.)[27,52] Similarly, Schriesheim et al. found the relative reactivity of a series of cyclic ketones in H_2O, at 0 °C and catalyzed by hydroxide to be $C_4 > C_5 > C_8 > C_7 > C_6$ with the relative rate constants for cyclobutanone/cyclohexanone to be 15.5.[46] More recent acetate-catalyzed enolization studies for series of ketones in aqueous solution, at 25 °C, $I = 2.0$M, found the relative reactivities to be $C_5 > C_6 > C_4 =$ acetone > 3-pentanone > C_7 where the relative reactivity of cyclobutanone/cyclohexanone was 0.50 and cyclobutanone/3-pentanone was 1.8.[72] The results presented here are in agreement with the Hegarty et al. work,[72] and it

(69) Kaatze, U.; Pottel, R.; Schumacher, A. *J. Phys. Chem.* **1992**, *96*, 6017–6020.
(70) Kaatze, U. *J. Chem. Eng. Data* **1989**, *34*, 371–374.
(71) Giese, K.; Kaatze, U.; Pottel, R. *J. Phys. Chem.* **1970**, *74*, 3718–3725.
(72) Hegarty, A. F.; Dowling, J. P.; Eustace, S. J.; McGarraghy, M. *J. Am. Chem. Soc.* **1998**, *120*, 2290–2296.

would appear as though the earlier studies[45,46] had overestimated the reactivity of cyclobutanone in some way during the course of their investigations. These observations suggest that the increased ring strain in **2** leads to an overall decrease in the rate constant of the general base-catalyzed enolization relative to larger cyclic ketones.



4

Rate Constants for the General Base-Catalyzed Deprotonation of 2 and Brønsted Correlation. Listed in Table 1 are the second-order rate constants for the general base-catalyzed deprotonation of **2** for a series of tertiary amine bases in D_2O, at 25 °C and I = 1.0 M (KCl). The original observation of general base-catalyzed deuterium incorporation into cyclobutanone found the second-order rate constant for the 3-quinuclidinone-catalyzed reaction to be $k_B = 3.3 \times 10^{-4}$ M^{-1} s^{-1} in D_2O, at 25 °C and I = 1.0 M (KCl).[47] Under similar conditions, the 3-quinuclidinone-catalyzed rate constants have been determined for acetone (**3**) ($k_B = 5.2 \times 10^{-4}$ M^{-1} s^{-1}) and for the methyl group of 2-(2′-oxopropyl)-benzaldehyde (**4**) ($k_B = 3.4 \times 10^{-4}$ M^{-1} s^{-1}). Statistical correction of the rate constant for **4** yields a rate constant very close to that observed for acetone suggesting that the methyl group of **4** was very acetone-like. If the rate constants listed above are corrected for the number of ionizable α-protons (p), the second-order rate constants for the general base-catalyzed deprotonation of **2**, **3** and **4**, by 3-quinuclidinone, are $k_B/p = 8.3 \times 10^{-5}$ M^{-1} s^{-1}, $k_B/p = 8.7 \times 10^{-5}$ M^{-1} s^{-1}, and $k_B/p = 1.1 \times 10^{-4}$ M^{-1} s^{-1}, respectively. These comparisons lead to the general conclusion that the barriers to deprotonation, for these three compounds under the same conditions, are similar to one another. This comparison can be extended as the rate constants for the general base-catalyzed deprotonation of **4**, for the tertiary amine bases listed in Table 1, have been determined in H_2O, at 25 °C, I = 1.0 M (KCl). If the potential for secondary solvent isotope effects are ignored, the second-order rate constants reported in ref 23 are similar in magnitude to those reported in Table 1 for cyclobutanone (see Table 1).

The similarity of these rate constants leads to the conclusion that the barrier to deprotonation (ΔG^*) is similar for all three compounds. Previous studies used the similarity of the rate constants for the general base-catalyzed deprotonation coupled with the structural similarity of the substrates themselves, to make the assumption that the relative energies of the transition state and the enolate intermediate to the keto-form are similar.[22,24,36,37,48] With this assumption in place, it was possible to estimate rate constants for the protonation of the enolate by the conjugate acid of the general base catalyst (k_{BH}, see eq 1) by comparison to systems with known pK_a's.[22,24,36,37,48] The complication, with an analysis of this type, occurs when the compounds being compared are no longer structurally similar. Thus, while the barrier to deprotonation was similar for all three compounds, no information about the nature of the transition state leading to the enolate intermediate and the relative energy of the enolate intermediate to the keto-form can be necessarily inferred from the data.

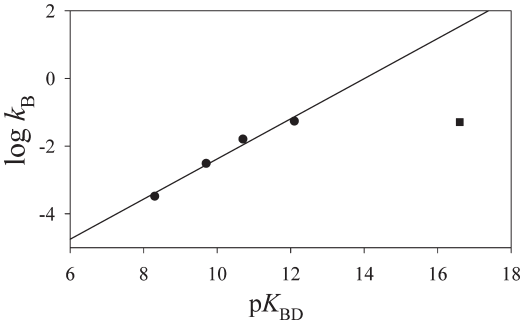


FIGURE 5. Brønsted correlation for the deprotonation of cyclobutanone by a series of substituted quinuclidine bases in D_2O, at 25 °C, I = 1.0 M (KCl). The deuteroxide (■, pK_{BD} = 16.6, not included in determination of Brønsted correlation) rate constant for deprotonation of cyclobutanone under the same conditions.

Richard and co-workers have, in part, addressed this issue by determining the second-order rate constant for the general base-catalyzed enolization for a series of tertiary amine bases, and plotting these rate constants in a Brønsted correlation.[36] With the β-value in hand, Richard et al. were able to make conclusions about changes in the nature of the transition state during proton removal in ethyl acetate, by a general base catalyst, and estimate the rate constant for the protonation of the enolate intermediate by the conjugate acid of the general base catalyst. The Brønsted correlation for the deprotonation of cyclobutanone by a series of substituted quinuclidine derivatives in D_2O, at 25 °C and I = 1.0 M (KCl), is shown in Figure 5. A linear correlation resulted, having a slope $\beta = 0.59$ for the deprotonation of cyclobutanone. This value can be compared to the β-value for the methyl group of **4** ($\beta = 0.55$, H_2O, at 25 °C, I = 1.0 M (KCl))[23] and for the deprotonation of hydroxymethyl group of dihydroxyacetone phosphate ($\beta = 0.48$; H_2O, at 37 °C, I = 1.0 M (KCl)) for the same series of general base catalysts.[73] Also, Amyes and Richard estimated the β-value for acetone to be $\beta = 0.5$ for the series of quinuclidine derivatives used, based upon literature values for several compounds.[36] The β-value of 0.59, determined from our general base-catalyzed deprotonation studies of cyclobutanone, suggests more advanced C−H bond cleavage in the transition state leading to the enolate, relative to acetone and the methyl group of **4**.

In addition, in the Brønsted plot shown in Figure 5, the point for the deuteroxide-catalyzed deprotonation of cyclobutanone has been included. As has been previously noted for other compounds,[23,36] the second-order rate constant for the lyoxide-catalyzed deprotonation of **2** does not correlate with the second-order rate constants determined for the tertiary amine bases. This lyoxide ion anomaly[74,75] is thought to result, in part, from the need for the strongly basic deuteroxide ion to partially desolvate in order to react.[74,76,77]

Nature of the Enolate of Cyclobutanone. In a paper discussing the concept of strain as it pertains to organic molecules, Wiberg[78] showed that the strain energy in cyclobutene

(73) Richard, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 4926–4936.
(74) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 683–692.
(75) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475–503.
(76) Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G.; Nakamura, C. *J. Am. Chem. Soc.* **1982**, *104*, 7045–7051.
(77) Hupe, D. J.; Wu, D. *J. Am. Chem. Soc.* **1977**, *99*, 7653–7659.
(78) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312–322.

(strain energy compared to cyclohexene was 28.8 kcal/mol) is slightly larger than the strain energy in exomethylenecyclobutane (strain energy compared to exomethylenecyclohexane was 28 kcal/mol). A similar comparison between cyclobutane (strain energy is 26.5 kcal/mol) and cyclohexane[78] leads to the conclusion that the incorporation of the double bond into the ring results in relatively small differences in energy due to strain. A later *ab initio* study determined the difference in strain energies between cyclobutene and cyclobutane to be ~5.75 kcal/mol as compared to cyclohexene and cyclohexane, respectively.[79] These results indicate that while the incorporation of the alkene into the 4-membered ring does destabilize the system relative to the 6-membered ring, the increase in strain energy does not appear to be significantly increased.

Acidity of α-Protons of Cyclobutanone. It is difficult to critically analyze the observed differences in the β-values and fully understand what these differences mean with regards to the transition state of the general base-catalyzed deprotonation and the relative energy of the enolate intermediate. It is well understood that a β-value of 0 indicates that there is no proton transfer in the transition state of the rate determining step of the reaction and a β-value of 1.0 indicates complete proton transfer in the transition state.[41] In the case of β-values approaching 1.0, it is thought that it is the separation of the ion pair (enolate/conjugate acid of the base) that is rate limiting.[36] Therefore, under these circumstances, protonation of the enolate would be a diffusion limited process or occur from a reorganization of solvent shell. Factoring these arguments together, it is not surprising that people have used the β-value as a measure of the degree of proton transfer in the transition state of the reaction.[80] (Such an analysis has been questioned,[76,77,81−83] however the use of β-values in this manner has continued.)

As stated above, the similarity of the rate constants (k_B) for acetone and **2**, indicates that the barriers to deprotonation, under the conditions of these studies, are very similar but the β-values indicates greater C−H bond breaking in the transition state for **2** and therefore a later transition state for **2** relative to acetone. If it were assumed that the potential energy surface leading to the transition state for the deprotonation of acetone is similar to that for the deprotonation of **2**, then the difference in β-values could be due to the difference in the relative energy of the enolates generated in these processes (see Figure 6). The enolate of cyclobutanone being slightly less stable than the enolate generated by deprotonation of acetone could explain the greater C−H bond cleavage in the transition leading to the enolate of **2** relative to that observed for acetone. The rate constant for the protonation of the enolate of acetone has been estimated to be $k_{BH} = 1.7 \times 10^8\ M^{-1}\ s^{-1}$ by the conjugate acid of 3-quinuclidinone in H_2O.[37] Whereas, a process with no barrier for the protonation of an enolate would be expected to be diffusion limited where values in the range of $(5-7) \times 10^9\ M^{-1}\ s^{-1}$ have been determined for the reaction of azide with a variety

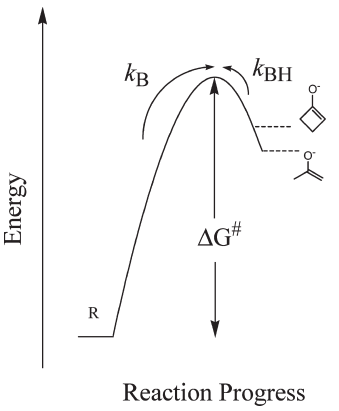
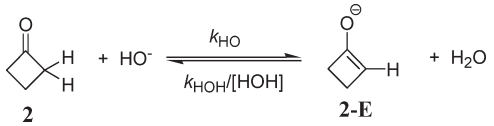


FIGURE 6. Reaction coordinate for the general base-catalyzed deprotonation of the cyclobutanone and acetone in D_2O where the barrier to deprotonation is similar for both ketones. The enolate of cyclobutanone lying in a more shallow energy well than the enolate of acetone leads to changes in the pK_a of the carbon acid.

SCHEME 4. Equilibrium for the ionization of cyclobutanone



of benzylic carbocations.[84−86] On the basis of the larger β-value and the strain analysis in the previous section, we conclude that the enolate of cyclobutanone is less stable, relative to the keto-form, than is the enolate of acetone. Thus, the k_{BH} value for the protonation of the enolate of **2** must lie between $k_{BH} = 1.7 \times 10^8\ M^{-1}\ s^{-1}$ and the diffusion limit. If a linear correlation between the β-values and these rate constants are assumed, limits for the rate constant for the protonation of the enolate of **2** by the conjugate acid of 3-quinuclidinone can be estimated for k_{BH} to be between 5×10^8 to $2 \times 10^9\ M^{-1}\ s^{-1}$.

An estimate for the pK_a of cyclobutanone can then be generated using eq 1. The fact that k_B was determined in D_2O rather than in H_2O has been acknowledged, however a small solvent isotope effect of $k_B^{HOH}/k_B^{DOD} = 1.1$ has been previously determined[73] for a similar system and a similarly small effect would be expected in these studies. When k_B, for the 3-quinuclidinone-catalyzed deprotonation of cyclobutanone, and the k_{BH} values from above are substituted into eq 1, the acidity of cyclobutanone in H_2O can be estimated to be pK_a = 19.7 - 20.2. This can be compared to the pK_a of 19.3 for acetone[27] and a pK_a of 19.6 for the methyl group of **4**.[24]

The lifetime of **2-E** in solution can be estimated on the basis of Scheme 4 and eq 9, where $k_{HO} = 0.036\ M^{-1}\ s^{-1}$ (using $k_{DO}/k_{HO} = 1.4$)[36] and a pK_a for **2** of 20.2, the upper limit of the reactivity of **2-E**. The rate constant for protonation of the enolate of **2** by water $k_{HOH} = 6 \times 10^4\ s^{-1}$, at 25 °C. Thus, the lifetime of **2-E** in solution is approximately

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1.6×10^{-5} s as compared to acetone whose approximate lifetime in aqueous solution is 2×10^{-5} s (based upon pK_a of 19.3[27] and $k_{HO} = 0.22\ M^{-1}\ s^{-1}$).[52]

$$K_{eq} = k_{HO}[HOH]/k_{HOH} = K_a^{k}/K_a^{HOH} \qquad (9)$$

Conclusions

The rate constants for the 3-substituted quinuclidine-catalyzed deuterium incorporation into the α-position of cyclobutanone have been determined in D_2O, $I = 1.0$ M (KCl) at 25 °C. The observation of general base catalysis of deuterium incorporation, in addition to other factors, supported the conclusion that the enolate of **2** was a free intermediate in solution. In all cases, the second-order rate constants determined for **2** were slower than those found for a 1-phenylacetone derivative (**4**),[23] whose reactivity is comparable to that of acetone. The second-order rate constant for deuteroxide-catalyzed deuterium incorporation into **2** was found to $k_{DO} = 0.051\ M^{-1}\ s^{-1}$ compared to $k_{DO} = 0.21\ M^{-1}\ s^{-1}$ for acetone, under the same conditions (D_2O, $I = 1.0$ M (KCl) at 25 °C). The similarity of the rate constants of base-catalyzed enolate formation indicated that the barrier to the deprotonation of cyclobutanone is similar to those of acetone and **4**. The β-value determined for cyclobutanone ($\beta = 0.59$) using a series of substituted quinuclidine bases indicated greater C−H bond breaking in the transition state relative to the β-value observed for **4**[23] and, potentially, a later transition state. A pK_a for cyclobutanone of 19.7−20.2 was predicted based upon the comparison of the general base-catalyzed rate constants for the enolization and β-values of **2**, **3**, and **4**.

Effect of Ring Strain? It is well-known that the induction of strain, like that found in small carbocycles, leads to greater s-character in the carbon contribution to the C−H bonds and an associated rise in the acidity of the hydrogens.[41] The results of prior studies determining the reactivity of cyclobutanone[45,46] generated outcomes that indicated **2** was significantly more reactive, with respect to enolization, than structural analogues. These results could be rationalized as an effect of the increased bond angle strain in the carbocycle, leading to an associated increase in the acidity/reactivity of the α-protons.

In contrast, we and others[47,72] have found the reactivity of the α-protons of cyclobutanone to be similar to that found for the α-protons of acetone and the methyl group of the phenylacetone derivative **4**. The results presented here clearly show that, over a range of pD and for a structurally similar series of tertiary amine bases, the barrier to the deprotonation of cyclobutanone is essentially the same as that found for acetone. That acetone, a strain-free system, would react with a rate constant similar to that observed for cyclobutanone suggests that ring strain is having no significant effect on the acidity of the α-protons. While this idea cannot be correct, as it has been well established that increases in ring strain have a significant effect on the acidity of the C−H bonds,[41] it is possible that strain may not be as significant in cyclobutanone as might be anticipated. For example, the similarity in the degree of hydration of acetone and cyclobutanone[62] suggests that any strain present in **2** does not have a significant effect on electrophilicity of the carbonyl group of **2** vs acetone.

Another factor that may lead to changes in the barrier to deprotonation is the alignment of the C−H bond on the α-carbon with the π-bond of the carbonyl. Such orbital overlap has been cited as central to decreasing the barrier to deprotonation both experimentally[87−92] and computationally.[42−44] While the entropic factors in cyclobutanone would be expected to be smaller compared to those of the comformationally unrestricted methyl group in acetone, the actual alignment of the α-protons with the carbonyl group in cyclobutanone is unknown. Does torsional strain between the α- and β-hydrogens have to be increased in **2** to provide better orbital alignment? If so, this would increase the barrier to deprotonation.

The combination of structural and dynamic factors that leads to the outcome discussed herein is not clear. However, for the enolization of cyclobutanone, ring strain does not apparently have a substantial effect on the velocity of reaction. We have postulated, based upon thermodynamic[78] and computational data,[79] that the ring size does destabilize the enolate generated upon deprotonation of cyclobutanone. Such destabilization results in a lower barrier to protonation of the enolate and a decrease in the acidity of cyclobutanone relative to that of acetone.

Experimental Section

Materials and Methods. The tertiary amines used were quinuclidine hydrochloride (97%), 3-quinuclidinone hydrochloride (99%), 3-quinuclidinol (99%), and 3-chloroquinuclidine hydrochloride (98%) which were purchased from commercial sources and purified by recrystallization as previously described.[23] Cyclobutanone (98+%), reagent grade acetone, deuterium oxide (99.9% D), potassium deuteroxide (40 wt % in D_2O, 98% D), potassium chloride, magnesium sulfate, potassium phosphate (tribasic), and deuterium chloride (35 wt % in D_2O, 99.5% D) were all purchased from commercial sources and used without further purification.

The reported pD's of all prepared solutions and those of the reaction solutions, after all the kinetic runs were completed, were obtained by adding 0.4 to the observed pH readings.[58] The [deuteroxide] was determined according to eq 8, using $K_w = 10^{-14.87}$, $\gamma_{OL} = 0.79$ as the apparent activity coefficient of lyoxide for these experimental conditions.[36]

Solution Preparation. Standard solutions of KOD and DCl were prepared by dilution, with D_2O, of concentrated stock solutions, where the concentration of the KOD or DCl had been determined by titration to the phenolphthalein end point using standard solutions.

The solutions used in the deuterium incorporation experiments were all prepared using the same general procedure, and as a result, the method will be described once, without individual detail. The quinuclidine buffers were recrystallized and dried prior to utilization. Before the solutions were prepared, all labile protons on the tertiary amines were exchanged by three successive washes with D_2O followed by removal of the solvent under vacuum, with final solvent removal performed under high

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vacuum at room temperature for at least 24 h. Solution preparation involved dissolving the deuterated amine in D_2O with additions of standardized DCl or KOD (depending on the amine used) added to reach the desired pD. The ionic strengths of all solutions were maintained at $I = 1.0$ M using KCl. The total concentration of all forms of the buffer in each of the standard solutions was 0.5 M, which was the solubility limit for most of the buffers used in these studies. The exception was the 3-chloroquinuclidine solution where the solubility of the amine limited the total buffer concentration to 0.1 M. The phosphate solutions also contained a total [phosphate] of 0.1 M.

Deuterium Incorporation Studies. All reactions were performed in D_2O in the presence of general base catalysts at 25 °C and $I = 1.0$ M (KCl). Prior to the initiation of any incorporation experiment, the kinetic solution was equilibrated in a water bath set to 25 °C for at least 15 min. An experiment was initiated by injecting neat cyclobutanone (10 mM final concentration) into the D_2O solution at zero time. At timed intervals a 1- or 1.5-mL aliquot of the reaction mixture was removed and acidified using DCl. A small excess of DCl was usually added to ensure that all the general base catalyst was in its conjugate acid form; otherwise, the tertiary amine would be extracted during the next stage. The resulting acidified solution was immediately extracted with ~1 mL of $CDCl_3$; after separation from the aqueous layer, the organic layer was dried by passage through a short column of $MgSO_4$ and stored in a sealed vial. The samples, so obtained, were stored at 4 °C until analyzed by ^{1}H NMR spectroscopy, without any apparent degradation over time. At least five and usually six time-dependent kinetic samples were collected and analyzed for each general base concentration studied. After the final sample was collected, the pD of the remaining reaction solution was measured to determine if the pD had changed during the course of the experiment.

Those experiments performed in the phosphate solutions were performed in the same manner as described above with both cyclobutanone and acetone having final concentrations of 5−7 mM.

^{1}H NMR Spectroscopy. The ^{1}H NMR analysis of each sample was performed using a 400 or 500 MHz spectrometer with the probe temperature maintained at 25 °C with all spectral data referenced to $CHCl_3$ at 7.27 ppm. The resonances for the α-protons of cyclobutanone were coupled to the β-protons yielding a set of peaks that became more complex upon deuterium incorporation. To simplify the resonance of the α-protons (3.11 ppm), the protons on the β-carbon (at 2 ppm) were subjected to inverse gated homonuclear decoupling during acquistion.[48,55] The spectrum simplified to yield a singlet at 3.11 ppm for the α-CH_2 and an upfield shifted triplet at 3.09 ppm ($J_{DH} = 2.2$ Hz) for the deuterated form of **2**. The relaxation times for the protons undergoing exchange were found to be approximately $T_1 = 5$ s, and thus, the delay time between pulses was set to 60 s to ensure a uniform population with each pulse.

The exchange of protium for deuterium in the α-position of cyclobutanone in D_2O was followed by monitoring the disappearance of the singlet at 3.11 ppm due to the α-CH_2's groups and the appearance of an upfield shifted triplet at 3.09 ppm for the α-CHD group. The progress of the reaction (R_{CH2}) was determined using eq 2,[56,57] where A_{CH2} and A_{CHD} are the integrated areas for the singlet and triplet peaks for the α-CH_2 and α-CHD peaks, respectively. Line broadening due to long-range coupling between the CHD group (C2 position) and the CH_2 group (C4 position) resulted in overlap between the observed singlet for the equivalent α-CH_2 positions and the triplet for the CHD group which resulted in only the area of the final peak of the triplet for the α-CHD group being accurately measured. Thus, A_{CHD} was determined by multiplying the area of the most upfield shifted triplet by 3. The area of A_{CH2} was determined by taking the total area of the singlet and triplet for A_{CH2} and A_{CHD} and then subtracting the A_{CHD} determined as described above.

The observed rate constants for deuterium exchange for a specific concentration of general base catalyst were determined by the slope of the linear correlation between the natural log of the reaction progress (R_{CH2}) vs time (according to eq 3). These plots were linear for exchange of up to 30% of the first proton of the α-CH_2 groups.

For the deuterium incorporation studies involving acetone and cyclobutanone, the amount of deuterium exchange into cyclobutanone was determined as described above. Deuterium exchange into acetone was performed as previously described[37] by following the disappearance of the singlet at 2.33 ppm (A_{CH3}) and the appearance of the upfield shifted triplet at 2.31 ppm (A_{CH2D}). The singlet and triplet peaks for the α-CH_3 and α-CH_2D were well resolved, and the areas of the peaks could be directly measured. The observed rate constants for deuterium incorporation were determined as shown in eqs 6 and 7, and plots of the natural log of reaction progress (R_{CH3}) were linear for exchange of up to ~30% of the first proton of the α-CH_3 groups.

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Supporting Information Available: Tables containing the observed rate constants of deuterium exchange into cyclobutanone as a function of the basic form of the tertiary amine for the reactions of 3-quinuclidinol, 3-chloroquinuclidine, and quinuclidine, plots of k_{obsd} vs basic form of the 3-substituted quinuclidine derivative for deuterium incorporation studies with cyclobutanone. This material is available free of charge via the Internet at http://pubs.acs.org.