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# Ring Strain and Its Effect on the Rate of the General-Base Catalyzed Enolization of Cyclobutanone

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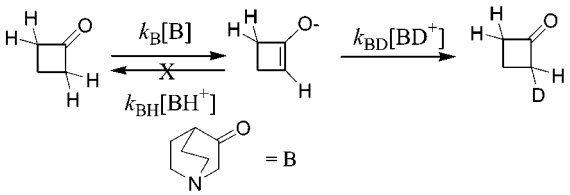
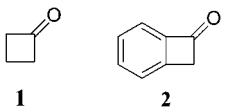
## ABSTRACT




**The 3-quinuclidinone-catalyzed (p$K_{BH}$ = 7.5) enolization of cyclobutanone (1) in $D_2O$ at 25 °C, $I$ = 1.0 (KCl) was followed by deuterium incorporation, which was determined by $^1$H NMR. The second-order rate constant for the buffer-catalyzed deprotonation of 1 was found to be $k_B = 3.3 \times 10^{-4}$ M$^{-1}$ s$^{-1}$, which is compared to rates for acetone and 2-(2′-oxopropyl)benzaldehyde under similar conditions. The data shows that ring strain has very little effect on the energy barrier to deprotonation of 1 vs the unstrained systems.**

Strained ring systems have long been of interest to chemists,[1] and for some this interest has focused on the hybridization and reactivity changes in the carbon−hydrogen bonds that are induced by ring strain.[2] Prior studies have established that as ring strain increases there is a resultant rise in the amount of s-character in the exocyclic bonds, which, when the substituents are hydrogen, leads to greater acidity.[2a] Only one study has specifically investigated the effect of ring strain on the reactivity of the α-protons of cyclic carbonyl systems that lead to endocyclic enolates and this study was performed in DMF.[3] Presented here are the results of our investigations of the rate of 3-quinuclidinone-catalyzed enolization of cyclobutanone (**1**) under aqueous conditions.




**1** **2**

Our interest in the effects of ring strain on the reactivity of the α-protons in cyclic carbonyl systems stems from studies involving benzocyclobutenone (**2**). The α-protons of **2** were found[4,5] to be much less reactive than compounds with similar structure.[5c] The lack of reactivity observed in **2** was rationalized on the basis of the generation of a carbanion wherein formation of the enolate increases the ring strain in the carbocycle and creates an antiaromatic π-system.[5c] Both factors would destabilize the transition state relative to the ground state, slowing the rate of deprotonation. In an attempt to dissect the relative importance of ring strain vs antiaromaticity as destabilizing factors in the rate of enolate production, we began our studies with cyclobutanone, which

(1) For a review, see: Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*; Academic Press: New York, 1978; Vol. 38.

(2) (a) Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965; Vol. 4. (b) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, 1987. (c) Carroll, F. A. *Perspectives on Structure and Mechanism in Organic Chemistry*; Brooks/Cole Publishing Company: New York, 1998.

(3) Shechter, H.; Collis, M. J.; Dessy, R.; Okuzumi, Y.; Chen, A. *J. Am. Chem. Soc.* **1962**, *84*, 2905−2910.

(4) (a) Amupitan, J. O.; Stansfield, F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1949−1951. (b) Bertelli, D. J.; Crews, P. *J. Am. Chem. Soc.* **1968**, *90*, 3889−3890. (c) Cava, M. P.; Muth, K. *J. Am. Chem. Soc.* **1960**, *82*, 652−654. (d) Hart, H.; Fish, R. W. *J. Am. Chem. Soc.* **1960**, *82*, 749−750. (e) Hart, H.; Hartlage, J. A.; Fish, R. W.; Rafos, R. R. *J. Org. Chem.* **1966**, *31*, 2244−2250.

(5) (a) Matsumoto, T.; Hamura, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1997**, *38*, 8985−8988. (b) Broadus, K. M.; Kass, S. R. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2389−2396. (c) Nagorski, R. W.; DeAtley, A. D.; Broadus, K. M. *J. Am. Chem. Soc.* **2001**, *123*, 8428−8429.

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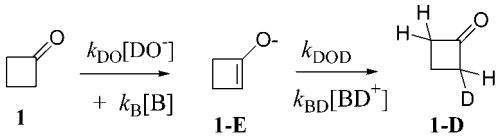
**Scheme 1**




is structurally similar to acetone (**3**), a well studied enolate source.[6]

Proton transfer at the α position of **1** (see Scheme 1) was followed by measurement of the amount of deuterium incorporation into **1** using an NMR technique developed by Richard and co-workers.[7] Deuterium incorporation studies were performed in $D_2O$ at 25 °C, $I = 1.0$ (KCl)[8] in the presence of the general-base catalyst 3-quinuclidinone ($pK_{BD} = 8.3$[7c]), with deuterium incorporation being monitored by $^1H$ NMR using a 400 MHz instrument.[9] Control experiments provided no evidence, by $^1H$ NMR, for significant formation of hydrated cyclobutanone when **1** was dissolved in 1 M KCl in $D_2O$.[9] This observation was in accord with studies by Wiberg and co-workers, who found the equilibrium constant for hydration of **1** to be $K = 2.18 \times 10^{-3}$ in $D_2O$ at 25 °C[10] as compared to $K = 1.4 \times 10^{-3}$ for acetone in $H_2O$ at 33 °C.[11] In addition, no evidence for formation of enolate addition products was observed during the course of the incorporation studies.

Deuterium incorporation at the α position of **1** results in a decrease in the intensity of the singlet for the α-methylene signals at 3.11 ppm[9] and the appearance of an upfield shifted triplet at 3.09 ppm ($J = 2.2$ Hz) for the CHD group for **1-D** (Scheme 1).[12] The relative amount of proton exchange was determined by comparing the areas of the α-CHD and α-$CH_2$ peak according to eq 1.[12,13] The observed rate of deuterium incorporation was determined by plotting $R_H$ according to eq 2 (see Figure 1).

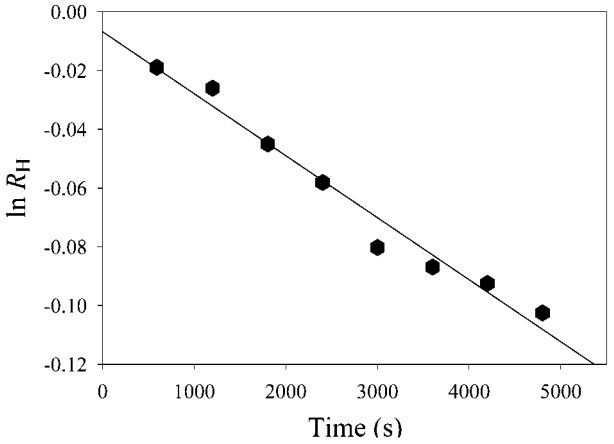



**Figure 1.** Representative natural logarithmic plot of $R_H$ vs time (s) for the exchange of protium for deuterium at the α position of cyclobutanone, as catalyzed by 3-quinuclidinone buffer ($[B + BH^+] = 0.5$ M, pD = 8.33) in $D_2O$ at 25 °C and $I = 1.0$ (KCl).

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

$$\ln R_H = \frac{-k_{obsd}t}{4} \quad (2)$$

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

The second-order rate constant for 3-quinuclidinone-catalyzed deprotonation was determined by plotting $k_{obsd}$ (from Figure 1) vs the concentration of the basic form of 3-quinuclidinone (Figure 2). Experiments performed at a different buffer ratio (pD = 9.3, see Figure 2) fall on the same correlation line as those performed at pD = 8.3. This observation leads to the conclusion that it is the basic form of the buffer that catalyzes deprotonation of **1** and also that $k_{DO}$, at the pD's of our experiments, is small compared to $k_B$ (see eq 3). If $k_{DO}$ were significant at the pD's of our experiments, then $k_{obsd}$ values performed at other pD's would have to be corrected for the deuterioxide reaction, and from

(6) Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 1990; p 399−480.

(7) (a) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 10297−10302. (b) Nagorski, R. W.; Mizerski, T.; Richard, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 4718−4719. (c) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 3129−3141. (d) Rios, A.; Richard, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 8375−8376. (e) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715−726. (f) Rios, A.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 9373−9385.

(8) (a) The deuterium incorporation studies were initiated by injecting 7.5 μL of neat cyclobutanone (10 mM final concentration) into the buffered $D_2O$ solution at zero time. At timed intervals a 1.0 mL aliquot was removed and acidified with DCl. This solution is immediately extracted with ~1 mL of $CDCl_3$. The $CDCl_3$ solution was separated from the aqueous layer and dried over a short column of $MgSO_4$. The pD of the reaction mixture was measured before the initiation of the reaction and after the reaction was complete. The pD was obtained by adding 0.4 to the observed pH reading (see ref 8b). (b) Glascoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188−190.

(9) (a) $^1H$ NMR spectra were obtained using a Varian Mercury 400 MHz instrument with the probe temperature maintained at 25 °C, and all spectra were referenced to $CHCl_3$ at 7.27 ppm. The NMR spectrum of the α-methylene protons was complicated by coupling to the methylene protons at the C3 position. To simplify the spectrum of the α-methylene protons, the protons in the C3 position (at 2 ppm) were subjected to inverse gated homonuclear decoupling (see refs 7e and 9b). (b) Sanders, J. K. M.; Hunter, B. K. *Modern NMR Spectroscopy*, 2nd ed.; Oxford University Press: Toronto, 1993.

(10) Wiberg, K. B.; Morgan, K. M.; Maltz, H. *J. Am. Chem Soc.* **1994**, *116*, 11067−11077.

(11) Hine, J.; Redding, R. W. *J. Org. Chem.* **1970**, *35*, 2769−2772.

(12) The line broadening due to the long-range coupling between the CHD group (C2 position) and the $CH_2$ group (C4 position) resulted in overlap between the singlet for the $CH_2$ group and the triplet for the CHD group, and as a result we could only accurately measure the area of the final peak of the triplet ($A_{CHD}$). The area of the triplet was calculated by multiplying the area of the measurable peak by three.

(13) (a) We have treated the four α-protons of **1** as being all equivalent. This analysis disregards the two potential dideuterated products that can be formed; however, these experiments are followed for exchange of 20% of the total α-protons, which is approximately 40% of the first α-proton of a single methylene unit. Similar experiments with acetone (see ref 7a) did not observe complicating dideuteration with similar incorporation percentages, and we did not observe any evidence suggesting this complication was occurring. (b) Halkides, C. J.; Frey, P. A.; Tobin, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 3332−3333. (c) Tobin, J. B.; Frey, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 12253−12260.

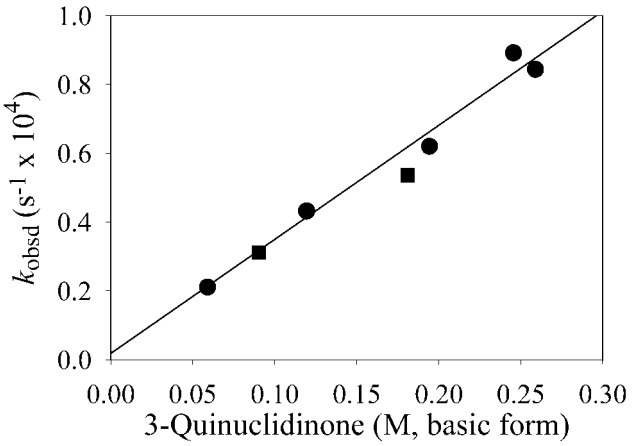
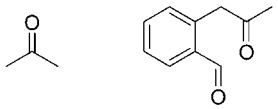



**Figure 2.** Dependence of the observed rate constant for deuterium exchange into the α position of cyclobutanone ($k_{obsd}$) on the concentration of the basic form of 3-quinuclidinone in $D_2O$ at 25 °C and $I = 1.0$ (KCl). (●) $k_{obsd}$ determined at pD = 8.3 ([B]/[$BH^+$] = 1.0); (■) $k_{obsd}$ determined at pD = 9.3 ([B]/[$BH^+$] = 10).

Figure 2 this is clearly not necessary. The second-order rate constant for the 3-quinuclidinone-catalyzed deprotonation of **1**, from Figure 2, was found to be $k_B = 3.3 \times 10^{-4}$ $M^{-1}$ $s^{-1}$.

This second-order rate constant for the deprotonation of **1** is in good agreement with second-order rate constants found for the 3-quinuclidinone-catalyzed deprotonation of acetone ($k_B = 5.2 \times 10^{-4}$ $M^{-1}$ $s^{-1}$)[7a] and the methyl group of 2-(2′-oxopropyl)benzaldehyde (**4**) ($k_B = 3.4 \times 10^{-4}$ $M^{-1}$ $s^{-1}$).[7b] However, the similarity of these results (rates are uncorrected for the number of ionizable protons) contrast the previous study that investigated the effects of ring strain on deprotonation leading to enolates.[3] Dessy and co-workers found the relative rate of deprotonation of cyclobutanone/4-heptanone was $k_{rel} = 290$ in DMF with 1 M triethylamine and 5 M $D_2O$ at 40 °C.[3]



**3** **4**

What are the factors that, when combined, generate this observed similarity in 3-quinuclidinone-catalyzed deprotonation rate constants of **1**, **3**, and **4**?

**(A) Hybridization Considerations.** The bond angles that are required by a four-membered carbon ring (especially where one of the carbons must be $sp^2$-hybridized to accommodate the carbonyl carbon) will lead to greater s-character in the C−H bonds. The usual observation upon increasing the s-character in a C−H bond is an associated drop in the p$K_a$ of these hydrogen, and this has been observed for cyclobutane (p$K_a = 50$) vs cyclohexane (p$K_a = 52$).[2b,14] The result of this greater s-character in **1** will be an α-carbon that is more able to support the developing negative charge that occurs during the early stages of deprotonation vs the α-carbon in **3**. The greater ability of the α-carbon in **1** to stabilize the developing negative charge should result in a decrease in the barrier to the deprotonation of **1** vs acetone.

**(B) Entropic Differences.** Computational studies of the deprotonation of acetaldehyde have found a transition state for proton abstraction wherein the orbitals of the proton being abstracted are parallel with the orbitals of the carbonyl $\pi$-system.[15] This alignment allows for distribution of the developing negative charge into the carbonyl group via resonance. Similarly, the coplanarity of the orbitals and lack of conformational freedom has been used to explain the rate difference of the hydroxide-catalyzed deprotonation of 2-indanone ($k_{HO} = 220$ $M^{-1}$ $s^{-1}$)[16] vs 2-benzosuberone ($k_{HO} = 3.7$ $M^{-1}$ $s^{-1}$).[16a,c] The carbocycle in **1** restricts the rotational freedom of the α-carbons, and as a result the α-protons are better aligned with the carbonyl $\pi$-system as compared to **3**, which has complete rotational freedom. Assuming that the solvation effects are the same for these two structurally similar systems, the lack of conformational mobility in **1** could lead to lower entropic requirements for proton removal relative to acetone and hence a lowering of the barrier to deprotonation of **1** vs **3**.

**(C) Ring Strain in the Transition State.** As the negative charge is generated on the α-carbon during deprotonation, stabilization of the developing charge via resonance into carbonyl group requires that the α-carbon reconfigure to $sp^2$ hybridization. In the case of **1**, such rehybridization would increase the ring strain within the system by creating two $sp^2$-hybridized carbons in **1-E** vs one $sp^2$-hybridized carbon in **1**. This would result in destabilization of the enolate intermediate and, depending on the degree of rehybridization and orbital overlap with the carbonyl $\pi$-system in the transition state,[15,17] increase the energy of the transition state relative to the ground state and thus slow the deprotonation of **1** relative to **3**.

We have shown that the rate of 3-quinuclidinone-catalyzed deprotonation of cyclobutanone in $D_2O$, $I = 1.0$ (KCl), at 25 °C is similar to those observed for the deprotonation of acetone (**3**) and 2-(2′-oxopropyl)benzaldehyde (**4**) under the same conditions. The similarities of these second-order rate constants indicate that there is no significant difference between the barriers for deprotonation of the unstrained systems vs cyclobutanone in our experiments, indicating that the predominant effect in **2** may be the destabilization due to antiaromaticity.[5c] A qualitative explanation of our observation involves the destabilizing effect of ring strain on the enolate intermediate being compensated by the increased s-character in the C−H bonds and possible entropic advantages due to the carbocycle. The apparent contradiction between our observations and those found by Shechter and

(14) (a) Streitwieser, J., A.; Young, W. R.; Caldwell, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 527−528. (b) Streitwieser, J., A.; Caldwell, R. A.; Young, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 529.

(15) (a) Perakyla, M. *J. Phys. Chem.* **1996**, *100*, 3441−3447. (b) Pranata, J. *J. Phys. Org. Chem.* **1996**, *9*, 711−716.

(16) (a) $I = 0.1$, at 25 °C in $H_2O$. (b) Keefe, J. R.; Kresge, A. J.; Yin, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8201−8206. (c) Eldin, S.; Pollack, R. M.; Whalen, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 1344−1349.

(17) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *27*, 119.

co-workers[3] can be rationalized by possible differences in the Bronsted $\beta$ slope between **1** and **3**, where **1** would be anticipated to have a slope larger than that observed for **3** as a result of destabilization of the enolate via ring strain ($\beta = 0.55$ for methyl group of 2-(2′-oxopropyl)benzaldehyde).[18]

**Acknowledgment.** This research was supported by an award from Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

(18) Richard, J. P.; Nagorski, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 4763−4770.

**Supporting Information Available:** Table of the observed rates for deuterium exchange into the α position of cyclobutanone as a function of the basic form of 3-quinuclidinone under the conditions of our experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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