

## Absolute and Relative Electrophilicities of a Carbonyl Group and Tertiary Ammonium Ions toward a Simple Enolate Ion

R. W. Nagorski, Tadeusz Mizerski, and John P. Richard\*

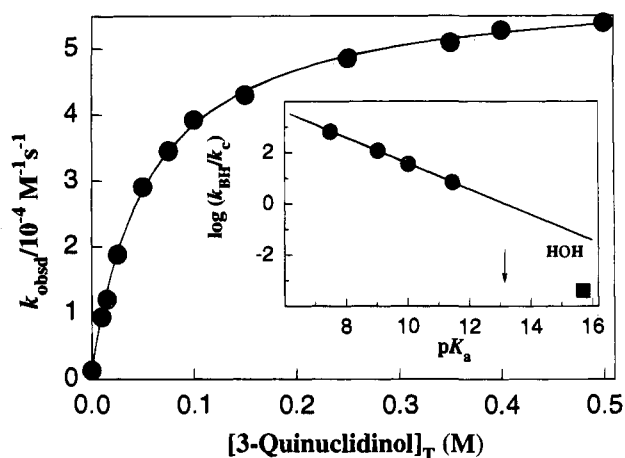
Department of Chemistry  
University at Buffalo, SUNY  
Buffalo, New York 14260-3000

Received January 17, 1995

Despite the prominence of addition reactions of enols and enolate ions to the carbonyl group in chemical syntheses<sup>1</sup> and enzyme-catalyzed reactions,<sup>2</sup> there have been few studies directed toward the determination of the chemical barriers to these fast reactions.<sup>3,4</sup> We report here the results of experiments to determine the absolute rate constant for intramolecular addition of the enolate ion **2** to its carbonyl group (Scheme 1) and the relative electrophilicities of Brønsted acids (water and tertiary ammonium ions) and this carbonyl group toward the simple enolate of **2**. The results show that a benzaldehyde-type carbonyl group is moderately reactive as an electrophile, with an electrophilicity toward a simple enolate ion that is comparable to that of weakly acidic tertiary ammonium ions.

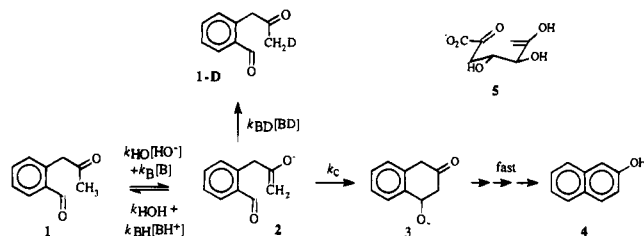
The conversion of **1**<sup>5,6</sup> into **4** in water was monitored by UV spectroscopy<sup>7a</sup> and HPLC analyses.<sup>7b</sup> The same pseudo-first-order rate constants,  $k_{\text{obsd}}$  ( $\text{s}^{-1}$ ), govern the disappearance of **1** and the appearance of **4**, and no reaction intermediates were observed by HPLC analyses. These observations show that the rate of conversion of **1** into **4** is limited by formation of the aldol addition product **3** and that subsequent steps for the conversion of **3** into **4** are fast (Scheme 1).

Proton transfer at the  $\alpha$ -carbonyl methyl group of **1** in  $\text{D}_2\text{O}$  at 25 °C and  $I = 1.0$  (KCl) was followed by 400 MHz <sup>1</sup>H NMR.<sup>8,9a</sup> Deuterium exchange catalyzed by  $>0.1$  M 3-quinuclidinone buffer is faster than aldol addition: for example, no **4** was observed by <sup>1</sup>H NMR during the conversion of 30% of **1** to **1-D** in the presence of 0.30 M 3-quinuclidinone buffer (50% free base,  $\text{pD} = 8.3$ ). By contrast, the deuterioxide ion-catalyzed exchange of deuterium into **1** to give **1-D** is slower than the formation of **4**. These experiments show that protonation of the enolate of **2** by the relatively acidic 3-quinuclidinone cation



**Figure 1.** Effect of increasing concentrations of 3-quinuclidinol buffer (50% free base) on  $k_{\text{obsd}}$  ( $\text{s}^{-1}$ ) for conversion of **1** into **4** in water at  $\text{pH} = 10.1$  and 25 °C,  $I = 1.0$  (KCl). Inset: Brønsted plot of  $\log(k_{\text{BH}}/k_{\text{c}})$  ( $\text{M}^{-1}$ , Scheme 1) against  $\text{p}K_{\text{BH}}$  for 3-substituted quinuclidine catalysts. The reactivity of water is expressed as a second-order rate constant and is calculated as  $k_{\text{HOH}}/55.5 \text{ M}$ . The arrow indicates the value of  $\text{p}K_{\text{BH}}$  for a hypothetical 3-substituted quinuclidine cation with the same reactivity in intermolecular protonation of the enolate of **2** as its carbonyl group in the intramolecular aldol addition reaction.

### Scheme 1



( $\text{p}K_{\text{BH}} = 7.5$ )<sup>10</sup> is faster than intramolecular addition of the enolate of **2** to its carbonyl group ( $k_{\text{BD}}[\text{BD}^+] > k_{\text{c}}$ , Scheme 1) but that protonation by the weaker acid water is slower than this competing cyclization ( $k_{\text{HOH}} < k_{\text{c}}$ ).

A second-order rate constant of  $k_{\text{B}} = 3.4 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$  was determined for deprotonation of **1** by 3-quinuclidinone.<sup>9b</sup> Statistical correction of the rate constant for deprotonation of acetone by 3-quinuclidinone in  $\text{D}_2\text{O}$  gives about the same value of  $k_{\text{B}} = 2.6 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$  for reaction of a single methyl group of acetone.<sup>11</sup> We conclude that the acidities of the methyl group of **1** and a single methyl group of acetone are similar and calculate  $\text{p}K_{\text{a}} \approx 19.6$  for deprotonation of **1** by making a statistical correction of the  $\text{p}K_{\text{a}} = 19.3$  for acetone.<sup>12</sup>

Figure 1 shows the effect of increasing concentrations of 3-quinuclidinol buffer (50% free base,  $\text{pH} = 10.1$ ) on  $k_{\text{obsd}}$  for

(1) Thebtaranonth, C.; Thebtaranonth, Y. In *The Chemistry of Enones*; Patai, S., Ed.; John Wiley & Sons: New York, 1989; Part 1, pp 199–280. Hajos, Z. G. In *Carbon–Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. 1, pp 1–79. Neilsen, A. T.; Houlikan, W. J. *Org. React.* **1968**, *16*, 1–438.

(2) Wong, C. H. *Biocatalysis* **1990**, 319–335. Horecker, B. L.; Orestes, T.; Lai, C. Y. In *The Enzymes*, 3rd ed.; Academic Press: New York, 1972; Vol. 7, pp 213–253.

(3) Guthrie, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 7249–7255.

(4) Miller, B. A.; Leussing, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 7146–7153. Cheong, M.; Leussing, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 2541–2549. Desper, J. M.; Breslow, R. *J. Am. Chem. Soc.* **1994**, *116*, 12081–12082.

(5) **1** was prepared by the reaction of 2-indanone (Aldrich) with methylmagnesium iodide to give 2-methyl-2-indanol (bp 84–86 °C/0.5 Torr), followed by dehydration with  $\text{P}_2\text{O}_5$  [Koelsch, C. F.; Johnson, P. R. *J. Am. Chem. Soc.* **1943**, *65*, 567–573] to give 2-methylindene and ozonolysis with a reductive workup [Garratt, P. J.; Vollhardt, K. P. C. *Synthesis* **1971**, 423–424] to give **1**.

(6) Hamer, N. K. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1285–1289.

(7) (a) The reaction of **1** was monitored spectrophotometrically by following the increase in absorbance at 340 nm due to the appearance of  $\beta$ -naphthol or the decrease in absorbance at 256 nm due to the disappearance of **1**. (b) HPLC analyses were performed as described previously.<sup>11</sup> The formation of **4** and the disappearance of **1** were monitored at 340 and 256 nm, respectively, using a Waters 996 photodiode array detector.

(8) These reactions were initiated by adding a 300-fold dilution of a solution of **1** in acetonitrile into 8 mL of  $\text{D}_2\text{O}$  buffered with 3-quinuclidinone at 25 °C and  $I = 1.0$  (KCl) to give a final concentration of 3.5–5.0 mM. Aliquots (1 mL) were removed at specified times and mixed with concentrated DCl in order to protonate the 3-quinuclidinone buffer. This solution was extracted with 1 mL of  $\text{CDCl}_3$ , and the extract was transferred directly to an NMR tube by filtration through  $\text{MgSO}_4$  in a Pasteur pipet with a glass wool stopper.

(9) (a) <sup>1</sup>H NMR spectra were obtained on a Varian VXR-400S spectrometer in  $\text{CDCl}_3$  at 25 °C. Chemical shifts were reported relative to 7.27 ppm for  $\text{CHCl}_3$ . The first reaction observed was the essentially complete exchange for deuterium from solvent of the benzylic protons of **1**. A second-order rate constant of  $k_{\text{B}} = 3.9 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$  was determined for this reaction catalyzed by 3-quinuclidinone. The subsequent exchange for deuterium of the methyl protons occurred at a slower rate and was followed by monitoring the appearance of the triplet at 2.311 ppm ( $J = 2.3 \text{ Hz}$ ) due to the  $\text{CH}_2\text{D}$  group of **1-D** and the quintet at 2.296 ppm ( $J = 2.3 \text{ Hz}$ ) for the  $\text{CHD}_2$  group resulting from exchange of the second proton of the methyl group, and the disappearance of the singlet at 2.327 ppm for the methyl group. (b) Details of the procedures used to determine first- and second-order rate constants for deprotonation of **1** from these deuterium exchange reactions are given in ref 11.

(10) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963–6970.

(11) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 10298–10302.

(12) Keeffe, J. P.; Kresge, A. J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; John Wiley and Sons: Chichester, 1990; p 457.

conversion of **1** into **4** in water at 25 °C and  $I = 1.0$  (KCl).<sup>7a</sup> The observation that this reaction is catalyzed by low concentrations of buffer but approaches a limiting velocity at high concentrations shows that there is a change from rate-determining buffer-catalyzed deprotonation of **1** when  $k_c > k_{\text{HOH}} + k_{\text{BH}}[\text{BH}^+]$  to rate-determining uncatalyzed cyclization of **2** at relatively high buffer concentrations when  $k_{\text{BH}}[\text{BH}^+] > k_c$ .

The rate constant for hydroxide ion-catalyzed aldol addition at pH = 10.1 is  $k_o = k_{\text{HO}}[\text{HO}^-] = (0.10 \text{ M}^{-1} \text{ s}^{-1})(1.6 \times 10^{-4} \text{ M}) = 1.6 \times 10^{-5} \text{ s}^{-1}$ .<sup>13a</sup> This is 36-fold smaller than the limiting rate constant observed at high concentrations of 3-quinuclidinol buffer at the same pH,  $k_{\text{lim}} = k_{\text{HO}}[\text{HO}^-](k_c/k_{\text{HOH}}) = 5.9 \times 10^{-4} \text{ s}^{-1}$  (Figure 1). Equation 1 gives the relationship between  $k_{\text{lim}}/k_o$  and  $k_c/k_{\text{HOH}}$  for partitioning of **2** between protonation by water ( $k_{\text{HOH}}$ ) and cyclization ( $k_c$ ). Substitution of  $k_{\text{HOH}} = k_{\text{HO}}(K_a)_w[\text{H}_2\text{O}]/(K_a)_c$  and  $k_o = k_{\text{HO}}[\text{HO}^-]$  gives eq 2, from which  $k_c = 1.6 \times 10^6 \text{ s}^{-1}$  can be calculated using  $(K_a)_c = 10^{-19.6}$  and  $(K_a)_w = 10^{-15.7}$  for the ionization constants of the methyl group of **1** and of water, respectively.

$$\frac{k_{\text{lim}}}{k_o} = \frac{k_{\text{HO}}[\text{HO}^-](k_c/k_{\text{HOH}})}{k_{\text{HO}}[\text{HO}^-]} = \frac{k_c}{k_{\text{HOH}}} \quad (1)$$

$$k_c = \frac{k_{\text{lim}}(K_a)_w[\text{H}_2\text{O}]}{(K_a)_c[\text{HO}^-]} \quad (2)$$

The value of  $k_c = 1.6 \times 10^6 \text{ s}^{-1}$  is in remarkable agreement with  $k_{\text{add}} = 1.4 \times 10^6 \text{ s}^{-1}$  estimated for conversion of a bimolecular encounter complex between the enolate of acetone and benzaldehyde to the aldol adduct.<sup>3</sup> The good agreement between these rate constants is consistent with an effective molarity of approximately unity for the intramolecular enolate addition reaction.

The solid line in Figure 1 shows the fit of data for catalysis of the reaction of **1** in water by 3-quinuclidinol buffer to eq 3 derived for Scheme 1 [(1 +  $k_{\text{HOH}}/k_c) = 1.03 \approx 1$  (see above);  $[\text{B}]_T$  is the total concentration of buffer, and  $K_{\text{BH}} = 9.6 \times 10^{-11} \text{ M}$  (ref 10) for deprotonation of the buffer acid] using values of

$$k_B = 1.9 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1} \text{ and } k_{\text{BH}}/k_c = 37.2 \text{ M}^{-1}.^{13b}$$

$$k_{\text{obsd}} = \frac{k_{\text{HO}}[\text{HO}^-](K_{\text{BH}} + [\text{H}^+]) + k_B K_{\text{BH}}[\text{B}]_T}{(K_{\text{BH}} + [\text{H}^+]) + (k_{\text{BH}}/k_c)[\text{H}^+][\text{B}]_T} \quad (3)$$

Values of  $k_B$  ( $\text{M}^{-1} \text{ s}^{-1}$ ) and  $k_{\text{BH}}/k_c$  ( $\text{M}^{-1}$ ) for a series of 3-substituted quinuclidine buffers were determined as described above. Brønsted plots of  $k_B$  ( $\text{M}^{-1} \text{ s}^{-1}$ ) for general base catalysis of deprotonation of the methyl group of **1** (not shown) and  $k_{\text{BH}}/k_c$  ( $\text{M}^{-1}$ ) for partitioning of **2** between protonation and cyclization (Figure 1, inset) against  $\text{p}K_{\text{BH}}$  are linear, with slopes of  $\beta = 0.53$  and  $-\alpha = -0.48$ , respectively. Extrapolation of the latter Brønsted correlation to  $\log(k_{\text{BH}}/k_c) = 0$  gives an estimated value of  $\text{p}K_{\text{BH}} = 13.2$  for a hypothetical substituted quinuclidine cation with the same reactivity in intermolecular protonation of the enolate of **2** as its carbonyl group in the intramolecular aldol addition reaction. That is, the benzaldehyde-type carbonyl group shows roughly the same electrophilicity as very weakly acidic tertiary ammonium ions toward a simple enolate ion.<sup>14</sup>

We conclude that the carbonyl group of **2** is (1) a *stronger electrophile* than water and (2) a *weaker electrophile* than tertiary ammonium ions ( $\text{p}K_{\text{BH}} < 13.2$ ) toward reaction with the enolate ion of **2**. The first conclusion is consistent with the observation that the enolate ion of **5**, a putative intermediate of the reaction catalyzed by dehydroquinase synthase, undergoes intramolecular addition to its carbonyl group faster than protonation by water and trapping by dehydroquinase synthase.<sup>15</sup> The second conclusion suggests that formation of enolate ion intermediates of enzymic aldol condensation in the presence of the conjugate acid ( $\text{p}K_a < 7.0$ ) of a catalytic base should be reversible and that carbonyl addition will be rate determining for the enzymatic reaction, unless the reactivity of the carbonyl group has been increased by other catalytic groups or metal cofactors at the enzyme.

**Acknowledgment.** This work was supported by Grant GM 47307 from the National Institutes of Health.

JA950145J

(13) (a) Deprotonation of **1** is the rate-determining step for the hydroxide ion-catalyzed cyclization reaction ( $k_c \gg k_{\text{HOH}}$ , Scheme 1). The concentration of hydroxide ion was calculated from the pH,  $K_w = 10^{-14} \text{ M}^2$ , and an experimentally determined activity coefficient of 0.79 for hydroxide ion in 1 M KCl [Amyes, T. L.; Richard, J. P., manuscript in preparation]. (b) The values of  $k_B$  ( $\text{M}^{-1} \text{ s}^{-1}$ ) and  $k_{\text{BH}}/k_c$  ( $\text{M}^{-1}$ ) were determined by fitting the data from Figure 1 to eq 3 derived for Scheme 1, using the Sigma plot nonlinear least-squares curve-fitting program from Jandel Scientific.

(14) This comparison is between the intermolecular reaction of the enolate ion with a Brønsted acid and its intramolecular reaction with a carbonyl group. A similar result is expected for a comparison between rate constants for intramolecular protonation of an enolate and addition to a carbonyl group, because the effective molarities for reaction of enolate ions with Brønsted acids are close to 1: Kirby, A. *J. Adv. Phys. Org. Chem.* **1980**, *17*, 183–278.

(15) Bartlett, P. A.; Satake, K. *J. Am. Chem. Soc.* **1988**, *110*, 1628–1630. Bartlett, P. A.; McLaren, K. L.; Marx, M. A. *J. Org. Chem.* **1994**, *59*, 2082–2085.