

Mechanism of Acetone Bromination in Methanol Containing Small Amounts of Water—Competition between Enol Path and Enol Ether Path

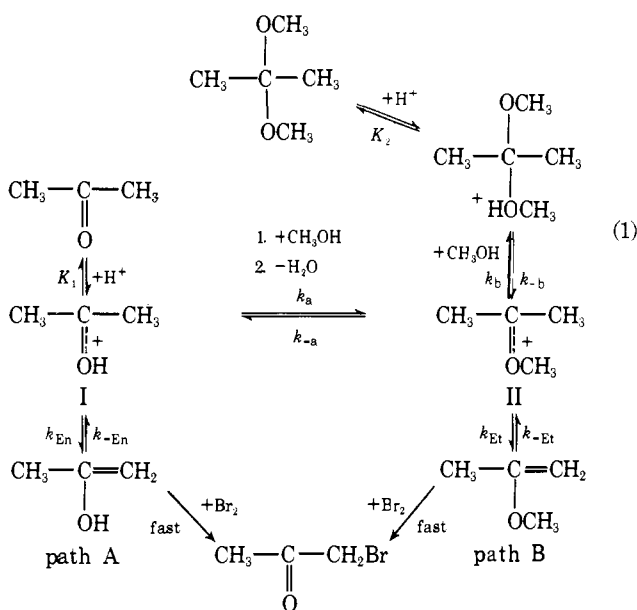
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Abstract: The acid-catalyzed bromination of the acetone-acetone dimethyl ketal system has been studied in methanol containing small amounts of water ($[H_2O] = 0.015\text{--}0.6\text{ M}$) at very low halogen concentration ($10^{-6}\text{--}10^{-5}\text{ M}$). For the lowest water concentrations, if the ketone-ketal system is equilibrated, the bromination rate is independent of halogen concentration, and is about 400 times faster than in water at the same acidity. Competition between the enol path and the enol ether path has been demonstrated in two studies: (a) influence of water concentration on the bromination rate constant of the equilibrated ketone-ketal system; and (b) bromination of a dynamic system, i.e., when equilibration occurs during the bromination. The partial rate constants of enolization and enol ether formation have been determined.

Significant differences in regioselectivity^{1,2} and stereoselectivity³ have been reported for acid-catalyzed halogenation of ketones in alcoholic media compared to other media. It has been proposed that one of the causes of these differences in behavior is the formation of enol ether (path B in eq 1)⁴⁻⁶ in-



stead of the enol (path A). There is, however, no direct evidence for such a mechanism nor, particularly, for its predominance relative to the classical mechanism via the enol. In this paper we shall determine which mechanism predominates when acetone is brominated in methanol containing a fully dissociated acid.

A priori, if paths A and B coexist, the proportions of A and B depend on the ratio of the ions I and II (hydroxy and alkoxy-carbenium ions) and the proton elimination rate constants, k_{En} and k_{Et} , for enol and enol ether formation. Therefore, if the bromination of the enol and the enol ether is fast relative to their formation, the rate of bromination of acetone, measured by the rate of bromine consumption, follows

$$-d[Br_2]/dt = k_{En}[I] + k_{Et}[II] \quad (2)$$

If the ketone-ketal system is rapidly equilibrated, concentrations of I and II are stationary and proportional to the concentrations of ketone and ketal, respectively; eq 2 can be expressed by

$$-d[Br_2]/dt = k_{exp}([ketone]_{eq} + [ketal]_{eq}) = k_{exp}[ketone]_T \quad (3)$$

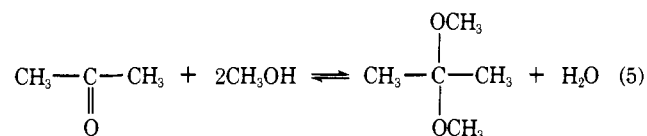
whether the two paths are in competition or if one is preferred ($[ketone]_{eq}$ and $[ketal]_{eq}$ are equilibrium concentrations of ketone and ketal, respectively; $[ketone]_T$ is the overall concentration). A kinetic study of acetone bromination in methanol cannot indicate the reaction mechanism directly. However, k_{exp} can be expressed by

$$k_{exp} = k_A[H^+](1 - x_{eq}) + k_B[H^+]x_{eq} \quad (4)$$

with

$$k_A = k_{En}/K_1 \text{ and } k_B = \frac{k_{Et}k_{-b}}{K_2k_b[CH_3OH]}$$

deduced from eq 2 and 3, where x_{eq} is the molar fraction of acetal ($x_{eq} = [ketal]/[ketone]_T$). There must therefore be a relationship between k_{exp} and x_{eq} . Since x_{eq} can be modified (see eq 5) by changing the water concentration, a study of the



effect of changing the water concentration upon the experimental rate constant, k_{exp} , is relevant. However, for this purpose it is necessary to estimate the influence of water on all the elementary rate and equilibrium constants in eq 4 (k_{En} , k_{Et} , k_{-b}/k_b , K_1 , and K_2).

A second approach to the problem, in which this difficulty does not occur, is to study the bromination of a "dynamic" ketone-ketal system, i.e., when the ketone and ketal concentrations tend during the bromination to the equilibrium ratio. In this case, particularly for low ketone concentrations, variations of the water concentration are negligible. We have performed such measurements by adding acetone ($\sim 10^{-3}\text{ M}$) to an acidic solution at very low bromine concentration ($\sim 10^{-6}\text{ M}$); the acid concentration has been chosen so that ketal formation is slow. The rate law, relative to the decrease of bromine concentration, is necessarily a function of the proportions of paths A and B.

Results

1. Ketone-Ketal Equilibration. Rate constants at 25 °C were obtained by acid-catalyzed hydrolysis of acetone dimethyl ketal by following spectroscopically the rate at which ketone appeared when equilibrium is displaced by water addition. The

Table I. Rate Constants for the Equilibration of Acetone with Acetone Dimethyl Ketal ($25 \pm 0.2^\circ\text{C}$)^a

| $10^3[\text{HBr}]$, M | $[\text{H}_2\text{O}]$, ^b M | $k_H + k_F$, ^c s^{-1} | $(k_H + k_F)/[\text{H}^+]$, $\text{M}^{-1}\text{s}^{-1}$ |
|---------------------------|--|---|--|
| 2.33 | 0.071, 0.068 | 0.115 | 49.3 |
| 2.28 | 0.135, 0.129 | 0.103 | 45.2 |
| 2.26 | 0.307, 0.298 | 0.094 | 41.6 |
| 2.25 | 0.543, 0.537 | 0.082 | 36.4 |
| 1.28 | 0.061, 0.057 | 0.0619 | 48.4 |
| 1.24 | 0.119, 0.113 | 0.0574 | 46.3 |
| 1.24 | 0.290, 0.270 | 0.0506 | 41.1 |
| 1.23 | 0.560, 0.553 | 0.0451 | 36.6 |
| 0.75 | 0.061, 0.057 | 0.0345 | 46.0 |
| 0.73 | 0.120, 0.114 | 0.0309 | 42.3 |
| 0.72 | 0.288, 0.278 | 0.0290 | 40.3 |
| 0.72 | 0.579, 0.571 | 0.0254 | 35.3 |

^a Initial concentration of acetone dimethyl ketal = 0.045 M.

^b Initial concentration, $[\text{H}_2\text{O}]_i$; final concentration, $[\text{H}_2\text{O}]_f$, taking into account the stoichiometric decrease. ^c The precision is estimated to be about $\pm 5\%$.

Table II. Bromination of the Equilibrated Acetone–Acetone Dimethyl Ketal System. Effect of Acid Concentration on the Experimental Rate Constant, k_{exp} ($25 \pm 0.1^\circ\text{C}$)^a

| $10^3[\text{HBr}]$, M | $[\text{H}_2\text{O}]$, ^b M | $10^6[\text{Br}_2]_0$, ^c M | $10^5 k_{\text{exp}}$, ^{d,e} s^{-1} |
|---------------------------|--|---|---|
| 50.0 | 0.037 | 15.2 | 59.5 |
| 25.0 | 0.041 | 7.3 | 28.0 |
| 10.0 | 0.032 | 2.4 | 11.3 |
| 5.0 | 0.037 | 2.3 | 5.8 |
| 2.0 | 0.037 | 2.3 | 2.35 |
| 1.0 | 0.037 | 1.1 | 1.18 |
| av 0.037 | | | |

^a $[\text{ketone}]_T = [\text{ketone}]_{\text{eq}} + [\text{ketal}]_{\text{eq}} = 1.3 \times 10^{-3}$ M. ^b Concentration just after the kinetic measurements, including water from ketal formation. In view of possible introduction of water to the methanol during sampling and the imprecision of the titration (Karl Fischer Method), the water content is considered to be constant. ^c Initial analytical bromine concentration, the sum of free bromine and Br_3^- . ^d Standard deviation about 2%. ^e Corrected for slow, spontaneous bromine uptake.

reaction was carried out in methanol containing small amounts of water with about 10^{-3} M hydrobromic acid as the catalyst. At the water concentrations used the reaction was always equilibrated; from the kinetic measurements the sum of the rate constants of ketal formation (k_F) and ketal hydrolysis (k_H) was obtained (Table I). The sum $k_H + k_F$ is proportional to H^+ concentration and is dependent on water concentration.

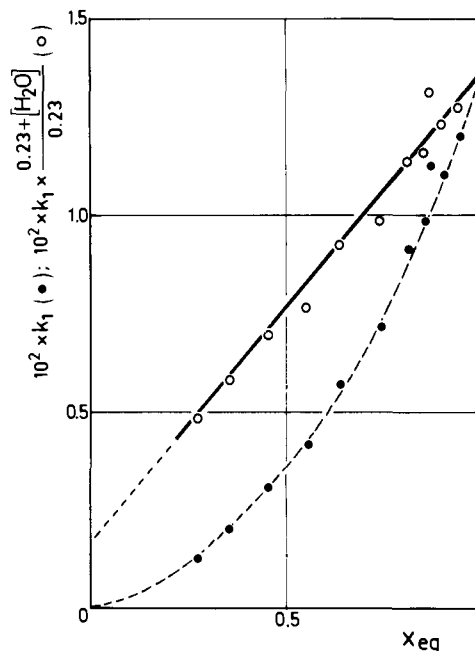
2. Bromination of the Equilibrated Ketone–Ketal System.

Rate Law. We have measured the rate of acid-catalyzed bromination of acetone in methanol with a large excess of ketone and very low bromine concentrations (from 10^{-6} M to 1.5×10^{-5} M) using the couloamperometric method.^{7,8} For the halogen concentrations used and for HBr concentrations between 10^{-3} and 5×10^{-2} M, the rate of bromine consumption is linear, corresponding to eq 3. From Table II, k_{exp} is proportional to acid concentration

$$k_{\text{exp}} = k_1[\text{H}^+] \quad (6)$$

with $k_1 = (1.16 \pm 0.02) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ for $[\text{H}_2\text{O}] = 0.037$ M as given by eq 4.

A comparison with the results previously obtained for acetone bromination in aqueous media shows that the reaction is

**Figure 1.** Effect of water concentration on the catalytic constant (k_1) for the bromination of acetone and acetone dimethyl ketal at equilibrium. $[\text{HBr}] = 10^{-2}$ M; 25°C .**Table III.** Bromination of the Equilibrated Acetone–Acetone Dimethyl Ketal System. Effect of Water Concentration on the Catalytic Rate Constant, k_1 ($25 \pm 0.1^\circ\text{C}$)

| $[\text{H}_2\text{O}]$, ^a M | x_{eq} ^b | $10^2 k_1$, ^c $\text{M}^{-1} \text{ s}^{-1}$ | % path A ^d |
|--|------------------------------|---|-----------------------|
| 0.015 | 0.94 | 1.20 | 0.9 |
| 0.027 | 0.90 | 1.105 | 1.6 |
| 0.037 | 0.87 | 1.13 | 2.1 |
| 0.042 | 0.85 | 0.99 | 2.4 |
| 0.058 | 0.81 | 0.91 | 3.2 |
| 0.085 | 0.74 | 0.720 | 4.8 |
| 0.139 | 0.63 | 0.575 | 7.6 |
| 0.195 | 0.55 | 0.415 | 10.4 |
| 0.291 | 0.45 | 0.307 | 14.8 |
| 0.435 | 0.35 | 0.201 | 20.7 |
| 0.628 | 0.27 | 0.129 | 27.8 |

^a Water concentration measured just after the kinetic measurements. ^b $[\text{ketal}]/([\text{ketone}] + [\text{ketal}])$. ^c $[\text{HBr}] = 10^{-2}$; $[\text{ketone}]_T = 0.0036$; $[\text{Br}_2]_0 \sim 2 \times 10^{-6}$ M. ^d See below.

much faster in methanol; the catalytic enolization rate constant in water ($(k_1)_w = 2.8 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$), analogous to k_1 , is a factor of about 400 less^{8,9} than k_1 for $[\text{H}_2\text{O}] = 0.037$ M.

Effect of Water Concentration. The results reported in Table III, concerning the effect of increasing the water concentration, show that the decrease of k_1 is much faster than that of the molar fraction of ketal (x_{eq}) (Figure 1).¹⁰ It is necessary, therefore, to take into account the influence of water on the elementary constants: k_{En} , k_{Et} , k_{-b}/k_b , K_1 , and K_2 .

Water does not intervene in the equilibrium between the conjugate acid of the ketal and the alkoxy-carbenium ion (II); the equilibrium constant k_{-b}/k_b is probably not affected by small amounts of water. On the other hand, the rate constants k_{Et} and k_{En} , corresponding to the elimination of proton by a base, water, or methanol, could be affected by increasing water concentration. However, a study of enol ether methanolysis, the reverse of ether formation, shows that only CH_3OH_2^+ intervenes;¹¹ for elimination in methanol containing small amounts of water, CH_3OH is much more important than H_2O

by the principle of microscopic reversibility. In other words, the difference between the basicities of water and methanol is not sufficient to counterbalance the large differences between the concentrations of these species. It seems probable, therefore, that the addition of small amounts of water does not cause significant variations in k_{Et} and k_{En} .

In contrast to the other elementary constants, the acidity constants K_1 of I and K_2 of II, must depend markedly on the water concentration. Acidity constants in methanol are known to be modified by small amounts of water.¹² An increase of water concentration causes changes in the distribution of the proton between water and methanol; CH_3OH_2^+ ions are progressively replaced by the less acidic ions H_3O^+ . The acidity constant K_a for an acid BH^+ can be calculated from

$$K_a = ((K_r + [\text{H}_2\text{O}])/K_r) (K_a)_m \quad (7)$$

where $(K_a)_m$ is the acidity constant in pure methanol^{12b,13} and $K_r (=0.23)$ is the distribution constant ($[\text{CH}_3\text{OH}_2^+][\text{H}_2\text{O}]/[\text{H}_3\text{O}^+]$) of the proton between methanol and water.¹²

From eq 3 and 7, eq 8 is deduced by taking into account the variations of K_1 and K_2

$$k_1((K_r + [\text{H}_2\text{O}])/K_r) = (k_A)_m(1 - x_{eq}) + (k_B)_m x_{eq} \quad (8)$$

where

$$(k_A)_m = \frac{k_{En}}{(K_1)_m} \quad \text{and} \quad (k_B)_m = \frac{k_{Et}k_{-b}}{(K_2)_m k_b [\text{CH}_3\text{OH}]}$$

If only path B is operative, eq 8 reduces to the second term; the plot of $k_1 \times (K_r + [\text{H}_2\text{O}])/K_r$ vs. x_{eq} would be a straight line with a zero intercept. Figure 1 shows that the straight line obtained has a nonzero intercept and therefore corresponds to the full equation (eq 8). Consequently, under these conditions, path B is predominant, but probably not exclusive.

Primary H/D Isotope Effect. In order to compare proton elimination from ions I and II in water and methanol, the bromination of acetone- d_6 was studied and the primary isotope effect, $(k_1)_H/(k_1)_D$, determined. A large modification of the isotope effect in methanol compared to water could reveal a significant change in the mechanism and explain the differences in behavior. In Table IV are listed the rate constants $(k_1)_D$ for different water concentrations; $(k_1)_D$ is compared with $(k_1)_H$ obtained by interpolation to the same water concentration. The isotope effect ($= 6.9 \pm 0.4$) is independent of water concentration and is of the same magnitude as that observed for acetone enolization in water ($=6.7$).⁹

3. Bromination of the Dynamic Ketone-Ketal System. The kinetic study of ketone-ketal equilibration indicates that, for 10^{-1} M acid, the half-equilibration time is about 0.1 s. When acetone is added rapidly to a well-stirred solution of bromine in methanol, the reaction must be almost instantaneous and the decrease in bromine concentration must be identical with that previously observed for bromination of the equilibrated ketone-ketal system. In fact, this is what is observed. The linear decrease of bromine concentration is in agreement with fast equilibration and shows that the mixing time is less than 0.2 s.

For lower acid concentrations (about 10^{-3} M), corresponding to slow ketal formation, the bromine concentration does not decrease linearly, instead it curves, as can be seen in Figure 2. This behavior is characteristic of a progressive increase in the bromination rate with ketal formation. Then, when the ketone-ketal system comes to equilibrium, the bromine concentration decreases linearly again. Such curves indicate that bromination of ketal is much faster than ketone.

If it is assumed that the two paths are followed as the preceding results seem to show, eq 2 must be considered to represent the rate equation, and then [I] and [II] have to be expressed as time-dependent functions.

Table IV. Bromination of the Equilibrated Acetone- d_6 -Acetone- d_6 Dimethyl Ketal System. CD/CH Isotope Effect (25 ± 0.1 °C)

| $[\text{H}_2\text{O}],^a$ M | $10^2(k_1)_D,^{b,c}$ $\text{M}^{-1} \text{s}^{-1}$ | $(k_1)_H/(k_1)_D^d$ |
|--------------------------------|---|---|
| 0.029 | 0.148 | 7.3 |
| 0.042 | 0.143 | 6.9 |
| 0.059 | 0.139 | 6.4 |
| 0.072 | 0.126 | 6.7 |
| 0.085 | 0.114 | 6.6 |
| 0.112 | 0.102 | 6.4 |
| 0.166 | 0.0720 | 6.9 |
| 0.223 | 0.0615 | 6.4 |
| 0.319 | 0.0430 | 6.6 |
| 0.459 | 0.0265 | 7.3 |
| | | av. 6.7 ± 0.4 (6.9) ^e |

^a See footnote b, Table III. ^b $[\text{HBr}] = 10^{-2}$; $[\text{CD}_3\text{COCD}_3]_T = 10^{-2}$ M, except $[\text{CD}_3\text{COCD}_3]_T = 3 \times 10^{-3}$ M for $[\text{H}_2\text{O}] = 0.029$ M; $[\text{Br}_2]_0 = \text{about } 10^{-6}$ M. ^c Deuterium content $99.5 \pm 0.1\%$. ^d The corresponding rate constants $(k_1)_H$ are calculated by interpolation from the results of Table III. ^e Extrapolated value from 99.5 to 100% deuterium content.

On the one hand, since the ketone protonation equilibrium is fast, [I] will be proportional to ketone concentration ($a(1 - x_t)$) (a is the initial concentration of acetone) at any moment of the reaction.

On the other hand, the [II]-time equation is not so simple if no assumption is made concerning the rate-determining step of ketone-ketal interconversion. Then, the concentration of the alkoxy-carbenium ion can be expressed by

$$[\text{II}] = \frac{[k_{-b}ax_t/K_2 + k_a[\text{CH}_3\text{OH}]a(1 - x_t)/K_1][\text{H}^+]}{k_b[\text{CH}_3\text{OH}] + k_{-a}[\text{H}_2\text{O}]} \quad (9)$$

This equation¹⁴ means that the rate law for bromine consumption might depend on the rate-determining step of ketone-ketal interconversion, which in turn depends on the relative values of $k_b[\text{CH}_3\text{OH}]$ and $k_{-a}[\text{H}_2\text{O}]$.

From a study of the rates of isotopic exchange of acetone dimethyl ketal, Cordès et al.^{5a,b,15} have shown that II reacts almost equally rapidly with H_2O and CH_3OH . Because of the large difference in water and methanol concentrations it can be assumed that: $k_b[\text{CH}_3\text{OH}] \gg k_{-a}[\text{H}_2\text{O}]$; the rate-determining step of ketal hydrolysis is then the addition of water to II. Therefore, II is always rapidly equilibrated with ketal; hence, the rate of formation of enol ether is proportional to ketal concentration (ax_t) at any moment of the reaction.

The ketal molar fraction is expressed by

$$x_t = [1 - e^{-(k_H+k_F)t}]x_{eq} \quad (10)$$

where k_F and k_H are the rate constants of ketal formation and hydrolysis, respectively, calculated from the equilibration measurements for the appropriate acid and water concentrations. Therefore, the bromination rate is given by¹⁶

$$R_t = -d[\text{Br}_2]/dt = k_A[\text{H}^+]a + (k_B - k_A)[\text{H}^+]ax_{eq}[1 - e^{-(k_H+k_F)t}] \quad (11)$$

At equilibrium

$$R_{eq} = k_A[\text{H}^+]a + (k_B - k_A)[\text{H}^+]ax_{eq} \quad (12)$$

Combination of eq 11 and 12 leads to eq 13, integration of which gives eq 14.

$$R_t = R_{eq} - (k_B - k_A)[\text{H}^+]ax_{eq}e^{-(k_H+k_F)t} \quad (13)$$

$$[\text{Br}_2]_0 - [\text{Br}_2] = R_{eq}t - (k_B - k_A)(ax_{eq}[\text{H}^+]/(k_H + k_F))[1 - e^{-(k_H+k_F)t}] \quad (14)$$

Table V. Bromination of the Dynamic Acetone–Acetone Dimethyl Ketal System. Partial Bromination Rate Constants via the Enol (k_A) and the Corresponding Enol Ether (k_B) (25 ± 0.1 °C)

| $[\text{H}_2\text{O}]^a$, M | $10^3[\text{HBr}]$, M | $10^3[\text{acetone}]_T^b$, M | $10^7 R_{\text{eq}}$, M s^{-1} | $10^2 k_1^c$, $\text{M}^{-1} \text{s}^{-1}$ | $k_H + k_F^d$, s^{-1} | Slope, ^e M | $10^2 k_A^f$, $\text{M}^{-1} \text{s}^{-1}$ | $10^2 k_B^g$, $\text{M}^{-1} \text{s}^{-1}$ | $10^2 (k_A)_m^h$, $\text{M}^{-1} \text{s}^{-1}$ | $10^2 (k_B)_m^h$, $\text{M}^{-1} \text{s}^{-1}$ |
|---------------------------------|---------------------------|-----------------------------------|---|---|------------------------------------|--------------------------|---|---|---|---|
| 0.041, 0.044 | 2.00 | 3.83 | 0.753 | 0.98 | 0.099 | 6.51 ± 0.12 | 0.14 | 1.13 | 0.17 | 1.35 |
| 0.046, 0.050 | 1.00 | 3.83 | 0.365 | 0.95 | 0.049 | 6.08 ± 0.13 | 0.17 | 1.11 | 0.21 | 1.36 |
| 0.050, 0.053 | 1.00 | 3.91 | 0.393 | 1.00 | 0.049 | 6.58 ± 0.16 | 0.18 | 1.19 | 0.22 | 1.46 |
| 0.055, 0.059 | 2.00 | 4.09 | 0.724 | 0.88 | 0.098 | 6.29 ± 0.05 | 0.13 | 1.07 | 0.17 | 1.34 |
| 0.056, 0.059 | 2.00 | 4.13 | 0.720 | 0.87 | 0.098 | 6.15 ± 0.07 | 0.14 | 1.05 | 0.18 | 1.32 |
| 0.084, 0.087 | 2.00 | 4.00 | 0.598 | 0.75 | 0.096 | 4.98 ± 0.04 | 0.15 | 0.97 | 0.21 | 1.33 |
| 0.108, 0.111 | 2.00 | 4.13 | 0.516 | 0.625 | 0.094 | 4.39 ± 0.03 | 0.12 | 0.85 | 0.19 | 1.27 |
| 0.165, 0.167 | 2.00 | 4.04 | 0.384 | 0.475 | 0.091 | 3.29 ± 0.04 | 0.11 | 0.73 | 0.18 | 1.27 |
| 0.221, 0.223 | 2.00 | 4.11 | 0.300 | 0.365 | 0.087 | 2.52 ± 0.03 | 0.10 | 0.62 | 0.19 | 1.22 |
| | | | | | | | | | av 0.19 ± 0.02 | av 1.33 ± 0.07 |

^a Initial concentration, final concentration (water is formed during the ketal formation). ^b $[\text{acetone}]_T = [\text{acetone}] + [\text{ketal}]$. ^c Calculated from R_{eq} (see eq 3 and 6). ^d Extrapolated values from ketone–ketal equilibration results. ^e Slope = $(k_B - k_A)ax_{\text{eq}}[\text{H}^+]/(k_H + k_F)$ (see eq 14). ^f Calculated from eq 15. ^g Calculated from slope and k_A values. ^h $(k_A)_m = (0.23 + [\text{H}_2\text{O}])k_A/0.23$ and $(k_B)_m = (0.23 + [\text{H}_2\text{O}])k_B/0.23$ are the constants for the paths A and B, respectively, corrected from the effect of water concentration on K_1 and K_2 , the acidity constants of I and II. They correspond to the extrapolated rate constants of path A and B in pure methanol. In these equations $[\text{H}_2\text{O}]$ is taken to be the final concentration.

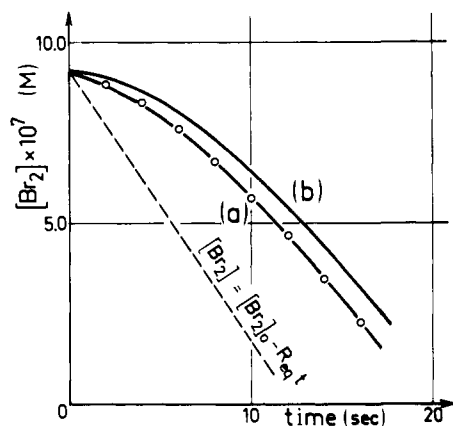


Figure 2. Bromination of the dynamic acetone–acetone dimethyl ketal system: O, experimental points. The dashed line corresponds to the linear decrease of bromine concentration after ketone–ketal equilibration. The solid lines are calculated curves using eq 14 (curve a) and eq 16 (curve b), the latter corresponding to the assumption that only the enol ether path applies. $[\text{HBr}] = 2 \times 10^3$; $[\text{H}_2\text{O}] = 0.041$; $[\text{acetone}]_T = 4.09 \times 10^{-3}$ M; 25 °C.

Returning to the experimental data, we observe a straight line (Figure 3) when $([\text{Br}_2]_0 - [\text{Br}_2] - R_{\text{eq}}t)$ is plotted against the term in square brackets. The slope is a function of the difference between the partial rate constants k_A and k_B . The constant k_A , for enol formation, is deduced from this slope and R_{eq} by means of

$$k_A = \frac{R_{\text{eq}}}{a[\text{H}^+]} - \frac{\text{slope}}{a[\text{H}^+]}(k_H + k_F) \quad (15)$$

which is deduced from eq 12 and slope = $(k_B - k_A)ax_{\text{eq}}[\text{H}^+]/(k_H + k_F)$.

The results for the experimental curve plotted in Figure 2 are listed in the first line of Table V.

Conversely, using these k_A and k_B values, the theoretical variations of $[\text{Br}_2]$ have been calculated (curve a, Figure 2); they fit remarkably well the experimental data. In contrast, if it is assumed that the enol route does not occur ($k_A \ll k_B$), the $[\text{Br}_2]$ variations calculated by eq 16 (deduced from eq 14) (curve b, Figure 2) depart distinctly from what is observed.

$$[\text{Br}_2]_0 - [\text{Br}_2] = R_{\text{eq}}t - (R_{\text{eq}}/(k_H + k_F)) [1 - e^{-(k_H + k_F)t}] \quad (16)$$

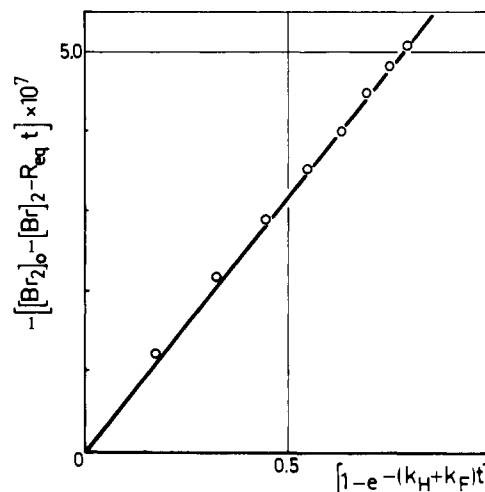


Figure 3. Bromination of the dynamic acetone–acetone dimethyl ketal system. Verification of the kinetic equation (eq 17). $k_H + k_F = 0.099 \text{ s}^{-1}$ (extrapolated from the experimental $k_H + k_F$ values given in Table I); $[\text{H}_2\text{O}] = 0.041$; $[\text{HBr}] = 2 \times 10^{-3}$ M.

We have performed similar kinetic measurements for several other water and acid concentrations. The results are listed in Table V. It must be pointed out that the ratio k_A/k_B is constant ($=0.14 \pm 0.01$) within experimental error and independent of water concentration.

Discussion

1. Influence of Water Concentration upon the Enol and Enol Ether Rates. The above results show that the partial rate constants, k_A and k_B , vary in parallel with the water concentration. Hence, the relative importance of the A and B paths can be calculated for all water concentrations. In Figure 4 the path A and the free ketone percentages are plotted against water concentration. In Table III are listed the percent of A with water content, corresponding to the water concentrations chosen for the study of the effect of water concentration on k_1 . In Figure 5, values of $(k_1 \times (\% \text{ path B}/100) \times ((K_r + [\text{H}_2\text{O}])/K_r))$ are plotted against the molar fraction of ketal (x_{eq}). The straight line observed, with a zero intercept, is considered to validate

$$k_1 \frac{\% \text{ path B}}{100} = (k_B)_m x_{\text{eq}} \frac{K_r}{K_r + [\text{H}_2\text{O}]} \quad (17)$$

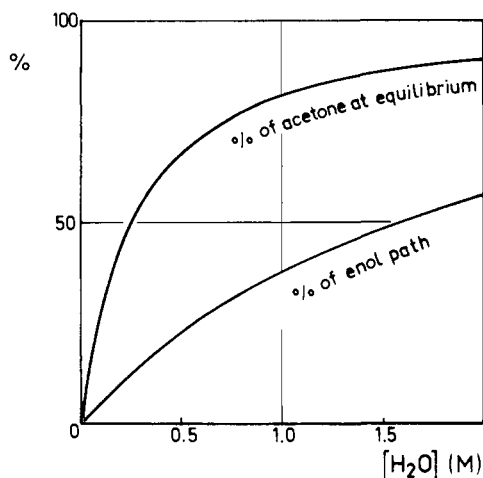
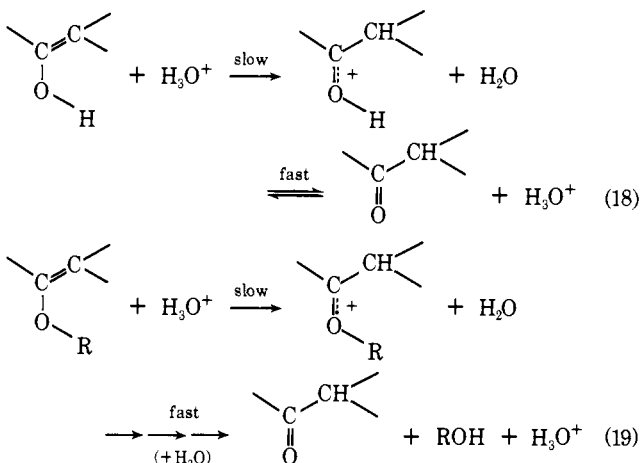


Figure 4. Equilibrium percentage of free acetone¹⁰ and percentage of enol path in terms of the water concentration, calculated from the following equation derived from eq 4: % path A = $100 k_A(1 - x_{eq}) / (k_A(1 - x_{eq}) + k_B x_{eq})$.

which comes directly from eq 8. The slope corresponds to the bromination rate constant in methanol: $(k_B)_m = (1.35 \pm 0.02) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$.

2. Explanation of the Predominance of the Enol Ether Path (B). It is evident from this study that it is mainly path B which is followed by the bromination of equilibrated ketone-ketal systems in methanol containing small amounts of water, e.g., 1% for A and 99% for B when $[\text{H}_2\text{O}] = 0.02 \text{ M}$. However, the predominance of this path is at first sight surprising in view of the quite similar stabilities and reactivities of the ions I and II. In particular, from the study of the reverse reactions, enol ketonization and enol ether hydrolysis corresponding to slow proton addition on enol (eq 18) or enol ether (eq 19), it can be



seen that the proton elimination rate constants, k_{Et} and k_{En} , must be of the same order of magnitude.

In this study, it has been shown that these two reactions are closely analogous and have comparable rate constants in water.^{8b,17,18} On the basis of similar isotope effects and Brønsted α 's (about 0.5) for ketonization and ether hydrolysis, we previously concluded that the extent of H^+ transfer in the transition state was similar in these reactions.⁹ On another hand, the identical isotope effects for k_1 in water⁹ and methanol (this work) can be explained by approximately the same transition-state symmetry in water and methanol. It follows that the approximate equation

$$\frac{k_{Et}}{k_{En}} = \left[\frac{k_{Et}/k_{-Et}}{k_{En}/k_{-En}} \right]^{1-\alpha} \quad (20)$$

in which k_{En} and k_{Et} are related to I-enol and II-ether equi-

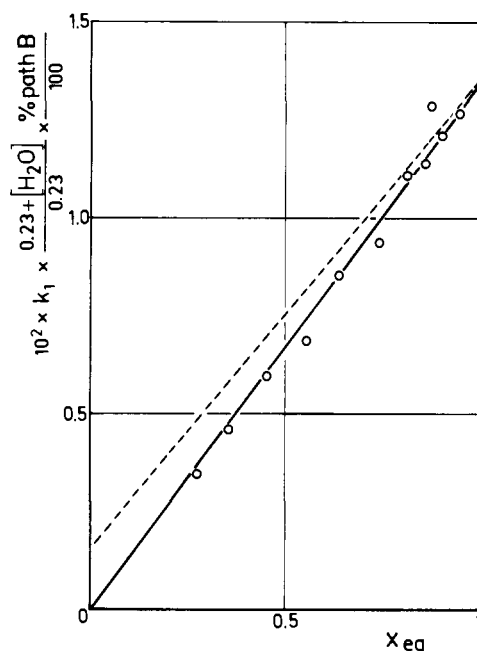


Figure 5. Enol ether formation rate constants vs. molar fraction of ketal at equilibrium. $(k_1 \times \% \text{ path B})$ is corrected for the variations in acidity with water concentration (solid line). The dashed line corresponds to k_1 variations (see Figure 1). $[\text{HBr}] = 10^{-2} \text{ M}$; 25°C .

librium constants, can be deduced (k_{-Et} and k_{-En} are the ether methanolysis, analogous to hydrolysis, and enol ketonization rate constants, respectively; α is the Brønsted exponent, which is assumed to be identical for both of these reactions).

In the same way, for the reverse reaction,

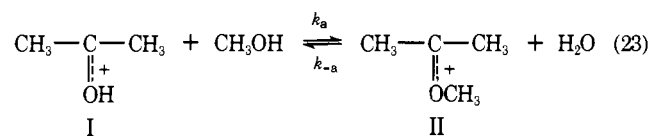
$$\frac{k_{-Et}}{k_{-En}} = \left[\frac{k_{En}/k_{-En}}{k_{Et}/k_{-Et}} \right]^\alpha \quad (21)$$

If α is taken equal to 0.5, corresponding to the theoretical maximum value observed for the kinetic isotope effect and corresponding to a symmetrical transition state (half-transferred proton),⁹ as is often assumed,

$$k_{Et}/k_{En} \approx k_{-En}/k_{-Et} \quad (22)$$

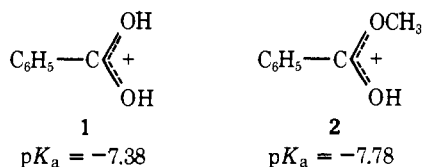
can be deduced. Taking into account the small differences observed between enol ketonization and ether hydrolysis rate constants,^{8b,17,18} k_{Et} and k_{En} must be about the same.

The essential reason for the predominance of path B must instead lie in differences in the relative concentrations of ions I and II at equilibrium. The large excess of CH_3OH , relative to H_2O , must cause a marked displacement of the $\text{I} \rightleftharpoons \text{II}$ equilibrium towards ion II (eq 23).



If it is assumed that $k_{Et} = k_{En}$, the equilibrium constant k_a/k_{-a} between the ions I and II can be estimated from the ratio of the partial rates ($k_{Et}[\text{II}]/k_{En}[\text{I}]$) of the two paths. Thus, when $[\text{H}_2\text{O}] = 0.02 \text{ M}$, for example, $k_{Et}[\text{II}]/k_{En}[\text{I}]$ is equal to 85. Otherwise, $[\text{II}]/[\text{I}]$ can be calculated from the equilibrium constant k_a/k_{-a} and the ratio of water and methanol concentrations: $[\text{II}]/[\text{I}] = (k_a/k_{-a}) \times ([\text{CH}_3\text{OH}]/[\text{H}_2\text{O}]) = 1250 \times k_a/k_{-a}$. Then, it can be deduced that $k_a/k_{-a} = 0.07$, corresponding to $\Delta G^\circ_{298} = 1.5 \text{ kcal/mol}$. This value is in agreement with that predicted by considering (a) the analogy between this equilibrium and the alcohol-ether equilibrium, for which ΔG°_{298} is reckoned to be about zero,¹⁹ and (b) the

positive charge can be better stabilized by an OH group than by OCH₃, as is shown by the acidity constants of ions **1** and **2**, derived from benzoic acid and its methyl ether.²⁰



It is interesting to note that the ratio of the two paths does not depend on the ketone-ketal equilibrium constant (K). Path B can predominate even when the ketal is not at all stable, i.e., when its equilibrium concentration is very small. In other words, ketal formation is a "dead end" in the mechanism of ketone bromination.

3. Enolization and Enol Ether Formation in Methanol Compared with Enolization in Water. Although the predominance of path B can be explained by considering the ratio $[\text{II}]/[\text{I}]$, the large ratio (about 500) of $(k_1)_m$ and $(k_1)_w$, the rate constants of enol ether formation and enolization, respectively, in methanol and water, cannot be explained in the same way. Furthermore, the constant $(k_A)_m$, which would correspond to enolization of acetone in pure methanol, is about $60(k_1)_w$.

In order to explain this last large effect we must examine the possible effects on k_{En} and K_1 . A first indication that the effect on K_1 is small is obtained by comparing the acidity function in these two solvents using indicators analogous to the hydroxycarbenium ion. Thus, for 4-nitroaniline, only a small difference is observed between $(H_o)_m$ and $(H_o)_w$ (for example, $(H_o)_w - (H_o)_m = 0.55$ for $[\text{HCl}] = 0.2 \text{ M}$),²¹ resulting from a small difference in acidity constants.²² Comparison of the rate constants for ethoxycarbenium ion formation from acetaldehyde diethyl acetal in water and ethanol confirms this conclusion. The rate constant for formation of this ion in water ($0.317 \text{ M}^{-1} \text{ s}^{-1}$)²³ has been obtained from the rate of acetal hydrolysis, the rate-determining step of which is ion formation from the conjugate acid of acetal. Using acetals labeled in the ethoxy group with carbon-14, Salomaa et al.⁴ have studied transacetalization, which corresponds to ion formation in ethanol; the rate constant obtained ($0.528 \text{ M}^{-1} \text{ s}^{-1}$) is almost equal to that observed for hydrolysis. This comparison must indicate that (a) the acidity constant of the conjugate acid of acetal is about the same in alcohol and water, and (b) there is only a small difference in the thermodynamic stabilities of the alkoxy-carbenium ions in alcohols and water. A similar conclusion must be valid for the analogous hydroxycarbenium ions.

The large difference between $(k_1)_m$ and $(k_1)_w$ must then be attributed essentially to an increase in the elimination rate constants, even though the reason of this effect is not obvious. It could be due to the greater stability of the enol in methanol. Unfortunately, the ketone-enol equilibrium constant cannot be measured because of the predominance of the ketal-ether system. In a subsequent publication, we shall examine the ketone-ketal-enol ether system at equilibrium to compare enol ether stability in methanol with that of the enol in water.

Experimental Section

1. Reagents. Methanol was obtained from technical methanol (Prolabo-France) by three successive distillations. Water is eliminated by distilling with magnesium, oxidizable impurities by distilling with bromine, and neutral methanol is obtained by distillation over sodium carbonate. The water concentration was measured after the kinetic measurements (Karl Fischer method). Differences between the water concentration after distillation and the water concentration after measurements were generally observed.

Methanolic solutions of hydrobromic acid were prepared by bubbling of gaseous HBr (Baker Chemical) and subsequent dilution. The acid concentration was determined just before the kinetic measurements. Acetone was R.P. (Prolabo-France). 2,2-Dimethoxypropane was 99% minimum (Aldrich).

The deuterium content of acetone- d_6 (Spin et Technique, Paris; 99.5% minimum) was checked by mass spectroscopy on a Thompson 206 C apparatus.

2. Kinetics Measurements. Ketone-Ketal Interconversion. The rate at which ketone appeared (ketal hydrolysis) was followed by monitoring the carbonyl absorption (at 280 nm) with a Cary 16 spectrophotometer. The contents of the thermostatted 1-cm cell was stirred by means of a small Teflon-coated magnet rotated by a motor located beneath the cell holder.

2,2-Dimethoxypropane was added to the stirred methanolic HBr solution. After equilibration, a weighed amount of pure water or a water-methanol solution was added to the solution for displacing the equilibrium. The rate of formation of acetone was followed until a new equilibrium was reached. From the curve of the increase of the absorbance, $k_H + k_F$, the sum of the rate constants for ketal hydrolysis and ketal formation was calculated by plotting $\ln(A_\infty - A)$ against time (A and A_∞ are the measured absorptions at time t and at infinite time, respectively); the slope of the straight line obtained corresponds to $k_H + k_F$. Another displacement of equilibrium is obtained by a further addition of water, and so on.

Bromination. Kinetic measurements were performed by the previously described coulometric method, which depends on the measurement of a diffusion current between two platinum electrodes.⁷ The anode was fixed and the cathode was rotated at 2500 rpm. The solution was stirred by the rotating electrode, which was paddle shaped. The mixing times were lower than 0.2 s and have been determined by addition of 2-ethoxypropene to aqueous bromine solution; the reaction was very fast and almost instantaneous. Bromine was produced by bromide ion electrolysis (constant current and measure of the electrolysis time).

For kinetic measurements on an equilibrated ketone-ketal system, 20 ml of an alcoholic solution of HBr was introduced into a thermostatted cell (Methrom 50-ml cell); argon was passed over the solution and then interrupted to avoid evaporation of halogen during the reaction. Bromine at about 10^{-6} M concentration was obtained by electrolysis during a few seconds. A slow, spontaneous decrease of bromine concentration, resulting probably from reactions with solvent impurities, was observed. After about 10 min, the bromine consumption was slower, constant, and concentration independent. By successive electrolyses (the electrolysis time was measured automatically by a numerical electronic chronometer) successive jumps in bromine concentration were obtained. For each step, the measure of the current (i_{amp}) provides a determination of the sensibility coefficient (α) of the electrode (this coefficient is about $10^{-7} \text{ M}/\mu\text{A}$). After the initial concentration has been adjusted, 50–100 μl of a methanolic solution of acetone (weighed) was added using a micro-syringe. When the bromine concentration was zero, it was necessary to wait some minutes for keto-ketal equilibration to occur. By another electrolysis, the bromine concentration was raised to a chosen value and the rate of bromine consumption was recorded. The rate constant k_{exp} was calculated (see the following equation) from the slope of the straight line obtained by taking into account the electrode sensibility coefficient and also the spontaneous decrease of bromine concentration ($(\Delta i_{amp}/\Delta t)_c$).

$$k_{exp} = \left[\frac{\Delta i_{amp}}{\Delta t} - \left(\frac{\Delta i_{amp}}{\Delta t} \right)_c \right] \frac{\alpha}{[\text{ketone}]^*}$$

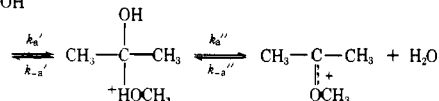
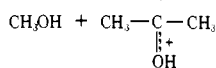
For measurements on a "dynamic" keto-ketal system, the method is the same. However, instead of adding diluted ketone, 5 μl of pure ketone (weighed) was injected rapidly. The curve of i_{amp} decrease with time was recorded immediately. After the equilibration of the ketone-ketal system, the bromine concentration was raised again by another electrolysis so that R_{eq} could be measured.

For all the measurements, the fraction of the ketone which reacted was very small. However, it was sometimes necessary to correct the ketone concentration. It is assumed that the α -bromo ketone is much less reactive than acetone, as is observed in water.²⁴

Acknowledgment. The authors are grateful to A. Adenier for technical assistance.

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- (6) Although step a is composite, with intermediate formation of the conjugated acid of hemiketal, it is not necessary for this purpose to distinguish the two



elementary steps a' and a'' . The rate constants k_a and k_{-a} can be expressed in the following form:

$$k_a = k_{a'}k_{a''}/(k_{-a'} + k_{a''})$$

$$k_{-a} = k_{-a'}k_{-a''}/(k_{-a'} + k_{a''})$$

Since the equilibrium hemiketal concentration is very low ($<1\%$),¹⁰ it is not necessary to take into account hemiketal formation.

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- (10) (a) The molar fraction of acetal (x_{eq}) is calculated from the equilibrium constant

$$K = \frac{[\text{ketal}]_{\text{eq}}[\text{H}_2\text{O}]}{[\text{ketone}]_{\text{eq}}[\text{CH}_3\text{OH}]^2} = \frac{x_{\text{eq}}[\text{H}_2\text{O}]}{(1 - x_{\text{eq}})[\text{CH}_3\text{OH}]^2}$$

- (b) $K = 4 \times 10^{-4} \text{ M}^{-1}$ (J. M. Bell, D. J. Kubler, P. Sartwell, and R. G. Zepp, *J. Org. Chem.*, **30**, 4284 (1965)).
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- (13) The apparent acidity constant in methanol containing small amounts of water is defined by the following equation

$$K_a = [\text{SH}^+][\text{B}]/[\text{BH}^+]$$

where $[\text{SH}^+] = [\text{CH}_3\text{OH}_2^+] + [\text{H}_3\text{O}^+]$. On the other hand, in pure methanol:

$$(K_a)_m = [\text{CH}_3\text{OH}_2^+][\text{B}]/[\text{BH}^+]$$

Equation 7 is directly deduced from these two equations, taking into account the $[\text{CH}_3\text{OH}_2^+]$ expression:^{12b}

$$[\text{CH}_3\text{OH}_2^+] = [\text{SH}^+][\text{H}_2\text{O}]/([\text{H}_2\text{O}] + 0.23)$$

- (14) Equation 9 assumes that proton elimination (rate constant, k_{Et}) is the rate-determining step of enol ether formation. This has been demonstrated for the following reaction:⁴



For acetone, the sum of the rate constants of ketone-ketal interconversion ($k_{\text{I}} + k_{\text{F}}$) for $[\text{HBr}] = 10^{-3} \text{ M}$ is about $0.05 \text{ M}^{-1} \text{ s}^{-1}$ (Table I), that is, a factor of 5×10^3 higher than k_{app} for the same acidity (Table II). Thus, $k_{\text{Et}}/k_{-a}[\text{H}_2\text{O}]$ is lower than 10^{-3} ; k_{Et} (II) is negligible compared to the other rates of formation and destruction of ion II.

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- (16) Given eq 10, eq 15 is deduced from the following equation

$$-d[\text{Br}_2]/dt = k_A[\text{H}^+]a(1 - x_1) + k_B[\text{H}^+]ax_1$$

where ax_1 and $a(1 - x_1)$ are the ketal and the ketone concentrations, respectively.

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Mechanism of Lithium Aluminum Hydride Reduction of Ketones. Kinetics of Reduction of Mesityl Phenyl Ketone¹

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Abstract: Pseudo-first-order kinetic studies on the reaction of LiAlH_4 , NaAlH_4 , and LiAlD_4 with mesityl phenyl ketone have been carried out in tetrahydrofuran at 25°C . The reactions were carried out in excess hydride and found to be first order in hydride and first order in ketone. LiAlH_4 is about ten times more reactive than NaAlH_4 which indicates the importance of the cation in the mechanism of the reaction. A deuterium kinetic isotope study involving the reaction of LiAlH_4 and LiAlD_4 with mesityl phenyl ketone gave a value of $k_{\text{H}}/k_{\text{D}}$ of 1.27 which implicates the transfer of the hydride from aluminum to the carbonyl carbon in the rate-determining step of the reaction. Entropies of activation for reduction of mesityl phenyl ketone by LiAlH_4 and NaAlH_4 indicate that the transition state is considerably more ordered for reduction by LiAlH_4 (-26.2 vs. -5.4 eu) and that the transition state is of considerably lower energy (10.5 vs. 18.1 kcal). These data further suggest that the lithium cation is associated with the carbonyl oxygen during reduction.

Introduction

After studying the stereochemistry of metal hydride reduction of a number of cyclic and bicyclic ketones under varying conditions of cation and anion size, concentration, stoichiometry, solvent, and temperature,³ it is clear that more information is needed about the transition state of the reaction

to explain the stereochemical results. Since the nature of the reagent and the mechanism of the reaction are both essential to the establishment of the nature of the transition state, it is clear that some understanding of the composition of LiAlH_4 in ether solvent and the mechanism of LiAlH_4 reduction of a model ketone is important to an understanding of the stereochemistry of the reaction.