THE JOURNAL OF Organic Chemistry®

VOLUME 41, NUMBER 21

OCTOBER 15, 1976

Rates and Equilibria in Hydration and Bisulfite Addition by 1,3-Dimethoxyacetone[1]

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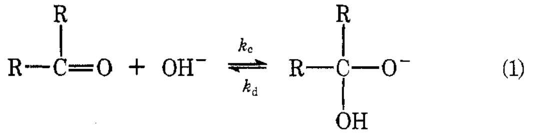
Received April 15, 1976

Equilibrium constants for the hydration of 1,3-dimethoxyacetone have been determined over the range 1.4–59.7 °C. The kinetics of hydration at 25 °C have been studied in cacodylic acid buffers around pH 6 and in triethylamine buffers around pH 11. The pK_a of the hydrate was found to be 13.17 at 25 °C. A study of equilibrium in bisulfite addition over the pH range 2.5–12.3 gave a pK_a of 9.89 for the hydroxylic hydrogen atom in $(MeOCH_2)_2C(OH)SO_3^-$ and an equilibrium constant of 880 M^{-1} for the formation of this anion from the ketone and bisulfite ion at 25 °C. The kinetics of the decomposition of the bisulfite addition compound at this temperature over the pH range 4.5–8.5 showed that the reaction involves largely rate-controlling decomposition of the dianion $(MeOCH_2)_2C(O^-)SO_3^-$, but leaves open the possibility of significant amounts of general catalysis of decomposition of the monoanion by the basic components of the buffers used. A method of determining the equilibrium constant for the hydration of the ketone was developed on the basis of the fact that bisulfite addition is much faster than hydration near pH 6. Stopped-flow measurements made when bisulfite addition was almost at equilibrium but very little hydration and dehydration had taken place gave equilibrium constants for hydration that confirmed the value obtained by injecting ketone into water and comparing initial and equilibrium absorbances. Rate constants for coodination of hydroxide ions and sulfite ions with the carbonyl carbon atom of 1,3-dimethoxyacetone were found to be smaller than analogous rate constants for reactions with aldehydes in cases where the reactions with the aldehydes had about the same equilibrium constants as the reactions with the ketone. This is attributed to steric hindrance being greater in the transition state than in the product of the reactions of these nucleophiles with aldehydes and ketones.

An earlier paper in this series dealt with correlations between rate constants and equilibrium constants for one-step Lewis acid–base reactions in which the electrophilic atom was carbon.[2] A plot of log k_c vs. log K_c for addition of hydroxide ions to acetone and seven aldehydes (eq 1) gave a reasonable approach to linearity. However, the compounds for which data were available were such that the effective size of the R's in eq 1 tended to decrease with increasing K. Therefore it seemed possible that the slope of the line was partly a result of systematic changes in steric effects. It was therefore of interest to obtain data on a ketone for which K_c is as large as it is for some of the aldehydes. Data on reactions involving nucleophilic reagents other than hydroxide ion were also of interest. For these reasons we have studied the kinetics of the hydration of and the addition of sodium bisulfite to 1,3-dimethoxyacetone. Use of 1,3-dimethoxyacetone as a model for the physiologically important compound 1,3-dihydroxyacetone also makes these studies of interest. The hydroxylic hydrogen atoms of 1,3-dihydroxyacetone so increase the number of ways that the compound can react that 1,3-dimethoxyacetone can provide some useful simplification of the possible reaction schemes.



$$R_2C{=}O + OH^- \underset{k_d}{\overset{k_c}{\rightleftharpoons}} R_2C(O^-)OH \qquad (1)$$

Results

Equilibrium in Hydration. The hydration reaction was first studied by a procedure[3,4] in which the ketone was dissolved in an aqueous solution and the absorbance near its uv absorption maximum monitored. In order to follow this rather rapid reaction over as wide a range of reaction as possible, the ketone was injected into an aqueous solution that was being stirred while in a spectrophotometer.[5] Points taken after about 5 s followed a first-order rate equation rather closely, but points taken earlier had too large an absorbance to fit the rate constant obtained from the later points. This deviation was attributed largely to the mixing process. Injection of acetone, which is almost negligibly hydrated in aqueous solution,[6] gave a comparable amount of excessive absorbance for about 5 s before the absorbance became essentially constant. The initial absorbance was obtained by extrapolation to zero time using the first-order rate equation and points taken after 5 s.[7] The part of the reaction thus neglected in these extrapolations ranged from the first 3.3% at 1.4 °C to the first 48% at 59.7 °C. The ratio A_∞/A_0 was taken to equal the fraction of ketone that is unhydrated at equilibrium.

$$\underset{C}{(MeOCH_2)_2CO} + H_2O \rightleftharpoons \underset{H}{(MeOCH_2)_2C(OH)_2} \qquad (2)$$

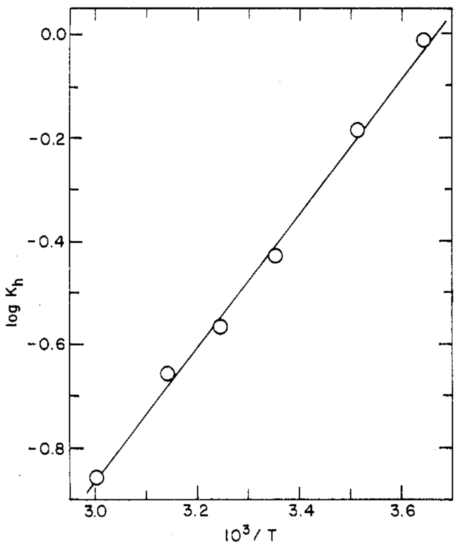


Figure 1. Plot of log K_h for the hydration of 1,3-dimethoxyacetone in aqueous solution vs. $1/T$.

Table I. Equilibrium Constants for Hydration of 1,3-Dimethoxyacetone in Aqueous Solution

Temp, °C	K_h	Standard deviation
1.4	0.975	0.013
11.5	0.652	0.010
25.0	0.373	0.003
35.0	0.271	0.004
45.1	0.219	0.002
59.7	0.139	0.006

Thus, using the symbols for the carbonyl and hydrate forms shown in eq 2, the dimensionless equilibrium constant for hydration may be expressed as shown in eq 3.

$$K_h = \frac{H}{C} = \frac{A_0}{A_\infty} - 1 \qquad (3)$$

Values of K_h obtained by injecting ketone into distilled water at various temperatures are listed in Table I and plotted logarithmically against $1/T$ in Figure 1. A least-squares calculation gave a ΔH value of -5.93 ± 0.1 kcal/mol and a ΔS value of -21.7 ± 0.3 eu, where the ± figures are standard deviations. The uncertainty in these values is probably significantly larger than the standard deviations, which take no account of systematic errors, errors that are linear in $1/T$, etc.

Kinetics of Hydration. At 25 °C 66 runs were made using cacodylic acid (HCa) buffers at ionic strength 0.289 over the pH range 5.13–7.32. The k_{obsd} values were fit to eq 4

$$k_{obsd} = k_H[H^+] + k_{HCa}[HCa] + k_{Ca}[Ca] + k_h[OH^-] + k_w \qquad (4)$$

which allows for general acid and base catalysis. Except for k_H, which was zero, the values obtained are listed in Table II. They fit the k_{obsd} values with a standard deviation of 3.2%. Since the k_h term is seen never to have contributed more than 4% to the overall reaction, and since the k_h value obtained is slightly smaller than its standard deviation, no reliable information on hydroxide ion catalysis was obtained. Setting k_h equal to zero did not significantly change the values obtained for k_{HCa}, k_{Ca}, and k_w or the fit to the experimental data.

The larger rate constants obtained using the cacodylate buffers were about as large as can be measured reliably using the technique described. Experiments using somewhat more basic buffers gave reactions that were too fast to follow by this technique. Therefore, we used a stopped-flow temperature-jump kinetic method, which could be applied to much more basic solutions. To make hydroxide ion catalysis dominant, the buffer base used was triethylamine, which is strongly basic but rather hindered. To minimize the effects of side reactions that degrade dimethoxyacetone in basic solutions, the temperature was jumped (from an initial 20 °C) within 2 s after stopped-flow mixing. The average final temperature, calculated from the magnitude of the overall change in absorbance and ΔH for hydration, for each of the buffers used was in the range 27 ± 3 °C. The variations of rate in this small range were obscured by the fairly large uncertainties in the rate constants obtained; standard deviations ran around 20% of the values of the constants. The results obtained are listed in Table III, where each observed rate constant is the average of at least five runs. In a least-squares fit of the data to eq 5

Table II. Catalysis Constants for Hydration of 1,3-Dimethoxyacetone in Water at 25 °C[a]

Constant	Value[b]	Max % contribution[c]
k_{HCa}	0.065 ± 0.004	45
k_{Ca}	0.296 ± 0.009	75
k_w	0.0185 ± 0.0006	48
k_h	5400 ± 5500	4

[a] At ionic strength 0.289. [b] These rate constants, for approach to equilibrium, are in $M^{-1}\,s^{-1}$, except for k_w, which is in s^{-1}. The ± figures are standard deviations. [c] To k_{obsd}.

Table III. Hydration of 1,3-Dimethoxyacetone in the Presence of Triethylamine Buffers[a]

$[Et_3N]_t$,[b] M	pH	Ionic strength[c]	k^d, s^{-1} Obsd	k^d, s^{-1} Calcd
0.0125	10.55	0.013	1.61	1.32
0.0200	10.59	0.020	1.43	1.50
0.0250	10.47	0.025	1.56	1.17
0.0345	10.52	0.035	1.42	1.34
0.0450	10.56	0.045	1.48	1.50
0.0375	10.615	0.101	1.71	1.80
0.0500	10.615	0.101	1.92	1.82
0.0750	10.67	0.101	1.89	2.09
0.1000	10.63	0.101	1.99	1.96
0.0250	10.945	0.101	3.9	3.8
0.0500	10.965	0.101	3.8	4.0
0.1000	11.08	0.102	4.0	5.3
0.1000	11.505	0.104	13.0	13.8

[a] In aqueous solution at 27 ± 3 °C. [b] Sum of protonated and unprotonated amine concentrations. [c] Sodium chloride added as needed to reach the ionic strength shown. [d] First-order rate constants for approach to equilibrium.

$$k_{obsd} = k_b[Et_3N] + k_h[OH^-] + k_w \qquad (5)$$

k_w was assumed to have the value listed in Table II. From the values 3240 ± 230 and 3 ± 4 $M^{-1}\,s^{-1}$ obtained for k_h and k_b, respectively, the first-order rate constants in the last column of Table III were calculated. No more than 5% of any of these values arose from the k_b term. This fact and the large standard deviation show that we have obtained no more than a rough upper limit for k_b. It is plausible that the catalysis constant for triethylamine should be so much smaller than that for hydroxide ions. The relative catalytic activities would be expected to be similar to those for the mutarotation of sugars. If the catalysis constant for triethylamine fits the Bronsted equation for the mutarotation of glucose at 18 °C given by Bell[9] it will be smaller than that for hydroxide ions by 620-fold. Steric hindrance, which has been observed in sugar mutarotations[10] and in catalysis by triethylamine,[11] should make the constant still smaller.

Acidity of the Ketone Hydrate. The acidity of the hydrate was determined by a method like that used previously for isobutyraldehyde,[12] in which the absorbance in the presence of sodium hydroxide is compared with the absorbance in neutral solution. The ketone and sodium hydroxide solutions were mixed by use of a stopped-flow spectrophotometer and "initial" absorbances (after ~0.3 s) measured. Under such conditions the hydration–dehydration equilibrium is reached as is equilibrium in the acid–base reaction (eq 6)

$$(\mathrm{MeOCH_2})_2\mathrm{C(OH)_2} + \mathrm{OH^-} \overset{K_{h^-}}{\rightleftharpoons} (\mathrm{MeOCH_2})_2\mathrm{C(OH)O^-} \qquad (6)$$

but complications from slower processes, such as aldolization, which become important only after several seconds, are negligible. The presence of sodium hydroxide uses up some of the hydrate via eq 6, and some of the ketone is then used up in restoring the hydration–dehydration equilibrium. Values of K_{h^-} were calculated from eq 7

$$K_{h^-} = \frac{(D_0 - D)(K_h + 1)}{DK_h[\mathrm{OH^-}]_e} \qquad (7)$$

where D_0 is the absorbance of a neutral solution of ketone and D is the absorbance in the presence of the equilibrium concentration of hydroxide ion $[\mathrm{OH^-}]_e$, corrected for a small amount of absorption by the sodium hydroxide solution. A K_{h^-} value of 6.8 with a standard deviation of 1.1 was obtained at 25 °C. This corresponds to a pK_a value of 13.17 ± 0.07 for the hydrate.

Equilibrium in Bisulfite Addition. The apparent equilibrium constant for the formation of total bisulfite addition compound from total ketone and total sulfite is defined in eq 8

$$K_{\mathrm{app}} = \frac{[\mathrm{adduct}]_t}{[\mathrm{ketone}]_t[\mathrm{sulfite}]_t} \qquad (8)$$

in which the subscript t's refer to all states of protonation and of hydration. Most of the values of K_{app} at 25 °C in the pH range 2.5–10.0 were obtained by dissolving the crystalline sodium bisulfite addition compound of the ketone in water and determining the extent of dissociation by quenching in cold acid and titrating the bisulfite formed iodometrically. Below pH 8.5 the equilibrium concentration of adduct was simply equal to the initial concentration minus the concentration of sulfite formed by dissociation. Above this pH, however, base-catalyzed oxidation by the traces of oxygen present, even though the experiments were carried out under nitrogen, removed some of the sulfite formed. Therefore, between pH 8.5 and 10.0 after the acid-quenched solution had been titrated to determine the concentration of sulfite formed by dissociation, excess iodine and sodium borate were added. At the resultant pH (~8) the adduct dissociated rapidly and the sulfite reacted with iodine. From the amount of excess iodine remaining the concentration of adduct could be determined. Above pH 10 the bases present in the solution interfered with the acid-quenching process (as had been observed previously in the case of isobutyraldehyde[12]). Base-catalyzed reactions of the ketone also appeared to give complications, especially in the higher part of this pH range. Therefore K_{app} values were measured by stopped-flow experiments using the ketone in one mixing syringe and a borate buffer or sodium hydroxide solution in the other. Equilibrium is rapidly established at these pH's, and absorbances at the ketone absorption maximum obtained after a few seconds remained constant for several minutes or more. After correction for small amounts of absorbing species in the sulfite solutions, these absorptions were used to calculate ketone and then adduct and sulfite concentrations. The plot of log K_{app} vs. pH in Figure 2 shows that the values obtained spectrophotometrically in the pH range 7–10 agree satisfactorily with those obtained titrimetrically.

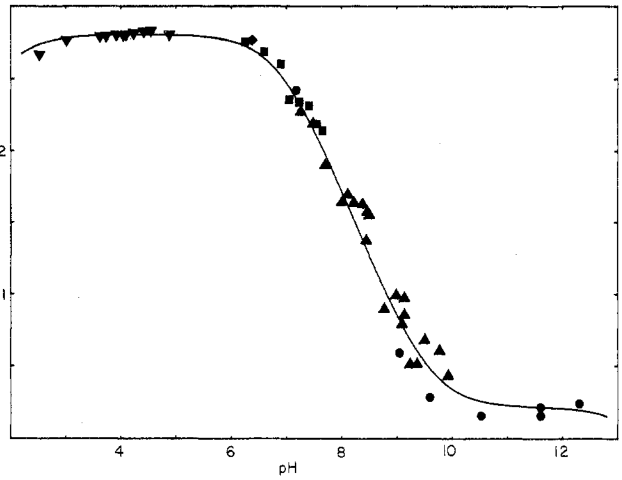


Figure 2. Plot of log K_{app} for addition of bisulfite to 1,3-dimethoxyacetone. Values were determined titrimetrically using acetate (▼), phosphate (♦), cacodylate (■), and borate (▲) buffers, and by stopped-flow spectrophotometry using borate buffers (●).

To express K_{app} in terms of more fundamental constants, we have assumed that all unicharged ions have the same activity coefficient γ and that the activity coefficient of a doubly charged ion is equal to γ^4. If the equilibrium constants for addition of bisulfite and sulfite ions to the ketone are denoted K_{SH} and K_{S2}, respectively

$$K_{\mathrm{SH}} = [\mathrm{R_2C(OH)SO_3^-}]/([\mathrm{R_2CO}][\mathrm{HSO_3^-}]) \qquad (9)$$

$$K_{\mathrm{S2}} = [\mathrm{R_2C(O^-)SO_3^-}]/([\mathrm{R_2CO}][\mathrm{SO_3^{2-}}]) \qquad (10)$$

then K_{app} may be expressed as shown in eq 11

$$K_{\mathrm{app}} = \frac{K_{\mathrm{SH}} + K_{\mathrm{S2}}K_{\mathrm{HSO_3}}/([\mathrm{H^+}]\gamma^4)}{[1 + K_h + K_hK_{h^-}K_w/([\mathrm{H^+}]\gamma^2)][1 + [\mathrm{H^+}]\gamma^2/K_{\mathrm{SO_2}} + K_{\mathrm{HSO_3}}/([\mathrm{H^+}]\gamma^4)]} \qquad (11)$$

in which $K_{\mathrm{SO_2}}$ and $K_{\mathrm{HSO_3}}$ are the first and second ionization constants of "sulfurous acid", K_w is the autoprotolysis constant of water, and K_h and K_{h^-} were defined in eq 3 and 6. Values of K_{SH}, K_{S2}, and $pK_{\mathrm{HSO_3}}$ were calculated so as to minimize the sum of the square of ($\log K_{\mathrm{obsd}} - \log K_{\mathrm{calcd}}$), with γ values calculated from the Davies equation.[13] The values obtained for K_{SH}, K_{S2}, and $pK_{\mathrm{HSO_3}}$ were 880 ± 56 M^{-1}, 2.26 ± 0.24 M^{-1}, and 7.31 ± 0.05, respectively, where the ± figures are standard deviations. The line in Figure 2 was based on these values and an ionic strength of 0.1. The deviations of the points from the line arise in part from the fact that they represent measurements at ionic strengths ranging from 0.026 to 0.159. The $pK_{\mathrm{HSO_3}}$ value is fairly close to the literature values 7.205 and 7.30.[14]

The slight decrease in K_{app} below pH 3 arises from the transformation of some of the bisulfite ions to sulfur dioxide ($pK_{\mathrm{SO_2}} = 1.89$[14]). The decrease that occurs on going above pH 6 arises from the transformation of bisulfite ions to sulfite ions. The decrease is halted as the hydroxylic hydrogen atom of the bisulfite addition compound becomes largely ionized above about pH 10. In fact, the ionization constant K_a for this hydrogen may be expressed as shown in eq 13. Our results give a pK_a value of 9.89.

$$K_a = [\mathrm{H^+}][\mathrm{R_2C(O^-)SO_3^-}]/[\mathrm{R_2C(OH)SO_3^-}] \qquad (12)$$

$$K_a = K_{\mathrm{HSO_3}}K_{\mathrm{S2}}/K_{\mathrm{SH}} \qquad (13)$$

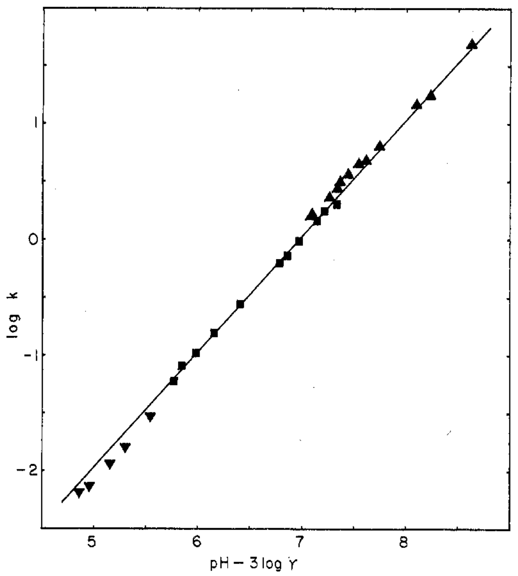


Figure 3. Plot of log k_{obsd} for the dissociation of the sodium bisulfite addition compound of 1,3-dimethoxyacetone in acetate (▼), cacodylate (■), and borate (▲) buffers vs. pH − 3 log γ.

Kinetics of Decomposition of the Bisulfite Adduct. The rate of decomposition of the bisulfite addition compound of the ketone was studied by stopped-flow spectrophotometric measurements in the presence of excess potassium triiodide, which reacts with the sulfite as soon as it is formed. The solutions were buffered and first-order rate constants were calculated from eq 14.

$$k_{obsd}t = \ln[([I_3^-]_0 - [I_3^-]_\infty)/([I_3^-] - [I_3^-]_\infty)] \quad (14)$$

If the reaction proceeds by rate-controlling decomposition of the conjugate base of the reactant as shown in eq 15 and 16

$$R_2C(OH)SO_3^- \overset{K_a}{\rightleftharpoons} H^+ + R_2C(O^-)SO_3^- \quad (15)$$

$$R_2C(O^-)SO_3^- \xrightarrow{k_d} R_2CO + SO_3^{2-} \quad (16)$$

the observed first-order rate constant may be expressed as shown in eq 17

$$k_{obsd} = k_dK_a/(\gamma^3 a_{H^+}) \quad (17)$$

where γ is the activity coefficient of a singly charged ion. To test this mechanism values of log k_{obsd} obtained using borate, cacodylate, and acetate buffers are plotted against pH − 3 log γ in Figure 3. (The pH never got close enough to pK_a for any significant fraction of the reactant to be present as the dianion.) The standard deviation of the 28 log k_{obsd} values from the line shown, which is based on the least-squares best k_dK_a value of $(1.08 \pm 0.18) \times 10^{-7}$ M s^{-1}, is 0.072. We regard this agreement as satisfactory, but the systematic nature of some of the deviations from the line suggests that the reaction may be subject to general base catalysis. Since the three significant bases present are all unicharged anions, general base catalysis gives eq 18

$$k_{obsd} = (k_dK_a/(\gamma a_{H^+}) + k_b[B^-] + k_{Ca}[Ca] + k_a[A^-])/\gamma^2 \quad (18)$$

in which A^- is acetate, B^- is borate, and Ca is cacodylate. (The first term in the equation corresponds to hydroxide ion catalysis; experiments in strongly acidic solution showed that the uncatalyzed reaction is negligible.) Least-squares treatment minimizing the sum of the squares of (log k_{obsd} − log k_{calcd}) gave values of $(9.00 \pm 0.26) \times 10^{-8}$ M s^{-1}, 355 ± 45 M^{-1} s^{-1}, 0.11 ± 0.04 M^{-1} s^{-1}, and zero for k_dK_a, k_b, k_{Ca}, and k_a, respectively, where the ± figures are standard deviations. These values gave log k_{calcd} values that fit the observed data with a standard deviation of 0.043. Although general base catalysis contributed as much as 34% to the overall reaction in the most favorable case, according to these rate constants, we do not regard it as definitively established. We did not make the systematic changes in concentration that would have been made in a study of general base catalysis, since we were just interested in the value of k_dK_a. Activity coefficients of doubly charged ions tend to deviate from activity coefficient equations at rather low ionic strengths. Perhaps the deviations from eq 17 seen in Figure 3 arise largely from this and other sources rather than from general base catalysis.

Combination of the k_dK_a values of 9×10^{-8} M s^{-1} with the pK_a value 9.89 gives a k_d value of 706 s^{-1}, which, when multiplied by K_{S2}, gives a k_c value of 1599 M^{-1} s^{-1}.

Equilibrium Constant for Hydration from Measurements Using Bisulfite. The preceding observations show that bisulfite ions have a rather large equilibrium constant for addition to dimethoxyacetone and that the addition reaction is much faster than hydration of the ketone around pH 6 or 7 (unless sulfite or bisulfite ions are unexpectedly good catalysts for hydration). These facts gave the basis for an independent way to determine the equilibrium constant for hydration. Aqueous sodium bisulfite and a phosphate buffer were put in one syringe and an aqueous solution of the ketone in the other syringe of the stopped-flow spectrophotometer. Very quickly after mixing, the absorbance at the carbonyl maximum decreases, reaching a minimum at time t_1 because part of the free ketone has been transformed to the equilibrium concentration of its bisulfite addition compound, but very little of the ketone hydrate has had time to lose water to replenish the supply of free ketone. As the concentration of bisulfite used is increased the concentration of free ketone present at time t_1 decreases. If the equilibrium constant for bisulfite addition were very large ($>10^6$ M^{-1}) the concentration of free ketone at time t_1 would essentially drop to zero when the bisulfite concentration became equal to the concentration of free ketone before reaction with bisulfite. Our equilibrium constant is not this large, but it is large enough to permit us to change the concentrations of reagents and, in essence, extrapolate to the situation that would prevail if the equilibrium constant were infinitely large. If, as previously, C represents the free ketone and f is defined as the fraction of C initially present that remains at time t_1

$$f = \frac{C_1}{C_0} \quad (19)$$

then K_{app} may be expressed as shown in eq 20

$$K_{app} = \frac{1 - f}{([HSO_3^-]_0 - (1 - f)C_0)f} \quad (20)$$

where the subscript zeros refer to concentrations before bisulfite addition begins. The initial free ketone concentration C_0 may be set equal to the total ketone concentration C_t (free and hydrated) divided by $1 + K_h$. Algebraic manipulation then gives eq 21

$$f[HSO_3^-]_0/(1 - f) = 1/K_{app} + fC_t/(1 + K_h) \quad (21)$$

which shows that a plot of $f[HSO_3^-]_0/(1 - f)$ vs. fC_t should give a straight line of slope $1/(1 + K_h)$ and intercept $1/K_{app}$. Data obtained at 25 °C and pH 6.4, using concentrations that varied f from 0.24 to 0.84, are plotted in Figure 4. The intercept and the slope give values of 688 M^{-1} and 0.362 for K_{app} and K_h, respectively. The latter value agrees well with the equilibrium constant for hydration at 25 °C listed in Table I, but eq 11 and our values of K_{SH}, K_{S2}, and K_{HSO_3} give a K_{app} value at pH 6.4 and ionic strength 0.16 that is 29% smaller than

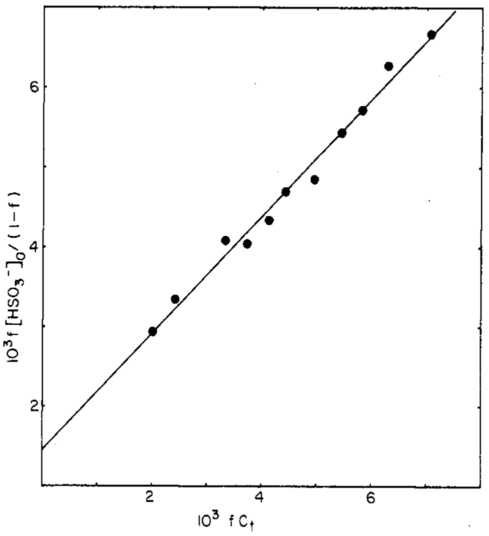


Figure 4. Plot for determination of the equilibrium constants for hydration (K_h) and bisulfite addition (K_{app}) by 1,3-dimethoxyacetone from stopped-flow spectrophotometric measurements.

the value obtained by these measurements. Calculations suggest that this deviation arises partly because the rate of establishment of the sulfite adduct equilibrium is not quite fast enough to make hydration of the aldehyde formed at time t_1 completely negligible.

Discussion

Hydroxide ions are assumed to catalyze the hydration of aldehydes and ketones simply by rate-controlling addition to the carbonyl carbon atom. The rate constant for such addition to dimethoxyacetone is then equal to k_h, the hydroxide ion catalysis constant for approach to equilibrium, multiplied by $K_h/(1 + K_h)$. This rate constant has been used in Figure 5, which contains extended Bronsted plots[2] for the additions of hydroxide and sulfite ions to aldehydes and ketones (eq 22).

$$R_2CO + N \overset{K_c}{\rightleftharpoons} \underset{\displaystyle N}{\underset{|}{R_2CO^-}} \qquad (22)$$

The data on addition of sulfite to benzaldehyde are from the work of Kokesh and Hall[15] and refer to 21 °C and ionic strength 1.0, instead of 25 °C and ionic strength zero like the other values. The data on sulfite addition to dimethoxyacetone are from the present work; the other data on sulfite addition,[16] addition of hydroxide ions to isobutyraldehyde,[12] and additions of hydroxide ions to other aldehydes and ketones[2] are also from the literature. The additions to dimethoxyacetone are seen to be slower than similar additions to aldehydes that have about the same equilibrium constants. It was noted previously that steric hindrance, as seen, for example, in the reactions of ortho-substituted triarylmethyl cations, produces such deviations in extended Bronsted plots.[2] In such cases steric effects are larger in the transition state than in the product, or, at least, a larger fraction of the equilibrium steric effects than of the equilibrium polar effects have appeared at the transition state. We believe that the deviations of the points for dimethoxyacetone from the lines roughly described by the points for the other compounds are probably largely steric in origin. Since there is a tendency for substituents to become smaller on moving to the right in Figure 5, these lines would probably have smaller slopes if steric effects were held constant.

It is interesting that the ratio of the equilibrium constant for addition of sulfite to the equilibrium constant for addition

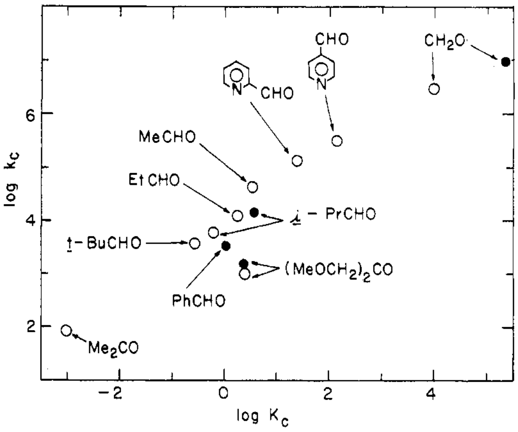


Figure 5. Rate–equilibrium plot for the addition of hydroxide ions (open circles) and sulfite ions (solid circles) to aldehydes and ketones in aqueous solution at 25 °C.

of hydroxide ions decreases steadily as hydrogen attached to the carbonyl group is replaced by alkyl or substituted alkyl groups. Thus $\log K_{SO_3} - \log K_{OH}$ decreases from 1.35 for formaldehyde to 0.78 for isobutyraldehyde to −0.05 for dimethoxyacetone. The ratio of *rate* constants, however, decreases much more slowly, $\log k_{SO_3} - \log k_{OH}$ being 0.53, 0.37, and 0.26 for formaldehyde, isobutyraldehyde, and dimethoxyacetone, respectively. Relatively constant values are required by the Ritchie equation (eq 23)

$$\log k = \log k_0 + N_+ \qquad (23)$$

which was originally applied to the combination of nucleophilic reagents with triarylmethyl and diazonium cations,[17,18] but has since been applied to attack on the carbonyl carbon atom of esters.[19] In eq 23 the value of N_+ depends on the nature of the nucleophile, the solvent, and the temperature, but not on that of the electrophile; k is the second-order rate constant for combination of the nucleophile and electrophile; and the value of k_0 depends only on the nature of the electrophile. Therefore, $\log k_{SO_3} - \log k_{OH}$ for reaction with any electrophile should just be equal to $(N_+)_{SO_3} - (N_+)_{OH}$, a constant. However, our values are 0.40 ± 0.14 instead of 7.90 − 4.75, or 3.15, as they should be according to the latest set of N_+ values.[19] Ritchie has noted other large deviations from eq 23 by the hydroxide ion and suggested that hydroxide ions are acting as general base catalysts of the reaction of water, removing a proton from water as its oxygen atom forms a bond to carbon.[19] Since hydroxide ion is the only base whose direct reaction with an electrophile gives the same product as the base-catalyzed reaction of water, these two alternative reaction paths in aqueous solution can be more readily distinguished with other bases. For this reason we plan to include data on a wide variety of nucleophiles in a forthcoming more general discussion of rate–equilibrium correlations in Lewis acid–base reactions.

Experimental Section

1,3-Dimethoxyacetone. The ketone was prepared by oxidation of 1,3-dimethoxy-2-propanol, which was made from epichlorohydrin and sodium methoxide by a method analogous to that of Abouzeid and Linnell.[20]

One procedure, which was not entirely reproducible, used the complex of chromium trioxide and pyridine.[21-23] In a typical run the complex from 160 g of chromium trioxide was dissolved in 2 l. of methylene chloride at 0 °C and 27 g of 1,3-dimethoxy-2-propanol added with stirring over a period of 10 min. After 10 min more the precipitate that formed was separated and washed with methylene chloride and the combined methylene chloride solutions concentrated and then vacuum distilled to give 12 g (45%) of 1,3-dimethoxyacetone: bp 89–90 °C (40 mm); 99.9% pure by GLC; ir 2990, 2985, 2930, 2910, 2820, 1740 (C=O), 1470, 1450, 1280, 1205, 1180, 1135, 1110, 1050, 990, and 950 cm^{-1}. 1,3-Dimethoxyacetone has been reported to boil at 78.0–78.5 °C (18 mm),[24] 62.5–63.0 °C (10 mm),[25] and 71.0–71.5 °C (16 mm),[26] but no spectral data seem to have been reported. ^{1}H NMR[27] ($CDCl_3$) δ 3.43 (s, 6, CH_3) and 4.18 ppm (s, 4, CH_2). The ^{1}H NMR spectrum in D_2O showed peaks at δ 3.40, 3.44, 4.30, and usually one at 3.39 ppm (relative to sodium 4,4-dimethyl-4-silapentane-1-sulfonate). The three (or two) peaks in the δ 3.39–3.44-ppm region were not sufficiently well resolved to measure their separate areas reliably, but their combined areas were about 2.23 times that of the peak at 4.30 ppm (at a probe temperature of about 40 °C). In a number of runs thought to have been carried out in the same way, the purity of the product was much poorer (sometimes, but not always, because of unoxidized starting material) or the yield was much lower.

The Moffatt–Pfitzner oxidation using *N,N'*-dicyclohexylcarbodiimide in dimethyl sulfoxide[28] was more reproducible. However, if no excess of dimethyl sulfoxide was used the product contained starting alcohol, and if more than about a 5% excess was used the product contained dimethyl sulfoxide. We could not remove much of either of these impurities by fractional distillation. In a typical successful run 24 g (0.20 mol) of alcohol, 120 g (0.58 mol) of *N,N'*-dicyclohexylcarbodiimide, 15 ml (0.21 mol) of dimethyl sulfoxide, and 3 ml of anhydrous phosphoric acid in 200 ml of methylene chloride were shaken in a 500-ml Erlenmeyer flask equipped with a drying tube. Occasional GLC analysis showed that reaction was complete in 5 days. Dicyclohexylurea and methylene chloride were removed by filtration and distillation, respectively. Distillation of the remaining liquid through a Vigreux column at 20 mm gave three fractions, all boiling at 82–83 °C. The middle 8-g fraction was 99.5% pure by GLC and the first (~5 g) and last (~2 g) fractions were somewhat less pure.

Some samples of ketone, upon standing for a few days, even in a freezer, acquired large amounts of impurities—sometimes white crystals separated. Other samples were rather stable to storage.

Kinetics of Ketone Hydration. A typical run below pH 9 was started by injecting 4 μl of ketone into 3 ml of aqueous solution from a 10-μl Hamilton syringe into a square topped 1-cm quartz cell in the thermostated cell compartment of a Cary spectrophotometer, Model 16. The syringe fit in the hole in a neoprene stopper, which fit through a hole in the top of the cell compartment into the top of the cell and kept light out of the cell compartment. The bottom of the cell contained a small Teflon-covered magnetic stirring bar, which was driven by a magnet in a motor below the cell.[5]

The runs above pH 9 were carried out using a Durrum-Gibson stopped-flow spectrophotometer with temperature-jump attachment. A 0.0055 M aqueous solution of dimethoxyacetone was put in one of the mixing syringes and a triethylamine buffer solution (made from recrystallized triethylamine hydrochloride and sodium hydroxide solution with sodium chloride added in some cases) was put in the other. Two seconds after stopped-flow mixing the capacitor, charged to 3.5 kV, was discharged for 0.1 s to heat the contents of the cell. The absorbance values at 275 nm were read starting 0.4 ms after the heating pulse ended. Over a period of time long enough to permit the absorbance to reach a maximum (and then decrease as the cell cooled), 4096 absorption values at constant time intervals were read into a Nicolet digital storage oscilloscope, Model 1090. Every 40th value was then transferred to the memory of an interfaced Hewlett-Packard calculator, Model 9830. A stored program then selected 20 values spaced as uniformly as possible in absorbance units between the minimum and maximum absorbances and used a nonlinear least-squares method[29] to calculate best values for the first-order rate constant, the infinite absorbance, and the change in absorbance.

The pH of solutions of dimethoxyacetone in triethylamine buffers tends to drift with time. The values listed in Table III were read as quickly as possible (about 1 min) after making solutions identical with those mixed in the temperature-jump experiments. The results deviated from those calculated on the basis of the known composition of the buffers and the pK_a of triethylammonium ions (10.67)[30] by an average of 0.068.

Determination of the Acidity of 1,3-Dimethoxy-2,2-propanediol. The acidity constant of the hydrate of 1,3-dimethoxyacetone was determined by stopped-flow spectrophotometric measurements in which an aqueous solution of dimethoxyacetone was in one of the two mixing syringes and aqueous sodium hydroxide in the other. The solutions used were of such strengths as to give sodium hydroxide concentrations of 0.12–0.58 M and total ketone concentrations (in all forms) of 0.003–0.009 M. The sodium hydroxide solutions used had an apparent extinction coefficient of 0.016 M^{-1} cm^{-1} and the apparent extinction coefficient of the ketone–hydrate equilibrium mixture at 25 °C is 16.1 M^{-1} cm^{-1}. In 23 runs an average K_{h^-} value of 6.8 M^{-1} and a standard deviation of 1.1 M^{-1} were obtained. After some initial small variations that were attributed to the mixing process the absorbance remained constant for several seconds, after which a slow increase could be noted. The absorbance values used were measured at about 0.3 s.

Equilibrium Constants for Addition of Sodium Bisulfite to 1,3-Dimethoxyacetone. Equilibrium in addition of bisulfite to the ketone was studied in a manner similar to that reported earlier for addition to isobutyraldehyde.[16] Most of the runs carried out below pH 10 were approached from the side of the bisulfite addition compound. In a typical preparation of the addition compound the distillate (which contained ketone and dimethyl sulfoxide) from the Moffatt–Pfitzner oxidation of 24 g of 1,3-dimethoxy-2-propanol by 50 ml of dimethyl sulfoxide was dissolved in 50 ml of methanol and 1 ml of pyridine. Addition of 20 g of sodium bisulfite was followed by heating to boiling, filtration, and removal of methanol from the filtrate under vacuum. Recrystallization of the resulting white powder from 95% ethanol and 8 h vacuum drying at room temperature gave 15 g of addition compound. Addition of weighed samples to ice-cold 0.5 M hydrochloric acid followed by iodometric titration showed that 1.6 ± 0.3% sodium bisulfite was present. Addition of sodium borate (to pH ~8) then liberated more sulfite whose iodometric titration showed that 76.6 ± 0.7% of sodium bisulfite addition compound was present. The remaining ~21% of the sample was assumed to be water and sodium sulfate. (Other bisulfite addition compounds are known to form hydrates from which water is not easily removed at room temperature.)[16]

A typical determination of K_{app} in the pH region 8.5–10.0, where the total amount of sulfite and adduct present was determined by two titrations rather than from the amount of adduct weighed out, was carried out as follows. Solutions of weighed amounts of the bisulfite addition compound were mixed under nitrogen with standard borate buffer solutions in a flask that was allowed to reach thermal equilibrium in a 25.0 °C constant temperature bath, where kinetic studies show that chemical equilibrium is reached in seconds in this pH range. Addition to ice-cold hydrochloric acid and titration gave the amount of free sulfite present and addition of sodium borate and retitration gave the amount that had been tied up as adduct.

When K_{app} was determined by a stopped-flow spectrophotometric measurements above pH 9 the absorbance of mixtures of ketone and buffer in the absence of sulfite was compared with the absorbance in the presence of sulfite.[16] This procedure was necessitated by the rapidity of the reaction. In the runs at pH 7.175, however, the reaction was slow enough that the initial absorbance (before any appreciable reaction) could be compared with the equilibrium absorbance.

Kinetics of the Decomposition of the Bisulfite Addition Compound. The kinetics of the decomposition of the sodium bisulfite addition compound of 1,3-dimethoxyacetone were followed in the same way that has been described for isobutyraldehyde.[16] Ionic strengths were around 0.10 for the acetate and cacodylate buffers and 0.01 for the borate buffers. Each run was carried out in triplicate.

Simultaneous Determination of K_{app} and K_h. In this method about 0.017 M 1,3-dimethoxyacetone was put in one stopped-flow syringe and a solution 0.0025–0.018 M in sodium bisulfite and 0.1589 M in total phosphate buffer in the other. Upon mixing the transmittance initially rapidly increased and then much more slowly decreased. The maximum values were read at about 1 s. The pH of the solutions was 6.406 ± 0.026.

Acknowledgment. We are indebted to Dr. William H. Sachs for creating the interface and computer program to use the HP 9830 calculator for stopped-flow and T-jump kinetics, and to Mrs. Karen Wang for making some of the calculations.

Registry No.—1,3-Dimethoxyacetone, 18664-32-9; 1,3-dimethoxy-2-propanol, 623-69-8; 1,3-dimethoxy-2,2-propanediol, 59907-40-3; sodium bisulfite, 7631-90-5.

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Selectivity in Cycloadditions. 5. Cycloadditions of Nitrile Oxides to Furan. Competing Mechanisms and Regiochemistry[1]

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Received April 12, 1976

Generation of benzonitrile oxide (BNO) in a large excess of furan gave a 91% yield of two regioisomeric monocycloadducts **1** and **2** in a 97:3 ratio and a 1% yield of the 1,3-addition product, **3**. The primary products can react further with BNO giving cycloaddition and fragmentation products, whose structures were established through spectroscopic evidence and chemical transformations. The cycloaddition with 2-methylfuran and cycloadditions of mesitonitrile oxide and *p*-nitro- and *m*-nitrobenzonitrile oxides to furan are also reported. Frontier orbital considerations allowed elucidation of the regiochemistry of the cycloadditions. A competing pathway stabilized by secondary orbital interactions is suggested for the formation of the 1,3-addition product.

In previous papers of this series we have evaluated the influence of polar and steric effects[3] as well as of π-conjugation[4] on nitrile oxide[5] cycloadditions. Although π-conjugation was remarkably effective in directing the regioselectivity of cyclopentadiene cycloadditions, nevertheless the two possible [4 + 2] cycloadducts of the dipole could be isolated. The results support the frontier orbital treatment of 1,3-dipolar cycloadditions,[6] which has recently led to a satisfactory understanding of regioselectivity and periselectivity phenomena.

Since the five-membered ring heteroaromatics, such as furan, thiophene, and pyrrole, have, in spite of their aromaticity, frontier orbital energies and shapes similar to those of cyclopentadiene[7]—which may be viewed as a cyclic diene aromatically stabilized through hyperconjugation[8]—it seemed to us interesting to extend our study to their dipolarophilic activities. A vast amount of material is available concerning the reactivity of heteroaromatics in substitution reactions[9] or in cycloadditions where the heteroaromatics enter as $_\pi 4_s$ components,[10] but the study of their dipolarophilic activities has been relatively scanty to date. A second aim of the studies was based on the well-known propensity of heteroaromatics toward substitution rather than addition reactions. If diradical or zwitterionic intermediates with a finite lifetime are ever involved in cycloaddition reactions, they would be expected to convert easily, perhaps quantitatively, to the substitution products because of the gain of aromaticity.

We have already given an account of the reactions of furan with nitrile oxides[11] and nitrile imines.[12] In this paper we report a more detailed study of the cycloaddition of nitrile oxides to furan, with particular attention directed at the regiochemistry of the reaction and to the detection of the substitution products.

Results

Furan is very slightly reactive toward nitrile oxides. Only the in situ preparation of benzonitrile oxide (BNO) in furan as solvent permitted isolation of a complex mixture of cycloadducts along with considerable amounts of diphenylfuroxan, the dimer of BNO, as well as 3,5-diphenyl-1,2,4-oxadiazole.

Because of the low reactivity of furan the primary monoadducts **1** and **2**, which have a reactive enol ether moiety,[6b,d] compete efficiently for BNO, even when furan is used as solvent. BNO also adds sluggishly on the C=N isoxazoline bonds of the bis adducts.

Chromatographic and fractional crystallization procedures led to isolation and characterization of not less than ten compounds. These products will be examined separately, depending upon whether they are 1:1 mono adducts or are derived from 2 mol of BNO and 1 mol of furan (bis adducts) or are further addition or transformation products.

Mono Adducts. On performing the reaction with a very small concentration of BNO (10^{-2} M) in furan in order to suppress any further reactions of the primary products, we obtained a 91% yield of the two cycloadducts **1** and **2** in a 97:3 ratio, and a 1% yield of the oxime **3**, as determined by GLC. In the normal runs (see Experimental Section) column chromatography gave the mono adducts in yields of 9–12, 0.3, and 0.1–0.2%, respectively.

The structures were assigned on the basis of chemical and NMR evidence. Acidic hydrolysis of **1** gives the isoxazoline