

Kinetics and Equilibria for the Reversible Hydration of the Aldehyde Group in Glyoxylic Acid

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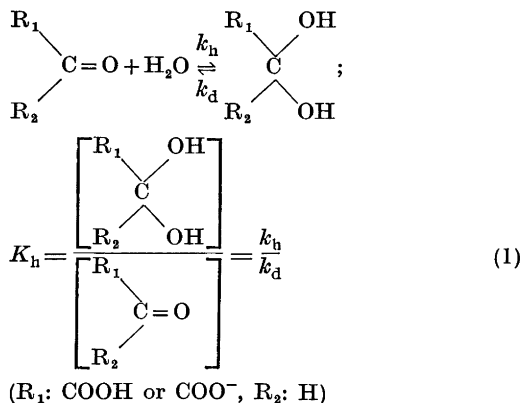
The kinetics of the dehydration of the hydrated aldehyde group in glyoxylic acid in aqueous solution have been studied at 298 K by means of a scavenger technique. In the pH-ranges 1–5.5 and 7–8.5 semicarbazide, followed by spectrophotometry, and sulphite, followed by pH-stat, were used as scavengers, respectively, and for a single experiment at pH = 6 hydroxylamine, followed by spectrophotometry, was found most suitable. The dependence of the first-order dehydration rate constant on pH and scavenger concentration indicated general acid-base catalysis and also showed that the rates of dehydration of hydrated glyoxylic acid and glyoxylate ion are different. The various spontaneous and catalytic rate constants are reported.

The equilibrium constants for the hydration of the two protolytic forms of glyoxylic acid were determined by combination of the present kinetic data with polarographic literature values. Thus, $K_h = [R_1R_2C(OH)_2]/[R_1R_2CO]$ for glyoxylic acid and glyoxylate ion are found to be 3.0×10^3 and 15.1, respectively.

The mechanism of the hydration process is discussed. The apparent existence of intramolecular catalysis by the carboxyl group may be attributed to activation entropy effects, caused by additional water molecules attached to this group, rather than to intramolecular general acid catalysis.

The study of intramolecular catalysis in simple molecules as models for more complicated catalytic phenomena such as enzyme activity has developed in recent years and has become an important discipline within chemical kinetics.¹ Thus, a very simple model for the function of the biological enzyme carbonic anhydrase – catalysing carbonyl group hydrations – might be a carbonyl compound possessing some catalytically active group, such as a carboxyl or an amino group. Suitable amino carbonyl

compounds are not particularly well known and will not be treated further in the present paper, but several well defined carboxylic carbonyl compounds are commercially available and a few have already been studied with respect to hydration of the carbonyl group, for example, pyruvic acid^{2-7,30} ($CH_3COCOOH$) and glyoxylic acid^{4,8,9} ($CHOCOOH$). Both of these compounds participate in metabolic processes in living organisms and the degree and rate of their hydration occupy a central position in this respect as pointed out by Davis.¹⁰ The kinetics and equilibria for the hydration of pyruvic acid have now been extensively investigated, but this is not the case for glyoxylic acid. In the polarographic work by Küta,⁹ where the limiting current at the dropping mercury cathode in certain pH-ranges is mainly determined by the rate of dehydration of the irreducible hydrated carbonyl group to the reducible free form only the quantity $k_d/K_h = k_d^2/k_h$ [for definition see eqn. (1)] could be determined.



More recently Ahrens⁹ has obtained data for the rate of dehydration of hydrated glyoxylic acid using a *t*-jump technique and for the degree of hydration using UV spectrophotometry, but the reliability of the rate constants seems to be rather limited, probably because of the many assumptions involved in explaining the experimental behaviour of the system.

The present paper reports the results of a more detailed study of the dehydration of hydrated glyoxylic acid using a scavenger technique. The same method was employed for the investigation of glycolaldehyde¹¹ (CHOCH₂OH), but in the case of glyoxylic acid the situation is somewhat more complicated by the dependence of the rate and equilibrium constants on the dissociation of the carboxylic group.

EXPERIMENTAL

Glyoxylic acid, monohydrate, cryst. (Fluka, *purum*) $M = 92.054$ was kept over P₂O₅ in a desiccator. The mean of three determinations of the molecular weight by titration with standard alkali (phenolphthalein as indicator) was $M = 92.6$. The compound was used without further purification. BDH Analar Na₂SO₃·7H₂O, Na₂S₂O₅, semicarbazide hydrochloride, and hydroxylamine hydrochloride were used for preparation of scavenger solutions. Analar NaCl for adjusting the ionic strength and doubly distilled water were used throughout.

In the pH-range 7–8.5 sulphite ($pK_A^{II} = 7.20$) was used as a scavenger by a pH-stat technique (Radiometer, Copenhagen), which has been described in detail earlier.^{11,12} The scavenger solutions had total sulphite concentrations in the range $1 \times 10^{-2} - 5 \times 10^{-2}$ mol dm⁻³ and ionic strengths (NaCl) 0.10–0.15. A 0.2 M solution of bisulphite was used as titrant and the initial concentration of glyoxylic acid in the reaction solution was about 5×10^{-3} mol dm⁻³ established by dilution of a 0.5 mol dm⁻³, neutral, aqueous stock solution of glyoxylic acid (glyoxylate ion).

Semicarbazide ($pK_A = 3.65$) was used as a scavenger in the pH-range 1–5.5, where a UV spectrophotometer (Beckman DB GT) recorded the appearance of the semicarbazone at its maximum absorbance, 255 nm. No other species present in the solution absorbed to an appreciable extent at this wavelength. At the higher pH-values (> *ca.* 2.6) a scavenger solution of known pH and total scavenger concentration ($10^{-2} - 10^{-1}$ mol dm⁻³, $I = 0.1$) was thermostated in a 1 cm silica cell and the reaction was initiated by adding 1–5 nm³ of a 0.1 mol dm⁻³ aqueous stock solution of glyoxylic acid. The same procedure was applied at the

lower pH-values (< *ca.* 2.6) but because of the risk of reduced scavenger capacity (discussed later) higher total scavenger concentrations were used ($5 \times 10^{-2} - 2.5 \times 10^{-1}$ mol dm⁻³, $I = 0.25$).

A single series of similar experiments with hydroxylamine ($pK_A = 5.97$) as a scavenger was carried out at pH = 6.0 (concentration range $1 \times 10^{-2} - 6 \times 10^{-2}$ mol dm⁻³, $I = 0.1$). The maximum of absorbance of the reaction product in this case was at 220 nm and there was no appreciable interference from other species in the solution at this wavelength.

All experiments in the present paper were carried out at 298.2 ± 0.2 K.

RESULTS AND DISCUSSIONS

The application of the scavenger principle, illustrated by the consecutive reaction scheme $A \rightleftharpoons B$ (I) and $B + C \rightarrow D$ (II), where the process (I) is to be studied and C is the scavenger, requires that B reacts with C much faster than it is converted to A. If this is so, the conversion of A to B will be the rate determining step and the velocity will be independent of the concentration of C (if this is not too small) apart from possible catalytic effects.

The kinetic curves for the dehydration of hydrated glyoxylic acid (A) were found to be of first order and there was no sign of incomplete scavenging in the concentration ranges used, but at the lower pH-values it was necessary to increase the total concentration of semicarbazide because of "deactivation" of this species due to conversion into the protonated form.¹² The observed rate constants (k_{obs}) could be obtained as $-\text{slope}/0.4343$ from plots of $\log |a_t - a_\infty|$ versus time, where a represents an arbitrary scale. The main results of the kinetic measurements are collected in Table 1. Table 2 contains results which can be used for calculation of catalytic constants of the scavengers in question except for hydroxylamine, which was not examined in detail. The values for the two protolytic forms of semicarbazide can easily be determined to a good approximation as the slopes of k_{obs} versus total scavenger concentration, which showed good linearity. This is so because semicarbazide at the extreme pH-values (2.00 and 5.20) exists mainly in its acidic and basic forms, respectively. The catalytic constants are given in Table 3 and it is worth noticing that $k_{RNH_3^+}$ and k_{RNH_2} apply to the catalysis of dehydration of the acidic and

basic forms of glyoxylic acid, respectively ($\text{p}K_A \approx 3.3$, see later).

For sulphite, the situation is less simple, but it can easily be shown¹¹ that the slope of the line k_{obs} versus total sulphite concentrations is

$$\text{slope} = \frac{f_{\text{SO}_3} f_{\text{H}} [\text{H}^+] k_{\text{HSO}_3} + f_{\text{HSO}_3} K_A k_{\text{SO}_3}}{f_{\text{SO}_3} f_{\text{H}} [\text{H}^+] + K_A f_{\text{HSO}_3}} \quad (2)^*$$

where f denotes activity coefficients (f_{HSO_3} and f_{SO_3} taken as 0.78 and 0.37, respectively¹⁴) and K_A is the thermodynamic dissociation constant for the bisulphite ion, $10^{-7.20}$ mol dm^{-3} at 298.2 K.¹⁵ Thus, k_{HSO_3} and k_{SO_3} can be determined by combining the slopes at two different pH-values. From the combinations at pH 7.20/7.40, 7.20/7.60, and 7.40/7.60, respectively, the following values were found for $k_{\text{HSO}_3}/k_{\text{SO}_3}$: $-0.050/0.187$, $-0.007/0.167$, and $0.061/0.154$. Therefore, k_{HSO_3} and k_{SO_3} can be taken as ≈ 0 and $0.17 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, respectively. These can be compared with the values of ≈ 0 and 0.30 and ≈ 0 and $0.22 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for glycol- and formaldehyde, respectively.^{11,12}

After correction for catalysis by the scavenger, *i.e.* after extrapolation to zero scavenger concentration, the rate of dehydration can be expressed in the following way for glyoxylic acid:^{**}

$$\text{Rate} = (k_0' + k_{\text{H}}' [\text{H}^+] + k_{\text{OH}}' [\text{OH}^-]) [\text{HA}] + (k_0 + k_{\text{H}} [\text{H}^+] + k_{\text{OH}} [\text{OH}^-]) [\text{A}^-] \quad (3)$$

where HA and A⁻ represent the acidic and the basic forms of hydrated glyoxylic acid, respectively, k_0 and k_0' are the "spontaneous" rate constants, *i.e.* the rate constants for catalysis by the solvent (H₂O), and k_{H} , k_{H}' , k_{OH} , k_{OH}' are catalytic constants for catalysis by H⁺ and OH⁻.

Using the relation $[\text{H}^+] [\text{A}^-] / [\text{HA}] = K_A$, where K_A now denotes the concentration acid dissociation constant for hydrated glyoxylic acid, eqn. (3) can be rearranged to

$$\text{Rate} = (k_0' + k_{\text{H}} K_A + k_{\text{H}}' [\text{H}^+]) [\text{HA}] + (k_0 + k_{\text{OH}} K_{\text{H}_2\text{O}} / K_A + k_{\text{OH}} [\text{OH}^-]) [\text{A}^-] \quad (4)$$

* As a simplification the ion charges of H⁺, OH⁻, HSO₃⁻, SO₃²⁻ and A⁻ are omitted when these ions are used as indices.

** Intermolecular catalysis by glyoxylic acid and glyoxylate ion is neglected which was shown experimentally to be reasonable because of the low concentrations ($< 5 \times 10^{-3}$ mol dm^{-3}).

By applying the relations $[\text{HA}] = [\text{H}^+] \times ([\text{HA}] + [\text{A}^-]) / (K_A + [\text{H}^+])$ and $[\text{A}^-] = K_A \times ([\text{HA}] + [\text{A}^-]) / (K_A + [\text{H}^+])$ to eqn. (4) and taking into account that the rate constants k_0' and k_{H} K_A cannot be separated experimentally ($k_0' + k_{\text{H}} K_A = k_{\text{HA}}^0$) – the same applies to k_0 and $k_{\text{OH}} K_{\text{H}_2\text{O}} / K_A$ ($k_0 + k_{\text{OH}} K_{\text{H}_2\text{O}} / K_A = k_{\text{A}}^0$) – eqn. (4) becomes:

$$\text{Rate} = k_{\text{obs}} ([\text{HA}] + [\text{A}^-]) \quad (5)$$

where

$$k_{\text{obs}} = \frac{k_{\text{HA}}^0 + k_{\text{H}}' [\text{H}^+]}{1 + K_A / [\text{H}^+]} + \frac{k_{\text{A}}^0 + k_{\text{OH}} [\text{OH}^-]}{1 + [\text{H}^+] / K_A} \quad (6)$$

which can also be written as

$$k_{\text{obs}} = \frac{k_{\text{HA}}^0}{1 + K_A f_{\text{H}} / 10^{-\text{pH}}} + \frac{k_{\text{H}}' 10^{-\text{pH}}}{f_{\text{H}} + K_A f_{\text{H}}^2 / 10^{-\text{pH}}} + \frac{k_{\text{A}}^0}{1 + 10^{-\text{pH}} / K_A f_{\text{H}}} + \frac{k_{\text{OH}} 10^{\text{pH} - \text{p}K_{\text{H}_2\text{O}}}}{f_{\text{OH}} + 10^{-\text{pH}} f_{\text{OH}} / K_A f_{\text{H}}} \quad (7)$$

or

$$k_{\text{obs}} = \frac{k_{\text{HA}}^0}{1 + 10^{\text{pH} - 3.38}} + \frac{k_{\text{H}}'}{10^{\text{pH} - 0.10} + 10^{2\text{pH} - 3.50}} + \frac{k_{\text{A}}^0}{1 + 10^{3.38 - \text{pH}}} + \frac{k_{\text{OH}}}{10^{13.88 - \text{pH}} + 10^{17.26 - 2\text{pH}}} \quad (8)$$

where f_{H} is taken as 0.83 and 0.79 at $I = 0.1$ and 0.25, respectively, and f_{OH} as 0.76.¹⁴ The value of K_A was determined by Kúta⁸ to be $10^{-3.30}$ (0.1 M citrate, 298 K).

The four rate constants in eqn. (8) were chosen so that the resulting values of k_{obs} – as a function of pH – fitted the experimental data in Table 1. This is shown graphically in Fig. 1, where the solid curve was calculated from the rate constants given in Table 3. The good agreement implies that the four rate constants are determined with fair accuracy and that the value 3.30 used for $\text{p}K_A$ of hydrated glyoxylic acid is reasonable.

These values can now be compared with the results obtained by Kúta⁸ and Ahrens.⁹ For the dehydration Kúta found $k_{\text{HA}}^0 / K_{\text{H}}^{\text{HA}} = 8.3 \times 10^{-5} \text{ s}^{-1}$, $k_{\text{A}}^0 / K_{\text{H}}^{\text{A}} = 3.65 \times 10^{-4} \text{ s}^{-1}$, and $k_{\text{OH}} / k_{\text{H}}^{\text{A}} = 2.8 \times 10^2 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, K_{H}^{HA} and K_{H}^{A} being the hydration equilibrium constants of glyoxylic acid and its anion, respectively, which combined with the results of the present paper give $K_{\text{H}}^{\text{HA}} = 3.0 \times 10^2$, $K_{\text{H}}^{\text{A}} = 15.1$, and

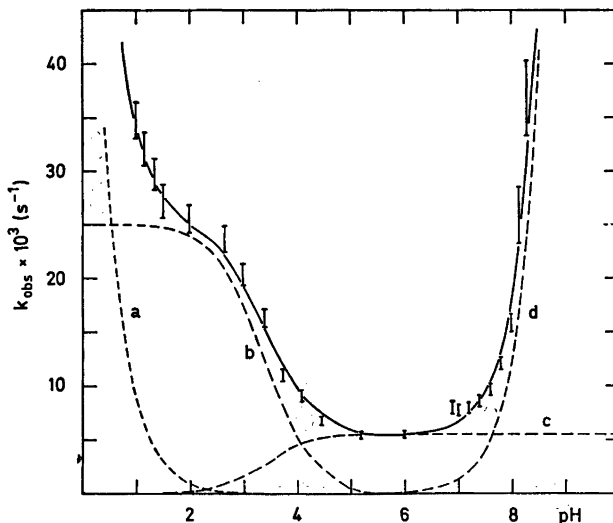


Fig. 1. Dependence of k_{obs} on pH. Experimental points are indicated with standard deviations. — calculated curve. - - - single terms of eqn. (8): a = k_{H^+} -term, b = k_{HA^0} -term, c = k_{A^0} -term, d = k_{OH^-} -term.

$K_{\text{H}^+}^{\text{A}} = 32.2$. These values are again comparable with $K_{\text{H}^+}^{\text{HA}} \approx 10^3$ and $K_{\text{H}^+}^{\text{A}} = 16.5$ given by Ahrens, who used a spectrophotometric technique for this purpose. It would seem that the most acceptable of these four values are $K_{\text{H}^+}^{\text{HA}} = 3.0 \times 10^2$ and $K_{\text{H}^+}^{\text{A}} = 15.1$ (16.5). The acid dissociation constant for dehydrated glyoxylic acid can now be determined as $K_{\text{A}} \times K_{\text{H}^+}^{\text{HA}} / K_{\text{H}^+}^{\text{A}} = 1 \times 10^{-2} \text{ mol dm}^{-3}$ which is in fair agreement with the value $1.3 \times 10^{-2} \text{ mol dm}^{-3}$ reported by Turjan.¹⁶

The agreement of equilibrium constants is within reasonable limits. However, this is not the case for the dehydration rate constants obtained by Ahrens and the present authors. Ahrens⁹ found $k_{\text{A}^0} \leq 6 \times 10^{-4} \text{ s}^{-1}$ [$(5.5 \pm 0.2) \times 10^{-3}$], $k_{\text{HA}^0} = (125 \pm 75) \times 10^{-3} \text{ s}^{-1}$ [$(25 \pm 1) \times 10^{-3}$], and $k_{\text{OH}^-} = (2.6 \pm 2) \times 10^5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ [$(9 \pm 1) \times 10^8$], where the figures in square brackets are results from the present paper. It is clear that the many assumptions and approximations involved in reducing the experimental "t-jump"-results by Ahrens to single rate constants tend to increase the uncertainty of these. We therefore believe that our results, which have been obtained in a much more direct way, are the more reliable.

Intramolecular catalysis of carbonyl hydration and keto-enol tautomerism by the carboxyl

group of α -keto acids has often been discussed. Thus, the considerably higher rates of spontaneous hydration and dehydration of pyruvic acid than, e.g., acetaldehyde (see Table 4), although the extent of hydration is approximately the same, has been attributed to intramolecular general acid catalysis by the carboxyl-group.^{2,17} Similarly, the higher rates of iodination of α -keto-acids compared with these for "normal" carbonyl compounds have been explained by such an effect.¹⁹⁻²¹ As can be seen from Table 4 pyruvic acid is not unique in this respect; glyoxylic acid can be conveniently compared with formaldehyde and shows higher rates of spontaneous reaction if the difference in the degree of hydration of the two substances is taken into account.

However, in a recent paper by Pocker *et al.*²² strong arguments against this theory are put forward. Investigation of the hydration kinetics of the methyl and ethyl esters of pyruvic acid, where no intramolecular acid catalysis is possible, showed that the rate constants for spontaneous hydration (273 K) were similar to that for the acid itself. Similarly, it was shown by Bell and Ridgewell,²⁶ Meany,²³ and by Fischer and Schellenberger²⁴ that the rates of keto-enol tautomerism of the methyl and ethyl esters of pyruvic acid were close to that of the free acid.

Table 1. Collected dehydration rate constants (s^{-1}) corrected for scavenger catalysis. The maximum standard deviation is ± 0.02 for pH and $\pm 5\%$ for k_{obs} apart from the last two values, where it is estimated to $\pm 10\%$ for k_{obs} .

pH	$k_{\text{obs}} \times 10^3$	Scavenger	
1.00	34.7		
1.15	32.0		
1.35	29.7		
1.50	27.0	semicarbazide	
2.00	25.5		
2.65	23.6		
3.00	20.3		
3.40	16.3		
3.75	10.9		
4.10	9.0	hydroxylamine	
4.46	6.7		
5.20	5.4		
6.00	5.4		
6.90	8.0		
7.00	7.7		
7.20	7.9		
7.40	8.5		sulphite
7.60	9.6		
7.80	12.0		
8.00	15.8		
8.15	25.9		
8.30	36.7		

We therefore believe that the pronounced catalytic effect of the carboxylic group in the hydration of α -keto-acids may be attributed to additional water molecules attached to the carboxylic group in the hydrated compound. It has been postulated and shown by various authors^{5,25,30,31} that the hydration equilibrium constant for pyruvic acid shows a third-power dependence on water concentration, which means that two molecules of water, in excess of the one used for hydration, are attached to the hydrated substance. A similar behaviour has been shown by Jen and Knoche²⁹ for the hydration of α -keto-glutaric acid and it may be reasonable to believe that it also applies to glyoxylic acid.

Bell and coworkers³²⁻³⁵ have clearly demonstrated that the transition state for the spon-

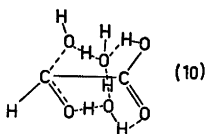
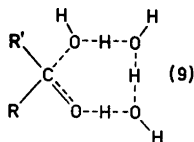


Table 2. Catalysis by scavenger substances.

$C_{\text{tot}} \times 10^2$ (mol dm ⁻³)	$k_{\text{obs}} \times 10^3$ (s ⁻¹)	$k_{\text{calc}} \times 10^3$ (s ⁻¹)
Semicarbazide; pH 2.00		
5	26.2	—
10	28.5	—
15	29.2	—
20	31.0	—
25	32.8	—
Semicarbazide; pH 5.20		
5	5.9	—
10	6.0	—
15	6.2	—
20	6.7	—
25	7.1	—
Sulphite; pH 7.20		
10	9.1	9.1
20	10.1	10.0
30	10.9	10.9
40	11.5	11.8
50	13.6	12.9
Sulphite; pH 7.40		
10	10.4	10.1
20	10.7	11.0
30	12.6	12.2
40	12.7	13.0
50	14.3	14.2
Sulphite; pH 7.60		
10	10.6	11.5
20	12.2	12.6
30	13.4	13.6
40	13.8	14.8
50	15.6	15.9

taneous hydration of simple carbonyl compounds undoubtedly consists of the carbonyl compound and at least three water molecules probably in a ring structure such as (9).

As a conclusion a plausible transition state for the hydration of α -keto-acids may be illustrated as (10), where the process proceeds *via* a transition state of ring structure as (9), but where this transition state is stabilized by hydrogen bondings to the carboxyl group as shown. As can be seen this mechanism does not necessarily imply acid-base activity of the carboxyl group and the catalytic effect would seem to be an entropy effect. This is shown experimentally by a comparison of activation entropy values for the hydration of pyruvic acid and acetaldehyde (Table 4). That for pyru-

Table 3. Collected catalytic constants, k_A and k_B , for the dehydration reaction. k_A and k_B are catalytic constants for the acidic and basic catalytic species, respectively. Temperature 298.0 K.

Compound	Catalyst(acidic species)	K_A (mol dm ⁻³)	$k_A \times 10^3$ (mol ⁻¹ dm ³ s ⁻¹)	$k_B \times 10^3$ (mol ⁻¹ dm ³ s ⁻¹)
Glyoxylic acid	H ₃ O ⁺	55.5	76 ± 5(k_H')	(25 ± 1)/55.5
	HSO ₃ ⁻	6.2 × 10 ⁻³	—	—
	N ⁺ H ₃ NHCONH ₂	2.24 × 10 ⁻⁴	30 ± 5	—
	H ₂ O	1.8 × 10 ⁻¹⁶	(25 ± 1)/55.5 ($k_{HA}^0/55.5$)	—
Glyoxylate ion	H ₃ O ⁺	55.5	—	(5.5 ± 0.2)/55.5
	HSO ₃ ⁻	6.2 × 10 ⁻³	≈ 0	170 ± 10
	N ⁺ H ₃ NHCONH ₂	2.24 × 10 ⁻⁴	—	6 ± 1
	H ₂ O	1.8 × 10 ⁻¹⁶	(5.5 ± 0.2)/55.5 ($k_A^0/55.5$)	(9 ± 1) × 10 ⁶ (k_{OH})

Table 4. Kinetic values and activation parameters for the hydration of various carbonyl compounds in aqueous solution of 298.2 K.

Carbonyl compound	Spontaneous rate constants		Hydration equil.const.	$\Delta H_{hydr.}^\ddagger$ (kJ)	$\Delta S_{hydr.}^\ddagger$ (J K ⁻¹ mol ⁻¹)	Ref.
	$k_{hydr.}^0$ (s ⁻¹)	$k_{dehydr.}^0$ (s ⁻¹)				
Acetaldehyde	9.0 × 10 ⁻³	6.1 × 10 ⁻³	1.49	37.2	-159	27, 28
Formaldehyde	10.2	5.1 × 10 ⁻³	2 × 10 ³	—	—	32
Glycolaldehyde	8.6 × 10 ⁻²	9.6 × 10 ⁻³	9	—	—	11
Pyruvic acid	1.56 × 10 ^{-1a}	9.6 × 10 ⁻²	1.63	39.3	-100	7, 25
Ethyl pyruvate	9.0 × 10 ⁻²	3.9 × 10 ⁻²	2.33	31.8	-89.5	22
Methyl pyruvate	1.15 × 10 ⁻¹	4.0 × 10 ⁻²	2.85	31.4	-89.0	22
Glyoxylic acid	7.5	2.5 × 10 ⁻²	3.0 × 10 ²	—	—	^b
Glyoxylate ion	8.3 × 10 ⁻²	5.5 × 10 ⁻³	15.1	—	—	^b
α-Keto-glutaric acid	1.75 × 10 ⁻¹	1.3 × 10 ⁻¹	1.35	—	—	29

^a Extrapolation from 273 K. ^b This paper.

vic acid is considerably less negative than that for acetaldehyde while the enthalpy of activation is actually slightly higher for pyruvic acid.

Furthermore, the apparent intramolecular catalysis in the methyl and ethyl esters of pyruvic acid may be explained in a similar way. Pocker *et al.*²² have reported that the hydration of the two esters shows a second-power dependence on water concentration so that at least one water molecule is attached to the ester group in the hydrated compound. The transition state for this reaction may be very similar to that for the pure acid [(10)] but less hydrogen bonded due to the replacement of -OH with -OR. Activation enthalpy and entropy considerations for the two esters (Table 4) also support this explanation as they

do for the free acid, although it is difficult to see why the esters should have less negative activation entropy values than pyruvic acid.

This explanation of intramolecular catalysis in α-keto-acids may also explain the lower degrees of hydration of the basic forms of these acids, *e.g.* glyoxylic acid/glyoxylate ion in Table 4, the carboxylate group having reduced hydrogen bonding capability and so is unlikely to bind the extra water molecules needed to facilitate the hydration of the carbonyl group. This also implies that the carboxylate ions do not show intramolecular catalysis and indeed the rate constants of hydration and dehydration of the glyoxylate ion are very similar to those of glycolaldehyde which shows no sign of intramolecular catalysis (Table 4).

Intramolecular catalysis of carbonyl hydration by carboxyl groups is not yet clear. The homologous series $\text{CO}_2\text{H}-(\text{CH}_2)_n-\text{CO}-\text{CH}_3$ studied by Bell and Fluendy¹⁸ with respect to iodination does not hydrate sufficiently for easy study. The only member of the series $\text{CO}_2\text{H}-(\text{CH}_2)_n-\text{CO}-\text{CO}_2\text{H}$, where carbonyl hydration is "activated" by the neighbouring carboxyl group in the manner already described, that has been studied, is α -keto-glutaric acid ($n=2$).²⁹ This compound shows higher rates of hydration and dehydration (Table 4) than pyruvic acid though not as high as might be expected if intramolecular catalysis also by the remote carboxyl group was important.

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