

The Effect of Methyl Substitution on the Kinetics of the Periodate Oxidation of Glyoxal¹

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Abstract: Second-order rate constants for the periodate oxidation of glyoxal, pyruvaldehyde, and 2,3-butanedione have been measured in aqueous acid solution at 26° and ionic strength 0.11. The over-all reaction rates decrease in the order glyoxal > pyruvaldehyde > 2,3-butanedione. pH-rate behavior is interpreted in terms of a nucleophilic attack on the carbonyl carbon atoms of the reductant by three forms of periodate, H₅IO₆, H₄IO₆⁻, and H₃IO₆²⁻. Acetate, phthalate, and glutamate ions catalyze the reaction. Activation parameters are given for the H₄IO₆⁻ reactions.

The literature on the kinetics of the periodic acid oxidation of glycols since the work of Duke³ is quite extensive.⁴ The kinetics of the oxidation of dicarbonyl compounds by periodate has received much less attention. Clutterbuck and Reuter⁵ have shown that the periodate oxidation of pyruvaldehyde (methylglyoxal) and 2,3-butanedione (dimethylglyoxal) leads to a mole each of formic acid and acetic acid in the first case and to 2 moles of acetic acid in the second case, along with the usual iodate product.

Shiner and Wasmuth⁶ studied the periodate oxidation of a series of α -diketones and could not detect the initial fast reaction, followed by a slow one, observed by Taylor and co-workers⁷ for 2,3-butanedione. The reactions were second-order over-all with no kinetically detectable intermediate such as that found in the case of glycols.³ The kinetics were explained on the basis of a nucleophilic attack on the carbonyl carbons by the several forms of periodate present in acid and slightly basic media.

Bunton and Shiner⁸ attempted to confirm the kinetic picture of a nucleophilic attack on the dione by periodate by using oxygen-18 as a tracer in H₂O¹⁸ solvent. While they preferred to view their data as confirmatory, they point out that other interpretations, such as reactions of hydrated diones, may also account for the observed behavior. In particular, their procedure utilized tetraethylammonium hydroxide-periodate buffers which would make speculation on mechanisms in the acid range tenuous at best.

Our study was undertaken to show what kinetic differences, if any, exist between the periodate oxidation of glyoxal and that of its methyl and dimethyl derivatives and to make comparisons between these data and those for methyl-substituted ethylene glycols.

Experimental Section

Materials. The periodic acid was obtained from the G. Frederick Smith Co. in 99% purity. The other inorganic materials were the best grades available.

Aqueous solutions of glyoxal (40%) and pyruvaldehyde (45%) were obtained from the Aldrich Chemical Co. in purities of 99.7 and 98.8%, respectively. Eastman White Label diacetyl (2,3-butanedione) was distilled at 750 mm and the fraction boiling at 87° was used (100% pure, by periodate oxidation).

The stoichiometry of the reaction between periodate and the dicarbonyl compounds was checked by allowing measured volumes of the glyoxals to stand in acetate-buffered solutions (pH 4) of periodate for various times and then measuring the periodate absorbance change at 222.5 m μ .

Kinetic Measurements. The arsenite-iodine titration method used earlier⁹ was found unsatisfactory in this work because of indefinite and fading end points. Therefore, the spectrophotometric procedure of Shiner and Wasmuth⁶ was utilized and the reactions were followed by observing changes in absorbance at 222.5 m μ on a Beckman DU spectrophotometer. The molar absorptivities (ϵ) at 222.5 m μ obtained in this work were identical with those of Crouthamel, *et al.*,¹⁰ with the exception of the value for H₄IO₆⁻ (10.39×10^3 compared to the literature¹⁰ value of 10.08×10^3).

All runs were followed over at least one half-life using the following procedure. To a 100-ml volumetric flask, with an additional mark at 92.28 ml, were added a measured volume of the standard solution of the dicarbonyl compound, the appropriate amount of buffer solution, and the volume of 1.0 M sodium perchlorate necessary to adjust the ionic strength to 0.11. The solution was then diluted to the 92.28-ml mark with distilled water. The flask, as well as a flask containing the standard periodate solution, was then placed in a constant-temperature bath and allowed to reach thermal equilibrium. The reaction was initiated by the addition of 7.72 ml of the standard periodate solution (to give a solution 8×10^{-5} M periodate). An electric timer was started immediately after the addition was complete. The reaction flask was then shaken vigorously for 15 sec and returned to the bath. For the more rapid reactions a single sample was pipetted into a cuvette and the absorbance at 222.5 m μ was measured at appropriate intervals, using a Beckman DU spectrophotometer equipped with a constant-temperature cell holder. For the slower reactions a new sample was pipetted from the reaction flask into the cuvette approximately every 200 sec. The reaction times were recorded at the time that the absorbances were read. The solution used as a blank contained all of the materials used in the reaction flask except the periodate. The initial absorbance was calculated from the initial concentration of periodate used and its molar absorptivity coefficient at that particular pH. The initial absorbance values agreed quite well with the values calculated by extrapolating the absorbances back to zero time.

The total periodate concentration at time t , $[P]_t$, was calculated from the expression

(9) V. C. Bulgrin and G. Dahlgren, *J. Am. Chem. Soc.*, **80**, 3883 (1958).

(10) C. R. Crouthamel, H. V. Meek, D. S. Martin, and C. V. Banks, *ibid.*, **71**, 3034 (1949).

(1) Work supported in part by Grant-P272 of the American Cancer Society.

(2) Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221.

(3) F. R. Duke, *J. Am. Chem. Soc.*, **69**, 3054 (1947).

(4) For example, see references in E. T. Kaiser and S. W. Weidman, *ibid.*, **86**, 4354 (1964); *Tetrahedron Letters*, 497 (1965).

(5) P. W. Clutterbuck and F. Reuter, *J. Chem. Soc.*, 1467 (1935).

(6) V. J. Shiner, Jr., and C. R. Wasmuth, *J. Am. Chem. Soc.*, **81**, 37 (1959).

(7) J. E. Taylor, B. Soldano, and G. A. Hall, *ibid.*, **77**, 2656 (1955).

(8) C. A. Bunton and V. J. Shiner, Jr., *J. Chem. Soc.*, 1593 (1960).

$$[P]_t = [P]_i \left[\frac{A_t - A_\infty}{A_0 - A_\infty} \right]$$

where $[P]_i$ = the initial total periodate concentration, A_t = the absorbance at time = t , A_0 = the absorbance at time = 0, A_∞ = the absorbance at time = ∞ .

All pH measurements were made at room temperature using a Beckman Model 76 expanded scale pH meter. The error in pH was assumed to be no greater than ± 0.03 pH unit.

The bath temperature was controlled to $\pm 0.05^\circ$ at 16.43° , to $\pm 0.03^\circ$ at 25.93° , and to $\pm 0.06^\circ$ at 38.93° .

All data from the various runs were processed in an IBM 1620 digital computer. The kinetic schemes and equations to which the data were fit are discussed in the following section. All slopes were computed using the method of least squares with the probable error assessed using a 50% probability. This error was found to vary between a maximum of $\pm 1.2\%$ and a minimum of $\pm 0.2\%$ for an individual run, with an average error of $\pm 0.4\%$. The reproducibility of identical runs was found to be $\pm 2.2\%$ for a test group of 10 runs.

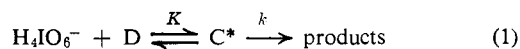
Results and Discussion

The rate of the over-all reaction of periodate with the dicarbonyl compounds decreased in the order glyoxal > pyruvaldehyde > 2,3-butanedione. Above pH 4 the pseudo-second-order rate constants increased rapidly with increasing pH for all three compounds.

For equimolar runs at pH 3.4 (where 99+% of the periodate exists in a univalent form, $H_4IO_6^-$ or IO_4^-) the second-order plots were excellent (typically within $\pm 0.4\%$ from least-squares linearity; see Experimental Section), with the slopes equal to the pseudo-second-order rate constants, k_2' . For runs in which the dicarbonyl compound was present in excess, excellent first-order and second-order plots were obtained with the slopes equal to the pseudo-first-order and pseudo-second-order constants, respectively.

Acetate, phthalate, and glutamate buffers were found to catalyze the reaction, an effect also observed in the case of acetate by Shiner and Wasmuth.⁶ A series of runs were made in which the total concentration of acetate buffer was varied at constant pH. A plot of the pseudo-second-order rate constants *vs.* the acetate ion concentration was linear with the slope equal to the catalytic constant for acetate ion, k_{OAc} (formally, a third-order constant), and the intercept equal to the pseudo-second-order rate constant for the uncatalyzed reaction. All of the constants reported in this work have been corrected for buffer catalysis. The acetate ion behavior will be discussed in a later section.

If we assume that $H_4IO_6^-$ is the reactant in the pH range 2.5–4.5 and if we further assume that the reactions follow the Duke kinetic scheme,³ then we may write



and the rate expression

$$-d[P]_T/dt = k[C^*] = kK[H_4IO_6^-][D] \quad (2)$$

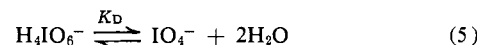
where $[C^*]$ = concentration of intermediate complex, $[D]$ = concentration of uncomplexed dicarbonyl, $[P]_T$ = concentration of total periodate in this pH range ($[H_4IO_6^-] + [IO_4^-] + [C^*]$). For runs in which the concentration of dicarbonyl compound is in sufficient excess over periodate (dicarbonyl concentration essentially constant during the course of a run) the first-order rate expression is

$$\frac{-d[P]_T}{dt} = \frac{kK[D]}{1 + K_D + K[D]} [P]_T = k_1' [P]_T \quad (3)$$

where k_1' = pseudo-first-order rate constant which equals

$$kK[D]/(1 + K_D + K[D]) \quad (4)$$

and K_D = dissociation constant for the equilibrium



The expression for k_1' may be written in the form

$$\frac{1}{k_1'} = \frac{1}{k} + \frac{1}{kK[D]}(1 + K_D) \quad (6)$$

A plot of the reciprocal of the pseudo-first-order rate constant *vs.* the reciprocal of the uncomplexed dicarbonyl concentration should be linear with a slope of $(1 + K_D)/kK$ and an intercept of $1/k$. However, our linear plots had zero intercepts and slopes equal to the reciprocal of the pseudo-second-order rate constants as required for the limiting case when $K_D + 1 \gg K[D]$ (the other limiting case, $K[D] \gg K_D + 1$, leads to zero-order dependence on the dicarbonyl concentration), or by simple second-order kinetics (complex formation rate determining), *viz.*

$$-d[P]_T/dt = k_1'[P]_T = k_2'[D][P]_T \quad (7)$$

and

$$1/k_1' = 1/k_2'[D] \quad (8)$$

The pseudo-second-order rate constants obtained from these reciprocal slopes at 26° in the univalent periodate range (dicarbonyl concentration in 5- to 20-fold excess over periodate) are compared with those obtained from the equimolar runs in Table I. The agreement is considered good.

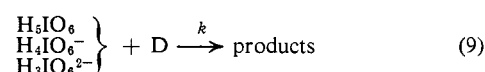
Table I. Pseudo-Second-Order Rate Constants for Periodate Oxidation^a

	$k_2', M^{-1} \text{sec}^{-1}$	
	Reciprocal plots	Equimolar runs ^b
Glyoxal	16.2	16.1
Pyruvaldehyde	7.97	8.15
2,3-Butanedione	0.635	0.617

^a Temperature 26° , $\mu = 0.11$, and pH 2.5–4.5 ^b Average of several runs with a variation of $\pm 2.2\%$.

In this work the dilute solutions used limited detection of complex formation to reactions with equilibrium constants greater than 100. Values for K of this order are not unreasonable since a range of 43 to 350 was observed for the ethylene glycol–periodate series.¹¹

If we accept H_5IO_6 , $H_4IO_6^-$, and $H_3IO_6^{2-}$ as the reactive periodate species in the acid range as suggested by Shiner and Wasmuth⁶ and if we assume that the reaction is second order over the entire acid range and not only in the univalent ion range as suggested above, then we may write for the reaction



(11) F. R. Duke and V. C. Bulgrin, *J. Am. Chem. Soc.*, **76**, 3803 (1954).

Table II. Second-Order Rate Constants,^a Acetate Catalysis Constant, and Thermodynamic Functions of Activation^b for the Periodate Oxidation of Dicarboxyl Compounds^c

Dicarboxyl	k_5	$k_4 \times 10^{-2}$	$k_3 \times 10^{-3}$	k_{OAc}^d	ΔH^*	ΔG^*	ΔS^*
Glyoxal	7.51 ± 1.06	7.14 ± 0.14	4.99 ± 0.57	225	+11.9	+13.6	-5.4
Pyruvaldehyde	11.8 ± 0.5	3.30 ± 0.03	2.99 ± 0.25	111	+10.7	+14.0	-11.1
2,3-Butanedione	1.46 ± 0.05 (0.74) ^e	0.157 ± 0.005 (0.133) ^e	0.639 ± 0.015 (0.350) ^e	5.02	+12.8	+15.9	-10.4

^a See text, eq 10, units of $M^{-1} \text{sec}^{-1}$. ^b Units of kcal/mole for ΔH^* and ΔG^* , eu for ΔS^* . Estimated error $\pm 1\%$. ^c Temperature 26° , $\mu = 0.11$. ^d Units of $M^{-2} \text{sec}^{-1}$. ^e Reference 6, 22° .

the rate expression

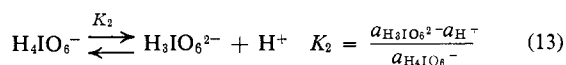
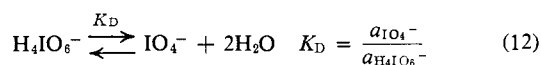
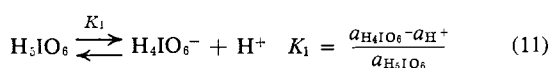
$$-\frac{d[P]_T}{dt} = \{k_5[H_5IO_6] + k_4[H_4IO_6^-] + k_3[H_3IO_6^{2-}]\}[D] \quad (10)$$

where over the acid range

$$[P]_T = [H_5IO_6] + [H_4IO_6^-] + [IO_4^-] + [H_3IO_6^{2-}]$$

$$[D] = [\text{dicarboxyl compound}]$$

From the dissociation equilibria



eq 10 becomes

$$-d[P]_T/dt = k_2'[P]_T[D] \quad (14)$$

where

$$k_2' = k_5/f_5 + k_4/f_4 + k_3/f_3 \quad (15)$$

and

$$f_5 = 1 + \frac{K_1 \gamma_{H_5IO_6}}{a_{H^+} + \gamma_{H_4IO_6^-}} + \frac{K_1 K_D \gamma_{H_5IO_6}}{a_{H^+} + \gamma_{IO_4^-}} + \frac{K_1 K_2 \gamma_{H_5IO_6}}{a_{H^+} + \gamma_{H_3IO_6^{2-}}}$$

$$f_4 = \frac{a_{H^+} + \gamma_{H_4IO_6^-}}{K_1 \gamma_{H_5IO_6}} + 1 + \frac{K_D \gamma_{H_4IO_6^-}}{\gamma_{IO_4^-}} + \frac{K_2 \gamma_{H_4IO_6^-}}{a_{H^+} + \gamma_{H_3IO_6^{2-}}}$$

$$f_3 = \frac{a_{H^+} + \gamma_{H_3IO_6^{2-}}}{K_1 K_2 \gamma_{H_5IO_6}} + \frac{a_{H^+} + \gamma_{H_3IO_6^{2-}}}{K_2 \gamma_{H_4IO_6^-}} + \frac{a_{H^+} + K_D \gamma_{H_3IO_6^{2-}}}{K_2 \gamma_{IO_4^-}} + 1$$

In eq 14 and 15 k_2' is the observed pseudo-second-order rate constant (after extrapolation of the rate constants to zero buffer concentration), γ is the activity coefficient for the subscript species, and the other symbols have their usual significance. The hydrogen ion activity, a_{H^+} , was determined directly from pH measurements.

The values for k_5 , k_4 , and k_3 were determined (using the least-squares method on an IBM 1620 computer) from the k_2' values obtained over the pH range 0.9–5.5 using the values of Crouthamel, *et al.*,^{10,12} for the equilibrium constants¹³ and activity coefficients. The rate constants so determined, the thermodynamic parameters of activation for the reaction of $H_4IO_6^-$ and the dicarboxyl compounds, along with values for

(12) C. E. Crouthamel, A. M. Hayes, and D. S. Martin, *J. Am. Chem. Soc.*, **73**, 82 (1951).

(13) A recent paper [S. W. Weidman and E. T. Kaiser, *ibid.*, **88**, (5820) (1966)] gives a different value for K_2 .

the catalytic constant for acetate ion, k_{OAc} , are recorded in Table II. The thermodynamic quantities for the reactions of H_5IO_6 and $H_3IO_6^{2-}$ were not determined because of the lack of sufficient data at temperatures other than 26° in pH regions where these species predominate. Calculated (eq 15) and observed values for k_2' are shown in Figures 1–3. Each of the observed points is the mean value of at least three runs and in several cases as many as 10 runs. The agreement between the observed and calculated values of k_2' for pyruvaldehyde and 2,3-butanedione is considered excellent. The agreement in the case of glyoxal is less and is probably due to the experimental difficulty in following this fast reaction.

The rate constants (k_3) obtained for the reaction of bivalent periodate, $H_3IO_6^{2-}$, are the least reliable because of the very low concentration of this species in the pH range studied. Slight errors in pH lead to sizable errors in the concentration of this species. For example, at a pH of 5.47 an error of ± 0.01 pH unit will lead to an error of 3% in the concentration of $H_3IO_6^{2-}$ and only 0.008% in the univalent species.

Conclusion

The reaction of periodate with glyoxal, pyruvaldehyde, and 2,3-butanedione in the pH range 2.5–4.5 is a second-order process (or a limiting second-order process with an upper limit of 100 for the equilibrium constant for complex formation) with $H_4IO_6^-$ as the most likely reactive univalent species. It is important to note here that our data are insufficient to permit us to extend this kinetic assignment to the entire acid range.

Our conclusions concerning $H_4IO_6^-$ are based on several observations. First, if the reaction is a nucleophilic attack by periodate on the dicarboxyl compounds,⁶ then the velocities of the reactions by the various periodate species should be in the same order as their nucleophilicities (roughly paralleling their basicities), or $H_3IO_6^{2-} > H_4IO_6^-$ or $IO_4^- > H_5IO_6$. However, when IO_4^- is selected as the exclusive univalent reactant the rates follow the order $H_3IO_6^{2-} > H_5IO_6 > IO_4^-$. When $H_4IO_6^-$ is selected the expected order is obtained. Secondly, the temperature coefficients for the reactions by univalent species are very nearly zero,¹⁴ which may be explained by the fact that the equilibrium expressed in eq 12 shifts to the right with increase in temperature (K_D ranges from 22.7 at 16.4° to 96.4 at 38.9°). Very small activation energies are obtained when IO_4^- is considered as the univalent reactant¹⁵ while activation enthalpies of the order of 10

(14) For example, the observed over-all reaction rate at pH 3.4 increases only slightly over 23° ($16\text{--}39^\circ$), 13.0 to 17.4 for glyoxal, 7.33 to 7.92 for pyruvaldehyde, and 0.324 to 0.435 for 2,3-butanedione.

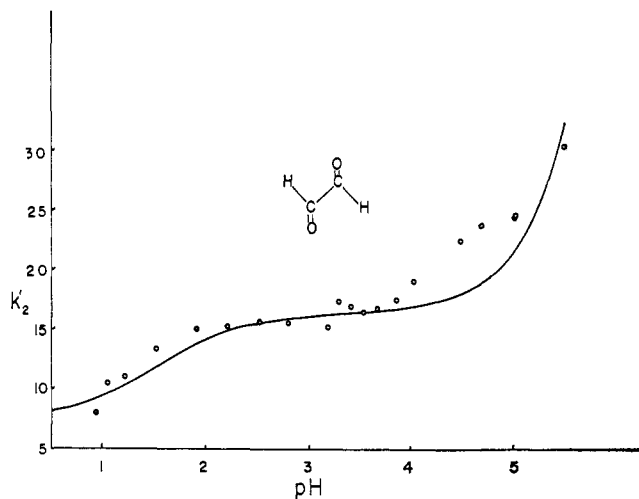


Figure 1. Glyoxal: variation of the pseudo-second-order rate constant with pH; temperature 26°, $\mu = 0.11$.

kcal/mole are obtained for $H_4IO_6^-$. In the periodate oxidation of 2,3-butanedione Shiner and Wasmuth⁶ observed a rate increase at 0° in going from pH 1 to 4, while at 22° they observed a rate decrease over the same pH range. They justified their selection of $H_4IO_6^-$ as the univalent reactant on the basis of a more nearly equal activation energy for the reactions of $H_4IO_6^-$ and H_5IO_6 than when IO_4^- was chosen (where the activation energy for IO_4^- was substantially smaller than that for H_5IO_6).

It can be seen from Table II that the rate constants for the reaction of $H_4IO_6^-$ (k_4) and $H_3IO_6^{2-}$ (k_3) with glyoxal are about twice those for the reaction of these species with pyruvaldehyde (7.14/3.30 and 4.99/2.99, respectively). Table II also shows that the constants for 2,3-butanedione oxidation are only a small fraction of the values for pyruvaldehyde. A possible explanation for this behavior is that the molecules are in the *s-trans* configuration and that reaction (attack on carbonyl carbon) occurs in essentially two directions of a single plane. In the case of glyoxal neither of these approaches is hindered significantly by hydrogen, whereas in pyruvaldehyde the single methyl group (factor of one-half), and in 2,3-butanedione the two methyl groups, shield the carbonyl carbon atoms. An equally plausible explanation can be based on the inductive influence of the methyl groups.

In both $H_4IO_6^-$ and $H_3IO_6^{2-}$ oxidations a decrease in rate with increase in substitution on the dicarbonyl compound is observed (Table II). Oxidation by H_5IO_6 exhibits an initial rate increase with the addition of one methyl group, followed by a decrease when the second methyl group is added. This same rate behavior

(15) As a matter of fact the activation energy may even become negative as in the periodate oxidation of 2-aminoethanol [G. Dahlgren and J. M. Hodsdon, *J. Phys. Chem.*, **68**, 416 (1964)]. In this case when $H_4IO_6^-$ is postulated as the reactant, instead of IO_4^- as reported, the activation energy becomes positive. Therefore, the prior equilibrium referred to by Dahlgren and Hodsdon is merely the equilibrium given in eq 12 of this work. The entropy of activation is also affected by the designation of $H_4IO_6^-$. In the 2-aminoethanol- IO_4^- case a questionably large negative entropy (-56 eu) was observed similar to that found for the cyclopentene glycol- IO_4^- series⁹ (-45 to -53 eu). Perhaps in these reactions entropy magnitudes are an indication of properly or improperly chosen kinetic reactants.

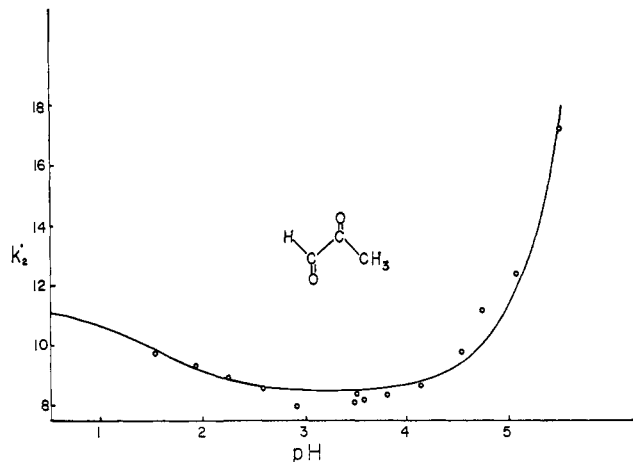


Figure 2. Pyruvaldehyde: variation of the pseudo-second-order rate constant with pH; temperature 26°, $\mu = 0.11$.

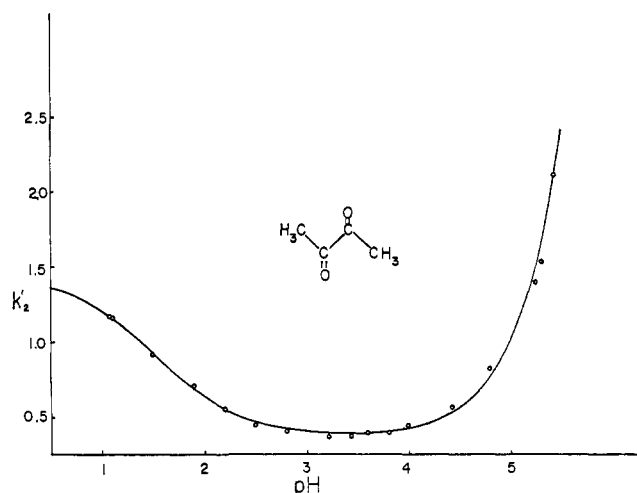


Figure 3. 2,3-Butanedione: variation of the pseudo-second-order rate constant with pH; temperature 26°, $\mu = 0.11$.

has been observed in the case of the lead tetraacetate oxidation of methyl-substituted *cis*-cyclohexanediol-1,2.¹⁶ Perhaps H_5IO_6 reacts by electrophilic attack of the carbonyl oxygen as might be expected for lead tetraacetate.

The role of buffer anions has not been studied extensively in this work. However, certain interesting observations warrant comment at this time. The fact that the constants for acetate catalysis and for $H_4IO_6^-$ oxidation vary in exactly the same fashion in going from glyoxal \rightarrow pyruvaldehyde \rightarrow 2,3-butanedione ($k_4/k_{OAc} = 3.1 \pm 0.1 M$) suggests that these substances are reacting in concert during some phase of the oxidation. The acetate ion may be involved with periodate in prior equilibria or perhaps its role is to function as a proton abstractor for the intermediate complex. Further work is contemplated in this area.

Since the mechanisms of the periodate oxidation of ethylene glycol and glyoxal appear to differ in kind, it was impossible to make valid comparisons between the two systems as originally planned.

(16) C. A. Bunton and M. D. Carr, *J. Chem. Soc.*, 770 (1963).