nated to the extent of 1% in the β-position, as determined by the isotopic dilution method.[12] By the use of the same technique, it was found that biphenyl affords 93.9 ± 2.4% of substitution in the 4-position.[13] With this information, and the usual statistical corrections, the partial rate factors, f_x, shown in the table, can be calculated. They are similar to those estimated for bromination in glacial acetic acid.[14]

The relative order of reactivities is one which might have been expected on general chemical grounds and which also agrees qualitatively with that predicted from the order of localization energies as calculated by the molecular-orbital method.[15] It is particularly noteworthy that the

(12) E. Berliner, F. J. Ochs and G. L. Zimmerman, J. Org. Chem., 23, 495 (1958).

(13) Unpublished results with G. L. Zimmerman and G. Pearson; from the senior honors thesis of Miss G. Pearson, 1959.

(14) P. B. D. de la Mare and J. H. Ridd, ref. 4b, pp. 157 and 176. The values for f_x, in the same order as in Table IV, are 1, 10^3, 3×10^2 and 10^5. Those for naphthalene utilize the data from ref. 12.

(15) M. J. S. Dewar, J. Am. Chem. Soc., 74, 3341 ff. (1952); M. J. S. Dewar in J. W. Cook, "Progress in Organic Chemistry," Vol. II, Academic Press, Inc., New York, N. Y., 1953, p. 1.

order 4-biphenyl > 2-naphthalene falls in the theoretical sequence, as it does in a variety of other reactions.[16] However, a plot of log f_x against $(N_0 - N_x)$, the so-called reactivity numbers,[17] though qualitatively correct, is by no means linear. Four compounds, to be sure, are not a sufficient number from which to draw any conclusions, but it seems that a better correlation is obtained when these partial rate factors are plotted against some other *measured* quantity, such as the rates of solvolysis of α-arylethyl chlorides.[18] A more detailed discussion will have to await the accumulation of more data.

(16) For a recent compilation of data see F. B. Deans, C. Eaborn and D. E. Webster, J. Chem. Soc., 3031 (1959); see also ref. 18.

(17) M. J. S. Dewar, T. Mole and E. W. T. Warford, J. Chem. Soc., 3581 (1956); also, the discussions in P. B. D. de la Mare and J. H. Ridd, ref. 4b, Chapters 13 and 17, and S. F. Mason, ref. 11.

(18) E. Berliner and N. Shieh, J. Am. Chem. Soc., 79, 3849 (1957).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE, NEWARK, DEL.]

Studies on the Mechanism of the Benzilic Acid Rearrangement; the Rearrangement of Alloxan (I)

BY HAROLD KWART AND ILYA M. SARASOHN[1]

Previous reports[15,16] on the alloxanic acid rearrangement had suggested that the reaction followed a simple course of rearrangement of the monoanion of alloxan (AH_3^{-1}). It is here shown that the reaction involves a more complex dependence on pH than hitherto elucidated, which suggests rearrangements not only in the monoanion but also the dianion (AH_2^{-2}) and trianion (AH^{-3}) (or its equivalent). The rate law based on this complex mechanism is derived and found to be in good agreement with the rate data. Rearrangements in AH_3^{-1} and AH_2^{-2} appear to be quite similar in character but decidedly different from the corresponding reaction in AH^{-3}, as judged by several kinetic criteria. For instance, general base catalysis is identified for AH^{-3} rearrangement but is absent in the cases of AH_2^{-2} and AH_3^{-1}. An unusual and exceedingly strong specific catalytic effect of borate buffer is demonstrated and its intensity characterized as a function of pH. The activation parameters of the borate-catalyzed, when compared to those of the hydroxide-catalyzed, rearrangement appear to indicate a cyclic intermediate is formed between substrate and borate monoanion as a preliminary to the rate-determining migration step. A discussion of these and other data is presented which arrives at the conclusions (i) that the driving force for both hydroxide ion and general base-catalyzed benzilic acid rearrangement is derived from a "*push*" on the migrating electron pair developed by electron pressure at the seat of reaction; and (ii) that the occurrence of specific ion catalysis of the rearrangement can be correlated with the presence of a reagent (such as borate) which can develop a "*pull*" on the migrating bond at the adjacent carbonyl center in concert with the relief of the electron pressures that are responsible for the "*push*."

Introduction

The familiar transformation of α-diketones by means of base to the salts of α-hydroxy acids is known as the "benzilic acid" rearrangement and is one of the oldest[2a] and most widely studied[2b] carbon–carbon bond cleavage reactions. Specific hydroxide ion catalysis of the cleavage in the parent compound, benzil, has been carefully documented in the work of Westheimer[3] and Roberts and Urey.[4] These authors established by a variety

(1) Part of this article is based on the thesis of I. M. Sarasohn submitted in partial fulfillment of the requirement of the Ph.D. degree at the University of Delaware, June, 1959. This material also was presented at the Meeting-in-miniature of the A.C.S. Delaware Valley Section, January, 1958.

(2) (a) J. von Liebig, Ann., 25, 27 (1838); (b) see, for examples, C. K. Ingold, Ann. Rep. on the Prog. Chem., 25, 124 (1928), and more recently M. M. Shemyakin and L. A. Shihukina, Quart. Revs., 10, 261 (1956).
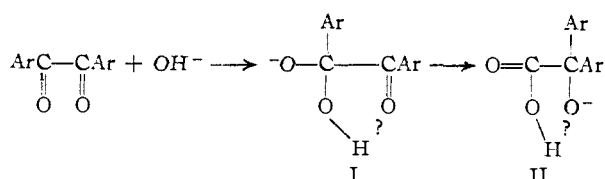
(3) F. H. Westheimer, J. Am. Chem. Soc., 58, 2209 (1936).

of rate[3] and tracer[4] studies the formation of an intermediate hydroxide ion adduct (I) of benzil. This intermediate had been isolated by Scheuing[5] and Lachman[6] and is capable of independent existence at lower temperatures in the absence of a polar medium.

The course of rearrangement proposed[3,4] as most consistent with these observations is also similar to one suggested earlier by Ingold[2b] and involved the rate-determining migration of an aryl group in the adduct I according to the indicated course resulting in II. Recently Hine and Haworth,[7] by means of rate studies in D_2O media, have eliminated the occurrence of a concerted participation of the conjugate acid with proton trans-

(4) I. Roberts and H. C. Urey, ibid., 60, 880 (1938).

(5) G. Scheuing, Ber., 56, 252 (1923).

(6) A. Lachman, J. Am. Chem. Soc., 45, 1509 (1923).

(7) J. Hine and R. D. Haworth, ibid., 80, 2274 (1958).

$$\text{ArC—CAr} + OH^- \longrightarrow \overset{Ar}{\underset{\overset{|}{O}}{\text{O—C}}}\text{—CAr} \longrightarrow \overset{Ar}{\underset{\overset{|}{O}}{\text{O=C}}}\text{—CAr}$$

I   II

fer in this transition state (as indicated by the ? symbol in the representation above).

The catalytic specificity previously noted[3-6] is made somewhat more understandable by the results of Doering and Urban[8] on the closely related benzilic ester rearrangement. Again, it was demonstrated that reaction occurs *via* initial attack by alkoxide ion on one of the benzil carbonyls with formation of an adduct analogous to I, followed by rate-determining rearrangement. Carbon–carbon cleavage, however, can only be observed in benzils *via* anions which are sufficiently basic to carry out the initial attack and create the intermediate adduct I. Weaker bases such as phenoxides[3] fail, presumably for lack of this capacity.

The source of driving force for the benzilic acid rearrangement is still largely undetermined. In the current view of the reaction mechanism, it cannot be decided whether the migration derives from the "*push*" of the migrating group from the electron-dense centers of the adduct or the "*pull*" from the residual electron-deficient carbonyl. The observations of Clark, Hendley and Neville[9] and of Roberts, Smith and Lee[10] establishing that the aryl ring substituted with electron-attracting groups migrates (preferentially) in the same order of ease as found for the rearrangement of unsymmetrical pinacols[11] and in the reverse order of that found for symmetrical pinacols[12] have received widely different interpretations.[9,10] These discussions have in fact suggested a possible doubt[9] as to the nature of the transition state and leave open to question that the intermediate I lies athwart the rearrangement path. Indeed, the preliminary reversible addition of hydroxide ion may constitute a parasitic equilibrium that explains only the O^{18} exchange between benzil and water.

In the interests of elucidating the driving forces of this and related $-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-$ bond cleavage reactions, we undertook to study the rearrangement of alloxan, one of the first "benzilic acid type" changes to be characterized by Liebig[1,13] and later by Biltz and co-workers.[14] Here the adduct III,

III   IV
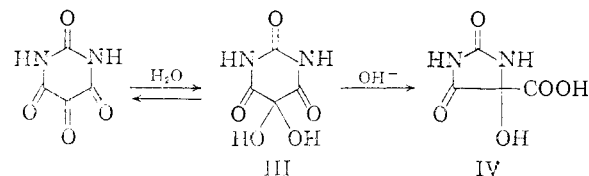
(8) W. von E. Doering and R. S. Urban, *J. Am. Chem. Soc.*, **78**, 5938 (1956); see, however, G. Swan, *J. Chem. Soc.*, 1408 (1948).

(9) M. T. Clarke, E. C. Hendley and O. K. Neville, *J. Am. Chem. Soc.*, **77**, 3280 (1955).

(10) J. D. Roberts, D. R. Smith and C. C. Lee, *ibid.*, **73**, 619 (1951).

(11) W. E. Bachmann and H. Sternberger, *ibid.*, **56**, 2081 (1934).

(12) W. E. Bachmann and F. H. Mosher, *ibid.*, **54**, 1134 (1932).

(13) F. Wöhler and J. von Liebig, *Ann.*, **26**, 241 (1838).

analogous to the Roberts and Urey intermediate I, represents the most stable form of the reagent in aqueous solution. The reaction occurs forming alloxanic acid (IV) with the great ease characteristic of the migration of all electron-attracting groups[9,10] in the benzilic acid rearrangement.

Previous Work on the Mechanism of Alloxan Rearrangement.—The formation of alloxanic acid has been followed kinetically by Richardson and Cannon.[15] They concluded that the rate constant is a linear function of the first acid constant of alloxan. More recently, Patterson, Lazarow and Levey[16] reinvestigated the kinetics of rearrangement using a spectrophotometric technique. The conclusion of the earlier workers was reaffirmed by their report that the velocity of reaction was first order in alloxan and that the decomposition of III is achieved by ionization of the first proton in alloxan (which was adduced to be a dibasic acid,[15] pK_a^1 7.20, pK_a^2 10).

A linear relation between log k_{obsd} and pH with unit slope would evidently be predicted for a rate-determining rearrangement of the monoanion of alloxan (assuming that only a small fraction of the initial concentration of alloxan is ionized). However, closer scrutiny of the actual data[15,16] reveals that this relationship is only approximately linear in the pH range 6.0–7.5 and the rate approaches almost pH independence between approximately 8.0 and 11.0 (see Fig. 1). We were of the opinion that this result could also be explained as a limitation on the ability of the oxidation–reduction electrode to follow the exceedingly fast rates while handicapped by slow attainment of electrode equilibrium and irreversible electrode side reactions in the strongly alkaline range. Clearly, the earlier kinetic conclusions[15,16] are subject to doubts that could only be resolved by pursuing the reaction by a variety of methods and this premise was the basis of the present report.

Results and Discussion

Kinetic results obtained by three independent methods, spectrophotometric, titrimetric and pH-static (see Experimental), showed good consistency over a pH range of approximately 6 to 14. This eliminated the doubts which arise in connection with the Richardson and Cannon data[15] with respect to the adequacy of the method of following the rapid rates of reaction encountered at higher pH values.

A. Alloxan and Hydroxide Ion.—The reaction between hydroxide ion and alloxan at constant pH was found to be first order in alloxan by all methods of reaction investigated. This is typically illustrated by the differential plot of the change in optical density (disappearance of alloxan) with time (Fig. 2), as well as by the plot in Fig. 3 of the same raw data processed by the Guggenheim method.[17] The first-order relationship in titrimetric data is almost identical.

The rate–pH profile for all runs (pH 6.0–13.5) is plotted on Fig. 1 for comparison with the

(14) M. Biltz, M. Heyn and M. Bergius, *ibid.*, **413**, 68 (1916).

(15) G. M. Richardson and R. K. Cannon, *Biochem. J.*, **23**, 68 (1928).

(16) J. W. Patterson, A. Lazarow and S. Levey, *J. Biol. Chem.*, **177**, 187 (1949).

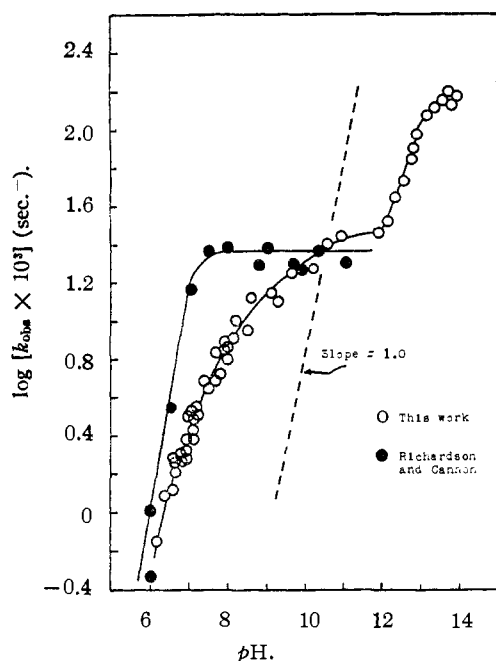(17) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

Fig. 1.—pH–rate profile: alloxanic acid rearrangement with hydroxide ion catalysis.
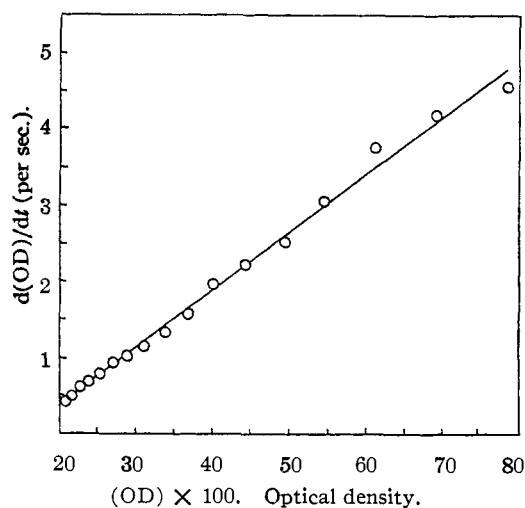

Fig. 2.—Typical differential plot: alloxan in KOH.

data of Richardson and Cannon. It is very apparent that our results do not agree with the picture inferred by these authors; for one, the slope is never unity as required for a simple mechanism of rearrangement of alloxan monoanion; for another, the slope of rate *vs.* pH is changing almost continuously with pH. Evidently, at any given pH several different anionic species may undergo rearrangement, judging from the complex dependence of the rate on hydroxide ion concentration.

One apparently suitable basis for understanding these results may be inferred from the fact that alloxan is a polybasic acid[15] which is able to develop at least three and possibly as many as four conjugate base functions with increasing concentrations of hydroxide ion. The anions resulting from successive interactions with hydroxide ion may be formed either through proton transfer to the hy-
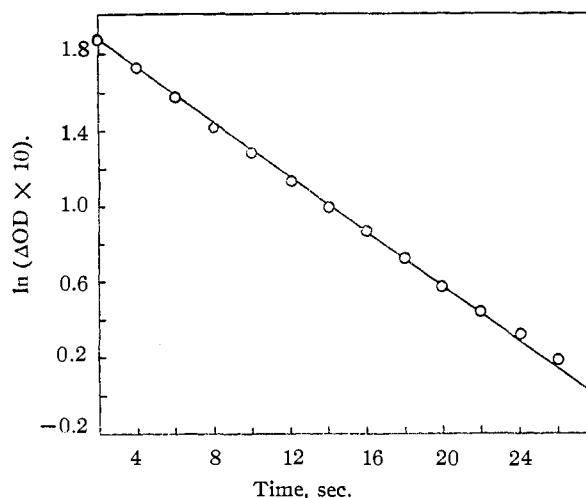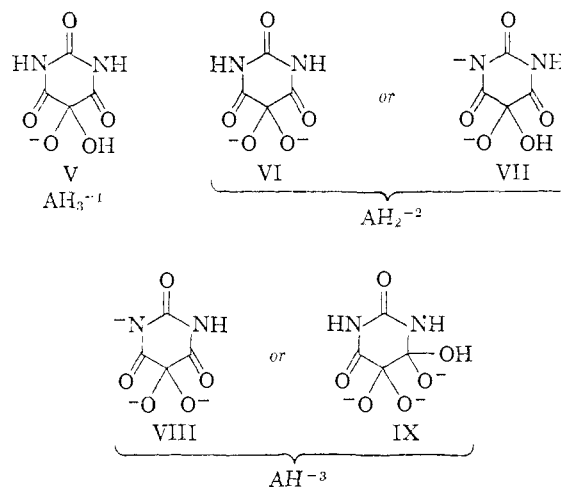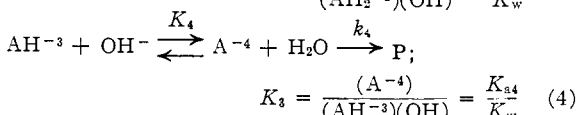

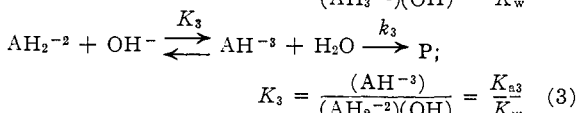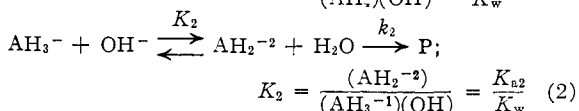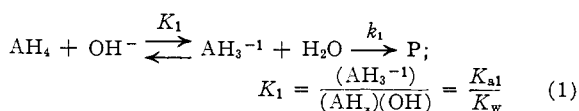Fig. 3.—Typical Guggenheim plot: alloxan in KOH.

droxide ion (alloxan possesses four such potential acid functions), or *via* hydroxide ion attack at a carbonyl center to produce an anionic adduct analogous to I. Some of the possible structures for the mono (AH_3^{-1}), di (AH_2^{-2}) and tri (AH^{-3}) anions are

In theory, the ability of any of these structures to undergo the electron displacements that occur in the "benzilic acid" change can be readily demonstrated.

B. The Rate Law.—We assumed, first, that each of the loops in the rate–pH profile (Fig. 1) approximately correlates with the rearrangement of a different ionic species or combinations of such species present in solution. We have designated the product as P; K_1, K_2, K_3, K_4 as the apparent equilibrium constants for reaction with hydroxide ion; K_{a1}, K_{a2}, K_{a3}, K_{a4} the corresponding apparent acid dissociation constants of the respective substances undergoing either proton transfer or the equivalent hydroxide ion acceptance; K_w as the autoprotolysis constant for water; and k_1, k_2, k_3, k_4 as the specific rate constants for the processes indicated in the rate equations (1) to (5).

The observed rate constant will then be a summation term composed of four concentration terms and four corresponding rate constants, assuming,

$$AH_4 + OH^- \underset{\longleftarrow}{\overset{K_1}{\rightleftharpoons}} AH_3^{-1} + H_2O \overset{k_1}{\longrightarrow} P;$$

$$K_1 = \frac{(AH_3^{-1})}{(AH_4)(OH)} = \frac{K_{a1}}{K_w} \quad (1)$$

$$AH_3^- + OH^- \underset{\longleftarrow}{\overset{K_2}{\rightleftharpoons}} AH_2^{-2} + H_2O \overset{k_2}{\longrightarrow} P;$$

$$K_2 = \frac{(AH_2^{-2})}{(AH_3^{-1})(OH)} = \frac{K_{a2}}{K_w} \quad (2)$$

$$AH_2^{-2} + OH^- \underset{\longleftarrow}{\overset{K_3}{\rightleftharpoons}} AH^{-3} + H_2O \overset{k_3}{\longrightarrow} P;$$

$$K_3 = \frac{(AH^{-3})}{(AH_2^{-2})(OH)} = \frac{K_{a3}}{K_w} \quad (3)$$

$$AH^{-3} + OH^- \underset{\longleftarrow}{\overset{K_4}{\rightleftharpoons}} A^{-4} + H_2O \overset{k_4}{\longrightarrow} P;$$

$$K_3 = \frac{(A^{-4})}{(AH^{-3})(OH)} = \frac{K_{a4}}{K_w} \quad (4)$$

Observed rate =
$$k_1(AH_3^{-1}) + k_2(AH_2^{-2}) + k_3(AH^{-3}) + k_4(AH^{-4}) \quad (5)$$

as usual, that all the equilibrium steps are very fast compared to subsequent reactions. Apparently, the final term involving the tetravalent anion is not realized in the pH region investigated thus far.

By means of certain approximations one can arrive at a very useful estimate of the magnitudes of the parameters of eq. 5 and the equilibrium constants of equations 1–4. These approximations are discussed in some detail in the appendix.

It is also possible to express the over-all rate in all pH ranges below 13.5 (with no approximations) on the basis of this assumed mechanism

$$\frac{dP}{dt} = \frac{d(AH_3^{-1} + AH_2^{-2} + AH^{-3} + AH_4)}{dt} =$$
$$k_1(AH_3^-) + k_2(AH_2^{-2}) + k_3(AH^{-3}) \quad (30)$$

$$(AH_4)_0 - (P) = (AH_4) +$$
$$(AH_3^{-1}) + (AH_2^{-2}) + (AH^{-3}) \text{ (mass balance)} \quad (31)$$

Substitution in eq. 30 for (AH_3^{-1}) from eq. 2 and (AH^{-3}) from eq. 3 gives the result (when properly factored)

$$\frac{dP}{dt} = \frac{k_1}{K_2 (OH)} + k_2 + k_3 K_3 (OH)(AH_2^{-2}) \quad (32)$$

Substituting for (AH_4) from eq. 1, (AH_3^{-1}) from eq. 2 and (AH^{-3}) from eq. 3 into eq. 31 yields, finally

$$[(AH_4)_0 - (P)] = \frac{(AH_2^{-2})}{K_1K_2(OH)^2} + \frac{(AH_2^{-2})}{K_2(OH)} +$$
$$(AH_2^{-2}) + K_3(AH_2^{-2})(OH) \quad (33)$$

Factoring out and solving for (AH_2^{-2}) and then substituting into eq. 32 gives successively

$$\frac{dP}{dt} = \left[\frac{k_1}{K_2(OH)} + k_2 + k_3K_3(OH) \right]$$
$$\left[\frac{(AH_4)_0 - (P)}{\frac{1}{K_1K_2(OH)^2} + \frac{1}{K_2(OH)} + 1 + K_3(OH)} \right] \quad (34)$$

and

$$[(AH_4)_0 - (P)]^{-1} \frac{dP}{dt} = \left[\frac{k_1 + k_2K_2(OH) + k_3K_2K_3(OH)^2}{K_2(OH)} \right]$$
$$\left[\frac{K_1K_2(OH)^2}{1 + K_1(OH) + K_1K_2(OH)^2 + K_1K_2K_3(OH)^3} \right] \quad (35)$$

Integration of eq. 35 produces directly

$$- \ln [(AH_4)_0 - (P)] =$$
$$\left[\frac{k_1K_1(OH) + k_2K_1K_2(OH)^2 + k_3K_1K_2K_3(OH)^3}{1 + K_1(OH) + K_1K_2(OH)^2 + K_1K_2K_3(OH)^3} \right] t + C \quad (36)$$

Invoking boundary conditions, solving for the constant of integration, and substituting gives

$$\frac{1}{t} \ln \left[\frac{(AH_4)_0}{(AH_4)_0 - (P)} \right] = k_{obsd} \quad (37)$$

where

$$k_{obsd} = \frac{k_1K_1(OH) + k_2K_1K_2(OH)^2 + k_3K_1K_2K_3(OH)^3}{1 + K_1(OH) + K_1K_2(OH)^2 + K_1K_2K_3(OH)^3} \quad (38)$$

The raw data were plotted and the best smooth line through the points was drawn. Points were picked off the plot every 0.2 pH unit and fed into the Bendix G-15 computer to solve for the parameters in eq. 38. The solution of eq. 38 was given such that the sum of the squares of the differences of the logarithms was minimized. Figure 1 shows the experimental points. The values of the points corresponding to the computer solution determine the curved line drawn in Fig. 1. Table I shows a comparison of the parameter values from the "approximation" calculations and computer solution.

TABLE I

A COMPARISON OF APPROXIMATION AND COMPUTER DETERMINED PARAMETERS

Parameter	Approximation	Computer
k_1	0.00358	0.00329
pK_{a1}	6.66	6.61
k_2	0.0192	0.0189
pK_{a2}	8.59	8.43
k_3	0.181	0.218
pK_{a3}	12.9	13.1

The values of the "approximation" parameters are in good agreement with those calculated by the computer and indicate both that the preceding approximations and the rate law expressed by eq. 38 are reasonable. It is also indicated that with reference to the data on the tail end of the curve (pH 13–14) the agreement between computed and experimental points falls off somewhat. These last four values were not included in the data fed to the computer because the spectrophotometer response time probably becomes significant in these very rapid reactions ($t_{1/2}$ = 7 seconds). These points are presently being re-evaluated and the pH range of investigation extended as well, by means of a stop-flow technique of kinetic measurement. Such results as are obtained will be reported in another concentration in a future publication from these laboratories.

While the value of pK_{a1} is in fair agreement with the various literature values (6.63,[18] 6.8–7.2,[16] 7.20[15]) the value of pK_{a2} is somewhat below that of ref. 15 which reports pK_{a2} = 10 by measurement of the pH of the (supposedly) half-neutralized reacting solution. From the data reported herein for the reacting solution the value of k_{obsd} at pH 10 is 0.0186 sec.$^{-1}$, corresponding to a half-life of 37.3 seconds. It would seem that attainment of electrode equilibrium in the experiment of R and C[15] is hardly possible in a system reacting this rapidly.

C. **The Neutral Salt Effect and General Base Catalysis.**—The Brönsted "kinetic salt" equation[19]

(18) J. K. Wood, *J. Chem. Soc.*, **89**, 1836 (1906).

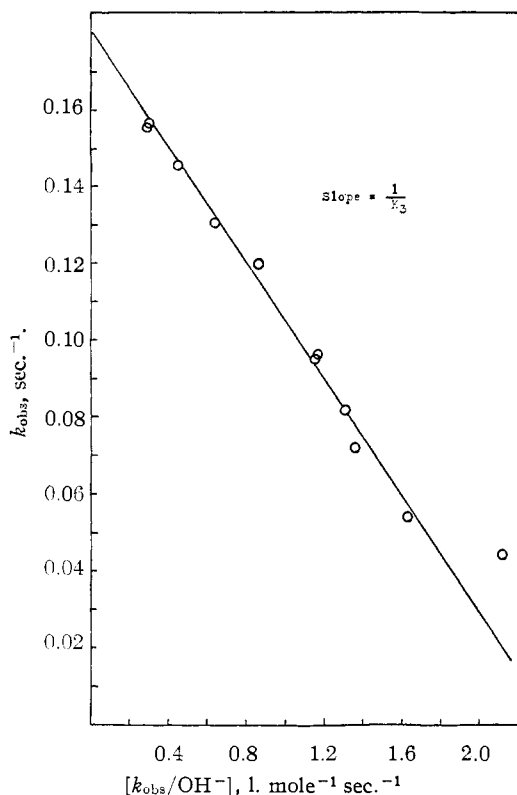(19) J. N. Brönsted, *Z. physik. Chem.*, **102**, 169 (1922); **115**, 337 (1925).

Fig. 4.—Data processed for equation 29.

predicts a linear relationship between log k_{obsd} and $\mu^{1/2}$. The validity of this relationship has been demonstrated in numerous cases.[20] The absence of a neutral salt effect of this nature would suggest, then, the absence of ionic interaction in the transition state. Tables II and III summarize the data on rate as a function of μ in the low and intermediate pH ranges 6.87 and 9.56, respectively. Clearly, the observed rate is independent of the

TABLE II

NEUTRAL SALT EFFECT IN THE LOW pH RANGE

Alloxan = 5.93×10^{-4} M, $(NaH_2PO_4)_0$ = 0.1997 M, pH 6.87 ± 0.03 (actually measured by glass electrode)

NaCl, g./25 ml.	k_{obs}, sec.
0	0.00214
0.0176	.00190
.0283	.00203
.0449	.00193
.0607	.00206
.1004	.00202
Av.	0.00201 ± 0.00007

TABLE III

NEUTRAL SALT EFFECT IN THE INTERMEDIATE pH RANGE

Alloxan = 4.91×10^{-3} M, $(NaH_2PO_4 + Na_2HPO_4)$ = 0.1000 M, pH 9.56 ± 0.02 (actually measured by glass electrode)

NaCl, mole/l.	k_{obs}, sec.
0	0.0189
0.0500	.0178
.1333	.0193
.2000	.0192
Av.	0.01888 ± 0.0005

(20) V. K. LaMer, Chem. Revs., 10, 179 (1932).
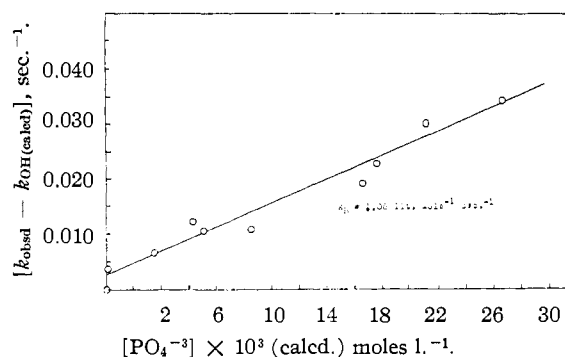
Fig. 5.—Phosphate ion (PO_4^{-3}) catalysis of alloxan.

ionic strength from μ = 0.2 to 0.4 (roughly the working concentrations of the buffer systems).

Both the nature and identity of response of the rates to added neutral salts in the low and intermediate pH range would support the mechanistic inference of unimolecular rearrangement (k_1 and k_2) of anions formed by rapid establishment of proton transfer equilibria (K_1 and K_2). At pH 11.00, however, a small positive salt effect is noted in the ionic strength range 0.0677 to 0.421, the slope of the line describing the relation between log k_{obs} and $\mu^{1/2}$ being only 0.28. Though this influence of neutral salt on the rate is far less than one could have expected for a transition state involving ionic interactions, there are many factors that might contrive to reduce the magnitude of the effect.[21] Suffice to mention here that the transition state for the rearrangement in the higher pH region is somewhat different from that of the low and intermediate cases. The nature of these differences is corroborated by the studies of general base catalysis of the several rearrangements.

Thus, if a rapid preliminary proton transfer equilibrium occurs prior to the rate-determining rearrangement, the absence of general base catalysis would be predicted. This is confirmed for the rearrangement reaction in both the low and intermediate pH range as demonstrated by the observation that the rates in $H_2PO_4^-/HPO_4^=$ buffers below pH 11.0 fall on the same line as do the specific hydroxide-catalyzed rates. In addition, the data on Table IV show that the observed rates in these buffers is independent of the buffer concentration at constant buffer ratio.

On the other hand, the appearance of general base catalysis must be regarded as indicative of the participation of hydroxide ion and other bases in the rate-determining step of the rearrangement. This occurrence is strongly manifested in phosphate buffer catalysis only in the neighborhood of pH 11.0, in contrast to the absence of such catalysis (as demonstrated above) for the pH region of lesser basicity. Figure 5 represents the familiar plot which is characteristic of general base catalysis, where the difference between the observed rate term and that due to hydroxide ion alone is linear with the calculated concentration of PO_4^{-3}. Scatter is undoubtedly due to the difficulties in obtaining an accurate measure of the hydroxide ion activity

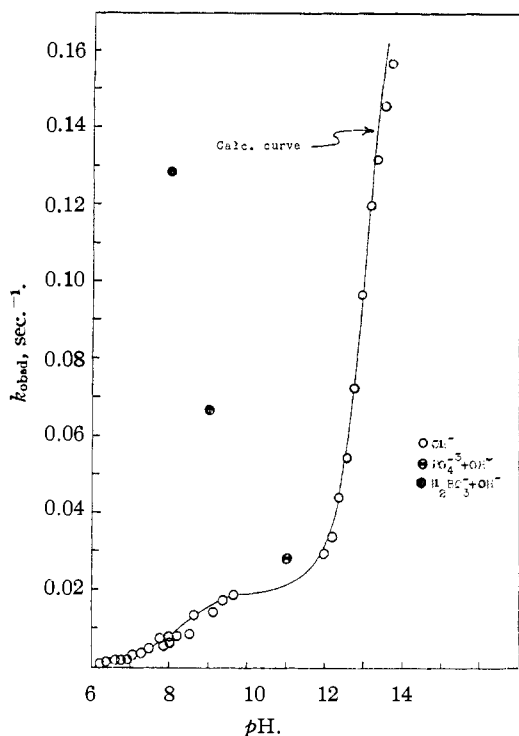(21) See for a full discussion and examples, A. R. Olson and T. R. Simonson, J. Chem. Phys., 17, 1167 (1949).

Fig. 6.—A comparison of experimental points with computer values.

corresponding to the various PO_4^{-3} concentrations. The fact that the line in Fig. 5 does not pass through the origin, therefore, is attributed to imprecision in measurement rather than to mechanistic significance.

TABLE IV

THE INDEPENDENCE OF THE RATE OF THE CONCENTRATION OF PHOSPHATE BUFFERS AT pH 7.06

Alloxan = 4.67×10^{-3} M, pH 7.06 ± 0.04

$(H_2PO_4^- + HPO_4^-)$, M	k_{obs}, sec.
0.09949	0.00319
.07879	.00329
.06566	.00307
.04596	.00317
.03283	.00319
Av.	0.00318 ± 0.00005

TABLE V

PHOSPHATE (PO_4^{-3}) CATALYSIS OF REARRANGEMENT

Initial alloxan = 5.06×10^{-3} M, $Na_2HPO_4 + Na_3PO_4 = 0.125$ M

pH	$10^2 (PO_4^{-3})^a$	k_{obs}, sec. $^{-1}$	$\dfrac{(k_{obs} - k_{OH}(OH)^-)}$
9.35	0.001	0.0172	0.000
9.51	.019	.0214	.0036
10.88	.345	.0264	.0066
11.19	.714	.0314	.0107
11.39	1.05	.0326	.0110
11.59	1.95	.0457	.0230
11.68	2.31	.0540	.0305
11.92	2.86	.0609	.0343

^{a} pK_a of phosphoric acid taken as 12.32.[22]

The fact that we do observe linearity of the rate with increasing (PO_4^{-3}), despite the obvious varia-

(22) Lange's "Handbook of Chemistry," 9th ed., Handbook Publishers, Sandusky, Ohio, 1956, p. 1201.
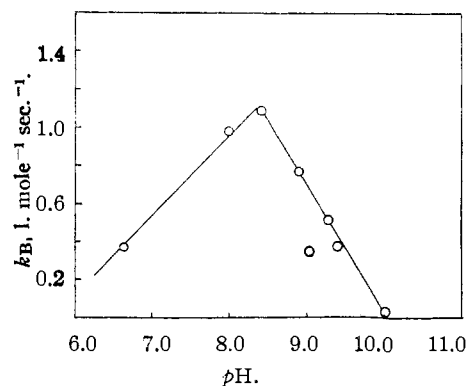

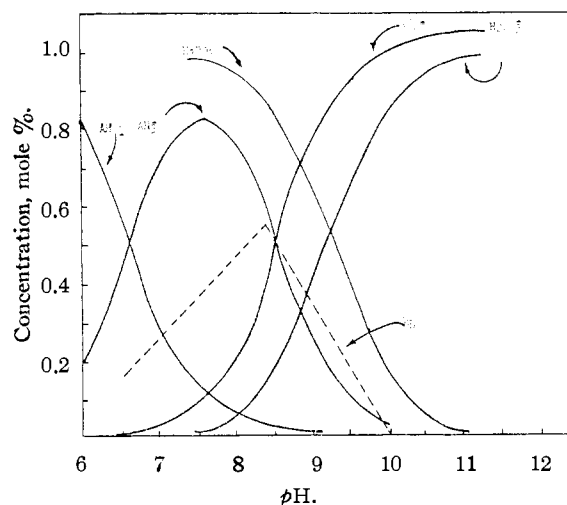Fig. 7.—Catalytic effect of borate buffers in alloxanic acid rearrangement.

Fig. 8.—Relative concentrations of reagents compared to borate catalytic coefficients as a function of pH.

tion of the (AH_2^{-3}) and (AH^{-3}) that occurs in the region of pH 9.5 to 11.8 (Table V) might be correlated with the mechanism of catalysis. It is clearly evident that only the strongest bases can react in the rate-determining step by which the rearrangement takes place in this pH range. The linearity observed here has been taken tentatively to indicate that the PO_4^{-3} reacts almost equally well with AH_2^{-2} and AH^{-3} whereas the hydroxide ion reaction is faster with AH^{-3} (see Table I). Verification of this awaits the outcome of studies in progress in the pH range beyond 13.0 where rate studies are attainable only by application of special techniques.

D. Specific Ion Catalysis by Borate.—A remarkable catalytic effect of boric acid–sodium borate buffers is observed in the rearrangement of alloxan in the pH range of ca. 6–10. Figure 6 affords appreciation at a glance of the magnitude of this effect by comparison with the effect of PO_4^{-3} ion at similar concentrations of the catalytic species.

The variation of the catalytic coefficient of borate catalysis (k_B) with pH as summarized in Table VI and plotted in Fig. 7 follows an interesting bell-shaped characteristic. Figure 8 displays this characteristic (dotted line) when plotted for comparison with the variation of concentration of

the several ionic species as a function of pH. This suggests that the catalytic activity may indeed correspond to the possibility for interaction of several different types of charged or neutral species in solution; for examples, H_3BO_3 and AH_2^{-2}, $H_2BO_3^-$ and AH_3^{-1}. In any event it is apparent that catalysis by borate buffer cannot be designated as "general base"[12] and does not derive from the same property that accounts for PO_4^{-3} catalysis. Rather it represents a specific interaction between borate buffer and substrate that is unrelated to the basicity of the catalyst and is of much greater magnitude than is observed for a general base catalysis.

TABLE VI

VARIATION OF BORATE CATALYSIS WITH pH

pH	k_B,[a] l. mole^{-1} sec.$^{-1}$
6.65	0.365
8.42	1.08
8.50	0.982
8.88	.760
9.03	.334
9.26	.510
9.40	.308
10.02	.026

[a] $k_B = \dfrac{k_{obs} - k_{OH}(OH^-)}{(H_3BO_3) + (H_2BO_3^-)}$.

In all likelihood the special activity of borate in catalyzing rearrangement here is related to the complex-forming abilities with vicinal diols and acyloins and the rapid rate of replacement of such ligands in the coördination sphere of borate.[23] The mechanistic possibilities by which catalysis by borate is effected will be discussed in an ensuing section of this report.

E. The Activation Parameters.—The rates as a function of temperatures in the range 20–42° were determined for both the hydroxide- and borate-catalyzed cases, where the activation parameters reflected the most widely different mechanisms of rearrangement that could result from variation of reaction conditions. The heats of activation were calculated from the familiar Arrhenius and the entropies of activation from the Eyring equation.[24] These results have been summarized in Table VII, where all symbols have their usual significance and units.[24]

TABLE VII

ACTIVATION PARAMETERS FOR ALLOXAN REARRANGEMENT

Catalyst	pH	ΔH^*	ΔS^*	$\Delta(\Delta S^*)$
Hydroxide ion	9.60	15.1	−16.7	−11.7
Borate	9.40	11.6	−28.4	

The most striking difference between the two cases is noted in the activation entropy terms. Since the more negative ΔS^* values are interpreted[24] usually to indicate a substrate experiencing loss in the number of degrees of freedom in rising to the transition state configuration, a likely explanation of the role played by borate in catalysis of the

(23) (a) J. O. Edwards, G. C. Morrison, V. F. Ross and J. W. Schultz, *J. Am. Chem. Soc.*, **77**, 266 (1955); (b) J. O. Edwards, *J. Chem. Ed.*, **31**, 270 (1954).

(24) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," 1st ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 14.

rearrangement is at hand. Thus, the transition state complex for borate catalysis must involve some highly ordered arrangement of the borate relative to the reacting centers in alloxan, suggesting, once again, some form of cyclization between borate and the vicinal diol or acyloin centers in alloxan.

The Mechanisms of Rearrangement. A. Rearrangement of AH_3^{-1} and AH_2^{-3}.—The structure of the respective anions formed *via* the rapid interaction of alloxan with two hydroxide ions (in the pH range below 8) is, of course, of the utmost interest for the mechanism of rearrangement. We have selected structures V and VI as most consistent with the available evidence (as follows).

Diphenyl triketone (monohydrate) (X) undergoes a rearrangement analogous to the alloxanic acid rearrangement in alkaline medium yielding benzoylmandelic acid. The reaction takes place at a significant rate at pH 6.0 and at pH 7.0 and has almost the same rate as the alloxanic acid rearrangement.[25] We infer, consequently, that the acidic dissociation of X at pH values below *ca.* 7.0 is quite similar in nature to that of alloxan in the same pH region. The anion XI and AH_3^{-1} are thus structurally similar conjugate bases and V is a satisfactory representation of AH_3^{-1}.

X ⇌ XI
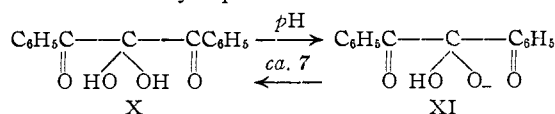
Dialuric acid (XII) is obtained from alloxan by a reduction in which one of the −OH groups is replaced by hydrogen. This hydrogen is the seat of the acidity in dialuric acid that has been characterized[26] by a pK_a value of 2.8. The protons on the nitrogen in the hybrid anion XIII are not readily

XII   XIII   etc.
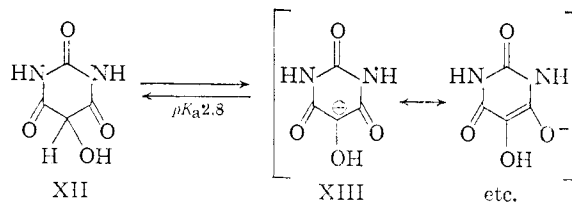
ionized; the associated pK_a values are greater than 11.0.[27] There is no apparent structural feature which would induce greater acidity associated with the protons on the nitrogen atoms in alloxan (III). Consequently, the most reasonable structure for the dianion AH_2^{-2} is represented by VI rather than VII. Dioxydianion structures such as VI are not unprecedented. Analogous intermediates have often been invoked in interpretations of the course of hydroxide ion and base-catalyzed cleavage reactions.[28]

(25) Unpublished results from these laboratories which will be discussed in a forthcoming article. See also R. de Neufville and H. von Pechmann, *Ber.*, **23**, 3375 (1890).

(26) G. Sartori and A. Liberti, *Atti Accad. naz. Lincei*, **1**, 94 (1946), as well as ref. 15.

(27) See ref. 16, p. 195, and references cited therein.

(28) (a) R. G. Pearson and E. A. Mayerle, *J. Am. Chem. Soc.*, **73**, 926 (1951); (b) R. G. Pearson and R. L. Dillon, *ibid.*, **70**, 1933 (1948); (c) C. Gustafson and M. Johanson, *Acta Chem. Scand.*, **2**, 42 (1948); (d) R. G. Pearson, D. H. Anderson and L. L. Alt, *J. Am. Chem. Soc.*, **77**, 527 (1955); (e) S. S. Biechler and R. W. Taft, Jr., *ibid.*, **79**, 4927 (1957).

Another line of evidence supporting the assignment of the dioxydianion structure VI is the similarity in kinetic behavior of AH_3^{-1} and AH_2^{-2}. Both rearrangements have been shown above to occur without salt effect or general base catalysis; in other words the ionization of the proton is not activation controlled, a property which is generally characteristic of oxygen–hydrogen bonds.[29] The subsequent rearrangement steps which have been shown above to occur (at higher pH) with general base catalysis obviously involve activation controlled proton transfer reactions.

The driving force of the alloxanic acid rearrangement can be perceived at once by comparing the rate constants for rearrangements of AH_3^{-1} and AH_2^{-2} (see Table I). The factor of about 6 which distinguishes the greater rearrangement facility of AH_2^{-2} can be said to arise from the greater electron pressure in the dianion. The tendency for delocalization of the bonding pair in the transition state is derived from a "*push*" and thereby a release of electron pressure (by transfer to a nearby receptor carbonyl center and formation of the resonance stabilized carboxylate anion).
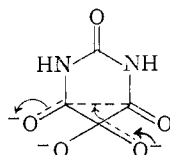
Transition State for AH_2^{-2} Rearrangement.—
The greater ease with which this reaction occurs in alloxan as compared to benzil is also partly attributable to the greater electron transport capacity of the displaced (—N—C=O) group vs. phenyl. These conclusions are clearly in harmony with the views of Clark, Hendley and Neville[9] on the mechanism of the benzilic acid rearrangement. These authors suggested that (in benzil) rearrangement accompanied the development of electron pressure as hydroxide ion approached the seat of reaction *in the transition state*. Although hydroxide ion is not directly involved in the transition state for AH_3^{-1} and AH_2^{-2} rearrangement, the same kind of forces appear to be at work in bringing about bond delocalization.

Hammond[30] has advanced the explanation that the greater migratory aptitude of electron-withdrawing groups in the benzilic acid rearrangement is attributable to the fact that the transition state resembles the unstable intermediate complex anion which is formed preferentially at the most electrophilic carbonyl. Clearly, however, this explanation does not suffice for α-triketone hydrates like alloxan or diphenyl-triketone where (i) the intermediate anion is more stable than in benzil, and (ii) where the migrating group in the transition state is of much more electron-withdrawing character, while the ease of migration is clearly much greater than in benzil. Furthermore, in terms of this[30] interpretation there is no explanation or basis for prediction of the observed greater rate of rearrangement as-

sociated with the anions of higher negative charge.

B. Borate Catalysis.—There are many alternative formulations of the mechanism of catalysis of the alloxanic acid rearrangement by borate buffer. However, if we assume that the data illustrated in Fig. 8 support a mechanism in which the monoborate anion,[23] ($B(OH)_4^-$ or H_2BO_3), and AH_3^{-1} are implicated, the following formulation appears to be very attractive. The complex XIV is the result of the very rapid interaction[23] of these anions and its stability may be assumed from the report by Moeller[31] on similar complexes between α-hydroxy-ketones and borate. The complex XIV
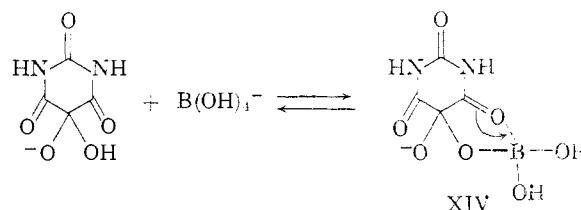
should rearrange much more readily than AH_3^{-1} with which it is in equilibrium. Coördination of the nearby carbonyl oxygen by the electrophilic boron introduces the feature which is not apparent in the rearrangement of AH_3^{-1}, namely, a "*pull*" on the migrating bonding pair *via* Lewis acid catalysis at the receptor carbonyl to coördinate with the "*push*" due to the comparatively undiminished electron pressure at the seat of reaction.

We have also examined the possibility of borate ion catalysis of benzil rearrangement in the presence of hydroxide ion. Table VIII summarizes these results. We observe here that borate not only fails to catalyze the rearrangement of benzil, it actually inhibits the normal hydroxide-catalyzed reaction.

TABLE VIII

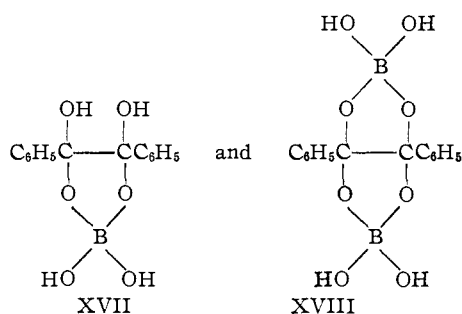ANION EFFECTS IN THE REARRANGEMENT OF BENZIL AT 71.80°

Initial (benzil), mole	Base	Concn. mole	Solvent	k_{obs}, l. mole^{-1} min.$^{-1}$
0.06014	NaOH	0.02872	Dioxane–H_2O^a	0.0255
.05894	NaOH Na$_2$B$_4$O$_7$	.02872 .006554	Dioxane–H_2O^a	.0139
.0339	NaHCO$_3$ Na$_2$CO$_3$	.02225 .02225	MeOH–H_2O^b	2.35 × 10^{-5}
.0339	NaHCO$_3$ Na$_2$CO$_3$ Na$_2$B$_4$O$_7$	.02225 .02225 .006554	MeOH–H_2O^b	No reacn. after 228 hr.

^{a} 66.7 volume % dioxane. ^{b} 70.0 volume % methanol. ^{c} Unimolecular rate constant (min.$^{-1}$) since reaction occurred here at constant concentration (buffer) of hydroxide ion.

At least part of the explanation for this can be correlated with the recent literature[32] which has noted extensive and rapid complexation between benzil and borate, where as many as two moles of borate are tried to each mole of benzil. Some likely representations of these complexes are given by the structures XVII and XVIII.

(29) See the following references for a fuller discussion of this point: (a) C. G. Swain and M. M. Labes, *J. Am. Chem. Soc.*, **79**, 1084 (1957); (b) C. G. Swain, J. T. McKnight and V. P. Kreiter, *ibid.*, **79**, 1088 (1957).

(30) G. S. Hammond, *ibid.*, **77**, 338 (1955).

(31) T. Moeller, "Inorganic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1952, p. 763.

(32) R. Pasternak, *Helv. Chim. Acta*, **30**, 1985 (1947).

HO   OH
   \ /
    B
   / \
  O   O
  | |
C_6H_5C————CC_6H_5 and C_6H_5C————CC_6H_5
  | | | |
  O   O   O   O
   \ /   \ /
    B   B
   / \   / \
 HO   OH   HO   OH
  XVII   XVIII

OH   OH
| |
C_6H_5C————CC_6H_5
| |
O   O

In neither is there a receptor carbonyl available toward which a displaced phenyl group could migrate. Conceivably, too, XVII is insufficiently acidic and XVIII possesses no potential for anion formation and the consequent electron pressures which constitute the driving force for the benzilic acid rearrangement, as discussed earlier in this article. Rough calculations, using the value of the equilibrium constant for complexation between borate and benzil,[32] indicate that the resultant decrease of benzil concentration in solution accounts for a large part of the rate reduction experienced (Table VIII).

C. Rearrangement in the Third State.—Here we propose to discuss the rearrangement of alloxan in the pH range where we have observed (in contrast to the lower pH range reaction) a kinetic salt effect and general base catalysis by PO_4^{-3} anion. These results are open to two alternative interpretations which are indistinguishable on the basis of present evidence: (i) the rate-determining removal by base of one of the nitrogen bound protons in AH_2^{-2} (cf. the ionization of analogous protons in dialuric acid[27]). In the act of proton abstraction by base the increased electron pressure thus generated in the molecule causes rearrangement to occur simultaneously (and with increased ease, cf. Table I); (ii) the rate-determining attack of hydroxide ion on one of the residual carbonyl groups in AH_2^{-2}. In this transition state the greatly increased electron pressures developed by OH^- approach causes migration of amido nitrogen to the adjacent carbon, where a bond to oxygen is displaced. It is obvious that carbon isotope
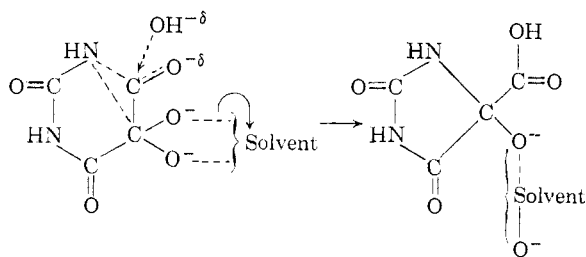
tracer experiments can distinguish these alternative mechanisms since different bonds have migrated in the respective product-forming steps. Such studies have been initiated in these laboratories.

Experimental

A. Preparations.—Alloxan monohydrate was prepared in accordance with the directions of Speer and Dabovich.[33] The purified product decomposed[33] at 250°.

(33) J. H. Speer and T. C. Dabovich, *Org. Syntheses*, **21**, 5 (1941).

$NaH_2PO_4 \cdot H_2O$ (General Chem. Corp., reagent grade), $Na_2HPO_4 \cdot 7H_2O$ and $Na_3PO_4 \cdot 12H_2O$ (Mallinckrodt analytical grade), $Na_2B_4O_7 \cdot 10H_2O$ (E and A purity reagent), Na_2CO_3 (General Chem. Corp. reagent grade), $NaHCO_3$ (Baker analyzed reagent) were used.

Benzil.—Eastman Kodak Co. white label benzil preparation was washed several times to remove small acid contaminants and then recrystallized before use.

Dioxane was prepared according to Fieser's[35] directions.

B. Product Analysis. 1. Alloxanic Acid.—In 50 ml. of warm water was dissolved 16 g. (0.1 mole) of alloxan monohydrate. A solution of 5.6 g. of KOH (0.1 mole) dissolved in 50 ml. of water was added slowly to the alloxan solution with stirring. The solution was allowed to stand overnight and a small amount of precipitate was filtered off. The solution then was evaporated to dryness at room temperature. The residue was taken up in 50 ml. of water and acidified with 10 ml. of 12 N HCl. The solution was evaporated to dryness and washed with small portions of acetone yielding 14 g. of dried product.

Preparation of alloxanic acid using an aqueous solution of K_2CO_3 was just as successful as with KOH.

2. Reaction Product from Alloxan in Buffered Solutions.—The ultraviolet spectrum of alloxanic acid prepared in the preceding section was identical with that of products obtained in all carbonate, phosphate and borate systems.

C. Instrumentation.—Ultraviolet absorption spectra were taken on an automatic recording spectrophotometer incorporating the standard Beckman quartz monochromator (model DUR). The instrument uses a single detector and a single fixed optical path, but mechanically reciprocates the sample and reference cells in the light beam at a frequency of 10 c.p.s. The instrument was designed and built by Process and Instruments Co.[36] and incorporates the Speedomax Recorder (type G) with full scale response time of 1.0 second. A water-cooled low-voltage hydrogen arc lamp was used as a light source (discharge current 1 to 1.3 amperes continuously: arc operating at 87 volts a.c. and 56 volts d.c. having a gas content of 0.55 cm.).

Maintenance of constant temperature was a closely checked factor throughout the work. The cell housing of the monochromator consisted of twin cored aluminum blocks which surrounded the cell holder. Water from a thermostat was circulated through the cell housing, presumably maintaining the temperature of the thermostating fluid. The temperature was maintained at 30.00 ± 0.05° in the cell holder proper as measured by placing a small calibrated thermometer directly in the cell block before and after each run. In later experiments a Leeds and Northrup direct current microvolt amplifier became available so that very accurate temperature measurements could be made in the cell block, and even directly in the reaction cell. For this purpose, a thermocouple was constructed from No. 28 Constantan solid advance thermocouple wire sheathed with copper tubing (0.0305 "o.d. × 0.0055" wall). A short length of copper sheath was removed, the Constantan wire stripped of glass wrap, bent back and silver soldered to the copper sheath. Another length was prepared in the same manner and like leads were connected together and cadmium soldered. One junction was always placed directly in the thermostat (reference) and the other in the cell block. The differential voltage was measured easily on the microvolt amplifier and the temperature differential was calculated. This method proved extremely valuable in measurements of cell temperature five or ten degrees removed from ambient room temperatures.

For rates run below 20°, a lively flow of dry nitrogen was fed through a flow meter into a tightly wound copper coil placed in the thermostat and then led into the cell block to keep the cell windows from fogging because of possible water condensation from the atmosphere.

The reaction vessel for ultraviolet studies was a two-stage system,[37] the lower stage of which was a standard 10 × 10 ×

(34) A. I. Vogel, "Practical Organic Chemistry," 2nd ed., Longmans, Green and Co., London, 1947, pp. 167 ff.

(35) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, pp. 368 ff.

(36) Known as the Recospec RS-3 by Process and Instruments, 15 Stone Ave., Brooklyn 33, N. Y.

(37) H. Kwart and M. M. Baevsky, *J. Am. Chem. Soc.*, **80**, 580(1958).

40 mm. silica cell. The concentration of the reagents was adjusted such that 3.000 ml. of substrate solution was microbureted or pipeted into the lower stage, and 3.000 ml. of base solution into the upper stage. The bulb was tightly stoppered and equilibrated 15 or 20 minutes in the thermostat. The vessel was then removed from the thermostat, rapidly dried with absorbant tissue, inverted several times, and inserted into the cell chamber of the spectrophotometer. The total operation involving removing, drying and inserting the reaction vessel never took more than six seconds. The absorbancy or optical density of the reaction solution was traced automatically by the recorder as a function of time. Appropriate points were picked off the trace and treated according to Guggenheim's method.[17]

pH measurements in earlier experiments were made with the Leeds and Northrup pH indicator (Cat. No. 7664) fitted with the L and N standard 1199–30 glass electrode, and calomel saturated KCl standard 1199–31 reference electrode. For later measurements, the Beckman model G pH meter was used with microelectrode (Beckman 290) and calomel reference (Beckman 270).

D. Rate Measurement by pH Maintenance.—For pH-Stat rate measurements a motor driven precision-screw, loaded syringe was constructed. The syringe bore was found to be very constant in diameter, so that the number of turns on the screw could be taken as a measure of the amount of delivery and could be read off a standard Veeder–Root counter. Delivery was reproducible to 2×10^{-4} ml. of titrant. The instrument was fitted with a variable speed clutch with both forward and reverse drives so that the amount of titrant could easily be controlled. In this manner it was possible to follow the course of the reaction by measuring the amount of titrant per unit time that had to be added to the reaction solution in order to maintain constant pH throughout the reaction. This quantity, $d(OH)$-/dt is proportional to $d(alloxan)/dt$, and the value of the specific rate constant calculated by Guggenheim's method was in good agreement with rates obtained by other methods.

E. Titrimetric Method.—Seligson[38] showed that alloxanic acid could be titrated in the presence of alloxan by adding an excess of ceric ion in 2 N sulfuric acid and then titrating the excess ceric ion with ferrous ammonium sulfate. Use of this method enabled the evaluation of a rate constant based on the rate of appearance of alloxanic acid rather than the disappearance of alloxan. These rates checked within experimental error those of alternate methods (see above).

F. Benzil Kinetic Measurements.—Benzil in NaOH solutions was followed by titrating aliquots of the reaction solution for disappearance of NaOH using phenolphthalein as indicator. For carbonate-buffered runs, each aliquot was acidified with a slight excess of HCl and evaporated to dryness. The residue was washed and evaporated successively with several portions of 50% MeOH–H₂O. Finally the residue was taken up in 10 ml. of H₂O and titrated with standard alkali using brom thymol blue indicator.

Appendix

Approximation Method for Estimation of Rate and Equilibrium Constants.

—Consider, first, the low pH range (pH 6.0 to 7.3). The literature value of pK_{a1} is about 7.0,[15,16] and it is not unreasonable to assume that the major species of alloxan in solution are AH_4 and AH_3^{-1} in this range of (OH^-), i.e., only the rate governed by k_1 is important in this range:

$$(AH_4)_0 = (AH_4) + (AH_4) + (AH_3^{-1}) + (P) \text{ (mass balance)} \quad (6)$$

$$\text{and } AH_3^{-1} \xrightarrow{k_1} P \quad (7)$$
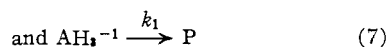
The rate law may be written

$$-d(AH_4)/dt - d(AH_3^{-1})/dt = k_1(AH_3^{-1}) \quad (8)$$

and further, assuming no significant storage in a reaction intermediate

$$-d(AH_4)/dt - d(AH_3^{-1})/dt = dP/dt$$

(38) D. Seligson and H. Seligson, *J. Biol. Chem.*, **190**, 647 (1951).

Substituting for (AH_4) in eq. 6 from eq. 1

$$(AH_4)_0 = \frac{(AH_3^{-1})}{(OH)K_1} + (AH_3^{-1}) + (P) =$$

$$\left[\frac{1}{K_1(OH)} + 1\right](AH_3^{-1}) + (P) \quad (9)$$

$$(AH_3^{-1}) = \left[\frac{(AH_4)_0 - (P)}{\frac{1}{(K_1(OH))} + 1}\right] \quad (10)$$

and substituting for (AH_3^-) from eq. 10 into eq. (8)

$$\frac{dP}{dt} = k_1\left[\frac{(AH_4)_0 - (P)}{\frac{1}{K_1(OH)} + 1}\right] \quad (11)$$

Integration of eq. 11 gives

$$-\ln[(AH_4)_0 - (P)] = k_1\left[\frac{1}{\frac{1}{K_1(OH)} + 1}\right] + C \quad (12)$$

Solution of eq. 12 for boundary conditions $t = 0$, and $(P) = 0$ gives

$$\ln\left[\frac{(AH_4)_0}{(AH_4)_0 - (P)}\right] = k_{obs} \times t \quad (13)$$

$$\text{where } k_{obs} = \frac{k_1 K_1(OH)}{1 + K_1(OH)} \quad (14)$$

To evaluate k_1 and K_1, eq. 14 is written as the reciprocal function

$$\frac{1}{k_{obs}} = \frac{1 + K_1(OH)}{k_1 K_1(OH)} = \frac{1}{k_1 K_1}\left[\frac{1}{(OH)}\right] + \frac{1}{k_1} \quad (15)$$

A plot of $1/k_{obs}$ vs. $1/(OH)$ should give a straight line of slope $1/k_1 K_1$ and intercept $1/k_1$ (recorded in Table I). It is interesting to note that the relationship fails to hold outside the region of approximation (i.e., pH 7.2) as expected.

Since the greatest amount of uncertainty is in the measurement of pH (making the error in $1/(OH)$ large) it is desirable to devise a somewhat less sensitive plot to evaluate these parameters; whence from eq. 15 we deduce by simple transformations

$$\log\left[\frac{1}{k_{obs}} - \frac{1}{k_1}\right] = \frac{1}{k_1 K_1 k_w} - pH \quad (16)$$

Using $k_1 = 3.60 \times 10^{-3}$ affords a straight line of unity slope as predicted by eq. 16 and, thereby, confidence in the k_1 value (Table I).

Consider now an intermediate pH range where two reactive species may be presumed to be present: (AH_3^{-1}) and (AH_2^{-2}): thus

$$(AH_3^{-1}) \xrightarrow{k_1} (P)$$

$$(AH_2^{-2}) \xrightarrow{k_2} (P)$$
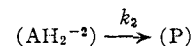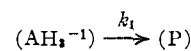
$$(AH_4)_0 = (AH_3^{-1}) + (AH_2^{-2}) + (P) \text{ (mass balance)} \quad (17)$$

where $(AH_4)_0$ and (AH^{-3}) are negligible. Then

$$\frac{dP}{dt} = \frac{d(AH_3^{-1} + AH_2^{-2})}{-dt} = k_1(AH_3^{-1}) + k_2(AH_2^{-1}) \quad (18)$$

Substitution for (AH_2^{-2}) in eq. 17 from eq. 2 yields

$$(AH_4)_0 = (AH_3^{-1}) + K_2(AH_3^{-1})(OH) + (P) \quad (18a)$$

and, therefore

$$(AH_3^{-1}) = \frac{(AH_4)_0 - (P)}{1 + K_2(OH)} \quad (19)$$

Also, substitution for (AH_3^{-1}) in eq. 17 from eq. 2 yields

$$(AH_4)_0 = \frac{(AH_2^{-2})}{K_2(OH)} + (AH_2^{-2}) + (P) \qquad (20)$$

Hence

$$(AH_2^{-2}) = \frac{(AH_4)_0 - (P)}{\dfrac{1}{K_2(OH)} + 1} \qquad (21)$$

Substituting the values for (AH_3^{-1}) and (AH_2^{-2}) from eq. 19 and 21 into eq. 18 results in

$$\frac{dP}{dt} = k_1 \left[\frac{(AH_4)_0 - (P)}{1 + K_2(OH)} \right] + k_2 \left[\frac{(AH_4)_0 - (P)}{\dfrac{1}{K_2(OH)} + 1} \right] \qquad (22)$$

which is transformed readily into

$$\frac{dP}{(AH_4)_0 - (P)} = \left[\frac{k_1 + k_2 K_2(OH)}{1 + K_2(OH)} \right] dt \qquad (23)$$

Integrating, solving for the integration constant, and resubstituting gives

$$\ln \left[\frac{(AH_4)_0}{(AH_4)_0 - (P)} \right] = k_{obs} \times t \qquad (24)$$

where

$$k_{obs} = \frac{k_1 + k_2 K_2(OH)}{1 + K_2(OH)} \qquad (25)$$

As a first approximation

$$K_2 = K_{a2}/K_w = 10^4 \text{ (lit.[15] value of } pK_{a\,2} = 10)$$

If $(OH) = 10^{-6}$, then $1 \gg K_2(OH)$, and thus eq. 25 reduces to

$$k_{obs} = k_1 + k_2 K_2(OH) \qquad (26)$$

A linear relationship of this nature is found to occur in the range of pH greater than 7 yet less than 8.5 having a slope equal to $k_2 K_2$ and intercept k_1. Table I gives the values of k_2, K_2 and pK_{a2} obtained therefrom.

In the high pH range the only species in appreciable concentration are (AH_2^{-2}) and (AH^{-3}); i.e.

$$(AH_4)_0 = (AH_2^{-2}) + (AH^{-3}) + (P) \text{ (mass balance)} \qquad (27)$$

$$(AH_2^{-2}) \xrightarrow{k_2} (P)$$

$$(AH^{-3}) \xrightarrow{k_3} (P)$$
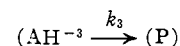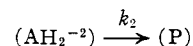
A derivation procedure similar to that given above produces

$$k_{obs} = \frac{k_2 + k_2 K_2(OH)}{1 + K_3(OH)} \qquad (28)$$

and if $k_{obs} \gg k_2$

$$k_{obs} = k_3 - (k_{obs}/K_3(OH)) \qquad (29)$$

The implied linear relationship can be viewed on Fig. 4 and this provides an estimate of k_3, K_3 and pK_{a3}.

Conversion of 3-Amino-1,2-quinones to 6-Hydroxypicolinic and Isocarbostyril-3-carboxylic Acids[1]

By J. H. Boyer[2] and L. R. Morgan, Jr.[3]

Both organic peroxyacids and paraperiodic acid transform 3-amino-1,2-quinones (VI) to corresponding 6-hydroxypicolinic and isocarbostyril-3-carboxylic acids (VII). Although peroxybenzoic acid transforms 3-aminobenzoquinone-1,2 (VIa) to 6-hydroxypicolinic acid (VIIa), the substitution of peroxyacetic for peroxybenzoic acid followed by hydriodic acid leads to the unexpected formation of pyridine and 2-hydroxypyridine. The latter is produced in similar reactions between this aminoquinone and peroxytrifluoroacetic or paraperiodic acid or more concentrated solutions of peroxyacetic acid.

In an enzymatic degradation of tryptophan, 3-hydroxyanthranilic acid (I) is converted by an unknown sequence to α-amino-β-carboxymuconic acid semialdehyde (II).[4] With decarboxylation and/or intramolecular cyclization the amino aldehyde gives quinolinic (III, R = R' = CO$_2$H), nicotinic (R = H, R' = CO$_2$H) and picolinic acids (III, R = CO$_2$H, R' = H).[5] Both 3,4-dihydroxyanthranilic acid (V, X = CO$_2$H, Y = Z = H)[6] and a fused ring peroxide (IV)[7] have been considered

$$(OCH(R)C(AH)(R')O)_m \xrightleftharpoons{} A - O, NR''$$

$$m \text{ RCHC(AH)R'} \xrightleftharpoons{} m \text{ RCHC(=A)R'}$$
$$\overset{|\;\;|}{O-O} \qquad\qquad \overset{|}{OOH}$$

as intermediates in the unknown sequence from I to II.

Chemical conversions of benzene derivatives to pyridine derivatives by cleavage of the carbocyclic ring and recyclization have not been developed.[8]

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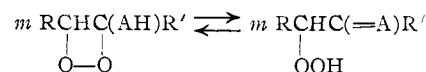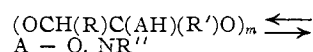(2) National Cancer Institute, Bethesda, Md.

(3) (a) This investigation was carried out during the tenure of a Pre-doctoral Fellowship from the National Heart Institute, U. S. Public Health Service, 1959–1960; (b) Chemistry Department, Imperial College, University of London, London, Eng.

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(7) B. Witkop, J. Am. Chem. Soc., 78, 2873 (1956). Peroxides from enols and oxygen have been assumed to be four-membered rings (W. von E. Doering and R. M. Haines, ibid., 76, 482 (1954)) and tautomeric

hydroperoxides (A. A. Patchett and B. Witkop, J. Org. Chem., 22, 1477 (1957)). In a similar way peroxides from eneamines and oxygen have been assigned structures as hydroperoxides (C. L. Stevens and R. J. Gasser, J. Am. Chem. Soc., 79, 6059 (1957)) and tautomeric cyclic four-membered rings (C. D. Lunsford, R. E. Lutz and E. E. Bowden, J. Org. Chem., 20, 1513 (1955)). Dimeric and/or polymeric olefin peroxides may be in equilibrium with monomeric enol and eneamine peroxides and, in certain examples, may conceivably supply the predominating species; cf. the peroxide (OCH₂CHClO)₂ from vinyl chloride and oxygen (M. Lederer, Angew. Chem., 71, 162 (1959)).

(8) Ozonolysis of a substituted aminomethylcatechol ether followed by cyclization accounts for the construction of ring III as a pyridone in the synthesis of strychnine (R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daenker and K. Scheinker, J. Am. Chem. Soc., 76, 4749 (1954)). Pyridine is reported to be one of the products from benzene and active nitrogen (P. M. Aronovich, N. K. Bel'skii