(50) F. H. Westheimer and A. Novick, *J. Chem. Phys.*, **11**, 506 (1943).
(51) J. W. Baker, "Hyperconjugation", Oxford University Press, Fair Lawn, N.J., 1952.
(52) M. J. S. Dewar, "Hyperconjugation", Ronald Press, New York, N.Y., 1962.
(53) The fully methylated 1,2,2,3,3-pentamethylcyclopropanol, 10^7 times as reactive as isopropyl alcohol, is with respect to chromic acid oxidation certainly the most reactive alcohol and quite possibly the most reactive organic compound known.
(54) H. Kwart and P. S. Francis, *J. Am. Chem. Soc.*, **77**, 4907 (1955).
(55) R. Brownell, A. Leo, Y. W. Chang, and F. H. Westheimer, *J. Am. Chem. Soc.*, **82**, 406 (1960).
(56) J. Rocek, F. H. Westheimer, A. Eschenmoser, L. Moldovanyi, and J. Schreiber, *Helv. Chim. Acta*, **45**, 2554 (1962).
(57) K. B. Wiberg and H. Schafer, *J. Am. Chem. Soc.*, **89**, 455 (1967); **91**, 927 (1969).
(58) W. Watanabe and F. H. Westheimer, *J. Chem. Phys.*, **17**, 61 (1949).
(59) M. Rahman and J. Rocek, *J. Am. Chem. Soc.*, **93**, 5462 (1971).
(60) K. B. Wiberg and S. K. Mukherjee, *J. Am. Chem. Soc.*, **96**, 1884 (1974).
(61) For a recent excellent review, cf. J. K. Beattie and G. P. Haight, Jr., in "Inorganic Reaction Mechanisms, Part II", J. O. Edwards, Ed., Interscience, New York, N.Y., 1972, p 93.
(62) S. E. Schaafsma, H. Steinberg, and T. J. DeBoer, *Recl. Trav. Chim. Pays-Bas*, **85**, 73 (1966).
(63) Cf. ref 56 for a more detailed discussion.
(64) V. Srinivasan and J. Rocek, *J. Am. Chem. Soc.*, **96**, 127 (1974).
(65) F. Hasan and J. Rocek, *Tetrahedron*, **30**, 21 (1974).
(66) J. Rocek and C.-S. Ng, *J. Am. Chem. Soc.*, **96**, 1522, 2840 (1974).
(67) P. M. Nave and W. S. Trahanovsky, *J. Am. Chem. Soc.*, **92**, 1120 (1970); **93**, 4536 (1971).
(68) K. B. Wiberg and H. Schafer, *J. Am. Chem. Soc.*, **91**, 933 (1969).
(69) K. B. Wiberg and G. Szeimies, *J. Am. Chem. Soc.*, **96**, 1889 (1974).
(70) K. B. Wiberg and S. K. Mukherjee, *J. Am. Chem. Soc.*, **96**, 6647 (1974).
(71) Chromium(VI) carbon–carbon cleavage of ditertiary glycols is well known.[72,73]
(72) Y. W. Chang and F. H. Westheimer, *J. Am. Chem. Soc.*, **82**, 1401 (1960).
(73) J. Rocek and F. H. Westheimer, *J. Am. Chem. Soc.*, **84**, 2241 (1962).
(74) G. A. Russell, *J. Am. Chem. Soc.*, **79**, 3871 (1957).
(75) P. D. Bartlett and G. Guaraldi, *J. Am. Chem. Soc.*, **89**, 4799 (1967).
(76) K. U. Ingold, *Pure Appl. Chem.*, **15**, 49 (1967).
(77) A. Streitwieser, "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962.
(78) A. S. Pell and G. Pilcher, *Trans. Faraday Soc.*, **61**, 71 (1965).

Specific Acid Catalysis in the Oxidation of 6,7-Diphenyl-8-methyllumazine by Permanganate

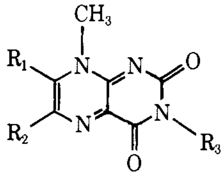
Ross Stewart* and Kiyotaka Oyama

Contribution from the Department of Chemistry, University of British Columbia, Vancouver, Canada.

Received February 19, 1975

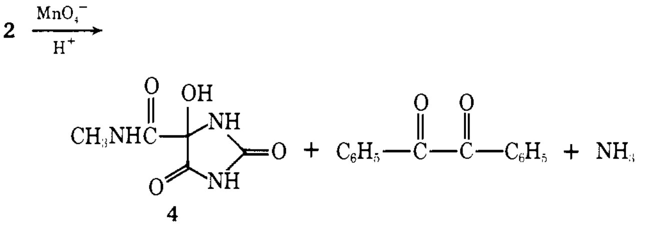
Abstract: The oxidation of 6,7-diphenyl-8-methyllumazine [6,7-diphenyl-8-methylpteridine-2(1*H*),4(3*H*)-dione] (**2**) by aqueous potassium permanganate is subject to specific acid catalysis and gives the methylamide of alloxanic acid, benzil, and ammonia. There are two pathways to the products; one is kinetically dependent on the permanganate concentration and the other is not. The latter reaction proceeds by rate-controlling hydration of **5**, the conjugate acid of **2**, followed by rapid reaction of permanganate with the hydrate. The former reaction proceeds either by reaction between permanganate ion and **5** or by reaction of **2** with an activated form of manganese(VII) formed by the action of acid on permanganate ion.

The kinetics of the acid-catalyzed permanganate oxidation of the riboflavine model compound 6,7,8-trimethyllumazine (**1**) are consistent with the existence of three paths, two of which are kinetically independent of the permanganate concentration and are believed to proceed via general acid catalyzed enolization and specific acid catalyzed hydration, respectively; the third is a permanganate-dependent path which is subject to specific acid catalysis.[1] In order to simplify the kinetics, we have studied the oxidation of 6,7-diphenyl-8-methyllumazine (**2**). This compound does not have enolizable protons and hence one of the three suspected paths is eliminated. Moreover, kinetic data for the hydration of 3,8-dimethyl-6,7-diphenyllumazine (**3**), a close structural analog of **2**, are available,[2] whereas corresponding information for **1** is not.



1, $R_1 = R_2 = CH_3$; $R_3 = H$
2, $R_1 = R_2 = C_6H_5$; $R_3 = H$
3, $R_1 = R_2 = C_6H_5$; $R_3 = CH_3$

The region of acidity covered in the present study is from pH 1.75 (aqueous phosphate buffer) to $H_0 = -0.42$ (10.8% sulfuric acid). The products of the reaction are the hydantoin **4** (the methylamide of alloxanic acid), benzil, and ammonia.



4

Results and Discussion

Using a large excess of permanganate, excellent first-order plots of the disappearance of **2** were observed in all cases, showing the oxidation to be first order in **2**. The order with respect to permanganate was then obtained by maintaining the acidity constant and varying the permanganate concentration. Plots of the pseudo-first-order rate constants against permanganate concentration give straight lines; extrapolations of these to zero permanganate concentration intercept the ordinate somewhat above the origin of the graph. This is observed over the whole acidity range studied and shows that permanganate-dependent and permanganate-independent paths exist. Typical plots of k_{obsd} against permanganate concentration are shown in Figure 1; such plots can be represented by the equation $k_{obsd} = k_1 + k_2[MnO_4^-]$.

In order to determine the acid dependency of these two paths, the intercepts k_1 and slopes k_2 of the plots of $\log_{obsd}$ against permanganate concentration were calculated by the method of least-squares and are shown in Table I. When

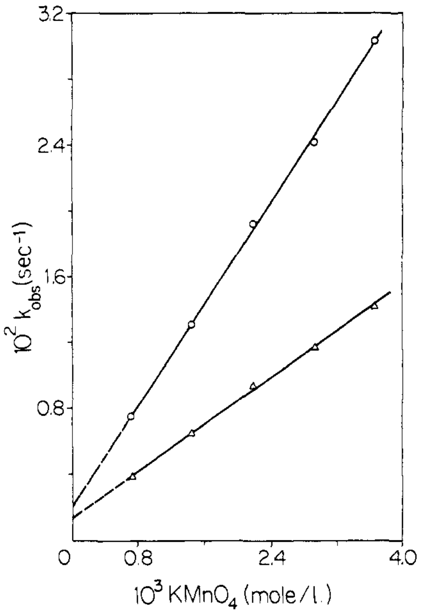


Figure 1. Effect of permanganate concentration on rate of oxidation of **2** at 25°; initial concentration of **2** = 5.00 × 10^{-5} *M*; H_0 = 0.28 (circles), pH 0.93 (triangles).

Table I. Rate Constants for the Permanganate-Independent Path (k_1) and the Permanganate-Dependent Path (k_2) of the Oxidation of 6,7-Diphenyl-8-methyllumazine (2) (T = 25°)

pH, H_0	α^f	k_2, l. mol^{-1} sec^{-1}	k_1, sec^{-1}	Correl coeff
pH, 1.75^a		0.764	2.36 × 10^{-4}	0.999
1.50^a	0.0758	1.29	4.37 × 10^{-4}	0.999
1.20^{a,b}	0.140	2.21	6.96 × 10^{-4}	0.998
1.20^c	0.137	2.20	7.16 × 10^{-4}	0.999
1.20^d	0.140	2.18	7.16 × 10^{-4}	0.999
1.20^e	0.144	2.19	7.36 × 10^{-4}	0.998
0.93^a	0.240	3.59	1.26 × 10^{-3}	0.999
0.83^a	0.322	4.54	1.31 × 10^{-3}	0.999
H_0, 0.48	0.433	6.51	1.55 × 10^{-3}	0.997
0.46	0.440	6.94	1.63 × 10^{-3}	0.998
0.39	0.488	7.03	1.65 × 10^{-3}	0.998
0.28	0.524	7.76	1.82 × 10^{-3}	0.999
−0.07	0.644	9.76	2.19 × 10^{-3}	0.999
−0.42	0.737	10.78	1.73 × 10^{-3}	0.999

^{a}Phosphate buffer, 0.02 *M*. ^{b}The oxidation rates in 0.02 and 0.10 *M* phosphate were identical within experimental error. $^{c-e}$Trichloracetate buffer, 0.10, 0.30, and 0.50 *M*, respectively. ^{f}Degree of ionization of 2, determined spectrophotometrically.

the logarithms of k_1 and k_2 are plotted against acidity of the solution (pH, H_0) a unit dependence on acidity is observed at lower acidities (Figure 2). At higher acidities, where the substrate is largely in the protonated form,[2] the expected leveling-off of both rates is observed.

In order to see whether the reaction is subject to specific or general acid catalysis, the effect on the rate of varying the buffer concentration was examined. As can be seen in Table I, the rates of both paths are independent of the buffer concentration. This result shows that both paths are subject to specific acid catalysis, which, in turn, is consistent with the conjugate acid **5** being an intermediate on both paths, although it does not require that this be so.

If the permanganate-independent oxidation path involves rate-controlling hydration to give, after proton loss, the hydrate **6**, the rate should be identical with the rate of hydration. Pfleiderer et al.[2] showed that the hydration rate at pH 2.96 and 20° for the closely related compound **3** has a value of −4.87 for log (rate). The oxidation of **2** at pH 2.96 is extremely slow, and so the rate has been obtained by extrapolating the linear part of the log k_1-pH plot in Figure 2 to this pH. A value of −4.58 is thus obtained for log k_1 at pH 2.96 and 25°. This value is in close enough agreement with the reported hydration rate of **3** at 20° that it is reasonable to conclude that the permanganate-independent oxidation route proceeds by way of rate-determining hydration.[3]

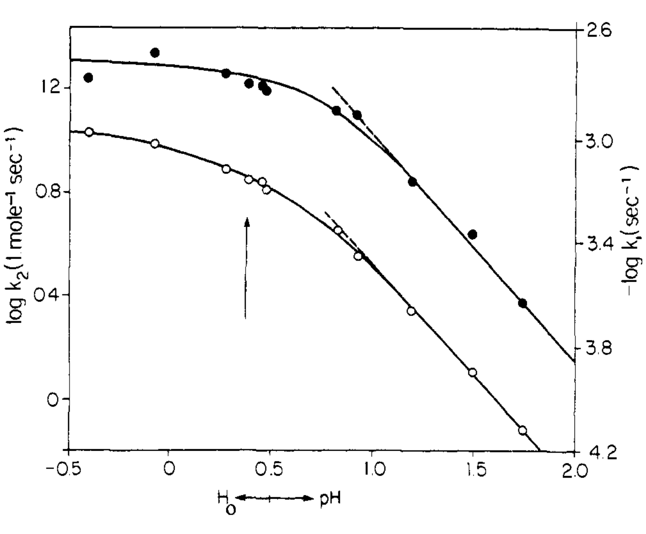
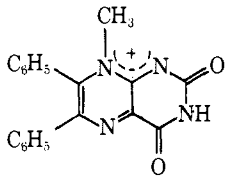
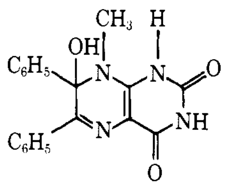
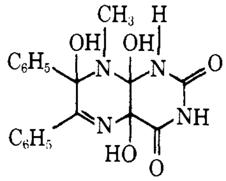


Figure 2. Relation between acidity and rate constants for the two permanganate oxidation routes for **2**. Upper curve represents permanganate-independent route (ordinate units on right); lower curve represents permanganate-dependent route (ordinate units on left). Arrow represents acidity at which **2** is half- protonated. The linear portion of each curve has been drawn with unit slope.


5


6


7

$$\mathbf{2} + H^+ \rightleftharpoons \mathbf{5}$$

$$\mathbf{5} + H_2O \xrightarrow{k_1} \mathbf{6} + H^+$$

$$\mathbf{6} + MnO_4^- \xrightarrow{\text{fast}} \text{products}$$

Hydration of **5** to give **6** serves to localize unsaturation at the ring juncture, making this site subject to rapid attack by permanganate. The resulting triol **7** would be expected to hydrolyze readily and lead by obvious routes to benzil, ammonia, alloxan, and methylamine. The latter two compounds are known to react together to give **4**.[1a,4]

Two kinetically equivalent mechanisms A and B are each consistent with the results obtained for the reaction whose rate is dependent on the permanganate concentration.

$$\text{mechanism A: } \mathbf{5} + MnO_4^- \longrightarrow \text{products}$$

$$\text{mechanism B: } H^+ + MnO_4^- \rightleftharpoons Mn(VII)^*$$

$$Mn(VII)^* + \mathbf{2} \longrightarrow \text{products}$$

Mechanism A involves rate-controlling attack by permanganate ion on the conjugate acid **5**; mechanism B involves activation of permanganate by acid to give a species designated here simply as Mn(VII)*, followed by rate-controlling attack on the neutral compound **2**.

Mechanism A can be envisaged as occurring by attack by permanganate ion on **5** at the partially positive carbon atom C-8 to form a permanganate ester, which subsequently decomposes and ultimately gives the reaction products. An analogous formation of a permanganate ester by combination of permanganate ion and a carbonium ion occurs in the acid catalyzed permanganate oxidation of aryl carbinols.[5]

Since acids almost invariably activate oxidants and only rarely do so to reductants,[5,6] mechanism B might seem, a priori, to be preferred. In more concentrated acid solutions, permanganate ion is converted to a powerful oxidant, Mn(VII)*, whose identity is a matter of conjecture but whose uv spectrum is distinctly different from that of permanganate ion.[7-11] The oxidation of fluoral hydrate in acid solution appears to involve this species, assumed earlier to be $HMnO_4$.[9] If the same species is also responsible for the oxidation of **2**, i.e., if mechanism B be correct, two points can be made. 1. The rate-controlling step in mechanism B would have to be extremely fast, well below the diffusion-controlled limit but extremely fast, nonetheless. (An exact calculation is difficult to make because of uncertainty with regard to the appropriate acidity function to use to calculate the pK of the activated permanganate species, Mn(VII)*, but the rate almost certainly must be greater than 10^5 l. mol^{-1} sec^{-1}.) 2. Whereas at pH 1.5 the acid catalyzed contribution to the fluoral hydrate–permanganate rate is small ($^1/_{30}$ of the uncatalyzed rate)[9] for **1** and **2**, it must be large (23 times larger than the uncatalyzed rate in the case of **1** and at least this great in the case of **2**).

A firm choice between mechanisms A and B for the permanganate-dependent path cannot be made at this time.

Experimental Section

6,7-Diphenyl-8-methyllumazine (**2**) was prepared by the method of Pfleiderer et al.,[2] mp 299-303° dec (lit.[2] 288-292°). Since the melting point is higher than that previously reported, an elemental analysis was obtained.

Anal. Calcd for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 68.80; H, 4.53; N, 17.01.

Product Determination. It was found that 1 mol of **2** is consumed by approximately $^2/_5$ mol of permanganate at pH 1.0. The products were isolated as follows.

To a suspension of **2** (200 mg, 0.55 mmol) in 100 ml of buffer (pH 1.0, $[Na_2HPO_4]$ 0.1 M) was added dropwise the stoichiometric amount of permanganate in the same buffer (35 mg, 0.22 mmol in 30 ml). In order to minimize involvement of the permanganate-dependent path, each drop was added after the color caused by the preceding drop had disappeared. After the addition was over, the color of the solution was a clear pale yellow with no indication of the presence of a manganese dioxide precipitate. The solution was made slightly basic (pH ~9) by addition of sodium bicarbonate powder, and the precipitated manganese hydroxide was filtered out. The filtrate was then extracted with ether which yielded after evaporation 76 mg (86%) of benzil, identical after recrystallization with an authentic sample.

The aqueous layer was worked up in the same way as previously described[1a] to give **4**, the yield of which based on the crude compound was 90 mg (85%). Ammonia was also detected using Nessler's reagent.

On the basis of the data in Table I, if one uses a 100-fold excess of permanganate at pH 1.0, 94% of the total reaction goes via the permanganate-dependent path and 6% via the permanganate-independent path. The oxidation was carried out under such conditions—200 mg (0.56 mmol) of **2** in 100 ml of buffer (pH 1.0, $[Na_2HPO_4]$ 0.1 M) plus 8.8 g (56 mmol) of permanganate in 30 ml of the same buffer. After 20 min, sodium bisulfite was added to the reaction mixture to quench the excess permanganate. The same work-up as before gave benzil and **4** in yields of 75 and 79%, respectively, on the basis of crude product.

Kinetic Procedure. The reaction rates were measured by following the disappearance of the 416-nm absorbance of **2**, essentially as previously described.[1b] However the water solubility of **2** is low, and stock solutions were prepared by dissolving accurately weighed samples in a known volume of buffer. To 2.5-ml aliquots of this solution, 10–50 μl of stock potassium permanganate solutions were added. In the more highly acidic region ($H_0 < 0.5$) manganese dioxide, the reduction product of permanganate, precipitates rather slowly, but when pH = $H_0 > 0.5$ the precipitation is rapid, making analysis of the kinetics difficult. This difficulty was overcome by the addition of a small amount of potassium phosphate (usually enough to make the solution 0.02 M).[12] The effect of added phosphate on the rate is negligible, provided the ionic strength of the solution is maintained at a constant value.

Acknowledgment. The financial support of the National Research Council of Canada is gratefully acknowledged.

References and Notes

(1) (a) K. Oyama and R. Stewart, *Can. J. Chem.*, **52**, 3879 (1974); (b) R. Stewart and K. Oyama, *ibid.*, **52**, 3884 (1974).

(2) W. Pfleiderer, J. Bunting, D. D. Perrin, and G. Nubel, *Ber.*, **99**, 3503 (1966).

(3) For thorough discussions of the chemistry of hydration of pteridines, see D. D. Perrin in "Advances in Heterocyclic Chemistry", Vol. 4, A. R. Katritzky, Ed., Academic Press, New York, N.Y., 1965, pp 43–73; A. Albert and W. L. F. Armarego, *ibid.*, pp 1–42; A. Albert, *Angew. Chem., Int. Ed. Engl.*, **6**, 919 (1967).

(4) H. Blitz and F. Lachmann, *J. Prakt. Chem.*, **113**, 310, 317, 318 (1926).

(5) F. Banoo and R. Stewart, *Can. J. Chem.*, **47**, 3199 (1969).

(6) L. S. Levitt, *J. Org. Chem.*, **20**, 1297 (1955); R. Stewart, "Oxidation Mechanisms: Applications to Organic Chemistry", W. A. Benjamin, New York, N.Y., 1964.

(7) N. Bailey, A. Carrington, K. A. K. Lott, and M. C. R. Symons, *J. Chem. Soc.*, 290 (1960).

(8) D. J. Royer, *J. Inorg. Nucl. Chem.*, **17**, 159 (1961).

(9) R. Stewart and M. M. Mocek, *Can. J. Chem.* **41**, 1160 (1963).

(10) A reassessment of the identity of this species is now under way in our laboratory; it now seems unlikely that it is permanganic acid.[11]

(11) N. A. Frigerio, *J. Am. Chem. Soc.*, **91**, 6200 (1969).

(12) R. Stewart in "Oxidation in Organic Chemistry", Vol. 1, K. B. Wiberg, Ed., Academic Press, New York, N.Y., 1965, p 6.