156. *The Mechanisms of Oxidation of Cyclohexanone under Acid Conditions. Part I. Two-electron Oxidants.*

By J. S. LITTLER.

The kinetics of the initial stages of the oxidations of cyclohexanone by iodine, bromine, mercury(II), thallium(III), and manganese(VII) in mineral acid have been studied. It is concluded that these two-equivalent oxidants attack the enol rather than the ketone form of the substrate.

THE rates of oxidation of ketones by bromine and iodine in acid solution have been shown in a few cases to equal the enolisation rate,[1] and the oxidation by permanganate is assumed to proceed *via* enolisation,[2] though the rates of oxidation and enolisation have not hitherto been compared. The present paper compares for cyclohexanone the apparent enolisation and oxidation rates, measured in a number of systems. Throughout the cyclohexanone has been used in large excess to ensure that reactions of secondary products are not kinetically significant. In all these systems the rate of oxidation has now been found to be of zero order in oxidant concentration, so that the oxidation step does not control the rate of the reaction, and hence it follows that the enolisation step is rate-determining.

RESULTS

The second-order enolisation rate constant k_2 (l. mole^{-1} sec.$^{-1}$) has been calculated, with appropriate assumptions about the stoicheiometry of the rapid initial reaction.

Then $\mathrm{d[Ketone]/d}t = -k_2\mathrm{[Ketone][H^+]} = \{d\mathrm{[Oxidant]/d}t\}/n$, where n is the number of molecules of oxidant consumed rapidly following the attack on a molecule of enol.

(1) Iodination of cyclohexanone is of zero order for 90% of the reaction and gives a value for k_2 of 31 × 10^{-6} (l. mole^{-1} sec.$^{-1}$) at 25° if the equation used is $I_2 + C_6H_{10}O \longrightarrow HI + C_6H_9OI$. This has always been assumed to measure the true enolisation rate for any ketone, independently of its structure. Section (*a*) of Table 1 shows that the usual acid-catalysed enolisation kinetics apply to cyclohexanone. Section (*b*) is for comparative purposes at 10°. Attempts to measure the rate of iodination in 4M-perchloric acid at lower ketone concentrations were not successful

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[1] Swain, Stivers, Reuwer, and Schaad, *J. Amer. Chem. Soc.*, 1958, **80**, 5885.

[2] Lejeune, *Compt. rend.*, 1926, **182**, 694.

owing to the reversibility of the reaction. The value of k_2 found is approximately twice that found from the mercury(II) oxidation but could be accounted for if a di-iodo-ketone is formed rapidly, *i.e.*, if $n = 2$. There appears to be no evidence in the literature on the extent of the rapid iodination of cyclohexanone. The reversibility of the iodination prevented confirmation of its stoicheiometry.

(2) Bromination of cyclohexanone (Table 2) gives a value of k_2 ($70{\cdot}5 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$) which is slightly more than twice as large as that given by iodination. Good zero-order reactions were observed for 90% of the reaction. When the reactants were mixed in the Br_2 : ketone ratio of 4·5 : 1, the decrease of bromine concentration followed a first-order curve for over 80% of the reaction, confirming that four, or possibly slightly more, moles of bromine were reacting rapidly with each mole of ketone (or enol). If $n = 4$, k_2 is $17{\cdot}6 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ at 25°.

TABLE 1.

Oxidation of iodine.

(*a*) $[I_2 + I_3^-] = 0{\cdot}0035$M. [Salt] = 1·05M. 25°.

$[H^+]$ (M)	1·00	0·60	0·20	1·00
[Ketone] (M)	0·0406	0·0406	0·0406	0·00356
$10^4 \times 1/$t.c. (sec.$^{-1}$)	33·4	22·0	8·1	3·13
10^5k_2 (l. mole^{-1} sec.$^{-1}$)	28·7	31·6	33·9	30

Mean value of $k_2 = 31 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ ($n = 1$).

(*b*) $[I_2 + I_3^-] = 0{\cdot}0035$M. [Ketone] = 0·049M. 10°.

$[H^+]$ (M)	1·0 ($HClO_4$)	0·85 (H_2SO_4)	
[Salt] (M)	4·05	0·90	
$10^4 \times 1/$t.c. (sec.$^{-1}$)	10·7	10·0	
10^5k_2 (l. mole^{-1} sec.$^{-1}$)	7·4	8·1	($n = 1$)

N.B. In all Tables t.c. = time taken to complete the consumption of oxidant; k_1 = first-order enolisation constant; k_2 = second-order, acid-catalysed enolisation constant. Mean values were obtained graphically.

TABLE 2.

Oxidation by bromine.

$[Br_2 + Br_3^-] = 0{\cdot}00272$M. $[H^+]$ = M ($HClO_4$). [Salt] = 1·05M. 25°.

[Ketone] (M)	0·00356	0·00356	$5{\cdot}93 \times 10^{-4}$
$10^4 \times 1/$t.c. (sec.$^{-1}$)	9·42	9·05	2·57
10^5k_2 (l. mole^{-1} sec.$^{-1}$): mean value = 70·5.			*ca.* 120.

(3) With mercuric perchlorate all runs were of zero order in oxidant for at least 50% of the reaction; in most cases 80—90% of the reaction was accurately of zero order. Section (*a*) of Table 3 shows that the reaction is of the first order in ketone; section (*b*) shows that it is of the first order in hydrogen ion; section (*c*) shows that it is slightly accelerated by increasing ionic strength; and section (*d*) is an approximate measurement for comparative purposes at high salt and acid concentrations. The enolisation rate constant k_2, calculated on the basis of the equation $2Hg^{2+} + C_6H_{10}O \longrightarrow Hg_2^{2+} + C_6H_{10}O_2$, was found to be $15{\cdot}9 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ at 25°. No metallic mercury was formed while spectrophotometric measurements were being made. Addition of sulphate or chloride ions strongly retarded the reaction, but oxidation of ketones by mercuric nitrate is known to occur.[3] In the reaction carried out to investigate the products, a further stage of oxidation occurred, and after a few hours finely divided globules of metal were precipitated. Investigation of the products showed that the α-diketone is an important product of the oxidation, which therefore probably proceeds *via* the acyloin. It was confirmed that the latter is readily oxidised by mercuric perchlorate.

(4) The reaction of thallic perchlorate also showed zero-order dependence on oxidant concentration. The equation $Tl^{3+} + C_6H_{10}O \longrightarrow Tl^+ + C_6H_{10}O_2$ gave a value of k_2 for the acid-dependent reaction of $11{\cdot}1 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ at 25°. Section (*a*) of Table 4 shows that the reaction is of the first order in ketone, and section (*b*) gives the acid-dependence.

(5) Potassium permanganate was generally used in sulphuric acid, as there was a greater tendency for manganese dioxide to be precipitated during the reaction if perchloric acid was

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[3] Zappi and Manini, *Anales Asoc. quim. argentina*, 1938, **26**, 89.

used. Table 5, section (*a*), shows that the reaction is of zero order in oxidant, although individual runs did not give good zero-order plots. Section (*b*) shows that it is of first order in ketone. If we assume, for the purposes of calculation, the equation $KMnO_4 + C_6H_{10}O \longrightarrow$ Products + Mn^{II}, then k_2 is 10·7 × 10^{-5} l. mole^{-1} sec.$^{-1}$ at 10·2° [cf. 4·05 × 10^{-5} sec.$^{-1}$ in

TABLE 3.

Oxidation by mercuric perchlorate.

(*a*) $[H^+]$ = 0·23M. [Salt] = 0·24M. $[Hg^{2+}]$ = 5 × 10^{-3}M. 25°.

[Ketone] (M)	0·0203	0·0406	0·102	0·152
10^4 × 1/t.c. (sec.$^{-1}$)	2·11	4·54	10·5	15·4
10^4k_1 (sec.$^{-1}$)	2·59	2·79	2·59	2·53

Mean value of k_1 = 2·6 × 10^{-5} sec.$^{-1}$.

(*b*) [Ketone] = 0·0406M. [Salt] = 1·24M. $[Hg^{2+}]$ = 5 × 10^{-3}M. 25°.

$[H_3O^+]$ (M)	0·23	0·63	0·83	1·23
10^4 × 1/t.c. (sec.$^{-1}$)	5·51	16·1	23·2	32·1
10^5k_1 (sec.$^{-1}$)	3·38	9·85	14·2	19·6
$10^5k_2 = k_1/[H^+]$	14·7	15·7	17·1	16·0

Mean value of k_2 = 15·9 × 10^{-5} l. mole^{-1} sec.$^{-1}$.

(*c*) [Ketone] = 0·0406M. $[H^+]$ = 0·23M. $[Hg^{2+}]$ = 5 × 10^{-3}M. 25°.

[Salt] (M)	0·24	0·74	1·24
10^4 × 1/t.c. (sec.$^{-1}$)	4·54	5·02	5·5
10^5k	2·79	3·08	3·38

k_1 = {2·63 + 0·6 [Salt]} × 10^{-5} sec.$^{-1}$

or k_2 = {11·5 + 2·6 [Salt]} × 10^{-5} l. mole^{-1} sec.$^{-1}$.

(*d*) [Ketone] = 0·0406M. $[H^+]$ = 5·1M. [Salt] = 5·1M. $[Hg^{2+}]$ = 5 × 10^{-3}M. 25°.
10^4 × 1/t.c. (sec.$^{-1}$) = 200.

∴ k_1 = 160 × 10^{-5} sec.$^{-1}$ and k_2 = 30 × 10^{-5} l. mole^{-1} sec.$^{-1}$.

TABLE 4.

Oxidation by thallic perchlorate.

(*a*) $[Tl^{III}]$ = 5·35 × 10^{-3}M. $[H^+]$ = 0·276M. [Salt] = 0·30M. 25°.

[Ketone] (M)	0·0203	0·051	0·102
10^4 × 1/t.c. (sec.$^{-1}$)	1·88	4·78	9·15
10^5k_1 (sec.$^{-1}$)	4·94	5·0	4·81

Mean value of k_1 = 4·87 × 10^{-5} sec.$^{-1}$.

(*b*) $[Tl^{III}]$ = 5·35 × 10^{-3}M. [Ketone] = 0·0406M. [Salt] = 1·3M. 25°.

$[H^+]$ (M)	0·276	0·476	0·676	0·876	1·076	1·276
10^5k_1 (sec.$^{-1}$)	7·81	10·3	11·7	14·8	16·3	19·2
10^5k_1 (calc.)	7·87	10·1	12·3	14·5	16·7	19·0

Expression used for calculation is k_1 (sec.$^{-1}$) = 4·8 × 10^{-5} + 11·1 × $10^{-5}[H^+]$.

TABLE 5.

Oxidation by acid permanganate.

(*a*) $[H^+]$ = 0·85M (H_2SO_4). [Salt] = 0·85M. [Ketone] = 4·9 × 10^{-2}M. 10·2°.

$[Mn^{VII}]$ (10^{-3}M)	4·65	2·79	0·93
10^4 × 1/t.c. (sec.$^{-1}$)	15·0	15·7	15·4
10^5k_1 (sec.$^{-1}$)	8·7	9·1	8·9

Mean value of k_1 = 8·9 × 10^{-5} sec.$^{-1}$. k_2 = 10·5 × 10^{-5} l. mole^{-1} sec.$^{-1}$.

(*b*) $[H^+]$ = 0·85M (H_2SO_4). [Salt] = 0·85M. $[Mn^{VII}]$ = 2·79 × 10^{-3}M. 10·2°.

[Ketone] (M)	0·0196	0·049	0·098	0·1274
10^4 × 1/t.c. (sec.$^{-1}$)	6·67	15·9	30·3	42·1
10^5k_1 (sec.$^{-1}$)	9·5	9·1	8·6	9·2

Mean value of k_1 = 9·1 × 10^{-5} sec.$^{-1}$. k_2 = 10·7 × 10^{-5} l. mole^{-1} sec.$^{-1}$.

(*c*) $[Mn^{VII}]$ = 4·6 × 10^{-3}M. [Ketone] = 4·9 × 10^{-2}M. $[H^+]$ = 4·0M ($HClO_4$). 10·2°. [Salt] = 4M.
10^4 × 1/t.c. (sec.$^{-1}$) = 34.

$10^{-5}k_1$ = 32·2 (sec.$^{-1}$); k_2 = 8·1 × 10^{-5} l. mole^{-1} sec.$^{-1}$.

Table 3(*b*) for diiodination]. Section (*c*) also shows that at higher acidity in perchloric acid $k_2 = 8{\cdot}1 \times 10^{-5}$ sec.$^{-1}$ [cf. $3{\cdot}75 \times 10^{-5}$ sec.$^{-1}$ from Table 3(*b*) under similar conditions]. This indicates that n is between 2 and 2·5.

(6) No oxidations were carried out with selenious acid or periodic acid. Duke's experiments[4] with the former give $k_2 = 0{\cdot}013 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$ at 47° for acetone, the reaction Se^{IV} + Ketone ⟶ Se + Oxidation products being assumed.

(7) Oxidation of ketones by periodic acid proceeds at a reasonable rate only when the α-hydrogen atom is doubly activated, as in β-diketones or benzyl ketones.[5] Oxidation of ketones by lead tetra-acetate in acetic acid is reported to proceed at the same rate and with the same kinetics as bromination in the same solvent.[6]

DISCUSSION

All the oxidants investigated above and also lead tetra-acetate show zero-order kinetics with respect to oxidant concentration, and the rates of oxidation are related to the rates of enolisation by factors appropriate to the particular oxidation and reasonable in view of the known chemistry of the systems.

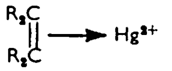
$$\begin{array}{rcll}
2Hg^{2+} + C_6H_{10}O & \longrightarrow & Hg^{2++} + C_6H_{10}O_2 & n = 2 \\
2I_2 + C_6H_{10}O & \longrightarrow & 2I^- + C_6H_8OI_2 & n = 2 \\
4Br_2 + C_6H_{10}O & \longrightarrow & 4Br^- + C_6H_6OBr_4 & n = 4 \\
Tl^{3+} + C_6H_{10}O & \longrightarrow & Tl^+ + C_6H_{10}O_2 & n = 1 \\
MnO_4^- + C_6H_{10}O & \longrightarrow & Mn^V + C_6H_{10}O & \\
Mn^V + Mn^{VII} & \longrightarrow & 2Mn^{VI} & \left.\right\} \text{or other products} \quad n = 2{\cdot}5 \\
Mn^{VI} + C_6H_{10}O & \longrightarrow & Mn^{II} + C_6H_8O_2 &
\end{array}$$

It can therefore be concluded that the rate-determining step of each reaction is the acid-catalysed enolisation of cyclohexanone, and that the enol form is rapidly attacked by the oxidant.

These reagents also react readily with olefins, and the mechanism of attack on the enol may be similar to that of attack on an isolated double bond. Olefin oxidation by iodine, by bromine, and by chromic acid is known to proceed through a complex of type (A), and stable complexes of the type (B) are known to be formed with mercury.[7] Similar

(A)

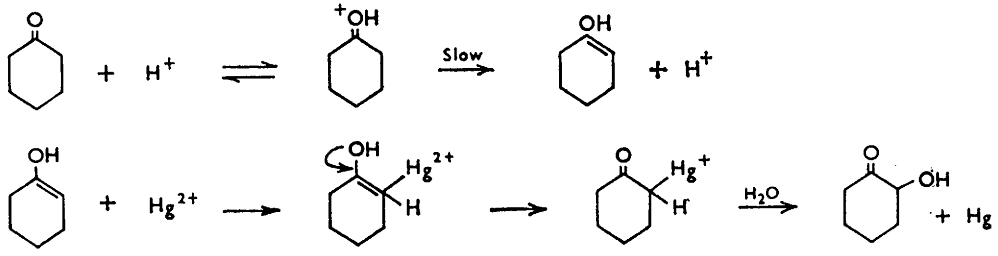
$R_2C{=}CR_2 \longrightarrow Br^+$



$R_2C{=}CR_2 \longrightarrow Hg^{2+}$

(B)

unstable complexes probably provide a route for the oxidation of olefins by thallium(III).[8] A typical mechanism for oxidation of a ketone by these reagents would then be as illustrated.



$$Hg^\circ + Hg^{2+} \rightleftharpoons Hg_2^{2+}$$

(cf. the electrophilic mercuration of phenols)

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[4] Duke, *J. Amer. Chem. Soc.*, 1948, **70**, 419.

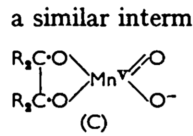
[5] Wolfrom and Bobbitt, *J. Amer. Chem. Soc.*, 1956, **78**, 2489; Felkin, *Bull. Soc. chim. France*, 1951, 915.

[6] Ichikawa and Yamaguchi, *J. Chem. Soc. Japan*, 1952, **73**, 415.

[7] Chatt, *Chem. Rev.*, 1951, **48**, 7.

[8] Grinstead, *J. Org. Chem.*, 1961, **26**, 238.

Oxidation of olefins by manganese(VII) is known [9] to proceed through the complex (C); a similar intermediate is possible in enol oxidation: it would break down to the hydroxyketone and eventually C–C fission products.



(C)

The acid-independent part of the oxidation by thallium(III) appears to be due to direct attack on the ketone, and may be due to the one-electron changes Tl^{III} to Tl^{II} or Tl^{II} to Tl^{I}, which are known to have a key role in some reactions of thallium salts.[10] This oxidation may well proceed by a mechanism similar to that suggested for oxidation by vanadium(V).

Manganic pyrophosphate, unlike manganic sulphate, appears to attack the enol, but although manganous sulphate did not retard the oxidation of cyclohexanone it did retard other oxidations by manganic pyrophosphate.[11] This indicates that some at least of the reactions of " manganic pyrophosphate " may be very fast reactions of a manganese(IV) pyrophosphate formed by disproportionation, for it is probable that pyrophosphoric acid stabilises Mn^{IV} in water to some slight degree:

$$Mn^{II} + Mn^{IV} \rightleftharpoons 2Mn^{III}$$

The above evidence consistently indicates that enol molecules are very easily oxidised by two-electron oxidants of electrophilic type. For these reagents there is no easily attacked site in the ketone molecule itself, but, if the oxidant is nucleophilic in nature, as in the Baeyer–Villiger reaction, attack on a ketone can of course occur. Decomposition of a ketone–oxidant complex by intramolecular hydride transfer (cf. the mechanism proposed for one-electron oxidants) is not likely as the electron-deficient transition state $-^{+}CH{\cdot}COR$ would be destabilised by the carbonyl group.

EXPERIMENTAL

Kinetic measurements were carried out as in the preceding paper. Concentration of oxidants were determined at the following wavelengths: For mercury, increase of Hg_2^{2+} absorption at 268 mμ.[12] For iodine, decrease of $I_2 + I_3^-$ absorption at 460 mμ.[13] For bromine, decrease of $Br_2 + Br_3^-$ absorption at 310 mμ.[14] For permanganate, decrease of MnO_4^- absorption at 532 mμ.[15]

The absorption of manganese(III) at 532 mμ may have contributed to the optical density towards the end of the oxidations by permanganate. Visually the solutions had the cherry-red colour of manganese(III) rather than the purplish colour of manganese(VII), but they were not sufficiently stable for the spectrum to be determined. It is probable that manganese(III) would be stable under the conditions used for permanganate oxidation.

Since thallium(III) could not be determined *in situ*, 0·05 ml. samples were taken by a micropipette and added to 1 ml. of 0·5M-sodium chloride. The chloro-complexes formed could then be estimated at 245 mμ.[16]

Oxidant Solutions.—Mercuric solutions were made by dissolving yellow mercuric oxide (99%) in " AnalaR " perchloric acid. Thallic solutions were made by dissolving freshly precipitated thallic hydroxide in perchloric acid. The thallic hydroxide was prepared by oxidation of an ice-cold aqueous solution of thallous nitrate with 100-vol. hydrogen peroxide in the presence of an excess of potassium hydroxide. The excess of peroxide was decomposed catalytically on gentle warming and the precipitate was washed repeatedly by decantation until the water was not detectably alkaline.

Product Study.—60% Perchloric acid (20 ml.), cyclohexanone (10 g., 1 mol.), and mercuric oxide (43·3 g., 2 mol.) were made up with water to 100 ml. and were kept at 50° for 20 hr., with occasional shaking. After about 3 hr. a considerable quantity of metallic mercury had

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[9] Waters, *Quart. Rev.*, 1958, **12**, 277.
[10] Higginson, Rosseinsky, Stead, and Sykes, *Discuss. Faraday Soc.*, 1960, **29**, 49.
[11] Drummond and Waters, *J.*, 1955, 496; Levesley and Waters, *J.*, 1955, 217.
[12] Higginson, *J.*, 1951, 1438.
[13] Awtry and Connick, *J. Amer. Chem. Soc.*, 1951, **73**, 1842.
[14] Gilbert, Goldstein, and Lowry, *J.*, 1931, 1092; Lewin, *Bull. Res. Council Israel*, 1952, **2**, 101.
[15] Drummond and Waters, *J.*, 1953, 435.
[16] Peschanski and Valladas-Dubois, *Bull. Soc. chim. France*, 1956, 1170; Peschanski, *ibid.*, p. 1574.

been formed, and eventually no mercuric oxide remained. The mixture was filtered and the brown aqueous layer was continuously extracted with ether. The ethereal solution was shaken with aqueous sodium hydroxide, and the aqueous layer was acidified and re-extracted with ether. After the ethereal solutions had been dried ($MgSO_4$) and evaporated, 6·8 g. of a neutral brown oil and 1·6 g. of an acidic tar were obtained. The neutral fraction was distilled at atmospheric pressure, yielding 2·2 g. of colourless material, b. p. 155—180°, which contained at least 0·64 g. of α-diketone (calculated as cyclohexanedione), together with a further 0·35 g. of yellow oil, b. p. 180—200°, containing 0·18 g. of diketone. The cyclohexane-1,2-dione was determined by gravimetric assay of the nickel dioxime complex, and a test with biacetyl showed that under the conditions used oxime formation is not quite quantitative. The figures obtained (above) indicate a yield of diketone approaching 10%. As further oxidation has obviously occurred and as diketones are themselves oxidised by mercuric perchlorate this was considered satisfactory evidence that this oxidation occurs at the position adjacent to the carbonyl group.

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THE DYSON PERRINS LABORATORY, OXFORD. [*Received, July 25th,* 1961.]