155. *The Mechanism of Oxidation of Cyclohexanone by Chromic Acid.*

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The kinetics of the initial stages of the oxidation of cyclohexanone by chromic acid in aqueous perchloric acid have been investigated. Comparative reaction velocities have been measured for cyclohexanone and 2,2,6,6-tetradeuterocyclohexanone in both water and deuterium oxide. Reasons are given for concluding that the oxidation of this ketone follows its enolization.

Rates of oxidation of ketones by chromic acid have been studied only by Petit,[1] who found that with a series of methyl ketones the rate increased progressively from acetone to heptyl methyl ketone. The present investigation was conducted to find out the mechanism of the oxidation and, if possible, to decide whether the reaction proceeds *via* enolization, as seems to be the case with so many other reactions of aliphatic ketones.

Results

The oxidation of cyclohexanone by chromic acid proceeded at a convenient rate for kinetic study in aqueous solution in the presence of 0·05—1M-perchloric acid, and when the ketone was present in excess the reduction of the chromium(VI) was found to be a first-order process for more than half the reaction. Table 1 shows that throughout this acidity range the reaction velocity is linearly dependent on the hydrogen-ion concentration in solutions of constant ionic strength. Table 2 shows that the dependence on cyclohexanone concentration is also of the first order. Table 3 shows that the dependence of the rate is nearly, but not exactly, dependent on the total chromic acid concentration for solutions containing a constant amount of perchloric acid although the hydrogen-ion concentrations of these solutions vary on account of the dissociation of the chromic acid as a strong monobasic acid (K_1 0·18). Calculation from the oxidation rates at constant acidity (Table 4, col. 3) shows that chromic acid is a more effective oxidant in dilute than in concentrated solution and indicates that in this reaction the rate is proportional to the concentration of the acid chromate anion, $HCrO_4^-$. This is confirmed by the figures of Table 4, col. 4, which have been calculated on the assumption that the association constant for dichromate formation ($K = [HCrO_4^-]^2/[Cr_2O_7^{2-}]$) has the value 0·01 at 50°

Table 1.

Acidity-dependence for the oxidation of cyclohexanone by chromic acid at 50°.

[Cyclohexanone] = 0·0712M. [CrO_3] = 0·005M.

The perchloric acid–sodium perchlorate mixtures had total ionic strength = 0·646.

[H$^+$] (M)	k_1 (hr.$^{-1}$)	k_1/[H$^+$]	[H$^+$] (M)	k_1 (hr.$^{-1}$)	k_1/[H$^+$]
0·646	1·74	2·67	0·484	1·33	2·71
0·388	1·15	2·92	0·323	0·91	2·78
0·258	0·677	2·57	0·161	0·484	2·92
0·129	0·345	2·57	0·0646	0·179	2·75

Average k_1/[H$^+$] = 2·73 l. mole^{-1} hr.$^{-1}$ = 7·58 × 10^{-4} l. mole^{-1} sec.$^{-1}$.

Table 2.

Cyclohexanone-dependence for the oxidation at 50°.

[CrO_3] = 0·005M. [$HClO_4$] = 0·646M.

[Ketone] (M)	k_1 (hr.$^{-1}$)	k_1/[Ketone]	[Ketone] (M)	k_1 (hr.$^{-1}$)	k_1/[Ketone]
0·0712	1·74	24·4	0·0534	1·32	24·7
0·0427	1·02	23·9	0·0321	0·811	25·3
0·0214	0·497	23·2	0·0107	0·246	23·0

Average k_1/[Cyclohexanone] = 24·1 l. mole^{-1} hr.$^{-1}$ = 67 × 10^{-4} l. mole^{-1} sec.$^{-1}$.

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[1] Petit, *Bull. Soc. chim. France*, 1945, **12**, 568.

TABLE 3.

Dependence on initial chromium(VI) in 0·0646M-perchloric acid at 50°.

[Cyclohexanone] = 0·0712M. k_0 is the initial rate of oxidation.

$[CrO_3]$ (M)	0·05	0·04	0·03	0·02	0·01	0·005
10^3k_0 (mole l.$^{-1}$ hr.$^{-1}$)	6·95	5·58	3·78	2·85	1·57	0·88
$k_0/[CrO_3]$ (hr.$^{-1}$)	0·139	0·139	0·126	0·142	0·157	0·176

TABLE 4.

Dependence of oxidation rate on chromium(VI), corrected to a total acidity of 0·0646M-H$^+$.

[In the experiments marked *a* the chromium(VI) was added as $K_2Cr_2O_7$; the other data are calculated from Table 3.]

Total $[CrO_3]$ (M)	10^3k_0 (mole l.$^{-1}$ hr.$^{-1}$)	k_0/total $[CrO_3]$ (hr.$^{-1}$)	$k_0/[HCrO_4^-]$ (hr.$^{-1}$)
0·05	3·92	0·0784	0·288
0·05 ^{a}	4·09	0·0818	0·301
0·04	3·47	0·0867	0·299
0·03	2·58	0·0860	0·258
0·025 ^{a}	2·36	0·0944	0·265
0·02	2·17	0·108	0·278
0·0125 ^{a}	1·56	0·125	0·271
0·01	1·36	0·136	0·272
0·00626 ^{a}	0·86	0·137	0·237
0·005	0·88	0·176	0·294

Average $k_0/[HCrO_4^-] = 0·276 \pm 0·039$ hr.$^{-1}$.

TABLE 5.

Effect of manganous ions on the oxidation of cyclohexanone.

[Cyclohexanone] 0·0712M. $[CrO_3]$ 0·005M. $[HClO_4]$ 0·646M. 50°.

$[Mn^{2+}]$ (M)	0·005	0·005	0·001	0·0
k_1 (hr.$^{-1}$)	1·45 ^{a}	1·55 ^{b}	1·73 ^{b}	1·61

^{a} Manganous salt used was a recrystallized sample of " AnalaR " manganous sulphate tetrahydrate. " Technical " grade manganese carbonate.

TABLE 6.

Effect of isotopic replacement on the oxidation of ketone.

(*a*) $[HClO_4] = 0·23$M. $[Cr^{VI}] = 5 \times 10^{-3}$N. 50°. Cyclohexanone.
(*b*) $[H_2SO_4] = 0·45$M. $[Cr^{VI}] = 5 \times 10^{-3}$N. 50°. Cyclohexanone.
(*c*) $[C_6H_4Me\cdot SO_3H] = 0·75$M. $[Cr^{VI}] = 15 \times 10^{-3}$N. 60°. Di-isopropyl ketone.

[Ketone]	Type	Solvent	k_1 (sec.$^{-1}$)	10^4k_1 [Ketone] (l. mole^{-1} sec.$^{-1}$)
		Reaction (*a*)		
0·186	H	H_2O	10·3	55
0·210	H	H_2O	11·6	55
0·135	D	D_2O	7·6	56
0·135	D	D_2O	6·7	50
0·198	H	D_2O	41·7	211
0·191	H	D_2O	41·2	212
		$k_H/k_D = 4·0$. $k_{D_2O}/k_{H_2O} = 4·3$.		
		Reaction (*b*)		
0·19	H	H_2O	14·25	75
0·172	H	D_2O	50	290
0·1412	D	D_2O	7·5	53
0·183	D	D_2O	8·6	47
0·156	D	H_2O	2·22	14·2
		$k_H/k_D = 5·5$. $k_{D_2O}/k_{H_2O} = 3·7$.		
		Reaction (*c*)		
0·0125	H	H_2O	3·36	239
0·0125	H	H_2O	3·69	
0·0125	H	H_2O	3·94	
0·0125	H	H_2O	3·43	
0·0125	H	D_2O	19·4	1210
0·0125	H	D_2O	18·2	
		$k_{D_2O}/k_{H_2O} = 5·2$.		

(cf. $K = 0·023$ at 25° [2] and 0·015 at 40° [3]). Again the figures marked *a* show that no adjustment of the acidity is needed if solutions are made up from potassium dichromate and a constant strength of perchloric acid.

These kinetic relations are similar to those found for oxidations of alcohols in this acidity

[2] Neuss and Riemann, *J. Amer. Chem. Soc.*, 1934, **56**, 2238.
[3] Westheimer, *Chem. Rev.*, 1949, **45**, 419.

range,[4] but Table 5 shows that the ketone oxidation differs from alcohol oxidation in that it is affected only slightly by the addition of manganous ion: these oxidations of cyclohexanone do not lead to the precipitation of manganese dioxide.

Table 6, gives the comparative rates of reduction of chromium(VI) by cyclohexanone and by 2,2,6,6-tetradeuterocyclohexanone in both water and deuterium oxide, with perchloric, sulphuric, and toluenesulphonic acid as sources of hydrogen ions. In both systems there is a definite primary isotope effect consequent on changing the α-CH groups to CD. There is also a solvent effect in changing from water to deuterium oxide. The latter of these effects is significant in the deduction of the reaction mechanism.

DISCUSSION

Chromic acid ultimately effects the oxidation of cyclohexanone to adipic acid, but throughout this investigation the cyclohexanone has been used in a sufficiently large excess to ensure that the rate of reduction of the chromic acid is proportional to the rate of the oxidation of the cyclohexanone itself, and not to the rate of destruction of any reactive organic intermediate, such as 1-hydroxycyclohexanone or cyclohexane-1,2-dione. Moreover since, under these conditions, the initial rate of consumption of chromic acid was always of the first order the rates of oxidation of intermediate products cannot be kinetically significant.

Now the kinetic measurements have shown that

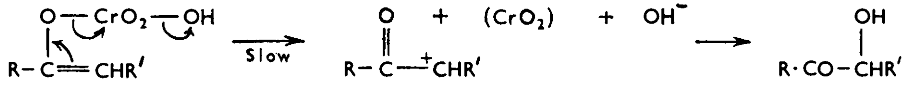
$$-\mathrm{d}[\mathrm{Cr^{VI}}]/\mathrm{d}t = k[\mathrm{Ketone}][\mathrm{HCrO_4^-}][\mathrm{H^+}],$$

which is also the rate equation for the oxidation of propan-2-ol in chromic acid solutions of low acidity. Since the chromic acid oxidations of primary and secondary alcohols occur by way of esterification the observed reaction kinetics would be consistent with the rapid formation and slow breakdown of an enol ester (I).

$$\text{(1)} \qquad \mathrm{R{\cdot}CO{\cdot}CH_2R' \rightleftharpoons R{\cdot}C(OH){:}CHR'}$$

$$\text{(2)} \qquad \mathrm{R{\cdot}C(OH){:}CHR' + H_2CrO_4 \rightleftharpoons R{\cdot}C(O{\cdot}CrO_2{\cdot}OH){:}CHR'\ (I) + H_2O}$$

(3)



Another possibility is that the attack of chromic acid on the enol is a concerted process (4), perhaps base-catalysed (5), which immediately gives an α-keto-chromite ester (II); this would hydrolyse (reaction 6) to the α-ketol and chromium(IV). Reaction (4) resembles the concerted reactions by which one can explain the rapid bromination and iodination of enols and is preferable to the reaction sequence (2–3) for it meets the criticism that, since enols are acids of comparable p*K* to phenols, their esterification (*i.e.*, the forward reaction 2) would be very small. Moreover, the concerted electrophilic reactions of enols do not require reagents as active as those needed for addition to olefins since *free* carbonium ions (cf. equation 3) are not generated.

A similar direct attack on an enol by selenious acid (7) is a very plausible stage in the selenium dioxide oxidation of the $\mathrm{CO{\cdot}CH_2}$ group (see 5, and footnote to p. 825).

However, the rate of oxidation of cyclohexanone by chromic acid is slower than its rate of enolization at the same acidity, and so these kinetic relations cannot show whether the ketone molecule or its enol is attacked, but merely indicate that the transition state of the rate-determining process involves the elements of a molecule of ketone and of a molecule of chromic acid, $\mathrm{H_2CrO_4}$.

The absence of any retardation of the rate of chromium(VI) reduction, or of precipitation of manganese dioxide in the mixtures to which manganous ions had been added, prevents conclusion whether compounds of chromium(IV) or chromium(V) are formed in

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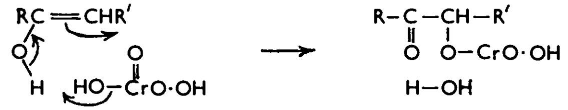
[4] Chang and Westheimer, *J. Amer. Chem. Soc.*, 1960, **82**, 406.

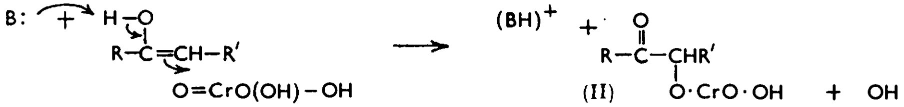
the rate-determining stage of the oxidation. This, however, may be due to the rapid reduction of the ketone by manganic ions, which would result from the reaction $Cr^{IV} + Mn^{II} \longrightarrow Cr^{III} + Mn^{III}$.

The primary isotope effect, k_H/k_D (found, 4·0 with $HClO_4$ and 5·5 with H_2SO_4 solutions), noted in changing from cyclohexanone to 2,2,6,6-tetradeuterocyclohexanone, in water or in deuterium oxide solution, shows that the fission of an α-C–H bond can be rate-controlling, but, as explained below, for oxidations carried out with freshly prepared solutions of the deuterated ketone this does not necessarily mean that the oxidation step involves a ketonic and not an enolic molecule.*

(4)

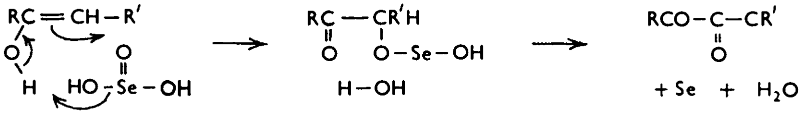


(5)



(6) $$\text{(II)} + \overset{\cdot}{\mathrm{H}}_2\mathrm{O} \longrightarrow \mathrm{R{\cdot}CO{\cdot}CHR'{\cdot}OH} + [\mathrm{CrO(OH)_2}]$$

(7)



The mechanism of acid-catalyzed enolization involves the reactions:

(8 $$\mathrm{R{\cdot}CO{\cdot}CH_2R'} + \mathrm{H_3O^+} \underset{k_{-8}}{\overset{k_8}{\rightleftharpoons}} \mathrm{R{\cdot}{}^+C(OH){\cdot}CH_2R'} + \mathrm{H_2O}$$

(9) $$\mathrm{R{\cdot}{}^+C(OH){\cdot}CH_2R'} + \mathrm{H_2O} \underset{k_{-9}}{\overset{k_9}{\rightleftharpoons}} \mathrm{R{\cdot}C(OH){:}CHR'} + \mathrm{H_3O^+}$$

where both the forward and the back reaction of equation 8 are instantaneous since they involve a proton exchange between oxygen atoms, whereas the forward reaction of equation 2 is slow, since it involves the fission of a C–H bond.[6] Thus the rate of formation of an enol should exhibit the same primary isotope effect as any other reaction that involves the fission of an α-C–H bond of a ketone. So any reaction proceeding through an enol with a velocity slower than the enolization rate should occur less easily with the deuterated molecule until the unattacked ketone has attained isotopic equilibrium with the solvent.

Indeed the rates of chromic acid oxidation of deuterated ketones (cyclohexanone and di-isopropyl ketone have been examined) do appear to accelerate in their later stages, but the disappearance of the chromic acid follows a first-order law for nearly 50% of the reaction.

Thus it follows that only the solvent isotope effect found by replacing water by deuterium oxide can be used to diagnose the reaction mechanism more fully.

Comparison of acid–base equilibria in water and deuterium oxide indicates that for any proton-catalysed reaction one should expect a solvent isotope effect, k_{D_2O}/k_{H_2O}, of

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[*] Corey and Schaefer[5] have made this erroneous conclusion in regard to the selenium dioxide oxidation of ketones; their argument is applicable only to equilibrated keto–enol systems.

[5] Corey and Schaefer, *J. Amer. Chem. Soc.*, 1960, **82**, 918; Duke, *ibid.*, 1948, **70**, 419.

[6] Bell, " The Proton in Chemistry," Methuen, London, 1959, p. 140.

about 2·0—2·5.[7] This solvent isotope effect, should favour all reactions involving molecular chromic acid, for the equilibrium (10) should be shifted by deuterium oxide so as to yield a higher concentration of H_2CrO_4 molecules than would be present in water.

$$(10) \qquad HCrO_4^- + H_3O^+ \rightleftharpoons H_2CrO_4 + H_2O$$

However, the observed solvent effects ($k_{D_2O}/k_{H_2O} = 3{\cdot}8$ in sulphuric acid, 4·3 in perchloric acid and 5·2 in toluenesulphonic acid) are almost double the above estimate, and in the perchloric acid this large discrepancy cannot be due to the participation of a second proton or of a protonated species such as $H_3CrO_4^+$, as appears to be the case for chromic acid oxidations of alcohols in strongly acid solutions;[4] for any such extra protonation would have been revealed by the kinetic measurements (Table 1 shows no deviation from first-order rate dependence on H^+). One must, therefore, infer that the pre-equilibrium involved in producing the rate-determining reaction complex of the chromic acid oxidation of cyclohexanone includes two different acid-catalysed processes. This is entirely consistent with the view that the oxidation proceeds through a reaction between an enol molecule and one of un-ionized H_2CrO_4, because the effects of isotopic substitution on the enol content and the reactivity of a freshly prepared aqueous solution of a ketone are as follows: (*a*) If the solvent is deuterium oxide rather than water the enolization constant $K = (k_8/k_{-8} \times k_9/k_{-9})$ should double, owing to the solvent effect on k_8/k_{-8}. The value of k_9 should not alter, as the base strengths of H_2O and D_2O are virtually identical, nor should the value of k_{-9} as the acid strengths of H_3O^+ and D_3O^+ are the same.[8] A value of k_{D_2O}/k_{H_2O} of 2·1 has been measured for the rate of acid-catalyzed enolization of acetone,[9] *i.e.*, $k_8k_9/k_{-8} = 2{\cdot}1$. (*b*) If the ketone is deuterium-substituted and the solvent is water, then K should be reduced to one-fifth of its value, owing to the primary isotope effect, which affects just k_9 (see p. 825). (*c*) If both the ketone and the solvent are deuterated, then both effects would occur.

Since for a chromic acid oxidation one also has a solvent isotope effect related to the ionization (10) the predicted relative oxidation rates should be as shown in Table 7.

TABLE 7.

Reaction involved		Predicted for C–H attack on ketone	Predicted for enolization initially	Found in		
				H_2SO_4	$HClO_4$	*k* $C_6H_4Me{\cdot}SO_3H$
In H_2O:	H-Ketone	1·0	1·0	1	1	1
	D-Ketone	0·2	0·2	0·18	0·25	—
In D_2O:	H-Ketone	2—2·5	4—5	3·7	4·3	5·2
	D-Ketone	0·4—0·5	0·8—1·0	0·7	1·1	—

EXPERIMENTAL

Materials.—Cyclohexanone was purified through its bisulphite compound. Di-isopropyl ketone was fractionated (b. p. 112·5°) and its purity confirmed by vapour-phase chromatography. Perchloric acid (Harrington's 60% acid), sodium perchlorate (recrystallized grade), and sulphuric acid were used without purification. The chromic acid solutions were prepared from "AnalaR" chromium trioxide or potassium dichromate and standardized immediately before use; the solubility of chromium trioxide in perchloric acid was so small that to obtain 0·1M-solutions concentrations of perchloric acid less than 30% had to be used.

2,2,6,6-*Tetradeuterocyclohexanone.*—Cyclohexanone (1 g.) and 99·8% deuterium oxide (from Norske Hydro) (2 ml.) were heated with 0·1 g. of anhydrous potassium carbonate for 24 hr. in a closed system at 100°. The aqueous layer was then removed, and replaced with a further 2 ml. of D_2O and a further 0·1 g. of catalyst. This should give a 97·3% exchange of the α-hydrogen atoms of the ketone. The aqueous layer was saturated with potassium carbonate, and the ketone was extracted with dry ether, dried ($MgSO_4$), and distilled, the fraction of b. p. 156°

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[7] Rule and La Mer, *J. Amer. Chem. Soc.*, 1938, **60**, 1974.

[8] Long and Watson, *J.*, 1958, 2019; Pocker, *Proc. Chem. Soc.*, 1960, 17.

[9] Reitz, *Z. phys. Chem.*, 1937, *A*,**179**, 119.

being collected and sealed in a glass ampoule until required. Analysis by combustion, followed by infrared spectroscopic estimation of the water produced, indicated that the material contained 98 ± 1% of $C_6H_6D_4O$ (we thank Drs. F. B. Strauss and G. D. Meakins for this analysis).

Deuterated toluene-*p*-sulphonic acid was prepared by crystallizing the "AnalaR" monohydrate from deuterium oxide and drying the product at 25°. No attempt was made to prepare deuteroperchloric or deuterosulphuric acid and consequently the reactions involving these substances and deuterium oxide were conducted in a solvent containing only about 95% of D_2O.

The kinetic experiments reported in Tables 1—5 were carried out titrimetrically; samples were quenched in an excess of ferrous sulphate solution and back-titrated with standard potassium dichromate. The data of Table 6 were obtained spectrophotometrically by using the absorptions of solutions at 349 mμ; 0·2 and 0·1 cm. cells were used in a Unicam S.P. 500 spectrophotometer fitted with an Adkins thermostat-controlled cell-block, and the reaction mixtures were prepared with the aid of an Agla micrometer syringe. Neutral aqueous solutions of the cyclohexanone were added to the acid chromate solutions just before the absorption measurements were made.

One of us (P. A. B.) thanks Imperial Chemical Industries Limited, Dyestuffs Division, for leave to participate in this work.

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