

523. The Mechanism of Oxidation of Cyclohexanone under Acid Conditions. Part III.¹ Corrected Enolization Rates and Kinetic Isotope Effects.

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New measurements show that the zeroth-order rates of bromination, iodination, and mercuric perchlorate oxidation of cyclohexanone are closely similar. The kinetic isotope effects for these three reactions have been measured for tetra α -deuterocyclohexanone. The isotope effects for both tritiation and detritiation of cyclohexanone have been measured by scintillation counting of samples of cyclohexanone oxime. These results accord with theoretical predictions.

IN Part I¹ evidence was presented to show that well-established ideas about the halogenation of ketones could be extended to their oxidation by 2-electron abstracting agents. However we now find that some of our conclusions concerning stoichiometries were erroneous. It has been necessary to rectify these before studying kinetic isotope effects.

Bromination.—We have isolated monobromocyclohexanone (50% yield) from the reaction between 1 mole of cyclohexanone and 1 mole of bromine in hydrobromic acid/potassium bromide solution. Consequently the zeroth order rates of bromination of cyclohexanone in the presence of perchloric acid at 25° were redetermined by both spectroscopic and titrimetric analyses, which are in accord and give $-\Delta[\text{Br}_2]/\Delta t = k_2[\text{ketone}][\text{H}_3\text{O}^+]$ where $k_{25^\circ} = (22.5 + 5.6 [\text{ClO}_4^-]) \times 10^{-5}$ l. mole⁻¹ sec.⁻¹ at low bromide-ion concentrations but is $31.3 \pm 0.3 \times 10^{-5}$ in hydrogen bromide-potassium bromide mixtures. (Tables 1 and 2.)

TABLE 1.
Bromination of cyclohexanone at 25°.

(i) Representative rate data in perchloric acid (titrimetric)

Initial Concentrations (M) $[\text{Br}_2] = [\text{Br}^-] = 0.0184$; $[\text{Ketone}] = 0.196$

$[\text{H}_3\text{O}^+]$ (M)	0.24	0.20	0.20	0.080	0.080	
$[\text{ClO}_4^-]$ (M)	0.24	1.00	1.80	2.48	3.28	
$10^5 k_2$ (l. mole ⁻¹ sec. ⁻¹)	23.7	28.1, 28.6	29.0	41.8	40.6	
$10^5 k_2$ (calc.*)	23.9	28.1	32.6	36.4	40.9	

* From equation $k_2 = (22.5 + 5.6 [\text{ClO}_4^-]) \times 10^{-5}$ l. mole⁻¹ sec.⁻¹; at this low bromide concentration spectrophotometric estimation is unreliable through shift of the equilibrium $\text{Br}_2 + \text{Br}^- \rightleftharpoons \text{Br}_3^-$ and evaporation of bromine (cf. Part I).

(ii) Representative data for hydrogen bromide solution (spectrophotometric)

$10^2 [\text{Br}_2]$ (M)	2.4	2.4	0.97	0.97	2.4	19.9
$10^2 [\text{Ketone}]$ (M)	2.58	1.29	1.29	1.29	1.29	19.6
$[\text{H}_3\text{O}^+]$ (M)	0.395	0.79	0.395	1.58	1.58	0.316
$[\text{Br}^-]$ (M)	0.40	0.75	1.15	1.58	1.58	1.30
$10^5 k_2$ (l. mole ⁻¹ sec. ⁻¹) *	33.2	32.7	31.1	31.0	31.0	29.5

* Mean of 14 results, 31.3 ± 0.3 .

TABLE 2.

Iodination of cyclohexanone at 25° (spectrophotometric).

Initial Concentrations (M), $[\text{HClO}_4] = 0.50$; $[\text{Ketone}] = 0.0129$; $([\text{I}_2] + [\text{I}_3^-]) = 1.86 \times 10^{-3}$; $([\text{I}^-] + [\text{I}_3^-]) = 7.5 \times 10^{-3}$

Total $[\text{ClO}_4^-]$ (M)	0.51	1.01	1.51	2.01	3.36
$10^5 k_2$ (found)	25.0	28.4	27.8	32.8	39.9
$10^5 k_2$ (calc.*)	25.1	27.6	30.1	32.7	39.7

* From $k_2 = (22.5 + 5.1 [\text{ClO}_4^-]) \times 10^{-5}$ l. mole⁻¹ sec.⁻¹.

Iodination likewise gave a zeroth order rate (Table 2). $k_{25^\circ} = (22.5 + 5.1 [\text{ClO}_4^-]) \times 10^{-5}$ l. mole⁻¹ sec.⁻¹.

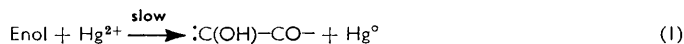
¹ Part II, Littler, J., 1962, 832. Part I, Littler, J., 1962, 827.

TABLE 3.
Kinetic isotope effects.
($10^5 k_2$ in l. mole⁻¹ sec.⁻¹)

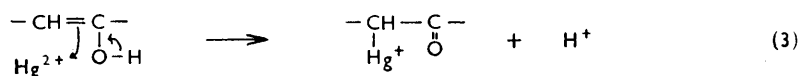
	Bromination *	Iodination †	Mercuration †
H-ketone	31.3, 31.3	24.9, 24.7, 24.1	23.9, 24.7, 24.9
D-ketone	6.36, 6.36	4.84, 4.86, 4.60	4.46, 4.66
k_H/k_D	4.9	5.2	5.4

* In 1.0M-hydrobromic acid. † In 1.0M-perchloric acid.

Oxidation with mercuric perchlorate, according to the data of Part I, has $k_{25^\circ} = \frac{1}{2}(23.0 + 5.2 [\text{ClO}_4^-]) \times 10^{-5}$ l. mole⁻¹ sec.⁻¹, it having been presumed that the reaction process was



the spectral change being due to the formation of mercurous cations, each one of which arises from two mercuric cations. However, as shown below, the measured reaction is



and the mercurated ketone, which has a distinct absorption spectrum, breaks down relatively slowly. Hence for mercuric perchlorate oxidation, too, Littler's¹ measurements give

$$k_{25^\circ} = (22.5 + 5.2 [\text{ClO}_4^-]) \times 10^{-5} \text{ l. mole}^{-1} \text{ sec.}^{-1}$$

and we now take this to be the enolization rate at 25°.

Avery, Morton, and Penner² have prepared compounds such as acetylmercuric iodide and found that they were hydrolysed only slowly even at 100° in aqueous acetic acid containing sodium acetate, and Miano³ has detected a similar complex in perchloric acid solution by Raman spectroscopy. We find that the soluble absorbing entity formed in the reaction between cyclohexanone and mercuric perchlorate has $\lambda_{\text{max.}}$ 226 m μ , $\epsilon_{\text{max.}}$ 8530, whilst that for the reaction with acetone has $\lambda_{\text{max.}}$ = 214 m μ , $\epsilon_{\text{max.}}$ 11,400. These values do not correspond exactly with the absorption of mercurous perchlorate ($\lambda_{\text{max.}}$ 209 and 236.5 m μ). The rate of attack on acetone by mercuric perchlorate was found to be of zeroth order with respect to Hg^{2+} : the rate constant at 25° in 1.0M perchloric acid was found spectroscopically to be 2.8×10^{-5} l. mole⁻¹ sec.⁻¹ (Table 4), whereas for monochlorination, -bromination, and -iodination the mean of published values (refs. 4—10) is 2.84×10^{-5} l. mole⁻¹ sec.⁻¹.

TABLE 4.

Mercuration of acetone at 25° by mercuric perchlorate in 1.0M-perchloric acid.

[Acetone] (M)	0.33	0.13	0.13	0.198
$10^2[\text{Hg}^{2+}]$ (M)	0.50	1.25	6.25	0.50
λ (m μ)	280	280	240	235
$10^5 k_2$ (l. mole ⁻¹ sec. ⁻¹)	3.0	2.6	2.5	2.79, 2.87, 2.83

² Avery, Morton, and Penner, *J. Amer. Chem. Soc.*, 1951, **73**, 3300.

³ Miano, *Diss. Abs.*, 1963, **23**, 3115.

⁴ Rice and Kilpatrick, *J. Amer. Chem. Soc.*, 1923, **45**, 1401.

⁵ Dawson, *Trans. Faraday Soc.*, 1928, **24**, 640.

⁶ Dawson and Key, *J.*, 1928, 2154.

⁷ Smith, *J.*, 1934, 1744.

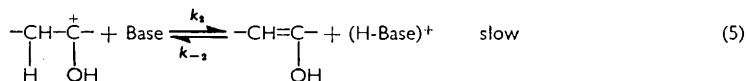
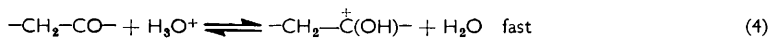
⁸ Reitz, *Z. phys. Chem.*, 1937, **A179**, 119.

⁹ Rice and Fryling, *J. Amer. Chem. Soc.*, 1925, **47**, 382.

¹⁰ Bell and Yates, *J.*, 1962, 1927.

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Kinetic Isotope Effects.—Having the assurance, summarized above, that halogenation and mercuric perchlorate oxidation rates for cyclohexanone measure the replacement of only one hydrogen (clearly that removed by the slow step (5) of an acid-catalysed enolization), we have measured the comparative rates of attack on cyclohexanone and



2,2,6,6-tetradeuterocyclohexanone by these three reagents. Our results (Table 3) give $k_{\text{H}}/k_{\text{D}} = 5.1 \pm 0.2$ at 25° , which is comparable with the value of 4.0 found by Best, Littler, and Waters¹¹ for chromic acid oxidation at 50° , but lower than the theoretical figure of 6.9 for linear stretching of C-H and C-D bonds at 25° ($\Delta E = 1.15$ kcal. mole⁻¹). However, the incomplete α -deuteration of any organic compound lowers considerably the directly measured $k_{\text{H}}/k_{\text{D}}$ values. Our deuterated ketone prepared by equilibration with deuterium oxide had an estimated purity of 98%; this introduces a 10% error in the kinetic isotope effect, which may therefore be about 5.6.

There is no such systematic error in measurements of isotope effects with tritium, since tracer techniques for tritium-counting can give $k_{\text{H}}/k_{\text{T}}$ values which are independent of the degree of tritiation of the organic molecule. With the enolization of a ketone, in contrast to its halogenation, the whole reaction process is described by equations (4) and (5), from which it can be shown that the exchange rates for detritiation of a tritio-ketone (T-ketone) in aqueous acid, and for tritiation of a normal ketone by tritiated water, should be similar.

TABLE 5.

(a) Detritiation of 2-tritio-cyclohexanone

Change of specific activity (S.A.) with time of oxime samples derived from 2-tritio-cyclohexanone. (Representative data—T. J. K.)

	Temp. $25.2 \pm 0.1^\circ$; $[\text{HClO}_4] = 1.94\text{M}$; $[\text{Ketone}] = 0.1875\text{M}$					
Time (10^3 sec.)	0	20.0	60.8	92.2	150.1	Infin.
S.A. (obs.) ($\mu\text{C g.}^{-1}$)	0.36	0.31	0.21	0.15	0.092	0.0031
S.A. (calc.) * ($\mu\text{C g.}^{-1}$)	0.37	0.30	0.20	0.15	0.087	0.0025

* From $k_1 = 9.60 \times 10^{-6}$ sec.⁻¹ (13 measurements). These data yield $k_2 = 4.95 \times 10^{-6}$ l. mole⁻¹ sec.⁻¹.

(b) Tritiation of cyclohexanone with active water (representative data)

Temp. = $25.1 \pm 0.1^\circ$; $[\text{HClO}_4] = 1.94\text{M}$; $[\text{Ketone}] = 0.1875\text{M}$, no added salt

Time (10^3 sec.)	0	14.4	30.9	65.0	86.4	107.5	172.0
S.A. of oxime of recovered ketone (S.A.) _t	0.0014	0.065	0.15	0.29	0.34	0.38	0.46
(S.A.) _t -(S.A.) _i (obs.)	0.56	0.50	0.41	0.27	0.22	0.18	0.10
(S.A.) _t -(S.A.) _i (calc.) *	0.56	0.48	0.40	0.28	0.22	0.18	0.09

* From $k_1 = 10.83 \times 10^{-6}$ sec.⁻¹ (18 measurements). Infinity value found for S.A. of recovered oxime, 0.563 ± 0.025 (6 measurements). The oxime would have attained an equilibrated specific activity of $0.640 \mu\text{C g.}^{-1}$ if statistical distribution of T atoms between all sites had been achieved: hence $K = 0.88$.

For detritiation. If a solution of cyclohexanone, molarity M , has $1/n$ of its solute molecules labelled in one of the four α -positions, then $[\text{T-ketone}] = M/n$ and $[\text{T-atoms}]/[\text{Exchangeable H atoms}] = 1/4n$.

The rate of enolization of T-ketone per available site is $k_2/F_d \times [\text{T-ketone}] \cdot [\text{H}_3\text{O}^+]/4$ where F_d is the kinetic isotope effect, $k_{\text{H}}/k_{\text{T}}$, for detritiation.

$$\text{Hence } \frac{(\text{Initial rate of tritium loss})}{(\text{Initial } [\text{T-ketone}])} = \frac{k_2}{4F_d} \cdot \frac{M[\text{H}_3\text{O}^+]}{n} \cdot \frac{n}{M} = \frac{k_2[\text{H}_3\text{O}^+]}{4F_d}$$

For tritiation. If the ketone, molarity M , is placed in aqueous acid with $1/x$ of its total hydrogen atoms replaced by tritium, then $3/x$ of the hydronium ions are present

¹¹ Best, Littler, and Waters, *J.*, 1962, 822.

as H_2TO^+ ; if a statistical distribution of tritium between ketone and solvent is eventually obtained, then the number of T-atoms per ketone molecule is finally $4M/x$ since M is fractional and the molarity of liquid water is 55.5. If there is non-statistical distribution, the number is $4KM/x$, where $K = (\text{observed final labelling})/(\text{statistical degree of labelling})$.

Now the rate of uptake of tritium from the solvent is

$$(k_{-2}/F_t) \cdot [\text{Enol}][\text{H}_2\text{TO}^+] \times (\text{chance of selecting T from } \text{H}_2\text{TO}^+).$$

$$= (k_{-2}/F_t)[\text{Enol}][\text{H}_3\text{O}^+] \cdot \frac{(3-1)}{x} \cdot \frac{1}{3}$$

where F_t is the kinetic isotope effect for tritiation.

But from the chemical equilibrium of equation (5), $k_2[\text{Ketone}] = k_{-2}[\text{Enol}]$, so that

$$\text{rate of tritium uptake} = k_2M[\text{H}_3\text{O}^+]/F_t x$$

and

$$\frac{(\text{Initial rate of tritium uptake})}{(\text{Final tritium content of ketone})} = \frac{k_2M[\text{H}_3\text{O}^+]}{F_t \cdot x} \times \frac{x}{4KM} = \frac{k_2[\text{H}_3\text{O}^+]}{4KF_t}$$

TABLE 6.

Acidity-dependences of isotope-exchange reactions (representative data).

[Ketone] = 0.1875M; $[\text{ClO}_4^-] = 1.94\text{M}$; Temp. = $25.1 \pm 0.1^\circ$

$[\text{HClO}_4]$ (M)	0	0.194	0.777	1.165	1.94
	(a) Detritiation				
Reaction time (10^3 sec.)	341	427	255	242	89.1
S.A. of oxime recovered ($\mu\text{C g}^{-1}$)	0.39	0.23	0.14	0.098	0.158
$10^6k/[\text{HClO}_4]$ (l. mole $^{-1}$ sec. $^{-1}$)	—	5.7	5.0	4.7	4.9 *
	* Mean of 7 measurements, 5.1.				
	(b) Tritiation				
Reaction time (10^3 sec.)	259	153	83.4	81.4	117.5
S.A. of oxime recovered ($\mu\text{C g}^{-1}$)	0.0007	0.097	0.194	0.253	0.384
$10^6k/[\text{HClO}_4]$ (l. mole $^{-1}$ sec. $^{-1}$)	—	6.4	6.6	6.3	5.6 *
	* Mean of 6 measurements, 6.3.				

The kinetic isotope effects, F_d and F_t , can therefore be determined by progressive tritium analysis of the ketone present in an equilibrating aqueous solution. Our experimental method has been to sample at intervals isomerizing solutions of cyclohexanone in perchloric acid, to convert the ketone into its oxime, and to determine the tritium content of the latter. Oximation is effected in an almost neutral buffer solution, which at once stops keto \rightleftharpoons enol interchange, and the oxime can be recrystallized from light petroleum so that no tritium exchange with the solvent occurs after any sample has been removed for analysis from the reacting acid solution. By this method the rate of both tritiation and detritiation of cyclohexanone have been shown to have a first-order dependence on acidity (Table 6).

Our rate measurements in 1.94M perchloric acid at 25° give

$$k_2/F_d = 2.05 \times 10^{-5} \text{ l. mole}^{-1} \text{ sec.}^{-1}; K = 0.88;$$

$$k_2/F_t K = 2.53 \times 10^{-5} \text{ l. mole}^{-1} \text{ sec.}^{-1}$$

$$\text{and hence } k_2/F_t = 3.04 \times 10^{-5} \text{ l. mole}^{-1} \text{ sec.}^{-1}$$

Taking $k_2 = (22.5 + 1.94 \times 5.2) \times 10^{-5} = 32.6 \times 10^{-5} \text{ l. mole}^{-1} \text{ sec.}^{-1}$, we therefore find $F_d = 15.6$ and $F_t = 10.7$ (or 13.6 for $K = 1$).

Swain, Stivers, Reuwer, and Schaad¹² consider that deuterium and tritium isotope effects should be related by the equation $k_{\text{H}}/k_{\text{T}} = (k_{\text{H}}/k_{\text{D}})^{1.442}$. This gives $F_d = 10.4$, if $k_{\text{H}}/k_{\text{D}}$ is assigned our experimental value of 5.1 or 12.3, and if the 10% correction is made for the incomplete deuteration of our ketone.

¹² Swain, Stivers, Reuwer, and Schaad, *J. Amer. Chem. Soc.*, 1958, **80**, 5885.

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In view of the experimental difficulty in measuring kinetic isotope effects we regard this agreement as satisfactory; it is similar to the isotope effect (9.7 at 98°, corresponding to 16.9 at 25°) reported by Swain and his colleagues for the detritiation of tritro- α -phenylisocaprophenone.

This concordance with theory constitutes independent evidence for our conclusion that the halogenation and mercuric perchlorate oxidation rates are true measures of the initial enolization-rate of cyclohexanone.

EXPERIMENTAL

Materials.—Cyclohexanone was purified through its bisulphite compound. Our preparation of 2,2,6,6-tetradeuterocyclohexanone has been described previously.¹¹

2-Tritrocyclohexanone. Purified inactive ketone (19 g.) was equilibrated with water (5 g.) of specific activity 2 mc/ml. by heating at 100° in the presence of potassium carbonate for 48 hr. in a flask fitted with a condenser and a mercury seal. The ketone layer was dried (Na_2SO_4) and inactive pure cyclohexanone (91 g.) was added. The combined ketone was then shaken with 5 portions of brine (each of 100 ml.) to remove water-soluble tritiated impurities. It was then dried (Na_2SO_4) and distilled (b. p. 153°/758 mm.).

Materials used in scintillation counting were supplied by Nuclear Enterprises Ltd.

The spectroscopic rate measurements were carried out as described in Part I.

Tritium Exchanges.—To 100 ml. of 2M-HClO₄ + 2M-NaClO₄ mixture in a flask immersed in a thermostat at 25° were added 1 ml. of water and 2 ml. of ketone, one of the last two substances being radioactive, depending on the direction of tritium transfer. Reactions were terminated at intervals by pouring the contents of the flask into sufficient iced sodium carbonate solution to neutralise almost all the acid. This solution was saturated with common salt and the ketone was extracted with ether (4 × 25 ml.). The combined extracts were washed with brine (2 × 25 ml.) to remove dissolved active water. The ether was evaporated and the residue was added to hydroxylamine hydrochloride (1.4 g.) and hydrated sodium acetate (1.4 g.) dissolved in the minimum of water. The flask was shaken and placed in an ice-bath. The oxime, which separated in 1–2 min., was filtered off and washed thrice with water. After being dried in a vacuum, it was recrystallised from light petroleum (b. p. 40–60°) until it attained m. p. 90°. The specific activity of the oxime was determined by dissolving a weighed portion in a conventional scintillator solution (10 ml.) [AnalaR toluene containing 2,5-diphenyloxazole (6 g. l.⁻¹) and 1,4-bis(2-5'-phenyloxazolyl)benzene (40 mg. l.⁻¹)], and measuring the coincident count rate of the light emission in a coincidence counter (model 2022, Isotope Developments Ltd.). The efficiency of the scintillator for counting a standard tritiated hexadecane in this instrument, also the quenching effect of the oxime itself upon the count rate, had previously been found.

The conversion of cyclohexanone into its oxime appeared to result in very little loss of activity; ketone of specific activity 165 $\mu\text{C mole}^{-1}$ afforded, on a number of separate conversions, samples with activities of 157, 155.5, 158, 159.5, and 157 $\mu\text{C mole}^{-1}$. Allowance was made for the small discrepancy where necessary.

Radioactive water was estimated with the aid of the scintillation system described by Hayes.¹³

Product Studies.—To a solution of cyclohexanone (0.0965 mole) in water (500 ml.) was added concentrated hydrobromic acid (47%; 100 ml.) and bromine (0.0970 mole) dissolved in 1.7M-aqueous potassium bromide. When the mixture had become colourless, the transparent oil which separated was salted out and extracted into ether. This solution was shaken with aqueous sodium carbonate and then water, and dried (Na_2SO_4). The ether was then removed and the residue was distilled (b. p. 70°/1.3 mm.). The yield of monobromocyclohexanone was 47% (Found: C, 40.6; H, 4.8; Br, 44.3. Calc. for C₆H₉OBr: 40.7; H, 5.1; Br, 44.2%).

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¹³ Hayes, *Internat. J. Appl. Radiation Isotopes*, 1956, **1**, 46.