Oxidizing Action of Hydroperoxides. VI. On the Oxidation of Ketones

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In the previous work[1], it was reported that hydroperoxides acted as a strong oxidizing agent in the presence of alkali hydroxide, and especially a vigorous reaction occurred with alkyl aryl ketone and resulted in a cleavage of C–C linkage between the carbonyl carbon and the alkyl carbon. The mechanism of this reaction must be different from the "Baeyer-Villiger" mechanism, because alkyl aryl ketone does not produce any phenolic products and diaryl ketone affords none of its reaction products.

From this point of view, the following three points were examined:

i) In the first place, it must be decided that the cleavage reaction of ketone with hydroperoxide can proceed by way of an intermediate complex, in which the hydroperoxide anion will be added to the carbonyl carbon atom of the ketone. And, if not, an active oxygen atom isolated from the hydroperoxide anion will be responsible for the cleavage reaction. In order to examine these points, a method of competitive reaction was employed; that is, with the selection of acetophenone-1-^{14}C (carbonyl ^{14}C) as a standard ketone, the reactivity among methyl derivatives of acetophenone, substituted on the methyl group, was compared.

ii) The influence of *p*-substituent to acetophenone towards the reactivity was confirmed.

iii) The progression of cleavage reaction was traced for some ketones — acetophenone, ethyl phenyl ketone and isopropyl phenyl ketone.

Experimental

Reagent. — Ketones used as reagents are all synthesized, as can be seen from the following tabulation.

Acetophenone-1-^{14}C was prepared from benzene and acetyl-1-^{14}C chloride. Acetyl-1-^{14}C chloride was synthesized from sodium acetate-1-^{14}C according to Anker's method.[2] The obtained acetophenone-1-^{14}C has b. p. 196~199°C (yield 75%). *tert*-Butyl-hydroperoxide was prepared from *tert*-butanol and

TABLE I

Ketones	(B. p.), [m. p.] °C	Semicarbazone m. p. °C	Oxime m. p. °C	2,4-Dinitrophenylhydrazone m. p.	Synthesized from
Ethyl phenyl	(105/20 mmHg), [21]				benzene and propionyl chloride
p-Chlorobenzyl phenyl	[138]		95~96		benzene and *p*-chlorophenylacetyl chloride
Isopropyl phenyl	[59~60]	175			benzene and isobutyloyl chloride
tert-Butyl phenyl	(220~222) (104~106/17 mmHg)			166~168	isopropyl phenyl ketone and methyl iodide (Halle's method)*
p-Methylacetophenone	(222)	205			toluene and acetyl chloride
p-Methoxyacetophenone	(138/14 mmHg) [38~39]	195			anisole and acetyl chloride
p-Phenylacetophenone	[120~121]		184~185		biphenyl and acetyl chloride
p-Chloroacetophenone	(99/7 mmHg), [20]	202~204			chlorobenzene and acetyl chloride
p-Bromoacetophenone	(130~131/12 mmHg) (51]				bromobenzene and acetyl chloride

* M. A. Halle and E. Bauer, *Compt. rend.*, **148**, 72 (1909).

1) K. Maruyama, This Bulletin, 33, 1516 (1960).

2) H. S. Anker, *J. Biol. Chem.*, **176**, 1333 (1948).

30% hydrogen peroxide according to Milas's method[3], b. p. 36°C/19 mmHg, n_D^{27} 1.3967.

Reaction Procedure. — *1) Competitive Reaction with Acetophenone-1-^{14}C.*—A three-necked 200cc. flask, equipped with a thermometer, a dropping funnel and a reflux condenser was placed in a thermostat, controlled to (70±1°C). A mixture of 0.01 mol. of acetophenone-1-^{14}C and 0.01 mol. of testing ketone, dissolved together in 50 g. of monochlorobenzene, was charged in the flask and the contents were agitated vigorously with a magnetic stirrer. When the temperature of the contents became constant, 0.062 mol. of finely powdered pure potassium hydroxide* was added and 0.06 mol. of *tert*-butylhydroperoxide, dissolved in 10 g. of monochlorobenzene, was dropped through a dropping funnel within three minutes. After one hour, the reaction was finished. The contents were cooled with ice, added with 50 cc. of ether and extracted with 20 cc. of water three times. The water extract was collected and acidified with 6N hydrochloric acid, and then precipitated benzoic acid was collected and purified. A hundred milligrams of the obtained benzoic acid was used for the counting** of the activity in each reaction.

2) Comparison of Reactivity of p-Substituted Acetophenone.—The same reaction apparatus as that described above was employed. A mixture of 0.02 mol. of ketone, 0.062 mol. of finely powdered pure potassium hydroxide dissolved in 50 g. of monochlorobenzene and a solution of 0.06 mol. of *tert*-butylhydroperoxide dissolved in 10 g. of monochlorobenzene was caused to react in the reaction vessel. After one hour, the reaction was ceased, the mixture was immediately cooled with ice, added with 50 cc. of ether, and extracted three times with 20 cc. of water each. The water extract was acidified with 14 cc. of 6N hydrochloric acid and extracted three times with 20 cc. of ether each. The ether extract was washed with 5 cc. of water three times, and then the ether extract was added with pure ethanol till the total volume became just 100 cc., and titrated with 0.054 N sodium hydroxide solution. Thus the obtained benzoic acid was determined.

3) Measurement of Progression of Cleavage Reaction.—In these reactions, 0.042 mol. of ketone, 0.056 mol. of *tert*-butylhydroperoxide and 0.056 mol. of finely powdered pure potassium hydroxide were used and reaction procedures were the same as in 2. The reaction mixture was not completely homogeneous, hence a pipetting-out method could not be used, and so the total reaction mixture was used for analysis after the definite time of reaction had elapsed. Therefore, to determine the cleavage velocity of a ketone, five reactions under the same conditions should be performed. In this method, the accuracy of the measurements was fairly good (see Fig. 2).

Results and Discussion

Competitive Reaction with Acetophenone-1-^{14}C. —The results are given in Table II. A relative reactivity derived from counting the amount of the benzoic acid obtained in each reaction is cited in column 4.

TABLE II. COMPETITIVE REACTION WITH ACETOPHENONE-1-^{14}C

	Ketone	Counting number*) (c. p. m.)	Reactivity
1.	$C_6H_5\cdot C(=O)\cdot CH_3$	1000±19	1
2.	$C_6H_5\cdot C(=O)\cdot CH_2CH_3$	514±15	2.9
3.	$C_6H_5\cdot C(=O)\cdot CH_2C_6H_4Cl(p)$	860±19	1.3
4.	$C_6H_5\cdot C(=O)\cdot CH(CH_3)_2$	707±19	1.8
5.	$C_6H_5\cdot C(=O)\cdot CH(CH_2{-}CH_2{-}CH_2{-}CH_2)$	1706±27	0.2
6.	$C_6H_5\cdot C(=O)\cdot C(CH_3)_3$	1111±19	0.8

*) A hundred milligrams of the obtained benzoic acid was used for the counting of the activity in every reaction.

Conditions of reactions: Temp. 70°C, reaction time 1 hr.

{acetophenone-1-^{14}C 0.01 mol. + ketone 0.01 mol.; *tert*-butyl hydroperoxide 0.06 mol.; powdered potassium hydroxide 0.062 mol.} dissolved in 60 g. of monochlorobenzene.

3) N. A. Milas and D. Sūrgenor, *J. Am. Chem. Soc.*, 68, 205, 643 (1946).

* After potassium hydroxide was added, the contents were slightly colored in brown, but soon decolorizeb when hydroperoxide was added.

** A G-M counter was applied.

TABLE III. COMPARISON OF REACTIVITY OF *p*-SUBSTITUTED ACETOPHENONE

	Ketone	Substituent	Titration neeeded volume of 0.054 N-NaOH soln. (V)
1.	$C_6H_5\cdot C(=O)\cdot CH_3$	-H	63.3
2.	$p\text{-}CH_3\cdot C_6H_4\cdot C(=O)\cdot CH_3$	$-CH_3$	34.0
3.	$p\text{-}CH_3O\cdot C_6H_4\cdot C(=O)\cdot CH_3$	$-OCH_3$	33.8
4.	$p\text{-}C_6H_5\cdot C_6H_4\cdot C(=O)\cdot CH_3$	$-C_6H_5$	65.0
5.	$p\text{-}Cl\cdot C_6H_4\cdot C(=O)\cdot CH_3$	-Cl	170.5
6.	$p\text{-}Br\cdot C_6H_4\cdot C(=O)\cdot CH_3$	-Br	212.4

Conditions of reactions: Temp. 70°C, reaction time 1 hr.
{ketone 0.02 mol., *tert*-butylhydroperoxide 0.06 mol., powdered potassium hydroxide 0.062 mol.} dissolved in 60 g. of monochlorobenzene.

From the above results, it may be seen that the successive methyl substitution on the methyl group of acetophenone produces a ketone which has the maximum reactivity upon *tert*-butylhydroperoxide in the series of acetophenone derivatives; that is, the relative reactivities of acetophenone, ethyl phenyl ketone, isopropyl phenyl ketone and *tert*-butyl phenyl ketone were about 1 : 3 : 2 : 1. On the other hand, the reactivity of *p*-chlorobenzyl phenyl ketone is one third of that of ethyl phenyl ketone. The same result is also seen in the comparison between isopropyl phenyl ketone and cyclohexyl phenyl ketone. The latter is about one tenth of the former in its reactivity. Moreover, *tert*-butyl phenyl ketone is even more reactive upon *tert*-butylhydroperoxide than cyclohexyl phenyl ketone is.

These results obtained above would lead to the conclusion that the steric effect of the alkyl group and the effect of the stability of the alkyl group as its cation are conversely responsible for the reactivity of alkyl phenyl ketone, that is, the size of the alkyl group obviously increases in the following order, $CH_3 < CH_2CH_3 < CH(CH_3)_2 < C(CH_3)_3$ and so the more bulky the alkyl group is, the larger is the steric hindrance of alkyl groups against the attack of *tert*-butylhydroperoxide on the carbonyl group (F-strain). On the other hand, the stability of the alkyl group as a cation is in the following order $CH_3 < CH_2CH_3 < CH(CH_3)_2 < C(CH_3)_3$. If the alkyl group of an alkyl aryl ketone is cleft as a cation*, the same order of the relative reactivity may be expected. Then, based on these considerations, it seems reasonable to suppose that the appearance of maximum reactivity in ethyl phenyl ketone depends upon the overlap of the conversely acting two effects.

Comparison of Reactivity of *p*-Substituted Acetophenones.—Relative reactivities of *p*-substituted acetophenones are given in Table III and their relation to Hammett's σ_p value is shown in Fig. 1. From the results obtained, it can be deduced that the more electron attractive the substituent of an acetophenone, the

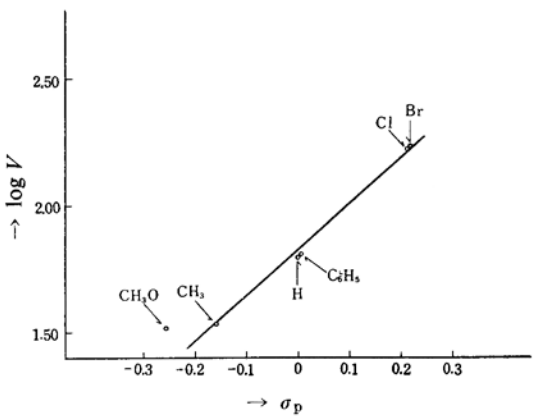


Fig. 1. The relation between σ_p value and reactivity of *p*-substituted acetophenones.

* This is also supported from the following facts: i) alcohol derived from the alkyl group was confirmed as a reaction product and ii) diaryl ketones could not be cleft by these reagents.

more reactive is the acetophenone derivative. Furthermore, Hammett's plot of log V to σ_p gives straight line (see Fig. 1). It may be deduced that, in general, an electron attractive substituent on the phenyl group raises the reactivity of acetophenone derivatives for *tert*-butylhydroperoxide.

Measurement of Progression of Cleavage.—In order to study the progression of reaction and to elucidate its mechanism, the cleavage reaction of acetophenone, ethyl phenyl ketone and isopropyl phenyl ketone was examined. From the results obtained, the following may be written (see Fig. 2).

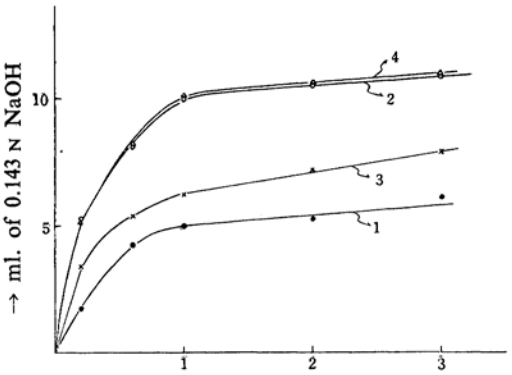


Fig. 2. Progression curve of reaction derived from titration curve of produced benzoic acid.

(1) $C_6H_5COCH_3$ 0.042 mol.
(2) $C_6H_5COC_2H_5$ 0.042 mol.
(3) $C_6H_5COCH\langle^{CH_3}_{CH_3}$ 0.042 mol.
(4) $C_6H_5COC_2H_5$ 0.042 mol.; As_2O_3 0.0005 mol.

Conditions of reactions: Temp. 70°C
ketone 0.042 mol.
tert-butylhydroperoxide 0.056 mol.
powdered potassium hydroxide 0.056 mol.
dissolved in 60 g. of monochlorobenzene.

i) There is no induction period for any reaction.

ii) The addition of arsenious acid to the reaction mixture has no effect.

iii) The reproducibility of these reactions is fairly good.

From the above three points, it might be possible to obtain the conclusion that the cleavage of ketones with hydroperoxides in the presence of alkali hydroxide is not a chain reaction.

Reaction Mechanism.—On the examination of reaction mechanism, the followings should be born in mind:

i) Alkyl aryl ketone is cleft with hydroperoxide cooperating with alkali hydroxide and produces benzoic acid derivative and alcohol derived from the alkyl group of ketone.

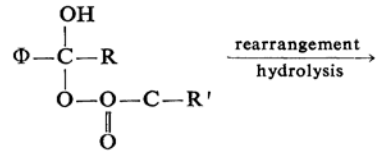
ii) Diaryl ketone (e. g. benzophenone, *p*-nitrobenzophenone and fluorenone) can not be cleft with this oxidizing reagent.

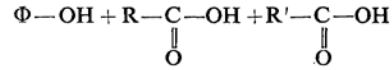
iii) In the series of methyl substituted derivatives of acetophenone having the substituent on the methyl group, a maximum reactivity is observed in ethyl phenyl ketone.

iv) In *p*-substituted derivatives of acetophenone, the more electron attractive the *p*-substituent is, the larger is the reactivity upon hydroperoxide.

v) These reactions have no induction period, and arsenious acid which is known as an inhibitor of the chain reaction has no effect.

In view of i) — iii), this cleavage reaction of ketone should be different from the "Baeyer-Villiger" reaction, which is a cleavage reaction of ketone by peracid, for the cleavage of ketone according to "Baeyer-Villiger" mechanism is of a rearrangement of carbanion to oxygen cation.

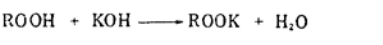




(1)

If this reaction, which is an oxidizing action of hydroperoxide cooperating with alkali hydroxide upon ketone, is supposed to follow the same mechanism as that of B. V., phenolic derivative and fatty acid must be produced, but, in fact, only benzoic acid derivative and fatty alcohol are obtained and so the C–C linkage between carbonyl carbon and phenyl carbon is not cleft. In order to explain these results conveniently, the following reaction mechanism seems very probable.

This mechanism implies that the hydroperoxide, first produces its potassium salt, and then this salt attacks carbonyl carbon and gives a complex (I), which is cleft by hydroxide anion to acid and alcohol. Reaction 3 should be a reversible reaction and the position of equilibrium would probably be settled under



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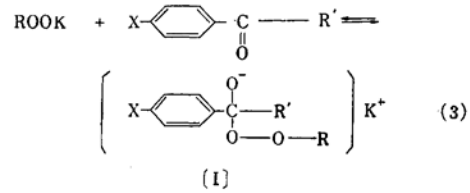

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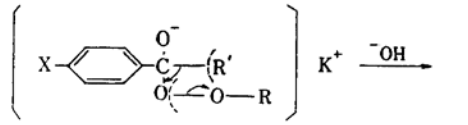
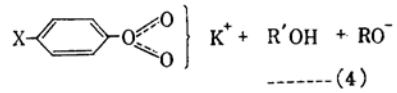
(I)





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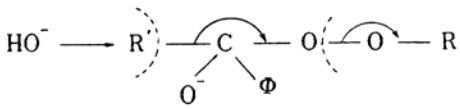
the influence of the size of alkyl group. F-Strain of alkyl group against the attack of hydroperoxide anion on the carbonyl carbon may act as a factor inhibiting the formation of complex [I]. On the other hand, the back-side attack of hydroxide anion on the alkyl group may play an important role* (Eq. 4) for the cleavage of complex I. The same equilibrium as in Eq. 3 may exist in the case of diaryl ketone, but the succeeding back-side attack of hydroxide anion would not act effectively, so that diaryl ketones could not be cleft. However, the cleavage reaction may be started by the scission of R'-cation from complex I, and a promoting action of HO^- anion for this, too, may act and at the same time the scission of RO^- anion may take place concertedly with the above process, that is:



As the result of this cleavage reaction, benzoic acid derivatives, R'OH and ROH are produced. According to this mechanism, it is quite possible that a maximum reactivity observed in ethyl phenyl ketone (discussion 3) is caused by a result of two counter-acting effects which are effects of R' cation and steric hindrance for the back-side attack of HO^- anion. Moreover, the increase of of F-strain, caused by the increase in size of the alkyl group, for the formation of complex I (Eq. 3) may contribute to the decrease of reactivity. On the other hand, the promoting action of an electron attracting substituent on the phenyl group can be explained as follows; that is, the increase of stability of the *p*-substituted benzoate anion by an electron attracting substituent may cause an increase of driving force for the cleavage reaction of the complex [I].

Contrary to the above mechanism, i) the possibility of contribution of radicals for the cleavage reaction of the complex [I], ii) the possibility of contribution of enol-type of ketone this cleavage reaction, and iii) the possibility of contribution of atomic oxygen isolated completely from ROO^- may be doubted. However, i) diaryl ketones can not be cleft and phenolic derivatives are not produced in any cleavage reaction, ii) *tert*-butyl phenyl ketone is cleft almost easily as acetophenone, and iii) when formaldehyde, acetaldehyde, propionaldehyde, acetone and methyl ethyl ketone are selected as carbonyl compounds, the decomposition velocity of hydroperoxide is strikingly different according to the structure of carbonyl compounds[5]. For example, *tert*-butylhydroperoxide did not decompose in the reaction with acetone (at 30°C), but the same hydroperoxide was decomposed in the reaction with methyl ethyl ketone under the same condition. If the isolated oxygen atom acts as an oxidizing agent, there must be no such phenomena.

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* In fact, it was confirmed that an increase of hydroxide anion, in homogeneous alkaline solution, accelerates the cleavage of the complex, which is inferred from the decomposition velocity of hydroperoxide, in the case of methyl ethyl ketone. The decomposition velocity of hydroperoxide was studied on the next two reaction mixtures;

A: methyl ethyl ketone 0.05 mol., *tert*-butylhydroperoxide 0.028 mol. and potassium hydroxide 0.03 mol. are all dissolved in 250 ml. of water.

B: methyl ethyl ketone 0.05 mol., *tert*-butylhydroperoxide 0.028 mol. and potassium hydroxide 0.06 mol. are all dissolved in 250 ml. of water.

The decomposition velocity of the hydroperoxide was in A: 0.30 mol./l hr., in B: 0.40 mol./l hr. at 35.0°C and in A: 0.49 mol./l hr., in B: 0.60 mol./l hr. at 40.2°C (unpublished work).

Cf. Maruyama, Goto and Kitamura, Oxidizing Action of Hydroperoxide III. under the contribution to *J. Chem. Soc. Japan, Pure Chem. Soc.* (*Nippon Kagaku Zasshi*).

5) O. Soga, K. Maruyama and R. Goto, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **81**, 668 (1960).