J. Chem. Soc. (B), 1971

Autoxidation of Ketones and Esters in Basic Solution

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The autoxidation of ketones and esters in aprotic solvents containing strong bases such as alkoxides was investigated extensively. Attention was paid to the autoxidation of other weakly acidic substrates such as nitriles. Schiff bases. and phenylhydrazones. The primary products are the α -hydroperoxides, which can be isolated in high yields when the oxidation is carried out at low temperatures, thus preventing their decomposition.

The first step of the reaction is ionization of the substrate to yield a resonance-stabilized anion, which subsequently reacts with oxygen.

A kinetic study showed that in some cases the oxidation is of the first order in anion and in oxygen, whereas in other cases (e.g., aliphatic esters) the ionization is the rate-determining step. Both oxidation and ionization show low activation energies (<10 kcal mol⁻¹) in aprotic systems. Arguments are advanced for a non-radical mechanism involving interaction of anion and O₂ to yield the hydroperoxide anion in one step. By considering the energies of the different steps involved it is shown that the autoxidation is favoured by the substrate being a weak acid as well as having a low C-H bond strength.

THE scope of autoxidations in basic systems has been greatly increased by the recent development of very strong bases.¹ While the older literature generally deals with substrates which are easily ionized, such as polyhydric² and hindered phenols,³ aliphatic nitro-compounds,⁴ and thiols,⁵ recent papers show that alkaline autoxidation can be extended to much weaker acids.⁶ The present work also reflects this development; it is mainly concerned with the products and mechanism of the autoxidation of esters and ketones. Other substrates with weakly acidic hydrogen atoms have been investigated only briefly.

¹ D. J. Cran, J. L. Mateos, F. Hauck, A. Langeman, K. R. Kopecky, W. D. Nielsen, and J. Allinger. *J. Amer. Chem. Soc.*, 1959, **81**, 5774, 5785.

² J. E. La Valle and A. Weissberger, J. Amer. Chem. Soc., 1947, **69**, 1567.

³ H. R. Gersmann and A. F. Bickel, J. Chem. Soc., 1959, 2711.

4 G. A. Russell, J. Amer. Chem. Soc., 1954, 76, 1595.

RESULTS

Product Studies .- Ketones. The first contribution to the alkaline autoxidation of ketones was by Doering and Haines 7 who, using t-butyl alcohol and potassium tbutoxide as solvent and base, respectively, obtained acids and aldehydes as the products. Scheme 1 was postulated to account for the results:



⁵ H. Berger, *Rec. Trav. chim.*, 1963, 82, 773.
⁶ (a) M. Avramoff and Y. Sprinzak, *Proc. Chem. Soc.*, 1962,
0; (b) H. R. Gersmann, H. J. W. Nieuwenhuis, and A. F. 150: Bickel, ibid., p. 279; (c) G. A. Russell, Adv. Chem. Sci., 1968, 75,

174. ⁷ W. von E. Doering and R. M. Haines, J. Amer. Chem. Soc., 1954, 76, 482.

Using the same solvent and base Bailey and his co-workers 8 obtained α -hydroperoxides from steroid ketones.

Our first experiments on simple aliphatic and aromatic ketones gave results essentially similar to those obtained by Doering and Haines. It was also found that most ketones with a secondary or tertiary α -hydrogen react very rapidly with oxygen, allowing of a considerably lower reaction temperature.

Even faster rates were obtained when t-butyl alcohol was partly or completely replaced by an aprotic * solvent such as 1,2-dimethoxyethane. It could be shown that in pure dimethoxyethane the ionization of most ketones is essentially complete in the presence of a slight excess of potassium t-butoxide. Autoxidation of the anions derived from ketones with tertiary α -hydrogen atoms gave the anions of the hydroperoxides; their decomposition is effectively prevented by the low temperatures employed (-10 to -80 °C). Yields were estimated by iodometric titration. In several instances the hydroperoxides were isolated by diketones may be responsible (see also Table 5). This reaction was investigated in more detail in the autoxidation of esters. Primary α -hydrogen in ketones is oxidized more slowly and in the case of asymmetric ketones such as isopropyl methyl ketone only the tertiary position is autoxidized.

Esters. Although esters are generally weaker acids than ketones and anion concentration is immeasurably small even in dimethoxyethane containing potassium t-butoxide, the autoxidation appeared to occur rapidly and again tertiary α -hydroperoxides could be obtained in high yields (Table 2). Avramoff and Sprinzak ^{6a} also obtained tertiary α -hydroperoxides from more strongly acidic substituted phenylacetates using trimethylbenzylammonium hydroxide in pyridine as base and solvent, respectively. Using phenylacetates we could also isolate secondary hydroperoxides with the potassium t-butoxide-dimethoxyethane system. A reaction temperature of -75 °C is required, while a small amount of t-butyl alcohol must be added to

TABLE 1

Oxidation	of ketones	with	α -tertiary	hydrogen	atoms	to α-ł	ivdrop	eroxides
							7 1	

Ketone (mmol)		KOBu ^t (mmol)	Solvent 	T/°C	Conversion of ketone $(\%)^{d}$	Yield on ketone converted (by titration) (%)
Isopropyl methyl ketone •	0.2	3	Α	0	100	94
Di-isopropyl ketone a	0.5	3	В	40	100	200 °
Di-isopropyl ketone	2	5	С	-5	100	65
2,6-Dimethylcyclohexanone	2.5	5	Α	-11	50	60
Isobutvrophenone	2	5	Α	10	50	65
b-Methoxyisobutyrophenone	4	10	в	-75•	86	82
Diphenylacetophenone	0.5	3	в	75°	100	80

^a The hydroperoxides from these ketones were isolated in larger scale experiments described in the Experimental section. ^b A, Dimethoxyethane-t-butyl alcohol (1:1, v/v); B, dimethoxyethane; C, 1,1-dimethylpropanol. ^e 100% dihydroperoxide. ^d Conversions were calculated from the oxygen uptake. ^e In these experiments *ca.* 20% toluene or ether was added to dimethoxyethane to avoid crystallization.

careful neutralization at low temperature and subsequent extraction, distillation, or crystallization. Results for a series of ketones with tertiary α -hydrogen are given in Table 1. From di-isopropyl ketone a mono- or a di-hydroperoxide can be obtained by applying protic or aprotic conditions, respectively. Ketones with secondary

TABLE 2

Oxidation of esters to α -hydroperoxides (0.5 mmol ester, 3 mmol potassium t-butoxide, 40 ml dimethoxyethane)

		Conversion	Yield by
		of ester	titration
Ester	T/°C	(%) a	(%)
t-Butyl isobutyrate	-40	100	>95°
t-Butyl (\pm) -2-methyl-	-40	100	>90 •
butyrate			
Ethyl phenylacetate ^b	— 75 d	100	21
t-Butyl phenylacetate	— 80 ª	100	>75°
Di-t-butyl t-butylmalonate	0	100	78

^a Conversions were calculated from the oxygen uptake. ^b 1 mmol potassium t-butoxide, 1.5 mmol t-butyl alcohol. ^c The hydroperoxides were isolated in larger scale experiments described in the Experimental section. ^d In experiments below -60 °C 20% ether or toluene was added to dimethoxyethane to avoid crystallization.

 α -hydrogen, though being rapidly autoxidized at a low temperature, only give very low hydroperoxide yields. In addition to the Doering reaction, a decomposition yielding

* An aprotic solvent is defined as a solvent which is not a proton acid under the reaction conditions.

avoid the decomposition of the hydroperoxide anion (see Experimental section).

In the rather tricky preparation of the secondary hydroperoxides derived from phenylacetates more attention was paid to the decomposition products obtained. Apart from the Doering reaction a considerable degradation to α keto-ester (phenylglyoxylate) was observed, particularly in the case of the methyl ester (Table 3).

Other compounds. In principle, the autoxidation described above is applicable to any compound containing **a** weakly acidic C-H bond. However, the isolation of the primary products often proved difficult.

Hydroperoxides could be isolated from nitriles (Table 4). These had previously only been prepared in one case *via* a rather cumbersome free-radical pathway.⁹ Phenylhydrazones autoxidized rapidly yielding very explosive hydroperoxides described by Busch and Dietz.¹⁰

No primary product could be isolated from the rapid aldehyde autoxidation. However, peroxidic products were obtained from Schiff bases.

Kinetics.—In order to elucidate the reaction mechanism the kinetics of the autoxidation were studied extensively. Preliminary experiments with a series of ketones (Table 5) clearly showed two trends: (a) primary α -hydrogen reacts less readily than secondary and tertiary α -hydrogen; and

⁸ J. E. Bailey, J. Elks, and D. H. R. Barton, Proc. Chem. Soc., 1960, 214.

⁹ M. Talât-Erben and Nevrat Onol, *Canad. J. Chem.*, 1960, **38**, 1154.

¹⁰ W. Busch and W. Dietz, Ber., 1914, 47, 3277.

(b) rates in the aprotic solvent are much higher than in t-butyl alcohol.

Final rate measurements have been carried out with ketones and esters having tertiary α -hydrogen in order to

TABLE 3

Oxidation of phenylacetates (1 mmol ester, 2 mmol potassium t-butoxide, 3 mmol t-butyl alcohol, 30 ml dimethoxyethane, 30 ml diethyl ether, temp. -80°)

	Product ratio (α-hydroperoxy-
Ester	$+ \alpha$ -hydroxy-ester) : glyoxylic ester
Methyl	12:88
Ethyľ	26:74
t-Butyl	72:28
-	

TABLE 4

Oxidation of various compounds in dimethoxyethane containing potassium t-butoxide

					Yield of
					hydro-
					peroxide
				Conver-	(by
Substrate		KOBu ^t /		sion ^a	titration)
(mmol)		mmol	T/°C	(%)	(%)
Isobutyronitrile	145	180	-40	30	50 b
Diphenylacetonitrile	1	3	-75ª	100	65 ^b
Cyclopentyl cyanide	2	3	-40	35	65
Acetone <i>p</i> -bromo- phenylhydrazone	1.4	10	-55	75	50 °
Acetophenone <i>p</i> -bromo- phenylhydrazone	1.5	10	-55	80	60 °
α-Methylindene	1.5	3	-75ª	100	~ 60
Isobutyraldehyde anil	1	3	- 75	60	80

^a Conversion was calculated from the oxygen uptake. ^b The hydroperoxides were isolated in larger scale experiments described in the Experimental section. ^e Product is very explosive. ^d See footnote to Table 2.

TABLE 5

Initial rate of oxidation of ketones in basic medium (40 ml 0·1N-potassium t-butoxide solution)

				Rate of
Ketone				oxygen uptake
(mmol)		Solvent	T/°C	(ml min ⁻¹)
Acetone	1	ButOH	40	0.5
Acetone	2	$(MeO)_{2}C_{2}H_{4}$	0	22
Acetophenone	1	Bu ^t OH	40	0.2
Acetophenone	2	$(MeO)_{2}C_{2}H_{4}$	0	$9 \cdot 2$
Ethyl methyl ketone	1	Bu ^t OH	40	2
Diethyl ketone	0.5	$(MeO)_{2}C_{2}H_{4}$	-40	> 10
Mesityl oxide	1	Bu ^t OH	40	> 15
Butyrophenone	1	ButOH	40	8·4 ª
2-Methylcyclo- hexanone	1	Bu ^t OH	40	> 15
3-Methylcyclo- hexanone	1	Bu ^t OH	40	>13
Di-isopropyl ketone	1	ButOH	40	3.8

^a Apart from the Doering decomposition products, phenylmethylglyoxal (32%) was isolated.

minimize hydroperoxide decomposition and its possible effects.

In all the runs the only variable was the substrate concentration [S], since base was always used in excess and its concentration could thus be considered constant, whilst effective stirring kept the oxygen concentration in solution in equilibrium with the constant oxygen pressure. The pseudo-first-order rate constant k' is calculated from the

equation -d[S]/dt = k'[S], where [S] is obtained from the oxygen consumption based on a l:l stoicheiometry of substrate and oxygen.

In general, the plots of log concentration against time give straight lines up to ca. 75% conversion.

The kinetics for isopropyl methyl ketone (Table 6) are of the first order in base and first order in oxygen pressure.

TABLE 6Oxidation of isopropyl methyl ketone

				Oxygen		
Ketone	Base		Sol-	pressure		
(mmol)	(mmol	l)	vent "	(mmHg)	$T/^{\circ}C$	$k_1/\min^{-1} b$
0.5	KOBu ^t	3	Α	760	0	0.115
0.5	NaOBut	3	Α	760	0	0.078
0.5	KOBut	2	Α	760	0	0.083
0.5	KOBut	4.5	Α	760	0	0.161
0.5	KOBu ^t	6	Α	760	0	0.270
0.5	KOBut	3	Α	420	0	0.062
0.5	KOBu ^t	3	Α	760	15	0.304
0.5	$KOBu^t$	3	Α	760	-10	0.076
0.5	KOBu ^t	3	Α	760	-13	0.053
0.5	KOBu ^t	3	в	760	0	2.33
0.5	KOBut	3	в	420	0	1.10
С	KOBu ^t	3	Α	760	0	0.034

^a t-Butyl alcohol-dimethoxyethane: A, 1:1(v/v); B, 1:9(v/v). ^b Pseudo-first-order rate constant; see text. ^c Diisopropyl ketone.

In addition, the strongly enhanced rate in 9:1 dimethoxyethane-Bu^tOH as compared with the 1:1 mixture should be noted.

Table 7 shows results for aliphatic esters in an aprotic medium. The pseudo-first-order rate constant is independent of the oxygen pressure and only slightly dependent on the base concentration.

TABLE 7

Oxidation of isobutyrates and 2-methylbutyrates (solvent, 40 ml dimethoxyethane; base, potassium t-butoxide)

-		-		
		$P(O_2)/$	Base	
Ester (0.5 mmol)	T/°C	mmHg	(mmol)	$k_1/\min^{-1} \sigma$
t-Butyl isobutyrate	-40	760	3	1.40
t-Butyl isobutyrate	-52	760	3	0.70
t-Butyl isobutyrate	-52	350	3	0.65
t-Butyl isobutyrate	-64	760	3	0.246
t-Butyl isobutyrate	-40	760	4.5	1.73
t-Butyl isobutyrate	-40	760	6	1.87
t-Butyl isobutyrate	-52	660	4.5	0.75
t-Butyl isobutyrate	-52	760	6	0.75
Isopropyl isobutyrate	-52	760	3	2.7
Ethyl isobutyrate	-52	760	3	~ 6.2
Methyl isobutyrate	-52	760	3	~ 8.7
t-Butyl 2-methylbutyrate	- 30	760	3	0.94
t-Butyl 2-methylbutyrate	30	350	3	0.88
t-Butyl 2-methylbutyrate	-40	760	3	0.60
t-Butyl 2-methylbutyrate	-40	350	3	0.59
t-Butyl 2-methylbutyrate	-40	760	4.5	0.72
t-Butyl 2-methylbutyrate	-40	760	6	0.72
t-Butyl 2-methylbutyrate	-52	760	3	0.24
t-Butyl 2-methylbutyrate	-52	350	3	0.24

" Pseudo-first-order rate constant.

Results on malonates in protic and aprotic media are given in Table 8. The pseudo-first-order rate constant is linearly dependent on the oxygen pressure. Since in this case the degree of ionization of the substrate is known, a second-order rate constant could be calculated from $-d[S^-]/dt = k_2[S^-][O_2]$. Arrhenius parameters for these reactions are in Table 9.

TABLE 8

Oxidation of malonates	(0.5 mmol	in 40	ml solvent)
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				Ioniz-			
Sol-		Base		ation	$P(O_2)/$	k_1	$k_2/1 \text{ mol}^{-1}$
vent ª	$T/^{\circ}\mathbf{C}$	(mmol)	(%)	mmHg	min ⁻¹ b	S-1 ¢
Di-t-bu	tyl t-but	tylmalona	te				
Α	25	$KOBu^t$	3	100	76	0.914	1.40
Α	11	KOBu ^t	3	100	76	0.461	0.72
Α	0	KOBut	3	100	76	0.246	0.38
Α	25	$KOBu^t$	3	100	15	0.174	0.290
Α	25	NaOBut	3	100	76	0.326	0.544
Α	25	KOBu ^t	1.5	100	76	0.715	1.19
в	39	KOBut	3	20 d	76	0.0306	0.22
в	35.5	KOBut	3	20	76	0.0200	0.145
\mathbf{B}	34.5	KOBut	3	20	76	0.0168	0.122
в	31	KOBut	3	20	76	0.0138	0.10
в	25.5	KOBu ^t	3	20	76	0.0081	0.058
в	20.8	KOBut	3	20	76	0.0033	0.023
Di-t-bu	ityl metł	nylmalona	te				
Α	16.5	KOBut	3	100	76	0.513	0.74
Ā	0	KOBut	3	100	76	0.278	0.40
A	-18.5	KOBut	3	100	76	0.965	0.14
Diethy	Diethyl t-butylmalonate						
A	0	KOBu ^t	3	100	76	0.024	0.032
	,		-				

^a A, Dimethoxyethane; B, dimethoxyethane-t-butyl alcohol (1:95 v/v). ^b Pseudo-first-order rate constant. ^c Second order rate constant. ^d The degree of ionization was measured at room temperature. It is assumed that the value does not show large differences in the temperature range studied.

TABLE 9

Arrhenius parameters of ionization and oxidation

Substrate	Reaction	Solvent	E_{exp}	$\log A$	<i>S</i> ‡
t-Butyl isobutyrate	Ionization	Aprotic	7300	5·2 *	- 37 *
t-Butyl a-methyl- butyrate	Ionization	Aprotic	6800	4 ∙3 *	-46 *
Isopropyl methyl ketone	Oxidation	Protic	9200	6·6 *	30 *
Di-t-butyl t-butyl- malonate	Oxidation	Aprotic	8600	6.4	-31
Di-t-butyl t-butyl- malonate	Oxidation	Protic	21,400	14.5	+6
Di-t-butyl methyl- malonate	Oxidation	Aprotic	6800	5	-37

* These values have no physical significance for the oxidation or ionization since the degree of ionization is not known.

DISCUSSION

Since the experimental results clearly indicate that the base-catalysed autoxidation proceeds via substrate anions, it is evident that the kinetics can be governed by either the ionization (1) or the oxidation (2) step.

$$RH + B^{-} \implies R^{-} + BH \qquad (1)$$

$$R^- + O_2 \longrightarrow \text{products}$$
 (2)

Ionization.—It is not possible to determine the acid strength of very weak acids in aprotic media, since the very low concentration of protons will be influenced by the method of measurement.¹¹ In these systems a comparison of acid strengths is best achieved by the quenching methods employed by House and Kramar¹² for asymmetric ketones.

The fact that the rate of autoxidation increased tremendously by going from protic to aprotic conditions led us to investigate whether measurable quantities of ketone and ester anions were present in aprotic media.

A priori chances of effecting ionization by e.g., potassium t-butoxide, did not seem favourable, since data on ketones in protic media indicated that they were generally much weaker acids than t-butyl alcohol. Surprisingly, it was found by i.r. spectroscopy that ketones could be ionized almost completely with a relatively small excess of potassium t-butoxide (Table 10). The i.r.

TABLE 10

Degree of	ionization of ketones by potassium t-butoxide
in	dimethoxyethane at room temperature

	Molar ratio	Ionization
Ketone	base : ketone	(%)
Acetone	1.7	91
Ethyl methyl ketone	2	95
Isopropyl methyl ketone	5	86
Isobutyl methyl ketone	5	100
Methyl t-butyl ketone	3.5	89
Diethyl ketone	$3 \cdot 3$	89
Di-n-propyl ketone	2	79
Di-isopropyl ketone	$3 \cdot 2$	97
Acetophenone	$2 \cdot 4$	100
Isobutvrophenone	3.3	91

spectra could be obtained in dimethoxyethane and also in benzene. A typical spectrum is shown in Figure 1. Owing to complications caused by ion-pair formation it has not yet been possible to give a complete analysis of the spectra. It could be shown, however, that an α proton is removed.

For simple aliphatic esters the independence of oxidation rate of oxygen pressure indicates that the rate of oxidation is equal to the rate of ionization. This is confirmed by chemical evidence, *viz.*, equality of oxid-



FIGURE 1 I.r. spectrum of acetone carbanion; full line, acetone with KOBu^t in benzene; broken line, acetone in benzene

ation rate and racemization rate of t-butyl (+)-isovalerate. The ionization being rate-determining, the anion concentration must be much smaller than in the case of ketones. In fact, ionization of esters was not detectable with i.r. spectroscopy, except in a few special cases such as malonates and phenylacetates.

Two distinct features of the ionization kinetics should be mentioned: (1) The activation energies are much

¹¹ R. Stewart, J. P. O'Donnell, D. J. Cram, and B. Rickborn, *Tetrahedron*, 1962, **18**, 917.

¹² H. O. House and V. Kramar, J. Org. Chem., 1963, 28, 3362.

smaller in completely aprotic medium than those measured by Cram et al.¹ for 2-methyl-3-phenylpropionitrile in dimethyl sulphoxide-methanol (9:1). This higher value is probably due to the protic solvent methanol. One can argue that in this case the ionization process first involves a desolvation of the base anion. (2) The rate of ionization decreases in the sequence methyl, ethyl, isopropyl, t-butyl esters.

As the rates of oxidation (equal to the rates of ionization) obtained for ethyl, isopropyl, and t-butyl esters (the methyl ester is ionized too quickly to obtain an accurate rate value) fit a Taft $\gamma^* \rho^*$ plot ($\rho^* = 4.6$), the influence of the alkyl group is obviously of a polar nature.13

In our experiments we invariably used an excess of base. Since the base consists of ion pairs which are

FIGURE 2 First-order rate constant in substrate in the autoxidation of di-t-butyl methylmalonate (values from Table 8); [S] = substrate concentration

probably associated, we neither expected nor found a great dependence on the base concentration.

Oxidation.—In those cases where a rate dependence on oxygen pressure was observed, it was concluded that the oxidation is rate-determining. This situation was encountered in practically all ketone oxidations (an exception being di-isopropyl ketone with sodium t-butoxide in dimethoxyethane) and in the oxidation of more acidic esters such as the malonates. Generally, a first order in oxygen pressure and a first order in substrate was found (Tables 5 and 8; Figure 2). Besides, in the protic medium the reaction is of the first order in base, which is logical because the base is well dissociated and the ketone is only slightly ionized under these conditions.

The observed kinetics can be explained by the simple mechanisms (3) and (4). However, there is some reluctance to accept such a mechanism, as it involves a

$$\mathbf{R}\mathbf{H} + \mathbf{B}^{-} \rightleftharpoons \mathbf{R}^{-} + \mathbf{B}\mathbf{H}$$
(3)

$$R^- + O_2 \longrightarrow ROO^-$$
 (4)

violation of the spin conservation 6c rule. Instead, a chain mechanism (5)—(9) has been suggested, in which

$$\mathbf{R}\mathbf{H} + \mathbf{B}^{-} \longrightarrow \mathbf{R}^{-} + \mathbf{B}\mathbf{H}$$
 (5)

$$R^- + O_2 \longrightarrow R^{\bullet} + O_2^-$$
 initiation (6)

$$R^{\bullet} + O_2 \longrightarrow ROO$$
 propagation (7)

$$ROO^{\bullet} + R^{-} \longrightarrow ROO^{-} + R^{\bullet} \int^{\text{propagation}} (8)$$

(9)

the important features are initiation by electron transfer from the carbanion to oxygen and a propagation step, again with electron transfer from the carbanion to the peroxy-radical. The latter step would explain why alkaline autoxidation can proceed at a much lower temperature than oxidation in a neutral system (where the corresponding step is a hydrogen abstraction by the peroxy-radical).

An alternative mechanism often suggested involves a catalyst as electron acceptor and donor. This mechanism was suggested for the autoxidation of hindered phenols and the kinetics were discussed in terms of reactions (10)-(13). A combination of this mechanism

$$\mathbf{R}\mathbf{H} + \mathbf{B}^{-} \mathbf{z} \mathbf{R}^{-} + \mathbf{B}\mathbf{H}$$
(10)

$$\mathbf{R}^- + \operatorname{cat} \longrightarrow \mathbf{R}^\bullet + \operatorname{cat}^- \tag{11}$$

$$R^{\bullet} + O_2 \longrightarrow ROO^{\bullet}$$
 (12)

$$ROO + cat^{\bullet} \rightarrow ROO^{-} + cat$$
 (13)

with the chain mechanism (5)—(9) can also occur. In that case the peroxy-radical accepts its electron not only from the reduced catalyst, but also from the carbanion.^{6c}

The fact that nitrobenzene can catalyse autoxidations in alkaline medium with formation of its anion radical has been used as an argument for the electron-transfer mechanism in the absence of a catalyst. This implies that nitrobenzene is a better electron acceptor than oxygen and should catalyse any autoxidation whose rate is not determined by ionization. In the case of the hindered phenols and of 2-methylhex-2-en-5-one, however, we found no catalysis by nitrobenzene. We consider it doubtful whether oxygen can accept an electron from a carbanion.

If one assumes exclusive termination by $R^{\bullet} + ROO^{\bullet}$ \rightarrow products (9) the chain mechanism (5)—(9) can also explain the observed kinetics. It is unlikely, however, that only (9) should be the termination step in all the systems investigated, since there is a large difference in rate on change of solvent. As the solubility of oxygen in the various solvents differs only slightly and no large effect is expected for the rates of reactions (7) and (9), one would expect to have $ROO^{\bullet} + ROO^{\bullet}$ termination in the slow reactions. The possibility of special preference for mixed termination cannot be excluded, however. We were able to settle this problem in favour of the direct mechanism by comparing products obtained on oxidation of suitable unsaturated esters under basic and free-radical conditions, respectively.¹⁴

¹³ P. R. Wells, *Chem. Rev.*, 1963, 63, 171.
¹⁴ H. R. Gersmann, H. J. W. Nieuwenhuis, and A. F. Bickel, Tetrahedron Letters, 1963, 1383.



Anion Reactivity.—From our kinetic study the general rule emerged that the rate of autoxidation increases as the acidity of the substrate diminishes. If one regards protonation as well as oxidation as an electrophilic attack on the carbanion this result seems plausible. Acidity is, however, not the only factor governing the oxidation rate. This becomes clear when one compares the hindered phenols with, *e.g.*, acetone: the more weakly acidic acetone is oxidized more slowly than the phenols. A rationalization of these results can be given by also taking into account the strength of the C–H bonds involved. We shall consider the energetics of the reaction and of a (hypothetical) free-radical oxidation route with the aid of Scheme 2. Proceeding via route



A-B-C we shall discuss the free energies of reactions A and C. The free energy of reaction A can be deduced from the acid strength of the substrate.¹⁵ Obviously, the weaker the acid the more positive the free energy of the ionized system $(R^- + H^+)$ will be with respect to the initial state.

Since the acid strengths of hydroperoxides will differ much less than those of the substrates (absence of resonance effects, less influence of polar effects) we assume that the free engery of process C is equal for different substrates.

Considering now route A'-B'-C' we discuss the energies of the different steps. The energy of reaction A' is determined by the strength of the C-H bond, whilst that of reaction B' involves a constant contribution from the transformation of the bonds in the O_2 molecule into the single peroxidic O-O bond and a contribution from the formation of a C-O bond. Data indicate that the latter contribution varies much less for different substrates than the C-H bond strength in reaction A'.¹⁶ We therefore assume it to be constant. Reaction C', involving the formation of the O-H bond, again gives a practically constant contribution for different substrates. In order to link routes ABC and A'B'C' for a discussion of reaction B we also assume that the entropy changes involved do not depend on the type of substrate. It follows that the free energy of reaction B is a function of the acid strength and of the strength of the substrate C-H bond.

For a weak acid RH also having a low C-H bond strength the free-energy level of $R^- + H^+$ will be high and that of ROO⁻ + H⁺ will be low both with respect to RH + O₂ and, consequently, the change in free energy of step B and its rate will be large. Extreme cases of the argument presented are depicted in Figure 3.

Interrelations between C-H bond strength and acidity exist and have the following consequences for carbanion oxidation. In comparison of acids from which resonance-stabilized carbanions are formed, more resonance stabilization corresponds with stronger acids and weaker CH bonds. The two factors are thus antagonistic in their effect on carbanion oxidation. Hence, the relative rate of carbanion oxidation is difficult to predict. In a given resonance-stabilized system, *e.g.*, the ketones, the esters, or the phenols, polar effects synergistically influence the effect of acid strength and C-H bond strength on autoxidation. For instance, electron-donating groups weaken acid strength and C-H bonds and this synergism could explain why alkyl substitution has such a marked



FIGURE 3 Energy levels; full lines, strong acid with strong C-H bond; broken lines, weak acid, weak C-H bond

effect on autoxidation rates (primary H oxidizes much more slowly than secondary or tertiary).

Apart from these thermodynamic considerations, the rates of autoxidation in basic media are also influenced by more subtle factors which cannot be discussed in this way. Important effects are believed to be caused by the charge distribution in the carbanion, the structure of ion pairs in solution, and (other) steric effects.

Scope of Autoxidation in Basic Media.—The preceding sections have shown that ionization is the key step in alkaline autoxidation. Strong bases are required to effect the ionization of the weakly acidic substrates. The KOBut-dimethoxyethane system is effective up to substrate acidities as encountered in diolefins. In that case already higher temperatures are necessary and the products become less defined. It is of course possible to use even stronger bases such as potassium amides and potassium triphenylmethide. Since these bases are themselves oxidizable they should ionize the substrate completely in stoicheiometric amounts. In many cases carbanions can therefore only be prepared by indirect methods, e.g., by way of the Grignard compounds. Generally the rate of autoxidation of these extremely weak acids is very high.¹⁷

Carbanions derived from stronger acids can easily be prepared, but are more stable towards oxygen. In these cases it is often possible to use an electron acceptor forcing the autoxidation into the free-radical (chain)

 ¹⁵ R. E. Dessy, J. Okuzumi, and A. Chen, J. Amer. Chem. Soc., 1962, 84, 2899, 2905.
 ¹⁶ T. L. Cottrell, 'The Strengths of Chemical Bonds,' Butter-

¹⁶ T. L. Cottrell, 'The Strengths of Chemical Bonds,' Butterworths, London, 1954.

¹⁷ Ch. Walling, H. Schwarz, and L. M. Marion, *J. Amer. Chem. Soc.*, 1953, **75**, 4372; S. A. Buckler, 1955, **77**, 6032.

mechanism. Representative electron acceptors are aromatic nitro-compounds, quinones, and transitionmetal ions. In our opinion oxygen is not an initiator for this reaction.

EXPERIMENTAL

Ketones.-These were commercial products. After removal of peroxides by washing with ferrous sulphate solution the ketones were distilled through a 2 m Vigreux column.

Diphenylacetophenone was prepared according to Yost.¹⁸ 2,6-Dimethylcyclohexanone was prepared by catalytic hydrogenation of 2,6-dimethylphenol and subsequent oxidation.¹⁹ p-Methoxyisobutyrophenone was prepared by acylation of anisole with an iodine catalyst according to Dominguez et al.²⁰

Esters.—Most of the carboxylic acids were commercial products. The t-butyl esters were prepared from the acids with isobutene in the presence of a small amount of dry hydrogen chloride.

(+)-2-Methylbutyric acid was prepared by oxidation of (+)-2-methylbutanol according to Marckwald.²¹ The commercial alcohol was about 80% pure, the impurity being mainly 3-methylbutanol. By distillation through a 100plate column the active alcohol was obtained pure $([\alpha]_p$ +5, 14°). The t-butyl ester had an optical rotation of $+6.12^{\circ}$ (5 cm).

t-Butylmalonic acid was prepared according to Van Woerden.22

t-Butyl Alcohol.-The commercial material was distilled through a 2 m Vigreux column. Only the fractions having m.p. $> 25 \cdot 4$ °C were used.

1,2-Dimethoxyethane.-The commercial product was refluxed for 72 h with potassium under nitrogen and then distilled. The distilled ether was heated with potassium and anthracene until the solution became blue owing to the formation of anthracene negative ion. The blue stock solution was kept under nitrogen and dimethoxyethane was distilled from it shortly before use, again under nitrogen.

Na and K t-Butoxides.-The alkoxides were prepared according to le Berre,23 the extra precaution being taken to keep the whole preparation carefully under nitrogen. The products were sublimed in a high vacuum at 150-180 °C. Rb and Cs t-butoxides were commercial. These compounds could not be purified by sublimation.

Hydroperoxides.— 2-Hydroperoxy-2,4-dimethylpentan-3one. Into a vessel provided with a separatory funnel and vibromixer, and connected to a gas burette filled with oxygen, was poured a solution of potassium t-butoxide (20 g, 0.18 mol) in t-butyl alcohol-dimethoxyethane (2:3, v/v). Di-isopropyl ketone (12 g, 0.1 mol) was added in one portion while the mixture was stirred in an oxygen atmosphere at -5 °C (bath temperature). With continued vigorous stirring at -5 °C, 2.51 of oxygen (0.1 mol) were taken up in 45 min. The mixture was then poured into ice-water (500 ml) followed by extraction with ether (500 ml). 65% Phosphoric acid (8 g) (after dilution) was added to the aqueous solution, which was then extracted with ether (250 ml). The combined ether extracts were dried

 (Na_2SO_4) and analysed for hydroperoxide by iodometric titration (0.085 mol). Ether was removed in vacuo at room temperature and the residue was taken up in pentane and cooled to -80 °C. The yield of crystalline product was 7.5 g (52%); m.p. 39-40 °C [Found: C, 57.5; H, 9.7%; equiv. (iodometric), 72.6. C₇H₁₄O₃ requires C, 57.5; H, 9.6%; equiv. 73].

3-Hydroperoxy-3-methylbutan-2-one. As above, isopropyl methyl ketone (10 g, 0.125 mol) was oxidized in t-butyl alcohol-dimethoxyethane (1:1, v/v) (500 ml) at -8 °C, 2.3 l of oxygen being taken up in 35 min. The mixture was poured into an ice-cold solution of NaHCO₃ (20 g), extracted with phosphoric acid (5 ml) at 0 °C and then with ether. The combined ether extracts were titrated The yield of hydroperoxide thus found was 65%. After removal of the ether, first in vacuo below 20 °C and then at 0.001 mmHg, the residue was taken up in pentane and the solution cooled to -80 °C to give the hydroperoxide (5.5 g; 40%), m.p. 26-27 °C (Found: C, 51.0; H, 8.8%; equiv. 61.8. $C_5H_{10}O_3$ requires C, 50.8; H, 8.5%; equiv. 59).

a-Hydroperoxide of p-methoxyisobutyrophenone. \mathbf{As} above, p-methoxyisobutyrophenone (10 g, 0.055 mol) was added to a solution of potassium t-butoxide (25 g) in dimethoxyethane (500 ml) in an atmosphere of oxygen at -75 °C. In 5 min 1.2 l of oxygen were taken up. The yield found by titration of the resulting ether solution was 85%. After removal of the ether and crystallization of the residue from hexane, the pure hydroperoxide, m.p. 63 °C, was obtained (4.57 g; 50%) (Found: C, 62.2; H, 6.7%; equiv. 111.6. C₁₁H₁₄O₄ requires C, 62.8; H, 6.7%; equiv. 105).

t-Butyl 2-hydroperoxyisobutyrate. Potassium t-butoxide (20 g, mmol) in dimethoxyethane (400 ml) was put into a vessel provided with a vibromixer and a separatory funnel and connected to a gas burette filled with oxygen. In an oxygen atmosphere t-butyl isobutyrate (10 g, 66 mmol) was then added in one portion with stirring at -10 °C. In 15 min, 1 l of oxygen (40 mmol) had been taken up. The mixture was then poured into a solution of sodium hydrogen carbonate (20 g) in water (200 ml), after which the solution was extracted with ether. After drying, the extract was analysed for hydroperoxide (31 mmol). When the ether had been removed in vacuo, the residue was taken up in pentane (50 ml) and the solution was cooled to -80 °C. The yield of crystalline hydroperoxy-ester was 62.5% on oxygen consumed; m.p. 47.5-48.5 °C [Found: C, 54.1; H, 9.2%; equiv. (iodometric), 88.9. $C_8H_{16}O_4$ requires C, 54.45; H, 9.1%; equiv. 88].

t-Butyl a-hydroperoxyphenylacetate. In an apparatus as described above t-butyl phenylacetate (5 g) was treated at -75 °C with 12.5 g of potassium t-butoxide (12.5 g) containing ca. 1 mol of t-butyl alcohol per mol of butoxide in dimethoxyethane (300 ml). The theoretical amount of oxygen was taken up in 3 min. To the mixture was then added a mixture, cooled to 0 $^{\circ}$ C, of phosphoric acid (5 g), ether (200 ml), and water (250 ml). The ether layer was dried (Na₂SO₄) and the ether removed in vacuo below 20 °C. The residue $(3\cdot 2 \text{ g})$ consisted of the crude α -hydroperoxide. The purity was ca. 90%. By recrystallization from

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- 22 H. F. Van Woerden, Rec. Trav. chim., 1963, 83, 920. 23 A. le Berre, Bull. Soc. chim. France, 1961, 1206.

¹⁸ R. S. Yost and Ch. R. Hauser, J. Amer. Chem. Soc., 1947, 69, 2325.
 ¹⁹ J. E. Nickels and W. Heintzelman, J. Org. Chem., 1950, 15,

^{1143.}

²⁰ X. A. Dominguez, B. Gormez, J. Slim, D. Giesecke, and E. Ureta, J. Amer. Chem. Soc., 1954, **76**, 5150.

pentane (b.p. 60—80 °C) the pure *hydroperoxide* was obtained; m.p. -9 °C (Found: C, 63.9; H, 7.2%, equiv., 112. C₁₂H₁₆O₄ requires C, 64.4; H, 7.2%; equiv. 112).

2-Hydroperoxyisobutyronitrile. In an apparatus described above isobutyronitrile (10 g, 145 mmol) in dimethoxyethane (500 ml) were treated with oxygen in the presence of potassium t-butoxide (20 g, 180 mmol) at -40 °C. After 10 min, 1100 ml O₂ (44 mmol) had been taken up. The reaction was quenched with phosphoric acid (15 g) in water (150 ml). Work up as usual gave crude hydroperoxide (2·3 g, 22 mmol). After evaporation of the solvent the yellow oil was distilled, b.p. 41° at 0·5 mm; yield 1·4 g; m.p. -3 to -4 °C (lit., $^{9}-8$ to -9°); $n_{\rm D}^{20}$ 1·4161 (lit., 1·4138) [Found: equiv. (titration): 114. Calc. for $C_4H_7NO_9$: equiv., 101].

 α -Hydroperoxydiphenylacetonitrile. As before, diphenylacetonitrile (1.93 g, 10 mmol) in dimethoxyethane (160 ml) were treated with oxygen in the presence of potassium t-butoxide (3.4 g) and t-butyl alcohol (7.5 ml) at -75 °C. The reaction was essentially complete in 1 min (O₂ consumption 230 ml). After quenching with acetic acid (3 mmol) in dimethoxyethane (10 ml) potassium acetate was filtered off. Iodometric titration showed a yield of 100% hydroperoxide on oxygen consumed. After removal of the solvent a 67% hydroperoxide concentrate was obtained. After crystallization from light petroleum with a little benzene, pure hydroperoxide (800 mg) was obtained; m.p. 88.5-89 °C [Found: C, 74.4; H, 4.9%; equiv. (iodometric), 220. C₁₄H₁₁NO₂ requires C, 74.7; H, 4.9%; equiv., 225].

Oxidation and Racemization of t-Butyl (+)-2-Methylbutyrate.—The experiments were carried out with ester (2 mmol) and potassium t-butoxide (6 mmol) at -52 °C. We chose these small quantities to avoid a slowing of the oxidation owing to acidic products. After reaction times of 1, 2, and 4 min the reaction was interrupted by neutralization with acetic acid in dimethoxyethane. After the potassium acetate had been filtered off, the filtrate was distilled to remove solvent. When *ca.* 1 ml of residue remained this was again filtered and the optical rotation was measured in a 5 cm micropolarimeter tube. The total ester content in the residue was determined by g.l.c.

After 40% oxidation the remaining ester had essentially retained its optical activity (errors were *ca.* 10%).

In the later stages some racemization occurred, which is obvious if we realize that the oxidation can be slowed by solvation of carbanions by the protic species formed. Carrying out the experiment under nitrogen we found that the amount racemized was ca. 8% higher than we would have expected from the oxidation.

Kinetic Measurements.—In the kinetic measurements in the strongly basic media great care had to be taken to avoid impurities. Most measurements were repeated several times and a reproducibility of 5% was reached. The apparatus is shown in Figure 4. Stirring was provided by an A.G. Chemische Apparatenbau Vibromixer. The rate of stirring was sufficient to keep the solution saturated with oxygen.

The apparatus was carefully dried by heating with a Philips i.r. lamp and evacuation. It was filled with nitrogen



and then with the reagents while under nitrogen, placed in a thermostat, and attached to a gas burette. Then nitrogen was replaced by oxygen and after temperature equilibrium had been reached the reactants were mixed by unscrewing the rod in the separatory funnel. As many reactions were very fast, a 5 s timing device was used for the readings of the gas burette. After each measurement the hydroperoxide formed was titrated.

The thermostat for the low-temperature measurements was a large Dewar vessel cooled by circulating methanol kept at -80 °C.

[0/2106 Received, December 11th, 1970]