AUTO-OXIDATION[1]

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During the past thirty years and since the important publication of Engler and Weissberg (1), a number of outstanding contributions have very ably summarized different phases of auto-oxidation as applied to both chemistry and biology. However, recent investigations of experimental as well as of theoretical importance seem to justify a summary of the field with due emphasis upon new and more recent developments. In view of the enormous amount of literature which has appeared on the various aspects of the subject during the past ten years, it will be beyond the scope of the present review to attempt to cover the field in detail. Furthermore, topics such as oxidation-reduction potentials, which have been adequately treated by Clark (2), Conant (3), Michaelis (4), and others, will be only briefly mentioned, while it is hoped that the entire field of auto-oxidation will be treated from a new point of view incorporating, as far as possible, recent ideas on activation and atomic physics.

I. INTRODUCTION

The simplest view concerning the mechanism of auto-oxidation regards it as the addition of molecular oxygen to the substance to be auto-oxidized with the subsequent formation of a highly reactive peroxide. Such a view was originally proposed by Engler and Wild (5, 1) and independently by Bach (6, 7; see also 8 and 9) and was later supported by the classical researches of Baeyer and Villiger (10), and by numerous other investigations of more recent date. In spite of all the evidence in favor of this simple interpretation, a rigorous adherence to it seems to lead to various ambiguities, and several serious objections can be raised in connection with auto-oxidations of a biological nature and of certain organic compounds such as alcohols, phenols, thioalcohols, thiophenols, hydrazobenzene, hydrazine, amino acids, methylene white, indigo white, etc. The apparent failure of these compounds to form isolable organic peroxides, their tendency to lose hydrogen atoms in the form of water or hydrogen peroxide, and the fact that they can be oxidized by other oxidizing agents in the complete absence of molecular oxygen led first Wieland (11, 12, 13) and later several other leading investigators

(14, 15) to propose that such oxidations are essentially dehydrogenations in which hydrogen atoms rather than molecular oxygen play the important rôle.

A very serious and fundamental objection which may be raised against this reasoning is the recognizable fact that dehydrogenations effected by methylene blue, indigo blue, benzoquinone, or by other so-called hydrogen acceptors are not strictly comparable to the oxidations effected by molecular oxygen. In the latter case intermediate peroxides of considerable activity are almost invariably formed; these peroxides may either result in more stable organic peroxides or liberate hydrogen peroxide. This fact will be made clearer in the main part of this review.

Some experiments of considerable significance bearing on the fundamental postulates of Wieland's theory have been recently described by Gillespie and Liu (16). They found that catalytically active palladium black prepared by the method of Gutbier (17) failed, in the complete absence of oxygen, to dehydrogenate hydroquinone. Furthermore, palladium black prepared in accordance with the method of Wieland (11) but subsequently purified by complete reduction in the presence of hydrogen also failed to dehydrogenate hydroquinone, even when this palladium had been treated with oxygen to oxidize completely the adsorbed hydrogen. The authors have also brought forward some other evidence from thermodynamic reasoning in support of their results. Obviously, therefore, it seems highly probable that the palladium which Wieland used in his researches was not sufficiently pure to warrant the conclusions he has drawn.

Moreover, the dehydrogenation theory has been the object of severe criticism by Warburg (18), Meyerhof (19), Milas (20), and others, who found it inadequate to account for oxidations effected by molecular oxygen. That dehydrogenations undoubtedly occur in many instances of biological and other auto-oxidations cannot be denied, but they occur, presumably, as secondary reactions between the primary products of auto-oxidation and the substrate.

Of the two leading interpretations of auto-oxidation which have been briefly discussed in the foregoing paragraphs, the

Engler-Bach interpretation appears to account, qualitatively at least, for a larger set of phenomena than the dehydrogenation theory. Yet, even this view, in its original form, is not adequate to account for the recent advances made in the various phases of auto-oxidation, such as, for example, negative catalysis (21, 22, 23, 24) including the chain mechanism (25, 26, 27, 28, 29) and the effect of narcotics or poisonous substances on biological oxidations (30, 19), the positive catalytic effect of peroxides and other positive catalysts (31, 32, 33), chemiluminescence (34, 35, 36), and in general, the different effects observed when kinetic studies are made of auto-oxidation reactions. Consequently, several modifications of the two leading theories have appeared in the literature from time to time to explain special cases. These will be taken up under their proper headings.

To propose a theory which will embrace all phenomena of auto-oxidation is an extremely difficult task at present, and the electronic interpretation recently proposed by Milas (20) makes an attempt to do this only in a qualitative way.

II. THE ELECTRONIC INTERPRETATION OF AUTO-OXIDATION

Briefly stated, this interpretation assumes that auto-oxidation proceeds by a preliminary addition of molecular oxygen to atoms or groups of atoms containing molecular valence electrons comparable to the molecular valence electrons of the various elements, with the subsequent formation of highly metastable or dative[2] peroxides which are characterized by high instability and energy content. Owing to their instability, these peroxides may transfer their excess energy to other molecules and thereby initiate new reaction chains either by reverting instantaneously to ordinary peroxides, or by causing intermolecular rearrangements with subsequent splitting of hydrogen peroxide or other organic peroxides.

This reasoning implies that auto-oxidations are possible only when the auto-oxidants possess unshared or "exposed" electrons

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[2] The term "dative" is used here, as elsewhere, to denote a type of covalence in which one of the atoms in the dative bond contributes both electrons. In this case the auto-oxidant contributes both electrons to the oxygen molecule.

having their spins[3] unpaired and therefore are assumed to be in reactive states. Moreover, some spectroscopic evidence in connection with electronic bands has been brought forward by Mulliken (43) and Birge (44) to show that the energy levels associated with valence electrons of molecules are analogous in all essential aspects with the valence electrons of atoms. In other words, molecular valence electrons are capable of existence in a series of electronic states.

Since these electrons are more loosely bound to the molecule than electrons whose spins are already paired, they may be assumed to be more easily affected by environmental disturbances, such as collisions with neighboring molecules or electrons, radiation, and temperature effects. It may be postulated, therefore, that *the first change which may occur in any auto-oxidation reaction* (or in any chemical reaction) *is the change in energy content of the molecular valence electrons.* This change will cause an immediate change in the vibrational energies of the molecule, thereby causing it to become activated or de-activated depending upon whether energy is added or removed.

Arrhenius was the first to point out that molecules should be in an activated state before they can take part in any chemical reaction. In the case of auto-oxidation reactions, the activation or deactivation of molecules may be governed by the following energy considerations: (*1*) The existence of activated molecules depends upon the energy levels of the molecular valence electrons present in these molecules. (*2*) The energy transfer among molecules under ordinary conditions is governed by the "resonance" relation of the quantum mechanics proposed by Kallmann and London (45). Furthermore, this energy transfer must be

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[3] The concept of spin moments of unpaired electrons as applied to chemical combination has arisen from some recent applications of quantum mechanics to chemical problems by Heitler (37), London (38), Slater (39), Pauling (40), and others, and the reader is referred to these for a detailed treatment of the concept. It may be remarked here that the electrons in unshared or "lone" electron pairs may be already loosely coupled, but activation might easily render them available for chemical combination. There exists considerable chemical evidence (41, 42) to indicate the existence of complex molecules formed by the addition of various reagents to substances containing molecular valence electrons.

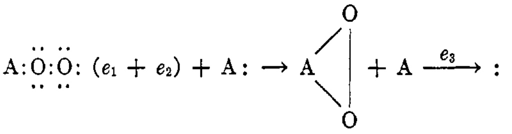
selective to account for the failure of various solvent molecules to de-activate the active molecules in question (46).

If A: represents a molecule of an auto-oxidant containing molecular valence electrons, e_1 the energy of activation, and e_2 the energy due to the pairing of spins of the electrons forming the dative bond, the changes which may occur during the first stages of the auto-oxidation of A: may be represented as follows:

$$A: + e_1 \rightarrow A \xrightarrow{e_1} : \qquad (1)$$

$$A \xrightarrow{e_1} : + \overset{..}{\underset{..}{O}}:\overset{..}{\underset{..}{O}}: \rightarrow A:\overset{..}{\underset{..}{O}}:\overset{..}{\underset{..}{O}}: (e_1 + e_2) \qquad (2)^4$$

The electrons which are directly responsible for the formation of the dative peroxide shown in equation 2 have probably undergone an increase in their principal quantum numbers due to the absorption of energy e_2. Molecules containing these electrons would be characterized by a very low energy of dissociation and extremely high instability. Mere collisions with other molecules will suffice to effect rearrangement or even decomposition of the dative peroxide with liberation of energy. This energy, according to Christiansen (25), may be utilized to initiate reaction chains.



$$A:\overset{..}{\underset{..}{O}}:\overset{..}{\underset{..}{O}}: (e_1 + e_2) + A: \rightarrow A\left\langle\begin{array}{c}O\\ |\\ O\end{array}\right. + A \xrightarrow{e_3} : \qquad (3)$$

where e_3 is the sum of e_1 and e_2. This energy increases with each subsequent reaction chain and eventually, according to Semenoff (27), may and probably does lead to explosive reactions.

If, instead of a normal auto-oxidant molecule, a normal inhibitor molecule which is in a "resonance" or "synchronous" relation with the dative peroxide should collide with it, all of its excess energy would be completely absorbed by the molecular valence

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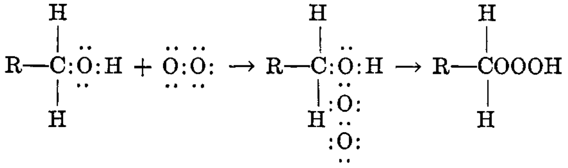
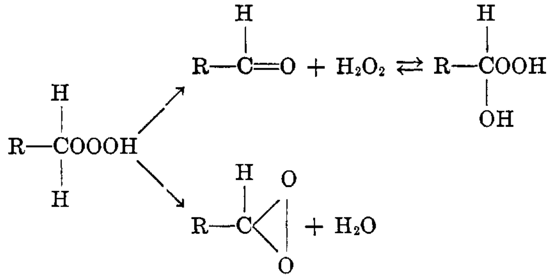
[4] It is not definitely certain that molecular oxygen reacts always in the form represented in equation 2. Oxygen represented by the "odd" electron formula proposed by G. N. Lewis (47) should not be excluded in auto-oxidation reactions, and Mithoff and Branch (48) suggested recently that little or no energy is required to activate molecular oxygen represented by this structure.

electrons of the inhibitor, which becomes partially activated. These activated molecules of the inhibitor may, then, be either oxidized by the organic peroxides, or by free oxygen, or may combine with auto-oxidant molecules forming unstable complexes which decompose, in some cases, to yield the original inhibitor molecules. Examples of all these will be found in later sections.

The theory developed in the foregoing paragraphs seems highly plausible and, in the opinion of the present author, has fewer objections than either of the two leading theories which have already been briefly discussed in the introduction. It seems to account satisfactorily for the mechanism of the auto-oxidation of substances, such as alcohols, thioalcohols, amino acids, and the like. Of particular interest is the interpretation of the auto-oxidation of alcohols, since the Engler-Bach view fails to account for the facts observed and Wieland postulates a dehydrogenation mechanism.



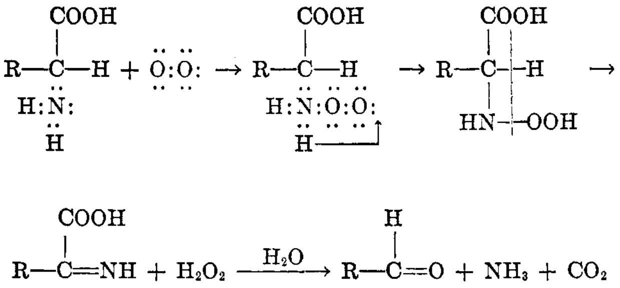
$$\mathrm{R{-}\underset{H}{\overset{H}{C}}{:}\ddot{\underset{..}{O}}{:}H + \ddot{\underset{..}{O}}{:}\ddot{\underset{..}{O}}{:} \longrightarrow R{-}\underset{H}{\overset{H}{C}}{:}\underset{:\ddot{O}:\,:\ddot{O}:}{\ddot{O}}{:}H \longrightarrow R{-}\underset{H}{\overset{H}{C}}OOOH} \qquad (4)$$



(5)

The primary addition of molecular oxygen to the hydroxyl oxygen to form a dative or oxonium peroxide (20a) will induce a positive charge on this oxygen which will have a tendency to repel the hydrogen atom originally attached to it and finally to eject it, resulting in the rearrangement shown in equation 4. The ejection of the hydrogen atom due to the coupling of the molecular valence electrons forming the dative bond may be also explained qualitatively in accordance with the recent quantum mechanical view of London (49). Such a peroxide as that which is represented by the last formula of equation 4 may be considered as a derivative of ozone and consequently assumed to be very unstable. It breaks down, yielding aldehydes and hydrogen peroxide usually, but it might also yield alkylidine peroxide and water. The aldehyde and hydrogen peroxide are known to recombine reversibly in an anhydrous medium forming α-hydroxy alkyl hydroperoxides (50). Hydrogen peroxide has been isolated from the oxidation products of alcohols by various investigators (51, 52), and very recently Conant and his students (53) postulated its formation in the allomerization (auto-oxidation) of chlorophyll, in which a secondary alcoholic group is assumed to have been auto-oxidized. That this process is an auto-oxidation phenomenon rather than a dehydrogenation is shown by its sensitiveness to foreign substances.

Analogously the oxidation of amino acids by free oxygen recently studied by Wieland and Bergel (54) may be expressed in the following manner



$$\mathrm{R{-}\underset{\underset{\displaystyle H}{H:\ddot{N}:}}{\overset{COOH}{C}}{-}H} + :\ddot{O}:\ddot{O}: \rightarrow \mathrm{R{-}\underset{\underset{\displaystyle H}{H:\ddot{N}:\ddot{O}:\ddot{O}:}}{\overset{COOH}{C}}{-}H} \rightarrow \mathrm{R{-}\underset{HN-OOH}{\overset{COOH}{C}}{-}H} \rightarrow$$

$$\mathrm{R{-}\overset{COOH}{C}{=}NH} + H_2O_2 \xrightarrow{H_2O} \mathrm{R{-}\overset{H}{C}{=}O} + NH_3 + CO_2$$

Numerous other examples may be cited but these two will suffice to show the adequacy of the view just presented. Furthermore, this view seems to give a rational explanation of the so-called activation of hydrogen usually referred to in connection with dehydrogenation reactions. Further applications of the present theory will be made in the appropriate place in this review.

III. METHODS OF STUDYING AUTO-OXIDATION REACTIONS

Auto-oxidation reactions, unlike other reactions, present numerous difficulties, owing to the formation of various intermediate products many of which can be isolated under suitable conditions. Kinetic studies of each reaction, in addition to isolation and identification of the products formed, are, therefore, very frequently necessary for the complete elucidation of the mechanism of such a reaction. The methods used for the study of auto-oxidation reactions may be divided into two classes: (*A*) those having to do with the quantitative estimation of the oxygen absorbed per unit time, and (*B*) those having to do with the estimation of the disappearance of the auto-oxidant or the progressive formation of the principal products of the reaction per unit time.

A. Quantitative methods for estimating oxygen absorption

Under this class come the various modifications of the static method. This method consists in following the oxygen absorption rate in a closed system, by determining either the decrease in volume at constant pressure or the decrease in pressure at constant volume. The simplest and most convenient, but by no means the most accurate, method, as will be shown later, is that in which the decrease in pressure is followed with time. Moureu, Dufraisse, and their collaborators (22b, 22c) and others (55) have amassed a great body of data by making use of this method. Their apparatus consists essentially of a barometric tube with the upper end bent in the shape of an inverted U-tube and connected to a small bulb containing the auto-oxidant. Pure oxygen is introduced until the pressure within the tube is the same as the atmospheric pressure. As soon as the reaction begins, the mercury within the tube rises; the degree of mercury rise is usually plotted against time. The results obtained with this method, however, are relatively accurate and useful only for purposes of comparison. The work of Reinders and Vlés (56), Reiff (57), Huber and Reid (58), Alyea and Bäckström (26b), and Milas (59) has raised certain objections against the use of this method.

The oxidation of organic liquid substances constitutes a two-phase system, and to determine the reaction rate between the two phases, the conditions must be such that the two phases are constantly in equilibrium with each other. In other words, the liquid phase must always be saturated with oxygen during the course of the reaction. Furthermore, there seems to exist a tendency in highly polymerized liquids, such as linseed oil or other "drying" oils, toward the formation of a surface film consisting chiefly of polymerized molecules which increase the viscosity of the surface layer and consequently diminish the diffusion rate of oxygen (60). Both of these objections may be overcome by rapid stirring or shaking of the reaction mixture.

Considerable changes in pressure during oxidation with oxygen are known to influence appreciably the rate of oxygen absorption. This fact has been clearly demonstrated recently by Chariton and Walta (61) and by Semenoff (62) in the case of the slow oxidation of phosphorus, by Vinogradov (63) in the case of the auto-oxidation of hydroquinone in the presence of phenolase, and by Vinogradov and Devyulin (64) in the case of the oxidation of tyrosine by oxygen. In the biological field Cook (65) has recently demonstrated that the oxygen intake by yeast cells is greatly diminished by reducing the oxygen pressure. The objection to the constantly changing pressure during the process of the reaction may, therefore, be overcome by working at constant pressure—preferably atmospheric—although the technique is slightly more difficult.

In several auto-oxidation reactions gaseous products are evolved which will not only influence the reaction, but will also increase the pressure of the system; the resulting effect would be an apparent decrease of the oxygen absorption rate. In biological oxidations this objection is overcome, in so far as the gas evolved consists of carbon dioxide, by the micro-apparatus of Barcroft and Haldane[5] (66) and that of Warburg[6] (67). In the case of other oxidations this difficulty has not yet been satisfactorily overcome.

[5] A recent description of this apparatus is given by Stephenson (68).

[6] A modified Warburg apparatus has been described recently by Hyde and Scherp (69).

B. Other methods for determining auto-oxidation

Most of the methods under this class are subject to some of the limitations described under class A. The estimation of the weight increase of the auto-oxidant with time constitutes one of the oldest methods still in use (70, 71, 72). Its use, however, is limited only to solids and liquids relatively free from any volatile products. Another method which is adaptable to substances of non-acidic nature, such as hydrocarbons and lubricating oils, deals with the estimation of organic acids formed in the course of the oxidation (73). Quite frequently other products, such as peroxides, aldehydes, alcohols, and esters, are formed which tend to diminish the accuracy of this method.

Still other methods include the use of density, refractive index, and viscosity measurements and the estimation of iodine numbers with time. These methods have been used especially in the determination of oxidation rates of "drying" oils (74). It must be borne in mind, however, that these methods are adequate only for measurements of the cumulative effect of auto-oxidation and polymerization, the latter being frequently more important with "drying" oils. Furthermore, when these methods are employed to determine the effect of inhibitors on these oils, they may lead to erroneous and often contradictory conclusions, since some inhibitors are known to affect selectively the process of auto-oxidation and polymerization.

The direct titration of the peroxides formed during the course of oxidation has been frequently employed to determine the rate of auto-oxidation reactions (75, 20a, 76). This method would be ideal and of a high degree of accuracy if the peroxides formed were sufficiently stable and did not lead to secondary reactions. Unfortunately, however, many of the peroxides are unstable and often lead to secondary oxidations. In spite of all these unavoidable difficulties, the method affords an excellent semi-quantitative comparison of the rates at which certain classes of substances oxidize. Its usefulness for the determination of the tendency of fats and oils to become rancid has been emphasized recently (76, 77).

Of particular interest are the methods which deal with the application of spectroscopy to the study of auto-oxidation problems. X-ray spectroscopy has been applied recently by Trillat (78) to the study of the auto-oxidation of unsaturated fatty acids; the results obtained are worthy of careful consideration. The method consists in spreading thin films of oils on lead plates and examining their x-ray spectra immediately, then after two to three hours, and finally after forty hours by means of the method of "turning crystal." The first and second stages gave remarkably intense x-ray spectra, while the last stage gave no spectra. The spectrum of the first stage was attributed to the lead salt of the acid under examination, the second to the formation of the "moloxide" and subsequent saturation of the double bonds, while the last stage corresponded to the complete polymerization of the acid, and therefore yielded no spectrum. Oleic, linoleic and linolenic[7] acids were chosen as typical examples. Some of the results are shown in table 1 in which d_1 and d_2 are the distances found between the planes in the space lattice before and after the addition of oxygen, and d_3 corresponds to a third x-ray spectrum found in the case of linolenic acid.

TABLE 1

X-ray data for the auto-oxidation of oleic, linoleic, and linolenic acids

SUBSTANCE	d_1	d_2	$d_2 - d_1$	d/O_2
	Å	Å	Å	Å
Oleic acid	29.8	37.5	7.7	7.7
(1 double bond)				
Linoleic acid	37.1	49.2	12.1	6.05
(2 double bonds)				
Linolenic acid	21.2[7]	28.0	6.8	6.8
(3 double bonds)		34.4 (d_3)	6.4 ($d_2 - d_3$)	6.4

These results, according to Trillat, show that the addition of a molecule of oxygen to a double bond in these acids causes an elongation of the molecule corresponding to approximately 6.78 Å. It would be of considerable interest if this method were

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[7] Linolenic acid oxidized so rapidly that it was impossible to obtain the spectrum of its lead salt. The spectra shown were those of the acid and its oxidation products.

further applied to the auto-oxidation of crystalline substances free from metallic salts such as ergosterol, abietic acid, and the like.

Molecular oxygen is known to combine with hemoglobin with extraordinary rapidity; the time interval involved is expressed in thousandths of a second. An accurate measurement of the rate of this reaction, therefore, presents a special problem requiring a special technique for its solution. A spectroscopic method of great accuracy, based on an application of the reversion spectroscope (79), has been worked out by Hartridge and Roughton (80) and successfully applied to the oxidation problem of hemoglobin. The principle involved in this method consists in a very rapid mixing of two solutions, one containing reduced hemoglobin and the other containing oxygen dissolved in water, before an appreciable combination between the two occurs. This was accomplished by forcing the solution through jets under considerable pressure and allowing them to come together at a high velocity within a restricted space. The mixture was then allowed to flow at a uniform rate through an observation glass tube, cross-sections of which were examined by the reversion spectroscope.[8] More recently the same authors have proposed a spectrophotographic method of greater accuracy than their original method (81).

IV. CRITERIA OF AUTO-OXIDATION

Very frequently auto-oxidation reactions are indistinguishable from any other chemical reaction and unless their characteristics are clearly understood their mechanism remains uncertain and highly doubtful. We have come to realize more and more, as a result of recent investigations, that there are certain criteria by which auto-oxidation reactions are usually recognized. (*A*) Auto-oxidation reactions are auto-catalytic. (*B*) They are susceptible to positive and negative catalysts. (*C*) They induce the oxidation of other substances relatively unaffected by free oxygen. (*D*) They induce the polymerization of various auto-

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[8] For a detailed description of this important method, the reader is referred to the original papers by the authors.

oxidants. (*E*) In numerous instances auto-oxidation reactions are chemiluminescent. (*F*) Susceptibility to auto-oxidation is frequently governed by the structure of the auto-oxidant. Although these characteristics are common to all auto-oxidation reactions, it must be emphasized here that not all of them are necessarily exhibited by the same reaction.

A. Auto-oxidation and auto-catalysis

1. Induction period. In section II it was shown that the rearrangement and subsequent decomposition of dative peroxides, occurring either spontaneously or by the interaction with other auto-oxidant molecules, leads to the liberation of a considerable quantity of energy in the form either of heat or of light. As a result, auto-oxidation reactions are usually found to be exothermic. Furthermore, these reactions proceed at first with a very slow, almost immeasurable, rate which increases gradually until it attains a maximum value, and then, if polymerization occurs simultaneously with the oxidation, falls off sometimes rapidly, and long before an appreciable amount of the auto-oxidant has been oxidized. Such reactions are auto-catalytic and of the chain type, and are said to be characterized by an induction period which is usually defined as the time necessary for the reaction to reach its maximum velocity. The induction period may be best illustrated by the auto-oxidation of anethole which has been studied recently by the author (24, 59). Curve 1 of figure 1 shows the uncatalyzed oxidation of anethole at 110° with an induction period of 16 minutes. The addition of 1 mole of benzoperacid to about 31 moles of anethole (curve 2) cut down the induction period to zero, while the addition of 1 mole of quinone or hydroquinone to 200 moles of anethole increased it to 169 minutes with the former (curve 3) and 388 with the latter (curve 4). Analogous results have been obtained by Brunner (82) with benzaldehyde, by Brunner and Rideal (83) with *n*-hexane, by Greenbank and Holm (84), and by Mattill (85) with fats and unsaturated fatty acids, by Dupont and Crouzet (86) with pinene, nopinene, carene, and limonene, and by Dupont and Levy (87) with abietic acid.

From these results one might conclude that the induction period is governed by the state of purity of the auto-oxidizable substance and its increase or decrease is controlled by the presence of negative or positive catalysts. This raises the question whether the induction period is an inherent property of the auto-oxidant or whether it depends upon the presence of traces of negative and positive catalysts. The answer is still vague. Michael, Scharf, and Voigt (88) claim that especially purified ethyl alcohol oxidizes with air more readily than alcohol having traces of impurities, while Brunnel (89) reports a more pronounced difference between the purified and unpurified *n*-propyl alcohol. We have had similar experiences with several substances which we purified. On the contrary, however, Kuhn and Meyer (90)

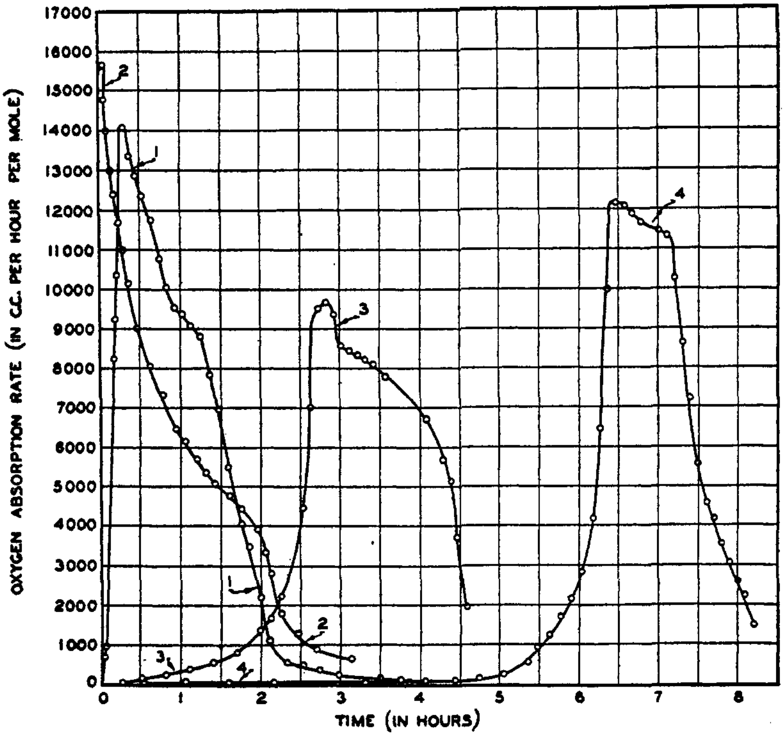


FIG. 1. AUTO-OXIDATION OF ANETHOLE

state that the auto-oxidation of benzaldehyde is essentially due to the presence of traces of heavy metals, and that when these are completely removed by careful purification benzaldehyde is obtained so pure that it no longer undergoes auto-oxidation. The conclusions of these investigators seem highly doubtful, since their determination of the auto-oxidation rates in a two-phase system, water–benzaldehyde, and in benzene is not free from inhibitory effects. Furthermore, the very recent experiments of Wieland and Richter (91) seem to indicate that although carefully purified benzaldehyde is rendered relatively inert towards oxygen when suspended in water, or when dissolved in benzene, it readily undergoes oxidation in the pure state. Moreover, benzoperacid (26a, 32) and benzoyl peroxide (33) are known to reduce the induction period of benzaldehyde and to accelerate its oxidation, yet they are free from any heavy metals. Besides, Dufraisse and Horclois (92) have found that certain iron salts have a definite inhibitory action on the oxidation of benzaldehyde, a fact which cannot be reconciled with the conclusions of Kuhn and Meyer.

B. Auto-oxidation and positive and negative catalysis

1. Positive catalysis. The acceleration of auto-oxidation reactions plays an extremely important rôle in numerous chemical and biological oxidations. Positive accelerators of auto-oxidation seem to fall under three main groups: (*a*) organic catalysts including peroxides and ozonides; (*b*) inorganic catalysts including metals, their salts, and metal complexes; and (*c*) radiation and high frequency sound waves.

(*a*) *Organic catalysts.* In the foregoing topic mention was made of the accelerating effect of benzoperacid and benzoyl peroxide, the former being far more effective than the latter. In view of its high instability when free from solvents, benzoperacid has not been widely investigated as an accelerating agent for auto-oxidations. Milas (32, 59) was the first to use it in a fairly pure form to accelerate the auto-oxidation of styrene and anethole. Benzoyl peroxide has been used by Berl and Winnacker (33) to accelerate the oxidation of benzaldehyde, and by van Loon (93) to stimulate various fermentations by yeast and *Aspergillus niger.* The observations of van Loon have recently been confirmed and extended by Proctor in collaboration with the author (94). These reactions are undoubtedly of the chain type, with the positive catalyst acting as a "trigger" to initiate the reaction chains or to increase their length. Perhaps one of the most important problems suggested in connection with organic peroxides is their application to biological oxidations. It is of particular interest to find out whether the respiration and metabolism of living tissues are really accelerated by these peroxides, and whether the mechanism of this acceleration is analogous to that of the oxidation *in vitro.* This problem is now being investigated in this laboratory with the coöperation of the biology department of the Institute.

As far as the author is aware, ozonides have not been used directly as "triggers" of auto-oxidation, while ozone has been employed, first by Semenoff and Rjabinin (95) in the oxidation of sulfur, and more recently by Spence and Taylor (96) in the auto-oxidation of ethylene. In the latter case the substance responsible for the acceleration was probably the ethylene ozonide.

A large number of organic catalysts which are closely associated with organic peroxides in plant and animal tissues are known as peroxidases and have been originally described by Schönbein (97). Inasmuch as the true chemical nature of these substances is still obscure and our present knowledge is very unsatisfactory, we shall refrain from any lengthy discussion. It may be well, however, to refer the reader to two excellent reviews on the subject recently published by Raper (98) and by Woker (98a).

Adrenaline has been found by several investigators (99,100,101) to act as a positive catalyst in various auto-oxidation reactions, especially with those taking place in living tissues. The mechanism of this catalysis is not known, although it is not unlikely that a dative peroxide formed by the addition of molecular oxygen to the nitrogen of the amino group of the adrenaline molecule may constitute the real catalyst. This view seems to find support in the recent experiments of Kisch (102), who finds that the oxidation of adrenaline by oxygen is an auto-catalytic reaction and can be accelerated by the presence of an as yet unknown oxidation product of adrenaline which is active even in dilutions of 1 to 10^8.

An important class of organic accelerators, which has been assumed to play a very significant rôle in respiration phenomena of the living cell, is that which includes compounds of the sulfhydryl group such as cysteine, glutathione, thioglycolic acid, thiolactic acid, thioglycine, etc. The importance of these substances as oxygen activators in auto-oxidation and metabolic processes has been emphasized by Thunberg (103), Hopkins (104), Abderhalden and Wertheimer (105), Meyerhof (19), and Michaelis (4). The mechanism of this catalysis is, at present, highly debatable. Warburg and Sakuma (106) maintain that the sulfhydryl catalysis is essentially a metal catalysis depending upon the oxidation of the metal complex by oxygen and its subsequent reduction by the tissue. Partial confirmation of Warburg's view is found in the experiments of Harrison (107) who found that the auto-oxidation of cysteine and glutathione is greatly diminished by removing the last traces of iron salts when subjected to careful purification in quartz vessels. The addition of small amounts of iron in the form of ferric chloride, or of hemin, produced marked changes on the oxygen absorption rate of these substances. Very recently Gerwe (108) prepared cysteine hydrochloride which contained less than 1 part of iron to 2×10^8 parts of the hydrochloride. When cysteine was freed from this salt, it was found to undergo auto-oxidation, although at a slow rate. These results seem to indicate that although the auto-oxidation of sulfhydryl compounds is highly sensitive to metallic salts, it does not depend entirely upon their presence.

Some experiments of considerable significance bearing on the catalytic effects of these substances have recently been published independently by Hopkins (109) and by Kendall, McKenzie, and Mason (110). These investigators prepared glutathione in a pure crystalline form. Contrary to early findings, this pure glutathione was shown by Dixon and Meldrum (111) to be physiologically inert. A confirmation of these results is to be found in the very recent work of Rosenthal (112) and of Voegtlin and Rosenthal (113), who found that the addition of crystalline glutathione to various tissue cells and to Baker's yeast failed to accelerate the oxygen absorption rate beyond that accounted for by the sulfhydryl compound. In addition to these results, Schöberl (114) reports a negative catalytic effect of both pure cysteine and pure glutathione on the auto-oxidation of leucomethylene blue in the presence of copper acetate as the positive catalyst. Since the auto-oxidation of sulfhydryl compounds is greatly influenced by hydrogen ion concentration, one cannot conclude, from Schöberl's results, that these compounds behave as negative catalysts in all auto-oxidation reactions, since he carried out his oxygen absorption measurements in solutions of acetic acid. In conclusion, we must admit that the sulfhydryl catalysis was in a rather unsatisfactory state at the time when this review was under preparation.

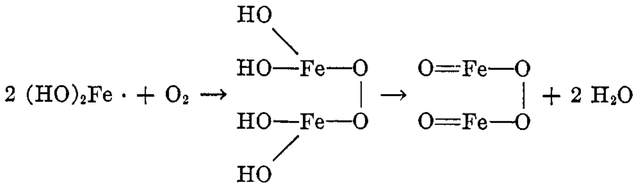
(*b*) *Inorganic catalysts, including metals, their salts, and their complexes.* A complete discussion of the positive catalytic effects of metals and metal salts on auto-oxidation reactions will be beyond the scope of this review; moreover, the subject has been adequately treated in well-known works on catalysis (115, 116).

In view of the great importance of iron catalysis in the auto-oxidation of the living cell, much work has been carried out recently both *in vitro* and *in vivo*, and under various conditions. Spoehr (117) and Spoehr and Smith (118) have shown that sodium ferro pyrophosphate is an excellent catalyst in the oxidation of glucose and other related sugars. Wieland and Franke (119) made an exhaustive study of the rate of auto-oxidation of several organic acids and other organic compounds in the presence of ferrous and ferric salts. They found that in many cases ferrous iron is more effective as a catalyst than ferric iron. In the same year Kuhn and Meyer (90) reported a marked acceleration of the auto-oxidation of benzaldehyde in the presence of iron salts. The same investigators (120) studied, in a two-phase system, the catalytic effect of hemin on the auto-oxidation of a great number of unsaturated compounds, such as fatty acids, sterols, and polyene pigments. These authors report the interesting fact that the oxidation rate of unsaturated compounds, in the presence of hemin, is governed by their structure. For example, oleic acid reacts fifty times faster than its geometric isomer, elaidic acid.

In connection with iron catalysis the recent work of Dufraisse and Horclois (92) deserves special consideration. Iron and its compounds have heretofore been considered uniquely as positive catalysts, and no one suspected otherwise until Berl and Winnacker (33) demonstrated the fact that colloidal iron acts as a negative catalyst in the auto-oxidation of benzaldehyde. To determine whether iron or any of its salts or complexes acted as negative catalysts, Dufraisse and Horclois set out to study a great number of iron salts and complexes with the following auto-oxidants: acrolein, benzaldehyde, furfural, styrene, turpentine, and sodium sulfite in slightly acid or in slightly alkaline solutions. As catalysts the authors used metallic iron, several ferrous and ferric salts, potassium ferricyanide and ferrocyanide, Prussian blue, and French blue in concentrations of 1/100; ferric acetyl acetonate in concentrations of 1/50; hemoglobin from horse and cattle blood in concentrations of 1/10, corresponding to an iron concentration of 35/100,000; oxyhemoglobin, methemoglobin, etc. Some typical examples of the results may be quoted here. Ferrous chloride is an accelerator while ferrous iodide is an inhibitor of the auto-oxidation of benzaldehyde and of acrolein. Ferrous oxide is an inhibitor of the oxidation of furfural; ferric hydroxide of sodium sulfite in slightly alkaline solution; ferric chloride of benzaldehyde and furfural; oxyhemoglobin and methemoglobin of furfural and to a less degree of acrolein. That ferrous iodide was found to be an efficient inhibitor is not difficult to understand. The perbenzoic acid formed during the auto-oxidation of benzaldehyde will undoubtedly liberate iodine from this iodide and the iodine thus formed will act as a negative catalyst. From their results the authors arrived at the conclusion that the catalytic activation of iron is variable in intensity and sign depending upon the chemical nature of the catalyst and that of the auto-oxidant. Wieland and Richter (91), on the other hand, found a slight acceleration of the oxidation rate of benzaldehyde in the presence of small quantities of ferric chloride. These investigators were able to isolate an intermediate complex of ferric iron and benzoperacid.

In biological oxidations Thunberg (121) was the first to show that small quantities of iron produced startling effects in the auto-oxidation of lecithin. Warburg (122, 18), Meyerhoff (19), and others have further demonstrated that iron salts are capable of accelerating oxidations even in the living cell.

In the catalysis of auto-oxidation reactions by iron the mechanism most frequently assumed is the activation of oxygen by the formation of an intermediate peroxide of iron. Manchot (123) was probably the first to propose that ferrous iron combines directly with molecular oxygen to form an unstable intermediate peroxide, FeO_2; more recently (124) he believes it to be Fe_2O_5 (cf. reference 125). Baudisch and Welo (126), on the other hand, proposed for the intermediate peroxide FeO_3 in the form of a coördination complex with water, $[\overset{\cdots\cdots O_2}{FeO_2}(H_2O)_5](OH)_2$. The auto-oxidation of ferrous compounds may be best explained, however, by assuming that ferrous iron, by virtue of its lone molecular valence electron, combines with oxygen like a free radical comparable to triphenylmethyl.



$$Fe_2O_4 + 2\ Fe(OH)_2 \rightarrow 2\ Fe_2O_3 + 2\ H_2O$$

A similar mechanism has been proposed recently by Hale (127), who claims to have conclusive evidence for the existence of Fe_2O_4. That the oxidation of ferrous salts is an auto-oxidation reaction is shown by the fact that it obeys the criteria set forth early in this section. Quite recently Lamb and Elder, Jr., (128) have shown that the auto-oxidation of ferrous sulfate can be inhibited by narcotics and accelerated by catalysts such as copper salts, platinum black, cocoanut charcoal, etc. In the case of cocoanut charcoal the authors isolated a peroxide which they believe is responsible for the accelerating effect of this catalyst. Still more recently Richter (129) has demonstrated that such an oxidation follows a chain mechanism, the chain length of which he measured in the case of benzyl and isopropyl alcohols as inhibitors.

Warburg (122), in proposing a mechanism for cell respiration, made the assumption originally that the primary reaction in the auto-oxidation of the living cell is that between molecular oxygen and iron, and that oxygen can react only through this reaction and not through a preliminary addition to the organic molecule. But in his latest view (130, 122b) Warburg assumes that the substance responsible for the catalytic activation of oxygen in cell respiration as a whole is an iron complex of hemin which he termed "respiration ferment." The reactions responsible for the activation of oxygen may be expressed as follows:

$$R \cdot Fe + O_2 \rightleftarrows R \cdot FeO_2$$

$$R \cdot FeO_2 + 2\,M \rightarrow R \cdot Fe + 2\,MO$$

where R·Fe represents the respiration ferment and M the respiring tissues. The strongest evidence in favor of this view, according to Warburg, lies in the fact that a large number of narcotics and poisonous substances, such as alcohols, ketones urethans, amides, and particularly hydrogen cyanide, hydrogen sulfide, and carbon monoxide, exert a strong inhibitory action on respiration and are also known to strongly inhibit most reactions catalyzed by iron. Hydrogen cyanide,[9] for example, in concentrations of 1/10,000 produces a definite inhibitory effect. These results seem to point strongly to the possibility that the auto-oxidation of the living cell might be of the chain type.

(c) *The effect of radiation and high frequency sound waves on auto-oxidation.* It is a well-known fact that radiation, especially

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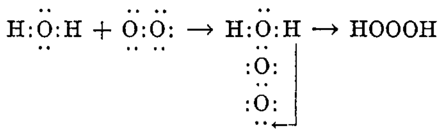
[9] Dixon and Elliot (131) have criticized Warburg's view on the grounds that it assumes complete inhibition of cell respiration by cyanide, whereas only 60 per cent inhibition is actually produced and 40 per cent must have another mechanism. Besides, an increase of cyanide concentration beyond a certain value failed to produce any noticeable effect on respiration. Warburg and Kubowitz (132) have already answered this criticism.

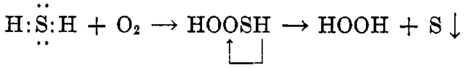
that of short wave-length, produces a marked acceleration in the rate of auto-oxidation reactions. Of recent date the investigations of Bäckström (26) with benzaldehyde, enanthaldehyde, and sodium sulfite, of Moureu, Dufraisse, and their collaborators (see section V, part A) with rubrene, of Milas (20a) with various ethers, and of Bowen and Tietz (133) with acetaldehyde fully illustrate this point. The experiments of Bäckström have shown that the photochemical oxidations as well as the thermal ones are susceptible to the action of inhibitors, and that both reactions are essentially chain reactions. Somewhat analogous results have been reported by Bowen and Tietz.

Some rather interesting and novel experiments on the acceleration of auto-oxidation reactions by ultrasonic radiation have been published recently by Schmitt, Johnson, and Olson (134). When aqueous solutions of potassium iodide, potassium chloride, potassium bromide, hydrogen sulfide, carbon tetrachloride, etc., were subjected, for a short period of time in the dark and in the presence of free oxygen, to ultrasonic radiation of high frequency —750,000 cycles per second—auto-oxidation ensued as determined by the liberation of iodine when starch-iodide was added to each solution. Even distilled water liberated iodine after a short exposure to this radiation. The mechanism of these auto-oxidations is readily understood if we apply the point of view developed in this review. Taking water and hydrogen sulfide as two typical examples we have



$$\mathrm{H{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}{:}H + \overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}{:} \rightarrow H{:}\overset{\cdot\cdot}{\underset{{:}\underset{{:}\underset{\cdot\cdot}{O}{:}}{O}{:}}{O}}{:}H \rightarrow HOOOH}$$

$$\mathrm{HOOOH + HOH \rightarrow 2\ H_2O_2}$$



$$\mathrm{H{:}\overset{\cdot\cdot}{\underset{\cdot\cdot}{S}}{:}H + O_2 \rightarrow HOOSH \rightarrow HOOH + S\downarrow}$$

$$\mathrm{HOOH + H_2S \rightarrow 2\ H_2O + S\downarrow}$$

The intermediate peroxide containing three oxygen atoms in the case of water and two in the case of hydrogen sulfide is expected to be much more active than hydrogen peroxide.[10]

2. Negative catalysis of auto-oxidation. The problem of negative catalysis has received tremendous attention during the past ten years and its solution is of inestimable practical and theoretical importance. In a period of eight years, between 1922 and 1930, Moureu, Dufraisse, and their collaborators amassed a great body of data concerning the inhibitory effect of small quantities of various substances on auto-oxidation reactions. In spite of some criticisms that may be raised against the experimental technique and the theoretical conclusions of these investigators, we must not belittle the importance of their contributions to the field as a whole. These contributions have been excellently summarized by Moureu and Dufraisse themselves (22a, 22b, 22c) and will not be described here again. Dhar (21), Taylor (23), Egerton (136), Bäckström (26), Milas (20, 24, 59), and others have also made notable contributions to the field.

Luther (137) was probably the first to propose a reasonable mechanism whereby negative catalysts or inhibitors are assumed to act by destroying the positive catalysts originally present in the auto-oxidizable substance. Moureu and Dufraisse found, however, that the Luther theory was inadequate to account for their results and proposed a general theory which is based on the mutual antagonistic destruction of the peroxides by the interaction of the original active peroxide of the auto-oxidant, A, and the negative catalyst or inhibitor, B. Assuming with Arrhenius that only the active molecules of the auto-oxidant react with molecular oxygen, this theory may be briefly outlined as follows:

$$A + O_2 \rightarrow A[O_2]$$

$$A[O_2] + B \rightarrow A[O] + B[O] \rightarrow A + B + O_2$$

or the inhibitor may be activated and oxidize directly with oxygen, as

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[10] That the oxidation of hydrogen sulfide by free oxygen is an auto-oxidation reaction having a chain mechanism has been shown very recently by Thompson and Kelland (135).

$$A + O_2 \rightarrow A[O_2];\ B + O_2 \rightarrow B[O_2]$$

$$A[O_2] + B[O_2] \rightarrow A + B + 2\ O_2$$

where the brackets indicate that the peroxide is active. Furthermore, the authors state that "it will be noted that A and O_2 have been taken from the state of activated molecules at the instant of their combination and returned to the mixture in an inactivated state."

Four main objections may be raised against this mechanism: (*a*) If activated molecules are removed from the mixture and allowed to go through the cycle represented by either one of the two sets of reactions and finally returned to the mixture inactivated, what happens to the energy of activation? Its disappearance is not accounted for. (*b*) The theory predicts a permanent inhibition which is contrary to experimental observations. In figure 1, it may be recalled, the inhibition produced on the auto-oxidation of anethole by quinone and hydroquinone is not permanent; after several hours the oxidation rate is observed to rise rapidly, and then to fall off again just as in the case of the uncatalyzed reaction. Similar results have been observed by several investigators, including Moureu and Dufraisse themselves. (*c*) If the antagonistic destruction of peroxides were true in connection with inhibitory phenomena, the addition of small quantities of an organic peroxide to a substance undergoing auto-oxidation should cause the liberation of oxygen and subsequent inhibition. This is not, however, the case and acceleration is actually observed. Furthermore, organic peroxides will not react with one another unless the oxidation potential of one is considerably higher than that of the other, and no such two peroxides will form simultaneously in a given auto-oxidation. Then, too, the interaction of the active peroxide $A[O_2]$ with B, the inhibitor, is not likely to lead to two active peroxides but presumably to two oxides partially or entirely devoid of peroxidic nature. (*d*) Finally, Christiansen (138) has shown from kinetic considerations that the mechanism proposed by Moureu and Dufraisse is not sufficient to explain the experimental facts unless it is supplemented by the assumption of some chain mechanism.

Various investigators including Dhar, Moureu and Dufraisse, Bäckström, and others, have further postulated the existence of some relationship between the inhibitory power of a negative catalyst and its oxidizability and have pointed out that the essential condition for a substance to act as a negative catalyst in auto-oxidation reactions is that it should be either "a good reducing agent" or "easily oxidizable." Numerous cases have been discovered recently in which this condition does not hold. Benzoquinone and anthraquinone are far from being easily oxidized, yet they exert a strong inhibitory action on the auto-oxidation of anethole (24). Furthermore, when anthraquinone is used as the negative catalyst it can be recovered quantitatively, within experimental error, at the end of the reaction, a fact which is at variance with the above condition. Some of the results are shown in table 2. Sulfuric acid is certainly not easily oxidized, yet in concentrations of 1/1000 in non-aqueous solvents it was recently found by Dupont and Levy (87b) to act as a strong negative catalyst in the auto-oxidation of abietic acid. Among other negative catalysts belonging to this class are ferric chloride (92), zinc chloride, mercuric chloride (91), iodine, disodium hydrogen phosphate, picric acid, trinitrotoluene, etc. Many of these inhibitors are known to form addition complexes with several auto-oxidants, and it is most likely that the formation of such complexes might prevent the propagation of reaction chains.

TABLE 2

A comparison of the amount of anthraquinone taken with the amount recovered

EXPERIMENTS	1	2	3
Anthraquinone taken in moles	0.01341	0.00268	0.000268
Anthraquinone recovered in moles	0.01313	0.00264	0.000211

Selective inhibitors are also common with many auto-oxidation reactions. For example, anthracene inhibits the auto-oxidation of benzaldehyde formed during the oxidation of styrene, or of anisaldehyde formed during the oxidation of anethole, but allows the oxidation of both styrene and anethole to proceed at a relatively high rate, similarly; iodine acts as a strong inhibitor towards benzaldehyde and as an accelerator towards styrene. Furthermore, inhibitors are far more effective during the initial stages of a given auto-oxidation than after oxidation has set in rapidly.

A critical examination of the various inhibitors, however, reveals the fact that all of them possess molecular valence electrons, but probably at different penetrations. An exchange of energy, therefore, between the inhibitor and the dative peroxide resulting in the partial activation of the former, is inevitable to inhibitory action. Moreover, this exchange of energy takes place only when the inhibitor is in a "resonance" or "synchronous" relation with the auto-oxidant. The activated molecules of the inhibitor can then be either oxidized by the organic peroxides or by free oxygen, or can combine with the active auto-oxidant molecules forming unstable complexes which may decompose to yield the original inhibitor molecules. This mechanism is in accordance with the electronic-chain interpretation of auto-oxidation proposed in section II.

A useful relationship connecting the maximum oxygen absorption rate of auto-oxidation (V_m) with the induction period (t), and the concentration of the inhibitor (C), has been proposed recently by the author (24), and has been shown to hold, within experimental error, with the auto-oxidation of anethole in which n is 2 when benzoquinone and anthraquinone are used as inhibitors. Assuming this relationship to hold, at least

$$V_m = K \frac{t}{C^{1/n}} \quad \text{or} \quad \frac{V_m C^{1/n}}{t} = K$$

with the auto-oxidation of anethole, the inhibitory constants (K) of some of the inhibitors used may be calculated. The reciprocals of these are shown in the last column of table 3.

This relationship leads one to conclude that at zero concentrations of the inhibitor the maximum oxygen absorption rate should approach infinity and the reaction should proceed explosively. This should be the case, however, only with reactions in which the reaction chains are not broken either on the walls of the reaction vessel or by other reactions proceeding simultaneously with the auto-oxidation. In the oxidation of anethole and other related substances, for example, three main reactions might be considered: the reaction between active molecules of anethole and oxygen; that between active anethole molecules themselves to form polymers which no longer react with oxygen; and that between the dative peroxide molecules themselves to form peroxide polymers. The last reaction has been proposed recently by Staudinger and Schwalbach (139).

An alternative mechanism of negative catalysis has been proposed by Reiff (57), Brunner (82), Rideal (140), and Bailey (141), who assume that auto-oxidation takes place, or is initiated at the surface of the reaction vessel, and is inhibited by the negative catalyst adsorbed in high concentration on this surface. This mechanism might be plausible with heterogeneous negative catalysis, but is quite improbable with homogeneous catalysis, although Bailey claims to have evidence that, in this case, the reaction is initiated at the gas-liquid interface and is inhibited there by the catalyst preferentially adsorbed at the interface.

TABLE 3

Inhibitory constants of various inhibitors of the oxidation of anethole

INHIBITOR	V_m	C CONCENTRATION OF INHIBITOR	t	$1/K$
	liters per hour per mole of anethole	*moles per mole of anethole*	*minutes*	
Hydroquinone	12.100	0.004998	388	434.8
Benzoquinone	9.624	0.004998	169	263.2
Anthracene	9.860	0.099980	17	5.4
Anthraquinone	6.038	0.099980	90	47.2
Phenanthrene	15.178	0.099980	8	1.6
Phenanthrenequinone	4.952	0.099980	30	19.2
Carbazole	8.408	0.099980	74	27.9
Anisaldehyde	16.272	0.099980	28	5.4

C. Auto-oxidation and induced oxidations

It has already been indicated in the foregoing topic that in many auto-oxidation reactions the inhibitor is oxidized during the oxidation, yet itself is relatively unaffected when exposed alone to free oxygen. This phenomenon is known as induced oxidation, and was probably first noticed by Schönbein (142), and described later by Kessler (143), van't Hoff (144), Jorissen (145), Traube (146), Engler and Wild (5), Job (147), Goard and Rideal (148, 125), Dhar (149), and by many others. Some specific examples are to be found in the recent experiments of Milas (24, 32) on the induced oxidation of anthracene to anthraquinone or of phenanthrene to phenanthrenequinone and thence to diphenic acid during the auto-oxidation of anethole or of styrene, of Bäckström (150, 26b) on the induced oxidation of isopropyl, *sec*-butyl, and benzyl alcohols to acetone, methyl ethyl ketone, and benzaldehyde respectively during the oxidation of sodium sulfite, of Mardles (151) on the induced oxidation of benzene to phenol, or of aniline, ethyl alcohol, etc., during the slow combustion of ethyl ether, ethane, or carbon bisulfide, of Jorissen and Van der Beek (152) on the induced oxidation of carbon tetrachloride to phosgene during the auto-oxidation of benzaldehyde, and of Jorissen (153) on the induced oxidation of several organic and inorganic substances during the oxidation of sodium sulfite.

It must be emphasized here again that not all inhibitors are necessarily inducedly oxidized, and the reverse is also known to hold in many cases. As a matter of fact, many substances which are inducedly oxidized are definitely known to accelerate auto-oxidation reactions. This is well exemplified by the induced oxidation of phenanthrene which accelerates the oxidation of anethole. Furthermore, this phenomenon is readily accounted for by the assumption that the induced oxidation will undoubtedly enhance, at least in the present case, rather than interrupt the propagation of reaction chains. Such a view may also hold with all auto-oxidation reactions in which an acceleration takes place when a foreign substance is added and the latter is inducedly oxidized. Even in oxidations in which inhibition occurs, it has not been definitely established whether it is the induced oxidation that interrupts the propagation of reaction chains, or the interaction of the oxidation products of the inhibitor with the active molecules of the auto-oxidant. The latter process seems more plausible, in the opinion of the author, in view of considerable evidence accumulated during the last few years in connection with the inhibitory effects of the oxidation products of certain inhibitors.

D. Auto-oxidation and polymerization

The effect of auto-oxidation on the polymerization of various unsaturated organic substances as exemplified by the "drying" oils in the paint and varnish industry (154), by the slow resinification of terpene-like substances and other essential oils in the presence of air, and by the gradual formation of rubber-like substances from isoprene, butadiene and its derivatives, etc., on exposure to air (155) has been known for some time. Engler and Weissberg (156) have pointed out the influence of auto-oxidation on the polymerization of styrene and its derivatives, cyclopentadiene, indene, cumarone, etc.

The elucidation of the mechanism of these reactions had its origin with the work of Stobbe and Posnjak (157), who arrived at the conclusion from kinetic studies of the polymerization of styrene to metastyrene, under the influence of light and heat, that the acceleration of such a polymerization was due to the initial formation of an "Autokatalysator" or a "Polymerizationskern." Almost simultaneously Heinemann (158) found that oxygen or ozone effected the polymerization of isoprene to rubber.[11]

Several years later Moureu, Dufraisse, and their coworkers (31) demonstrated the existence of a relationship between the auto-oxidation of acrolein and its polymerization to disacryl. No polymerization of this substance was found to occur in the dark provided oxygen was excluded, whereas either light or

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[11] Since the work of Heinemann, numerous other patents, taken in various countries, describe the polymerization of several organic substances in presence of oxygen, organic peroxides, ozone, and ozonides. In connection with this work the following recent contributions are of interest: the polymerization of styrene catalyzed by benzoperacid (32); that of isoprene, under high pressures, catalyzed by organic peroxides (159); that of vinyl acetate catalyzed by benzoyl peroxide (160); that of styrene, indene, etc. catalyzed by octylene ozonides (161); and that of styrene and cyclopentadiene catalyzed by benzoyl peroxide and diphenylethylene peroxide (162).

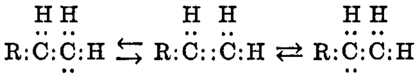
oxygen alone readily effected the polymerization. When oxygen was present in excess the photopolymerization was inhibited, most of the acrolein being oxidized rather than polymerized (cf. reference 163). This is not at all unusual, as Bäckström (164) has already pointed out, since there exists a competition between the auto-oxidation and polymerization reactions, and the active acrolein molecules are likely to react, under these conditions, more readily with oxygen than with one another to form polymers.

Polymerizations of the type here described, like auto-oxidations, are susceptible to negative catalysts, and a given negative catalyst like hydroquinone may inhibit both of these reactions at the same time. However, negative catalysts are known which will inhibit the polymerization, but allow the auto-oxidation to proceed at a relatively high rate. Anthracene, for example, inhibits completely the polymerization of styrene, but allows its oxidation to proceed at a relatively high rate.

That polymerizations of the type here described have a chain mechanism was first suggested from various considerations by Milas (165), and later confirmed by Starkweather and G. B. Taylor (160) and by H. S. Taylor and Vernon (163). In the acceleration of polymerizations by organic peroxides, the latter seem to behave as "trigger" catalysts, initiating reaction chains by reacting directly with the auto-oxidizable substances. With oxygen, polymerization is undoubtedly effected by the energy liberated during the formation of the dative peroxides, their subsequent rearrangement and decomposition of the rearranged product, their polymerization, or their reaction with the active unoxidized molecules of the auto-oxidants. Furthermore, the energy liberated as the result of polymerization of the unoxidized molecules should not be overlooked.

In cases in which polymerization and auto-oxidation occur simultaneously three possible reactions should be considered: (*a*) Auto-oxidation of the unsaturated substance. Under ordinary conditions and in the dark, this reaction is indispensable to polymerization, and usually precedes the latter. (*b*) Polymerization of or through the aid of the dative peroxides. This reaction has been particularly advocated by Staudinger (166, 139, 162) in connection with the auto-oxidation of ketenes and *unsym*-diphenylethylene, and by Morrel and Marks (167) in connection with the polymerization of "drying" oils. Staudinger further believes that the monoxides, formed from the monomer peroxides, undergo polymerization to polyoxides, but it has not been definitely established whether monoxides are ever formed or polymerize in the manner described. Direct experimental evidence in favor of the monoxide formation through auto-oxidation is certainly lacking, especially in the field of unsaturated oils. (*c*) Finally, direct polymerization of the active unsaturated molecules. In accordance with the reasoning developed in section II, these reactions may now be illustrated as follows:

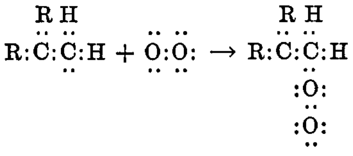
(*a*) *Auto-oxidation reaction.* The active auto-oxidant molecules may be represented by structures II and III, and the carbon atom to which the oxygen molecule initially adds depends entirely upon the nature of the group R. In auto-oxidants having symmetrical structure both II and III are likely to be present, while substances with unsymmetrical structure like styrene, *unsym*-diphenylethylene, etc., may be represented by II only.



$$\mathrm{R}{:}\overset{\mathrm{H}}{\ddot{\mathrm{C}}}{:}\underset{\cdot\cdot}{\overset{\mathrm{H}}{\ddot{\mathrm{C}}}}{:}\mathrm{H} \leftrightarrows \mathrm{R}{:}\overset{\mathrm{H}}{\ddot{\mathrm{C}}}{::}\overset{\mathrm{H}}{\ddot{\mathrm{C}}}{:}\mathrm{H} \rightleftarrows \mathrm{R}{:}\underset{\cdot\cdot}{\overset{\mathrm{H}}{\ddot{\mathrm{C}}}}{:}\overset{\mathrm{H}}{\ddot{\mathrm{C}}}{:}\mathrm{H}$$

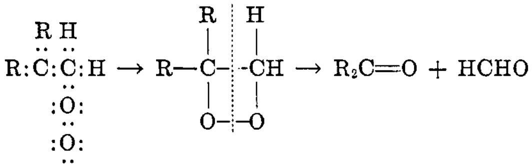
II I III

The dative peroxide for *unsym*-diphenylethylene, for example, R representing the phenyl group, is formed as follows:



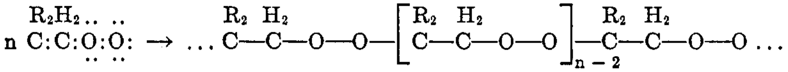
$$\mathrm{R}{:}\underset{\cdot\cdot}{\overset{\mathrm{R}}{\ddot{\mathrm{C}}}}{:}\overset{\mathrm{H}}{\ddot{\mathrm{C}}}{:}\mathrm{H} + \underset{\cdot\cdot}{\ddot{\mathrm{O}}}{:}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}{:} \rightarrow \mathrm{R}{:}\overset{\mathrm{R}}{\ddot{\mathrm{C}}}{:}\overset{\mathrm{H}}{\ddot{\mathrm{C}}}{:}\mathrm{H}\quad\begin{matrix}{:}\ddot{\mathrm{O}}{:}\\ {:}\underset{\cdot\cdot}{\ddot{\mathrm{O}}}{:}\end{matrix}$$

This dative peroxide, which is highly active and is assumed to exist only momentarily, may (*1*) rearrange to form a relatively inactive peroxide which tends to break down with liberation of energy, (*2*) undergo polymerization, or (*3*) react with active unoxidized molecules resulting in mixed polymers. In each case its excess energy is liberated and made available for the activation of other molecules, and the initiation of new reaction chains.



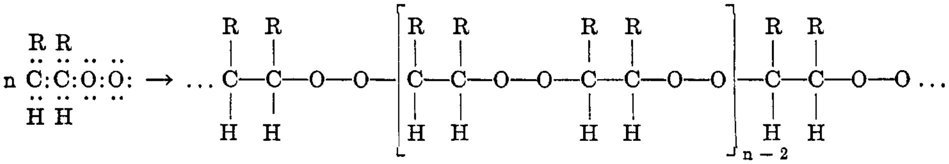
$$\begin{array}{c}R\,H\\ R{:}\ddot{C}{:}\ddot{C}{:}H\\ :\ddot{O}:\\ :\ddot{O}:\end{array} \rightarrow R\text{—}\underset{O-}{\overset{R}{C}}\text{-}\vdots\text{-}\underset{-O}{\overset{H}{C}}H \rightarrow R_2C{=}O + HCHO$$

(*b*) *Polymerization of or through the aid of the dative peroxide.* Staudinger's formulation is adopted here, not because it is free from any criticisms, but because it seems the simplest and most probable formulation at present.



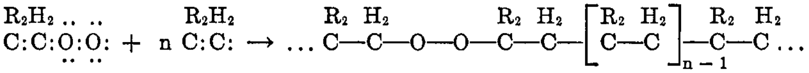
$$n\ \overset{R_2H_2\cdot\cdot\ \cdot\cdot}{C{:}C{:}\underset{\cdot\cdot}{O}{:}\underset{\cdot\cdot}{O}{:}} \rightarrow \ldots \overset{R_2}{C}—\overset{H_2}{C}—O—O—\left[\overset{R_2}{C}—\overset{H_2}{C}—O—O\right]_{n-2}—\overset{R_2}{C}—\overset{H_2}{C}—O—O\ldots$$

For a somewhat symmetrical structure as in the case of "drying" oils the following formulation is possible:



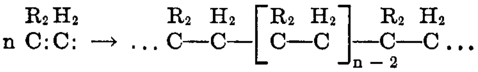
$$n\ \underset{H\,H}{\overset{R\,R}{\ddot{C}{:}\ddot{C}}}{:}\ddot{O}{:}\ddot{O}{:} \rightarrow \ldots \underset{H}{\overset{R}{C}}—\underset{H}{\overset{R}{C}}—O—O—\left[\underset{H}{\overset{R}{C}}—\underset{H}{\overset{R}{C}}—O—O—\underset{H}{\overset{R}{C}}—\underset{H}{\overset{R}{C}}—O—O\right]_{n-2}—\underset{H}{\overset{R}{C}}—\underset{H}{\overset{R}{C}}—O—O\ldots$$

and for the mixed peroxide-auto-oxidant polymer,



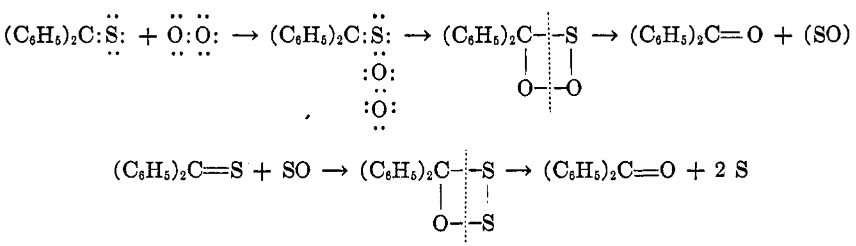
$$\overset{R_2H_2\cdot\cdot\ \cdot\cdot}{C{:}C{:}\underset{\cdot\cdot}{O}{:}\underset{\cdot\cdot}{O}{:}} + n\ \overset{R_2H_2}{C{:}C{:}} \rightarrow \ldots \overset{R_2}{C}—\overset{H_2}{C}—O—O—\overset{R_2}{C}—\overset{H_2}{C}—\left[\overset{R_2}{C}—\overset{H_2}{C}\right]_{n-1}—\overset{R_2}{C}—\overset{H_2}{C}\ldots$$

(*c*) *Direct polymerization of the active auto-oxidant molecules.* That polymerizations of this type are exothermic may be readily shown by a simple calculation of the heats of polymerization from the heats of combustion of the monomers and polymers. Besides oxygen, peroxides, ozone, or ozonides, light, especially that of short wave length, can initiate and accelerate this reaction. It may be briefly formulated as follows:



$$n\ \overset{R_2H_2}{C{:}C{:}} \rightarrow \ldots \overset{R_2}{C}—\overset{H_2}{C}—\left[\overset{R_2}{C}—\overset{H_2}{C}\right]_{n-2}—\overset{R_2}{C}—\overset{H_2}{C}\ldots$$

A very interesting polymerization induced by a preliminary auto-oxidation is that of thiobenzophenone recently studied by Staudinger and Freudenberger (168). When thiobenzophenone is allowed to oxidize slowly the following substances are formed: benzophenone, the dimer of thiobenzophenone, sulfur in *statu nascendi*, polymerized sulfur, and very small amounts of sulfur dioxide indicating, according to the authors, that the oxygen molecule had originally added to the carbon atoms rather than in the usual manner. We are inclined to disagree with this interpretation, and our analysis of the reaction leads us to the following alternative view in which molecular oxygen adds initially onto the sulfur atom.



$$(C_6H_5)_2C{:}\underset{\cdot\cdot}{\ddot{S}}{:} + \underset{\cdot\cdot}{\ddot{O}}{:}\underset{\cdot\cdot}{\ddot{O}}{:} \longrightarrow \underset{\substack{:\underset{\cdot\cdot}{O}: \\ :\underset{\cdot\cdot}{O}:}}{(C_6H_5)_2C{:}\ddot{S}{:}} \longrightarrow \begin{array}{c}(C_6H_5)_2C - S\\ |\qquad |\\ O - O\end{array} \longrightarrow (C_6H_5)_2C{=}O + (SO)$$

$$(C_6H_5)_2C{=}S + SO \longrightarrow \begin{array}{c}(C_6H_5)_2C - S\\ |\qquad |\\ O - S\end{array} \longrightarrow (C_6H_5)_2C{=}O + 2\ S$$

Part of the SO, however, will further oxidize to SO_2 and in certain cases (34) even to SO_3. All these reactions will undoubtedly liberate enough energy to induce the polymerization of thiobenzophenone to its dimer which will react will nascent sulfur to form the trisulfide.

E. Auto-oxidation and chemiluminescence[12]

Perhaps one of the earliest and well-known examples of chemiluminescence associated with auto-oxidation phenomena is that

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[12] Although chemiluminescence is produced by several other oxidations—e.g., the oxidation of pyrogallol by hydrogen peroxide in the presence of alkali (169) or peroxidases (170); the Wedekin reaction (171) consisting of the oxidation of phenylmagnesium bromide or iodide by chloropicrin which gives an intense green luminescence; the oxidation of Grignard compounds with other nitro compounds, recently studied by Gilman and his students (172); and the interesting reaction recently discovered by Albrecht (173) relating to the oxidation of aminophthalic hydrazide and some of its derivatives, which produces a rather strong luminescence visible even in concentrations of 10^{-8} mole—only those in which molecular oxygen is concerned will be discussed here.

of the auto-oxidation of white phosphorus.[13] As far back as 1877 Radziszewski (176) reported the evolution of light when substances like formaldehyde, aldehyde of ammonia, several amides, etc., auto-oxidize in the presence of alkali. A little later Perkin (177) showed that when ether vapor mixed with air was allowed to impinge on the surface of a heated copper ball, a faint bluish luminescence appeared provided the ball was not hot enough to cause ignition of the ether. The same phenomenon was observed with a number of other organic substances which have since been reported to have a tendency to promote "knocking" when used as motor fuels (178, 151).

Thorpe and Rodger (179) have found that thiophosphonyl fluoride, a colorless gas, inflamed spontaneously when mixed with air, while more recently Delépine (34) (see also Billeter and Wavre (180)) has shown that the property of chemiluminescence is general with the auto-oxidation of numerous organic sulfur compounds, especially with thiosulfocarbonates of the general type $S{=}CR_2$ where R can be methoxyl, ethoxyl, SCH_3, $N(CH_3)_2$, etc. Like other auto-oxidation reactions these are influenced by both negative and positive catalysts. For example, the addition of alkalis or ammonia intensifies the evolution of light, whereas the addition of ether, ethylene and butylene oxides, turpentine, ethyl and methyl alcohols, benzene, etc. diminishes it.

The auto-oxidation of organomagnesium halides affords another interesting example of chemiluminescence. Notable contributions to this field have been made by Moeller (181), Lifschitz (182), Evans and Dufford (183), and by Dufford and coworkers (184). The last named investigators studied over sixty different Grignard compounds, and their findings may be summarized as follows: The chemiluminescence accompanying the auto-oxidation of Grignard compounds depends upon the presence of magnesium (although calcium compounds show faint luminescence) and its direct attachment to an unsaturated car-

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[13] An excellent and thorough discussion of this reaction has been given recently by Bäckström (26a); since then, Miss Miller (174), and Bowen and Cavell (175) have carried out further some very interesting experiments on the oxidation of phosphorus.

bon atom.[14] The nature of the solvent seems to affect the intensity but not the wave-length of the emitted light, while both the wave-length and the intensity are influenced by the nature of the halogen and the organic radical attached to the magnesium atom. Furthermore, the brightness of chemiluminescence is affected by the position and nature of the second substituent group in the benzene ring. For example, p-ClC_6H_4MgBr shows a brightness of 2400 microlamberts, whereas the corresponding meta and ortho compounds show a brightness of only 205 and 14 (?) microlamberts respectively. The light given off when the Grignard compounds are oxidized with chloropicrin is different from that obtained with oxygen. When oxidized with organic peroxides, notably benzoyl peroxide, these compounds gave faint luminescence, although the authors did not try a truly active organic peroxide like benzoperacid. In this connection Lifschitz and Kalberer (182a) found benzene triozonide to be active. It is very unfortunate that the chemistry of these interesting auto-oxidations is very vague, owing to the fact that they have always been studied in solvents and that the latter have been found to be simultaneously oxidized (186). More work is, therefore, needed before a satisfactory explanation of the mechanism of these reactions can be given.

Still another source of chemiluminescence is to be found in the oxidation of silicon compounds, especially that of silikone, a solid mixture of siloxene ($H_6Si_6O_3$) and its oxidation products, studied by Kautsky and his students (35). Silicobromoform was recently reported by Schumb and Young (187) to be spontaneously inflammable on exposure to air, but its luminescence has not been further investigated. To account for chemiluminescence in oxidation reactions, Kautsky (35a) proposed the following explanation. The energy which is set free during the oxidation first remains associated with the oxidation products, which may emit part of it in the form of light or transfer it without light

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[14] Dufford (185) himself found recently that this generalization is not quite true, since several aliphatic Grignard compounds, such as methyl, ethyl, propyl and butyl compounds in which the magnesium is attached to a saturated carbon atom, give faint luminescence on auto-oxidation.

emission to neighboring molecules, raising them to higher energy levels. These, then, may revert to a state of lower energy content by emitting their excess energy as light.[15]

Chemiluminescence of another type, usually known as bioluminescence, is associated with the respiration phenomena of certain types of insects, such as the fire-fly, small crustaceans, such as *cypridina*, and numerous bacteria. It has been found by Harvey (36, 189) and others that the luminescence is emitted as a result of the oxidation of definite chemical substances produced in the luminous cell. In *cypridina*, for example, the luminescence is due to the auto-oxidation of two chemical substances, luciferin and luciferase, the latter being an enzyme. The chemical properties of these substances are excellently summarized by Harvey (189) who points out that oxygen and luciferase acting together on luciferin are indispensable to light production. No light is produced when luciferin is rapidly auto-oxidized in the absence of luciferase, nor is it produced in the presence of this enzyme when luciferin is oxidized by oxidizing agents other than molecular oxygen. He further concludes that the reaction is an oxidative dehydrogenation analogous to that of leuco-methylene blue and may be formulated as follows:

$$RH_2\text{(luciferin)} \rightarrow R\text{(oxyluciferin)} + H_2$$

$$H_2 + 1/2\ O_2 \rightarrow H_2O$$

Perhaps we ought to be reminded here that the oxidation of leuco-methylene blue with oxygen has been found recently by Macree (190) to be a true auto-oxidation reaction in which the oxygen adds initially onto methylene white to form a dative peroxide. Analogously luciferin may be assumed to auto-oxidize forming a dative peroxide rich in energy content, which rearranges and decomposes in the presence of luciferase in such a manner as to liberate part of its energy as light. That this might be the case is borne out by the work of Moureu and his collaborators (191) on the chemiluminescence emitted during the decom-

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[15] For an excellent theoretical treatment of chemiluminescence, see Griffith and McKeown (188).

position of rubrene peroxide (see p. 340). Harvey himself has proposed a mechanism involving the transfer of energy, but only from the active water molecules to luciferase which, then, re-emits it in the form of light. It is not certain, however, that water is the initial product of the auto-oxidation of luciferin, consequently the latter mechanism may not be entirely justifiable.

F. Auto-oxidation and structure

The structure of auto-oxidizable substances plays an exceedingly important rôle in determining their susceptibility to the action of molecular oxygen. Qualitatively it has been known for a long time that, other factors being constant, substances having different groups in their molecules behave differently towards molecular oxygen. However, only few quantitative studies are available in the literature. Staudinger and his students (192) studied the absorption of oxygen when weighed samples of certain aromatic aldehydes were kept in sealed tubes in excess of oxygen at 130–131°; at the end of fifteen hours the percentage of oxygen absorbed was determined. Table 4 shows some of the results obtained, which are the average of two runs for each aldehyde.

Comparative rates of auto-oxidation of several aldehydes have recently been published by Bogert and Davidson (193). Table 5 shows some of their results. The figures given represent the average maximum oxygen absorption rate in cubic centimeters of moist oxygen per minute per 4 cc. of each aldehyde. These authors have also determined the oxidation rates of several aliphatic aldehydes, and came to the conclusion that with one exception (octanal) the aliphatic aldehydes oxidize less rapidly than benzaldehyde.

The results of both groups of investigators seem to indicate that a free hydroxyl group attached to the benzene nucleus (*p*-hydroxybenzaldehyde, vanillin) has a retarding influence on the oxidation of the aldehyde. A group in the ortho position is likewise more effective than one in the para or meta positions. In making such comparisons, however, the polymerization of the aldehyde during the oxidation should not be overlooked. For example, phenylacetaldehyde (194) and *p*-nitrobenzaldehyde (192) oxidize comparatively slowly, yet they polymerize rapidly. Therefore the auto-oxidation rate alone does not determine the activity of the aldehyde group.

TABLE 4

Comparative oxidizability of certain aromatic aldehydes

ALDEHYDE	OXYGEN ABSORBED PER 15 HOURS
	per cent
Benzaldehyde	81.1
p-Acetoxybenzaldehyde	81.1
m-Methoxybenzaldehyde	72.2
p-Methoxybenzaldehyde	53.2
o-Methoxybenzaldehyde	44.4
p-Dimethylaminobenzaldehyde	31.4
p-Hydroxybenzaldehyde	5.6

TABLE 5

Maximum auto-oxidation rates of certain aldehydes

ALDEHYDE	MAXIMUM OXYGEN ABSORPTION RATE PER 4 CC. OF ALDEHYDE	
	At 22°	At 100°
	cc. per min.	*cc. per min.*
α-Amylcinnamic aldehyde	5.4	....
Cinnamic aldehyde	2.2	....
Benzaldehyde	1.6	....
p-Methoxybenzaldehyde	0.00	4.0
Piperonal	....	2.0
Vanillin	....	0.12
Ethylvanillin	....	0.10
Salicylaldehyde	....	0.00

Although different groups exert some influence on the auto-oxidation of unsaturated substances, the position of the double bond seems to be of greater significance. Isoeugenol and isosafrole, for example, are much more readily oxidizable than their corresponding isomers, eugenol and safrole. The following order with decreasing oxidizability has been found by the present author to hold for six unsaturated substances: anethole > styrene

> isoeugenol > isosafrole > eugenol > safrole. These results indicate that end double bonds are less reactive than internal ones. Similar conclusions have been reached by Kuhn and Meyer (120) with regard to the auto-oxidation of certain unsaturated fatty acids, and by Hyman and Wagner (75) in connection with the auto-oxidation of the amylenes. The reason for the difference in activity of the two types of double bonds is not well known. With unsaturated substances as with aldehydes, the polymerization rates should not be overlooked.

TABLE 6

Formation of peroxides in oxidizing ethers

ETHER	PEROXIDIC OXYGEN FORMED PER MOLE OF ETHER IN 40 HOURS
	grams
tert-Butyl benzyl	2.326
sec-Butyl ethyl	0.760
tert-Butyl ethyl	0.600
n-Butyl ethyl	0.496
Isobutyl ethyl	0.440
tert-Butyl *n*-propyl	0.360
n-Dibutyl	0.320
tert-Butyl methyl	0.117
p-Methyl cresol	0.0225
o-Methyl cresol	0.0184
Phenetole	0.0176
Anisole	0.0094
Diphenyl	0.0024

The rate with which molecular oxygen combines with ethers to form oxonium peroxides seems to be influenced largely by the nature of the groups to which the ether oxygen is attached. Aromatic groups (diphenyl ether) impart a rather high stability to the ether oxygen, whereas aliphatic groups especially when the two groups are unlike (*tert*-butyl benzyl ether) impart to it a high instability towards molecular oxygen. Table 6 shows some preliminary results recently published by the author (20a) on the auto-oxidation of certain ethers under the influence of ultraviolet radiation. With the majority of ethers studied, the total peroxide formed increases, for long periods of time, proportionately with the time of irradiation, so that the figures given in table 6 correspond to the total peroxide formed at 45°, and at the end of forty hours of irradiation calculated in grams of peroxidic oxygen formed per mole of each ether.

Numerous other examples of more or less qualitative nature are to be found in the literature, but space does not permit their discussion in this review.

V. CLASSES OF AUTO-OXIDATION REACTIONS

Auto-oxidation reactions may be conveniently divided into two classes: (*A*) Reversible auto-oxidations, sometimes termed oxygenations,[16] including those in which the oxygen addition compounds of the auto-oxidants show considerable dissociation at lower pressures or higher temperatures than those under which they are formed. (*B*) Irreversible auto-oxidations comprising those in which the molecular oxygen forms with auto-oxidants non-dissociable but often highly unstable peroxides which may rearrange or spontaneously decompose to form simpler products.

A. Reversible auto-oxidation reactions

1. Hemoglobin. For a long time hemoglobin has been the classical example of this class of auto-oxidation reactions, and its unique property of combining reversibly with molecular oxygen seems to control the entire respiratory function of the blood. In view of three excellent reviews published recently on this subject by Barcroft (196), by Hastings (197), and by Anson and Mirski (198), it would be unnecessary to discuss this topic here at any great length.

That a chemical change occurs when oxygen combines with

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[16] Conant (195) prefers to term these oxidations oxygenations, but the present author believes that this term would be confused with that used by Moureu, Dufraisse, and their collaborators to include all auto-oxidation reactions. For lack of a better term we prefer the one established by long usage, viz., auto-oxidation.

hemoglobin is evident by (*a*) the heat evolved,[17] (*b*) the change of color from dark reddish purple to scarlet, and (*c*) the increase in acidity which has been attributed to an increase in the dissociation constant of one of the hydrogen atoms in the hemoglobin molecule (201). In the oxidation of hemoglobin the assumption has been made that one molecule of oxygen combines reversibly with one molecule of hemoglobin, and such a reaction has been found to obey the mass action law.

$$\mathrm{Hb + O_2 \rightleftarrows HbO_2} \qquad (1)$$

This view requires that the equilibrium curve should be a rectangular hyperbola. However, equation 1 was deduced on the assumption that hemoglobin has a molecular weight of 16700 as determined from its content of iron, which is present to the extent of one atom to each molecule of oxygen absorbed. But recent determinations of the molecular weight of hemoglobin by two independent methods (202, 203) have shown that the molecular weight is not 16700, but four times this value. This, of course, necessitates that equation 1 should be written as follows:

$$\mathrm{Hb_4 + 4\ O_2 \rightleftarrows Hb_4O_8} \qquad (2)$$

The equilibrium curve represented by equation 2 is no longer a rectangular hyperbola, but one with a large inflection. Such a formulation, therefore, introduces a difficulty which can be overcome only by making the assumption that the reaction takes place in steps in which the existence of intermediate compounds is postulated.

$$\mathrm{Hb_4 + O_2 \rightleftarrows Hb_4O_2} \qquad (3)$$

$$\mathrm{Hb_4O_2 + O_2 \rightleftarrows Hb_4O_4} \qquad (4)$$

$$\mathrm{Hb_4O_4 + O_2 \rightleftarrows Hb_4O_6} \qquad (5)$$

$$\mathrm{Hb_4O_6 + O_2 \rightleftarrows Hb_4O_8} \qquad (6)$$

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[17] The heat evolved when one gram molecule of oxygen combines with hemoglobin has been determined by several investigators (Barcroft (196), page 186), but no two seem to agree; the values given vary from 5,350 calories at 38° (199) to 15,000 calories at 34° (200). It would be of interest to compare this value with that obtained when one gram molecule of oxygen combines with benzaldehyde to form benzoperacid, a non-reversible peroxide. This has been estimated by Bäckström (26a) to be about 47,000 calories.

The intermediate compounds Hb_4O_2, Hb_4O_4, Hb_4O_6, according to Conant and McGrew (195), would be expected to be more soluble than the completely auto-oxidized product, and might be easily separated from it. An attempt made by these investigators to isolate the intermediate products was entirely unsuccessful. Therefore, the present mechanism of the reversible auto-oxidation of hemoglobin seems to rest still entirely on the possibility of the existence of these intermediate products.

The question may now be raised, if hemoglobin forms a compound with oxygen, what type of union has been established? Is it non-polar, or is it a dative or coördinated union like that postulated under section II? If it is the latter, is it between the iron atom and the oxygen molecule, or is it between some other highly unsaturated part of the hemoglobin molecule and oxygen? It is well known that removal of the iron atom from hemoglobin deprives the latter of the property of combining reversibly with oxygen. Yet when hemoglobin is subjected to a series of careful purifications, it becomes less and less active towards oxygen for every successive purification, until finally it loses its power to combine reversibly with the latter, though it still contains iron. Moreover, oxyhemoglobin does not behave like a peroxide although under certain conditions it might be made to act as though it contained active oxygen.[18] For example, Roaf and Smart (204), and independently Quagliarello (205), found that the addition of acid to oxyhemoglobin caused the liberation of only 50 per cent of the oxygen bound to it; the remaining 50 per cent caused the conversion of oxyhemoglobin to methemoglobin which they represented by HbO. It is now known that substances containing peroxides cause this transformation to take place (206), and one might conclude that in the case cited above some of the oxygen of the oxyhemoglobin had been converted into active oxygen. This is not at all surprising since the respiration ferment of Warburg (130), which, according to him, is closely related to hemin, the iron complex portion of

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[18] If all the oxygen bound to hemoglobin were of peroxidic nature, the active oxygen would be less than 0.1 per cent, an amount which is very small yet easily detectable.

hemoglobin, activates oxygen, and in so doing develops oxidizing and catalytic powers. Hemoglobin differs from this ferment in that it has no catalytic powers; it even fails to utilize its oxygen on the way from the lungs to the tissues.

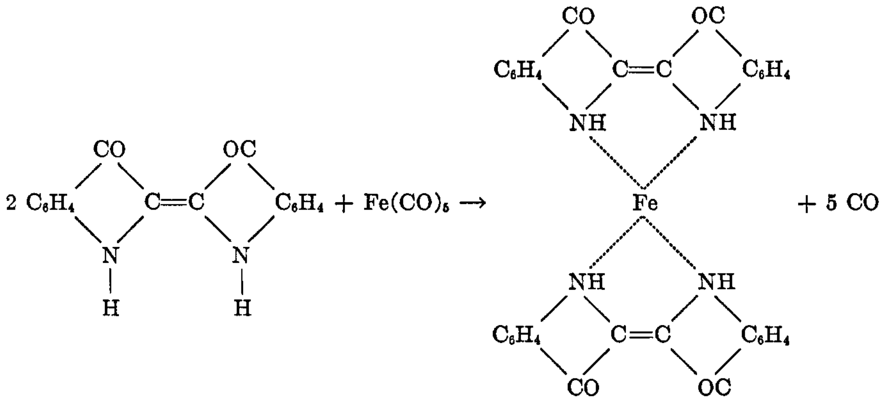
From what has been said in the foregoing paragraph, one may conclude that the valence problem as applied to oxyhemoglobin is not as simple as it may seem. Its solution may be facilitated only by a thorough study of simpler auto-oxidants of known structure possessing the property of combining reversibly with oxygen.

2. Hemocyanin. Hemocyanin is another substance of biological nature which combines reversibly with oxygen (207, 208).

$$\mathrm{Hcy} + \mathrm{O_2} \rightleftarrows \mathrm{HcyO_2} \qquad (1)$$

This property of hemocyanin has been found to be responsible for the control of the respiratory function of the blood of certain classes of invertebrate animals such as crabs, lobsters, snails, etc. The mechanism of oxygen transport in the blood of these animals is subject to the same laws as that in the blood of vertebrates. The only apparent difference between hemocyanin and hemoglobin is that the former contains a copper–pyrrole complex rather than iron, and that the ratio of copper to the bound oxygen is two atoms of the former to one molecule of the latter. However, with hemocyanin as with hemoglobin, we are confronted with the same difficulty when we attempt to examine the nature of the union between oxygen and this substance.

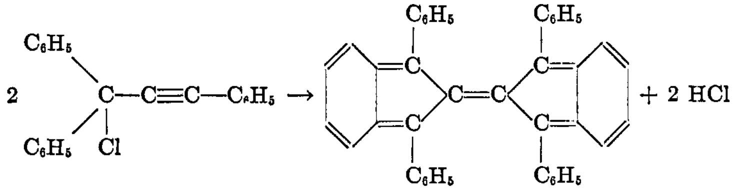
3. The synthesis of a "respiring model." Quite recently Kunz and Kress (209) made the important synthesis of an iron complex of indigo blue, which, according to these investigators, is capable of combining reversibly with oxygen. They prepared it by allowing iron carbonyl in excess to react with indigo blue in an anhydrous pyridine solution. The product is a yellowish red crystalline substance containing one atom of iron to two moles of indigo blue. One may formulate the reaction as follows:



The iron in such a complex is assumed to be held very loosely by the subsidiary valences of the nitrogen atoms (cf. Kuhn and Machemer (210) and Machemer (211)), since dilute acids and even water decompose the complex with regeneration of indigo blue. On bubbling dry oxygen through a pyridine solution of the complex, the red color of the solution becomes green and a compound is formed containing one molecule of oxygen to one atom of iron. At low pressures and moderate temperatures, all the oxygen is removed and the solution turns red again. If, however, the green solution is kept on ice for some time, the oxygen becomes firmly bound and cannot be removed either by vacuum or by heat. On long standing at room temperature, the green solution becomes red, the oxygen having been utilized to oxidize some of the indigo to isatin and a colorless by-product. This reaction is facilitated by heat. Dry hydrogen cyanide inhibits the addition of oxygen to the complex, and only by very long bubbling of oxygen does the solution change in color to green. Unlike hemoglobin or the respiration ferment of Warburg, the indigo complex fails to form an addition compound with carbon monoxide, although it does combine with nitric oxide.

From the foregoing remarks one may easily conclude that the mechanism of the auto-oxidation of the iron–indigo complex might be analogous to that of the auto-oxidation of hemoglobin. Furthermore, the primary oxygen addition seems to be very loose and has a tendency to become more firmly bound. According to Kunz and Kress, the oxygen molecule adds on to the metal of the complex, but there seems to be no experimental evidence to corroborate this view. The fact that isatin is formed by the oxidation of the complex indicates that oxygen might have added on to the double bond of the indigo group. This is readily understood by assuming that the occupation of the molecular valence electrons of the nitrogen atoms by the iron tends to activate the double bonds of the indigo groups and render them more accessible to molecular oxygen. This reasoning may also apply to hemoglobin and allied substances.

4. Rubrene. Reversible auto-oxidation reactions are not limited to metallic complex substances, such as those discussed in the foregoing topics, but are also found among substances entirely free from any metals. Perhaps one of the leading syntheses in organic chemistry made recently by Moureu, Dufraisse, and Dean (212), is that of a colored hydrocarbon, rubrene, which is capable of fixing one molecule of oxygen to form a dissociable peroxide (oxyrubrene). The importance of the discovery of this remarkable substance may be indicated by more than twenty-eight publications which have already appeared, all of them in French, describing its unusual properties and derivatives. The empirical formula of rubrene, as deduced from analytical data, is $C_{42}H_{28}$, and the structural formula in closest agreement with its behavior is that proposed by Willemart (213, 214). Rubrene was first prepared by heating in vacuum at 100–120° phenylacetylenediphenylchloromethane; two molecules of hydrogen chloride split off and rubrene, an orange-red solid hydrocarbon, was formed along with some resinous material. Its synthesis, leaving out all possible intermediate stages (213a, 215), may now be formulated as follows:



Another method of preparation has been recently worked out by Robin (216), and the difficulties encountered with the original method of preparation have been very recently discussed by Moureu, Dufraisse, and Lotte (217).

In solution, rubrene is not appreciably oxidized in the dark, but in the presence of light the oxidation proceeds rapidly followed by the evolution of heat[19] and by the disappearance of the red color and the yellow fluorescence of the solution. Inhibitors such as hydroquinone, pyrocatechol, etc., retard this oxidation. Oxyrubrene separates out as a colorless crystalline compound with solvent of crystallization (219); it dissociates under a high vacuum. The dissociation of oxyrubrene into its components, under various conditions of pressure and temperature, is always accompanied by emission of light, and the critical dissociation pressure, at 16°, has been found to be about 5 mm. (220). Partial reduction of oxyrubrene yields a non-dissociable oxide (metrubrene) containing one oxygen atom per molecule of rubrene (221, 222). Metrubrene can also be prepared by direct oxidation of rubrene with oxidizing agents other than free oxygen. Under no circumstances were the authors able to isolate metrubrene as an intermediate product in the formation of oxyrubrene, or to produce the latter by its auto-oxidation.

An attempt has been made recently by Dufraisse and Badoche (222) to determine the type of union between the oxygen molecule and rubrene in oxyrubrene by allowing the latter to react with the Grignard reagent and subsequently isolating the products formed. The reaction, however, was too complicated to yield any decisive conclusions, but as a result of it a second non-dissociable oxide of rubrene (isooxyrubrene) was produced containing two atoms of oxygen and possessing entirely different properties from oxyrubrene. Inasmuch as this oxide could be easily reduced to rubrene, the authors concluded that it must

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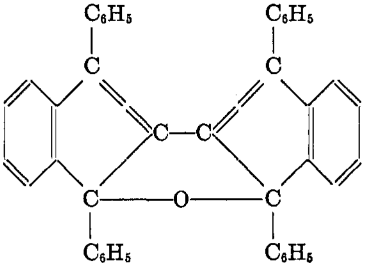
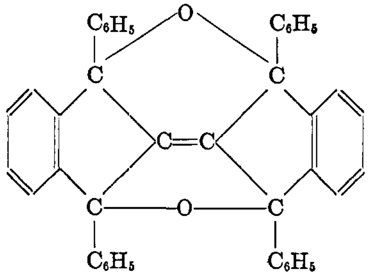
[19] Dufraisse and Enderlin (218) calculated recently the heat evolved when one gram molecule of oxygen combines with rubrene to form oxyrubrene. This is 23,000 calories, which is more than that evolved when oxyhemoglobin is formed but less than the heat (about 50,000 calories) evolved when one gram molecule of oxygen is introduced into the ethylene bond.

have its skeleton structure, and that the oxygen atoms are connected in such a way as to form two furane rings. The authors represented the structure of metrubrene and isooxyrubrene as follows:

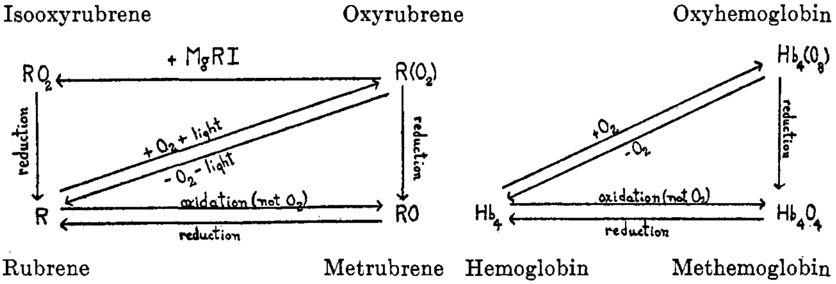


Metrubrene



Isooxyrubrene

The evidence for the presence of furane rings in metrubrene and isooxyrubrene is, in the opinion of the present author, inconclusive, and the possibility of two ethylene oxide groups resulting from a splitting off of a moloxide has not been entirely overruled. Summarizing the conversion of rubrene to its different oxides and their mutual transformations, and comparing these with analogous transformations of hemoglobin, we have:



It may be clearly seen that the analogy between hemoglobin and rubrene is far from being perfect, yet enough similarity exists between the two to warrant the assumption, which Moureu, Dufraisse, and their collaborators have repeatedly emphasized, that in oxyhemoglobin the oxygen molecule might be bound not to the iron atom, as it has been assumed hitherto, but to some other unsaturated part of the molecule. The fact that the iron in hemoglobin is bivalent and does not undergo a valence change during the oxygen transfer in the blood seems to support this view. In no case, however, has the nature of the union been definitely established.

One other not so well-defined case of reversible auto-oxidation has been reported recently by La Lande (72). A peroxide of abietic acid, formed by absorption of oxygen under ordinary conditions, was found to lose part of its oxygen when subjected to high vacuum and moderate temperature. It was not ascertained, however, whether abietic acid was being regenerated at the same time that oxygen was being lost.

B. Non-reversible auto-oxidation reactions

1. *Auto-oxidation of saturated hydrocarbons.* The direct oxidation of hydrocarbons, especially gaseous hydrocarbons, is of inestimable theoretical and practical importance, and the complete elucidation of the mechanism involved would constitute an important contribution to chemical knowledge. So much has been done and written in this field that a complete account of it will not be attempted.[20] That the oxidation of several saturated hydrocarbons follows a chain mechanism has been shown recently by Pease (224), Pope, Dykstra, and Edgar (225), and by Fort and Hinshelwood (226). The last named investigators reported that whereas the oxidation of methane is greatly influenced by its concentration, the oxygen concentration played a minor rôle. A chain propagation was assumed to take place when the intermediate "oxygenated" products (peroxides or aldehydes) collide with fresh molecules of the hydrocarbon, while collision with oxygen molecules results in the destruction of the reaction chains. Unfortunately, however, the high temperatures employed in all of these investigations made it impossible to isolate and identify the initial or intermediate products of each reaction. In practically all cases the products reported consist of aldehydes, steam, and the oxides of carbon, and in some instances minute traces of peroxides.

[20] The reader is referred to two recent papers (223) which aim to review the field up to 1929.

The use of oxides of nitrogen to accelerate the oxidation of saturated hydrocarbons has been published recently by several investigators (227), but no further evidence regarding the identity of the initial products has been produced.

The work of Riesenfeld and Gurian (228) on the oxidation of methane is of interest inasmuch as these investigators were able definitely to isolate hydrogen peroxide, the formation of which was attributed to the interaction of oxygen with atomic hydrogen resulting from the dissociation of methane. Ozone was also formed in small quantities, but its concentration was entirely conditioned by the decomposition of hydrogen peroxide.

Very recently Bone (229) has again challenged the validity of the peroxidation theory of hydrocarbon combustion proposed independently by Callender (230), and by Moureu, Dufraisse, and Chaux (231), and has with added assurance revived the importance of his hydroxylation theory (232). In a re-investigation of the slow combustion of ethane at temperatures between 290° and 323° and at initial pressures between 440 and 780 mm., Bone and Hill (233) found that the reaction is characterized by a well-defined induction period which is considerably affected by the addition to the dry reaction mixture of 1 per cent of the following substances: water, ethyl alcohol, iodine, nitrogen tetroxide, formaldehyde, and acetaldehyde, the last one causing an instantaneous explosion. An increase of the initial pressure of the mixture also shortened the induction period, while the latter was increased with increased oxygen concentration. The products found were chiefly aldehydes, steam, oxides of carbon, and traces of peroxides which were assumed to form in the aldehyde stage. In spite of these results the authors maintained that ethyl alcohol, rather than a peroxide of the hydrocarbon, was the initial product of the oxidation. An apparent experimental support of this view is found in the recent experiments of Landa (234), who succeeded in isolating alcohols as well as aldehydes from the slow oxidation of higher paraffin hydrocarbons at 280° to 300°. More recently Bone (229) himself described an experiment performed by Newitt and Haffner on the combustion of a 9:1 methane–oxygen mixture at 360° and under a pressure of about 100 atmospheres. Of the total methane oxidized 17 per cent appeared as methyl alcohol, about 0.6 per cent as formaldehyde, and the remainder as oxides of carbon and steam. Neither free hydrogen nor a peroxide was found among the products of the reaction. These results, according to Bone, constitute "undeniable evidence" in favor of the hydroxylation theory. It will be shown later, however, that the isolation of alcohols from these experiments is not necessarily at variance with the peroxidation theory.

Perhaps the most important published experimental evidence in favor of the peroxide theory is to be found in the recent work of Mondain-Monval and Quanquin (235). These investigators succeeded in isolating organic peroxides having the properties of the alkyl α-hydroxy alkyl peroxides, ROOCH(OH)R, from the slow combustion of pentane, hexane, octane, or even gasoline in air, using the flow method, at about 300°, or a few degrees below the temperature at which white fumes began to evolve. Out of 100 cc. of hexane, for example, they obtained 20 cc. of an oily yellow mixture consisting chiefly of organic peroxides, acids, aldehydes, and acetals. The mixture had strong oxidizing powers, oxidizing potassium iodide and hydroquinone instantly. Upon distillation under vacuum, the mixture decomposed exothermically with a blue luminescence, yielding formaldehyde and other aldehydes. When treated with strong alkalis, it liberated hydrogen, a reaction which is peculiar to α-hydroxy alkyl peroxides (50, 236, 237).

The study of the mechanism of the auto-oxidation of hydrocarbons has also been undertaken in this laboratory in collaboration with Dr. George Thomson (238), and our preliminary results seem to support the peroxidation theory. With pure and dry n-heptane, for example, the oxidation was effected with a measurable rate, under the influence of ultra-violet radiation, at as low as 50°, using the quartz apparatus previously reported from this laboratory (20a). The peroxide formed after 12.22 and 82.47 hours of irradiation was found to be 0.378×10^{-3} g. and 1.89×10^{-3} g. of peroxidic oxygen respectively per 5 cc. of the hydrocarbon. Our analytical results, especially the benzidine reaction (20a), seem to indicate that the peroxides are of the α-monohydroxy alkyl type, and neutral peroxides presumably of the type reported by Mondain-Monval and Quanquin. The work is still in progress and complete identification of the products will be reported shortly.

From the point of view developed in this review, saturated hydrocarbons will not add molecular oxygen directly to form peroxides because of the absence of molecular valence electrons. It is well known, however, that hexaphenylethane and other free radical producing hydrocarbons absorb oxygen very readily only in their free radical form, and their dissociation may be determined quantitatively by measuring the oxygen absorbed (239). The existence of free radicals in hydrocarbon flames has already been detected spectroscopically by Bonhoeffer and Haber (240), while more recently Paneth and Hofeditz (241) have actually measured the half-life period of free methyl radicals obtained from the decomposition of lead tetramethyl.[21] The very recent work of Norris and Thomson (243) seems to indicate that in many instances the decomposition of hydrocarbons occurs in the C-C bond rather than in the C-H bond, and this is to be expected from the heats of dissociation of these bonds, which is given by Grimm (244) as 71,000 and 92,000 calories respectively. In oxidations, however, activation of these bonds might be sufficient to expose the necessary electrons for combination with oxygen, and from the study of explosion temperatures Sagulin (245) found the heat of activation of the C-H bond to be about 64,000 calories, which is in fairly close agreement with the heat of activation of methane (61,500 calories) recently calculated by Fort and Hinshelwood (226). A mechanism of the oxidation of hydrocarbons therefore should take into account not only all the foregoing considerations but also the stability of the initial peroxides formed. As an illustration, the oxidation of methane may be considered here.

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[21] In a very recent publication Schultze and Müller (242) seem to cast some doubt on the results of Paneth and Hofeditz.

$$H_3CH \begin{cases} \xrightarrow{\text{activation}} H_3C{:} \rightarrow H \\ \xrightarrow{\text{dissociation}} H_3C\cdot + H\cdot \end{cases} \tag{1}$$

$$H_3C{:} \rightarrow H + O_2 \rightarrow H_3COOH \tag{2}$$

$$2\ H_3C\cdot + O_2 \rightarrow H_3COOCH_3 \tag{3}$$

$$2\ H\cdot + O_2 \rightarrow HOOH \tag{4}$$

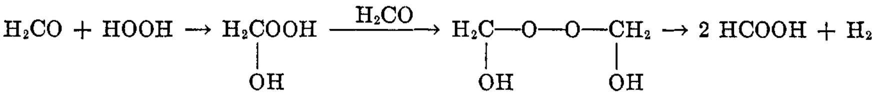
Since activation precedes dissociation, methyl hydroperoxide may form in larger quantities than either of the other two peroxides. Both methyl hydroperoxide and dimethyl peroxide are known and their properties have been studied. They decompose spontaneously, according to Rieche (50), as follows:

$$H_3COOH \rightarrow CH_2O + H_2O \tag{5}$$

$$H_3COOCH_3 \rightarrow CH_3OH + CH_2O \tag{6}$$

The formaldehyde thus formed may undoubtedly combine with either methyl hydroperoxide or hydrogen peroxide to form hydroxy peroxides of the type isolated by Mondain-Monval and Quanquin, and Milas and Thomson. That these peroxides may decompose to yield the products indicated in equations 7 and 8

$$H_3COOH + H_2CO \rightarrow H_3COOCH_2OH \begin{cases} \rightarrow CH_3OH + HCOOH \\ \rightarrow CH_2O + HCOOH + H_2 \end{cases} \tag{7}$$



$$H_2CO + HOOH \rightarrow \underset{\text{OH}}{H_2COOH} \xrightarrow{H_2CO} \underset{\text{OH}}{H_2C}\text{—O—O—}\underset{\text{OH}}{CH_2} \rightarrow 2\ HCOOH + H_2 \tag{8}$$

has been shown by Rieche (50), and by Wieland and Wingler (236). Although this mechanism may seem more complicated than the one resulting from the hydroxylation theory, it is more plausible than the latter. Per-acids are also likely to form by the direct auto-oxidation of the aldehydes, and these may lead further to per-esters and per-acetals. With higher hydrocarbons than methane the mechanism of the oxidation is essentially the same except that the free radicals formed by the splitting off of C-C bonds should also be considered.

An additional reaction which may occur when the oxidation is carried out under high pressure is the reduction of formaldehyde by the free hydrogen to methyl alcohol. To determine whether formaldehyde is actually reduced by hydrogen, under pressure, to give methyl alcohol, we carried out the following experiments.[22]

These experiments indicate clearly that formaldehyde is reduced by hydrogen under pressure to form methyl alcohol. We feel, therefore, that the experiment described by Bone (229) is insufficient evidence to prove that methyl alcohol is the initial product formed in the oxidation of methane under pressure.

2. Auto-oxidation of unsaturated hydrocarbons. During the past few years much emphasis has been centered on the slow oxidation of simple hydrocarbons such as acetylene and ethylene. Kistiakowsky and Lenher (246) studied the acetylene–oxygen reaction at temperatures between 250° and 315° and found it to be a homogeneous reaction of the chain type exhibiting an induction period and almost entirely suppressed in glass-packed vessels. The products isolated consisted of glyoxal, formaldehyde, and oxides of carbon, together with small quantities of hydrogen. To explain the formation of glyoxal, the authors assumed a three-body collision between two molecules of acetylene and one

TABLE 7

Reduction of formaldehyde under pressure at 360°

EXPERIMENT 1	EXPERIMENT 2
"Enduro" bomb 800 cc.	Steel bomb 1679 cc.
Paraformaldehyde 55 g.	Paraformaldehyde 48.3 g.
Hydrogen to make up pressure of 2800 lbs. at 360°	Hydrogen to make up pressure of 1390 lbs. at 360°
Running time 4 hours	Running time 6 hours
Chief products:	Chief products:
(1) 54.2 liters of gas (CO_2, CO, H_2)	(1) 60 liters of gas (CO_2, CO, H_2)
(2) 17 cc. liquid (60 per cent CH_3OH)	(2) 31 cc. liquid (69 per cent CH_3OH)

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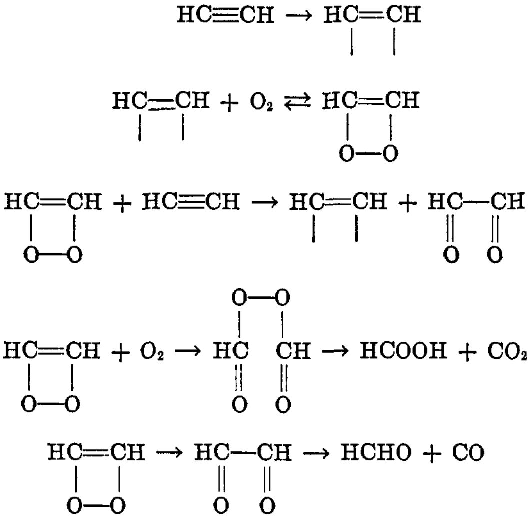
[22] We are greatly indebted to Professor E. W. Brugmann and his associates of the Research Laboratory of Applied Chemistry for carrying out for us the high pressure experiments.

of oxygen. The reaction seems to proceed in a step-wise sequence somewhat analogous to that proposed by Bone and Andrew (247). A fairly plausible explanation of the oxidation mechanism of acetylene has been put forward recently by Bodenstein (248), who formulated the several reactions as follows:



$$\mathrm{HC{\equiv}CH} \longrightarrow \begin{array}{c}\mathrm{HC{=}CH}\\ |\quad|\end{array} \qquad (1)$$

$$\begin{array}{c}\mathrm{HC{=}CH}\\ |\quad|\end{array} + O_2 \rightleftarrows \begin{array}{c}\mathrm{HC{=}CH}\\ |\quad|\\ \mathrm{O{-}O}\end{array} \qquad (2)$$

$$\begin{array}{c}\mathrm{HC{=}CH}\\ |\quad|\\ \mathrm{O{-}O}\end{array} + \mathrm{HC{\equiv}CH} \longrightarrow \begin{array}{c}\mathrm{HC{=}CH}\\ |\quad|\end{array} + \begin{array}{c}\mathrm{HC{-}CH}\\ \|\quad\|\\ \mathrm{O}\quad\mathrm{O}\end{array} \qquad (3)$$

$$\begin{array}{c}\mathrm{HC{=}CH}\\ |\quad|\\ \mathrm{O{-}O}\end{array} + O_2 \longrightarrow \begin{array}{c}\mathrm{O{-}O}\\ |\quad|\\ \mathrm{HC}\quad\mathrm{CH}\\ \|\quad\|\\ \mathrm{O}\quad\mathrm{O}\end{array} \longrightarrow \mathrm{HCOOH} + CO_2 \qquad (4)$$

$$\begin{array}{c}\mathrm{HC{=}CH}\\ |\quad|\\ \mathrm{O{-}O}\end{array} \longrightarrow \begin{array}{c}\mathrm{HC{-}CH}\\ \|\quad\|\\ \mathrm{O}\quad\mathrm{O}\end{array} \longrightarrow \mathrm{HCHO} + \mathrm{CO} \qquad (5)$$

Equations 4 and 5 have been slightly modified to account more clearly for the products formed. These reactions can also be explained by the general scheme given in section II. The reversibility of equation 2, for example, is more probable in the dative peroxide stage than in the more stable moloxide stage. The formation of performic acid and its possible interaction with the unsaturated bonds to form monoxides should not be overlooked.

More recently Lenher (249) found that the auto-oxidation of acetylene in the presence of nitrogen oxides proceeds between 170° and 250°, the main product of the reaction being the trimeric glyoxal.

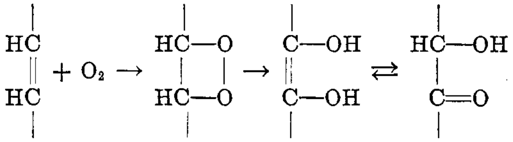
The slow combustion of ethylene has also been found to be a chain reaction by Thompson and Hinshelwood (250, 96). The authors suggested that the initial stage consists in the formation of an unstable peroxide, which collides with other ethylene molecules to form unstable hydroxylated substances. Recently Lenher (251) investigated this reaction at somewhat lower temperatures (300–525°) and was able to isolate, in addition to the usual products found, ethylene oxide and dihydroxymethyl peroxide, $HOCH_2OOCH_2OH$. The principal primary products have been assumed to be ethylene oxide and formaldehyde, while dihydroxymethyl peroxide, acetaldehyde, formic acid, oxides of carbon, hydrogen, and steam are secondary reaction products. We are of the opinion, however, that both formaldehyde and ethylene oxide are also secondary reaction products, the former resulting from the decomposition of the primary ethylene moloxide, and the latter from the interaction of form-peracid with ethylene.

Several other investigations have been published recently on the auto-oxidation of higher unsaturated hydrocarbons, including the amylenes (252, 75), cyclohexene (253), cyclohexadienes (254), and benzene (255).

3. Auto-oxidation of "drying" oils. Owing to the importance of auto-oxidation in connection with drying oils, considerable work has been done recently in an attempt to elucidate its mechanism. An excellent résumé of the field is to be found in the recent publication of Eibner (154). The criteria of auto-oxidation set forth in section IV of this review are applicable to the drying process of unsaturated oils.

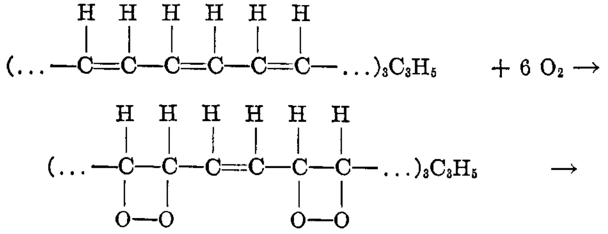
It has long been recognized that organic peroxides, presumably of the moloxide type, are formed during the initial stages of the oxidation of oil films, but to produce a stable film, a further change of the peroxide is invariably necessary. Accordingly, the suggestion was made by Fahrion (256) and others (257) that interaction between the moloxides so formed and the unoxidized oil results in monoxides which may further polymerize, probably in accordance with the scheme proposed by Staudinger (166a). The alternative suggestion, that this reaction results in the production of 1, 4-dioxane ring systems, has been made by Marcusson (258) and by Eibner and Munzert (259). That these views are untenable is shown by the properties of the oil film (167 b), and particularly by the total oxygen absorbed, which corresponds to two atoms of the latter per ethylene linkage (260). It is not at all surprising, however, to find present in the oil film small amounts of monoxides or their rearranged products, resulting from the interaction of per-acids with the unoxidized oil. The formation of per-acids may be easily accounted for by the direct oxidation of the aldehydes which are formed by the decomposition of moloxides. Both aldehydes and several other volatile products consisting of fatty acids, mono and dibasic alcohols with 3, 4, and 6 carbon atoms, hydrogen peroxide (261), and, presumably, organic peroxides (262) have been detected by various investigators in oxidizing oil.

Another view consisting in the rearrangement of the moloxide into a substance containing keto-hydroxy groups has been suggested by Ellis (263). This may be formulated as follows:



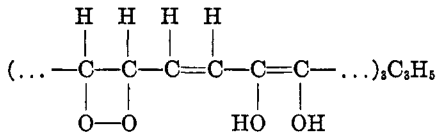
$$\begin{array}{c}|\\ \mathrm{HC}\\ \|\\ \mathrm{HC}\\ |\end{array} + O_2 \rightarrow \begin{array}{l}|\\ \mathrm{HC{-}O}\\ |\quad\;\;|\\ \mathrm{HC{-}O}\\ |\end{array} \rightarrow \begin{array}{l}|\\ \mathrm{C{-}OH}\\ \|\\ \mathrm{C{-}OH}\\ |\end{array} \rightleftarrows \begin{array}{l}|\\ \mathrm{HC{-}OH}\\ |\\ \mathrm{C{=}O}\\ |\end{array}$$

The view of Ellis finds ample support in the important experimental contributions of Morrell and Marks (167). From the auto-oxidation of β-eleostearic acid, these authors succeeded in isolating an oxidation product containing one peroxide (moloxide) group, one hydroxyl group, one carbonyl group, and one double bond. The action of methyl alcohol in the presence of gaseous hydrogen chloride on the oxidized glyceride yielded a keto-hydroxy peroxide ester and a keto-methoxy peroxide ester. The chemical transformations involved may be summarized as follows:



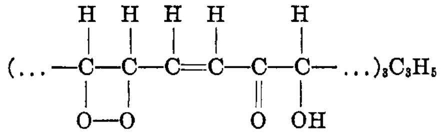
$$(\ldots{-}\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}{=}\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}{-}\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}{=}\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}{-}\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}{=}\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}{-}\ldots)_3C_3H_5 \quad + 6\,O_2 \rightarrow \qquad (1)$$

$$(\ldots{-}\underset{\lfloor\mathrm{O}}{\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}}{-}\underset{\mathrm{O}\rfloor}{\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}}{-}\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}{=}\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}{-}\underset{\lfloor\mathrm{O}}{\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}}{-}\underset{\mathrm{O}\rfloor}{\overset{\mathrm{H}}{\overset{|}{\mathrm{C}}}}{-}\ldots)_3C_3H_5 \quad \rightarrow \qquad (2)$$



$$(\ldots-\overset{H}{\underset{O-}{C}}-\overset{H}{\underset{-O}{C}}-\overset{H}{C}=\overset{H}{C}-\underset{HO}{C}=\underset{OH}{C}-\ldots)_3C_3H_5 \qquad (3)$$

↓↑



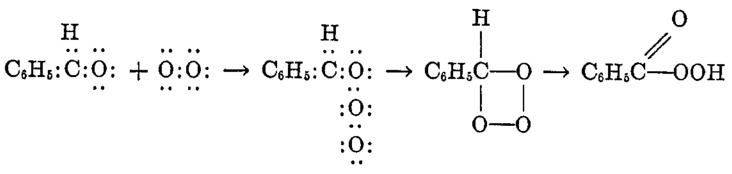
$$(\ldots-\overset{H}{\underset{O-}{C}}-\overset{H}{\underset{-O}{C}}-\overset{H}{C}=\overset{H}{C}-\underset{\overset{\|}{O}}{C}-\overset{H}{\underset{OH}{C}}-\ldots)_3C_3H_5 \qquad (4)$$

There seems to be some evidence to show that methylation of (3) yields different methyl esters than those produced by the methylation of (4). The two moloxide groups in (2) differ in chemical properties from one another. The moloxide remote from the glyceride group is of "basic" character stable in the presence of acids, but unstable towards alkalis, which cause it to split into two aldehyde groups. The near moloxide, on the other hand, is decidedly "acidic," showing keto-enol tautomerism and forming colored salts. The yellowing of drying oils, according to these investigators, is due to rancidity consequent on the disruption of the remote moloxide and the formation of keto-enol groups in the near moloxide. Elm (167b), however, finds no experimental support of this view, and concludes that yellowing results from the hydrolysis of the moloxides with subsequent rearrangement of the monoxides formed and polymerization of the final keto-product. That yellowing might be due to the polymerization of the aldehydes formed should also be considered, since the latter are known to turn yellow on slow oxidation and polymerization.

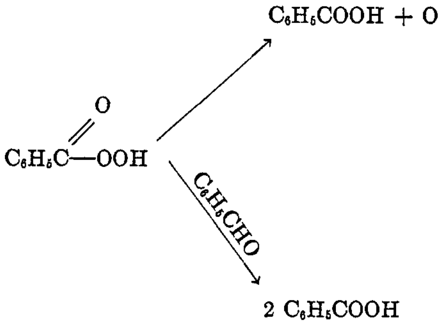
In spite of all the work that has been done in this field recently, the mechanism of the auto-oxidation of unsaturated oils is, in our opinion, still relatively obscure, owing to the complexity of the oxidation products and the uncertainty of their structure.

4. The auto-oxidation of aldehydes. Reference has already been made to the influence of structure on the auto-oxidation of various aldehydes, but nothing was said regarding the mechanism of this oxidation. Benzaldehyde has become the subject of numerous investigations ever since the classical observation of Wöhler and Liebig (264) revealed the rapid formation of benzoic acid, especially in the presence of light, when oxygen was allowed to come in contact with it. Bach (265) was, presumably, the first to propose the formation of an intermediate peroxide consisting of one molecule of oxygen added on to the carbonyl double bond, while Bodländer (266) and Baeyer and Villiger (10) assumed benzoperacid to be the primary product of the oxidation of benzaldehyde. Engler and Steinkopf (267) made the significant observation that indigo is decolorized much faster by a mixture of benzaldehyde and oxygen than by benzoperacid, and arrived at the conclusion that benzoperacid is not the primary product but probably the peroxide proposed by Bach. Similar conclusions have been drawn recently by Jorissen and van der Beek (268), who observed that benzoperacid failed to oxidize carbon tetrachloride to phosgene, in spite of the fact that the latter was formed during the auto-oxidation of benzaldehyde in the presence of carbon tetrachloride. That benzoperacid is formed from the oxidation of benzaldehyde has been conclusively shown by these authors (152), who are of the opinion that it is not the primary product.

Both in the liquid (26) and in the vapor (269) phase the mechanism of the auto-oxidation of benzaldehyde has been shown to be of the chain type. It is quite reasonable, therefore, to assume that both indigo blue and carbon tetrachloride could be activated during the initial stages of the oxidation of benzaldehyde and be more easily oxidized either by the active dative peroxide or by the benzoperacid. Accordingly, the auto-oxidation of benzaldehyde may be formulated as follows:



(1)



(2a)

(2b)

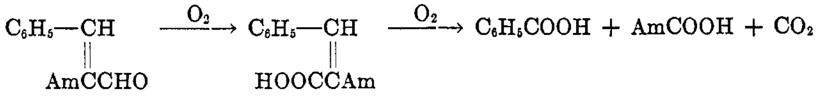
That benzoperacid decomposes, on heating, in accordance with (2a) has been shown by Erlenmeyer (270). At low temperatures and in the presence of benzaldehyde, reaction 2b occurs probably through the intermediate formation of a per-ester.

The oxidation of formaldehyde (269) and acetaldehyde (133, 248) has also been shown to be of the chain type. Furthermore, in the case of acetaldehyde Bodenstein found that the course of the main reaction could be expressed mathematically as follows:

$$\frac{d[P]}{dt} = K \cdot \frac{[A]^2}{[O_2] + 150}$$

in which P denotes the concentration of peracetic acid and A that of acetaldehyde.

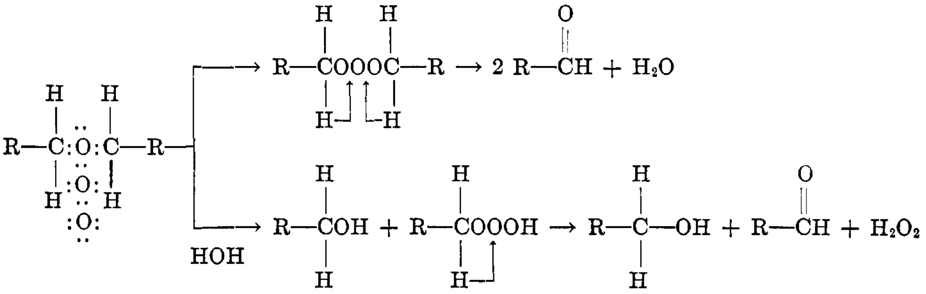
In connection with the auto-oxidation of *trans*-α-amylcinnamic aldehyde Bogert and Davidson (271) recently made the very interesting observation that in the course of the reaction the *trans*-aldehyde is simultaneously oxidized and transmuted to the *cis*-α-amylcinnamic acid.



$$\begin{array}{c} C_6H_5\text{—}CH \\ \| \\ AmCCHO \end{array} \xrightarrow{O_2} \begin{array}{c} C_6H_5\text{—}CH \\ \| \\ HOOCCAm \end{array} \xrightarrow{O_2} C_6H_5COOH + AmCOOH + CO_2$$

The inversion is accomplished, according to the authors, by the absorption of energy liberated during the initial stages of the oxidation.

5. The auto-oxidation of ethers. The auto-oxidation of ethers has been the subject of several recent investigations (272, 236, 273, 20a). Perhaps the mechanism of this oxidation may be best interpreted on the basis of the oxonium peroxide theory (20a), which assumes the initial addition of the oxygen molecule onto the ether oxygen, and the subsequent rearrangement and decomposition of the dative peroxide, as follows:



$$R{-}\overset{H}{\underset{H}{C}}{:}\underset{\underset{:\ddot{O}:}{:\ddot{O}:}}{\ddot{O}}{:}\overset{H}{\underset{H}{C}}{-}R \begin{cases} \longrightarrow R{-}\overset{H}{\underset{H}{C}}OOO\overset{H}{\underset{H}{C}}{-}R \rightarrow 2\,R{-}\overset{O}{\overset{\|}{C}}H + H_2O \\ \xrightarrow[HOH]{} R{-}\overset{H}{\underset{H}{C}}OH + R{-}\overset{H}{\underset{H}{C}}OOOH \rightarrow R{-}\overset{H}{\underset{H}{C}}{-}OH + R{-}\overset{O}{\overset{\|}{C}}H + H_2O_2 \end{cases}$$

The presence of α-hydroxy alkyl peroxides and hydroperoxides in the oxidation products of ethers is easily accounted for by the interaction of the hydrogen peroxide formed with the aldehydes in the ratio of 1:2 or 1:1. Per-acids and per-esters are also formed as a result of the further oxidation of the aldehydes, although the formation of the latter has not been generally accepted (274).

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