CATALYSIS AND AUTO-OXIDATION

ANTI-OXYGENIC AND PRO-OXYGENIC ACTIVITY

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CONTENTS

INTRODUCTION

Oxygen is the most abundant element in the crust of the earth, of which it constitutes nearly half of the mass. In a free state it forms an essential part of the atmosphere, and due to its great reactivity it tends to act upon the substances with which it comes in contact. It is therefore quite natural to find the study of this element, by Lavoisier, at the very beginning of the science of chemistry.

[1] Translated from the French by John R. Johnson, University of Illinois, Urbana, Illinois.

113

This element plays a fundamental rôle in nature, and among natural phenomena there is none of greater importance than spontaneous oxidation by free oxygen, commonly known as auto-oxidation. Respiration, the essence of life itself, might be conceded to fall into the domain of auto-oxidation.

Oxygen may act upon living organisms or inanimate objects in a multitude of ways. According to the need of man, its effects may sometimes be useful, sometimes harmful. Thus, man may wish to favor or to deter its action, and for this purpose a number of instruments have been employed, especially catalytic influences. Among the latter (the only ones with which we shall be concerned) we have called anti-oxygenic activity (negative catalysis), that which inhibits the action of oxygen, and pro-oxygenic activity (positive catalysis), that which accelerates it.

1. Résumé of Experimental Observations

I. HISTORICAL REVIEW

It would probably be possible to trace the employment of anti-oxygens and of pro-oxygens to the most ancient times. One would find among the various recipes and formulas which have been handed down from the old alchemists, certain ones which have for their purpose the exaltation or inhibition of the action of oxygen. The discussion which follows will be concerned only with observations resulting from the use of scientific methods. Even thus restricted, the task of preparing a complete bibliography of this subject is exceedingly difficult. We have limited our field to anti-oxygenic catalysis, of which very little discussion is found in the general treatises on catalysis, and refer for pro-oxygenic catalysis to the general works in this field.[2]

Phosphorus. Berthollet in 1797 made the curious observation that traces of the vapors of sulfur compounds prevented the luminescence of phosphorus in a dilute atmosphere of oxygen. This is the first observation of anti-oxygenic action that has been

[2] Among the works which treat of the historical aspect of catalysis may be cited: Paul Sabatier, "Catalysis in Organic Chemistry," transl. by E. Emmet Reid. D. Van Nostrand Co., New York, 1922.

found.[3] This phenomenon was studied later by a number of investigators.[4]

Sulfur compounds. The oxidation of phosphorus and its prevention are very closely related to the recent observations of Delepine, who showed that traces of the vapor of ether, acetaldehyde, and other substances, hinder the luminescence of certain sulfur compounds (methyl dithiocarbonate, etc.).[5]

Explosive gas mixtures. The researches of Davy[6] in 1817 and of other investigators[7] have shown that the detonation of an explosive mixture of hydrogen and oxygen (two volumes of hydrogen and one volume of oxygen), or the slow combustion of hydrogen under the influence of platinum, is prevented by the presence of relatively small amounts of certain gases, such as ethylene and carbon monoxide.

Oxidizable gases or vapors. Observations analogous to those cited above have been made with other gases and inflammable vapors. Thus, Frankland observed that ethylene diminished markedly the inflammability of carbon disulfide vapor.[8]

Chloroform. Rump in 1868 was the first to report that traces of alcohol protected chloroform against atmospheric oxidation.[9] This observation has served as the basis of a practical method for the stabilization of anesthetic chloroform and has resulted in lessening the dangers attendant upon its use in surgical operations.

Sodium sulfite. Auto-oxidation of this substance and means of preventing it have been the object of many important studies.

[3] Journ. de l'Ecole polytechn., series 3, 277 (1797).

[4] It would be out of place to give here a detailed bibliography of this special topic. The following is a list of the principal workers in this field: Thenard, Graham, Schoenbein, Joubert, Centnerszwer, Scharff, Thorne and Tutton, Vant' Hoff, Jungfleisch, Jorissen, Lord Rayleigh.

[5] Bull. soc. chim. (4) **31**, 762 (1922).

[6] Trans. Roy. Soc. London, 1817, 45; Ann. chim. phys. (2) **4**, 347 (1817).

[7] W. Henry, Edw. Turner, Faraday, Graham, etc., and more recently Tanatar, Jorissen.

[8] E. Frankland, Chem. News, **6**, 3 (1862); see also the work of Turpain (1890) and of Dixon (1925).

[9] "Ueber die Prufung des Chloroforms," Hanover, 1868. The stabilization of chloroform has also been studied by: Regnauld, Villejean, Breteau and Woog, Baskerville, Clover, and others.

The first was that of Bigelow[10] in 1898, who observed that a number of substances, such as benzyl alcohol, benzaldehyde, butyl alcohol, glycerol, mannite, cresols, aniline, et cetera, possessed the property of retarding the atmospheric oxidation of solutions of sodium sulfite. A considerable amount of research has been carried out on this subject.[11]

Stannous chloride. Young[12] in 1901 observed a number of facts concerning the action of stannous chloride which were analogous to those observed by Bigelow with sodium sulfite.

Oxalic acid. It was observed by Jorissen and Reicher in 1903 that hydroquinone and resorcinol, among other substances, exerted a strong inhibitory action on the oxidation of solutions of oxalic acid by air.[13]

Alkaloids. Richard and Malmy in 1921 observed that sulfurous acid had a stabilizing influence on solutions of adrenaline.[14] There is reason to believe, although the authors do not so state, that this is an anti-oxygenic action. The same may be said of the interesting observations of Bridel in 1923, on the preservation of solutions of various alkaloids by means of sodium bisulfite.

Many other substances, more or less clearly defined in their chemical composition, are also subject to oxidation in the air. In some instances their use is limited by this serious inconvenience. Various practices, which involve an anti-oxygenic action, have been employed to avoid these undesirable effects.

Paraffin. Siebeneck[15] has recently observed that traces of sulfur prevented any oxidation of paraffin in free oxygen up to a temperature of 135°.

Fats and oils. Deschamps in 1843 showed that fresh lard containing gum benzoin or populin, did not become rancid as did pure

[10] "Effect of Catalytic Action on the Velocity of Oxidation of Sodium Sulfite by Atmospheric Oxygen," Z. phys. chem., **26**, 493 (1898).

[11] Young (1901), Titoff (1903), Lumiere and Seyewetz (1905), Dhar (1922).

[12] "Studies on Solutions of Stannous Salts. II. The Oxidation of Solutions of Stannous Chloride by means of Free Oxygen;" S. W. Young, J. Am. Chem. Soc., **23**, 119 (1901). Mittra and Dhar also worked on this subject (1922).

[13] Handel Vlamsch Natuur- en Geneesk Congres, Ghent, Sept. 27, 1903.

[14] J. Pharm. Chim. (7), **23**, 209 (1921).

[15] Petroleum, **18**, 281 (1922).

lard.[16]   The cause of this preservation is attributed by the present authors to the anti-oxygenic action of phenolic substances present in benzoin (vanillin), or in the poplar buds (saligenin and derivatives).

Chevreul[17] pointed out that he found oak wood to be a remarkable anti-drying agent for linseed oil; that poplar wood seemed to have this same property in a less degree; and pine wood in a slighter degree.   It has been shown by the authors that phenols are excellent anti-drying agents for linseed oil, and that they act as anti-oxygens.   We attribute the facts discovered by Chevreul to the presence of a certain quantity of tannin in the wood which he used, especially since it is well known that a considerable amount of tannin is present in oak.

Rubber.   Several substances have been found to aid in the preservation of rubber.   It is stated in a German patent[18] that synthetic rubber is protected against auto-oxidation by the presence of phenolic substances.

Silk.   Silk, as well as other animal fibres, is subject to more or less rapid alteration, especially when it has been impregnated with salts of tin.   Various substances are claimed to act in a protective manner: thiocyanic acid, its salts, and other derivatives.[19]

Living tissues.   It appears that Claude Bernard[20] was the first to note the inhibitory effect of small quantities of hydro-

[16] J. Pharm. Chim. (3), **4,** 201 (1843).   According to Sisley, (1922), acetyl-thiourea also prevents fats and oils from becoming rancid.

[17] Ann. chim. phys. (3), **47,** 209 (1856).

[18] Badische Aniline und Soda Fabrik, D. R. P. 330, 741 (1918).   Other observations have also been made: Baeyer and Co., D. R. P. 366, 114 (1918); Helbronner, French pat. 509, 667 (1919), mentions an empirical procedure of vulcanization which depends as we shall show later, on an anti-oxygenic property.

[19] Soc. Anon. cooperativa per la stagionature e l'assaggio delle sete ed affini, French pat. 347, 689 (1904).   The same problem was studied later by Herzog (1909), Otto Meister (1910), Berg and Imhoff (1910), Gianoli (1911), Sisley (1911), Korselli (1917).

[20] "Lecons sur les effets des substances toxiques et médicamenteuses," (1857). That the action of hydrocyanic acid is manifestly anti-oxygenic in nature, has been shown by other investigators, who did not work with such complex chemical materials as living tissues, but with pure chemical individuals (Abderhalden, Warburg, etc.).

cyanic acid upon oxidation by means of free oxygen in living organisms.

No doubt many other facts are scattered throughout the literature on this subject, and perhaps there are some which have escaped attention. There are a number of instances where the facts are difficult to understand, and cases where anti-oxygenic action does not appear sufficiently well defined have not been considered.[21]

It is evident that the problem of avoiding the undesirable activities of atmospheric oxygen, has led to many interesting observations. The publication by the present authors of numerous facts concerning anti-oxygenic catalysis, has drawn attention to the possibility of avoiding these oxidations and the resulting inconveniences. The publication of a theory as to their mode of action has served not only to coordinate the known facts and to guide the development of investigations, but has stimulated research upon the part of other scientists and in the industries, that has led to important discoveries. The present authors are collecting these experimental results as they are published, but will wait for some time before bringing them together into a systematic survey.

The wide extent of the field of anti-oxygenic action has been indicated by the variety of facts presented in the fore-going résumé. Our investigations in this field, which are summarized below, have indicated that a complete body of doctrine may be evolved about the phenomena of anti-oxygenic action. Instead of an unusual or rare occurrence, as one might be led to believe from the facts that have been presented thus far, we are dealing with an extremely general phenomenon that plays a rôle of great importance in natural processes. In fact, one might have been

[21] Thus, certain materials which are contaminated with products of pyrogenation and are consequently liable to contain phenolic substances, are less susceptible to the action of air than the same substances in a high state of purity. This is the case when one compares certain salts of pyroligneous acid with the pure acetates. In the same way, disinfection by means of sulfur candles may often, in addition to the usual antiseptic effects, have an anti-oxygenic action about which little is known.

led long ago to suspect something of this nature, from a consideration of the simple fact that organic matter, endowed with a great reactivity toward oxygen, is capable of existing alongside this element in a free state in the atmosphere. Does it not seem probable that strong catalytic influences must be opposing these reactions, at least in a great number of cases, where until recently, we have been satisfied with the too vague notion of *passive resistance?*

II. OUR RESEARCHES

Origin of the study

In our first publication on the anti-oxygens,[22] which appeared in 1922, we presented the fact that a wide variety of auto-oxidizable substances were protected against the action of oxygen by an entire class of chemical compounds; namely, substances having at least one free phenolic group. We announced at this time that the phenomenon was catalytic in nature, and that substances other than phenols might have the property of acting as anti-oxygens.

In a very fortuitous way, this subject presented itself in the study of a problem of the war. In order to make possible the use of acrolein, it was necessary to prevent the alteration of this extremely unstable substance. In spite of the investigations of a number of able scientists, the instability of acrolein remained as closely associated with it as its irritant properties. Furthermore, the product of its alteration, disacryl, is a stable resin from which it is impossible to regenerate acrolein. These facts proved to be serious difficulties in the use of acrolein; it was necessary to use the material immediately after preparation, and it could not be made in large quantities and stored.

After an empirical process of stabilization[23] had been found, we were successful in discovering by means of a systematic study, that phenols prevented the transformation of acrolein into disacryl. The protective action of certain phenols was very

[22] "Sur l'autoxydation: les Antioxygènes." Compt. rend. **174**, 258(1922).
[23] Ch. Moureu and A. Lepape, Compt. rend. **169**, 705 (1919).

powerful; for example, in the presence of one part of hydroquinone in ten thousand, acrolein remained absolutely transparent and unaltered, whereas a control sample soon became opaque and rapidly changed to an inert mass of disacryl.

The problem of the stabilization of acrolein was thereby completely solved and it was possible to manufacture this substance in large quantities in the French factories. In one factory it was possible to produce one thousand kilograms of acrolein per day, whereas the greatest quantity of acrolein which had been obtained before this work was that used by Emil Fischer in his celebrated synthetic work on the sugars. For this work Fischer used a quantity of two kilograms, which was considered at that time as an enormous amount of acrolein.

One might well ask, what relationship exists between the alteration and stabilization of acrolein and the problem of auto-oxidation? At the time of these investigations we did not suspect that our researches bordered on the field of auto-oxidation in its broadest conception. This is but another instance where a systematic scientific investigation has led into the most unexpected fields.

In attempting to elucidate this curious action of phenols we were led to the realization that auto-oxidation was the key to the mystery. It would be superfluous to mention the details and the difficulties encountered in the circuitous route that led to the idea of the following experiment,[24] apparently quite absurd, which was carried out in our laboratory on October 21st, 1917. In a barometer tube containing an atmosphere of oxygen over a mercury reservoir, was placed a sample of acrolein, which is known to absorb oxygen readily, and a trace of a substance of the type of pyrogallol, which is commonly used for the absorption of oxygen, was added with the hope that under these conditions oxygen would not be absorbed. The idea of this paradoxical experiment was the result of a careful analysis of many experimental observations; we were not surprised to note that the mercury level remained constant and consequently no oxygen was

[24] On this subject consult: "Les alterations de l'acroléin et les antioxygènes," Bull. soc. chim. (4), **31**, 1152 (1922).

absorbed.   A trace of a substance as easily oxidized as pyrogallol is thus capable of rendering oxygen inert toward another substance which is readily oxidizable in a pure state.

We trust that the description of the circumstances which were the origin of our researches on auto-oxidation will not be found out of place.   This seems to us a typical example of the advantage of a thorough investigation of a phenomenon of which the nature is unknown.

Survey of the principal results

Preliminary experiments along various lines soon indicated that the phenomenon of anti-oxygenic action was extremely general in character.   Although one might be led to believe the contrary from the small number of isolated and apparently unrelated experiments which were previously reported, anti-oxygenic action is widespread and is quite common.   It is probable that under suitable conditions all oxidizable substances may act as anti-oxygens.   Thus, in actual practice, perhaps an anti-oxygenic action is not exceptional, but rather the absence of all anti-oxygenic impurities is exceptional, in the system: auto-oxidizable substance plus oxygen.

Before taking up an investigation of the vast field of research which had thus been opened, we attempted to set up a theory which might serve as a guide to the immense number of experiments which would be necessary.   From these theoretical considerations, which will be discussed in the second section, we undertook a systematic series of experiments with varied auto-oxidizable substances and catalytic agents.

We are now in the midst of the development of this problem which touches upon many of the different fields of chemistry, and our theory has thus been subjected to rigorous trial.   By means of our theory, we have not only been able to explain every fact which we have encountered, but we have also been able to predict certain effects which would have been difficult to visualize without it.   We shall consider this subject at length in the theoretical discussion, and it will suffice to point out here, three particularly striking results:

1. Relationship of the two inverse catalyses. The rational development of our theory led us to believe that a very close relationship existed between the two inverse catalyses of auto-oxidation, negative catalysis (anti-oxygenic action) and positive catalysis (pro-oxygenic action), and that there was probably a common underlying causation, such that a given catalyst might, according to the conditions, act either as an accelerator or an inhibitor of auto-oxidation. Our experimental results were in complete accord with this prediction.

The hydroiodide of methyl amine, for example, acts as an anti-oxygen toward benzaldehyde, but as a pro-oxygen toward styrol. Ethylxanthogenamide inhibits the auto-oxidation of an aqueous solution of sodium sulfite if the latter is slightly alkaline, but it behaves as an accelerator if the solution is slightly acid. It has been noted that substances which are the most active as anti-oxygens, are also the most active when they become pro-oxygens.

According to the particular case, a given catalyst may thus act either as an anti-oxygen or a pro-oxygen, and one cannot say that a given substance is an anti-oxygenic catalyst, or that another is a pro-oxygenic catalyst. To both of these, one must apply the generic term, auto-oxidative catalyst, since the sense of the catalysis, positive or negative, is dependent upon the conditions of the experiment and not upon the nature of the catalyst. The only property which is dependent upon the nature of the substance acting upon an oxidizable material, is that of being able to act as an auto-oxidative catalyst.

It is scarcely necessary to remark that the property of inversion of the sense of auto-oxidative catalysts has no connection with the well known reversibility of catalytic action. For example, hydrogen ions are known to catalyze the esterification of an alcohol with an acid (formation of an ester and water), as well as the hydrolysis of an ester by water (regeneration of the acid and alcohol), so that the final state of stable equilibrium, defined by the respective concentrations of the four constituents—alcohol, acid, ester, water—is the same whether it is attained from the system, alcohol plus acid, or the system, ester plus water, without

the intervention of a catalyst (although in reality a much longer time would be required). In auto-oxidative catalysis, on the contrary, there is not a state of equilibrium between the constituents and there can be no reversibility in the classical sense of the term. No catalyst has the power of regenerating benzaldehyde from the ultimate product of its auto-oxidation, benzoic acid. We shall return to this subject in the following section to discuss it from the standpoint of energy relationships.

2. The catalytic properties of a substance are related to its susceptibility toward oxidation. As we shall point out in the following section, our theory of auto-oxidative catalysis rests entirely upon the relationship between the suceptibility of a substance toward oxidation and its catalytic properties. We mention here a single striking example: phosphorus sesquisulfide (P_4S_3), which is used in the manufacture of matches on account of its great reactivity toward oxygen, acts as an effective anti-oxygen toward benzaldehyde at a dilution of one part per thousand.

3. Generalization of anti-oxygenic and pro-oxygenic phenomena. We have found more or less accentuated catalytic properties, under favorable circumstances, among several hundred compounds, all of which are susceptible to oxidation. We have succeeded in demonstrating by a direct method, that the catalytic activity was localized in that portion of the molecule which was oxidizable under the conditions of the experiment. All of our observations lead us to believe, as we might predict from the theory, that we could extend our list of catalysts almost indefinitely, from the most common chemicals to the rarest of them. In principle, any oxidizable substance whether its reactivity toward oxygen be great or slight, should be capable of acting as an auto-oxidative catalyst under the proper conditions. This idea confirms the statement made above; namely, that anti-oxygenic catalysis is a very general phenomenon, since we have everywhere matter which is susceptible to oxidation. We might even go further and state that an auto-oxidizable substance may act either as a positive or negative auto-oxidative catalyst toward itself.

Experimental Technic and Observations

Anti-oxygenic action. 1. Let us take a glass barometric tube, with the upper end bent in the shape of an inverted U and connected to a small bulb containing pure benzaldehyde, a substance which oxidizes rapidly in the air. Pure oxygen is introduced into the barometer tube until the mercury column within the tube is at the same level as that of the exterior. The mercury column within the tube soon starts to rise gradually. After several hours, when the height of the column indicates an internal pressure of 50–60 millimeters, the rise becomes slower and slower, and after twenty-four hours the internal pressure is still 20 to 30 millimeters. This phenomenon is due to the transformation of benzaldehyde, by the fixation of oxygen, into its peroxide and finally into benzoic acid.

If this experiment be repeated with benzaldehyde containing a small amount of hydroquinone (of the order of one part per thousand), the mercury does not rise and there is no absorption of oxygen. Thus, a trace of hydroquinone prevents the fixation of oxygen by benzaldehyde.

We have observed analogous results of approximately the same order of intensity, in replacing hydroquinone by other phenols, as well as a large number of other substances extremely varied in nature; on the other hand, these catalysts were found to exhibit a similar anti-oxygenic action toward a great variety of auto-oxidizable substances. Among the catalysts may be cited: catechol, pyrogallol, naphthols, tannins; iodine, inorganic iodides, ammonium iodide and substituted ammonium iodides, alkyl iodides, iodoform, carbon tetraiodide; sulfur, phosphorus sesquisulfide, inorganic sulfides, thioethers, mercaptans; aliphatic and aromatic amines, nitriles, amides, ureas, urethanes, substituted hydroxylamines, and dyes. Among the auto-oxidizable substances were the following: simple aliphatic aldehydes, such as acetaldehyde and heptaldehyde; substituted aliphatic aldehydes, such as acrolein and chloral; cyclic aldehydes, such as benzaldehyde, cinnamic aldehyde, and furfural; unsaturated hydrocarbons, such as styrol, phenylbromoethylene, diphenyl-

ethylene, spinacene, essence of turpentine; complex organic substances, such as caoutchouc, fats and oils; sodium sulfite, and other inorganic salts.[25]   The anti-oxygenic activities were, of course, found to vary considerably according to the nature of the auto-oxidizable substance and the nature of the catalyst, as well as with the concentration of the latter.

In practice, a number of experiments was carried out in series. A number of modified barometric tubes were sealed, side by side, to a horizontal tube which was connected with a mercury reservoir.   Special auxilliary connections were arranged in such a way that the series of bulbs and tubes could be evacuated to a very low pressure and filled with pure oxygen (fig. 1).   The heights of the mercury columns were noted at regular intervals, varying from several minutes, or hours, to several days or weeks, according to the rate of absorption.   In every set of tubes one

[25] Charles Moureu, Charles Dufraisse, and others: Sur l'autoxydation: les Antioxygènes, Compt. rend. 174, 258 (1922); II Le pouvoir antioxygène. Phènomènes divers se rapportant a l'action antioxygène., Ibid., 175, 127 (1922); III Les altérations de l'acroléine et les antioxygènes, Bull. soc. chim. (4) 31, 1152 (1922); IV Autoxydation et Action Antioxygène, Anales soc. espan. fis. quim., 20, 383 (1922); V Essai sur le mécanisme de l'action antioxygène, Compt. rend. 176, 624 (1923); VI Propriétés catalytiques de l'iode et de ces composes, Ibid., 176, 797 (1923); VII Propriétés catalytiques de l'iode et de ces composes. Genéralisation du phénomène, Ibid., 178, 824 (1924); VIII (with Panier des Touches) Propriétés catalytiques des phénols iodes, Ibid., 178, 1497 (1924); IX Propriétés catalytiques du soufre et de ces composés, Ibid., 178, 1861 (1924); X (with M. Badoche) Propriétés catalytiques du soufre et de ces composés. Généralisation du phénomène, Ibid., 179, 237 (1924); XI Activation et Desactivation de l'oxygène, Rec. trav. chim., 43, 645 (1924); XII (with M. Badoche) Recherches sur la forme active autoxydable de l'acroléine, Compt. rend. 179, 1229 (1924); XIII Recherches sur la désactivation de l'acroléine par hydroquinone. Expériences a la lumière: l'action désactivante de l'hydroquinone ne peut suffire à expliquer son action anti-oxygène, Bull. soc. chim. (4) 35, 1564 (1924); XIV (with M. Badoche) Recherches sur l'activation de l'acroléine par la lumière, Ibid. (4) 35, 1572 (1924); XV (with M. Badoche) Recherches sur l'activation de l'acroléine par l'oxygène et par la lumière et sa désactivation par l'hydroquinone, du point de vue de sa condensation en disacryle, Ibid., (4) 35, 1591 (1924); XVI (with P. Lotte) La propriété catalytique est localisee dans la partie oxydable de la molécule du catalyseur, Compt. rend., 180, 993 (1925); XVIII (with M. Badoche) Actions catalytiques des composés azotés. Considérations générales, Ibid., 182, 949 (1926); Reports of the Solvay International Council on Chemistry, April, 1925.

bulb contained a pure sample of the substance under investigation, which was used as a control.

The accompanying curves (figs. 2 and 3) give an idea of the effects which were observed. It is worthy of note that one of the catalysts chosen as an illustration (fig. 3), namely, sulfur, is as powerful an anti-oxygen toward benzaldehyde as hydroquinone; considering the feeble reactivity of sulfur at ordinary temperatures, this pronounced activity seems quite remarkable.
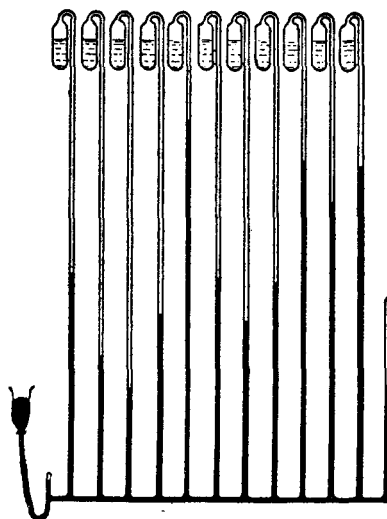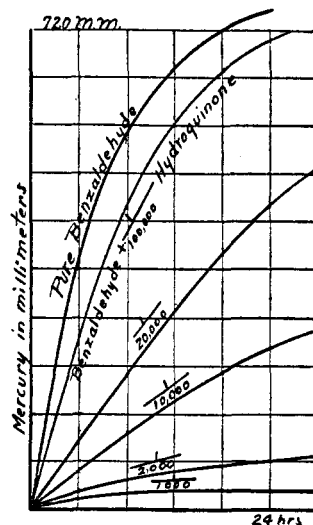

FIG. 1   FIG. 2

When the substance under investigation has a high vapor tension the general aspect of the curves is slightly different (fig. 4). With acrolein (b.p. 52°) the mercury rises in the control tube containing the pure substance, but in the tube containing the catalysts the mercury level falls until a certain level is reached, on account of the diffusion of acrolein vapor.

2. The above method often permitted us to distinguish quite sharply, differences between relatively slight variations in the concentrations of the anti-oxygen. In several instances, we were able to determine the sensitiveness of the anti-oxygenic activity, and it was found to vary considerably with the various catalysts.

The accompanying table (fig. 5) illustrates the effect of varying concentrations of hydroquinone upon the auto-oxidation of acrolein over a period of twenty-four hours. One will note that an appreciable effect is observed even in a concentration of one part per million.

If methylamine hydroiodide is used in place of hydroquinone, the effects are of the same order of magnitude (fig. 7).
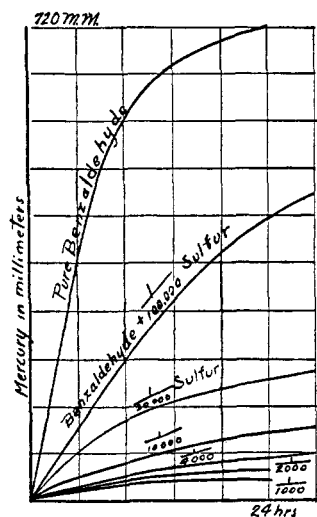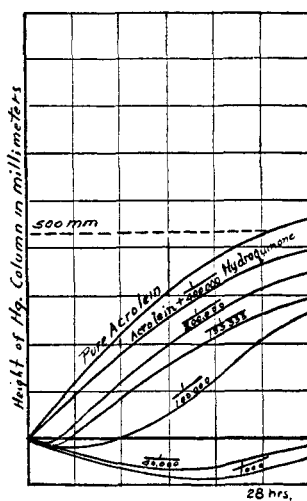

FIG. 3   FIG. 4

FIGS. 3 AND 4. CURVES SHOWING RISE OF MERCURY DURING OXIDATION IN THE PRESENCE OF HYDROQUINONE

3. As we have just pointed out, the intensity of anti-oxygenic activity of a given catalyst is dependent upon the concentration. This leads to a consideration of the duration of this protective action, when the auto-oxidation appears to have been suppressed by a sufficiently high concentration of the anti-oxygen. If no special phenomenon occurred and the anti-oxygen remained intact, the protective effect should last indefinitely. In reality, it is found after a long period of time, that the anti-oxygen becomes altered by chemical reaction with the oxidizable substance, especially if fresh quantities of oxygen are frequently admitted

into the system; the quantity of anti-oxygen corresponding to this slow depletion is thus irreparably lost for catalysis. Nevertheless, our observations indicate that in a great many cases, such as acrolein containing one part of hydroquinone per thousand, the protective action may be considered to be practically indefinite.

A priori, it would appear quite simple to determine in a precise manner, whether an auto-oxidation which appears to be inhibited, is actually completely stopped, or only greatly retarded. It should be sufficient to prolong the experimental observations over an extended period of time; unfortunately, however, a parasitic reaction vitiates the results of such observations. If we continue to observe a series of tubes containing a substance under
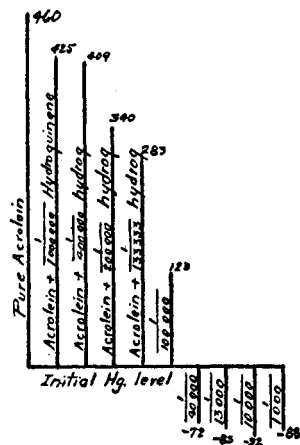

FIG. 5. TABLE SHOWING HEIGHT OF MERCURY AFTER TWENTY-FOUR HOURS

investigation with various catalysts, after a certain length of time (perhaps several days or weeks, or in some cases only after several months or years) we note an appreciable rise of the mercury column, indicating evidently a certain absorption of oxygen. On closer examination we find that a progressive condensation of the substance has occurred on the walls of the vessel and on the surface of the mercury, where it gradually collects. Obviously, it is the fraction of the material thus removed from the protective influence of the anti-oxygen which is responsible for the absorption

of the oxygen. This physical difficulty has limited the period of observation of our experiments and has prevented us from determining whether anti-oxygens actually stop the process of auto-oxidation or simply decrease the velocity of the reaction.

A simple experiment will serve as another illustration of the disturbing effect caused by vaporization and subsequent condensation of the auto-oxidizable substance. In our laboratory we have observed a corked bottle one-third filled with benzaldehyde, containing one part of hydroquinone per thousand, which has been allowed to stand undisturbed over a period of six years. Although the liquid appears unaltered except for a slight discoloration, the upper part of the bottle is coated with crystals of benzoic acid which evidently is formed by the oxidation of benzaldehyde which condenses upon the walls of the container (fig. 6).
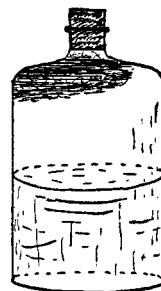

FIG. 6

A careful examination of the curves will show that the absorption of oxygen is never completely inhibited. Even under the most favorable circumstances a slight rise of the mercury column is observed if the experiment be sufficiently prolonged. We have now in progress a series of experiments in which the foregoing physical difficulty has been eliminated. The results of these observations will permit us to obtain precise data on the true velocity of oxidation in the presence of anti-oxygens.

Pro-oxygenic action. 1. Iodine and a number of iodine compounds act as positive catalysts toward the auto-oxidation of styrol. Similar behavior was observed toward linseed oil, as one might expect from the presence of double bonds in the latter, which make it analogous to styrol.

The green sulfide and the anhydrous pink sulfide of manganese accelerate considerably the auto-oxidation of benzaldehyde. Cobalt sulfide is also an accelerator but is less active than the sulfides of manganese.[26] Other positive catalysts for the auto-

[26] Conversely, iron sulfide and nickel sulfide behave as anti-oxygens. It appears that this activity is not a specific property of the metallic ion, which may pro-

oxidation of benzaldehyde are carbon disulfide, sodium sulfide, and diethyl thiocarbonate.

Among certain interesting facts which have resulted from our observations may be mentioned the following:

Ethyl sulfide acts as a pro-oxygen toward acrolein, although ethyl mercaptan is a strong anti-oxygen toward this substance.

Phosphorus sesquisulfide, thiophenol, ethyl mercaptan, antimony sulfide, act as positive catalysts toward styrol.

Thiophenol and the green sulfide of manganese are accelerators toward essence of turpentine.

Phosphorus sesquisulfide and the green sulfide of manganese are accelerators toward linseed oil.

2. In general, the activity of pro-oxygenic catalysts was found to be relatively slight, although we have encountered instances where the speed of auto-oxidation was increased one hundred fold. Usually the coefficient of acceleration falls between 2 and 20. We have not ordinarily taken into account any cases where the coefficient was less than 2.

One must not confuse the phenomena of pro-oxygenic activity with certain others of a somewhat similar nature which are distinctly different. Numerous substances which are practically inactive toward free oxygen, are readily oxidized in the presence of an appropriate catalyst. The latter first auto-oxidizes, then gives up to the substance the oxygen thus acquired, and is itself regenerated in its original unoxidized state; the cycle then recommences and goes on indefinitely.

A clear cut example of this type of oxidative catalysis (involving preliminary auto-oxidation of the catalyst) is furnished by the oxidation of glucose by free oxygen in the presence of cerium salts, discovered by Job.[27] A solution of glucose containing a trace of a cerous salt, oxidizes in the air according to the mechanism just described, and the cerous salt acts in this instance as an *auto-oxidizing catalyst.*

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duce either one of the two opposite effects. In fact, we have observed that the chlorides of nickel and manganese are accelerators toward benzaldehyde, but the iodides are inhibitors. It can also be seen that manganese does not always have pro-oxygemic activity as one might be led to believe a priori.

[27] Ann. chim. phys. (7) 20, 205 (1900).

Many other examples involving auto-oxidizing catalysts are known, such as the oxidation of hydroquinone and pyrogallol under the influence of traces of manganous salts, or under the influence of laccase, a soluble enzyme containing manganese.[28]

Inversion of the catalysis. 1. On account of the close relationship which exists between the two opposite types of catalytic action, an inversion of the sense of catalysis frequently occurs. Our investigations on this subject have resulted in a number of sharply defined observations. In addition to those which have already been mentioned are the following:

Iodine, which is a powerful anti-oxygen toward benzaldehyde, is a pro-oxygen toward styrol.

Iodoform, which is a pro-oxygen toward styrol, is an anti-oxygen toward furfural.

Phosphorus sesquisulfide, which is an anti-oxygen toward benzaldehyde, is a pro-oxygen toward linseed oil.

Thiophenol, which is an anti-oxygen toward benzaldehyde, is a pro-oxygen toward essence of turpentine.

Sulfur and diethylene disulfide, which inhibit the auto-oxidation of sodium sulfite in alkaline solution, behave as accelerators if the solution is slightly acid.

2. Ordinarily, in these inversions, the most powerful anti-oxygens become also the most active pro-oxygens. For example, methylamine hydroiodide is an extremely active anti-oxygen toward acrolein; conversely, it is a highly active catalyst as a pro-oxygen toward styrol.

3. In certain observations of the action of a catalyst upon the auto-oxidation of a given substance, it was noted that the sense of the catalysis changed during the course of the experiment.

The behavior of iodine and iodine compounds toward acrolein furnished a number of examples of this inversion. The catalysis, at first negative, changed to positive after a certain length of time, which varied from several minutes or hours, to days or weeks, depending upon the particular catalyst and the concentration. This occurrence was observed in the following instances;

[28] Bertrand, Ann. chim. phys. (7) 12, 115 (1897).

methylene iodide, one per cent (negative catalysis during 15 minutes); iodoform, one per cent (20 hours); carbon tetraiodide, one per cent (several days); ethylene iodide, one per thousand (8 hours); acetylene di-iodide, one per thousand (18 hours); iodol, one per thousand (90 hours); benzyl iodide (70 hours).

The accompanying graph (fig. 7) shows the remarkable results obtained with methylamine hydroiodide in high dilutions. There was observed at first an intense anti-oxygenic activity, then oxida-
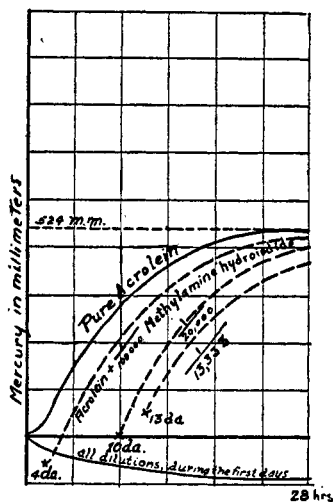

FIG. 7. CURVES SHOWING RISE OF MERCURY DURING OXIDATION IN THE PRESENCE OF AN HYDROIODIDE

The dotted curves have been brought toward the y-axis by parallel transposition.

tion started suddenly at a rapid rate which was about the same as that of the control tube of pure acrolein. In this case there was no well defined pro-oxygenic action, since the oxidation was not markedly accelerated, probably on account of the very great dilution of the catalyst. The positive activity being slight, did not appear distinctly in such very low concentrations, but the inversion was too distinct to leave any doubt.

Among other anomalous results which were noted are the following:

Phosphorus sesquisulfide acts toward turpentine, first as an accelerator, then as an anti-oxygen. Thiophenol acts in a similar manner toward linseed oil. Conversely, thiolactic acid and thioglycolic acid exert first, an anti-oxygenic effect toward acrolein, followed by a pro-oxygenic activity.

These are but a few of the numerous examples of this type.

Secondary phenomena of auto-oxidation and anti-oxygenic action. Auto-oxidation is very often accompanied by secondary reactions such as molecular condensation, which is manifested by resinification, or the development of colorations, precipitates, or rancidity. When an anti-oxygen prevented the fixation of oxygen, we observed a simultaneous inhibition of these secondary reactions. Thus, furfural, which usually becomes rapidly discolored, remains almost colorless; acrolein does not become turbid from the precipitation of disacryl; styrol remains fluid and mobile, instead of being resinified with the formation of metastyrol; linseed oil, upon exposure to the air in thin films, remains fluid after three years; butter, and other fats and oils, do not, in general, turn rancid.

It appears that the immediate agency which produces these secondary phenomena, is not free oxygen itself, as one might suppose, but is combined oxygen from a peroxide which is first formed from the auto-oxidizable substance. This has been rigorously demonstrated in the case of acrolein in the following way.

If acrolein which has been exposed to the air, is freed from dissolved gases by thorough evacuation and is then preserved in a high vacuum, condensation and formation of disacryl proceed in the same manner as in the presence of air. Therefore, free gaseous oxygen is not responsible for this alteration, but contact with air has sufficed to inoculate acrolein with a mortal poison. On the other hand, if we allow acrolein containing a small quantity of an anti-oxygen to stand in contact with free oxygen, there is no condensation; consequently, it is not free oxygen which causes the alteration, but combined oxygen. We conclude from the above facts, that the catalytic agent which effects the conversion of acrolein into an insoluble resin is a peroxide.

Auto-oxidation of vapors. It would be natural to expect that the vapor of an auto-oxidizable substance, such as benzaldehyde, when mixed with an excess of gaseous oxygen, would be oxidized rapidly. If one were dealing with a system in which an excess of auto-oxidizable liquid were present, so that the depletion of vapor could be replenished as rapidly as oxidation occurred, one might think that the absorption of oxygen would proceed with greatest intensity in the vapor phase.

If we consider our experimental technic, in which the essential instrument is a barometer tube, and we examine the case of a catalyst which completely inhibits oxidation, one conclusion appears to be inevitable: the vapors of an auto-oxidizable substance do not undergo oxidation. In fact, with our experimental procedure, it would have been impossible to observe anti-oxygenic action,—at least in those most common cases where the anti-oxygens under investigation did not have an appreciable vapor pressure, and could not exert an anti-oxygenic influence in the gaseous phase. If there had been an appreciable oxidation in the gaseous phase we would have been unable to note a diminution in the rate of absorption of oxygen.

Our experiments have revealed very definite anti-oxygenic action, and at the same time, have established, not only that the vapor of an auto-oxidizable substance does not oxidize rapidly, but apparently that oxidation does not occur at all in the vapor phase (under the conditions of our experiments).[29] This is a rather important and altogether unexpected result.

Repercussions in various fields. Anti-oxygenic and pro-oxygenic catalysis may play an important rôle in the chemical processes involved in a multitude of natural phenomena, both in inanimate matter and in living organisms. We shall enumerate and discuss certain special cases.

1. Contact catalysis—the so-called poisoning of catalysts. We shall be concerned here with contact catalysis only inasmuch as it involves phenomena of auto-oxidation. Outside of living organisms, with which we shall be concerned later, this is true

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[29] Experiments relative to this point are now in progress.

in a certain number of cases, particularly those of catalysis by free metals. In these cases, we suppose that the catalyst auto-oxidizes to give an unstable oxide, which in turn gives up its oxygen and regenerates the metal. It has long been known that platinum in a finely divided state (platinum sponge, platinum black, platinized asbestos, and colloidal platinum), is an active catalyst for a variety of oxidations. Other metals of the platinum group, particularly palladium, may behave in a similar manner, and the same is true of gold, silver, and copper.

We can consider in the same light other catalytic agents wh'ch undergo preliminary auto-oxidation. For example, recent studies have shown that a large number of organic substances may be completely oxidized at ordinary temperatures in the presence of charcoal; mixtures of metallic oxides, such as "hopcalite," which has been extensively studied in America, have the property of oxidizing carbon monoxide at room temperature.

It is well known that such catalytic activity is often inhibited by traces of certain substances which behave as catalyst poisons. Thus, small quantities of certain gases or vapors (ethylene, carbon monoxide, hydrogen sulfide, and others), prevent platinum sponge from effecting a violent combination of hydrogen and oxygen at room temperature. We believe that these inhibitory substances exert the same anti-oxygenic influence upon the transitory oxidation of platinum, that hydroquinone exerts toward benzaldehyde, and we would apply the general mechanism of anti-oxygenic action which will be discussed later, to explain this so-called "poisoning" of oxidizing catalysts.[30] We believe that our interpretation may also be applied to a number of other instances of the poisoning of oxidizing catalysts.

2. "Anti-knock" agents. The recent discoveries of the American chemist, Midgley, have shown that small amounts of various substances have a remarkable effect in preventing knocking in motors. We believe that here also, one is dealing with an anti-oxygenic action which is quite comparable with those that have already been described.[30a] We might add in this connection, that

[30] Moureu and Dufraisse, J. Chem. Soc., **127**, 1 (1925).
[30a] Cong. Soc. Chim. Ind., Paris; October, 1925.

tetraethyl lead, which is a powerful anti-knock agent, is also capable of acting as an anti-oxygen toward benzaldehyde at room temperature. Tetraethyl lead acts as a moderator to the action of oxygen at a high temperature upon the explosive gas mixtures of motors, and it exerts the same moderating influence on auto-oxidation under the usual conditions of our experiments. Its mode of action would seem to be the same in both cases.

3. Biological considerations. On account of the fundamental interest of auto-oxidation in vital phenomena, from the very first we were able to perceive numerous applications of the facts which we had discovered to several general conceptions of biology.

Phenols. Phenols are present in many living organisms, but from this standpoint there are two distinct categories of organisms; those in which phenols are quite common and wide spread, and those in which phenols are rare. The first group is made up of plants and trees, where one encounters an abundance of the most varied phenolic compounds; monohydric and polyhydric phenols and their derivatives, among which the tannins merit special notice, on account of their general distribution and occurrence in large quantity. The second group is made up of animals; among these, very few phenols occur, and always in very small amounts. Plants are precisely the organisms of slowest metabolism, and those in which the phenomena of auto-oxidation do not have the same intensity as in animals, and it is but natural to suppose that in animals, the phenols act as protective agents against a too vigorous oxidizing action. One cannot help but remark the fact that the tannins, which are very active phenolic substances, are present in greatest amounts in those parts of the plant in which metabolism is at the lowest ebb.

Among the most interesting experiments which suggested themselves for consideration, was the auto-oxidation of hemoglobin. We have carried out a number of experiments in this field, with hemolysed blood, and with the liquid resulting from the hemolysis of washed red corpuscles, and with solutions of hemoglobin which had been purified by crystallization. Our results were negative with the various phenols investigated, namely, phenol, naphthols,

catechol, guiacol, resorcinol, hydroquinone, pyrogallol, gallic acid. Hemoglobin which had been reduced by evacuation at 40° was found to oxidize as really in the presence of phenols as in their absence. We observed what appeared to be a mutual destruction of both the phenol and hemoglobin.

One must not necessarily conclude from these results that phenolic substances are without action on the auto-oxidation of hemoglobin. The speed of auto-oxidation of hemoglobin is enormous, perhaps comparable with the neutralization of a strong acid with a strong base; it is therefore quite possible that the antagonistic action of the phenols was too weak to be noticeable under the conditions of our experiments.

Nevertheless, it is probable that phenolic substances play some part in a stage of the oxidative mechanism of higher animals. This contention is supported by the toxicity of the phenols; those which are the most active anti-oxygens are the most toxic, and the symptoms of poisoning are similar to those of asphyxia.

It seems likely that the antiseptic properties of phenols may be due to their anti-oxygenic activity, which perhaps affects microörganisms by interfering with their oxidative processes.

When one considers the extremely minute quantities of an anti-oxygen which are capable of producing very definite effects, one can scarcely avoid comparing their activity to that of toxins and venoms. A certain number of the latter cause death by asphyxiation, and this leads to the idea that they may act as anti-oxygens. This viewpoint would be supported by the fact that quinone has been encountered in certain venoms.

Finally, we cannot omit to mention certain consequences which may result from the application of this new notion of anti-oxygens to pharmacology. It is particularly remarkable that phenols are antipyretics, no doubt, on account of the fact that they attenuate the intensity of oxidative metabolism. This is perhaps the key to the physiological action of antipyretics in general. In fact, it happens that antipyretics used in therapy are aromatic substances, and it has been observed that aromatic compounds may be oxidized in the body to give phenolic substances. It is evident that a knowledge of the anti-oxygenic properties

of phenols may be of such a nature as to modify the interpretation of certain therapeutic effects which are observed to follow their administration.   From this conception one cannot help but note the favorable results often obtained by the use of phenolic substances (creosote, guiacol and its derivatives, and others) in the treatment of a malady which closely affects the oxidation processes of the organism, namely, pulmonary tuberculosis.   It would fall into the domain of workers in this field to determine whether or not these substances act in moderating respiratory hyperactivity, as well as destroying microörganisms.

Iodine and its derivatives.   It is well known that iodine is widely diffused throughout the mineral kingdom.   There are considerable amounts of iodides in sea water, in which we find innumerable living organisms which accumulate this metalloid in their tissues.   We also find iodine in all forms of life, plant or animal, and it is ordinarily considered as one of the elements which are necessary for life (A. Gautier, Baumann, Gley, and others).

From our experiments one might suppose that iodine acts in a number of cases as a regulative agency for the phenomena of oxidation.   Small quantities of energy would suffice to change iodine from the state of a negative catalyst to that of a positive catalyst, and vice versa, according to the needs of the organism.

Although the higher animals live in an environment very low in iodine, they concentrate this element in a special organ, the thyroid gland, to which we attribute precisely the rôle of regulating oxidative metabolism.

Hence it was natural to extend our experiments to extracts of the thyroid gland.   Our results were quite well defined, but it is difficult to interpret them correctly, on account of the complexity of the material which we used.   We hope to be able to investigate the behavior of thyroxin, the active principle isolated by Kendall, but we have not yet been able to obtain a sample of this substance.

Sulfur and its derivatives.   Sulfur is present in many substances which occur in living organisms and is found in one of the most important groups of organic compounds of natural origin, the proteins.
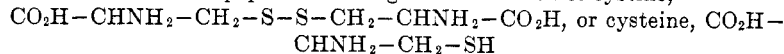
The recent work of Hopkins[31] and his collaborators has drawn attention to the presence of glutathione in practically all animal tissues. According to Hopkins, glutathione[32] can exist in two forms, an oxidized form $R-S-S-R$ and a reduced form $R-S-H$, which are readily interconvertible. He states that this substance acts as an oxidizing catalyst, but differs from hemoglobin, which is an oxygen carrier, in that it is a hydrogen carrier. The latter transports hydrogen from an oxidizable substance to free oxygen and the result amounts to an oxidation of the oxidizable substance.

When an equilibrium between a substance X and its oxidation product Y, occurs among the phenomena of a catalytic oxidation, we have found that it is not necessarily this reversible transformation which is the basis of the catalytic activity. We have demonstrated that X and Y each have a specific catalytic influence. In the case of thiophenol, a catalyst which we have observed to be converted into diphenyl disulfide during the course of certain catalytic oxidations, the passage from $R-S-H$ to $R-S-S-R$ and vice versa, is in reality an accessory phenomenon of the catalysis, contrary to the statement of certain authors. Catalytic activity is produced according to a mechanism (which we shall discuss later) involving much more rapid reactions, which consequently result in much more intense catalytic effects.

Nitrogen compounds. From a biological standpoint nitrogen compounds are of much greater importance than any other substances, either organic or inorganic, which have been mentioned thus far. Nitrogen in various forms is an essential constituent of all living tissues and is present in the principal compounds

[31] "The Mechanism of Oxidation in Living Organisms"—Lecture before the International Conference on Pure and Applied Chemistry; Cambridge, 1923, published in Bull. soc. chim. biol., **5**, 761 (1923); compare also Hopkins, Biochem. J., **15**, 286 (1921), Hopkins and Dixon, J. Biol. Chem., **54**, 529 (1922); Hopkins, Biochem. J., **19**, 787 (1925).

[32] Glutathione is a dipeptide resulting from the union of cystine,
$$CO_2H-CHNH_2-CH_2-S-S-CH_2-CHNH_2-CO_2H,$$ or cysteine, CO_2H-
$$CHNH_2-CH_2-SH$$
with glutamic acid, $CO_2H-CH_2-CH_2-CHNH_2-CO_2H$.

which are elaborated by the organism. It is of fundamental importance in the movement of oxygen in higher animals. On account of the great complexity of many of these compounds one would scarcely expect to find their activity to be simple in nature. Studies which are now in progress may lead us to certain generalizations on this subject.

Practical applications. We have pointed out the desirability of being able, at will, to accelerate or diminish the reactivity of oxygen. Our experiments lead to hope that this problem may be solved easily. In our own experience we have been able to inhibit a number of undesirable oxidative effects and thus avoid their harmful consequences. We have been able to preserve many alterable compounds, such as unsaturated hydrocarbons, aldehydes, delicate perfumes, caoutchouc, fats and oils, et cetera.

We employ anti-oxygens currently in our laboratory for the stabilization of various auto-oxidizable substances. A striking example of the practical service which anti-oxygens render almost every day, is the case of furyl ethylene, $C_4H_3O - CH = CH_2$. This extremely sensitive substance was the starting point in a study which was undertaken in our laboratory with the collaboration of an American student. If we had not been able to stabilize furyl ethylene and to assure ourselves of a sufficient supply of this material, it would have been necessary to renounce the work and we would have been unable to achieve the goal, which was furyl acetylene, $C_4H_3O - C \equiv CH$.

The advantages of the use of anti-oxygens are not limited to the preservation of sensitive substances against oxidation. Traces of peroxides are often known to produce disastrous catalytic effects upon the yields in certain chemical operations, particularly on account of many condensation reactions which they bring about. It is therefore advantageous to utilize anti-oxygens, even with substances that are comparatively unreactive toward oxygen, when it is necessary to allow an auto-oxidizable substance to come into contact with air. It has been found that acrolein gives much better yields in a Grignard reaction if it has been preserved against auto-oxidation by an anti-oxygen, rather than

simply stored out of contact with air.[33] An analogous result was obtained in the transformation of essence of turpentine into camphor.

Scientists in various parts of the world have honored our work by the utilization of anti-oxygens in their researches. Many were kind enough to write and inform us of the beneficial results which were obtained. Nevertheless, in the utilization of these catalysts one must not lose sight of the close relationship which exists between the two opposite senses of the catalysis: according to the conditions and to the influences of minute quantities of reagents, one may produce a pro-oxygenic instead of an anti-oxygenic catalysis. A catastrophe is thus brought about in the attempt to avoid it. In this connection one may recall, with a slight deformation of its meaning, an old saying: "The Tarpeian rock is near the Capitol."

2. THEORIES OF ANTI-OXYGENIC ACTION

Let us consider the system composed of an auto-oxidizable substance A, and oxygen O_2. The stable state of this system corresponds with the formation of a stable oxide, AO_2, since the inverse reaction $AO_2 \rightarrow A + O_2$, is not possible unless energy is furnished to the system. Let us add a catalyst B to the system— if we observe a diminution in the velocity of formation of AO_2, we state that this activity which we call anti-oxygenic action, is a negative catalysis.

We have indicated in the preceding chapter, that the two modes of catalysis (positive and negative) mentioned here, are not to be confused with catalysis in the two opposite senses produced by the same catalyst in the well-known phenomenon of the inversion of catalytic action. In fact, if one considers this inversion one realizes that the action of the catalyst is always positive from the standpoint of the energy relationships—both when it accelerates the direct and the reverse reaction—since in each case it tends to bring the system into a state of stable equilibrium.

[33] The yield of vinylmethylcarbinol was increased from 25 per cent to 52 per cent by the use of acrolein containing one part of hydroquinone per thousand; Daudrenghein, Bull. soc. chim. Belg. **31**, 160 (1922).

In the case of auto-oxidation the facts are not apparently so simple from the energetic point of view. Pro-oxygenic activity is undoubtedly a positive catalysis, since it favors the displacement of the system $A + O_2$ toward its stable state of equilibrium, corresponding to the stable oxide AO_2. But what is anti-oxygenic activity? We have used in this connection the term *negative catalysis*, which is not particularly appropriate. In reality the term negative catalysis, which we did not create, does not appear especially fortunate. Although it expresses very well the superficial appearance of the phenomenon, that is, the production of an effect opposite to that produced by positive catalysis, it presents the serious inconvenience of lending itself to an inexact interpretation. It seems to imply the idea of a catalysis in the wrong direction; a catalysis which would give to the reaction an impulse in the opposite direction to that given by positive catalysis. In the case of a movable object, if one designates displacement in a certain sense positive, the corresponding velocity is positive, while a velocity corresponding to displacement in the opposite sense is negative.

It is evident that here an analogous point of view would be grossly erroneous. No catalyst is able, without the addition of external energy, to reverse the course of spontaneous chemical reactions which are accelerated by positive catalysts, for it is impossible to raise the potential of a system without the expenditure of energy, and the laws of thermodynamics require that when a phenomenon takes place spontaneously (that is, without the application of external energy to the system) it always takes place with liberation of energy. A diminution of potential, negative catalysis in the literal sense of that expression, is therefore impossible. For instance, no catalyst is able to regenerate from benzoic acid the initial mixture of benzaldehyde and oxygen. This would be in the strict sense of the word a true negative catalysis.

It follows that if anti-oxygenic activity is really a catalysis, as we have already called it by anticipation, it can be no other than a positive catalysis; that is, a catalysis impelling the system toward a state of equilibrium, a phenomenon permitting a lowering of potential.

In the case of reversible reactions, one can easily conceive that a catalyst might be capable of producing two inverse chemical reactions, depending upon whether it impels the reaction in one direction or in the reverse direction. Here, on the contrary, in the case of anti-oxygenic and pro-oxygenic activities we do not have an analogy, since we are dealing not with a reversible reaction but with the irreversible change, $A + O_2 \rightarrow AO_2$. We are therefore confronted with the problem of finding a mechanism for anti-oxygenic catalysis such that we shall deal with an equilibrium which is impelled in a sense opposite to that of pro-oxygenic catalysis, the only one of which we are able to perceive the result. In fact, if one considers the case of a stone on the side of a hill, one can compare positive catalysis to an agency which facilitates its sliding downward, but it is difficult to imagine a catalysis, also positive (corresponding to anti-oxygenic action) which would facilitate a movement that would result in maintaining the stone in its original position. That is, the mode of action must be such that as a result of the movement the stone returns to its original position. This problem of paradoxes is capable of solution, and we believe that it can easily be solved by the present resources of physical chemistry.

Before examining the possible interpretations, we shall consider first an hypothesis for the mechanism of anti-oxygenic action which does not involve a catalysis.

I. NON-CATALYTIC THEORY OF ANTI-OXYGENIC ACTIVITY

Does the action of anti-oxygens consist in a neutralization of the action of positive catalysts?

Various observations have led to the supposition that the process of auto-oxidation requires the aid of a positive catalyst. Such substances would always be present in a system whether or not one succeeds in demonstrating their precise rôle. The action of the walls of the vessels, minute amounts of impurities, and traces of moisture, appears to be essential in many reactions. It has, for example, been established that oxidations are difficult to

carry out with thoroughly dried oxygen;[34] that it is impossible to bring about the detonation of absolutely dry mixtures of carbon monoxide and oxygen, that a carbon monoxide flame is extinguished by absolutely dry air;[35] and that carbon and oxygen rigorously dried do not combine at 1000°.[36]

Theory of Titoff. If, in certain cases, the presence of traces of appropriate impurities is necessary and sufficient to permit auto-oxidation, it should be comparatively simple, by the addition of small amounts of impurities to extinguish their effects. It was thus that Titoff[37] explained the hindering effect caused by traces of benzyl alcohol, benzaldehyde, mannite, glycerol, and various phenols, in the auto-oxidation of dilute solutions of sodium sulfite; he showed that copper is an extremely active positive catalyst for this reaction, and he came to the conclusion that the rôle of a negative catalyst is simply to paralyze (by complex formation) the action of a positive catalyst.

In a like manner, Warburg[38] concluded that iron in many biological and similar processes is neutralized by various substances, especially by hydrocyanic acid.

Although such explanations may appear sufficient in certain isolated cases, they are in general inadequate. If one remembers, for example, that traces of hydroquinone protect a great number of diverse substances against the action of oxygen, it is difficult to suppose that this substance really has the power in each case, to neutralize the positive catalyst.

In the first place, it is quite certain that in general, the positive catalyst which is neutralized cannot be water, as in certain examples cited above, since anti-oxygens are not dehydrating agents, and since moreover, they may act in aqueous solution.

In the second place, if hydroquinone owes its activity to a neutralizing action upon a positive catalyst, one would be forced to suppose that the most diverse substances susceptible to auto-

[34] Dixon, Trans. Roy. Soc. London, **37**, 56 (1884).
[35] Traube, Ber. **18**, 1890 (1885).
[36] Baker, J. Chem. Soc., **47**, 349 (1885); Proc. **1**, 37 (1885).
[37] Titoff, Zeit. phys. chem., **45**, 641 (1903).
[38] Warburg, Ber. **58**, 1001 (1925).

oxidation, owe this susceptibility to the presence of the same impurity, or at least to impurities belonging to the same category; and this appears very improbable. On the other hand, as we have shown (we shall return to this in more detail later), first, a common property of all anti-oxygens, and one which appears an essential condition for anti-oxidative activity, is oxidizability; second, according to the conditions, the same catalyst may act either to diminish or accelerate auto-oxidation, i.e., either as an anti-oxygen or as a pro-oxygen. These are two remarkable properties of anti-oxygens and they are very difficult to account for by means of the above hypothesis.
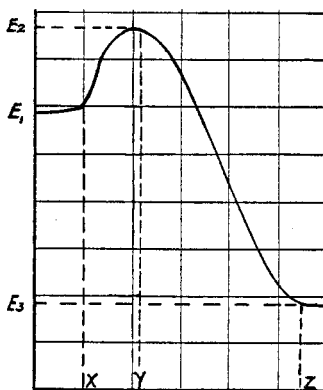

FIG. 8

II. THEORIES INVOLVING A CATALYTIC MECHANISM

If one is to conceive of anti-oxygenic action as a catalysis, the latter must necessarily be positive, and it is essential to concede that the phenomenon of auto-oxidation of a substance A, does not consist in a continual drop of potential of the system $A + O_2$ until oxidation is complete. One does not escape the fatality that the process is obliged to imply an increase of potential at a certain moment. It is at this phase that an anti-oxygen will oppose the ensemble of auto-oxidation processes by a positive catalytic action, that is by favoring a lowering of potential.

The accompanying curve (fig. 8) is a graphical representation,

in which time is the abscissa, and the ordinate is the potential energy of the mixture of the two molecules A and O_2 which are to react with each other. It is in the portion of the curve projected in XY that anti-oxygenic action would occur.

This conception was not invented by us for the needs of the moment. It is a relatively old notion of the great Swedish theorist Arrhenius, which is coming to play an increasingly important part from day to day in our modern physical theories. Due to its basis of solid experimental facts, none could be better suited to the interpretation of our results.

It is well known that physical and chemical observations have led to the inference that in a fluid (liquid or gas) made up of a definite chemical species, all of the molecules are not in the same state. From the standpoint of energetics the states of the individual molecules are distributed around a mean state and the proportion of molecules in a given state varies inversely with the difference from the mean state. Molecules removed from the mean state are called *activated*. In most chemical reactions all of the molecules present cannot interact simultaneously, and at a given moment only a small portion of the entire number can enter into reaction. The velocity of a reaction is regulated precisely by the proportion of active molecules, and by the speed with which they are formed in the ensemble of the mass. Due to developments of this theory by Berthoud, Marcelin, Lewis, Perrin, Langevin, and others, one may calculate the excess of energy which must be acquired by the molecules in a mean state to become activated for a given reaction. This minimum additional energy requirement is called the *critical increment of energy*.

The especially favorable condition of the active molecules is acquired at the expense of the average energy, in accordance with statistical laws.[39] Although the curves which we have given above may appear somewhat fantastic at first, they are readily explained on this basis. The average molecules are found at the level E_1; those which react must pass through the level E_2 before descending to the level E_3, which represents the stable state of

[39] Moureu and Dufraisse, Reports of the Solvay International Council on Chemistry, Brussels, April (1925), p. 529ff.

auto-oxidation. At the moment of the obligatory passage through the level E_2, two catalyses are possible, both positive of which the effects are diametrically opposite: one, pro-oxygenic action favoring movement to E_3; the other, anti-oxygenic action favoring return to E_1. Thus, it is evident that if one succeeded in causing a constant retrogression of the molecules at the level E_2 to the level E_1, the entire phenomenon of auto-oxidation would be suppressed.

This representation of the process of anti-oxygenic action readily explains one of the most striking characteristics of the phenomenon, namely, that a very small number of molecules of an anti-oxygen can prevent oxidation of an enormous number of molecules of an auto-oxidizable substance in contact with oxygen. There is something truly disconcerting about this fact; for example, one molecule of hydroquinone suffices to prevent the oxidation of forty thousand molecules of acrolein, and considerable effects may be observed at dilutions much greater than this. Such a disproportion between the number of molecules which tend to be oxidized and the number of antagonistic molecules leads to the conclusion that the former must pass through some critical transitory stage where they are particularly vulnerable, and that it is only in such a transitory stage that the opposing molecules are present in sufficient number.

Direct inactivation

Do anti-oxygens act through a process of direct inactivation of the molecules of either the auto-oxidizable substance, or of oxygen?

It is evident from the foregoing paragraphs that if one succeeded through any agency in diminishing the concentration of active molecules of a chemical species, one would diminish the velocity of reaction in the same measure. It would then be rational, a priori, to think of a simple mechanism in which the anti-oxygen, which we shall designate as B, would act in catalyzing the return of active molecules, either of the auto-oxidizable substance A, or of oxygen O_2, to the mean energy level of the ensemble. From the outset we have been occupied with this

suggestion which has been put forward and supported by various scientists. In particular, Professor Hugh S. Taylor[40] in a paper on this subject, has made certain very suggestive calculations based upon our experimental results, and has presented a series of experiments in support of his views.

We have shown with benzaldehyde, for example, that a proportion of one part of hydroquinone per thousand produces very marked anti-oxygenic effects, so that at this very low concentration, benzaldehyde is practically stable in the air. Taylor points out that if, instead of reasoning from the total number of molecules of benzaldehyde, one consider only the molecules which are ready to react (i.e., the number of active molecules, which he determined by the speed of oxidation) hydroquinone is not only present in the liquid in stoichiometric superiority, but is present in an overwhelming proportion when compared with the number of active molecules of benzaldehyde. It would suffice, therefore, that the molecules of hydroquinone enter into a transitory combination with active molecules of benzaldehyde, and that this combination dissociate later with liberation of a molecule of benzaldehyde in an inactive state.

In order to support this theory with experimental evidence, Taylor investigated the tendency of benzaldehyde to form molecular complexes with various substances which we had found to act as anti-oxygens toward this aldehyde, and he sought the property of anti-oxygenic activity among substances which were known to form molecular complexes with benzaldehyde. Along with an undeniable measure of success, he encountered certain practical difficulties.

Notwithstanding, this theory is very interesting, and we have already refuted certain criticisms which have been advanced.[41] In our opinion it seems necessary to supplement this theory by the following observations:

Selective attraction. We believe that the difficulties encountered by Taylor are centered in his idea of the tendency toward forma-

[40] J. phys. chem., **27**, 322 (1923).

[41] Moureu and Dufraisse, *Reports of the Solvay International Council on Chemistry, Brussels,* April (1925) p. 554.

tion of molecular complexes. As he justly stated, the molecular complexes which he studied, either were too stable, and consequently unable to fulfill the condition of being readily dissociated (such as the complex, benzaldehyde: trichloroacetic acid), or were too unstable (such as those whose existence is based uniquely upon the examination of solidification curves). In the latter case, the reactivity of the catalyst toward the auto-oxidizable substance is far too feeble to allow observation of its activity in the high dilutions which are used. In our opinion, the essential condition is the union of the catalyst with the active molecules, and not with the mass of molecules in the mean state. This latter condition would even be prejudicial, since the molecules held in a stable complex would be lost for catalytic activity. The ideal anti-oxygen would be one which was deprived of all reactivity toward average molecules of the auto-oxidizable substance, but would have a great power of attraction for active molecules. It would be exceedingly difficult to adduce experimental evidence of combinations of this type, and one must not be surprised that Taylor was able to discover only a rather vague relationship between the anti-oxygenic activity of a substance and its tendency to form molecular complexes with average molecules of benzaldehyde.

We would go one step further, in that we believe that no theory of anti-oxygenic catalysis can avoid the necessity of invoking a selective (if not exclusive) attraction of the anti-oxygen for at least one of the active members of the transformation (active molecules of oxygen, or of the auto-oxidizable substance, or of the first products of their union). One can readily see objections to any other explanation of the protective action of one molecule of hydroquinone upon forty thousand molecules of an auto-oxidizable substance. First, a protective action would obviously be impossible if the forty thousand molecules were able to react with oxygen simultaneously. Second, it is essential that as soon as one of the molecules enters into reaction, the anti-oxygen reach it surely and immediately, in order to act before an irreparable injury has resulted.

In bringing about an inactivation the anti-oxygen must not

hesitate between active molecules and the others, nor waste time in the formation of sterile combinations. It must act as a magnet to seek exclusively and rapidly, those molecules which are on the point of undergoing a definite transformation. *This result can only be obtained by a marked power of selective attraction, which we believe to be indispensable for anti-oxygenic activity.*

One can scarcely object to the concept that a reacting molecule may choose, among the mass of surrounding molecules, those which are in an activated state. In so doing, the reacting molecule would but imitate oxygen itself, which combines with active molecules to the exclusion of all others.

The need of another theory. Notwithstanding the interesting theories based upon a pure and simple inactivation of the auto-oxidizable substance, we do not believe that they can account for the mechanism of anti-oxygenic action except in certain special cases.

At the outset, they have against them the wide variety of anti-oxygens and auto-oxidizable substances. It would be necessary to suppose that such widely different substances as sodium iodide, sulfur, hydroquinone, thiohydracrylic acid, *et cetera*, act upon a single substance such as benzaldehyde, in modifying it in the same manner. It would be necessary to admit also, that the substances in such a varied collection as the following; benzaldehyde, acrolein, essence of turpentine, sodium sulfite and linseed oil, undergo the same transformations on contact with the same reagent, such as ethyl xanthogenamide. It is evident that one of these suppositions is as unlikely as the other.[42]

An experimental proof that anti-oxygens do not act by the inactivation of auto-oxidizable substances would be highly desirable. One realizes the experimental difficulties which must be surmounted, when one considers that we are dealing with researches involving ephemeral molecules which are probably present in almost infinitesimal amounts (probably of the order of one per million, or even less).

[42] In any case, the second objection would have less force against a theory based upon the inactivation of oxygen, since in all the infinite variety of auto-oxidative phenomena, this is the only thing which remains identical.

In one special case, through a combination of favorable conditions, we had the good fortune to be able to determine directly, whether or not an auto-oxidizable substance was inactivated by an anti-oxygen. The case was that of acrolein to which hydroquinone had been added.[43] We came to the definite conclusion that the inactivating effect of hydroquinone toward acrolein, if it existed was quite insufficient to explain its anti-oxygenic action. Although such a cause may intervene (which is possible, but would need to be demonstrated), there is certainly another which is much more important. Further, it would be extraordinary if we had just happened to fall upon an exception in the example just mentioned. In any event, since one cannot explain the action of hydroquinone upon acrolein as an inactivation of the latter, another theory is necessary, and it is this theory which we propose to discuss in the following paragraph.

Indirect Inactivation

A general theory of anti-oxygenic action: a process of indirect inactivation

From the debut of our researches we were occupied with the formulation of a mechanism to account for the peculiar action of anti-oxygens. Very early we conceived the following theory which has served as a valuable guide in the orientation of our investigations.

We suppose, with the majority of authors (Engler and Wild, Bach, and others), that auto-oxidation starts with the union of an oxygen molecule, O_2, with a molecule of the auto-oxidizable substance A, giving rise to the peroxide $A[O_2]$, which we shall call the primary peroxide. Our notion of this combination differs considerably, however, from that of our predecessors. To us, this peroxide or first term of the successive transformations which an auto-oxidizable substance takes with oxygen, is formed with an absorption, and not a liberation, of energy. The peroxide results from the union of active molecules of A and O_2, not of average molecules, and the union is effected with loss of very little energy.

From the standpoint of energetics the combination $A[O_2]$,

[43] Reference 25, III, and XII–XV.

formed by elevation of potential from the system $A + O_2$, must be placed toward the summit of the curve representing the phenomenon (see fig. 9). In the formula, oxygen is enclosed in brackets in order to indicate that it is present in an activated state. We shall follow the same designation for other oxides ($M[O_2]$ or $M[O]$) when we wish to indicate this particular state of oxygen.

On this basis we believed that anti-oxygens must act in catalysing the inverse reaction of the formation of the peroxide $A[O_2]$, that is, its destruction. In addition to the liberation of free oxygen from combined oxygen, it would be necessary that the reaction be very rapid and also complete (since one molecule of hydroquinone can protect forty thousand molecules of acrolein
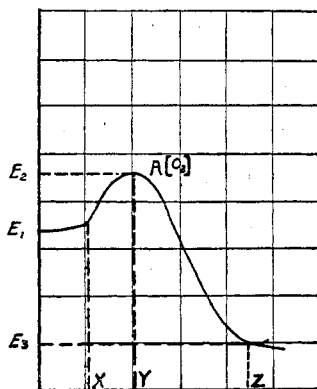

FIG. 9

from auto-oxidation), and we immediately thought of the mutual destruction of peroxides—well known reactions in which oxygen is almost totally and instantly liberated from such compounds.

Thus we have come to the following explanation of the mechanism of the action of anti-oxygens:

We suppose that the peroxide $A[O_2]$, oxidizes the anti-oxygen B, with the formation of a peroxide $B[O]$, while it is itself transformed into another peroxide $A[O]$. The two peroxides $A[O]$ and $B[O]$ are antagonistic, and mutually destroy each other, (as has been observed for numerous antagonistic peroxides)

with regeneration of the three original molecules, $A + B + O_2$, in their original state. This notion of anti-oxygenic action is summarized in the three equations which follow:

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

$$A[O] + B[O] \rightarrow A + B + O_2$$
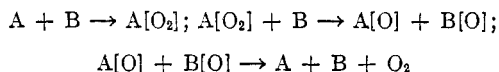
We should not exclude the hypothesis of a direct auto-oxidation of the anti-oxygen; in this case, we would have the following cycle:

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

$$A[O_2] + B[O_2] \rightarrow A + B + 2 O_2$$
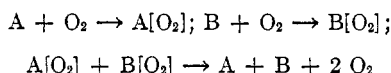
It will be noted that A and O_2 have been taken from the state of *activated molecules* at the moment of their combination, and returned to the mixture in an inactivated state. Our so-called negative catalysis is thus, in reality, a positive catalysis with its normal effect, since it favors a drop of potential. This action corresponds to the portion of the curve (fig. 9) projected in XY, where the potential energy falls from the value E_2, to the value E_1.

We have thus a rational solution of the paradoxical problem which was presented at the opening of this section; i.e., that of an impelling force corresponding to a positive catalysis, which has the effect of leaving the stone undisturbed on the side of a hill. It suffices to suppose that the resistance which opposes accelerated descent is none other than irregularities of contour. The stone must slide over each of these irregularities before being able to fall. Therefore, when the stone is at the summit of an irregularity, if there is a cause which facilitates its return to the original lower level, this corresponds to a true positive catalysis involving a loss of potential energy, and the stone will not proceed on its course downward. We have in this particular causation, the picture of a true positive catalysis of which the apparent effect on the general course of the reaction is negative.

This mechanism of indirect inactivation is essentially different than a separate inactivation of the auto-oxidizable substance or

oxygen, which was mentioned above. In these two inactivations, one considers that either the auto-oxidizable substance alone, or the oxygen alone, is inactivated by the activity of the anti-oxygen. In pure acrolein, for example, the concentration of active molecules would be diminished simply by contact with the anti-oxygen, and the same would be true for oxygen. According to our theory, on the contrary, acrolein could only be inactivated by anti-oxygens in the presence of oxygen, and oxygen could only be inactivated in the presence of an auto-oxidizable substance. In brief, by mutual interaction we simultaneously inactivate both oxygen and the auto-oxidizable substance.

This theory allows the prediction of numerous results, of which a certain number have already been found in good accord with experimental observations:

1. However strange it may seem, the power of preventing the action of free oxygen must belong to oxidizable substances. In fact, we have found this property among more than three hundred oxidizable substances (phenols, inorganic and organic compounds of iodine, sulfur, nitrogen, etc.). Let us recall in this connection, the remarkable example of phosphorus sequisulfide, a highly oxidizable substance which acts as a powerful anti-oxygen toward benzaldehyde.

2. This catalytic property can be possessed exclusively by oxidizable substances. To our knowledge, there is not a single anti-oxygen which is not capable of oxidation.[44]

3. The activity of an anti-oxygen is localized in the oxidizable portion of the molecule.

We have been able to demonstrate this in the case of sulfur.[45] For instance, dimethyl sulfide, $(CH_3)_2S$, hinders the oxidation of benzaldehyde, and this activity is due to the sulfur, which is the oxidizable portion of the molecule, and not to the methyl groups. This is shown by the fact that on oxidation of the sulfur in this molecule, by conversion to dimethyl sulfone $(CH_3)_2SO_2$, its oxi-

[44] Mittra and Dhar in 1922 made the independent observation that the auto-oxidation of sodium sulfite and of stannous salts was inhibited only by oxidizable substances.

[45] Moureu, Dufraisse and Lotte, reference 25, XVI.

dizability is suppressed, and we observed that its anti-oxygenic activity was destroyed at the same time, although the general structure of the molecule remained unchanged. Analogous results were observed with other substances containing sulfur and with oxidizable substances other than benzaldehyde.

4. The catalytic activity of an anti-oxygen should increase with increase of oxidizability.

In accordance with this prediction we have observed, for example, that bromides are in general much less active than iodides, and that chlorides and fluorides are practically without action.[46]

5. Every oxidizable substance should be able to act as an anti-oxygen under favorable conditions. This property would be a general one associated with all oxidizable substances; the favorable conditions would vary according to the nature of the substances selected.

In the case of any two auto-oxidizable substances that are placed in contact with each other, it should be possible to find conditions under which one may play the rôle of an anti-oxygen toward the other.

It is even possible to imagine a case in which a substance acts as an anti-oxygen toward itself.[47] One may suppose that the substance can give rise to two antagonistic peroxides, either directly or after a spontaneous transformation:

$$A[O]^+ + A[O]^- \rightarrow 2A + O_2$$
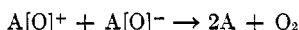
Since oxygen itself is capable of forming a peroxide (ozone, O_3, is none other than a peroxide of oxygen, $O_2[O]$), it may act in certain cases as the anti-oxygen B:

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

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

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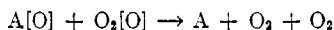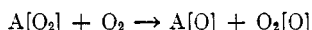
[46] The oxidizability that we invoke here as an essential condition of catalytic activity, requires that an antioxygen have a certain reactivity toward oxygen. This is not entirely sufficient; other conditions dependent upon the nature of the auto-oxidizable substance and external conditions (temperature, etc.) must be fulfilled. We cannot yet state exactly what these conditions are, although we have many interesting observations on this subject.

[47] This prediction, and the one following, are illustrated by a subtle analysis, of the auto-oxidations of sulfur compounds and of phosphorus, made by Delepine. Bull. soc. chim. (4) **31**, 762 (1922).

The auto-oxidation of phosphorus is an example of this kind. It is known that this auto-oxidation is prevented by an excessive concentration of oxygen. To us, oxygen plays the part of an anti-oxygen, according to the above scheme. Let us recall the well known fact that during the course of this auto-oxidation, formation of a peroxide of oxygen has been demonstrated by the formation of ozone.
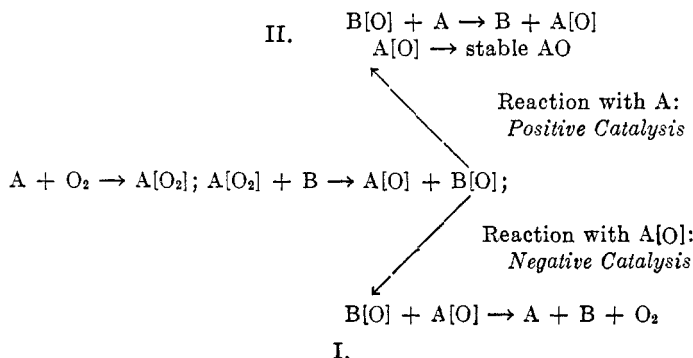
6. A logical development of this theory leads to the following conclusions: (i) the two inverse senses of catalysis, positive (pro-oxygenic action) and negative (anti-oxygenic action), are closely related to each other, and at the outset at least, they follow an analogous mechanism; (ii) the sense of catalysis is determined by experimental conditions, and a slight change of the latter may result in an inversion of the sense.

Let us reconsider the second phase in the scheme which we have presented for the mechanism of anti-oxygenic action. There are formed two transitory peroxides, A[O] and B[O], which are very reactive toward each other and are going to pass through a series of transformations. What are the possible transformations? We have described one according to which A[O] and B[O], being antagonistic, react immediately with each other, causing a mutual reduction with liberation of oxygen. This is anti-oxygenic action. But one must realize that other reactions may also occur with the same ease. In particular, let us remark that the peroxide B[O] is surrounded by a mass of molecules of A, which are strong reducing agents. B[O] may thus be strongly drawn toward the reaction $B[O] + A \rightarrow B + A[O] \rightarrow AO$ (stable).[48] B, which is liberated after this cycle of reactions, may then recommence in the same way and there results a positive catalysis of the oxidation of A under the influence of B. It is evident that B will act

[48] Among other reactions which may be imagined, we shall mention only the following, rather important one. The transitory peroxide B (O), before acting upon A(O) (negative catalysis) or upon A (positive catalysis), may tend to pass into a stable form (stable BO), in which case the molecule B which has undergone this transformation, is irreparably lost for catalysis. We have explained in this way certain characteristics of the phenomena of auto-oxidation; namely, coupled reactions (see reference 25 (XII) and exhaustion of the catalyst, which is a more or less well defined occurrence in all of our experiments.

as a positive or a negative catalyst, depending upon whether the peroxide B[O] prefers to act upon A[O] or upon A.

The following diagram indicates the two cycles:

$$\text{II.} \quad \begin{aligned} &B[O] + A \rightarrow B + A[O] \\ &A[O] \rightarrow \text{stable AO} \end{aligned}$$

Reaction with A:
Positive Catalysis

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

Reaction with A[O]:
Negative Catalysis

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

I.

The first two steps of the reactions are common to both modes of activity, since the sense of the catalysis is not determined until the third step is reached. The respective probabilities of the reactions I and II determine the sense of the catalytic effect; reaction I is favored by its velocity, reaction II by the concentrations.

With regard to reaction I, it may be said that reactions between antagonistic peroxides are rapid and complete, if we judge by such examples as the mutual decomposition of hydrogen peroxide and permanganates. In the latter we are dealing with stable peroxides that would be expected to be much less reactive than the transitory peroxides which we have formulated in the above diagram. This would lead us to expect greater velocities of reaction between the transitory peroxides A[O] and B[O], if such a thing is possible. Further, the probability of an increased velocity of reaction between the two antagonistic molecules A[O] and B[O], is increased by the fact that they are produced in the same reaction and in close proximity to one another, so that no time is lost in effecting contact of the two substances.

With regard to reaction II, it is clear that if the circumstances are such that B[O] separates from A[O] even for an instant before reaction, the chances for reaction between B[O] and A become

preponderant, since B[O] immediately finds itself in the zone of action of an enormous number of reducing molecules A, and this obviously gives to the reaction II the important advantage of concentration.

In principle, then, very slight changes may suffice to determine the sense of the catalysis. It is to be assumed that the two reactions can be effected simultaneously in the same medium, and the proportion of each will vary according to its inherent tendency to occur. The apparent sense of the catalysis (acceleration or retardation) will be the net effect, i.e., the algebraic sum of the effects of the two inverse catalyses.

What factors will determine the preponderance of one or the other of these two characteristic reactions, and consequently decide between an anti-oxygenic and a pro-oxygenic action? Manifestly, the experimental conditions play an important part. Let us attempt to analyze the situation. First, we must consider the nature of the substances present; namely, oxygen, common to all cases, an auto-oxidizable substance A, and a catalyst B, (either of the latter two extremely varied in nature). Other variables are temperature, light effects, concentration, and certain other characteristics of the media, of which certain ones are beyond our control, e.g., action of the walls of the vessels. It is quite certain that the individual nature of A and B is of great importance in the orientation of the phenomenon, but on account of the slight modification required to change this orientation, it is to be assumed that a knowledge of A and B will not suffice to determine the behavior of the system, and consequently other variable conditions may also play a decisive rôle.

A priori, it is impossible to assign definitely to any given catalyst B, the property of anti-oxygenic or pro-oxygenic activity. In practice, B will behave as a positive or a negative catalyst, according to the nature of the substance A with which it is in contact, and according to the conditions of observation of the action of oxygen upon the mixture of A and B.

Another source of complication is the fact that a catalyst may become altered during the course of the experiments, in which case one must expect that the observed facts may be even differ-

ent, since B will have been converted to a new substance B′ which will react in place of B.   In this case, if one does not have experimental indications of such an alteration, one will attribute to B the effects which are actually due to B′.   In our opinion this is the explanation of certain modifications of the nature of catalysis that are produced in the course of experiments in which no apparent change has been made in any of the conditions; e.g., the same auto-oxidizable substance A, the same catalyst B, the same external conditions, the same reaction vessel, and the duration of contact as the only variable.   Instead of a regular procedure, anomalies are observed in the oxidation curves, which may even go so far as an inversion of the sense of catalysis. Certain characteristic examples have already been mentioned in the first chapter.   We have experimental evidence that this inversion of catalysis in the course of a single experiment is due to an alteration of the catalyst, in observing the behavior of iodine and a number of iodine derivatives toward acrolein.   These catalysts produced first an anti-oxygenic action, which was followed rather suddenly by a more or less intense pro-oxygenic action, after an interval of time varying with the nature of the iodine compound used, and its concentration.   In fact, with iodine compounds there was always observed at first a reddish yellow coloration (similar to that given by free iodine), and the pro-oxygenic phase did not occur until after complete decolorization of the liquid.

Let us add also, that the course of a catalysis may be modified by the alterations previously cited in connection with the exhaustion of a catalyst through oxidation into products which may themselves possess specific catalytic properties, or be without any activity.   We have called attention to these facts apropros the passage of the thiol group, $-S-H$, into the disulfide, $-S-S-$, and vice-versa, in the case of certain sulfur-containing catalysts.[25,39]

The close relationship of the two inverse catalyses, and an easy inversion of the sense of the catalysis, are two unexpected but ineluctable consequences of our theory.

No one would challenge the theoretical and practical impor-

tance of these deductions, and the experimental demonstration of these points was of fundamental importance. An abundance of facts reported in the first chapter serves to establish these concepts with certainty.

One realizes from the foregoing that it would be exceedingly difficult in practice, to foresee the sense of the effect produced by this veritable "oxidizable impurity" which acts as the catalyst B; either an acceleration or a retardation of auto-oxidation may result from its presence. We have not so far succeeded in developing a rule which is sufficiently general to permit predictions of the sense of the catalysis. It has even happened, as one might theoretically foresee, that the same catalyst may behave toward the same oxidizable substance, either as an anti-oxygen or a pro-oxygen, depending upon the experimental conditions. We may remark that the useful acquisition, both from a theoretical and a practical standpoint, is the simple fact that we are warned of the possibility of such an inversion.

We are pursuing our experiments in a systematic manner, and perhaps they will lead to the formulation of rules that may be applied to new cases for the prediction of their behavior.

In résumé, one can see that our general conception of the mechanism of anti-oxygenic action is in satisfactory accord with the experimental observations. Our theory has not only enabled us to account for all the facts already known, but also to foresee a multitude of others, which but for it, would have been entirely unexpected.[49] We may be permitted to emphasize the fact that this theory has allowed a passage without transition, from the phenols to other categories of anti-oxygenic substances of an entirely different nature, such as inorganic and organic compounds of iodine, sulfur, nitrogen, et cetera.

We believe also, that our conception will be easily able to account for numerous facts which are still regarded as mysterious, and we have already been able, in diverse cases, to propose a rational interpretation of existing facts.

[49] It may be pointed out that certain other scientists (A. Gillet and others) have already successfully applied our conceptions to problems in which they were interested.

CONCLUSION

To characterize this long study in a few words, perhaps one would say that it abounds in surprises and improbabilities. To this we reply, that in science even more than in the theatre, according to the celebrated quotation of Boileau: *"le vrai peut quelque fois n'etre pas vraisemblable"* (the truth may sometimes not seem probable).

Is there a man of thought and reflection, to whom Nature does not appear vastly more marvelous, and stranger than all that which he may draw from the most profound depths of his own knowledge?

Let us recall our beginnings—by what tortuous ways we were led over a narrow and obscure path to the negative catalysis of auto-oxidation—how, in the search for a directing light, we built up a theory which made possible not only a facile interpretation of facts already known, but also the prediction of a number of others, which without it, would have been entirely unexpected. We have pointed out what significance this work has in the diverse fields of speculative science, industry, and biology.

It is not surprising to see our horizon thus continually enlarging. We live in oxygen, the essential agent of respiration; oxygen bathes all the bodies and objects which surround us, and its great reactivity is well known.   If then one were to effect by any means, a moderation or an excitation of the universal avidity of such an element, would there not result new perspectives in the chemistry of Nature, living and dead?

The general phenomenon of auto-oxidation appears to be favored by certain agencies and deterred by others. A continual struggle goes on between the positive and negative catalysts of this reaction, and anti-oxygenic activity appears along with the action of chlorophyll, the regenerator of oxygen, as an equilibrating factor in the movements of oxygen on the surface of the earth.

We may remark further, concerning our theory, that it constitutes a direct application by way of experimental research, of the idea of active molecules. It appears difficult to arrive at a conception of anti-oxygenic action without a belief in the

existence of active molecules, just as it was difficult before the introduction of that concept, to have a correct idea of the slowness of reactions. In this way, the experimental facts upon which our theory rests may be regarded as experimental evidence of an entirely different order, for the reality of chemical activation of molecules.

Along another line of thought, it seems reasonable to suppose that in addition to anti- and pro-oxygenic activity, one may encounter corresponding effects with other elements, or even with certain compounds; for example, anti-chloric, anti-sulfic, anti-plumbic activities. Certain phenomena are already known that could be placed under the above terms. Is it not to an anti-chloric or an anti-bromic activity of oxygen that the retarding action observed in certain reactions may be referred? Without doubt these observations may be profitably used in diverse fields of pure and applied chemistry.

The domain is enormous. The more one reflects, the more one is persuaded that the discovery of traces of impurities and the study of their influences will give us a true understanding of a multitude of chemical phenomena, if not to chemical reaction itself, envisaged in its most general aspect. No doubt in work of this kind, the most fruitful light will come from precise data concerning the physico-chemical structure of molecules, which will come to us chiefly through studies of energetics, utilizing the methods of photochemistry and thermochemistry.

What great questions to resolve! What vast fields to cultivate! The imagination takes flight. . . . . Who knows? After all its magnificent conquests, may not the science of chemistry, due to the study of catalysis, inaugurated by Davy and Berzelius, and reanimated after half a century of quiescence by Sabatier and Senderens—may it not again be but as at the dawn of a new era? But let us pause. For on such a delicate subject, as Dumas remarked, one always risks saying too much, however little one says. This much is certain: that the domain of the unknown is without limit in extent or depth, and that our knowledge will never equal our desire to know nor our joy to discover.