The Kinetics and Mechanism of Metal-Catalyzed Autoxidation[1]

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ABSTRACT

The autoxidation of organic compounds, RH, occurs by a radical-catalyzed chain reaction to give hydroperoxides, RO_2H, as primary products. The initial rate is $-d[O_2]/dt = k_p[RH]\{k_i[Cat]/k_t\}^{1/2}$, or in the presence of an inhibitor, (In), $k_p[RH](k_i[Cat]/k_I[In])$, where k_p is the chain propagation rate; $k_i[Cat]$, the rate of radical catalysis; k_t chain termination rate; $k_I[In]$ rate of inhibitor action. As oxidation proceeds the hydroperoxides break down to give further catalytically active radicals and eventually an autoxidation may reach a maximum rate of $k_p^2[RH]^2/fk_t$, independent of the concentration or nature of the catalyst. Photosensitization, by forming singlet oxygen, can catalyze autoxidation by forming peroxides. Compounds of many transition metals, e.g., Co, Mn, Fe, act as secondary catalysts by promoting the rapid formation of radicals from RO_2H molecules by a one-electron transfer reaction $RO\text{-}OH + M^{2+} \rightarrow RO\cdot + M^{3+} + OH^-$ and the M^{3+} ions are then reconverted to M^{2+} ions giving further radicals. The overall catalytic activity of a metallic ion is controlled by the slower step of the $M^{2+} \rightleftharpoons M^{3+} + e$ redox cycle and depends on the electronic structures of the two ions concerned and on the ligand groups attached to them. These effects are discussed in detail since ligand molecules for transition metal ions can be selected so as either to promote or inhibit autoxidation. Special reference is made to biological catalysts, such as the porphyrins, found in food products. Direct activation of oxygen by metallic complexes rarely seems to occur, but direct oxidation of substrates by metallic compounds is possible. This leads to another redox cycle which is utilized in copper-containing enzymes.

INTRODUCTION

The preservation of foodstuffs has always been a major problem for human civilization. With the continual increase in world population and its urbanization it becomes more and more difficult to achieve, particularly for highly industrialized countries such as Great Britain which have to import large tonnages of perishable foodstuffs from regions as far away as New Zealand.

Now foodstuffs deteriorate from the moment of collection by the agricultural producer, the hunter or the fisherman on account of (a) bacterial action, (b) enzyme-catalyzed hydrolysis or oxidation and (c) direct chemical attack by oxygen, i.e., autoxidation. Although modern techniques of sterilization and cold storage can very largely overcome the effects of (a) and (b), if they are employed rapidly enough, autoxiation cannot so easily be checked since it is a chemical chain reaction with a very low overall activation energy and consequently, unlike an enzyme reaction, is not greatly diminished in rate by lowering the temperature of food storage to practicable limits. Again, for many reasons, the total storage of all food in the complete absence of oxygen is quite impracticable.

Of the chemical components of foodstuffs it is the lipids which are the most prone to autoxidation but the eventual deleterious effects of this oxidation, which occurs slowly at normal temperatures, are more widespread since peroxidic products of lipid oxidation can attack chemical molecules of other types and many of the unwelcome characteristics eventuating from autoxidation are due to secondary reactions. The overall damage to foodstuffs that can be traced to initial oxidation of lipids is far more serious in relation to the preservation of meat and of fish than it is for vegetable foodstuffs, not only because animal foods have microscopic admixtures of lipids with proteins but because they contain small but significant percentages of heavy metals, principally iron, but including also copper, cobalt and manganese combined in complex molecules such as hemoglobin, the cytochromes and the prosthetic groups of many enzymes. These compounds of the transition metals, which typically have a variable valency, can be autoxidation catalysts. Unfortunately modern food packing processes, such as canning, and even the early handling operations, such as evisceration, on the farm or fishing vessel can enhance this contamination and, at the same time, may remove some of the natural inhibitors of autoxidation which are present in the tissues of living animals and plants.

The autoxidative deterioration of organic compounds is nefarious outside the foodstuff industries. For instance it is responsible for the slow gumming of mineral oils, especially lubricants, for the perishing of rubber and for the deterioration of both natural and artificial textiles, especially when dyed. Consequently oil chemists should view autoxidation research, its catalysis and inhibition, as a much wider problem than that of lipid preservation and appreciate that it is concerned with understanding the outcome of a general reaction between the hydrocarbon chains of organic compounds and atmospheric oxygen.

Problems concerning autoxidation have engaged the attention of chemists for over a century, but it is little more than 30 years since the way in which oxygen gas reacts with organic compounds at room temperature was correctly understood. Today generalized accounts of the mechanism of oxidation of organic compounds are to be found in most standard textbooks of organic chemistry and chemical kinetics, but there have been many significant theoretical developments of the subject in recent years. The outstanding features of these developments, and present trends of thought concerning autoxidation and its catalysis are outlined in the following pages.

GENERAL CHARACTERISTICS OF AUTOXIDATIONS OF ORGANIC COMPOUNDS

The autoxidation of an organic compound normally effects the insertion of a molecule of oxygen into a C-H bond of a hydrocarbon chain to give a hydroperoxide that is generally formulated as $R_3C\text{-}O\text{-}OH$, but sometimes is abbreviated as R-O-OH. These hydroperoxides are also active oxidants, capable of reacting at room temperature with other molecules. The attack of oxygen on hydrocarbon chains does not occur spontaneously, but requires a catalyst capable of producing free radicals of carbon, $R_3C^{\cdot}$, which immediately combine with the normal, or triplet form of oxygen gas. A reaction chain is then set up (see following sections) which is autocatalytic on account of the

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thermal instability of the hydroperoxides $R_3C\text{-}O\text{-}OH$, and so, when once started, an autoxidation reaction can continue for an appreciable time, consuming many molecules of oxygen, unless a specific "inhibitor" molecule is adjacent to the reactive center to break the chain sequence.

Though most autoxidation catalysts lead directly to the formation of active free radicals, some colored substances, including chlorophyll, act indirectly by absorbing radiant energy and then using it to convert oxygen gas to a more reactive singlet electronic state. This singlet form of oxygen is quite short-lived but it can attack, selectively, many unsaturated organic compounds again to give peroxides which too are autoxidation catalysts. Sunlight therefore can initiate the autoxidation of some lipid foodstuffs.

Since oxygen is a gas, autoxidation, initiated as indicated above, usually starts at or near the surface of a lipid and then spreads through its bulk as oxygen molecules diffuse to the reaction centers. Often the rate of oxidation is diffusion controlled and consequently with animal foodstuffs or emulsified lipids, such as butter, sensitivity towards autoxidation may be as much a feature of microscopic structure as of chemical composition. Nevertheless the rates of autoxidation processes are structure dependent. In general it can be said that the more unsaturated a lipid molecule the greater will be the rate of its autoxidation.

The Chain Reaction

Satisfactory kinetic theories to explain the main features of autoxidations of organic compounds were formulated some 20-30 years ago. Our problems today, especially with reference to metal catalysis, are concerned with the elaboration of these theories in the light of more sophisticated modern concepts of the inorganic chemistry of the transition metals and of much more factual knowledge.

In the autoxidation of any organic compound RH the dominant chain carrier is a peroxy radical $RO_2\cdot$ for which the rate-determining reaction 1 becomes exothermic because the radical $R\cdot$ is to some degree stabilized by electron delocalization (resonance) as in allylic systems, -CH-CH-CH-, derived from unsaturated compounds.

$$RO_2\cdot + RH \rightarrow RO_2H + R\cdot \quad \text{(rate constant } k_p) \qquad [1]$$

$$R\cdot + O_2 \rightarrow RO_2\cdot \qquad [2]$$

Although reaction 2 is extremely fast the normal triplet ($^3\Sigma_g$) or diradical form of oxygen, $\cdot O\text{-}O\cdot$ is much less reactive than the mono-radical $RO_2\cdot$. Consequently a free radical catalyst (Cat.) is needed for the initial generation of radicals $R\cdot$ or $RO_2\cdot$ and chain termination occurs by combination of two $RO_2\cdot$ radicals except at very low oxygen pressures (1). This termination involves the formation of an unstable tetroxide R_2O_4, but this in part yields some active radicals as it decomposes (2). Under the following circumstances

A. Rate of Autoxidation $= k_p[RH]\{[Cat]k_i/k_t\}^{1/2}$. Where k_i is the chain initiation rate and k_t the chain termination rate, but if an inhibitor (In) is present to remove $RO_2\cdot$ radicals singly, i.e., $RO_2\cdot + In \rightarrow$ Product, then

B. Rate of Inhibited Autoxidation $= k_p[RH](k_i[Cat]/k_{In}[In])$. Both rate equations A and B are independent of $[O_2]$; consequently most autoxidations are equally effective (or deleterious) in air as in free oxygen. Hence the storage of foodstuffs in closed containers such as refrigerators does not significantly check autoxidation.

The structural features of autoxidation depend essentially on reaction 2 and are governed by factors of energetics. Thus (a) oxygen adds preferably to the ends of an extended allylic system so as to give a conjugated allylic hydroperoxide, i.e.,

$$-CH{=}CH\text{-}CH_2\text{-}CH{=}CH- \rightarrow CH{=}CH\text{-}CH{=}CH\text{-}CH(OOH)-$$

(b) the *cis-trans* configuration of olefins may be altered (1,3-5); (c) mixtures of both structurally and stereochemically isomeric hydroperoxides are formed even from pure starting products. Another kinetic feature of autoxidation that merits mention is the finding that with mixtures the individual components may synergistically accelerate each other's autoxidation, often to a remarkable extent (6). Correspondingly, mixtures of inhibitors may synergistically enhance each other's efficacy (7). The mathematical theory of this synergism has been worked out, but is difficult to apply to practical examples.

Photo-Catalysis

Any substance capable of producing radicals which can attack RH molecules, as in 1, or can combine with oxygen as in 2, is a direct catalyst of autoxidation. Typical substances are diacyl or dialkyl peroxides which slowly decompose thermally to give reactive oxy-radicals, $R\text{-}O\cdot$ as in 3:

$$R\text{-}O\text{-}O\text{-}R \rightarrow 2\ R\text{-}O\ ;\ R\text{-}O\cdot + H\text{-}R \rightarrow R\text{-}OH + R\cdot \text{ (fast)} \qquad [3]$$

Now cyclic dialkyl peroxides may be produced by the photosensitized oxidation of conjugated dienes, $-CH{=}CH\text{-}CH{=}CH-$. This direct oxidation involves the "singlet" ($^1\Delta_g$), or double-bond form (O=O) of oxygen and has quite different characteristics from autoxidation (8) for it is not a chain reaction. However it does produce dialkyl peroxides of the type R-O-O-R which by decomposing homolytically by reaction 3 can generate free $R\text{-}O\cdot$ radicals and so initiate autoxidation chains of the normal type, (reactions 1 and 2).

Fortunately even the highly unsaturated lipids, such as many fish and some vegetable oils, have their double bonds disposed in extended allylic systems, $-CH{=}CH\text{-}CH_2\text{-}CH{=}CH-$, rather than in conjugated systems and so do not react rapidly with singlet oxygen. However even mild heat treatment can effect bond rearrangement with consequent increase in reactivity towards oxygen. For example boiled linseed oil oxidizes much more rapidly than raw linseed oil and so is used to speed the drying of oil-bound paints.

The biological oxidation of certain highly unsaturated fatty acids to yield hormones of the prostaglandin group is a notable example of a reaction sequence that undoubtedly involves the action of "singlet" oxygen. This type of biosynthesis clearly is not involved in the normal pathways of lipid metabolism.

As mentioned earlier, singlet oxygen is formed by the interaction of oxygen gas with an irradiated coloring matter of suitable structural type. Many more synthetic than natural coloring matters can effect this photosensitization which requires the short wavelengthed radiation present in direct sunlight or fluorescent lighting. Consequently to check the onset of photo-catalysis of autoxidation it is advisable to curtail the use of many colored food additives and also to avoid the exposure of lipid foodstuffs on brightly illuminated market shelves.

CATALYSIS BY TRANSITION METAL IONS

The thermal decomposition of hydroperoxides, R-O-O-H, can give the radicals $R\text{-}O\cdot$ and $H\text{-}O\cdot$ both of which are active enough to attack the C-H bonds of organic compounds, but the decomposition reaction is slow and kinetically complex (9). However the ions of a number of the transition metals are effective as secondary catalysts of autoxidation. Initially they act as one-electron donors to

give RO• radicals by reaction 4.

$$R\text{-}O\text{-}O\text{-}H + M^{2+} \rightarrow RO\bullet + M^{3+} + OH^- \quad [4]$$

With the effective catalysts this oxidation of M^{2+} to M^{3+} is followed by a second radical-producing reaction (5, 6 and 7 are all possibilities) which regenerates M^{2+} so that a second chain sequence is set up.

$$R\text{-}O\text{-}O\text{-}H + M^{3+} \rightarrow R\text{-}O\text{-}O\bullet + M^{2+} + H^+ \quad [5]$$

$$M^{3+} + RH \rightarrow R\bullet + M^{2+} + H^+ \quad [6]$$

$$M^{3+} + {}^-O\text{-}CO\text{-}R' \rightarrow M^{2+} + CO_2 + R'\bullet \quad [7]$$

If 4 is the rate-determining catalytic reaction then A becomes C.

C. Catalyzed Autoxidation rate =

$$k_p\left\{k_{cat}[RO_2H]\ [M^{2+}]/k_t\right\}^{1/2}$$

$$= k'[RH]^{3/2}[M^{2+}]^{1/2}$$

but since 4 destroys RO_2H molecules a limiting state is soon reached in which reactions 1 and 4 balance. Then

D. $[RO_2H]_{lim} = k_p^2[RH]^2/(k_{cat}k_t[M^{2+}])$

from which it follows that there is a limiting autoxidation rate E which is independent of the concentration or the reactivity (k_{cat}) of the metal catalyst (10,6).

E. $-d[O_2]/dt_{lim} \approx -d[RH]/dt_{lim} = k_p^2[RH]^2/k_t$

If other reactions such as 6 or 7 are rate-determining then E is still valid, except that k_t then needs a modifying numerical factor, (fk_t) (6). With active metallic compounds the limiting oxidation rate may be reached with less than 0.5% of added catalyst.

For the catalytic reaction chain of $M^{2+} \rightarrow M^{3+} \rightarrow M^{2+}$ represented by equations 4 and 5-7 above the controlling rate is that of the slower reaction and the metallic ion is mainly in the valence state corresponding to this. Thus for a cycle of reactions 4 and 5

F. $-d[RO_2H]\,dt = \left\{2ak_4/(1+a)\right\}[M][RO_2H]$

where [M] is the total concentration of metallic ion and $a = k_4/k_5$ (11). Though the ratios $[M^{2+}]/[M^{3+}]$ have rarely been determined during catalyzed autoxidations, colorimetric observations usually show that the metal is predominantly in the more highly oxidized state. Now the rates of oxidation and reduction of the metallic ion are governed by rates of one-electron transfers. The free energies, but not necessarily the rates of these reactions can be correlated by reference to the redox potentials of Table I. This however gives only a general guide to possible catalytic reactivity as it does not refer to the true conditions (solvent, acidity, temperature, ionic structures, etc.) under which autoxidations are actually carried out.

This Table shows that in their higher valence state the active catalysts (Co, Mn) do not oxidize RO_2H to $RO_2\bullet$ in aqueous solution but can oxidize H_2O_2 to $HO_2\bullet$ because the latter is an acid and its anion $(:O_2\bullet)^-$ is a strong reducing agent whereas $RO_2\bullet$ does not dissociate. Consequently equation 5, though valid for the Haber-Weiss theory of catalase action, is unlikely to be involved in autoxidations.

Direct oxidation of the substrate RH (reaction 6) or of an available reaction product, e.g., the alcohol ROH, is however thermodynamically feasible, and Bawn and Jolley (12) have shown kinetically that this is the rate-controlling step in the cobalt acetate catalyzed autoxidations of aldehydes in acetic acid. Recent measurements have indicated that it may also occur in the cobalt catalyzed oxidations of olefinic compounds (13). Reaction 7, direct radical production from the transition metal salts of carboxylic acids, has also been substantiated by our work at Oxford (14) for *inter alia* we have been able to trap the hydrocarbon radical R'• from the anion $(R'CO_2)^-$ by use of bromoform and also establish radical transfer, R'• + RH→R'H + R• to an autoxidizable substrate such as toluene.

TABLE I

Approximate Redox Potentials in Water (Volt)

Complex ion	E_o	
$e + Co^{3+} \rightleftharpoons Co^{2+}$	-1.8	$e + R\bullet \rightleftharpoons R^- \overset{H^+}{\rightleftharpoons} RH$
$e + Ce^{4+} \rightleftharpoons Ce^{3+}$	-1.6	$e + RO\bullet \rightleftharpoons RO^- \overset{H^+}{\rightleftharpoons} ROH$
		.....
$e + Fe^{3+} \rightleftharpoons Fe^{2+}$	-0.75	$e + RO_2\bullet \rightleftharpoons RO_2^- \overset{H^+}{\rightleftharpoons} RO_2H$
		.....
$e + Cu^{2+} \rightleftharpoons Cu^+$	-0.17	$e + O_2 \rightleftharpoons (O_2\bullet)^- \overset{H^+}{\rightleftharpoons} \bullet O\bullet OH$
		.....
$e + Ti^{4+} \rightleftharpoons Ti^{3+}$	+0.04	$e + R^+ \rightleftharpoons R\bullet$

Table 1 also shows that hydrocarbon radicals, R•, are good reducing agents, and indeed this has been shown by direct experiments with both ferric and cupric salts (15-17), i.e., Equation 8:

$$M^{3+} + R\bullet \rightarrow M^{2+} + R^+ \rightarrow M^{2+} + R^+ \rightarrow ROH \quad [8]$$

Consequently alcohols, and their oxidation products, aldehydes and ketones, rather than hydroperoxides are the major products of metal-catalyzed autoxidations. The unpleasant odors of rancid oils and fats are mainly due to aliphatic aldehydes and acids of fairly low molecular weight produced by the eventual oxidative scission of the long hydrocarbon chains of lipid molecules.

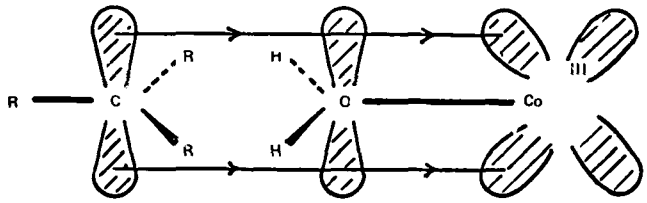
Effects of Ligand Groups on Catalytic Reactivity

Presently it is well known that different compounds of the same transition metal may differ greatly in catalytic activity. This is understandable because free metalic cations do not exist in solution: they are always surrounded by solvent molecules or by other ligand groups so that to oxidize or reduce a transition metal an electron has to be extracted from, or added to the *d* shell of the metal by way of a ligand. There are two general routes for this electron transfer viz. outer sphere and inner sphere reaction processes.

Outer sphere oxidations by the high-spin form of hydrated cobalt (III) are illustrated by Figures 1 and 2.

An unfilled t_{2g} orbital of the cobalt atom can accept one further electron and this can pass in from a *p* electron of an organic radical or from a π electron of an olefin, by hybridization with the unshared sp^3 electrons of the water ligand provided that a linear path for the electron flow is available. This electron flow can be blocked in particular directions by replacing the water molecule by a ligand like NH_3 which has no electrons to act as conductors of the electronic charge, or by a tightly bound anion such as fluoride which immobilizes its unshared electrons. If 4 or 5 positions are blocked, as with iron in hemoglobin, then the electron flow is restricted to one stereochemical direction with respect to the complex ion. During this electron transfer weakly bound ligands such as water may be displaced or even transferred to the attacking reagent. This is illustrated by Figure 3.

Inner sphere reactions are two-stage processes in which the attacking reagent first displaces a ligand group. Following this the path for electron movement to or from the metal atom is easy. Thus reaction 4 may well involve stages 9 and 10:



The arrows show the direction of electron flow.

FIG. 1.

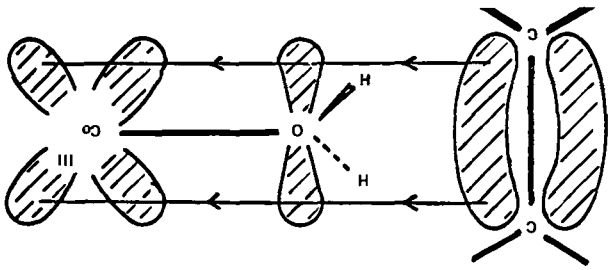


FIG. 2.

$$RO\text{-}OH + H_2O\text{-}M^{II}L_5 \rightleftharpoons RO\text{-}O\text{-}M^{II}L_5 + H_3O^+ \text{ fast equilibrium} \quad [9]$$

$$RO\text{-}O\text{-}M^{II}L_5 \rightarrow RO\cdot + {}^{-}O\text{-}M^{II}L_5 \quad \text{slow} \quad [10]$$

where the arrows show single electron movements (11).

The oxidation of a carboxylic acid (including α-hydroxy and α-amino acids) by cobaltic ions in water is definitely to be represented by 11 and 12:

$$R'\text{-}CO\text{-}OH + Co^{III}(H_2O)_6^{3+} \rightleftharpoons R'\text{-}CO\text{-}O\text{-}Co^{III}(H_2O)_5^{2+} + H_3O^+ \quad [11]$$

$$R'\text{-}CO\text{-}O\text{-}Co^{III}(H_2O)_5 \rightarrow R'\cdot + CO_2 + Co^{II}(H_2O)_5^{2+} \quad [12]$$

because these reactions exhibit Michaelis-Menten kinetics (Equation G below) (14) which is found also with enzyme-catalyzed reactions.

G. $-d[Co^{III}]/dt = [k_{12}[Co^{III}]\cdot K_{11}[R'CO_2H]/([H^+]+K_{11}[R'CO_2H])$

Spectroscopic evidence for the existence of the intermediate complex has been obtained in some cases (18); notably in enzyme chemistry it has been shown decisively that intermediate compounds are involved in the decomposition of peroxides by catalase (19,20).

Now Equation G shows that the ease of electron transfer depends on the equilibrium constant K for the ligand displacement process (Equations 9 and 11). The displacement of water by other groups is easy, though pH dependent, but it is possible to deactivate a metallic ion by surrounding it by tightly bound ligands that cannot be replaced by reagents such as hydroperoxide. Substances like EDTA, 8-hydroxyquinoline and other corrosion inhibitors that are now used as additives to lubricating oils act in this way, though of course 8-hydroxyquinoline is itself a phenolic inhibitor of autoxidation. Citric and tartaric acids probably act in this way when used as additives in oily salad dressings or in baking mixtures. They both form strongly bound complexes with ferric and cupric ions, but of course they are also useful for pH control. Lecithin may act similarly and is quite a good antioxidant.

The single reactive position around iron in the porphyrins such as hemoglobin and the cytochromes can easily be blocked by combination with groups like CN, CO or NO. The nitric oxide adducts of both hemoglobin and cytochrome-c give electron spin resonance spectra (g = 2·006; a_N = 18 gauss) (21,22) which show that they are structurally similar to organic nitroxide free radicals and have an unpaired electron which is more closely associated with the NO group than with the iron. Since organic nitroxides are inhibitors of autoxidation (23), one could achieve in this way both a stereochemical and a functional blocking of the catalytic reactivity of metal-containing biological systems. I suggest that this type of ligand replacement occurs when meat is cured in the making of ham or corned beef, for fat autoxidation is undoubtedly catalyzed both by blood pigments and by cytochrome enzymes and can drastically be checked by the curing process.

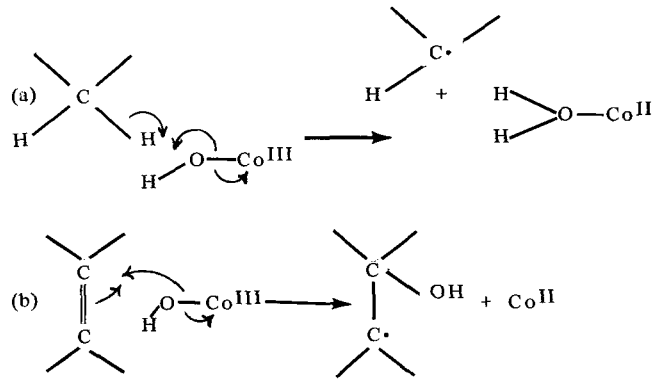


FIG. 3. (a) Hydrogen transfer from the substrate, e.g., the oxidations of paraffins or of ethers by cobaltic perchlorate. (b) Hydroxyl (or water) transfer from the oxidant, e.g., oxidation of olefins.

Polar Effects of Ligands

Ligands can also alter catalytic reactivity by altering the electron density at the metallic center of a complex ion and so its redox potential. Since, in electronic language, oxidation is equivalent to electron loss and reduction to electron gain it follows that metallic ions with vacant *d* orbitals of low energy level and a high localized positive charge are strong oxidizers, e.g., $\{Co^{III}(H_2O)_6\}^{3+}$. Consequently if one surrounds a metallic cation by several closely grouped anions, such as fluoride its oxidizing power is diminished:

$$Fe^{3+}aq. + 6F^- \rightarrow (FeF_6)^{3-} + aq. \quad [13]$$

In the same way ligands such as ammonia and other bases which coordinate by bond formation effect a similar charge transfer but this is partly offset by the dipolar character of the bond which is formed, e.g., 14:

$$Cu^{2+}aq. + :NH_3 \rightleftharpoons (Cu \leftarrow NH_3)aq^{2+} \text{ or } (Cu^+ - \overset{+}{N}H_3)aq \quad [14]$$

In such cases a comparison of the extent of charge transfer should be made with the ligand which has been displaced from the same stereochemical position. Thus, as a ligand, ammonia causes more charge transfer than water because it is a stronger base, i.e., a better electron pair donor.

However heterocyclic bases act in the opposite way as ligands and increase the oxidizing power of metallic ions. This is due to π bonding between filled t_{2g} orbitals of the metal and unfilled π orbitals of the ligand whereby electronic charge is drawn away from the metallic atom (Fig. 4).

Table II shows the effects of ligand groups on redox potentials, but gives only the overall effect of replacing water by another group. It must be remembered that the polar effect of introducing any one ligand group into a complex ion influences as a vector the reactivity of other

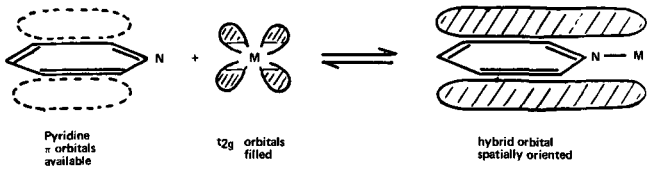


FIG. 4.

ligand groups in the same ion. Consequently *trans* replacement of a ligand has a greater effect than *cis* replacement; in another connection this has been studied extensively with complexes of the porphyrin and corrin types (24).

It is now appreciated that biological metal-containing enzymes, e.g., hemoporphyrins, cytochromes, can act as autoxidation catalysts in foodstuffs but their consideration is outside the scope of this review. The redox potentials of these substances are such that in their lower valence states they can reduce hydroperoxides (reaction 4) but not free oxygen, while their reduction from the higher valence state can probably not be effected by autoxidizable lipids but requires other highly reducing organic compounds present in biological tissue, though probably not in the lipid phase.

Hydroperoxides, or more certainly the RO• radicals to which they give rise in catalyzed autoxidation, are such active oxidants that they are prone to attack not only the major substrates of autoxidizable systems but also many of the organic molecules that are of value as ligands capable of solubilizing transition metal salts in lipid or hydrocarbon solvents. For this reason there are technical limitations to the choice of complexing agents in promoting autoxidation: as autoxidation proceeds the complexes are slowly destroyed and the metallic compounds separate as an inactive sludge. This occurs in engine oils. Conversely corrosion within machinery or metallic containers can promote autoxidation, except in aluminum vessels, by producing transition metal ions. To check this it is necessary to add complexing agents which inactivate metal ions (see above). This procedure, which is regularly adopted for the production of high grade lubricating oils, is cogent for food packing in appropriate circumstances.

However in meat products and in emulsified foodstuffs the consequences of phase separation have to be considered. The aqueous phases of foodstuffs contain many reducing compounds such as glucose and other soluble carbohydrate derivatives, including salts of hydroxy-acids, which rapidly destroy oxidizing metal ions and free radicals but do not react with molecular oxygen. Consequently in such foodstuffs autoxidation is confined to the lipid phase, though the aqueous phase may act as a reservoir to facilitate the transport of dissolved oxygen. Though metallic ions will preferably exist in the aqueous phase their complexes with proteins and fatty acids may concentrate on the phase boundaries and so be able to act as autoxidation catalysts of the lipid particles. Hence in the applied chemistry of the foodstuff industries it is essential to adopt a critical approach to application of the foregoing theories concerning autoxidation, for they have all been developed for one-phase systems which can be studied kinetically.

AUTOXIDATIONS IN AQUEOUS SOLUTION

The following sections deal with autoxidations that can occur in aqueous solution. They do not comprise the oxidations of lipids as such; nevertheless they are important in connection with the applied chemistry of lipids, because the aqueous phases of natural foodstuffs contain the bulk of the inhibitor molecules which allow living organisms to synthesize compounds prone to undergo chemical autoxidation at normal temperatures. The destruction of a natural

TABLE II

Effects of Ligands on Redox Potentials[a]

Complex ion	E_{δ}
$e + \{Cu(H_2O)_4\}^{2+} \rightleftharpoons Cu^{1+}aq$	-0.17
$e + \{Cu(NH_3)_4\}^{2+} \rightleftharpoons \{Cu(NH_3)_2\}^{+} + 2NH_3$	+0.58
$e + \{Co(H_2O)_6\}^{3+} \rightleftharpoons Co\ aq^{2+}$	-1.8
$e + \{Co(NH_3)_6\}^{3+} \rightleftharpoons \{Co(NH_3)_6\}^{2+}$	-0.1
$e + \{Co(CN)_6\}^{3-} \rightleftharpoons \{Co(CN)_6\}^{4-}$	+0.8
$e + \{Fe(H_2O)_6\}^{3+} \rightleftharpoons \{Fe(H_2O)_6\}^{2+}$	-0.77
$e + \{Fe(CN)_6\}^{3-} \rightleftharpoons \{Fe(CN)_6\}^{4-}$	-0.36
$e + \{Fe(\underline{o}\text{-Phen})_3\}^{3+} \rightleftharpoons \{Fe(\underline{o}\text{-Phen})_3\}^{2+}$	-1.1
(e + Methaemoblobin ⇌ Haemoglobin	ca. -0.2 at pH 7)

[a]Data from Reference 25.

inhibitor is usually the first stage in the autoxidation of a natural product. Unfortunately many of the commercial techniques of lipid food processing, such as oil clarification, deodorization, partial bleaching and fat hardening lead to the removal of natural inhibitors of autoxidation, for these include carotenoids and tocopherols as well as plant pigments of flavonoid type.

Reactions of Oxygen With Metallic Complexes

Much stronger reducing agents (E_o positive) are required to reduce free oxygen than to reduce hydroperoxides (Table I). Consequently transition metal ions do not act as autoxidation catalysts by the direct conversion of triplet oxygen to a more active mono-radical. Though several paramagnetic complex ions can combine directly with oxygen they rarely give effective peroxy catalysts of structure M-O-O• (where M is a metal). Many cobalt(II) complexes react with oxygen in this way (e.g., Equation 15) but the initial products are strong reducing agents and the following reaction (16) becomes so fast that the M-O-O• radicals are destroyed before they can attack organic substrates (25,26).

$$\{(NH_3)_5Co^{II}\}^{2+} + O_2 \rightarrow \{(NH_3)_5Co^{III}\text{-}O\text{-}O\bullet\}^{2+} \quad [15]$$

$$\{(NH_3)_5Co^{III}\text{-}O\text{-}O\bullet\}^{2+} + \{Co^{II}(NH_3)_5\}^{2+} \rightarrow \{(NH_3)_5Co^{III}\text{-}O\text{-}O\text{-}Co^{III}(NH_3)_5\}^{4+} \quad [16]$$

Paramagnetic hemoglobin combines with oxygen to form oxy-hemoglobin but this, though still a derivative of Fe^{II} is diamagnetic and so cannot have a structure of the paramagnetic M-O-O• type; it is probably a substance of singlet oxygen type with an O=O bond (25).

Copper Catalyzed Autoxiations

There is however a second mechanism for the chain autoxidation of organic compounds from that which involves hydroperoxide formation. In this the metallic ion in its higher valence for is the prime oxidizing agent. This mechanism is typified by the copper catalysis of the autoxidation in alkali of ascorbic acid and of many other α-ketols or polyphenols of the catechol type. Phytochemically it is an important reaction and, with copper-containing enzymes, it operates to destroy many of the naturally formed antioxidants present in fresh vegetable foodstuffs.

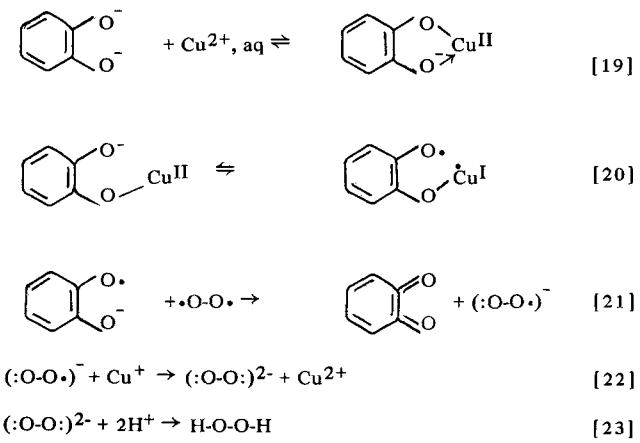
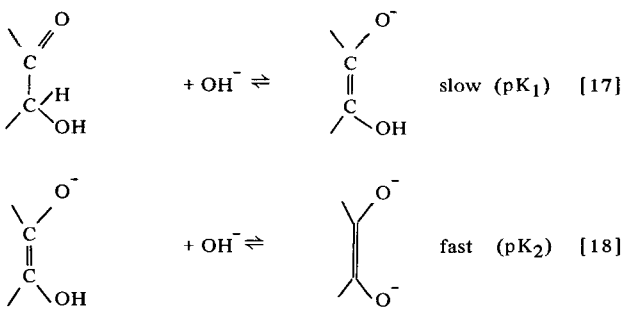


FIG. 5. Copper-catalyzed autoxidation of catechol.

α-Ketols, such as acetoin, benzoin, ascorbic acid and other reductones enolize slowly, equation (17), and this is often the rate-determining stage in their autoxidations (27,28). In alkaline solution the ene-diols ionize further to a slight extent depending on the pK_2 for the equilibrium (18),

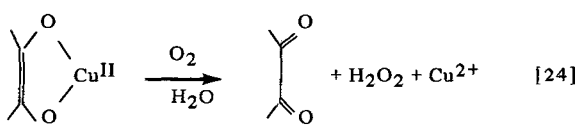


and these dianions can them form chelate complexes with cupric ions (19).

Similar complexes are formed in dilute alkali with catechol and analogous *ortho* diphenols many of which, such as the widely distributed flavonoids, are naturally occurring plant products. Now these cupric chelate complexes are mesomeric with cuprous complexes of enol-oxy radicals (Fig. 5) and some slight dissociation to these radicals can occur (Equation 20).

They are powerful enough reducing agents to be able to transfer an electron to oxygen, with the formation of an α-diketone, or *o*.quinone and the $(\cdot O_2)^-$ radical-ion (Equation 21), but this then abstracts a further electron from the cuprous ions which have been formed and is further reduced to the anion of hydrogen peroxide, regenerating a cupric ion (Equations 22 and 23).

Very probably the whole of the reactions involving the enol-oxy radical from the cupric chelate, the attack by oxygen and the reformation of the cupric ion occurs within a solvent cage, so that the overall copper-catalyzed reaction can be represented by Equation 24,



because the free copper ions in the solution remain almost entirely in the cupric state and the hydrogen peroxide does not get further reduced. Kinetically these autoxidations proceed at rates proportional to the square of the hydroxide ion concentration, showing that the dianion of the ene-diol is the autoxidized species (27,29,30). Fortunately, in foodstuffs autoxidations of this type can be checked by maintaining a low pH; this is one role of the naturally occurring plant acids.

With alkaline solutions of catechol the one-electron oxidation mechanism of autoxidation has been substantiated by identification of the radical anion ($\cdot O \cdot C_6H_4 \cdot O^-$) by electron spin resonance spectrometry (31). Alkaline solutions of hydroxylamines undergo copper-catalyzed autoxidation in exactly the same way, and with them it has been possible to follow the course of the reaction both by oxygen uptake measurements and by monitoring the change in concentration of the intermediate free radicals (32).

Inspection of the redox-potential table (Table I) shows why this type of autoxidation seems to be unique to copper. A stronger oxidant, such as the ferric ion would directly oxidize both the ene-diol and the transient organic radical anion so that this would not have a sufficient free life-time to be able to be attacked by free oxygen, while weaker oxidants than the cupric ion, even if they did form chelate complexes, would not be able to oxidize the ene-diols.

Linked Catalytic Systems

In conclusion, mention should be made of the fact that both synergistic and antagonistic effects upon the rates of metal-catalyzed autoxidations have been observed when two different metals are used together as catalysts. Linked catalytic systems are particularly important with biological systems in which metal-containing enzymes are involved, but they are also involved in some industrial autoxidations, significantly in connection with its inhibition by organic additives (7).

Although the redox potentials of transition metal compounds can be listed to show the thermodynamic order of oxidizing or reducing power this sequence does not give the kinetic order of reactivity towards other molecules for, as explained above, the reaction mechanisms may differ. For example cupric ions are much better oxidizers of free alkyl radicals (15,17) and of the $(O_2\cdot)^-$ ion (33) than are ferric ions. Consequently traces of copper ions have a synergistic effect on iron-catalyzed reactions of hydroperoxides (33) and can promote the formation of different end-products, as for example in reactions between olefins and organic hydro-peroxides.

Under the alkaline conditions of copper-catalyzed autoxidations of ene-diols, iron complexes effect the decomposition of hydrogen peroxide by reactions of the catalase type [25,26] which do not produce radicals of oxidizing character.

$$Fe^{III} + {}^-O\text{-}OH \rightarrow Fe^{II} + \cdot O\text{-}OH \qquad [25]$$

$$Fe^{III} + (\cdot O\text{-}O:)^- \rightarrow Fe^{II} + \cdot O\text{-}O\cdot \qquad [26]$$

Catalase is invariably present in multi-component enzyme systems and, by acting as a peroxide destroyer, its net effect is the enhancement of the specificity of other metal-catalyzed oxidations in cellular systems. It is probably to catalase control that one should attribute the fact that living plants and animals are able to synthesize quite large amounts of many highly unsaturated and very easily autoxidizable organic compounds. So many enzyme reactions are linked together in living cells that the kinetic interpretation of oxidation in vivo can as yet be given only in qualitative terms.

GENERAL OBSERVATIONS

In the 30 years that have elapsed since the chain reaction mechanism of autoxidation was first propounded, satisfac-

tory kinetic theories for explaining both its catalysis and its inhibition have been developed for homogeneous systems. The newer theories of the coordination chemistry of the transition metals are proving to be particularly helpful in relation to the understanding of autoxidation catalysis.

In fields of applied chemistry autoxidation now comprises one of the main procedures used by the petrochemical industries in upgrading their crude hydrocarbons to more valuable commercial products and a vast bulk of scientific information has been garnered in this field. Fortunately for the petroleum chemists, most of their chemical reactions can be carried out in homogeneous liquid or gaseous systems to which kinetic theories are quantitatively applicable, but this is seldom the case for the food processing industries. Though lipid chemists can only apply quantitative theories of autoxidation to problems concerned with the storage and utilization of extracted vegetable and fish oils it is significant to recall that much of our basic knowledge of autoxidation originally came from the experimental study of esters of oleic, linoleic and linolenic acids (1), so that unquestionably information obtained from the study of mineral oils is relevant to lipid chemists.

In previous sections two major restrictive features of applied lipid chemistry have been indicated, the fact that no animal and few lipid foodstuffs are homogeneous liquids, and the fact that all materials of biological origin are complex mixtures containing small and variable amounts of trace metal catalysts and organic autoxidation inhibitors which cannot completely be removed by any rational food processing. So, in regard to the whole of lipid chemistry, scientific explanations as to the cause, or rate, of autoxidation reactions, and suggestions for effecting improvement in the storage quality of foodstuffs can only be given in qualitative terms.

Yet pure chemistry provides the basic theories on which both biochemistry and commercially applied chemistry rely for their development. So much is known today about the pure chemistry of autoxidation reactions that its theoretical interpretation is securely based. Consequently it is hoped that this article which has surveyed the present outlook will prove to be of service to lipid chemists in broadly indicating ways in which they should consider their particular problems.

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