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Activation of Molecular Oxygen by Metal Complexes and Its Role in the Mechanism of Liquid Phase Oxidation

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Problems of the involvement of molecular complexes of oxygen with variable-valence metal compounds in the liquid-phase oxidation of organic compounds, including the chain initiation reactions in radical chain oxidation, via the interaction of such complexes with the hydrocarbon are considered. The possibility of the operation of mechanisms resembling those of enzymic oxidation is analysed. Despite the lack in many instances of unambiguous evidence for the occurrence of the oxidation reaction via a mono- or di-oxygenase mechanism, one can assume that the reaction conditions and mechanisms in many chemical systems are close to those in biological systems.
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I. INTRODUCTION

The catalytic oxidation reactions of organic substances in the liquid phase constitute one of the commonest types of chemical reactions. The study of their mechanisms is important both for the creation of new selective processes in chemical technology and for the understanding of many biochemical processes.

The liquid-phase catalytic oxidation reactions of organic substances in the presence of the majority of variable-valence metal compounds proceed via a radical chain mechanism.[1-3] The catalyst can then participate in all the elementary oxidation stages—chain branching, chain propagation, and chain termination. The acceleration of the catalytic reaction compared with the non-catalytic reaction is associated mainly with the increase of the rate of chain branching as a result of the radical decomposition of hydroperoxides by variable-valence metal compounds.[4]

When the oxidation reaction has a radical chain mechanism, the introduction of homogeneous or heterogeneous catalysts can influence the selectivity of the oxidation through interaction of the catalyst with free radicals, which in many instances alters both the rate and the composition of the chain propagation reaction products.

The ratio of the oxidation products can also vary owing to alteration of the chain length. Since an increase of free radical formation rate in the presence of the catalyst entails a decrease of the oxidation chain length, the free radical recombination products accumulate in large amounts in these oxidation reaction mixtures.[5]

The use of metal complexes as oxidation catalysts, which have a fairly pronounced peroxidase function, is usually complicated by the rapid oxidation of the ligand by peroxides or free peroxy-radicals,[6-8] which leads to the replacement of the ligand in the early stages of the oxidation process and hence can alter the oxidation reaction pathway in the course of the reaction.

Evidently the involvement of active free radicals in catalytic liquid-phase oxidation reactions cannot ensure a sufficiently high process selectivity because of the high reactivity, which leads to a large number of different reactions of the starting materials and the intermediates.

Nevertheless, in the words of Academician N.M.Emanuel', "the problem of the effective employment of natural raw materials is of prime importance in the chemistry of our time. The high selectivity and rate of a chemical reaction accompanied by small energy expenditures and in apparatus of minimal size have become the principal criteria of the likely usefulness of the chemical process from the practical point of view".[5]

From the standpoint of the increased selectivity of the oxidation reactions, the creation of conditions ensuring the direct insertion of oxygen in a C–H bond of the molecule of the organic substance with formation of alcohols, hydroperoxides, and other oxygen-containing compounds would be most promising.

In the absence of a catalyst, oxygen, which exists in a triplet ground state, is incapable of reacting with substrates in the singlet state because such a process infringes the spin conservation rule. The formation of molecular complexes of oxygen with variable-valence metal compounds removes the spin restriction and the direct reaction of oxygen with the substrate accompanied by the formation of hydroperoxides,

$$RH+O_2 \rightarrow ROOH$$

or alcohols,

$$RH_2+O_2+DH_2 \rightarrow HROH+H_2O+D \quad , \qquad (1)$$

where DH_2 is a cofactor (or cosubstrate), which serves as the reducing agent, becomes possible, in principle, in this system.

The problem of the activation of molecular oxygen by variable-valence metal complexes has been the subject during the last decade of numerous investigations devoted to various aspects of the structure of such complexes,[9,10] their reactivity, and the mechanism of their interaction with substrates undergoing oxidation.[11-15]

Variable-valence metal compounds readily interact in many instances with molecular oxygen, forming adducts in which oxygen is present in the form of the superoxide ion O_2^- or the peroxide ion O_2^{2-}. The peroxo-complexes can in their turn contain either one metal atom (when the metal can serve as a donor of two electrons, $M\begin{smallmatrix}O\\|\\O\end{smallmatrix}$) or two metal atoms (for metals which undergo a change in valence only by unity, the μ-peroxo-complexes M–O–O–M). Metal oxo-complexes (M=O) and μ-oxo-complexes (M–O–M), containing one oxygen atom, can also be formed. However, such complexes

are as a rule inactive in oxygen transfer processes. From the standpoint of their employment as oxidants, transition metal peroxo- and super-oxo-complexes of oxygen are the most promising.

II. INITIATION OF OXIDATION CHAINS BY VARIABLE-VALENCE METAL SUPEROXO-COMPLEXES

Despite the large number of studies which have been made on the mechanisms of the activation of molecular oxygen, it is at present fairly difficult to relate the mechanism of the oxidation of organic substances in the presence of complexes of molecular oxygen with the catalyst to the structure of such complexes. It has been suggested that paramagnetic mononuclear complexes of the type $M...O_2^-$ (superoxo-complexes) can serve as electron transfer agents:[16,17]

$$RH_2 + M \cdots O_2^- \rightarrow M \cdots O_2^{2-} + RH_2^+$$

or can participate in the radical substitution reaction[15]

$$RH_2 + M \cdots O_2^- \rightarrow M \cdots HO_2^- + RH^\cdot \qquad (2)$$

and can thus ensure the initiation of radical chain reactions.

The reactions of O_2^- coordinated in the titanium(IV) coordination sphere to various organic substrates have been investigated by EPR using a flow technique.[17] Although the authors did in fact observe that only compounds with comparatively weak C–H, N–H, or O–H bonds, such as *p*-toluidine, *p*-aminophenol, and 3,5-dihydroxybenzaldehyde, react with the complex $Ti(IV).O_2^-$, a direct relation between the rate of reaction and the bond dissociation energy apparently does not exist. Thus the dissociation energy of the C–H bond in toluene is approximately equal to the O–H bond energy in phenol, while the C–H bond energy in benzaldehyde is significantly lower. Nevertheless, only phenol is oxidised in the process of $Ti(IV).O_2^-$.

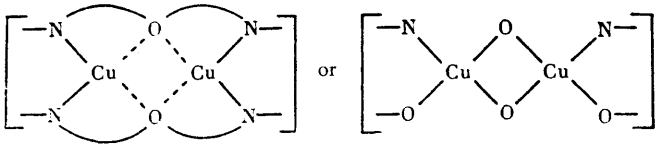
At the same time, a satisfactory quantitative correlation has been observed between the reaction rate constant and the ionisation potential of the substrate. The results obtained made it possible to suggest that at least in aqueous solutions at room temperature the rates of the radical substitution reactions (2) of the complexes $Ti(IV).O_2^-$ [17] and $Zr(IV).O_2^-$ [18] are negligibly low compared with the rate of electron transfer with formation of the coordinated dianion $Ti(IV).O^{2-}$ and the radical-cation of the substance being oxidised:

$$Ti(IV) \cdot O_2^- + RH_2 \rightarrow Ti(IV) \cdot O_2^{2-} + RH_2^+ .$$

The rate constants for the interaction of the complex $Zr(IV).O_2^-$ with amines and phenols are close to the corresponding constants for the complex $Ti(IV).O_2^-$.[18]

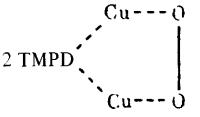
The oxidation of *NNN'N'*-tetramethyl-*p*-phenylenediamine (TMPD) by oxygen in the presence of square planar complexes of bivalent cobalt, such as the cobalt complexes of Schiff bases (CoL_2), leads to the formation of a coloured compound, whose electronic spectrum is the same as that of the complex $[Cl(L)_2TMPD^+]$.[16] Electron transfer takes place only in the joint presence in the solution of TMPD, O_2, and $Co(L)_2$, which suggests that the reaction proceeds in a ternary complex via a concerted mechanism.

Dinuclear copper complexes with chelate units



in which the distance between the copper atoms is not less than 3–3.5 Å, exhibit a high catalytic activity in the oxidation of TMPD by molecular oxygen.[19] The catalytic activity of these complexes is determined by their reduction potential: the more positive the reduction potential, the higher the activity of the catalyst.

Increasing the distance between the copper atoms above 3.5 Å causes the catalytic activity of the complex to fall rapidly. The maximum initial rate of oxidation is attained for the ratio [TMPD]:[catalyst] = 2:1. It has been suggested that the oxidation proceeds with two-electron reduction of oxygen to O_2^{2-} via an intermediate stage in which is produced the complex



The transfer of two electrons in such a complex can occur in one stage via a concerted mechanism.[19]

Despite the fact that at room temperature in aqueous solutions[17] the rate of electron transfer is probably significantly higher than the rate of the radical substitution reaction (2), chain initiation via reaction (2) can take place at least in the presence of certain copper, nickel, and coblat complexes.

The problem of demonstrating the involvement of complexes of molecular oxygen with variable-valence metal compounds in the oxidation chain initiation stage in many cases cannot be solved unambiguously primarily because almost all variable-valence metal compounds can decompose hydroperoxides into free radicals at rates greatly exceeding the rate of formation of radicals via reaction (2), which creates considerable difficulties for the identification of reaction (2) against the background of chain branching even in the presence of traces of hydroperoxides and imposes particularly stringent requirements on the degree of elimination of traces of hydroperoxides from hydrocarbons. In order to reach clear-cut conclusions about the role of reaction (2) in the oxidation process, it is necessary to carry out a quantitative comparison of the observed rates of oxidation with the rates which can be ensured by chain branching in the presence of the catalyst.

In addition, there are virtually no unambiguous methods whereby one could demonstrate a non-radical reaction pathway. The method of inhibitors widely employed in non-catalytic oxidation frequently fails to yield information in the presence of catalysts because, on the one hand, inhibitors (phenols or aromatic amines) can behave as promoting agents, or catalytic poisons, forming complexes with the catalyst, and, on the other hand, for sufficiently high rates of chain initiation, large concentrations of the inhibitor must be introduced into the reaction in order to obtain effects beyond experimental error, which can lead to its intense oxidation by oxygen. Thus, when the method of inhibitors is used to investigate the mechanism of catalytic oxidation, in each individual case it is necessary to have evidence that the inhibitor reacts in the given catalytic system only with the free radicals (i.e. that the introduction of the inhibitor does not alter the structure of the metal compound and that the rate of consumption of the inhibitor is independent of its initial concentration).

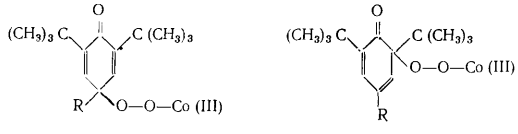
The occurrence of reaction (2) in the oxidation of α-methylstyrene in the presence of the copper complex of α-phthalocyanine has been postulated[20,21] on the grounds that the copper complex of α-phthalocyanine can be an active catalyst of the oxidation of α-methylstyrene, although it does not in

fact accelerate to any appreciable extent the degree of decomposition of the peroxide formed in this process.

Kinetic evidence for reaction (2) has been obtained in the study of the oxidation of styrene in the presence of cobalt stearate, which is also inactive in the decomposition of the polyperoxide formed.[22]

The complex of vitamin B_{12} and O_2 [a mononuclear paramagnetic cobalt(II) superoxo-complex[9]] can interact with hydroquinone and ascorbic acid to form free radicals from the substrate.[23]

Direct evidence for the occurrence of reaction (2) has been obtained by EPR in the oxidation of 2,6-di-t-butyl-4-R-phenols in the presence of bivalent cobalt complexes with Schiff bases (CoL_2).[24] It has been shown that the concentration of the superoxo-complexes, formed in the interaction of molecular oxygen with CoL_2 and detected by EPR, falls sharply when phenols are added to the solution. Under anaerobic conditions, one can then observe the formation of the corresponding free phenoxy-radicals. In an atmosphere of oxygen the reaction is not catalytic and leads to the formation of quinones:



with insertion of the Co(III)OO group in the *p*-position of the phenol for R = CH_3, C_2H_5, iso-C_3H_7, or t-C_4H_9 or in the *o*-position for R = $C_6H_{11}R'$. The phenoxy-radicals formed in the first stage of the process are apparently reduced by cobalt(II) ions with formation of the corresponding phenoxides, which react further with molecular oxygen at high rates.

The possibility of the involvement of the catalyst in the oxidation chain initiation stage, apparently owing to the preliminary formation of superoxo-complexes, has been demonstrated in relation to the oxidation of ethylbenzene in the presence of nickel bis(acetylacetonate).[25] The rate of chain initiation measured by the method of inhibitors proved to be 4×10^{-7} and 9×10^{-6} mol litre^{-1} s^{-1} in this process at 120 °C and catalyst concentrations of 3×10^{-3} and 2×10^{-2} M respectively. These rates are significantly higher than the rate of chain initiation in the absence of catalysts (1.5×10^{-9} mol litre^{-1} s^{-1}).[26]

Such high rates of formation of free radicals in the catalytic process could not be ensured by the decomposition of hydroperoxides, since nickel bis(acetylacetonate) exhibits only a weak activity in their decomposition reaction. In order to attain the above rates of formation of free radicals, the content of hydroperoxides in the system should have been not less than 0.01 M,[27] while the experimental concentration $[ROOH]_0$ in ethylbenzene at the beginning of the process did not exceed 1×10^{-4} M.

The addition of electron-donating ligands [alkali metal stearates,[28,29] dimethylformamide (DMF), hexamethylphosphoramide, or *N*-methyl-2-pyrrolidinone[30]], which form complexes with nickel bis(acetylacetonate), leads to an appreciable increase (by a factor up to 3) of the rate of formation of free radicals, although the rate of decomposition of hydroperoxides in the presence of electron-donating ligands diminishes.[28] As for the cobalt(II) complexes,[31,32] the coordination of electron-donating ligands apparently increases the equilibrium formation constant of the complex of molecular oxygen with the catalyst and lowers its oxidation-reduction potential, which creates in its turn more favourable conditions for reaction (2).

Free radicals are apparently formed in the interaction of RH_2 with metal superoxo-complexes in the oxidation of ethylbenzene in the presence of copper complexes of *o*-phenanthroline (*o*-phen).[33] The rate of absorption of oxygen (W_{O_2}) in this system depends greatly on the concentration of the dissolved oxygen and is described by the empirical equation

$$W_{O_2} = a(b + c[O_2])^{1/2},$$

where *a*, *b*, and *c* are constants.

The observed rate law agrees qualitatively with the following oxidation mechanism:

$$\mathrm{Cu(II)}(o\text{-phen})_n \xrightarrow{\mathrm{ROOH}} \mathrm{Cu(I)}\,(o\text{-phen})_n,$$

$$\mathrm{Cu(I)}\,(o\text{-phen})_n + O_2 \rightarrow \mathrm{Cu(II)}\,(o\text{ phen})_{n-1}O_2^{\cdot} + (o\text{-phen}),$$

$$\mathrm{Cu(II)}\,(o\text{-phen})_{n-1}O_2^{\cdot} + RH_2 \rightarrow HR^{\cdot} + HO_2^{\cdot} + \mathrm{Cu(I)}\,(o\text{ phen})_{n-1},$$

$$HR^{\cdot} + O_2 \rightarrow HRO_2^{\cdot},$$

$$HRO_2^{\cdot} + RH_2 \rightarrow HROOH + HR^{\cdot},$$

$$2HRO_2^{\cdot} \rightarrow \text{chain termination}.$$

The porphyrin complexes of nickel, iron, and manganese can also serve as initiators of the free-radical oxidation reaction.[34-36]

III. THE MONOXYGENASE OXIDATION MECHANISM

The monoxygenase oxidation mechanism is the term which has come to be given to the mechanisms of catalytic reactions with participation of molecular oxygen in which one oxygen atom is consumed in the oxidation of the substrate, while the other is reduced to water. The reaction takes place without the intermediate formation of free radicals in accordance with the overall equation

$$RH_2 + O_2 + DH_2 \rightarrow HROH + D + H_2O.$$

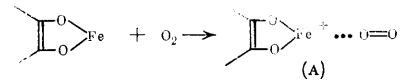
The enzymes catalysing such oxidation reactions have come to be called monoxygenases.

When a cofactor does not participate in the process, i.e. when the reaction proceeds in accordance with the overall equation

$$RH_2 + O_2 \rightarrow R{=}O + H_2O,$$

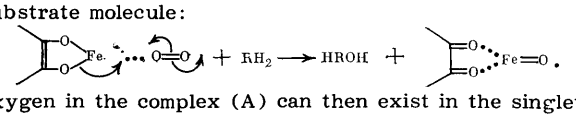
the monoxygenases of this type are referred to as internal monoxygenases.[37]

It has been suggested that in catalysis by monoxygenases oxygen is inserted in the substrate molecule via an intermediate stage involving the formation of oxenoid complexes (by analogy with carbenoid complexes), in which the oxygen atom has six electrons.[38] The hydroxylation of alkanes and aromatic compounds as well as the epoxidation of olefins can proceed via the oxenoid mechanism. For example, in the hydroxylation of substrates in the presence of iron compounds, electron transfer from iron to oxygen could give the intermediate complex (A)



(A)

resulting in the transfer of an oxygen atom with six electrons to a substrate molecule:



The oxygen in the complex (A) can then exist in the singlet form, which facilitates the reaction without the intermediate formation of radical products.

One of the chemical systems whereby it is possible to model the action of monoxygenases is apparently the hydroxylation of aromatic compounds by molecular oxygen in the presence of molybdenum hexacarbonyl $Mo(CO)_6$.[39,40] This reaction is accompanied by the formation in the first macrostage of the process of an arenemolybdenum tricarbonyl in accordance with the scheme

$$Mo(CO)_6 = Mo(CO)_5 + CO\,,$$
$$Mo(CO)_5 + ArH \rightarrow Mo(CO)_5(ArH)\,,$$
$$(ArH)Mo(CO)_5 \rightleftarrows (ArH)Mo(CO)_4 + CO\,,$$
$$(ArH)Mo(CO)_4 \rightleftarrows (ArH)Mo(CO)_3 + CO\,.$$

The formation of the complex $(ArH(Mo(CO)_3$ can be detected by ultraviolet and infrared spectroscopy. The rate-limiting stage in this macrostage of the process is the dissociation of $Mo(CO)_6$ with elimination of one CO molecule, which has been confirmed by the weak dependence of the rate of oxidation on the substrate concentration.

The final reaction products (phenols or naphthols) are formed in the interaction of arenemolybdenum tricarbonyl with oxygen. The rate of this macrostage depends on the oxygen concentration. It has been suggested[39-41] that the rate-limiting stage in the oxidation of arenemolybdenum tricarbonyl is the formation of the intermediate complex $(ArH)Mo(O_2)(CO)_3$. The formation of a ternary complex, in which both reactants (O_2 and the substrate) are coordinated to a zerovalent molybdenum atom, facilitates the insertion of one oxygen atom in the molecule of the aromatic compound:

$$(ArH)Mo(O_2)(CO)_3 \rightarrow ArOH + Mo(O)(CO)_3\,.$$

The molybdenum dioxo-complexes O=Mo=O can also serve as effective catalysts of the oxidation of many organic substances via a non-radical mechanism.[42-46] Thus the complexes $MoO_2(S_2CNR_2)_2$ can catalyse the oxidation of trialkyl- and triphenyl-phosphines by molecular oxygen with formation of the corresponding oxides. In the absence of oxygen, the reaction is stoichiometric and leads to the formation of the inactive complex $Mo_2O_3(S_2CNR_2)_4$:

$$MoO_2(S_2CNR_2)_2 + PR_3 \rightarrow MoO(S_2CNR_2)_2 + R_3PO\,,$$
$$MoO_2(S_2CNR_2)_2 + MoO(S_2CNR_2)_2 \rightarrow Mo_2O_3(S_2CNR_2)_4\,.$$

In the presence of oxygen, the oxidation of tertiary phosphines becomes catalytic owing to the regeneration of the dioxo-complex on interaction of oxygen with $Mo_2O_3\cdot(S_2CNR_2)_4$:[47]

$$Mo_2O_3(S_2CNR_2)_4 + O_2 \rightarrow Mo_2O_3(O_2)(S_2CNR_2)_4\,,$$
$$Mo_2O_3(S_2CNR_2)_4 + Mo_2O_3(O_2)(S_2CNR_2)_4 \rightarrow 4MoO_2(S_2CNR_2)_2\,.$$

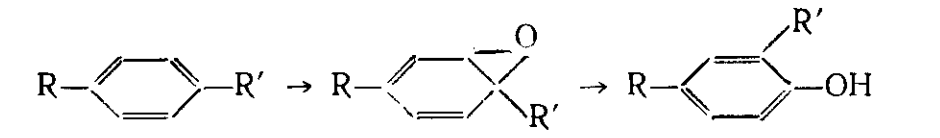
Reactions involving oxidation by molecular oxygen using cytochrome P-450 as the catalyst have attracted much attention because cytochrome P-450 forms part of the composition of microsomal oxidative systems.[37]

The cytochrome P-450 structure has been investigated by various methods and can now be regarded as fairly reliably established.[48-50] The iron atom in the complex is surrounded by four nitrogen atoms in equatorial positions; the axial ligands consist of cysteinyl sulphur and histidine.

It has been suggested that catalysis by porphyrins, metal complexes of azaporphyrins, and cytochrome P-450 ensures the development of the process via a non-radical pathway. In model systems cytochrome P-450 exhibits mainly a hydroxylating capacity, i.e. behaves similarly to monoxygenases, catalysing the incorporation of one oxygen atom in the substrate molecule.

Apart from the hydroxylation of aromatic and paraffinic hydrocarbons, the commonest reactions with participation of cytochrome P-450 as the catalyst involve the dealkylation of *S*-, *N*-, and *O*-substituted compounds.[37]

One of the most significant pieces of evidence showing that cytochrome P-450 catalyses the development of oxidative reactions via a non-radical mechanism is the high regioselectivity of such reactions, which is as a rule not characteristic of radical chain processes. As an example, one may point out that the hydroxylation of paraffinic hydrocarbons apparently proceeds with the preferential formation of 2-alkanols.[37] Examples of the oxygenation of substituted aromatic compounds, accompanied by a change in the position of the substituent in the aromatic ring, are known.[51] It has been suggested that the reaction proceeds via the intermediate formation of epoxides:



In the hydroxylation of aromatic compounds, the isomeric composition of the phenols formed is considered as one of the pieces of evidence for the molecular (monoxygenase) mechanism of the action of both cytochrome P-450 and other hydroxylating systems.

For many catalytic hydroxylating systems, incorporating iron(II), iron(III), copper(I), and titanium(III) ions as well as ligands with redox activity (the ascorbate ion, thiosalicylic acid, etc.), the proportions of the isomeric *ortho*- *para*-, and *meta*-phenols differ significantly from those of the corresponding isomers produced by the interaction of aromatic substrates with $\dot{O}H$ radicals.[52-56] This discrepancy can evidently be regarded as important evidence in support of the view that free hydroxy-radicals are not involved in the hydroxylation, but it cannot indicate unambiguously the interaction of the substrate with activated oxygen.

One of the important features of chemical hydroxylating systems is their ability to catalyse the epoxidation of olefins by molecular oxygen. Since this property is as a rule characteristic of enzymes (monoxygenases), it too can be regarded as evidence in support of a non-radical oxidation pathway.[57]

The hydroxylation of various substrates by molecular oxygen in the presence of cytochrome P-450 and NADPH(DH_2) is believed to proceed in several stages. A molecular complex of cytochrome P-450 with the substrate ($Fe^{3+}...RH_2$), which undergoes one-electron reduction on interaction with NADPH with formation of the $Fe^{2+}...RH_2$ species, combining with molecular oxygen, is formed in the first stage of the process. The ternary complex $RH_2...Fe^{2+}...O_2$ is reduced via a one-electron mechanism:

$$RH_2 \cdots Fe^{2+} \cdots O_2 \xrightarrow{\bar{e}} RH_2 \cdots Fe^{2+} \cdots O_2^- \rightleftarrows RH_2 \cdots Fe^{3+} \cdots O_2^{2-}\,.$$

The complex $RH_2...Fe^{3+}...O_2^{2-}$ contains iron in the formal +5 oxidation stage:[58]

$$Fe^{3+} \cdots O_2^{2-} \rightleftarrows Fe^{5+} \cdots O_2^{4-}\,.$$

This complex can be reduced via the oxenoid mechanism with the simultaneous transfer of two electrons to the oxygen molecule or via the peroxidase mechanism with the consecutive transfer of two electrons:[41]

$$[Fe^{3+} \cdots O_2^{2-} \equiv Fe^{5+} \cdots O_2^{4-}] \xrightarrow{\bar{e}} [Fe^{3+} \cdots O_2^{3-} \equiv Fe^{4+} \cdots O_2^{4-}] \xrightarrow{\bar{e}} Fe^{3+}$$
$$[Fe^{5+} \cdots O_2^{4-}] \xrightarrow{2\bar{e}} Fe^{3+}\,.$$

However, the concept of the monoxygenase mechanism of the oxidation of organic substrates in the presence of cytochrome P-450 is in certain cases inconsistent with experimental data. Thus, according to Akhrem et al.,[41]

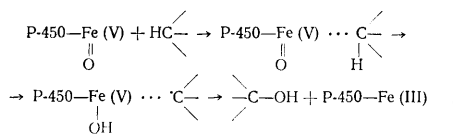
metal-O_2 complexes behave as hydroxylating agents only in aprotic media. In this case the transfer of an oxygen atom takes place via the oxenoid mechanism and the rate of the hydroxylation reaction is limited by the insertion of oxygen in the substrate molecule; in aqueous or other protic media, the hydroxylation takes place with participation of the free radicals $\dot{O}H$ or $H\dot{O}_2$. An important element in the oxidation via the oxenoid mechanism in a ternary substrate–catalyst–oxygen complex is the activation of both reactants.[41]

The intermediate formation of radical species has been suggested also in the oxidation of norbornene in the presence of cytochrome P-450.[59] In this case oxidation by molecular oxygen leads to the formation of *exo*- and *endo*-2-norborneols in proportions of 3.4 : 1. The appreciable kinetic isotope effect (k_H/k_D = 11.5), found for this reaction, suggested[59] that the rate-limiting stage is the abstraction of a hydrogen atom from the norbornene molecule with the intermediate formation of an alkyl radical.

When oxygen interacts with cytochrome P-450, the oxo-complex P-450–Fe(V) of the formally quinquevalent iron is

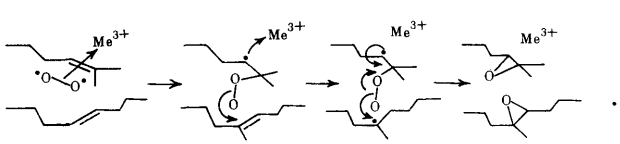


formed in the first stage and then reacts with the hydrocarbon via the mechanism



In many investigations involving the use of metal-phthalocyanines as oxidation catalysts, the conclusion that oxygen can be activated by such complexes is based on the ability of metal-phthalocyanines to form complexes with oxygen.[60,61] However, the observed effects can be frequently attributed to the possibility of the formation of a catalyst–substrate complex and not the activation of oxygen. Thus the rates of oxidation of squalene and the composition of the products in the advanced process in the presence of cobalt-octaethylporphyrin, i.e. Co(OEP), and cobalt(III) and iron(III) tris(acetylacetonates), which cannot form complexes with molecular oxygen, are virtually identical.[62] Furthermore, it is known that there is an almost complete electron transfer in the molecular complexes of cobalt(II)-octaethylporphyrin with molecular oxygen to form a superoxide ion coordinated to a tervalent cobalt ion.[63] The interaction of this complex with an olefin should have led to the formation of the octaethylporphyrin complex of tervalent cobalt, which is incapable of coordinating oxygen, i.e. the oxidation in the presence of Co(OEP) should have been non-catalytic. Nevertheless, the number of substrate molecules reacting per catalyst molecule reaches 100.

The principal squalene oxidation products are epoxides; allyl alcohols and ketones, which are the main products of the oxidation of low-molecular-weight olefins, are virtually absent from the oxidation reaction mixture.[63] Since squalene is associated in solution[64] and a parallel arrangement of the chains is characteristic of the associated species, it has been suggested that the bimolecular interaction of the free-peroxy-radical with the double bond of a second squalene molecule plays an important role in the oxidation mechanism:



The dependence of the rate of oxidation W of pyridine solutions of ascorbic acid (H_2A) on the oxygen concentration in the presence of catalytic amounts of iron(III), copper(II),[65] UO_2^{2+},[66] VO_2^+,[67] and zinc(II)[68] complexes is described by the law

$$W = \frac{(k_1 + k_2[\mathrm{Py}])[\mathrm{HA}^-][\mathrm{O_2}][\mathrm{cat}]}{[\mathrm{H}^+](1 + K_a[\mathrm{HA}^-])},$$

This suggested[65–67] that the process proceeds via a non-radical mechanism as a result of the activation of molecular oxygen. It is evident, however, that an analogous dependence might have been obtained also for a radical non-chain mechanism[69] if it is assumed that the first stage of the process involves the formation of a molecular complex of the catalyst with the ascorbate anion HA^-, which dissociates in the coordination sphere of the catalyst with formation of the dianion A^{2-}. The oxidation of the coordinated dianion by molecular oxygen leads to the formation of the radical-anion $A^{\cdot-}$, which then disproportionates in the system. Indeed, it has been found that the $A^{\cdot-}$ concentration measured by EPR in the solution being oxidised is virtually identical with that calculated on the assumption of a radical non-chain oxidation mechanism.[69]

Among porphyrin complexes of both cobalt and iron, the highest activity in the oxidation reaction is shown by complexes having the composition M–P : O_2 = 1 : 1:

$$\mathrm{LCo{-}P} + \mathrm{O_2} \rightleftarrows \mathrm{LCo{-}P \cdots O_2}, \qquad (3)$$

where L is an axial ligand and P is a porphyrin.

The hydroxylating activity of the catalyst falls appreciably on dimerisation (disproportionation) of mononuclear complexes:

$$\mathrm{LCo{-}P \cdots O_2 + LCo{-}P \rightleftarrows LCo{-}P(O_2)P{-}CoL}. \qquad (4)$$

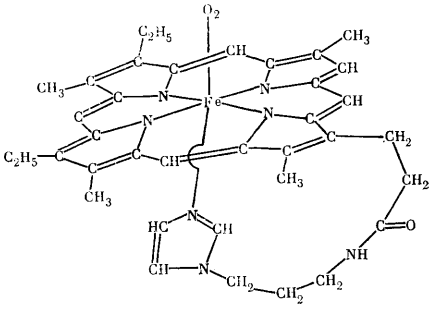
Depending on the reaction conditions, both mononuclear[70] and dinuclear,[71,72] complexes can be formed in solution. The formation of mononuclear 1 : 1 complexes with oxygen is characteristic of cobalt(II) complexes of protoporphyrin IX, while the irreversible reaction (4) takes place on raising the temperature.[73] It has been suggested that reaction (4) is preceded by a rearrangement of the complex LCo–P...O_2 in which the length of the O–O bond increases and its multiplicity diminishes.

The structure of the complex, in particular, the presence of a fairly strong base in the axial position, has a considerable influence on the complex-forming capacity of porphyrins in the reaction with molecular oxygen. In the complex formation reaction of Co(II)–P′ (where P′ is protoporphyrin IX) with oxygen, a satisfactory correlation is observed between the enthalpy of complex formation and the basicity of the axial ligand L[73] in the following sequence: benzimidazole < 4-t-butylpyridine < imidazole < 1-methylimidazole. The marked difference between the rate constants for reaction (4) with L = pyridine and imidazole suggested[73] that the stability of the oxygen complexes incorporating imidazole is ensured by the formation of hydrogen bonds between imidazole and O_2^- in the complex with the metal-porphyrin.

The presence of imidazole in the axial-position in haem-containing compounds has different effects on the rate constants for the complex formation reactions of haems with oxygen and carbon monoxide.[74,75] Thus the replacement of pyridine by imidazole hardly alters the rate constant for the formation of a complex of CO with mesohaem, while the corresponding rate constant for oxygen increases at least by a factor of 3.8×10^3.[76] In order to account for this effect, it has been suggested that the high π-basicity of imidazole plays a major role in the process. It strengthens the π-bond (compared with other bases) between iron ions and

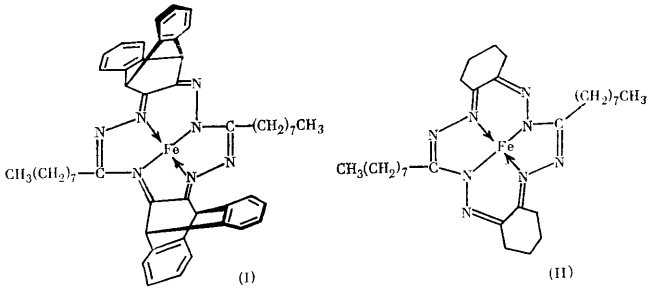
the unoccupied oxygen π* orbitals. The strength of the π-bond between iron and the A–B molecule (CO or O_2) should increase with increasing σ-basicity of the A–B molecule. Since the σ-basicity increases on passing from CO to O_2, the replacement of pyridine by imidazole should have a greater influence on the complex formation reaction of LCo–P with oxygen than with carbon monoxide.

The role of structural factors has been noted in a study of the stability of the complexes of O_2 with a synthetic section of the active centre of myoglobin:[77]



The possibility of the formation of this complex with molecular oxygen is also determined to a large extent by the presence of imidazole in the 5-position.

The influence of the structural factor on the complex formation reactions involving oxygen and also on the stability of oxygen complexes has been demonstrated.[78] The study of the interaction of O_2 with two complexes differing in the depth of the "cavity" formed by the ligand in which the iron atoms are located has shown that compound (I), in which the depth of the "cavity" is 5 Å, forms with oxygen reversible bright cherry-red 1:1 complexes. Compound (II), in which the depth of the "cavity" is 2.2 Å, combines irreversibly with oxygen in the stoichiometric proportions O_2:Fe = 0.5:1:



(I) (II)

The study of the mechanism of the oxidation of organic substances in the presence of rhodium(I) complexes has attracted much attention from the standpoint of the possibility of the activation of molecular oxygen. It has been suggested that the oxidation of olefins in the presence of chlorotris(triphenylphosphine)rhodium(I) takes place via the monoxygenase mechanism.[79–84] Triphenylphosphine, which is oxidised to the corresponding oxide under these conditions, functions as the reducing agent in the above process.

In one of the early studies of this cycle,[85] it was shown that chlorotris(triphenylphosphine)rhodium is an effective catalyst of the oxidation of aromatic compounds at temperatures above 100 °C.

An interesting feature of the process is the marked dependence of the rate of oxidation on the oxygen pressure,[85,86] which is not characteristic of catalytic oxidation via a radical chain degenerate branched mechanism. Such a dependence presupposes the involvement of oxygen in the rate-limiting stage of the reaction.

Although chlorotris(triphenylphosphine)rhodium and chlorocarbonylbis(triphenylphosphine)rhodium greatly accelerate the decomposition of hydroperoxides,[85,87] this does not rule out the possibility of the involvement of complexes of molecular oxygen with rhodium compounds both in the chain initiation stage [via reaction (2)] and in non-radical oxidation reactions of the substrates.

Lines due to the formation of species comprising rhodium(II) and O_2^-,[87,88] possibly the superoxo-complexes Rh(II).O_2^-, can be identified in the EPR spectra of solutions of $Rh(PPh_3)_2$.COCl, saturated with oxygen, at 77 K. The concentration of these species increases greatly in the presence of cumenyl hydroperoxide,[87] apparently as the result of the facilitation of electron transfer from rhodium(I) to O_2 in the ternary complex:

$$ROOH \overset{\curvearrowright}{\cdots} Rh(I) \overset{\curvearrowright}{\cdots} O_2 .$$

The oxidation of cyclohexene by molecular oxygen in the presence of rhodium complexes activated by cumenyl hydroperoxide leads to the formation of cyclohexenyl hydroperoxide with a selectivity up to 95%.[86] Calculation of the rate of oxidation by the formula

$$W_{O_2} = (k_2/k_6^{1/2})[RH]\,W_i^{1/2} ,$$

where W_i is the rate of formation of free radicals in the decomposition of the hydroperoxide and k_2 and k_6 are respectively the rate constants for the oxidation chain propagation and termination, i.e. on the assumption of a radical chain oxidation mechanism, showed that the calculated W_{calc} is virtually identical with experimental W_{exp} only at the beginning of the process (at $t \to 0$); in later stages $W_{exp}/W_{calc} > 3$. This finding as well as the decrease of the reaction order with respect to the concentrations of cumenyl hydroperoxide (activator), the catalyst, the olefin, and oxygen from 1 to 0 as the concentration of the corresponding reactant increases suggested that the olefin is oxidised via a non-radical mechanism involving the formation of a ternary catalyst–substrate–oxygen complex after the preliminary modification of the catalyst in accordance with the scheme

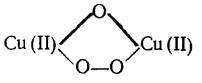
$$Rh(CO)Cl(PPh_3)_2 + ROOH \rightleftarrows Rh(CO)Cl(PPh_3)(ROOH) + PPh_3 ,$$
$$Rh(CO)Cl(PPh_3)(ROOH) + O_2 \rightleftarrows Rh(II)(CO)Cl(PPh_3)(ROOH)\cdot O_2^- ,$$
$$Rh(II)(CO)Cl(PPh_3)(ROOH)\cdot O_2^- + RH \to$$
$$\to Rh(II)(CO)Cl(PPh_3)(ROOH)\cdot O_2^-(RH) ,$$
$$Rh(II)(CO)Cl(PPh_3)(ROOH)\cdot O_2^-(RH) \to$$
$$\to ROOH + Rh(I)(CO)Cl(PPh_3)(ROOH) .$$

The catalyst in the initial form as well as rhodium(III) complexes and salts catalyse the radical chain oxidation pathway, which apparently explains the appearance of long induction periods after the introduction of different inhibitors at the beginning of the reaction in the presence of univalent rhodium compounds.[89] It is significant that the effectiveness of the modification of the catalyst by hydroperoxides depends greatly on the structure of the latter. For example, cyclohexenyl hydroperoxide hardly modifies the rhodium catalyst.[86]

The results of experiments using labelled oxygen must be regarded as the most reliable evidence in support of the mechanism involving the direct oxidation of substrates by molecular oxygen. With the aid of this method, combined with a series of kinetic methods, the possibility of the activation of molecular oxygen by high-spin complexes of bivalent nickel with a macrocyclic nitrogen-containing ligand has been demonstrated unambiguously.[90,91]

The hydroxylation of aromatic compounds, in particular cresols, in the presence of such complexes in an atmosphere of $^{17}O_2$ in solution in $H_2{}^{18}O$ showed that the phenol formed contains a ^{17}O atom, i.e. that oxygen is inserted in the direct interaction between ArH and O_2.

The possibility of the effective utilisation of a series of dimeric univalent copper complexes as models of monoxygenases has been demonstrated in recent years.[92–95] The formation of the dinuclear peroxo-complexes



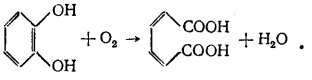
plays an important role in the mechanism of the activation of oxygen by such complexes.[96]

IV. MODELS OF THE ACTION OF DIOXYGENASES

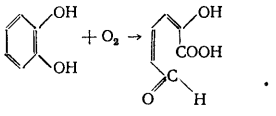
Enzyme systems catalysing the insertion of both atoms of molecular oxygen in the molecule of the substrate being oxidised (S) have come to be called dioxygenases. As a rule, such reactions do not require the participation of an extermal reductant in the process and are formally described by the equation

$$S + O_2 \rightarrow SO_2 .$$

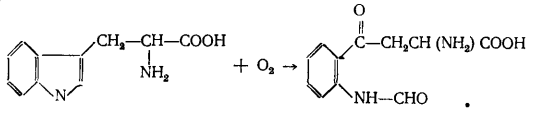
The most typical dioxygenases are catechol dioxygenases, protocatechuate dioxygenases, and tryptophan oxidases. The active centre in catechol 1,2-dioxygenase and protocatechuate 2,3-dioxygenase is a high-spin Fe^{3+} ion.[97–99] In the presence of these enzymes, the oxidation reaction proceeds with the dissociation of a C–C bond and, for example, in the oxidation of catechol leads to the formation of muconic acids:[100]



The metapyrocatechases—catechol 2,3-dioxygenases and protocatechuate 4,5-dioxygenases—contain iron in the form of Fe^{2+} and catalyse the *meta*-cleavage of catechols:[101]



Tryptophan 2,3-dioxygenase, whose composition includes the Cu^+ ion, catalyses the oxidative cleavage of the indole ring in tryptophan:[102]



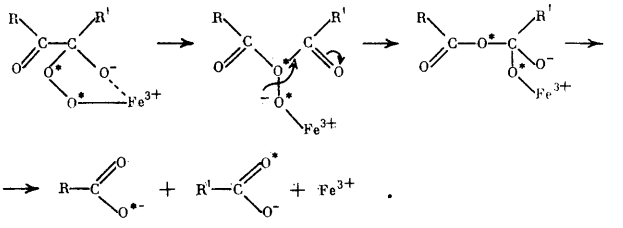
The mechanism of the action of all three enzyme systems involves many different intermediate stages, associated, in particular, with the rearrangement of the enzyme–substrate complexes formed initially.

The mechanism of the action of catechol 1,2-dioxygenases has been studied in greatest detail.[100,103,104] Experiments with $^{18}O_2$ have shown[100,103] that, in the course of the oxidation of catechols in the presence of catechol 1,2-dioxygenase, both atoms of molecular oxygen are incorporated in the oxidation product and no isotope exchange with the medium is observed. The reaction is accompanied by the formation in the first stage of an enzyme–substrate complex, which reacts further with molecular oxygen:[100,104]

$$E + S \rightleftarrows ES + O_2 \rightleftarrows ESO_2 \rightarrow ESO_2^* \rightarrow EP \rightleftarrows E + P,$$

where E is the enzyme, S the substrate, and P the reaction product.

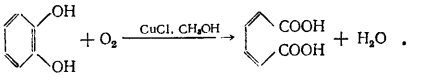
In certain cases, the formation of a "primary" complex with oxygen (ESO_2) may be detected in the system. However, in most systems the complex ESO_2 rapidly rearranges to form the "secondary" oxygen complex (ESO_2^*), and the rate of reaction is so high that the formation of the "primary" complex cannot be detected even by the stopped flow method and its formation can be inferred only indirectly on the basis of kinetic data.[100] The structures of the complexes ESO_2 and ESO_2^* have not been established. However, it is known that the formation of the intermediate complex ESO_2^* and its decomposition are accelerated when electron-donating substituents are introduced in the *para*-position in the benzene rings of catechols. This and also the finding that there is no change in the valence [oxidation state] of iron during the oxidation of catechols suggested that the reaction product is formed as a result of the insertion of oxygen in the C–C bond and is accompanied by the migration of an acyl group:



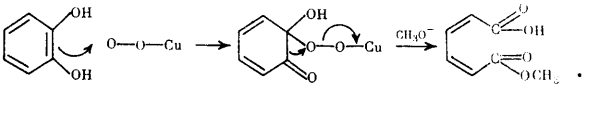
In the above formula the astericks denote the atoms of molecular oxygen.

Very few chemical models of the action of dioxygenases, in which the dioxygenase mechanism of the oxidation by molecular oxygen is demonstrated, have been described in the literature and as a rule the evidence presented cannot be regarded as unambiguous.

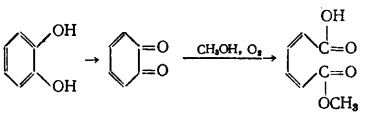
Copper(I) chloride catalyses the oxidation of catechol to muconic acid by oxygen in methanol in the presence of amines:[105]



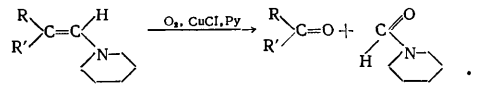
Although formally this reaction can be regarded as a model of the action of catechol 1,2-dioxygenase, in reality experiments with $^{18}O_2$ have shown that only one atom of the oxygen molecule enters into the composition of muconic acid.[105] The reaction can proceed via the intermediate formation of a peroxo-complex.[105] Its product is formed as a result of the interaction of the peroxo-complex with the anion CH_3O^-:



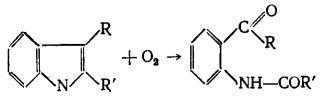
It has been suggested[106] that muconic acid is formed in the consecutive reaction



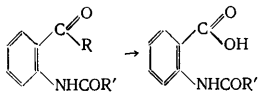
In pyridine solutions copper(I) chloride catalyses the oxidation of various substrates by molecular oxygen[107–109] at room temperature. For example, enamines are oxygenated with cleavage of the double bond and the formation of a ketone and *N*-formylpiperidine:[107]



The CuCl + amine system can serve as an effective catalyst of the oxidation of tryptophan and substituted indoles[108] at 25 °C. The reaction is accompanied by the dissociation of the double bond:



This system can be regarded as a model of tryptophan 2,3-dioxygenase which is capable, as pointed out above, of catalysing the oxidation of tryptophan [R = $CH_2CH(NH_2)$.COOH, R' = H]. However, formylkynurenine, which is a product of the enzymic oxidation of tryptophan, accumulates in the model chemical system in very small amounts (up to 1%) owing to its instability in relation to oxygen in the presence of pyridine complexes of univalent copper. The carbonyl compounds formed initially are oxidised at high rates and with a selectivity up to 60% to 2-acetamidobenzoic acid:[108]

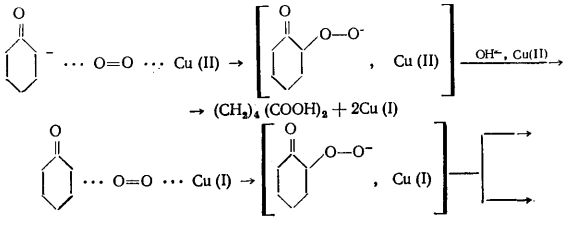


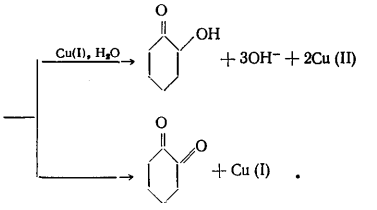
Thus the chemical system is less selective. The dinuclear μ-peroxo-complex Cu...O_2...Cu apparently serves as the oxygen transferring agent in the CuCl + O_2 + pyridine system.[110,111] The role of pyridine reduces to increasing the degree of dissociation of the dimeric form of copper(I) chloride $(CuCl)_2$, which is inactive in the reaction with molecular oxygen.

Certain cobalt complexes with Schiff bases[112] and with porphyrins[113] can also be regarded as models of tryptophan 2,3-dioxygenase.

The oxidation of alcohols and ketones in alkaline solutions in the presence of copper(II) complexes of *o*-phenanthroline can apparently also proceed via the dioxygenase mechanism.[33,114,115] The rate of oxidation of ketones in such a system increases linearly with increasing alkalinity of the medium,[116,117] i.e. as in the enzymic oxidation of catechols;[118] the deprotonation of the substrate plays a significant role in this process.

The reaction takes place via a non-radical mechanism, as shown, in particular, by the sequence in the formation of the reaction products, which is unusual for a radical-chain oxidation reaction: in the initial stages of the oxidation of cyclohexanone, the only oxidation products are adipic acid and cyclohexane-1,2-dione.[117] The latter is oxidised at rates much lower than the rate of accumulation of adipic acid, so that both products are formed via parallel (in relation to the substrate oxidised) pathways:





The rate of oxidation of ketones and the process selectivity (reaching 90–95% in the presence of *o*-phenanthroline) decrease greatly when 5-nitro-1,10-phenanthroline is used as the ligand,[116] which makes it possible to regard the reaction

$$RO^- + Cu(II)L_2 \rightarrow RO^{\cdot} + Cu(I)L_2 ,$$

whose rate should increase on passing from *o*-phenanthroline to 5-nitro-1,10-phenanthroline, as insignificant.

The increase of the rate of formation of free radicals when cyclohexane-1,2-dione is introduced at the beginning of the reaction also reduces the rate and selectivity of the oxidation of ketones.

The hypothesis of the involvement of superoxide ions in the process[114] is also inconsistent with experiment, since it is known that the complex Cu(*o*-phen)$_2$ can play the role of superoxide dismutase[119] and the O_2 [O_2^-?] concentration in solution should therefore be negligible. Furthermore, the superoxide ion can react rapidly with *o*-phenanthroline,[120] which should have led to its consumption during the oxidation process. Nevertheless the concentration of *o*-phenanthroline hardly changes in the oxidation of ketones.

Thus the $CuCl_2$ + *o*-phenanthroline + base catalytic system can be regarded as one of the systems in which the simultaneous activation of both oxygen and the substrate by the catalyst leads to the operation of a non-radical oxidation mechanism, ensuring a high process selectivity close to room temperature.

The examples quoted above demonstrate the practical feasibility of liquid-phase oxidation processes at high rates and with high selectivities via a non-radical mechanism at comparatively low temperatures (close to room temperature) using as catalysts relatively simple catalytic systems modelling the action of biological enzymes.

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