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Mechanisms of the Hydroxylation of Aromatic Compounds

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A systematic account is given of various mechanisms for the hydroxylation of aromatic compounds in the liquid phase, and they are discussed critically. Similarities and differences are emphasised in the mechanisms of the action of Fenton's reagent, enzymes, and models of the latter in the hydroxylation of aromatic systems. Mechanisms of radiolytic hydroxylation are examined in detail, and questions concerning the nature of the attacking species and the distribution of the resulting isomeric phenols are discussed. Kinetic data and the mechanism of the hydroxylation of aromatic systems during oxidation together with aliphatic alcohols are examined in detail. A list of 211 references is included.

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I. INTRODUCTION

The concept of "aromaticity" in organic chemistry implies the ability of a substance to undergo substitution readily while being stable to the action of oxidants. This concept arose from a study of the properties of benzene, which, although formally unsaturated, readily undergoes substitution and is very resistant to oxidising agents [1]. The great stability of the aromatic ring in homolytic oxidations is explained also by the fact that benzene and its derivatives do not form the corresponding hydroperoxide, which, by decomposing into free radicals, might have initiated further oxidation. Finally, the oxidation of aromatic compounds yields phenols and their reaction products, which act as inhibitors in the chain oxidation of hydrocarbons.

The direct preparation of hydroxy-derivatives of aromatic compounds in a single stage is of great practical importance, since no effective single-stage process has yet been developed e.g. for obtaining phenol from benzene, there are no methods for producing naphthols by the direct oxidation of naphthalene, and only the direct preparation of anthraquinone from anthracene is of importance in industrial organic synthesis [2]. Yet it is known to be possible in principle to oxidise benzene and its derivatives to phenols under mild conditions: for example, there are enzymes which oxidise phenylalanine to tyrosine; micro-organisms assimilate aromatic compounds, converting them into *o*- and *p*-diols and then cleaving the rings to form aliphatic acids [3]; under certain conditions benzene can be oxidised to give a quite high yield of phenol [4].

We shall not discuss here the oxidation of benzene to phenol in the gas and liquid phases by various methods, since a detailed survey of this question has appeared [4]; nor shall we be concerned with oxidation processes involving destruction of the benzene ring [5]: we shall concentrate our attention on the mechanism of the first stage in the oxidation of aromatic compounds—the hydroxylation of aromatic rings with the formation of phenolic derivatives. In several cases the nature of the hydroxylating agents and the mechanism of their interaction with the aromatic systems are not entirely clear. The aim of the Review is to show the similarities and the differences in the mechanisms of hydroxylation by Fenton's reagent and various catalytic systems which simulate the action of enzymes and the mechanisms of hydroxylation in radiation-chemical processes and also in initiated and combined oxidations involving aromatic compounds. Examination of the mechanisms of the hydroxylation of aromatic compounds will enable a deeper insight to be obtained into processes involving their oxidation and also supplement our knowledge of substitution in the aromatic series.

II. MECHANISM OF HYDROXYLATION BY FENTON'S REAGENT AND ITS ANALOGUES

At a certain ratio of its components Fenton's reagent ($Fe^{2+} + H_2O_2$) is a source of reactive HO$^\cdot$ radicals, this being confirmed by its initiation of the polymerisation of vinyl compounds and oxidation of aliphatic and aromatic substances. The following mechanism has now been proved and accepted [6-10] for the interaction of iron(II) ions with hydrogen peroxide:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + HO^\cdot \quad (0)$$

$$Fe^{2+} + HO^\cdot \rightarrow Fe^{3+} + HO^- \quad (1)$$

$$H_2O_2 + HO^\cdot \rightarrow HO_2^\cdot + H_2O \quad (2)$$

$$Fe^{2+} + HO_2^\cdot \rightarrow Fe^{3+} + HO_2^- \overset{H^+}{\rightleftarrows} H_2O_2 \quad (3)$$

$$Fe^{3+} + HO_2^\cdot \rightleftarrows Fe^{2+} + H^+ + O_2 \quad (4)$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2^\cdot + H^+ \quad (5)$$

In the presence of excess of Fe^{2+} ions reactions (0) and (1) take place; with excess of hydrogen peroxide in acid solutions, when reactions (4) and (5) can be neglected, reactions (0), (2), and (3) occur. Comparable concentrations of Fe^{2+} and H_2O_2 in acid media result in reactions (0)–(3). The stoichiometry of the reaction is $2Fe^{2+}$ and H_2O_2. The rate constant of reaction (0) has been given as $k_0 = 4.45 \times 10^8 \exp(-9400/RT)$ M^{-1} s^{-1}. Thus with excess of the Fe^{2+} ion in acid media Fenton's reagent and its analogues are efficient sources of HO$^\cdot$ radicals.

A large amount of work has been done on the hydroxylation of aromatic systems by Fenton's reagent and its analogues ($Cu^{2+} + H_2O_2$, $Ti^{3+} + H_2O_2$, etc.). [11-26] Studies have been made of the hydroxylation of benzene [11-15,18,20], naphthalene [21], toluene [18,22,24], anisole [24], fluorobenzene [23], phenol and its substituted derivatives [23,25], nitrobenzene [12], and acetanilide [23].

Early papers [11,15] suggested the following mechanisms of interaction between the HO· radical and an aromatic compound:

$$XC_6H_4H + HO^{\cdot} \rightarrow XC_6H_4^{\cdot} + H_2O$$
$$XC_6H_4^{\cdot} + Fe^{3+} + HO^- \rightarrow XC_6H_4OH + Fe^{2+}$$
$$XC_6H_4^{\cdot} + XC_6H_4^{\cdot} \rightarrow XC_6H_4{-}C_6H_4X.$$

The reaction results in the formation of phenol and biphenyl (derivatives of the latter are not formed in nearly neutral media in the presence of oxygen). If oxidation does involve detachment of a hydrogen atom in conformity with the above scheme, an isotope effect should be observed in the reaction between HO· and completely deuterated benzene C_6D_6, provided that the detachment of a hydrogen or deuterium atom limits the rate of formation of reaction products. However, no isotope effect was observed experimentally in the oxidation of hexadeuterobenzene by Fenton's reagent [18], which indicates either that detachment of a hydrogen atom does not occur or that this step does not limit the overall rate of the process. It is noteworthy that removal of a hydrogen atom may occur to a slight extent with rise in temperature, as is indicated by the increase in k_H/k_D from 1.25 (at 20°) to 1.37 (70°C) in the oxidation of a mixture of ordinary and deuterated benzene [27].

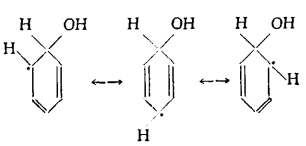
Proskurin and his coworkers [28] were the first to suggest that the HO· radical adds to the benzene ring to form the complex radical $C_6H_6O{\cdot}H$. The existence of this radical was demonstrated by pulse radiolysis combined with flash spectroscopy [29], its absorption spectrum (λ_{max} = 313 nm) has been determined, and the addition rate constant calculated as $(4.3 \pm 0.9) \times 10^9\ M^{-1}\ s^{-1}$ at 25°C.

The use of ^{18}O to investigate oxygen transfer in the reaction of benzene with Fenton's reagent and its analogue $Cu^{2+} + H_2O_2$ showed that 15–23% of oxygen is incorporated from water into the phenol if no oxygen is present in the gas phase, and 5% of oxygen from the gas phase if the latter contains oxygen [20]. The results are consistent with the mechanism

$$H_2O_2 + Fe^{2+} \rightarrow HO^{\cdot} + Fe(OH)^{2+}$$
$$C_6H_6 + HO^{\cdot} \rightarrow (C_6H_6OH)^{\cdot} \rightarrow PhOH + H$$

The limiting step is the formation of HO· radicals, not their interaction with benzene.

Dixon and Norman [19] used electron spin resonance to study the free radicals formed in the systems—$H_2O_2 + Ti^3$ and $H_2O_2 + Ti^3 + C_6H_6$—and found that the hydroxy-radicals disappear in the presence of benzene. New radicals appear, to which these workers attributed the structure

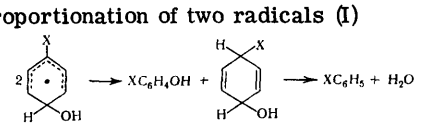


All the above results confirm that the first stage in the reaction between HO· and C_6H_5X (where X is a substituent) is the addition of hydroxyl to the benzene ring with formation of a cyclohexadienyl type of radical. The radical $XC_6H_5O{\cdot}H$ (I) is then able to react in three ways [18]—

(*A*) formation of phenolic compounds

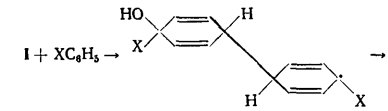
$$I + Fe^{3+} \rightarrow XC_6H_4OH + Fe^{2+} + H^+ \quad (6)$$
$$I + O_2 \rightarrow XC_6H_4OH + HO_2^{\cdot} \quad (7)$$

(*B*) disproportionation of two radicals (I)



(8)

(*C*) formation of biphenyl compounds



(9)

Three mechanisms can be suggested [30,31] for the formation of biphenyl compounds—removal of a hydrogen atom from the C_6H_5X molecule followed by recombination of the phenyl radicals, addition of the radical (I) to C_6H_5X with simultaneous detachment of hydrogen (as shown in scheme *C*), and slow formation of an intermediate complex by addition of the radical (I) to C_6H_5X with a subsequent rapid reaction due to attack by another radical or by the action of an oxidant (HO·, Fe^{3+}, or O_2 with the formation of H_2O, $Fe^{2+} + H^+$, and $HO_2^{\cdot}$ respectively)—among which the third mechanism appears to be the most probable [32,33].

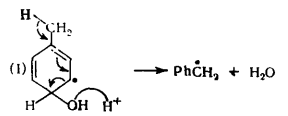
In the presence of oxygen the most probable route for the formation of phenol is reaction of the radical (I) with an oxygen molecule, the rate constant of which is quite large—$(5.0 \pm 0.6) \times 10^8\ M^{-1}\ s^{-1}$ at 23°C [34]—so that disproportionation of two radicals (I) (scheme *B*) is improbable. The formation of phenol in preference to biphenyl compounds in the presence of molecular oxygen is explained by the more rapid reaction of (I), with this oxidant than with C_6H_5X (scheme *C*). In the absence of oxygen biphenyl compounds are formed, and also phenol by reaction (1) with Fe^{3+} and by disproportionation (scheme *B*).

Table 1.

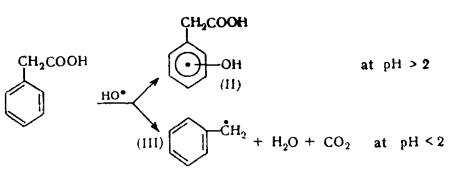
pH	Yield of products × 10^5 (moles)	
	1,2-diphenylethane	cresols
1.3	60	2.7
2.1	16	4.4
3.6	1.5	34

The pH of the medium has a great effect on the rate of oxidation by Fenton's reagent and on the composition of the products. The distribution of isomeric phenolic derivatives is maintained with variation in pH, but the proportions of phenolic and biphenyl products change substantially [24]. Table 1 gives the variation in the composition of the products for the oxidation of toluene.

Large quantities of 1,2-diphenylethane are formed in acid media in the absence of molecular oxygen. This is due to the acid-catalysed conversion of the corresponding cyclohexadienyl radical into a benzyl radical:



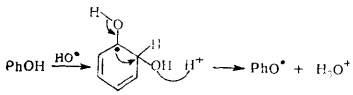
The cyclohexadienyl radical formed by the interaction of HO· with phenylacetic acid behaves similarly:



The radical (III) has been recorded in strongly acid media by electron spin resonance, and the radical (II) in less acid media.

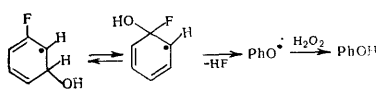
The acid-catalysed fragmentation of cyclohexadienyl radicals is a general phenomenon. Investigation of the reactions of anisole, acetanilide, fluorobenzene, and certain substituted phenols in the Ti^{3+}–H_2O_2 system showed that the adduct of HO· and phenol is recorded by e.s.r. only at pH > 1: in more acid media this adduct is not recorded, but the spectrum of the phenoxy-radical C_6H_5O· is clearly developed. Cyclohexadienyl radicals corresponding to the other benzene derivatives studied were not recorded at all in acid media[23].

These facts are explained by fragmentation of the radicals in acid media:



This last reaction is confirmed also by the pulse radiolysis of phenol in aqueous solutions[35]: the absorption spectrum of the adduct of HO· with phenol (λ_{max} = 330 nm) and the spectrum of the phenoxy-radical (400 nm) are recorded. At 20°C the adduct decomposes with a rate constant of 5000 s^{-1}, while phenoxyl accumulates at the same rate. The rate of conversion of the adduct into phenoxyl is substantially dependent on the pH and the temperature.

The above fragmentation of cyclohexadienyl radicals explains the formation of phenol when such compounds as fluorobenzene are oxidised by Fenton's reagent[23]:



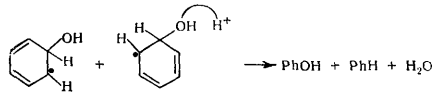
The fact that metal ions (Fe^{2+}, Fe^{3+}, Ti^{3+}) are not responsible for the influence of pH on the composition of the products is proved by results for the hydroxylation of toluene by hydrogen peroxide exposed to ultraviolet radiation[24]. Table 2 shows that the yield of cresols increases with pH, and that this effect is not due to the action of ions.

Table 2.

pH	5.4	3.0	2.0	1.0	0.2
Relative yield of cresols	10	4.2	2.5	0.9	trace

It is interesting that in strongly acidic media the yield of hydroxy-derivatives of anisole is far smaller than the yield of phenol from benzene under the same conditions[24]. The adduct of HO· with benzene is obviously more stable in acid media than is its adduct with anisole. This is confirmed by the clear e.s.r. spectra of C_6H_6O·H in the Ti^{3+} + H_2O_2 system[19], whereas the corresponding adduct of anisole is not recorded by e.s.r.[23]

Variation in pH affects the molar proportions of biphenyl and phenol produced by the ultraviolet irradiation of the C_6H_6 + H_2O_2 system (Table 3).[24] The relative increase in the yield of phenol can be explained by the fact that, in acid media, most of the phenol is formed by disproportionation, which is facilitated by hydrogen ions:



Thus the influence of pH on the composition of the products conforms to the same rules in oxidation by Fenton's reagent and in hydrogen peroxide exposed to ultraviolet radiation.

Table 3.

pH	5.5	3.0	2.0	0.5
[PhPh]/[PhOH]	0.5	0.4	0.23	0.02

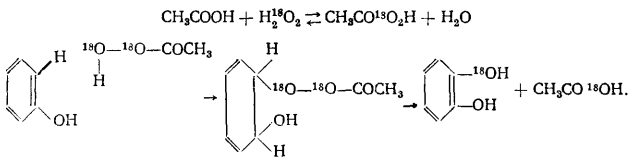
Metal ions (Fe^{3+} and Cu^{2+}) may play an important part in oxidation by Fenton's reagent, since their reactions with organic radicals are well known[36,37]. Additions of Cu^{2+} and F^- ions to Fenton's reagent have been made in the oxidation of anisole, and the effect on the yield of phenols has been examined. The yield is increased by the addition of copper ions, but fluoride ions lower the yield, since they form a stable complex with the Fe^{3+} ions which would have oxidised cyclohexadienyl radicals to phenols.

Important parameters of the species which attacks the benzene ring are the distribution of isomeric products which are formed and the relative reactivities of monosubstituted benzene derivatives and benzene itself towards this species. For example, most monosubstituted benzenes are more reactive than benzene itself towards the phenyl radical, independently of the polar character of the substituent[38]. The sequence of reactivities with Fenton's reagent is[22]

$$PhOCH_3 : PhH : PhCl : PhNO_2 = 6.35 : 1 : 0.55 : 0.14$$

This reactivity series differs from the order for phenylation[38], and indicates that the HO· species is electrophilic. The above reactivity sequence is maintained with hydrogen peroxide exposed to ultraviolet radiation.

The electrophilic nature of the HO· radical is confirmed by the distribution of isomeric phenolic products resulting from the oxidation of substituted benzenes. Table 4 shows that substituents of the first kind orient the group HO· mainly *ortho* and *para*, which is typical of electrophilic substitutions in the benzene series. Not only the HO· radical but also peroxy-acids (peracetic and trifluoroperacetic acids) may act as electrophilic agents[25,26]. Thus the oxidation of phenol by hydrogen peroxide in the presence of acetic acid and $H_2{}^{18}O_2$ yields catechol[25]:



Oxygen is incorporated into the catechol from the oxidant: free hydroxy-radicals are not formed in the reaction.

The action of Fenton's reagent involves attack by the radical HO· as has been noted many times. Several workers have recently obtained e.s.r. spectra of this radical in systems which act similarly to Fenton's

reagent. Table 5 lists the characteristics of the e.s.r. spectra and the conditions under which they have been obtained. It shows that the $Ti^{3+} + H_2O_2$ system generates HO· radicals in concentrations sufficient for detection by this method. The e.s.r. spectrum of the HO· radical differs from that of $HO_2^·$. The $Ce^{4+} + H_2O_2$ system produces solely $HO_2^·$ radicals by the reactions

$$Ce^{4+} + H_2O_2 \rightarrow Ce^{3+} + H^+ + HO_2^·$$
$$Ce^{4+} + HO_2^· \rightarrow Ce^{3+} + H^+ + O_2$$

and is considerably less effective than Fenton's reagent in the hydroxylation of benzene. From this Norman and Smith [18] concluded that $HO_2^·$ radicals are less reactive than HO· towards aromatic systems. However, Coppinger had shown [16] that the $HO_2^·$ radical is able to attack the benzene ring quite effectively.

Table 4. Distribution of isomers in the hydroxylation of substituted benzenes by Fenton's reagent.

Compound	Conditions	Phenols, %			Ref.
		ortho	*meta*	*para*	
Toluene	$Fe^{2+} + H_2O_2$, N_2	55.5	15.0	29.5	24
Toluene	$Fe^{2+} + H_2O_2$, air	71.0	5.0	24.0	18
Anisole	$Fe^{2+} + H_2O_2$, N_2, pH 2.5	81.0	0.5	18.0	24
Anisole	$Cu^{2+} + H_2O_2$	84.0	3.0	13.0	24
Anisole	Fe^{2+}-EDTA + H_2O_2	84.0	—	16.0	22
Anisole	Fe^{2+}-ascorbic acid + H_2O_2	88.0	—	12.0	17
Chlorobenzene	Fe^{2+}-EDTA + H_2O_2	42.0	29.0	29.0	22
Fluorobenzene	Fe^{2+}-EDTA + H_2O_2	37.0	18.0	45.0	22
Nitrobenzene	Fe^{2+}-EDTA + H_2O_2	24.0	30.0	46.0	22
Nitrobenzene	H_2O_2 + ultraviolet	24.0	30.0	46.0	22
Acetanilide	Fe^{2+}-EDTA + H_2O_2	47.0	3.0	50.0	39
Naphthalene	$Fe^{2+} + H_2O_2$	79.2 (1-naphthol)		20.8 (2-naphthol)	21

Table 5. Electron spin resonance spectra of HO· and $HO_2^·$ radicals and their characteristics.

Conditions of recording of spectrum	*g*	ΔH, oersteds	Species	Ref.
1% H_2O_2 soln. + ultraviolet from −70° to +60°C	2.015	1.0	HO·	40
$TiCl_4 + H_2O_2$		1.0	HO·	43
$Ti^{3+} + H_2O_2$, in flow	2.0128	0.7 (28°)	HO· in Ti^{4+} complex	41
	2.0114			
$TiCl_3 + H_2O_2$, rapid mixing at room temp.	2.0117		in Ti^{4+} complex	42
	2.0102			
$Ce(HSO_4)_4 + H_2O_2$, in flow, ice	2.0160	27	$HO_2^·$	44
H_2O_2, β-rays, −187°			HO·	46
$Ti^{3+} + H_2O_2$		1	$HO_2^·$	46
$Ti^{3+} + H_2O_2$ (different ratios)		1.5	HO· and $HO_2^·$ in different ratios	48
$Ti^{3+} + H_2O_2$	2.0115	0.8	$[TiO·OH]^{2+}$	47
	2.0130		$[TiO·O_2H]^{2+}$	45

Many experimental results indicate nevertheless that the principal active species in oxidation by Fenton's reagent is the radical HO·. This is confirmed by the distribution of isomeric phenolic products, by the reactivity sequence of substituted benzenes towards Fenton's reagent, by the similarity with reactions with hydrogen peroxide exposed to ultraviolet radiation, and by the direct recording of the e.s.r. spectra in systems analogous to Fenton's reagent. However, recent e.s.r. studies of such systems as $Ti^{3+} + H_2O_2$ under flow conditions have shown that the e.s.r. signals originate, not from free HO· or $HO_2^·$ radicals but from their complexes with compounds of quadrivalent titanium [45]. It is probable that complexes of this type may also be hydroxylating species, acting as electrophilic agents.

III. MECHANISM OF RADIOLYTIC HYDROXYLATION

Many studies have been made of the hydroxylation of aromatic compounds under the influence of various kinds of radiation—the photochemical oxidation of benzene in aqueous solution on exposure to a mercury lamp [49,50], the oxidation of phenols under the same conditions [51–54], the photolysis of benzene in the gas phase on ultraviolet irradiation [55–59], and the oxidation of benzene and phenol in aqueous solution subject to ultrasonic vibrations [60]—but most of the investigations have used more penetrating, harder radiations—the oxidation of benzene to phenol by the action of neutrons and α-particles [61] and in aqueous solution by the action of X-rays [62–65]. The radiolysis of aromatic compounds in aqueous solution has been effected in many cases by means of cobalt-60 γ-rays [60–101]: studies have been made of the oxidation of benzene [66–92], toluene [93], naphthalene [95], chlorobenzene [97], nitrobenzene [101], anisole [100], *p*-nitrophenol [98] and benzoic acid [99].

In aqueous solution at room temperature, in the absence of oxygen and metal ions, the oxidation of aromatic compounds is effected by products of the radiolysis of water—H_2O_2, HO·, and $HO_2^·$—independently of the type of radiation employed [62,63,68]. The yields of phenols are low, 2.64–2.94 mM kr^{-1}. [67,68] In the presence of oxygen, however, the yield of phenol from benzene increases to G = 2 mol./100 eV. [68] It was first established in 1955 [49,68] that the addition of iron ions (Fe^{2+} or Fe^{3+}) to the aqueous solution increases the yield of phenol, which under certain conditions (oxygen pressure of 10 atm) may reach 6 mol./100 eV. [68] Raising the temperature from 20° to 220°C with the addition of iron ions enables phenol to be obtained from benzene in a yield of 0.035 M with a ratio of water to benzene of 32 : 1. [68] Resins containing both phenolic derivatives and polyphenylenes are formed together with the phenol. After the termination of exposure the reaction develops autocatalytically, and the authors assume that at high temperatures the oxidation of benzene is a branched chain process [68].

Exposure of a solution of benzene to X-rays in the absence of oxygen yields phenol and biphenyl, but in the presence of oxygen hydrogen peroxide and dialdehydes are also obtained [63,64]. Phenol and muconaldehyde are formed in parallel and in equal quantities [64]: G_{ph} = 1.8 and G_{diald} = 1.5.

Before considering the mechanism of the hydroxylation of aromatic compounds in the radiolysis of aqueous solutions, we must discuss the mechanism of the radiolysis of such systems as H_2O–O_2 and H_2O–O_2–Fe^{2+}–Fe^{3+}, since the facts given above make it clear that oxygen and iron ions play a very important part in the oxidation of aromatic compounds in radiolytic systems.

Analysis of the steady states arising in the radiolysis of water and their dependence on various input parameters has shown that the experimental results can be described correctly on the hypothesis that an excited species—an

exciton (ext)—takes part in the radiation-chemical process [102]. In contrast to earlier schemes [103], therefore, the mechanism of the radiolysis of the H_2O–O_2 system involves the reactions [102]

$$H_2O \rightsquigarrow H_2,\ H_2O_2,\ ext,\ H \quad (1)$$
$$ext + O_2 \rightarrow H_2O_3 \quad (2)$$
$$ext + H_2O_2 \rightarrow H_2O + 2HO^{\cdot} \quad (3)$$
$$ext \rightarrow H_2O \quad (4)$$
$$H_2O_3 + H_2O_2 \rightarrow H_2O + O_2 + H_2O_2 \quad (5)$$
$$HO^{\cdot} + H_2O_2 \rightarrow H_2O + HO_2^{\cdot} \quad (6)$$
$$HO^{\cdot} + H_2 \rightarrow H_2O + H \quad (7)$$
$$2HO_2^{\cdot} \rightarrow H_2O_2 + O_2 \quad (8)$$
$$H + O_2 \rightarrow HO_2^{\cdot} \quad (9)$$
$$HO_2^{\cdot} \rightleftarrows H^+ + O_2^- \quad (10)$$
$$O_2^- + H_2O_2 \rightarrow O_2 + HO^{\cdot} + HO^- \quad (11)$$

The above mechanism provides a good quantitative description of the radiolysis of solutions of oxygen at pH 0–6.5. The mechanism of the process at higher pH-values probably differs significantly, owing to the conversion of hydrogen atoms and excitons in alkaline medium into solvated electrons:

$$H + OH^- \rightarrow e_{aq}^- + H_2O \quad (12)$$
$$ext + HO^- \rightarrow e_{aq}^- + HO^{\cdot} \quad (13)$$

A solvated electron is extremely effective in breaking down hydrogen peroxide with formation of the radical-ion O_2^- by the reaction

$$e_{aq}^- + O_2 \rightarrow O_2^- \quad (14)$$

In solutions of Fe^{2+} and Fe^{3+} in sulphuric and perchloric acids saturated with hydrogen and oxygen under pressure the radiation efficiencies of oxidation are extremely high, reaching 100 mol./100 eV under optimum conditions [104,105]. This is evidently due to the chain character of oxidation. The radiolysis of such solutions involves the reactions [102]

$$H_2O \overset{\gamma}{\rightsquigarrow} H,\ \dot{O}H,\ H_2O_2,\ H_2 \quad (0)$$
$$HO^{\cdot} + H_2 \rightarrow H_2O + H \quad (7)$$
$$Fe^{2+} + HO^{\cdot} \rightarrow Fe^{3+} + HO^- \quad (15)$$
$$H + O_2 \rightarrow HO_2^{\cdot} \quad (9)$$
$$Fe^{2+} + HO_2^{\cdot} + H^+ \rightarrow Fe^{3+} + H_2O_2 \quad (16)$$
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + HO^{\cdot} \quad (17)$$
$$Fe^{3+} + H \rightarrow Fe^{2+} + H^+ \quad (18)$$
$$HO_2^{\cdot} \rightleftarrows H^+ + O_2^- \quad (10)$$
$$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2 \quad (19)$$

The cycle formed by reactions (7), (9), (16), and (17) regenerates a certain quantity of HO· radicals, which lays the foundation for development of a chain process. Chain termination takes place by reactions (15), (18), and (19). The conditions for chain propagation are determined by the relation between the reactions involving the growth and the termination of chains. Under certain conditions reaction (16) should be replaced by reaction (8).

Great progress has been made during recent years in the study of radiation processes in aqueous solutions, this being due in considerable measure to the successful application of pulse radiolysis, which permits determination of the absolute rate constants of many reactions involving intermediate products of radiolysis and their characterisation from the absorption spectra recorded during radiolysis [106–112].

When discussing the mechanism of the radiation hydroxylation of aromatic compounds we have repeatedly required a knowledge of the rate constants of the elementary reactions in the radiolysis of aqueous solutions. Rate constants for several primary reactions are therefore listed in Table 6. Thus the radiolysis of water and aqueous solutions involves formation of the radicals HO· and $HO_2^{\cdot}$, which in principle can be hydroxylating agents in the water–aromatic compound system. In the first stage of hydroxylation, as in the action of Fenton's reagent, the HO· radical "adheres" to the benzene ring [29,34,64].

Table 6. Rate constants of elementary reactions in the radiolysis of aqueous solutions (20–25 °C).

Reaction	Rate constant, $M^{-1}\,s^{-1}$	Ref.
$H + O_2$	$(0.53 \div 2.6)\cdot 10^{10}$	113
$H + Fe^{3+}$	$9.0\cdot 10^7$	114
$H + e_{aq}^-$	$2.5\cdot 10^{10}$	115
$HO^{\cdot} + Fe^{2+}$	$2.6\cdot 10^8$	118
$HO_2^{\cdot} + Fe^{3+}$ (0.5 M H_2SO_4)	$7.3\cdot 10^5$	108
$HO_2^{\cdot} + Cu^{2+}$ (pH 2,3)	$1.5\cdot 10^7$	109
$HO_2^{\cdot} + HO_2^{\cdot}$ (pH $\leqslant 3$)	$(1.9 \div 2.7)\cdot 10^8$	111, 116
$O_2^- + O_2^-$ (pH $\geqslant 5$)	$(1.35 \div 1.70)\cdot 10^7$	111
$e_{aq}^- + O_2$	$1.9\cdot 10^{10}$	117
$e_{aq}^- + N_2O$	$9.0\cdot 10^9$	117
$HO^{\cdot} + H_2O_2$	$4.5\cdot 10^7$	118

This reaction has been investigated with many benzene derivatives by pulse radiolysis with recording of the absorption spectra of the cyclohexadienyl radicals [29,34,117–129]. Table 7 gives the spectra of these radicals and the rate constants for reaction between the HO· radical and the aromatic compounds.

Table 7. Rate constants of reaction between HO· and C_6H_5X, and absorption spectra of cyclohexadienyl radicals $C_6H_5X(^{\cdot}OH)$.

Compound	λ_{max}, nm ($HOC_6H_5X^{\cdot}$)	$10^{-9}k_{OH + C_6H_5X}$ at 25 °C, $M^{-1}\,s^{-1}$	Ref.
C_6H_6	313	4.3 ± 0.9	34
		3.3	120, 126
C_6D_6	—	4.7 ± 0.9	34
$C_6H_5NO_2$		1.7	101
		2.0	120
		4.7 ± 0.5	126
C_6H_5COOH	350	2.1	120, 128
	347	4.3 ± 0.8	124
$C_6H_5COO^-$	328		129
C_6H_5Cl	324	4.2	34, 120
C_6H_5Br	326		34
$C_6H_5CH_3$	317	3.0	34, 120
$C_6H_5OCH_3$	—	3.6	120
$C_6H_5NH_2$	—	5.3	120
HOC_6H_4OH	320	12.0	122
C_6H_5OH	320	5.1	34, 120
» pH 7.4	—	14.03	121
» pH 6—7		10.6 ± 0.3	121
» pH 9	330	5.1 ± 0.3	35, 121

The reactivities of substituted benzenes towards HO· have been compared under the same conditions as for the reaction of this radical with *p*-nitrosodimethylaniline. The

rate constants $k_{(HO^{\cdot} + C_6H_5X)}$ have been calculated, as well as the ratios

$$\frac{k_{(HO+C_6H_5X)}}{k_{(HO+C_6H_6)}} = \gamma^{120}.$$

A linear dependence of $\lg\gamma$ on σ_p and σ_m has been obtained for deactivating substituents X and a similar dependence of $\lg\gamma$ on σ_p for other substituents X. The coefficient ρ in the Hammett equation has been calculated as 0.41. The correlation of $\lg\gamma$ with the Hammett σ-parameter and the negative value of ρ confirm the electrophilic character of the radical HO$^{\cdot}$. However, a significant defect of this work [120] is the lack of an analysis of the isomeric phenols, so that σ is compared with the total phenol concentrations, not with the quantities of *para*- and *meta*-isomers formed.

In the absence of oxygen and iron ions the cyclohexadienyl radicals are able to react with the hydrocarbon C_6H_5X and with themselves. In the presence of oxygen and iron ions the radicals are consumed also by reactions with these additions. In acid media the unimolecular conversion of HOC_6H_5X into phenoxyl is also possible [121,122]:

$$HOC_6H_5X \xrightarrow{H^+} C_6H_5O^{\cdot} + H_2X^+$$

The mechanisms of the disproportionation of cyclohexadienyl radicals of type (I), their reaction with hydrocarbons, and also the unimolecular transformation of the radicals in acid media have been discussed in sufficient detail in Section II, and particular features of radiolytic systems have no significant influence on the mechanisms of the above processes.

The pulse radiolysis method has enabled the rates of disproportionation of radicals (I) and of their reaction with oxygen to be measured under identical conditions, and the effect of substituents X on these rates to be established [125]. The values of these rate constants in Table 8 have been used to correlate the quantities

$$\alpha = \frac{k_{(HO^{\cdot}C_6H_5X+O_2)}}{k_{(HO^{\cdot}C_6H_5+O_2)}} \quad \beta = \frac{k_{(2HO^{\cdot}C_6H_5X)}}{k_{(2HO^{\cdot}C_6H_6)}}$$

with the Hammett σ-parameters for the *meta*- and *para*-positions. Good linearity was obtained, and the coefficients in the Hammett equation were calculated as $\rho_\alpha = -1.0$ and $\rho_\beta = -0.75$. [125] Thus electron-donor substituents X tend to increase the rate of reaction of the radicals with molecular oxygen and with one another, whereas electron-acceptor substituents retard these reactions.

In the absence of oxygen a radical of type (I) may be oxidised to phenol by radicals (HO$^{\cdot}$, $HO_2^{\cdot}$) or by Fe^{3+} (Cu^{2+}) ions:

$$I + HO^{\cdot} \rightarrow XC_6H_4OH + H_2O \quad (20)$$

$$I + Fe^{+3} \rightarrow XC_6H_4OH + Fe^{2+} + H^+ \quad (21)$$

The rate constant of reaction (21) has been estimated as $k_{Fe^{3+} + HO^{\cdot}C_6H_6} = 7000\ M^{-1}\ s^{-1}$ at room temperature on the basis of the kinetic scheme set up for the oxidation of benzene in aqueous solutions in the presence of Fe^{2+} ions (0.001 M) on exposure to γ-rays. [76] The occurrence of reaction (21) is confirmed by a study of the effect of the concentration of potassium hexacyanoferrate(III) on the yield of hydroxybenzoic acids in the radiation hydroxylation of benzoic acid in aqueous solution in the presence of nitrous oxide [99]

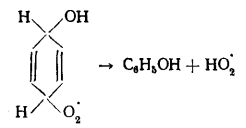
$$(HOC_6H_5COOH)^{\cdot} + Fe(CN)_6^{3-} \rightarrow HOC_6H_4COOH + Fe(CN)_6^{4-} + H^+.$$

The rate constant (7000) of reaction (21) is much smaller than that of the reaction between the radical (I) and molecular oxygen (Table 8): i.e. addition of oxygen to the radical (I) is more rapid than the transfer of an electron by reaction (21).

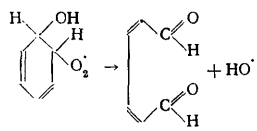
Table 8. Effect of substituent X on rate of reaction of cyclohexadienyl radicals $HO^{\cdot}C_6H_5X$ (I) with oxygen and with each other.

X	$10^{-6}k_{I+O_2}$, $M^{-1}s^{-1}$	$10^{-8}k_{I+I}$, $M^{-1}s^{-1}$	E_{I+I}, kcal mole^{-1}
NO_2	2.5	5.0	6.0
CN	2.9	3.9	4.7
COC_6H_5	3.7	3.66	4.7
$COCH_3$	3.82	4.20	4.3
SO_2NH_2	4.2	3.68	5.1
COOH	5.25	3.95	4.3
I	7.0	4.0	5.0
Cl	7.95	4.86	3.5
Br	9.6	4.2	3.9
OH	4.9	11.0	6.7
OCH_3	16.4	5.73	5.8
NH_2	25.4	16.0	3.9
H	400	4.55	3.5
CH_3	390	3.85	3.0
C_2H_5	555	4.2	3.6

A radical of type (II) ($HO.C_6H_5.XO_2^{\cdot}$) differs from cyclohexadienyl radicals (I) in absorbing at shorter wavelengths [34]. Such radicals are able to decompose by the unimolecular reactions (22) and (23) to form phenol and dialdehydes respectively [78,79]:

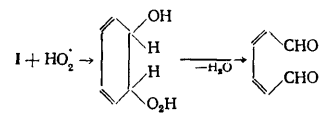


$$\rightarrow C_6H_5OH + HO_2^{\cdot} \quad (22)$$



(23)

Reaction (23) was first proposed by Kartasheva and Pikaev [78]. These workers have since shown that, in the radiolysis of benzene in aqueous solution containing iron ions and oxygen, the ratio $k_{22}/k_{23} = 1.4$. Muconaldehyde can be formed not only by reaction (23) but also by the reaction



(24)

Kartasheva and Pikaev [80] consider that, in the oxidation of benzene, the radical (II) may be involved in the reaction

$$O_2^{\cdot}C_6H_6OH + Fe^{2+} + H^+ \rightarrow HOOC_6H_6OH + Fe^{3+} \quad (25)$$

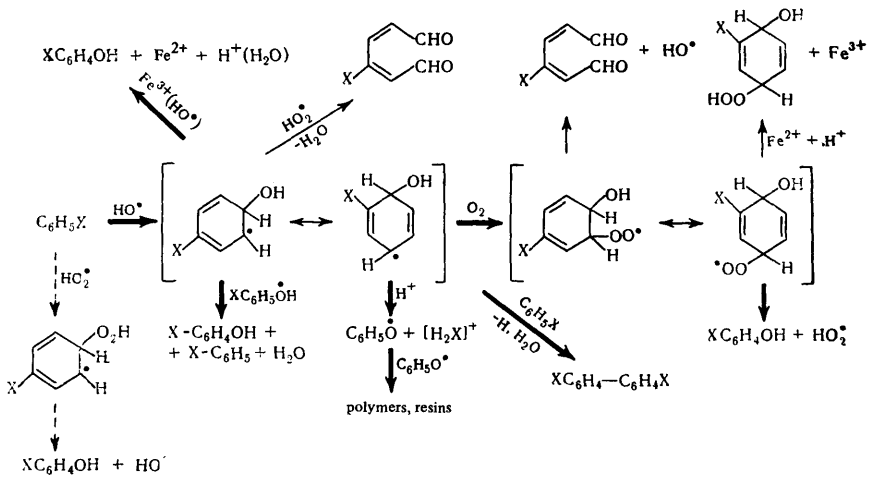
They give the ratios $k_{25}/k_{22} = 6300\ M^{-1}$ and also $k_{25}/k_{23} = 9000\ M^{-1}$: i.e. with 0.001 M Fe^{2+} the rate of reaction (25) will exceed those of reactions (22) and (23) by factors of 6 and 9 respectively. The hydroperoxide formed by reaction (25) may react in two ways:

$$HOOC_6H_6OH \rightarrow HO^{\cdot} + \dot{O}C_6H_6OH \quad (26)$$

$$HOOC_6H_6OH + Fe^{2+} \rightarrow Fe^{3+} + HO^- + \dot{O}C_6H_6OH \quad (27)$$

According to these workers [80] $k_{27}/k_{26} = 5900\ M^{-1}$.

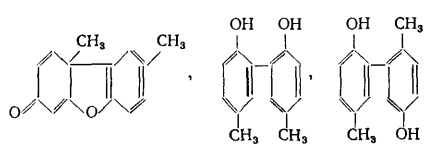
Scheme 1



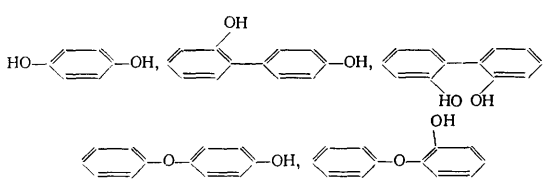
Every possible reaction in the radiation-chemical hydroxylation of benzene and its derivatives is shown in Scheme 1. Reliably demonstrated reactions of molecules and radicals are indicated by thick arrows; reactions which have been introduced into kinetic schemes, and are characterised by the constants of relatively reliably demonstrated processes, are denoted by ordinary arrows; and finally hypothetical reactions [75] are indicated by broken arrows.

Let us consider in greater detail the formation and reactions of phenoxy-radicals. As already noted [35], in acid media the adduct of the radical HO· with phenol is converted to phenoxyl with the elimination of water. The radicals $HOC_6H_4O^{\cdot}$ and $^{-}OC_6H_4O^{\cdot}$ (λ_{max} = 415 and 425 nm respectively) are recorded in the pulse radiolysis of quinol; they are formed from the adduct of HO· and quinol with a rate constant of $(4.6-8.8) \times 10^4$ s^{-1}. [122]

Phenoxy-radicals interact with one another. At 20°C the radicals $HOC_6H_4O^{\cdot}$ react with a rate constant of 1.09×10^9 M^{-1} s^{-1} to form quinone and quinol (disproportionation); [122] and tolyloxy-radicals $CH_3C_6H_4O^{\cdot}$ dimerise with a rate constant of 6.5×10^9 M^{-1} s^{-1}. [119] The recombination of tolyloxy-radicals has been proved [52] to yield dimers of the three types



The compounds



have been detected among the products of the photolysis of phenol [54].

It is very important to examine the effect of the reaction conditions—presence or absence of oxygen, addition of nitrous oxide, etc.—on the distribution of phenolic isomers in the radiation-chemical oxidation of substituted benzenes. Table 9 gives the distribution of isomeric phenols formed by the γ-irradiation of dilute aqueous solutions of benzoic acid, nitrobenzene, and anisole, and includes for comparison the distribution of isomers resulting from the hydroxylation of these compounds by Fenton's reagent.

Table 9. Distribution of isomeric phenols on γ-irradiation of dilute aqueous solutions of substituted benzenes at room temperature.

Compound	Conditions	Isomers			Ref.
		ortho	*meta*	*para*	
C_6H_5COOH	N_2O, $K_3Fe(CN)_6$	29	12	59	99
$C_6H_5NO_2$	air	50	31	19	101
$C_6H_5NO_2$	0.02 M N_2O	40	21	39	101
$C_6H_5NO_2$	0.014 M N_2O + 0.00023 M O_2, Fenton's reagent	51	31	18	110
$C_6H_5NO_2$	0.00023 M O_2	24	30	46	22
$C_6H_5OCH_3$	0.02 M N_2O	37	0	63	100
$C_6H_5OCH_3$	Fenton's reagent	80	0	20	100
$C_6H_5OCH_3$		81	1	18	24

Table 9 shows that the distribution of isomers varies with the conditions of hydroxylation: the distribution obtained on exposure in an atmosphere of nitrous oxide coincides with that obtained with Fenton's reagent, since the same species—the HO· radical—is the hydroxylating agent in this case. In the presence of nitrous oxide the reaction

$$e_{aq}^{-} + N_2O \rightarrow HO^{-} + N_2 + HO^{\cdot}$$

takes place with $k = 9 \times 10^9$ M^{-1} s^{-1} (Table 6). In an atmosphere of oxygen or air the reaction

$$e_{aq}^{-} + O_2 \rightarrow O_2^{-} \xrightarrow{H^+} HO_2^{\cdot}$$

occurs with $k = 1.9 \times 10^{10}$ M^{-1} s^{-1} (Table 6), and in my view the main hydroxylating species is now the $HO_2^{\cdot}$ radical, which produces a change in the distribution of isomers. Both radicals—HO· and $HO_2^{\cdot}$—operate in the presence of nitrous oxide and oxygen, since the reactions of the solvated electron with oxygen and with nitrous oxide are competitive. The hydroxylation of naphthalene at 55 to 120°C (on γ-irradiation) yields a little 2-naphthol (7–10%) at low temperatures, but with rise in temperature the

quantity increases to 75% (at 170°C), which is evidently due to a change in the relative proportions of HO· and $HO_2^·$ radicals with rise in temperature [95]. Thus the distribution of phenolic isomers in radiation hydroxylation indicates that two radicals—HO· and $HO_2^·$—may be active species.

The radiation oxidation of benzene and toluene in the presence of iron and copper ions at 100–200°C is especially interesting [84–94]. Iron(II) sulphate ensures a high yield of phenol (2.5% on the initial benzene) both with and without irradiation. On catalysis by the Fe^{3+} ion phenol is formed in considerable quantities only above 180°C. When copper(II) sulphate is used the yield of phenol is equally high (up to 3.7% on the initial benzene) with and without irradiation. Iron and copper chlorides are less active catalysts than are the sulphates [86,87]. The quantity of phenol formed is greatly diminished by addition of the anions Cl^- and SO_4^{2-}, but increasing the concentration of copper(II) sulphate from 0.0001 M to 0.01 M at 198°C increases the yield of phenol. Although phenol is the main reaction product, small quantities ($\sim 10^{-4}$ M) of such compounds as benzene diols, maleic, acetic, and formic acids, acetone, and acetaldehyde are also formed [90]. The oxidation of toluene under similar conditions (1 ml of toluene in 15 ml of an aqueous solution of an iron or a copper salt under 30 atm of oxygen at 100 to 200°C) yields $(2.5–4.0) \times 10^{-4}$ M benzaldehyde, $(0.2–2.1) \times 10^{-5}$ M benzyl alcohol, $\sim 0.5 \times 10^{-5}$ M benzoic acid, and up to 0.4×10^{-5} M cresols [93].

Study of oxygen transfer by means of ^{18}O showed that oxygen is incorporated into phenol both from water and from the gas phase [91]. Isotopic analysis of the phenol formed from an equimolecular mixture of benzene and hexadeuterobenzene gave $k_H/k_D = 1.2$. The small isotope effect suggests that detachment of a hydrogen atom from benzene occurs to a slight extent in the limiting step. On the basis of experimental results and published data Japanese investigators have suggested a mechanism for the oxidation of benzene and toluene, transferring without reservation to higher temperatures (180–200°C) a scheme adopted for radiation oxidation at room temperature. At high temperatures the reaction

$$HO·C_6H_5X + O_2 \rightarrow HOC_6H_5XO_2^· \rightarrow HOC_6H_4X + HO_2^·$$

is most probably able to occur in a single step without formation of a peroxy-radical of type (II). Iron and copper ions act at high temperatures as initiators of oxidation, since they generate radicals by the reactions

$$Fe^{2+} + O_2 \rightarrow Fe^{3+} + O_2^- \xrightarrow{H^+} HO_2^· \quad (28)$$

$$Fe^{3+} + H_2O \rightarrow Fe^{2+} + H^+ + HO· \quad (29)$$

The possible occurrence of reaction (29) has been shown by several workers [130,131]. Japanese authors attribute to iron ions also the role of stabilisers of peroxy-radicals (II), but even the existence of these radicals at high temperatures is doubtful.

The inhibiting action of chloride ions is explained by the reaction

$$Cl^- + HO· \rightarrow Cl· + HO^- \quad (30)$$

the rate constant of which is 1.8×10^8 M^{-1} s^{-1} at pH 2 and 25°C, increasing in 0.8 *N* sulphuric acid by a factor of 8. [118] The rate constant for the reaction between the radical HO· and benzene is 4.3×10^9 M^{-1} s^{-1}, and if the temperature variation of this constant is assumed to be the same as that of k_{30}, the reactions of HO· with benzene and with the chloride ion may compete with one another at high temperatures.

Japanese authors consider the oxidation of benzene and toluene to be a branched chain process. On the basis of published results [132] they suggest the scheme of branching

$$PhO· + PhH \rightarrow PhOH + Ph· \quad (31)$$
$$Ph· + O_2 \rightarrow PhO_2^·$$
$$PhO_2^· + PhH \rightarrow PhOOH + Ph·$$
$$PhO_2H + Fe^{3+} \rightarrow PhO_2^· + Fe^{2+} + H^+$$
$$PhO_2H + Fe^{2+} \rightarrow PhO· + Fe^{3+} + HO^-$$
$$PhO_2H \rightarrow PhO· + HO·$$

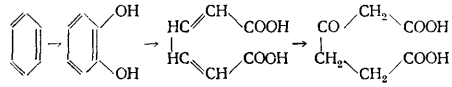
There are several grave objections to this scheme. Reaction (31) cannot occur at an appreciable rate, since the $C_6H_5O·$ radical is relatively inactive, while the carbon–hydrogen bond in benzene is stable. This reaction is endothermic (17 kcal $mole^{-1}$) and is unable to compete successfully with such reactions of the phenoxy-radical as oxidation or addition to benzene. The hydroperoxide C_6H_5OOH does not exist as a molecular compound (especially at high temperatures), and therefore all reactions involving it are irrelevant. The mechanism of the acceleration of the oxidation of benzene in the presence of iron and copper ions will be considered in detail in Section IV dealing with the catalytic oxidation of aromatic compounds.

With regard to the part played by iron (copper) ions in radiation hydroxylation in aqueous solution, the addition of iron ions at room temperature ensures that a certain quantity of the hydroxylating agent (HO· radicals) is regenerated (reactions 16 and 17). The oxidised form of the ion (Fe^{3+} or Cu^{2+}) oxidises radicals of type (I) to phenol. At high temperatures the metal ions also initiate oxidation, since they generate HO· and $HO_2^·$ radicals by reaction with oxygen. At high concentrations of Fe^{2+} ions inhibition of the oxidation of benzene may become possible, since $k_{Fe^{2+} + HO·} = 2.6 \times 10^8$ (Table 6), while other results indicate that $k_{HO· + C_6H_6}/k_{HO· + Fe^{2+}} = 3.2$ at 25°C. [133,134]

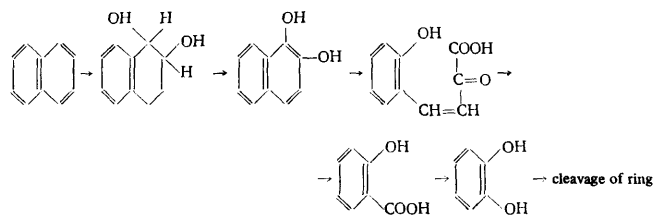
IV. CATALYTIC HYDROXYLATION

A. Enzymatic Hydroxylation of Aromatic Compounds

As already noted, micro-organisms are able to assimilate aromatic compounds, converting them into *o*- and *p*-benzenediols and then cleaving the ring to give aliphatic acids [3,135]. The oxidation of benzene yields catechol, and phenol and *cis-cis*-muconic acid accumulate [136]. Benzene oxidase has been extracted from cells grown on benzene, which it transforms according to the scheme [137]



Cultures of five different micro-organisms break down naphthalene as follows [138]:



A detailed account of the mechanism of the microbiological oxidation of aromatic and heterocyclic compounds has been published [139], but the first, most decisive stage of oxidation—hydroxylation of the aromatic ring—is not entirely understood. This stage usually involves active catalysis by enzymes, which transfer oxygen to the reaction product. Table 10 gives some examples of the hydroxylation of aromatic compounds by means of enzymes.

Table 10.

Substrate	Enzyme	Reaction product	Ref.
Salicylic acid	peroxidase + dihydroxyfumaric acid	2,4-dihydroxybenzoic acid	146
Phenylalanine	tyrosinase	tyrosine	146
3,4-Xylenol	tyrosinase	4,5-dimethylcatechol	142

In the above cases oxygen is incorporated into the hydroxy-group from molecular oxygen—not from water or hydrogen peroxide [140,142]—and the new hydroxy-group enters the *ortho*-position relative to orienting substituents of the first kind in the benzene ring. The oxygen molecule is a weak oxidant, since oxidation must involve rupture of the strong bond between the oxygen atoms, which are bound to one another by one two-electron bond and two three-electron bonds [sic]. The addition of two electrons to the oxygen molecule, as occurs on reduction to O_2^{2-} or H_2O_2, weakens the bond between the oxygen atoms. This function of reductants for the oxygen molecule is performed by metal ions, which are inevitably present in redox enzymes (Table 11). [143]

Table 11.

Metal-containing enzyme	No. of metal ions per enzyme mol.
Peroxidase	1 Fe
Tyrosinase	3-4 Cu
Catalase	4 Fe
Cytochrome oxidase	2 Fe + 2 Cu

The activation of molecular oxygen is not the only function of metal ions [144]: they may also stabilise structures, initiate chain processes, form catalytic units having qualitatively new catalytic functions, etc.

We shall consider below mechanisms of the activation of molecular oxygen and the schemes of the hydroxylation of aromatic systems which are known for peroxidases and tyrosinase [141]. Iron(II) and copper(I) ions allow the O–O bond to be ruptured by a mechanism involving reduction of the first pair of electrons. The ferrous ion combines with oxygen to form a perferryl ion FeO_2^{2+}, in which the bond between the oxygen atoms is less stable than in molecular oxygen, since electrons pass from iron to the oxygen.

Evidence of the existence of an intermediate perferryl ion has been obtained in work [144–148] on the kinetics of the oxidation of Fe^{2+} by oxygen, which is represented by the equations

$$Fe^{2+} + O_2 \rightleftarrows FeO_2^{2+}$$

$$FeO_2^{2+} + Fe^{2+} + H_2O \rightarrow Fe^{3+}OOH + Fe^{2+}OH$$

The bond in the perferryl ion may be broken with the formation of a ferryl ion FeO^{2+}. Bray and Gorin [149], from kinetic data for the reaction

$$2Fe^{3+} + H_2O_2 \rightleftarrows Fe^{2+} + FeO^{2+} + H_2O$$

suggested the existence of this ion in inorganic reactions.

There is evidence that FeO^{2+} or a similar ion of the same degree of oxidation may be present in biological systems [150]. The $FeOOH^{2+}$ ion, like the $FeOH^{2+}$ ion, is well known in inorganic chemistry from its charge-transfer spectra in solutions containing H_2O_2 and Fe^{3+}. Thus enzymes may contain iron ions of different degrees of oxidation:

$FeOOH^{2+}$ or $FeOH^{2+}$ (iron 5) – complex I,
FeO^{2+} (iron 4) – complex II,
FeO_2^{2+} – complex III,

Chance [151] showed that catalase reacts with hydrogen peroxide to form the complex (I), which reacts further with hydrogen peroxide to form molecular oxygen and water. One-electron reduction of the complex (I) yields the ferryl ion (complex II):

$$FeOOH^{2+} + H^+ + e \rightarrow FeO^{2+} + H_2O.$$

In the case of peroxidases complex (I) acts as a one-electron oxidant, the most probable mechanism being

$$Fe^{3+} + H_2O_2 \rightarrow FeOOH^{2+} + H^+$$

$$FeOOH^{2+} \xrightarrow[-H_2O]{H} FeO^{2+}$$

$$FeO^{2+} + PhH \rightarrow PhOFe^+ + H^+$$

$$PhOFe^+ + H^+ \rightarrow PhOH + Fe^{2+}$$

The hydroxylating species is the ferryl ion (complex II).

Copper is able to form complexes analogous to complexes (I)–(III) of iron-containing enzymes. It is present in tyrosinase as the univalent ion [152]; direct reaction of molecular oxygen yields the percupryl ion CuO_2^+, the analogue of complex (III) in iron-containing enzymes. The percupryl ion is then reduced to the complex (II) (the cupryl ion), which hydroxylates the benzene ring by transferring one of the atoms of the oxygen molecule to the substrate. Such a process is typical of enzymes which have been termed "oxidases of mixed function". [153] The mechanism of the action of tyrosinase is represented by the scheme [141]

$$Cu^+ + O_2 \rightleftarrows CuO_2^+ \quad \text{or} \quad Cu^+O_2Cu^+$$

$$CuO_2^+ + 2e + 2H^+ \rightarrow CuO^+ + H_2O$$

$$CuO^+ + PhH \rightarrow PhOCu^+ + H^+$$

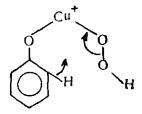
$$PhOCu^+ + H^+ \rightarrow PhOH + Cu^+$$

Evidence of the existence of the cupryl ion in tyrosinase has been obtained from the denaturation of the enzyme by acid and from kinetic investigations [154].

B. Models of Hydroxylase Biocatalysts and the Mechanism of Their Action

The detailed mechanism of the action of hydroxylases can be elucidated by means of models. Konecny, Havinga, and others [155–159] studied models of complex (I). Hydrogen

peroxide and the cupric ion hydroxylate benzene and sodium benzoate to phenol and salicylic acid respectively [155]. Studies have been made [156–159] of the copper-catalysed hydroxylation of phenols and aniline in the presence of amines. This model resembles tyrosinase: both the model and tyrosinase contain copper and hydroxylate in the *ortho*-position. A mechanism was proposed [156] in which the oxidant was hydrogen peroxide formed by the successive oxidation of certain reaction products. The Cu^{2+} ion, phenol, and the peroxide form the complex (I), which directs hydroxylation to the *ortho*-position. The Cu^{2+} ion is acting here as an acid catalyst, polarising the O–O bond so that it is cleaved with the formation of ions, the pair of electrons remaining on the oxygen near the copper atom. The action of the copper ion in this reaction resembles that of the two protons in acid-catalysed oxidations by hydrogen peroxide [160]. Complex (I) containing copper



like the iron-containing complex (I), may take part in free-radical reactions. It was suggested [156] that the hydroxylating agent in the copper–amine–phenol system was the OH^+ ion, formed by the breakdown of complex (I) and acting as an electrophilic agent. It will be shown below that this is incorrect.

Oxidative coupling of phenols is possible in the presence of amine–copper catalysts, e.g. [161]

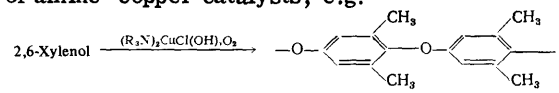


Table 12 gives the results of a study of models of peroxidases which hydroxylate aromatic compounds [162–165].

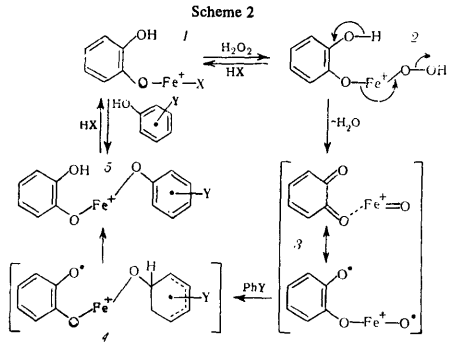
Table 12. Hydroxylation by systems (Fe^{3+}–H_2O_2–benzenediol) simulating peroxidases.

System	Substrate	Distribution of phenols			Ref.
		ortho	*meta*	*para*	
$Fe^{3+} - H_2O_2$ — Catechol	anisole	64	3	33	162
Catechol	nitrobenzene	48	26	26	164
Catechol	chlorobenzene	45	15	40	164
$Fe^{3+} - H_2O_2$ — Quinol	anisole	65	5	35	162

From a comparison of the resulting distribution of isomeric phenols with that obtained by the action of Fenton's reagent (Table 4) and a detailed kinetic investigation of hydroxylation involving the Fe^{3+}–H_2O_2–catechol system [163,164] it can be confidently stated that neither the radical HO· nor the radical $HO_2^·$ is the hydroxylating species in this case: hydroxylation occurs by the mechanism of Scheme 2. [164]

In this mechanism the overall rate of the process is limited by the formation of complexes *2* and *3*. The latter complex is a hybrid of all possible states of the metal, which explains its stability. It reacts as a radical, giving a distribution of isomeric phenols which is typical of radical attack on an aromatic ring. The ligands used to make complex *3* capable of hydroxylation were catechol, quinol, 3,4-dihydroxybenzoic acid, 3-methoxycatechol, etc. Phenol, ascorbic acid, and benzoquinone exhibit less catalytic activity or none at all, owing to the instability of the complex *3* when the above ligands are used. The interaction of form *3* with organic solvents involving removal of a hydrogen atom explains the inhibiting effect of the latter on hydroxylation.

Scheme 2



The relation between the above system and the action of such enzymes as peroxidase and catalase is that, according to George [166,167], the oxygen atom is bound to iron in the same way in these enzymes as in form *3*. In peroxidase and catalase this form is evidently stabilised by porphyrins having redox characteristics closely similar to those of catechol.

Table 13. Hydroxylation by systems (containing molecular oxygen) simulating oxidases.

System containing O_2	Substrate	Distribution of phenols, %			Ref.
		ortho	*meta*	*para*	
Fe^{2+} + EDTA + ascorbic acid	anisole	43	18	39	17
Fe^{2+} + 2,4,5-triamino-6-hydroxypyrimidine	anisole	49	13	38	169
$TiCl_3$	acetanilide	35	32	33	171
Sn^{2+}/HPO_4^{2-}	acetanilide	36	35	29	33
Fe^{2+} + 2-mercaptobenzoic acid	acetanilide	57	3	40	175
Fe^{2+} + 2-mercaptobenzoic acid	toluene	61	13	26	175
Microsome + NADP	toluene	59	13	28	175

Several enzymes (tyrosinase, etc.) act as "mixed-function oxidases", [153] which are characterised by the transfer of an oxygen atom from molecular oxygen to a substrate RH in conformity with the equation [168]

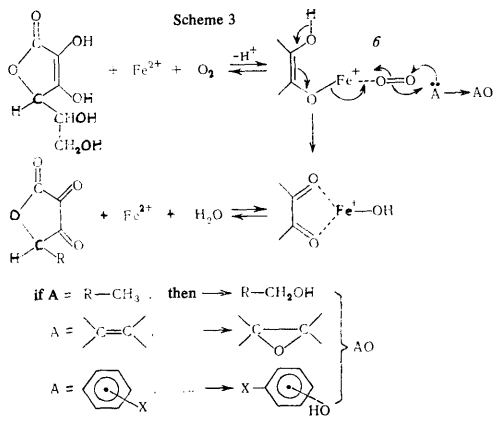
$$RH + DH_2 + O_2 \rightarrow ROH + D + H_2O$$

where DH_2 is a hydrogen donor. Such oxidases hydroxylate aromatic compounds to phenols, oxidise aliphatic compounds to alcohols, and epoxidise ethylenic compounds, which immediately excludes the radical HO· as a possible agent in their action. Several systems have been investigated which might be regarded as models of mixed-function oxidases [17,39,169–175]. These models help to answer the questions how molecular oxygen is activated,

how electrons are transferred to the oxygen molecule, and how this transfer is connected with hydroxylation of the substrate [176]. We shall first consider results (summarised in Table 13) for the hydroxylation of aromatic compounds by molecular oxygen in which such model systems are involved.

Table 13 shows that, for several substrates, the distribution of isomeric phenols differs from that for hydroxylation by Fenton's reagent (Table 4): i.e. the radical HO· is not in this case the hydroxylating species. Several papers have shown that hydrogen peroxide is not an intermediate product which might be formed and be responsible for hydroxylation [39,167,174]. Hence a special mechanism of hydroxylation is applicable to these models. The hydroxylating species in the O_2–$TiCl_3$–acetanilide system was assumed [171] to be the $HO_2^{\cdot}$ radical, which is less electrophilic than HO·, and will therefore give a distribution of isomeric phenols characteristic of nuclear attack by radicals. However, with other systems (e.g. O_2–Sn^{2+}–HPO_4^{2-}), which not only hydroxylate aromatic compounds but also oxidise aliphatic compounds, the $HO_2^{\cdot}$ radical cannot be accepted as the attacking species. Therefore several workers [39,170,174] suggest a mechanism consisting essentially in the reduction of molecular oxygen by metal ions to a so called "oxenoid" capable of transferring an oxygen atom to the substrate mostly by an electrophilic mechanism. According to Hamilton [170] the model of a mixed-function oxidase (Fe^{2+} + O_2 + ascorbic acid) acts by the mechanism of Scheme 3.

Scheme 3



According to Scheme 3 the oxidising agent is the complex *6*, where the function of the iron ion is to combine with the reducing agent and oxygen, transmitting electrons to the latter in the transition state. The iron ion enables a singlet oxygen atom to be transferred from the bound oxygen molecule to the substrate in such a way that intermediate diradicals are unnecessary. If a triplet oxygen atom were transferred, the process would be less advantageous energetically owing to the formation of a triplet reaction product, which would be less stable than a singlet product. Simultaneous transfer of the proton of ascorbic acid to the complex with molecular oxygen and transfer of electrons by means of the iron ion probably occur in complex *6*, leading to oxidation of the complex ascorbate and reduction and stabilisation of the oxygen atom not transferred to the substrate. But the other oxygen atom, having six electrons (hence analogous to carbenes CR_2 and nitrenes NR, which also have six electrons around the carbon or nitrogen and are very reactive), is incorporated into the substrate. This way a four-electron exchange is accomplished with minimum movement of nuclei.

There are in general two principal ways in which "oxene" :Ö: can act as an oxidant: (1) four-electron reduction of molecular oxygen and two-electron oxidation of the substrate take place in a single step:

$$DH_2 \cdot A \cdot O_2 \rightarrow D \cdot AO \cdot H_2O$$

(2) the same act can occur in two steps:

$$DH_2 \cdot A \cdot O_2 \rightarrow DO \cdot A \cdot H_2O$$
$$DO \cdot A \cdot H_2O \rightarrow D \cdot AO \cdot H_2O$$

In these schemes DH_2 represents the reduced form either of the enzyme or of the coenzyme, and AO the product of reaction between the substrate A and oxygen. Study of model systems shows [170] that both mechanisms are possible.

C. Mechanism of the Oxidation of Benzene to Phenol catalysed by Iron and Copper Ions in Aqueous Solution at 180–220°C

Studies of oxidation in the presence of copper and iron ions in aqueous solution have been made on the conversion of benzene into phenol at 180–220°C, [177-183] of phenol into catechol and quinol at 110°C, [184] and of ethylbenzene [185]. However, a detailed investigation of the kinetics and the mechanism of such catalysed oxidation has been made only on benzene [177-183]. Oxygen at 35–50 atm was used to oxidise benzene dissolved in water. In the absence of copper and iron ions no oxidation is observed in aqueous solution at 180–200°C, but in the presence of these ions benzene is oxidised to phenol, whose accumulation is clearly autocatalytic in character [177-187]. Phenol is an intermediate product in the reaction, which is proved by experiments in which phenol is introduced into the initial oxidising mixture. Resins and small quantities of compounds of low-molecular weight—acetone, acetaldehyde, acetic acid, etc.—are formed from phenol.

The introduction of small quantities of phenol into the initial mixture accelerates the oxidation of benzene in aqueous solution, whereas in hydrocarbon media phenol inhibits oxidation. It has been shown convincingly [180] that the phenol undergoing oxidation is responsible for the autocatalysis in the accumulation of phenol from benzene.

The valency state of the iron ions changes during the reaction: if Fe^{3+} ions are introduced into the initial aqueous solution of benzene, Fe^{2+} ions appear during the reaction; and conversely. All kinetic rules are very similar for catalysis by copper and by iron ions [177,178]: with increase in the benzene concentration the maximum reaction velocity passes through a maximum, while the maximum phenol concentration increases linearly. With increase in the catalyst concentration W_{max} passes through a maximum, while the maximum phenol concentration increases in the case of copper ions. The reaction velocity decreases with increase in the hydrogen-ion concentration. Under optimum conditions the yield of phenol is 57% based on the benzene consumed.

The mechanism of the oxidation of benzene is closely connected with that of the oxidation of phenol and the valency changes undergone by the catalytic ions. A detailed study was therefore made [181] of the mechanism of

the oxidation of phenol by oxygen catalysed by iron ions. This showed that the simultaneous occurrence of three modes of oxidation of phenol—by Fe^{3+} ions, by molecular oxygen, and by free radicals—in sulphuric acid solution at 200°C. The following mechanism was proposed for the oxidation of phenol in the presence of iron ions in aqueous solution:

$$PhOH + O_2 \rightarrow PhO^{\cdot} + HO_2^{\cdot} \quad (0')$$

$$PhOH \overset{K_0}{\rightleftarrows} PhO^- + H_3O^+$$

$$PhO^- + O_2 \rightarrow PhO^{\cdot} + O_2^- \quad (0'')$$

$$PhO^- + Fe^{3+} \rightarrow PhO^{\cdot} + Fe^{2+} \quad (1')$$

Free radicals are formed in the oxidation of Fe^{2+} ions by the reactions [145–148,186,187]

$$Fe^{2+} + O_2 \rightarrow Fe^{3+} + O_2^- \quad (2')$$

$$Fe^{2+}\,aq \overset{K_0}{\rightleftarrows} FeOH^+ + H^+$$

$$FeOH^+ + O_2 \rightarrow FeOH^{2+} + O_2^- \quad (2'')$$

$$H^+ + O_2^- \rightarrow HO_2^{\cdot}$$

$$HO_2^{\cdot} + Fe^{2+} \rightarrow HO_2^- + Fe^{3+}$$

$$HO_2^- + H^+ \rightleftarrows H_2O_2$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^{\cdot} + HO^-$$

The resulting radicals $HO^{\cdot}$ and $HO_2^{\cdot}$, which are indistinguishable kinetically and will henceforward be denoted by $r^{\cdot}$, react with Fe^{2+} and phenol:

$$Fe^{2+} + HO^{\cdot} \rightarrow Fe^{3+} + OH^- \quad (3)$$

$$PhOH + r^{\cdot} \rightarrow PhO^{\cdot} + rH \quad (4)$$

The resulting phenoxy-radicals either recombine or are oxidised to products [52,54,119,122].

Comparison of the above scheme with experiment showed that the rate of oxidation of Fe^{2+} by oxygen was

$$4\,[Fe^{2+}]\,[O_2]\,(k_{2'} + k_{2''}K_2[H^+]^{-1}),$$

and the overall rate of oxidation of phenol

$$W = (2k_0[O_2] + k_1[Fe^{3+}] + k_4[r^{\cdot}])[PhOH]_0,$$

where

$$k_0 = k_{0'} + k_{0''}K_0[H^+]^{-1}, \quad k_1 = k_{1'}[H^+]^{-1}.$$

Experimental results obtained at 200°C were used to determine the values of $k_{0'}$, $k_{0''}K_0$, $k_{2'} + k_{2''}K_2$, and $k_{1'}$, and to estimate the proportions of the three reactions in the total consumption of phenol.

Benzene when present reacts with the radicals $HO^{\cdot}$ and $HO_2^{\cdot}$ to form phenol:

$$C_6H_6 + HO^{\cdot} \xrightarrow{O_2} PhOH + HO_2^{\cdot}$$

$$C_6H_6 + HO_2^{\cdot} \rightarrow PhOH + HO^{\cdot}$$

The relative part played by each radical in the hydroxylation of benzene cannot be determined from the experimental results. However, it is clear that the catalytic oxidation of benzene in aqueous solution at 180–220°C is a coupled autocatalytic radical-ion oxidation of benzene and phenol involving short chains (4–6 steps). This conclusion was reached after a detailed study of the mechanism of oxidation of the phenol formed from benzene and an estimate of the contributions of the different reactions to the total formation of radicals in the system [182,183]. This estimate showed that, in the initial stages of the process, iron (or copper) ions act as initiators for the oxidation of benzene, forming radicals by reaction with oxygen (2′ and 2″). When the process has developed, the oxidation of phenol by oxygen (reactions 0′ and 0″) begins to play the main part in the generation of free radicals. Thus the role of accelerator of the reaction passes to phenol, while the metal ions may merely promote conversion of the radical $HO_2^{\cdot}$ into $HO^{\cdot}$.

V. HYDROXYLATION OF AROMATIC COMPOUNDS ON OXIDATION TOGETHER WITH ALCOHOLS AND HYDROCARBONS

The oxidation of hydrocarbons involves the accumulation of peroxides, which decompose with the formation of radicals. It may therefore be expected that aromatic compounds will undergo hydroxylation in the presence of easily oxidisable hydrocarbons and alcohols. Emanuel' and Denisov [188,189] were the first to demonstrate the fundamental possibility of oxidising liquid benzene to phenol under pressure at temperatures below the critical point (288°C), and discovered that such additives as cyclohexane and cyclohexanone (2 vol.%) could initiate the oxidation of benzene. The introduction of these compounds, which undergo oxidation by a chain mechanism, accelerates significantly the accumulation of phenol from benzene, but the oxidation of benzene remains self-inhibiting and cannot be conducted to high degrees of conversion.

Considerable rates of accumulation of phenol from benzene can be achieved by increasing the proportion of easily oxidisable substance. Thus when benzene is oxidised together with cyclohexane (10–20 mole %) in air (60 atm) at 220–250°C the rate of accumulation of phenol is $\sim 10^{-5}$ M s^{-1}. [190–192]. A kinetic study of the combined oxidation of benzene with cyclohexane, cyclohexanol, and cyclohexanone showed that autocatalysis in the oxidation of benzene was due to the autocatalytic oxidation of the additives [190–192]. In this case the developed reaction comprises the combined oxidation of cyclohexane and cyclohexanone and of benzene and phenol. The reaction remains self-inhibiting, owing to the inhibiting effects of benzene and of the resins formed from phenol. Other additives—methyl- and ethyl-cyclohexane, toluene, and *p*-xylene—may also exert an inhibiting action. Attempts to stimulate the oxidation of benzene by readily oxidisable organic additives have been undertaken also in the catalysed oxidation of benzene in aqueous solution [179]: the oxidation in aqueous copper(II) sulphate solution (0.125 M) at an oxygen pressure of 35 atm and 180°C is accelerated by the addition of cyclohexane and cyclohexanone (2 vol.% based on the benzene), whereas similar additions of cyclohexanol, propan-2-ol, cumene, and cyclohexene lengthen the induction period in the formation of phenol from benzene. Japanese workers [193] have made a systematic investigation of the simultaneous oxidation of benzene and toluene with the addition of ethylbenzene, cumene, cyclohexane, cyclohexene, n-hexane, t-butyl alcohol, propan-2-ol, and ethanol in solutions of iron(II) sulphate under 30 atm of oxygen at 180°C. They established that small additions of all the compounds diminish the yield of phenol from benzene and of benzaldehyde from toluene, but the yield of these products is increased by increasing the proportion by volume of the additives.

In all the above investigations the simultaneous oxidation of benzene and the additives was accompanied by hydroxylation of the benzene. However, several workers have found [194–196] that the addition of aromatic compounds diminishes the rate of oxidation of the other component, and phenolic products are not observed. Phenol is formed by the combined oxidation of benzene and a readily oxidisable additive only at sufficiently high temperatures—at 180–200°C in aqueous solution and at 220–250°C in

organic media. At lower temperatures phenol is not formed, and benzene either behaves as an inhibitor of oxidation [196] or simply changes the dielectric properties of the medium [197].

The kinetics and the mechanism of the hydroxylation of aromatic compounds have been studied when oxidised together with alcohols [198–204]. The combined oxidation of benzene and of the phenol formed from it by oxygen in aqueous solution has been established at 180–240°C; [198] a detailed study of the kinetics of the process showed that phenol was directly involved in the oxidation of benzene. To establish the character of the oxidation of benzene to phenol in aqueous solution it is important to compare the rates of oxidation of the two compounds under similar conditions. For this purpose the oxidation of benzene at 200°C was investigated on a sample which had initially been primed with phenol at its kinetically equilibrium concentration under these conditions. The rate of consumption of phenol was then equal to its rate of formation so long as there was no significant decrease in the benzene concentration. The rate of oxidation of benzene was 4.5×10^{-5} M s^{-1}, whereas the rate of oxidation of phenol at the kinetically equilibrium concentration but in the complete absence of benzene was 1.9×10^{-5} M s^{-1} under otherwise similar conditions. Thus the rate of oxidation of benzene is more than double that of phenol under analogous conditions, which indicates that the oxidation of benzene is a chain reaction. A detailed kinetic investigation of the oxidation of phenol by oxygen in phosphoric-acid solution (pH 1.55) supported the reaction mechanism [197,200]

$$\mathrm{PhOH} + \mathrm{O_2} \rightarrow \mathrm{PhO^{\cdot}} + \mathrm{HO_2^{\cdot}} \qquad (0')$$

$$\mathrm{PhOH} \rightleftarrows \mathrm{PhO^-} + \mathrm{H^+}$$

$$\mathrm{PhO^-} + \mathrm{O_2} \rightarrow \mathrm{PhO^{\cdot}} + \mathrm{O_2^-} \qquad (0'')$$

$$\mathrm{O_2^-} + \mathrm{H^+} \rightleftarrows \mathrm{HO_2^{\cdot}}$$

$$\mathrm{PhOH} + \mathrm{HO_2^{\cdot}} \rightarrow \mathrm{PhO^{\cdot}} + \mathrm{H_2O_2} \qquad (1)$$

$$\mathrm{PhOH} + \mathrm{H_2O_2} \rightarrow \mathrm{PhO^{\cdot}} + \mathrm{H_2O} + \mathrm{HO^{\cdot}} \qquad (2)$$

$$\mathrm{PhOH} + \mathrm{HO^{\cdot}} \rightarrow \mathrm{PhO^{\cdot}} + \mathrm{H_2O} \qquad (3)$$

$$\mathrm{PhO^{\cdot}} + \mathrm{PhO^{\cdot}} \rightarrow \mathrm{Products}\ .$$

Comparison of this scheme with the experimental relations enabled the rate constants of reactions (0′), (0″), and (2) to be evaluated as (in $M^{-1} s^{-1}$) $k_{0'} = 4.9 \times 10^8 \exp(-25\,600/RT)$, $k_{0''} = 3.5 \times 10^{12} \exp(-17\,000/RT)$, and $k_2 = 7.3 \times 10^{10} \exp(-23\,700/RT)$. The phenoxide ion reacts with oxygen at 200°C with a rate constant exceeding the rate constant of reaction (0′) by a factor of 10^7, but in acid media the two reactions occur at comparable rates, since the concentration of phenoxide ions is very small. The oxidation of phenol by oxygen is accompanied by the formation of $HO_2^{\cdot}$ radicals and hydrogen peroxide, which then reacts with the phenol. The rate constants of reactions (0′) and (2) can be used to calculate kinetically the equilibrium concentrations of hydrogen peroxide, and compare the results with the experimental values. Such a comparison has been made at 157° and 180°C, and shows good agreement between experimental and calculated quantities of hydrogen peroxide, which supports the above mechanism.

The radicals $OH^{\cdot}$ and $OH_2^{\cdot}$, formed by the oxidation of phenol, hydroxylate benzene. Whereas the hydroxylating power of the former radical is well known, the similar part played by $HO_2^{\cdot}$ in the combined oxidation of aliphatic alcohols and aromatic compounds has been demonstrated quite recently [201–204]. For this purpose benzene was introduced into two systems—comprising hydrogen peroxide and an initiator together with water and with methanol and molecular oxygen—in which $HO_2^{\cdot}$ radicals are generated continuously but no $HO^{\cdot}$ radicals are formed [201]. Under these conditions $HO_2^{\cdot}$ is formed by the reaction of initiator radicals and peroxy-radicals of methanol $RO_2^{\cdot}$ with hydrogen peroxide. Evidence has been obtained [205,206] of the rapid exchange $R^1OO^{\cdot} + R^2OOH \rightarrow R^1OOH + R^2OO^{\cdot}$. The radicals $RO_2^{\cdot}$ in the oxidisable alcohol exchanged for $HO_2^{\cdot}$ in the hydrogen peroxide formed, the degree of this substitution depending on the ratio of the rate constants $k_{RO_2^{\cdot} + H_2O_2}/k_{HO_2^{\cdot} + RH}$. At 30°C, for example, 0.11 to 0.47 M ROOH is sufficient for complete exchange of peroxy-radicals with the hydroperoxide during oxidation of the hydrocarbon [207]. It is therefore most likely that at 110–220°C there will be complete exchange of peroxy-radicals with hydrogen peroxide taken in the same concentrations, for the H–O bonds to be broken have almost the same strength in the hydroperoxides as in hydrogen peroxide.

In the presence of an initiator and hydrogen peroxide, phenol is formed from benzene both in water (in an atmosphere of argon) and in oxidisable methanol (in oxygen). Phenol is formed only by the reaction of benzene with free radicals: in the absence of an initiator hydrogen peroxide does not hydroxylate benzene under the experimental conditions, since no appreciable decomposition of the peroxide with the formation of $HO^{\cdot}$ radicals takes place. Therefore the formation of phenol from benzene in the systems—H_2O–H_2O_2—initiator and CH_3OH–H_2O_2–initiator–O_2—must be regarded as proof of hydroxylation by the radical $HO_2^{\cdot}$. Kinetic study of the combined initiated oxidation of methanol and benzene showed that the initial rate of accumulation of phenol $W_0^{C_6H_5OH}$ is directly proportional to the square root of the initial concentration of the initiator: i.e. it increases linearly with the concentration of free radicals in the system. Three types of free radicals—those from the initiator, $\diagdown\!\!\diagup C(OH)OO^{\cdot}$, and $HO_2^{\cdot}$—are present in the oxidisable alcohol (the concentration of $\diagdown\!\!\diagup C(OH)^{\cdot}$ radicals is very small in the presence of molecular oxygen and they can be ignored). Experiments in water showed that in the presence of hydrogen peroxide an initiator does not ensure the hydroxylation of benzene: i.e. the initiator radicals are not involved in hydroxylation. In methanol undergoing oxidation, therefore, benzene can be hydroxylated by $\diagdown\!\!\diagup C(OH)OO^{\cdot}$ and $HO_2^{\cdot}$ radicals. Experiments in methanol with different initial concentrations of hydrogen peroxide showed that this factor has hardly any effect on $W_0^{C_6H_5OH}$: i.e. benzene is hydroxylated either by both peroxy-radicals or by $HO_2^{\cdot}$ alone. The hydroxylation of benzene in the H_2O–H_2O_2–initiator system, in which $\diagdown\!\!\diagup C(OH)OO^{\cdot}$ radicals are in general absent, again proves that $HO_2^{\cdot}$ is able to hydroxylate benzene. Thus the hydroxylating power of the $HO_2^{\cdot}$ radical has been demonstrated.

The oxidation of alcohols involves the formation of hydrogen peroxide, which may yield $HO_2^{\cdot}$ radicals by reaction with the peroxy-radicals of the alcohol. Hydroxylation of benzene can therefore be expected when it is oxidised in the presence of alcohols. In fact phenol is formed in all cases of such oxidation in air at 50 atm and 200°C. [202,204] Its rate of accumulation shows a well defined autocatalytic character.

In order to obtain quantitative parameters a study was made of the initiated oxidation of mixtures of alcohols and benzene at 145°C. Measurements were made of the initial rates of accumulation of phenol $W_0^{C_6H_5OH}$ and of

the total oxidation products of the alcohol W_0^{alc}. The initial stages of oxidation of an alcohol mixed with the benzene were shown [201] to be described by the equation for chain reactions with quadratic termination:

$$W_0^{alc} = (k_2/\sqrt{k_6})_{alc}[R-OH]_0\sqrt{W_i},$$

where $[ROH]_0$ is the initial alcohol concentration, k_2 the rate constant of chain growth, k_6 the termination rate constant, and W_i the rate of initiation. The oxidation of benzene was characterised by the parameter $(k_2/k_6^{1/2})_b$, calculated by means of the equation

$$W_0^{PhOH} = (k_2/\sqrt{k_6})_b[C_6H_6]_0\sqrt{W_i}.$$

Table 14. Initiated oxidation of benzene–alcohol mixtures in air at 50 atm and 145°C in the presence of 0.054 M t-butyl peroxide ($W_i = 1.18 \times 10^{-5}$ M s^{-1}).

Alcohol	M	Benzene, M	$10^4 W_0^{alc}$, M s^{-1}	$10^3(k_2/k_6^{1/2})_{alc}$	$10^6 W_0^{C_6H_5OH}$, M s^{-1}	$10^{-4}(k_2/k_6^{1/2})_b$	No. of steps
Propan-2-ol	9.15	3.35	5.80	18.4	3.84	3.32	49
Ethanol	13.7	2.25	1.80	3.80	1.70	2.20	15
Methanol	19.7	2.25	1.82	2.70	0.47	0.61	15
t-Butyl alcohol	8.5	2.25	0.16		0.10		1—2

Experimental results for the initiated oxidation of mixtures of benzene and alcohols are given in Table 14, from which it follows that the rate of accumulation of phenol is a maximum for the initiated oxidation of benzene in propan-2-ol.

The oxidation of mixtures of propan-2-ol and benzene or toluene has been studied at 110–150°C. Rates of initiation were calculated for various temperatures by means of the equation $W_i = k_i[TBP]_0$, where TBP represents t-butyl peroxide and $k_i = 4.4 \times 10^{14}\exp(-35\,000/RT)$ s^{-1}. [208] The initial rates of accumulation of phenol, benzaldehyde + benzyl alcohol, cresols, and acetone were used to calculate the rate constant ratios $k_2/k_6^{1/2}$ for benzene, toluene at the methyl group, cresols, and propan-2-ol: for a toluene–propan-2-ol mixture

$$(k_2/\sqrt{k_6})_{i\text{-PrOH}} = 1.30 \cdot 10^4 \exp(-11000/RT),$$
$$(k_2/\sqrt{k_6})\ \text{at}\ CH_3 = 3.20 \cdot 10^2 \exp(-9600)/RT),$$
$$(k_2/\sqrt{k_6})_{\text{cresols}} = 17.8\exp(-9100/RT),\ M^{-1/2}\,s^{-1/2}.$$

and for a benzene–propan-2-ol mixture

$$(k_2/\sqrt{k_6})_{i\text{-PrOH}} = 2.40 \cdot 10^3 \exp(-9800/RT),$$
$$(k_2/\sqrt{k_6})_b = 4.25 \cdot 10^2 \exp(-11700/RT),\ M^{-1/2}\,s^{-1/2}.$$

The hydroxylation of monosubstituted benzene derivatives in the course of the initiated oxidation of propan-2-ol has been studied at 137°C in air at 50 atm. The experimental results are listed in Table 15.

The mechanism of the oxidation of alcohols has now been thoroughly investigated [209]. The primary oxidation products are hydroperoxides, which break down into hydrogen peroxide, and carbonyl-containing compounds—acetone, formaldehyde, and acetaldehyde from propan-2-ol, methanol, and ethanol respectively. Hydrogen peroxide accumulates in considerable concentrations in the oxidation of secondary and primary alcohols, the quantity depending on the nature of the alcohol. In fact, in benzene–alcohol mixtures with the same conditions of initiation at 145°C, the quantity of hydrogen peroxide and its rate of accumulation increase in the sequence—methanol < < ethanol < propan-2-ol. Peroxy-radicals react with hydrogen peroxide to form hydroperoxy-radicals. Thus $HO_2^\cdot$ radicals are formed in mixtures of alcohols with benzene and its derivatives as a consequence of a series of reactions such as

$$\text{Initiator} \xrightarrow{k_i} r^\cdot \xrightarrow{RH} rH + R^\cdot \qquad ROOH \rightarrow H_2O_2 + \rangle C{=}O$$
$$R^\cdot + O_2 \rightarrow RO_2^\cdot \qquad RO_2^\cdot + H_2O_2 \rightarrow HO_2^\cdot + ROOH$$
$$RO_2^\cdot + RH \rightarrow ROOH + R^\cdot \qquad HO_2^\cdot + RH \rightarrow H_2O_2 + R^\cdot \text{ etc.}$$

These radicals hydroxylate the aromatic compounds and react with one another:

$$XC_6H_5 + HO_2^\cdot \rightarrow XC_6H_4OH + HO^\cdot \qquad 2\,HO_2^\cdot \rightarrow H_2O_2 + O_2.$$

Table 15. Initiated oxidation of propan-2-ol (70 ml) mixed with monosubstituted benzenes (30 ml) at 137°C in the presence of 0.108 M di-t-butyl peroxide.

C_6H_5X	$[C_6H_5X]_0$, M	Length of chain	$10^2(k_2/k_6^{1/2})_{alc}$	$10^4(k_2/k_6^{1/2})_{ar}$	$10^4(k_2/k_6^{1/2})_{ar}$	
					ortho	*m + p*
C_6H_6	3.36	50	1.44	2.51	—	—
$C_6H_5CH_3$	2.82	53	2.09	2.24	1.12	1.12
C_6H_5Cl	3.11	64	2.14	3.43	1.48	1.94
$C_6H_5NO_2$	2.94	12	0.39	0.83	0.42	0.41
C_6H_5OH	0.50	3	0.11	—	—	—

At later stages the $HO_2^\cdot$ radicals react with the phenols which are formed, and both the latter and the resins which accumulate from them tend to inhibit oxidation [202].

The concentration of $HO_2^\cdot$ radicals in alcohol–benzene mixtures is $(\alpha W_i/k_6)^{1/2}$, where α represents the completeness of exchange of $RO_2^\cdot$ for $HO_2^\cdot$ radicals. Thus with the same initiation the concentration depends on α and k_6. The constant k_6 is greatly influenced by the medium [197], and α by the ease of oxidation of the alcohol. The combined effect of these factors is that the $HO_2^\cdot$ concentration, and hence the rate of hydroxylation of aromatic compounds $W = k_2^{ar}[XC_6H_5]_0[HO_2^\cdot]$, increase in the sequence—methanol < ethanol < propan-2-ol—corresponding to the ease of oxidation of the alcohols. Table 15 show that, in propan-2-ol undergoing oxidation, all monosubstituted benzenes are hydroxylated with formation of the corresponding phenols. The isomeric distribution of the resulting substituted phenols differs substantially from that obtained on hydroxylation by Fenton's reagent (Table 16). This indicates that in the present systems the benzene ring is attacked not by the $HO^\cdot$ radical, as with Fenton's reagent, but by another species—the $HO_2^\cdot$ radical.

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A detailed examination of the mechanisms of the hydroxylation of aromatic compounds shows that various species can act as hydroxylating agents depending on the conditions—the $HO^\cdot$ radical (Fenton's reagent and radiolytic systems), the $HO_2^\cdot$ radical (catalytic conversion of benzene into phenol at high temperatures, the combined oxidation of aromatic compounds together with alcohols and hydrocarbons, and also perhaps in radiolysis at high temperatures), and complexes of iron-containing enzymes with oxygen. In many papers different mechanisms are

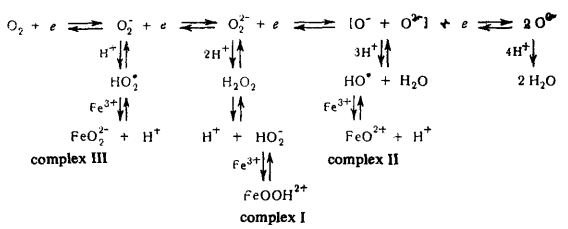
often sharply contrasted with one another; however, we shall attempt to show the relation between them by systematically examining the reduction of an oxygen molecule and the fate of the resulting intermediate species in the presence of ions of variable valency, e.g. iron. Scheme 4 shows the stepwise reduction of an oxygen molecule and the formation of every possible hydroxylating species.

Table 16. Distribution of isomers in the hydroxylation of benzene derivatives in propan-2-ol undergoing oxidation and by means of Fenton's reagent.

XC_6H_5	Combined oxidation of benzene and propan-2-ol			Fenton's reagent			Ref.
	ortho	*meta*	*para*	*ortho*	*meta*	*para*	
$C_6H_5CH_3$	50	25	25	55.5	15.0	29.5	24
		meta—para					
C_6H_5Cl	43	57		42	29	29	22
$C_6H_5NO_2$	51	49		24	30	46	22

According to George [167] the oxidising power of oxygen varies with the stage at which oxidation terminates. If molecular oxygen is reduced to the superoxide anion, and the latter is unable to react further, oxygen is a weak oxidising agent. A higher degree of oxidation is achieved when the superoxide ion combines with a proton to form $HO_2^{\cdot}$. In the reduction of hydrogen peroxide oxygen behaves as an oxidant of medium strength, approximately the same as Fe^{3+}. [176] In the presence of Fe^{3+} ions (or Ti^{4+}, etc.) $HO^{\cdot}$ and $HO_2^{\cdot}$ radicals are able to form complexes with the metals, and thus become stabilised. The ferryl ion FeO^{2+} can be regarded as an $HO^{\cdot}$ radical stabilised by the Fe^{3+} ion. Scheme 4 shows the possible hydroxylating agents and their modes of interconversion.

Scheme 4



A very important aspect of the hydroxylation of aromatic compounds is the nature of the attack on the ring. Although the $HO^{\cdot}$ radical attacks the ring by an electrophilic mechanism, as indicated by the distribution of isomers produced by Fenton's reagent and in radiolytic systems, the $HO_2^{\cdot}$ radical will give a distribution of isomers which is more typical of radical substitution in the benzene ring. Very contradictory results are obtained for the distribution of isomeric hydroxylation products with model systems of mixed-function peroxidases and oxidases and with the enzymes themselves. However, this discrepancy can be eliminated when it is remembered that the agents which attack the benzene ring in these cases are able to react in different forms—as radicals and as ions of different signs. Hamilton considers [170] that the character of the attack on the benzene ring, and hence the distribution of isomers, may change with model systems from radical to electrophilic and even to nucleophilic. It all depends on which state—ionic or radical—predominates with the given hydroxylating species. This state depends on the type of metal and especially on the ligand surrounding it. For example, hydroxylation by means of Fe^{2+}–mercaptobenzoic acid–O_2 yields a distribution of isomers which is characteristic of electrophilic reactions; the same distribution of isomers is obtained by the hydroxylation of toluene in the toluene–t-butyl hydroperoxide–$AlCl_3$ system [210], in which the benzene ring is attacked by the t-butyloxonium cation $[(CH_3)_3COH_2]^+$ by a definitely electrophilic mechanism. However, replacement of the ligand in the Fe^{2+}–EDTA–ascorbic acid–O_2 system produces a sharp change in the distribution of isomers, since the nature of the attacking species changes. There are in general many forms of the attacking complex in the latter case, so that it is necessary to consider the state of the complex as a whole and to know which form is the most significant, for this form will determine the character of the attack on the benzene ring.

We note in conclusion that the study of hydroxylation mechanisms is especially valuable in biochemistry, since reactions of this type occur widely in biological systems. Work during recent years has shown that the mechanism of free oxidations, which play a part in temperature control and several specific metabolic functions, such as the formation of metabolites by oxidation, the detoxication of poisonous compounds, etc., consists in hydroxylation of the substrate [211]. The most widespread is hydroxylation accomplished by a special respiratory chain comprising enzymes of free [non-phosphorylating] oxidation. This system is present in liver microsomes, where foreign compounds and several natural metabolites are converted into non-toxic polar products, the initial stage in these transformations being hydroxylation of the molecule.

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