Russian Chemical Reviews **64** (12) 1105–1129 (1995) ©1995 Russian Academy of Sciences and Turpion Ltd

UDC 541.128 + 541.49 + 547.97

Iron compounds and the mechanisms of the homogeneous catalysis of the activation of O_2 and H_2O_2 and of the oxidation of organic substrates

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Abstract. Experimental data on the homogeneous catalysis by iron compounds of the activation of O_2 and H_2O_2 and of their oxidation of organic substances, and the current ideas on this subject are described. Data concerning the formation of various intermediate species and of their role in these processes are analysed. A series of catalytic systems simulating the functional activity of certain enzymes are considered at a model level. The bibliography includes 338 references.

I. Introduction

The activation of O_2 and H_2O_2 by aquoiron ions and iron complexes in biological, environmental, and industrial oxidation–reduction processes has been the subject of numerous publications. The experimental results available on this question have been partly surveyed in monographs and reviews.[1–5] The mechanisms of model and real processes have been investigated mainly at a qualitative level and only rarely at a semi-quantitative level. This situation is due to the complexity of the systems investigated, the multivariability of the possible routes followed by the processes, and the dependence of the latter on many parameters. Molecular oxygen and hydrogen peroxide, which are ecologically ideal oxidants, are reduced in the presence of iron compounds, generating highly reactive superoxide and hydroxyl radicals as well as species of the ferryl type $LFe^{IV}=O^{2+}$. The rapid reaction of these species in biological or nonbiological processes, the difficulty of their identification, their specific and nonspecific activity, and the influence of various parameters (temperature, the nature of the solvent and the ligand L, pH, the ratio of the ligand and iron ions, the characteristics of the oxidant, the concentrations of the components, etc.) create significant difficulties in the study of the mechanisms of the catalytic processes in which they participate. Nevertheless, during the last 10–15 years vigorous studies have been performed on the mechanisms of catalytic reactions involving the oxidation of various substrates by environmentally pure oxygen and hydrogen peroxide, on the mode of these reactions, and in particular on the elucidation of the role of iron compounds as catalysts in these reactions. Conditions have been developed for the optimisation of the processes and foundations have been laid for the prediction of the paths in the reactions of the substrates. The role played by iron compounds in the manifestation of toxicity by the products of the conversion of O_2 in vivo has been explained at a model level.

In order to establish the mechanisms of the catalytic oxidation of the various organic substances, it is important to have information about the radical and nonradical intermediates formed under these conditions, for example the ferryl complexes. The experimental data concerning the latter refer mainly to the 1980s.

II. Iron compounds and the mechanisms of catalytic decomposition of H_2O_2

1. Catalysis by Fe^{2+} and Fe^{3+} aquo-ions

After the demonstration of the catalytic activity of aquoiron ions in the H_2O_2 decomposition reactions (see the relevant reviews[1,3]), a detailed study was made of the $Fe^{2+}-H_2O_2$ system (the Fenton reagent)[2] and the mechanism of this process was analysed and discussed.[1–3,6–14] Numerous studies have been devoted to the kinetics of the decomposition of H_2O_2 by the Fe^{3+} aquo-ions.[1,3,6,7,9,15–19, etc.]

The study of the $Fe^{2+}-H_2O_2$ system (and also the $Fe^{2+}-H_2O_2$–substrate systems) made it possible to develop mechanisms for the decomposition of H_2O_2 catalysed by aquoiron(II) ions. All the reactions considered in this respect are compiled in Table 1. The question of the generation of the $^{\bullet}OH$ radicals in the $Fe^{2+}-H_2O_2$ system is of fundamental importance. It has now been demonstrated unambiguously that such radicals are formed in this process. The experimental data obtained (surveyed in a monograph[3] and partly presented in Scheme 1 and in Table 1) made it possible to determine the elementary stages in the decomposition of H_2O_2 by Fe^{2+} aquo-ions and their sequence depending on the experimental conditions.

Scheme 1 (p. 1107) presents the reactions involved solely in the H_2O_2 decomposition process in the $Fe^{2+}-H_2O_2$ system.[3]

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Received 18 May 1995
Uspekhi Khimii **64** (12) 1183–1208 (1995); translated by A K Grzybowski

Table 1. The rate constants for the elementary reactions and the acid–base equilibrium constants in the $Fe^{2+}-H_2O_2$ system.

Reaction	Constant[a]	Ref.	Reaction	Constant[a]	Ref.
$Fe^{2+}+H_2O_2 \longrightarrow Fe^{3+}+{}^{\bullet}OH+OH^-$	68	20	$(H_2O)_4(OH^-)Fe^{2+}(H_2O_2) \longrightarrow$	3×10^5	47
	76.5	21	$\longrightarrow (H_2O)_4(OH^-)FeO^{2+}+H_2O$		
	62	22			
	53	8, 23			
	58	24	$(H_2O)_5Fe(H_2O_2)^{2+} \longrightarrow$	2.8×10^3	47
	66	25	$\longrightarrow (H_2O)_5(OH^-)Fe^{3+}+{}^{\bullet}OH$		
	79	26			
	49.5	27			
	73	28	$(H_2O)_5Fe(H_2O_2)^{2+}+Fe^{2+}(H_2O)_6 \longrightarrow$	3×10^5	47
	76	29	$\longrightarrow 2(H_2O)_5Fe^{3+}(OH^-)+H_2O$		
	56.2	30			
	41.7	31			
	61.7	32	$Fe^{2+}+O_2^{\bullet-} \xrightarrow{H^+} Fe^{3+}+HO_2^-$	7.3×10^5	45
	60.3	33			
	50.1	34, 35	$Fe^{3+}+H_2O_2 \longrightarrow Fe^{2+}+HO_2^{\bullet}+H^+$	9.1×10^{-7}	48
$Fe^{2+}+{}^{\bullet}OH \longrightarrow Fe^{3+}+OH^-$	2.6×10^8	36			
	5.1×10^8	37	$Fe^{3+}+H_2O_2 \rightleftharpoons FeHO_2^{2+}+H^+$	2×10^{-3}	49
	3×10^8	29, 40			
	5×10^8	38	$Fe^{3+}HO_2^- \longrightarrow Fe^{2+}+HO_2^{\bullet}$	2×10^{-3}	50
	3.2×10^8	38, 39, 41		1.6×10^{-3}	20
	2.5×10^8	42	$FeHO_2^{2+}+FeOH^{2+} \longrightarrow$	5	20
	2.7×10^8	43	$\longrightarrow 2Fe^{2+}+H_2O+O_2$		
	3.3×10^8	44			
$Fe^{2+}+HO_2^{\bullet} \longrightarrow Fe^{3+}+HO_2^-$	7.2×10^5	45	$Fe^{3+}+HO_2^{\bullet} \longrightarrow Fe^{2+}+H^++O_2$	7.3×10^5	45
	1.5×10^6	46		2.1×10^6	51
				3.3×10^5	30
$Fe^{3+}+{}^{\bullet}OH \longrightarrow Fe^{4+}+OH^-$	7.9×10^7	3, 42	$Fe^{3+}+O_2^{\bullet-} \longrightarrow Fe^{2+}+O_2$	4×10^8	52
				1.29×10^9	51, 53
${}^{\bullet}OH+H_2O_2 \longrightarrow HO_2^{\bullet}+H_2O$	4.5×10^7	36		1.1×10^9	50
	1.7×10^7	37		5×10^7	30
	3×10^7	42		1.9×10^9	46
${}^{\bullet}OH+{}^{\bullet}OH \longrightarrow H_2O_2$	5.3×10^9	29	$H_2O_2 \rightleftharpoons HO_2^-+H^+$	2.63×10^{-12}	58
	5.02×10^9	54			
	8×10^9	36	$HO_2^{\bullet} \rightleftharpoons H^++O_2^{\bullet-}$	3.55×10^{-5}	59
	6×10^9	52			
${}^{\bullet}OH+O_2^{\bullet-} \longrightarrow OH^-+O_2$	1×10^{10}	3, 42	$HO_2^{\bullet}+H^+ \rightleftharpoons H_2O_2^+$	$(3.16-3.98)\times10^{-5}$	55, 56
${}^{\bullet}OH+HO_2^{\bullet-} \longrightarrow H_2O+O_2$	1.4×10^{10}	3, 42	${}^{\bullet}OH \rightleftharpoons O^{\bullet-}+H^+$	1.02×10^{-12}	60
$HO_2^{\bullet}+HO_2^{\bullet} \longrightarrow H_2O_2+O_2$	1.9×10^6	55	$Fe^{2+}+OH^- \rightleftharpoons FeOH^+$	$K=3.63\times10^5$	61
	2.2×10^6	56			
	8.1×10^5	57	$Fe^{3+} \rightleftharpoons FeOH^{2+}+H^+$	2×10^{-3}	62
				1.4×10^{-3}	63
$O_2^{\bullet-}+O_2^{\bullet-} \xrightarrow{H^+} O_2+HO_2^-$	< 0.35	38		1.83×10^{-3}	64
$HO_2^{\bullet-}+O_2^{\bullet-} \longrightarrow HO_2^-+O_2$	8.5×10^7	38	$(H_2O)_5Fe^{2+}(H_2O)+H_2O_2 \rightleftharpoons$	1.8×10^{-2}	47
$HO_2^{\bullet}+H_2O_2 \longrightarrow H_2O+O_2+{}^{\bullet}OH$	0.2	3	$\rightleftharpoons (H_2O)_5Fe(H_2O_2)^{2+}+H_2O$		
	3.7	3			
			$(H_2O)_5Fe(H_2O_2)^{2+} \rightleftharpoons$	6×10^{-5}	47
			$\rightleftharpoons (H_2O)_4(OH^-)Fe(H_2O_2)^{2+}+H^+$		
			$Fe^{2+}+HO_2^{\bullet} \rightleftharpoons FeHO_2^{2+}$	2.1×10^6	51

[a] The rate constants are expressed in litre mol^{-1} s^{-1}, the decomposition constants in s^{-1}, and the equilibrium constants in mol $litre^{-1}$.

The following set of consecutive reactions in the $Fe^{2+}-H_2O_2$ system is nowadays regarded as generally accepted.

Scheme 2

1. $Fe^{2+}+H_2O_2 \longrightarrow Fe^{3+}+HO^{\bullet}+OH^-$
13. $Fe^{2+}+{}^{\bullet}OH \longrightarrow Fe^{3+}+OH^-$
20. ${}^{\bullet}OH+H_2O_2 \longrightarrow HO_2^{\bullet}+H_2O$
18. $Fe^{3+}+HO_2^{\bullet} \longrightarrow Fe^{2+}+H^++O_2$
19. $Fe^{3+}+O_2^{\bullet-} \longrightarrow Fe^{2+}+O_2$
14. $Fe^{2+}+HO_2^{\bullet} \longrightarrow Fe^{3+}+HO_2^-$

This series of stages occurs under the following conditions: $0.5 < [H_2O_2]/[Fe^{2+}] < 200$, pH > 2. The catalytic decomposition of H_2O_2 by Fe^{2+} aquo-ions proceeds in accordance with a radical-ion cyclic mechanism (a characteristic feature of this mechanism is the equality of the rates of the chain initiation and propagation stages) when $0.5 < [H_2O_2]/[Fe^{2+}] < 3\times10^6$ and in accordance with a radical-chain mechanism {only in this case it is possible to differentiate clearly the chain initiation [reaction (1)], propagation [reactions (20) and (21)], and termination [reaction (18) and/or (19)] steps} when $[H_2O_2]/[Fe^{2+}] > 3\times10^6$.

Scheme 1

A. Processes with participation of Fe^{2+}

1. $Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$
2. $Fe^{2+} + H_2O_2 \longrightarrow FeO^{2+} + H_2O$
3. $Fe^{2+} + H_2O_2 \longrightarrow Fe^{4+} + 2OH^-$
4. $FeOH^+ + H_2O_2 \longrightarrow Fe^{3+} + {}^{\bullet}OH + 2OH^-$
5. $FeOH^+ + H_2O_2 \longrightarrow FeO^{2+} + H_2O + OH^-$
6. $(H_2O)_5Fe(H_2O)^{2+} + H_2O_2 \rightleftharpoons (H_2O)_5Fe(H_2O_2)^{2+} + H_2O$
7. $(H_2O)_5Fe(H_2O_2)^{2+} \xrightarrow[-H^+]{} (H_2O)_4(OH^-)FeO^{2+} + H_2O$
8. $(H_2O)_5Fe(H_2O_2)^{2+} \xrightarrow[-H^+]{} (H_2O)_5(OH^-)Fe^{3+} + {}^{\bullet}OH$
9. $(H_2O)_5Fe(H_2O_2)^{2+} + Fe^{2+}(H_2O)_6 \longrightarrow 2\,(H_2O)_5Fe^{3+}(OH^-) + H_2O$
10. $Fe^{2+} + HO_2^- + H_2SO_4 \longrightarrow Fe(SO_4H)(OOH) + H^+$
11. $Fe^{2+}SO_4 + H_2O_2 \longrightarrow FeSO_4(H_2O_2)$
12. $Fe(SO_4H)(OOH) + H_2O_2 \longrightarrow Fe(SO_4H)(OH) + H_2O + O_2$
13. $Fe^{2+} + {}^{\bullet}OH \longrightarrow Fe^{3+} + OH^-$
14. $Fe^{2+} + HO_2^{\bullet} \longrightarrow Fe^{3+} + HO_2^-$
15. $Fe^{2+}(H_2O_2)(HO_2) \rightleftharpoons Fe^{2+}(HO_2^{\bullet})(HO^+) + OH^-$
16. $Fe^{2+}(HO_2^{\bullet})(HO^+) \rightleftharpoons Fe^{3+}(HO_2^{\bullet})(HO^{\bullet})$
17. $[Fe_2(OH)_2]^{2+} + H_2O_2 \longrightarrow [Fe_2(OH)_2]^{4+} + 2OH^-$

B. Processes with participation of Fe^{3+}

18. $Fe^{3+} + HO_2^{\bullet} \longrightarrow Fe^{2+} + H^+ + O_2$
19. $Fe^{3+} + O_2^{\bullet-} \longrightarrow Fe^{2+} + O_2$

C. Processes with participation of ${}^{\bullet}OH$, $HO_2^{\bullet}$ ($O_2^{\bullet-}$)

(in addition to those listed above)

20. ${}^{\bullet}OH + H_2O_2 \longrightarrow HO_2^{\bullet} + H_2O$
21. $HO_2^{\bullet} + H_2O_2 \longrightarrow O_2 + H_2O + {}^{\bullet}OH$

D. Processes with participation of Fe^{4+}

22. $FeO^{2+} + H_2O_2 \longrightarrow Fe^{2+} + O_2 + H_2O$
23. $Fe^{4+} + OOH^- \longrightarrow Fe^{2+} + O_2 + H^+$
24. $Fe^{4+} + HO_2^- \rightleftharpoons FeOOH^{3+} \longrightarrow Fe^{3+} + HO_2^{\bullet}$
25. $(H_2O)_4(OH^-)Fe^{2+}O + H_2O \longrightarrow (H_2O)_4(OH^-)_2Fe^{3+} + {}^{\bullet}OH$
26. $(H_2O)_4(OH^-)Fe^{2+}O + Fe^{2+} \longrightarrow 2\,Fe^{3+}(OH^-)(H_2O)_5$
27. $Fe^{4+} + Fe^{2+} \longrightarrow 2\,Fe^{3+}$
28. $FeO^{2+} + H_2O_2 \longrightarrow HO_2^{\bullet} + OH^- + Fe^{3+}$

E. Acid–base equilibria

29. $Fe^{2+} + H_2O \rightleftharpoons FeOH^+ + H^+$
30. $2\,Fe^{2+} + 2\,H_2O \rightleftharpoons Fe_2(OH)_2^{2+} + 2\,H^+$
31. $H_2O_2 \rightleftharpoons HO_2^- + H^+$
32. $HO_2^{\bullet} \rightleftharpoons H^+ + O_2^{\bullet-}$
33. $(H_2O)_5Fe(H_2O_2)^{2+} \rightleftharpoons (H_2O)_4(OH^-)Fe(H_2O_2)^{2+} + H^+$

According to a series of data,[16,20,46,50,65–73] the decomposition of H_2O_2 by Fe^{3+} aquo-ions (Ruff's system)[74,75] in an acid medium (at pH $\leqslant$ 2) proceeds via a radical-chain mechanism. A different mechanism of this process has sometimes been suggested.[45,49,51–53,57,76–81] All the possible steps of the process occurring in the $Fe^{3+}-H_2O_2$ system, proposed by various investigators, are presented in a monograph.[3]

Of the principal experimental evidence in support of the operation of a radical-chain mechanism of the decomposition of H_2O_2 in the $Fe^{3+}-H_2O_2$ system, we shall mention the following: (a) evidence based on the inhibiting effects of various organic substances;[16,17,20,50,66–73,82] (b) evidence indicating (directly or indirectly) the generation of the ${}^{\bullet}OH$ radicals[72,73,83–89] and/or $O_2^{\bullet-}$ radical-ions[16,50,66–68,82,90] in the system; (c) evidence confirming the existence of one-electron transfer steps which include the oxidation-reduction cycle

$$Fe^{3+} \underset{-\bar{e}}{\overset{\bar{e}}{\rightleftharpoons}} Fe^{2+},$$

(the assumption[91,92] of the formation of Fe^{2+} has been confirmed[16,20,85,92]).

The question arises of the evidence used by the supporters of the ion-molecule mechanism. The principal evidence is believed to be[49,76–79,81,93–95] the formation in the reaction medium of active intermediate compounds and primarily peroxo-complexes. Indeed the peroxo-complex $FeHO_2^{2+}$ *is formed in the system.*[49,51,76–79,81,94–98] However, it has been shown[3] that this does not conflict with the occurrence of the process by a radical-chain mechanism.

Purmal'[16] demonstrated qualitatively and quantitatively that, among all the possible reactions considered in the literature as steps in the H_2O_2 decomposition by Fe^{3+} aquo-ions,[3] only the series of consecutive steps presented in Scheme 3 actually occur. This scheme is nowadays generally accepted to be the description of the mechanism of the decomposition of H_2O_2 by Fe^{3+} aquo-ions.

Scheme 3

Initiation

$FeHO_2^{2+} \longrightarrow Fe^{2+} + HO_2^{\bullet}$

$FeHO_2^{2+} + FeOH^{2+} \longrightarrow 2\,Fe^{2+} + O_2 + H_2O$

Chain propagation

$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$

${}^{\bullet}OH + H_2O_2 \longrightarrow HO_2^{\bullet} + H_2O$

$O_2^{\bullet-} + Fe^{3+} \longrightarrow Fe^{2+} + O_2$

Chain termination

$Fe^{2+} + HO_2^{\bullet} \longrightarrow Fe^{3+} + HO_2^-$

$Fe^{2+} + {}^{\bullet}OH \longrightarrow Fe^{3+} + OH^-$

$HO_2^{\bullet} + HO_2^{\bullet} \longrightarrow H_2O_2 + O_2$

Acid–base equilibria

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

$HO_2^{\bullet} \rightleftharpoons H^+ + O_2^{\bullet-}$

$Fe^{3+} + H_2O \rightleftharpoons FeOH^{2+} + H^+$

$Fe^{3+} + H_2O_2 \rightleftharpoons FeHO_2^{2+} + H^+$

Analysis of the literature devoted to studies of the kinetics and mechanisms of catalytic decomposition of H_2O_2 by Fe^{2+} and Fe^{3+} aquo-ions demonstrated, firstly, the complexity of the reactions occurring in the $Fe^{2+}-H_2O_2$ and $Fe^{3+}-H_2O_2$ systems; secondly, it demonstrated the possibility of kinetic studies on such systems and the limitations of this possibility; thirdly, it made it possible to devise procedures for the determination, discrimination, and justification of the reaction mechanisms in complex systems including a set of a large number of consecutive elementary stages.

When iron ions are replaced as catalysts by their coordination compounds, the decomposition of H_2O_2 is in many cases accelerated.[1,3,16,99,106] The catalytic activity of the Fe^{3+} complexes is in many cases higher than that of aquoiron ions. Among the iron complexes with a catalase-like activity, the coordination compounds of Fe^{3+} with triethylenetetramine ('inorganic catalase') exhibit the highest activity in the hydrogen peroxide decomposition reaction.[3]

Complex formation promotes the occurrence of the process by different mechanisms depending on the nature of the ligand. This can be seen from the data presented in Table 2.

The oxidation-reduction decomposition of H_2O_2 by iron(III) complexes can also proceed via different mechanisms: radical-chain (I), ion-molecule (II), and chain-nonradical (III). A general scheme for the reactions occurring in the Fe^{3+} – ligand – H_2O_2 systems is presented in Scheme 4.

Cycle I. The free radical species $O_2^{\cdot-}(HO_2^{\cdot})$ and $^{\cdot}OH$ are generated during the process and the one-electron transfer stages

$$L''Fe^{3+} \underset{-\bar{e}}{\overset{\bar{e}}{\rightleftharpoons}} L'''Fe^{2+}$$

occur. The rate of gas evolution (w_{O_2}) appreciably exceeds the rate of initiation (w_i). This mechanism operates in the Fe^{3+}–2,2′-Bipy – H_2O_2,[3,15,107] Fe^{3+} – EDTA – H_2O_2,[117–119] Fe^{3+} – H_2LM – H_2O_2[3,113,120] Fe^{3+} – Acid Chrome Dark-Blue – H_2O_2,[2] Fe^{3+} – ethylenediamine – H_2O_2,[119,121] Fe^{3+} – glutamic acid – H_2O_2,[122,123] and certain other systems.

Cycle II. The main process does not include the reactions of the $^{\cdot}OH$ and $O_2^{\cdot-}$ radical species. The two-electron transfer stage

$$L'Fe^{2+} \underset{-2\bar{e}}{\overset{2\bar{e}}{\rightleftharpoons}} L'Fe^{4+}$$

takes place. As in cycle I, $w_{O_2} \gg w_i$.

This mechanism operates, in particular, in the decomposition of H_2O_2 by the coordination compounds of Fe^{3+} with triethylenetetramine[3,104–106] and histidine.[3,111,124–126]

Cycle III. The catalytic process proceeds via the formation of mono- and di-peroxo-complexes. In the course of the reaction, the oxidation state of the central ion in the complex catalyst remains unchanged and the $^{\cdot}OH$ and $HO_2^{\cdot}$ ($O_2^{\cdot-}$) radical species are not generated in the reaction medium. It has been shown that the decomposition of H_2O_2 by the coordination compounds of Fe^{3+} with 4′,4″,4‴-tetrasulfophthalocyanine (PTS),[116] *N,N′*-bis-(2-methylpyridyl)ethylenediamine,[127] and quaterpyridyl[127] proceeds in accordance with this mechanism.

Analysis of published data[3] made it possible to arrange systematically the factors determining the catalytic activity of the Fe^{2+} and Fe^{3+} ions on complex formation and the characteristic features of the catalytic processes in the presence of coordination compounds of iron. The hydrolytic stability of iron ions, their electrochemical properties, and the lability of the coordination sphere change on complex formation. All this leads ultimately to a change in the catalytic activity of the aquoiron ions.

2. Oxidation of organic substrates by the $Fe^{2+}(LFe^{2+})$–H_2O_2 system

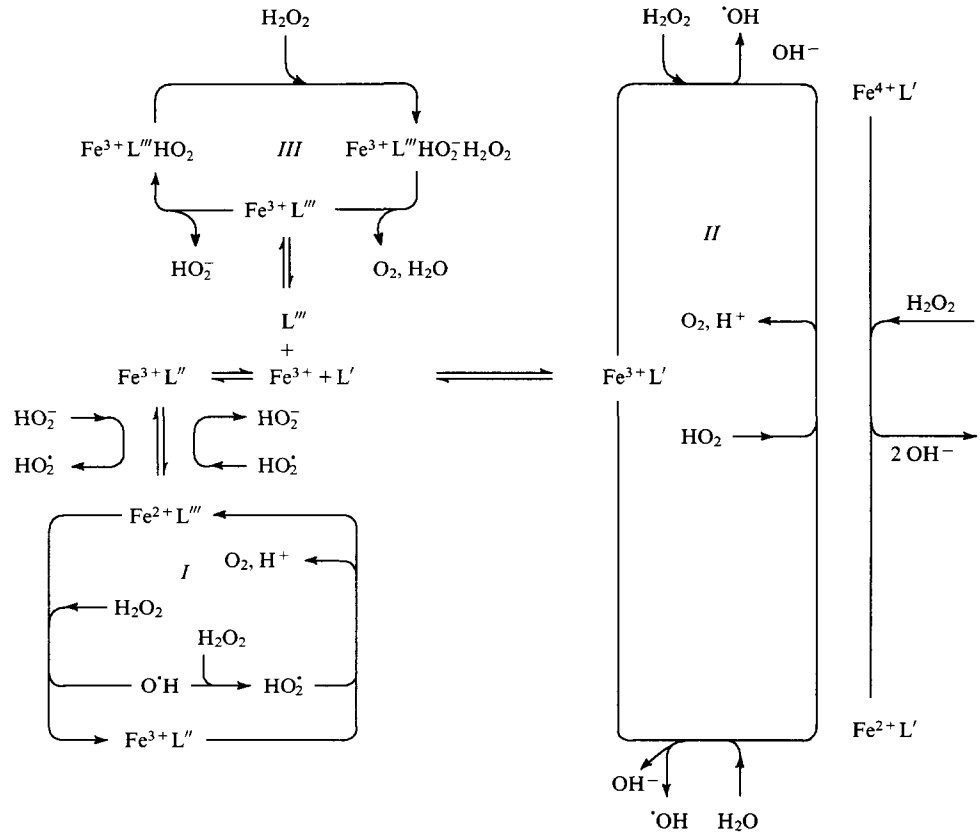
The results of the numerous studies devoted to the elucidation of the mechanisms of the oxidation of organic substrates by the Fe^{2+} – H_2O_2 system have been arranged systematically to the fullest extent by Walling.[29] However, the scheme which he presented does not embrace the entire wide variety of such mechanisms. The question of the nature of the substrate (S) is considered to only a limited extent in his communication,[29] the influence of the formation of a complex between the substrate

Table 2. The mechanisms of the interaction of the iron(II) complexes with H_2O_2.

System[a]	Elementary mechanism of the interaction with H_2O_2	Process mechanism	pH of medium	Ref.
Fe^{2+} – Bipy – H_2O_2	$FeBipy_n^{2+} + H_2O_2 \longrightarrow FeBipy_n^{3+} + {}^{\cdot}OH + OH^-$	radical-chain	4–6	107
Fe^{2+} – Phen – H_2O_2	$FePhen^{2+} + H_2O_2 \rightleftharpoons FePhenH_2O_2^{2+} \longrightarrow$	radical-ion	4–5	108
	$\longrightarrow FePhen^{3+} + O^{\cdot}H + OH^-$			
	$FePhen_n^{2+} + H_2O_2 \longrightarrow FePhen_n^{3+} + {}^{\cdot}OH + OH^-$	"	2–5	109
Fe^{2+} – His – H_2O_2	$Fe(His)_2 + H_2O_2 \longrightarrow Fe(His)_2^+ + {}^{\cdot}OH + OH^-$	"	2–5	110
	$Fe^{2+}(His)_2 + H_2O_2 \longrightarrow Fe^{4+}(His)_2 + 2\,OH^-$	ion-molecule	7–8	111
Fe^{2+} – H_4T – H_2O_2	$H_2TFe^{2+} + H_2O_2 \longrightarrow H_2TFe^{3+} + {}^{\cdot}OH + OH^-$	radical-ion	2–4	112
Fe^{2+} – DFH_4 – H_2O_2	$FeDFH_3^+ + H_2O_2 \longrightarrow FeDFH_3^{2+} + {}^{\cdot}OH + OH^-$	cyclic radical-ion	2–4	112
	$FeDFH_2 + H_2O_2 \longrightarrow FeDFH_2 + {}^{\cdot}OH + OH^-$	"	2–4	112
Fe^{2+} – H_3Cit – H_2O_2	$FeHCit + H_2O_2 \longrightarrow FeHCit^+ + {}^{\cdot}OH + OH^-$	radical-ion	2–4	112
Fe^{2+} – H_2LM – H_2O_2	$Fe^{2+}HLM + H_2O_2 \longrightarrow Fe^{4+}HLM + 2\,OH^-$	radical-chain	2–5	113
Fe^{2+} – EDTA – H_2O_2	$EDTAFe^{2+} + H_2O_2 \longrightarrow EDTAFeO^{2+}$	ion-molecule	4–6	2, 114
Fe^{2+} – TETA – H_2O_2	$TETAFe^{2+} + H_2O_2 \longrightarrow TETAFe^{4+} + 2\,OH^-$	"	7–8	106
Fe^{2+} – CN^- – H_2O_2	$[Fe(CN)_5H_2O]^{3-} + H_2O_2 \longrightarrow [Fe(CN)_5(H_2O)]^{2-} + {}^{\cdot}OH + OH^-$	radical-ion	3–5	115, 116

[a] The following notation has been adopted: Bipy = α,α′-bipyridyl, Phen = 1,10-phenanthroline, His = histidine, H_4T = tartaric acid, DFH_4 = dihydroxyfumaric acid, H_3Cit = citric acid, H_2LM = lumomagneson, EDTA = ethylenediaminetetraacetic acid, and TETA = triethylenetetramine.

Scheme 4



L', L'', and L''' are ligands of different kinds.

and Fe^{2+} on the oxidation mechanism is not considered, and no account is taken of the fact that the oxidation proceeds under aerobic conditions (under the influence of oxygen), as usually happens in real systems involving the use of the Fenton reagent and in other similar systems. The problem of the change in the mechanism of the oxidation of organic substrates following the introduction of an additional ligand into the system also requires special consideration. In order to take into account the above factors, it is essential to analyse the results obtained in typical ferroperoxide systems, which are listed below.

1.	$Fe^{2+} - H_2O_2 - S(S_1)$	$S(S_1)$ = noncomplex-forming or weakly complex-forming substrate. In contrast to S, the substrate S_1 has pronounced reducing properties
2.	$Fe^{2+} - H_2O_2 - S - O_2$	Aerobic system
3.	$Fe^{2+} - L - H_2O_2 - S$	The additional ligand L has been introduced into the system
4.	$Fe^{2+} - L - H_2O_2 - S - O_2$	Aerobic system with additional ligand
5.	$Fe^{2+} - H_2O_2 - S_L$	S_L = substrate which functions simultaneously as a ligand
6.	$Fe^{2+} - H_2O_2 - S_L - O_2$	Aerobic system with S_L
7.	$Fe^{2+} - L - H_2O_2 - S_L$	System incorporating L and S_L
8.	$Fe^{2+} - S_L - H_2O_2 - S$	System incorporating S_L and S
9.	$Fe^{2+} - S_L - H_2O_2 - S - O_2$	Aerobic system incorporating S_L and S

These systems can be divided into two groups. In the first group (systems 1–4), the substrate being oxidised does not form a complex with Fe^{2+} or forms it very ineffectively. Here there is little overlap of the electron orbitals of Fe^{2+} and S. The oxidation reaction in systems of this group should proceed via an outer-sphere route (outside the first coordination sphere of Fe^{2+}, i.e. in the reaction volume). In the second group (systems 5–9), the substrate is also a ligand. Here one should expect the formation of intermediate compounds with the substrate and inner-sphere electron transfer. Such subdivision into two groups reflects only the extreme manifestations of complex-forming properties and there is a possibility of a series of intermediate versions.

We shall analyse briefly the data obtained in the study of some typcial systems.

a. The $Fe^{2+} - H_2O_2 - S(S_1)$ system

Organic substances (S and S_1) without a chelating capacity towards iron ions or forming relatively unstable complexes with the latter are oxidised by the Fenton reagent.[3,128–134] Analysis of the results shows that, when the chosen substrate (S) or the substrate radical formed (R$^{\cdot}$) has no reducing properties (and the latter also has oxidising properties), the process mechanism includes the following stages:

Scheme 5

1. $Fe^{2+} + H_2O_2 \xrightarrow{k_1} Fe^{3+} + {}^{\cdot}OH + OH^-$
2. ${}^{\cdot}OH + S \xrightarrow{k_2} R^{\cdot}$
3. ${}^{\cdot}OH + H_2O_2 \xrightarrow{k_3} HO_2^{\cdot} + H_2O$
4. $Fe^{3+} + HO_2^{\cdot} \xrightarrow{k_4} Fe^{2+} + H^+ + O_2$
5. $Fe^{2+} + HO_2^{\cdot} \xrightarrow{k_5} Fe^{3+} + HO_2^-$
6. $Fe^{2+} + {}^{\cdot}OH \xrightarrow{k_6} Fe^{3+} + OH^-$

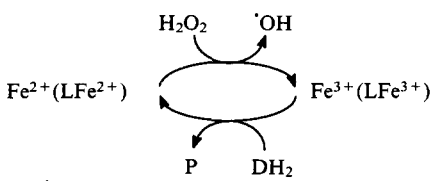
It is not difficult to demonstrate that, when $[S]/[H_2O_2] \geqslant 0.01$ (recalling that k_2 is 2–3 orders of magnitude higher than k_3), only the first two stages will occur in the system — in this case, because $k_6 = 3 \times 10^8$ litre mol^{-1} s^{-1}, $[S]/[Fe^{2+}]$ should be greater than

unity.[29] Consequently the rate of oxidation of the substrate under such conditions is defined by the following expression:

$$w_S = k_1[Fe^{2+}][H_2O_2][S]^{1\to 0}.$$

In this case, Fe^{2+} and S are actually oxidised in the system by hydrogen peroxide via a radical and not a chain mechanism. After the conversion of the initial Fe^{2+} into Fe^{3+}, the oxidation of the substrate also ceases. Since the rate constants for all the elementary stages in Scheme 4 are known, it is possible to calculate theoretically the necessary Fe^{2+}, H_2O_2, and S concentrations in each specific case for the catalytic process to occur via the radical-ion cyclic mechanism. Only when this mechanism operates can one expect the effective oxidation by the Fenton reagent of substrates of the type considered. The effectiveness of the oxidation may be increased also by the additional introduction into the reaction medium of a substance capable of reducing Fe^{3+} to Fe^{2+}, i.e. of regenerating the initial form of the catalyst. The addition of the appropriate reductant (DH_2) leads to the appearance of an oxidation-reduction (OR) cycle in which the $^{\cdot}OH$ radicals, oxidising the substrate, are generated.

Scheme 6



P = product.

Similar OR cycles arise also in the $Fe^{3+}(LFe^{3+}) - H_2O_2 - S$ systems. Such systems, containing $Fe^{2+}(LFe^{2+})$ ions (or other transition metal ions, for example Cu^{2+}),[47] hydrogen peroxide, and the reductant, have been called 'reversible' and have been described, in particular, in the monographs of Dolgoplosk and Tinyakova.[11,13] Various sugars, dienols, rongalite, hydrazine, cysteine, and a series of other organic and inorganic compounds are used as reductants. For example, ascorbic acid (AH_2) increases appreciably the effectiveness of the oxidation of ethyl alcohol by the Fenton reagent[135] ($Fe^{2+} - S_L - H_2O_2 - S - O_2$ is a typical system).[3]

The oxidation reactions of substrates with reducing properties are of greatest interest in the analysis of systems of the type considered because they play a decisive role in the formation of a reversible OR cycle incorporating the following reactions:

Scheme 7

1. $Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + {}^{\cdot}OH + OH^-$
2. $^{\cdot}OH + S_1 \longrightarrow R_1^{\cdot}$
3. $Fe^{3+} + S_1 \longrightarrow R_1^{\cdot\prime} + Fe^{2+}$

$R_1^{\cdot\prime}$ = substrate radical.

As a consequence of this, the substrate undergoes effective catalytic oxidation.

When the reactivity of the substrate radicals (including the reactivity with respect to O_2) is low, the oxidation mechanism (Scheme 7) does not include additional stages. It does not change under aerobic conditions either—conditions are considered where $[S_1]/[H_2O_2] \geqslant 0.1$, since otherwise it is also necessary to take into account the possible occurrence of stages 3–6 (Scheme 5). A similar mechanism has been adopted also in the anaerobic and aerobic oxidation of indigocarmine (IC), indigotetrasulfonate (ITS) and Methylene Blue (MB) by the Fenton reagent.[136] Since the ability of these substrates to form complexes with Fe^{2+} (the OR potential of the Fe^{3+}/Fe^{2+} couple hardly changes when the dye is added), one may assume that the catalyst in the $Fe^{2+} - H_2O_2 - IC(MB, ITS)$ systems is the Fe^{2+} aquo-ion.

A more complex picture is observed (and a greater variety of products are accordingly formed) when the substrate radical in the $Fe^{2+} - H_2O_2 - S(S_1)$ systems is reactive (it possesses mainly reducing properties).

The mechanism of the oxidation of type $S(S_1)$ substrates under anaerobic conditions in the typical $Fe^{2+} - H_2O_2 - S(S_1)$ systems has been investigated in numerous studies, which have been surveyed in the monograph of Sychev and Isak.[3] It has been most fully elucidated, justified qualitatively, and generalised in the publications of Walling and coworkers.[137–140] It has been suggested that the $^{\cdot}OH$ radical formed in the system as a consequence of the interaction of Fe^{2+} with H_2O_2.

Analysis of the possible steps occurring in the $Fe^{2+} - H_2O_2 - S(S_1)$ systems under anaerobic conditions, where the reactive substrate radical is formed, combined with allowance for other data[29,139,140] leads to the following series of consecutive steps:[3]

Scheme 8

Step	Reaction	k_i/litre mol^{-1} s^{-1}
1	$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\cdot}OH + OH^-$	53
3	$^{\cdot}OH + H_2O_2 \rightarrow HO_2^{\cdot} + H_2$	3×10^7
4	$Fe^{3+} + HO_2^{\cdot} \rightarrow Fe^{2+} + H^+ + O_2$	2.1×10^6
5	$Fe^{3+} + HO_2^{\cdot} \rightarrow Fe^{3+} + HO_2^-$	1.5×10^6
6	$Fe^{2+} + {}^{\cdot}OH \rightarrow Fe^{3+} + OH^-$	4×10^8
7	$Fe^{3+} + S_1 \rightarrow Fe^{2+} + R_1^{\cdot}$	–
8	$^{\cdot}OH + R_\alpha H^* \rightarrow R_\alpha^{\cdot} + H_2$	$\sim 10^9$
9	$^{\cdot}OH + R_\beta H^* \rightarrow R_\beta^{\cdot} + H_2$	$\sim 10^9$
10	$^{\cdot}OH + R_\gamma H^* \rightarrow R_\gamma^{\cdot} + H_2$	$\sim 10^9$
11	$R_\alpha^{\cdot} + Fe^{3+} \rightarrow Fe^{2+} + P$	$\sim 10^8$
12	$R_\alpha^{\cdot} + H_2O_2 \rightarrow ROH + {}^{\cdot}OH$	1.6×10^5
13	$R_\alpha^{\cdot} + {}^{\cdot}OH \rightarrow ROH$	$\sim 10^{10}$
14	$R_\gamma^{\cdot} + Fe^2 \rightarrow RH + Fe^{3+}$	–
15	$2R_\beta^{\cdot} \rightarrow$ products (dimers)	–
16	$RH + HO_2^{\cdot} \rightarrow R^{\cdot} + H_2O_2$	–
17	$R^{\cdot} + O_2 \rightarrow RO_2^{\cdot}$	$\sim 10^9$

Organic compounds (hydrocarbons, alcohols, aldehydes, acids, etc.), the interaction of which with $^{\cdot}OH$ in the positions indicated (α-, β-, or γ-) results in the abstraction of a hydrogen atom, are designated by an asterisk (RH*).

If the rate constants for the elementary stages presented and the concentrations of the corresponding species are known, it is possible to estimate which reactions make the main contribution to the process under consideration. It is easy to demonstrate that, in a specific instance involving certain concentrations, Scheme 8 reduces to Walling's scheme, which is well known in the literature and has been proposed for the oxidation of organic compounds of different classes under anaerobic conditions.[29] If account is taken of data[29,130,137,138,141–145] indicating the addition of $^{\cdot}OH$ to the substrate and the formation of 'adhesion' radicals, the following additional steps must be included in the mechanism:

Scheme 9

8. $R_iH + {}^{\cdot}OH \longrightarrow R_i^{\cdot}HOH$
10. $R_kH + {}^{\cdot}OH \longrightarrow R_k^{\cdot}HOH$
11. $R_i^{\cdot}HOH + Fe^{3+} \longrightarrow R_i^{\prime}HO + Fe^{2+} + H^+$
14. $R_k^{\cdot}HOH + Fe^{2+} \xrightarrow{H^+} R_k^{\prime}H_2OH + Fe^{3+}$
17. $R_j^{\cdot}HOH + R_jH \longrightarrow R_j{-}R_j + H_2O$

R_i = substrate radical with reducing properties, R_k = oxidant radical, and R_j = radical tending to dimerise.

The mechanism in each specific case must be determined by specified concentration conditions with allowance for the established reaction kinetics, the data concerning the types of

substrate radicals formed in the systems and their reactivities, as well as information about the intermediates obtained and the rate constants for elementary reactions. The problem of obtaining complete information for a particular system is difficult to solve: it is rare to achieve an unambiguous experimental determination of all the types of substrate radicals formed and it is as a rule impossible to detect the intermediates; the rate constants for any elementary stages of the oxidation process are frequently unknown. For this reason, the mechanisms of oxidation of organic substrates by the Fenton reagent under anaerobic conditions have been at the present time justified only at a qualitative level. Nevertheless the overall mechanism (Schemes 8 and 9) makes it possible to describe more fully and adequately the mechanism of the oxidation of organic substrates than Walling's scheme.

b. The $Fe^{2+}-H_2O_2-S-O_2$ system

The process mechanism under aerobic conditions becomes even more complicated when molecular oxygen is involved in the oxidation. In this case, the amount of H_2O_2 consumed in the presence of O_2 on the oxidation of a specific amount of S diminishes, while the amount of the accumulated product of the oxidation of S in the presence of O_2 exceeds the theoretical maximum value established from the amount of H_2O_2 consumed.

The question arises how molecular oxygen influences the oxidation process. It has been established experimentally that the aerobic oxidation of substrates in the absence of Fe^{2+} and H_2O_2 hardly occurs (although iron ions are a universal contaminant and it is virtually impossible to get rid of them).

The available data on the activation of O_2 by Fe^{2+} aquo-ions indicate that the process includes the reactions[2]

$$18.\ Fe^{2+} + O_2 \underset{k_{-18}}{\overset{k_{18}}{\rightleftharpoons}} (FeO_2)^{2+},$$

$$\left(K = \frac{k_{18}}{k_{-18}} = 10^{-10}\ \text{litre mol}^{-1}\right),$$

$$19.\ (FeO_2)^{2+} + Fe^{2+} \overset{k_{19},\ 2H^+}{\rightleftharpoons} 2Fe^{3+} + H_2O_2,$$

$$(k_{19} = 10^6\ \text{litre mol}^{-1}\ \text{s}^{-1}).$$

However, the influence of O_2 is exerted via the intermediates formed in the $Fe^{2+} - H_2O_2 - S$ system and not via the initial components (the last two stages may be neglected[3]). The primary product of the oxidation of organic substances by the Fenton reagent is the substrate radical R$^{\bullet}$, which possesses mainly reducing properties. Consequently, it can react effectively with O_2. Thus, in the typical systems considered, the radicals R$^{\bullet}$ formed may be consumed via the reactions with H_2O_2, Fe^{3+}, and O_2. If the interaction of $^{\bullet}OH$ with ethanol results in the formation of the alkoxy-radical $CH_3C^{\bullet}HOH$ ($R^{\bullet}_{\alpha}$), i.e.

$$20.\ C_2H_5OH + {}^{\bullet}OH \xrightarrow{k_{20}} CH_3C^{\bullet}HOH + H_2O,$$

$$(k_{20} = 1.6 \times 10^9\ \text{litre mol}^{-1}\ \text{s}^{-1}),$$

then the following reactions involving its consumption may be considered:

Step	Reaction	k_i/litre mol^{-1} s^{-1}	Ref.
12	$R^{\bullet}_{\alpha} + H_2O_2 \xrightarrow{k_{12}} ROH + {}^{\bullet}OH$	$k_{12} = 1.6 \times 10^5$	146
21	$R^{\bullet}_{\alpha} + Fe^{3+} \xrightarrow{k_{21}} P + Fe^{2+} + H^+$	$k_{21} = 2.7 \times 10^8$	147
22	$R^{\bullet}_{\alpha} + O_2 \xrightarrow{k_{22}} RO^{\bullet}_2$	$k_{22} = 4.6 \times 10^9$	148

Comparative analysis of stages 12, 21, and 22 permits the conclusion that under aerobic conditions the radicals $R^{\bullet}_{\alpha}$ are almost fully consumed on the interaction with O_2. Consequently, in contrast to the mechanism operating under anaerobic conditions (Scheme 7) and also Walling's general mechanism,[29] the above scheme should include new elementary stages involving the formation and further reactions of the peroxyl radical $CH_3C^{\bullet}H(OO)OH$ ($RO^{\bullet}_2$) derived from the alcohol. The complete mechanism of the oxidation of ethanol under aerobic conditions (an example of a typical $Fe^{2+} - H_2O_2 - S - O_2$ system), put forward by Sychev et al.,[149] is given in Scheme 10.

Scheme 10

$$1.\ Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$$

$$20.\ {}^{\bullet}OH + C_2H_5OH \longrightarrow R^{\bullet}_{\alpha} + H_2O$$

$$22.\ R^{\bullet}_{\alpha} + O_2 \longrightarrow RO^{\bullet}_2$$

$$23.\ RO^{\bullet}_2 \longrightarrow CH_3CHO + HO^{\bullet}_2$$

$$24.\ RO^{\bullet}_2 + ROH \longrightarrow CH_3CH(OOH)OH + R^{\bullet}_{\alpha}$$

$$25.\ RO^{\bullet}_2 + Fe^{2+} \xrightarrow{H^+} Fe^{3+} + CH_3CH(OOH)OH$$

$$26.\ HO^{\bullet}_2 + C_2H_5OH \longrightarrow R^{\bullet}_{\alpha} + H_2O_2$$

$$5.\ HO^{\bullet}_2 + Fe^{2+} \xrightarrow{H^+} Fe^{3+} + H_2O_2$$

$$4.\ HO^{\bullet}_2 + Fe^{3+} \longrightarrow Fe^{2+} + O_2 + H^+$$

$$27.\ CH_3CH(OOH)OH \longrightarrow CH_3CHO + H_2O_2$$

On the basis of this scheme, it is possible to derive an expression for the initial rate of formation of acetaldehyde on the assumption that $k_{25}[Fe^{2+}] \leqslant k_{23} + k_{24}[ROH]$ and $k_{26}[ROH] \ll k_5[Fe^{2+}] + k_4[Fe^{3+}]$:

$$w_{o,A} = \frac{k_1[Fe^{2+}][H_2O_2]}{(1 + k_{27}[H_2O_2])(1 + k_{24}[ROH]/k_{23})}.$$

It is consistent with the experimentally observed features.[149]

The participation of oxygen in the aerobic oxidation of organic substrates by the Fenton reagent and the complication of the reaction mechanism under these conditions has also been noted in other studies.[2, 3, 144, 150–153]

A similar mechanism operates in the oxidation of substrates also in the typical $Fe^{2+}-S_L-H_2O_2-O_2$ and $L-Fe^{2+}-H_2O_2-S-O_2$ systems with the sole difference that the coordination compounds of Fe^{2+} with S_L and L respectively function as catalysts in this case.[3]

The following features should be included in the experimental evidence for the occurrence of the process under aerobic conditions according to Scheme 10:

(1) the difference between the rates of oxidation of the substrate in the aerobic and anaerobic systems;

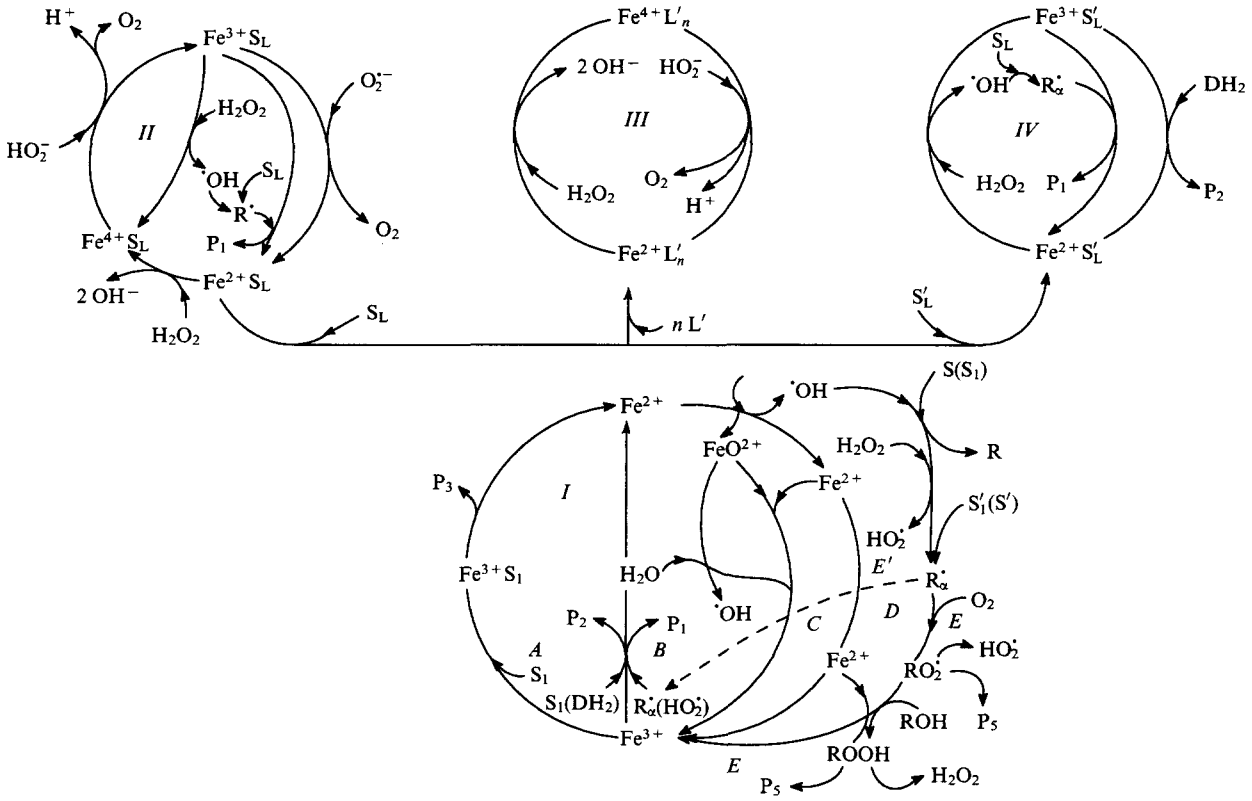
(2) the greater amount of the substrate oxidation product compared with the amount of disproportionated H_2O_2;

(3) the generation of $^{\bullet}OH$ radicals, the decrease in the Fe^{2+} concentration during the reaction, and the accumulation of Fe^{3+}.

Thus one may postulate that the mechanism of the oxidation of organic substrates under aerobic conditions by the $^{\bullet}OH$ radicals generated by ferroperoxide systems in cases where an active radical (of the type $R^{\bullet}_{\alpha}$) is formed can be described by Scheme 10. Consequently the role of H_2O_2 in the aerobic oxidation of organic substrates (especially alcohols) reduces to the preparation of the latter for their subsequent oxidation by oxygen (in the case of alcohols, for the conversion of ROH into $R^{\bullet}_{\alpha}$).

On the basis of the analysis of literature data, the mechanisms of the decomposition of H_2O_2 and of the oxidation of substrates can be represented by the generalised Scheme 11.[3]

Scheme 11



If iron(II) coordination compounds serve as the catalyst, the general mechanism assumes as a rule a form (mainly in acid and weakly acid media) analogous to fragment *I* of Scheme 11 ($Fe^{2+}L_n$ participates in the reaction instead of Fe^{2+}).

For simplicity, not all possible reactions of the $^{\bullet}OH$ radicals generated have been included in fragments *II*, *IV*, and also *I* (sequence *C*) (they are all analogous to the reactions presented in sequence *E* of fragment *I*).

The ferroperoxide systems may be classified in terms of different features: in terms of the effectiveness of their action, in terms of the complex-forming capacity of the substrate relative to Fe^{2+}, and in terms of the mechanisms of the disproportionation of H_2O_2 and the oxidation of the substrate.

If the substrate S introduced and the substrate radical $R^{\bullet}$ formed have no reducing properties, then the oxidation process decays as a function of time and reaches completion after the conversion of all the Fe^{2+} into Fe^{3+} (sequence *D* or *C* occurs — see Scheme 11). If the substrate S_1 and/or the substrate radical $R^{\bullet}_{\alpha}$ formed are effective reductants, then quantitative oxidation of the substrate takes place under anaerobic conditions, the process being more effective the higher the reducing 'strength' of the latter (or of the corresponding substrate radical). Such processes include the reaction sequences *D* (or *C*), *E*, and *B* (Scheme 11). The formation of an active substrate radical increases the effectiveness of the oxidation of the substrate also under aerobic conditions as a consequence of the realisation of sequences *D* (or *C*), *E*, and *B*. In such cases, the role of hydrogen peroxide consists merely in preparing the substrate (via the formation of $R^{\bullet}_{\alpha}$) for the subsequent interaction with O_2. It is possible to infer which of the mechanisms operates in the oxidation of a particular substrate by ferroperoxide systems, provided that the rate constants for the elementary stages of the interaction of the substrate and substrate radicals with $^{\bullet}OH$ and O_2 are known.

The role of the added inert ligand consists in enhancing the oxidising capacity of the ferroperoxide systems and of ensuring their operation in weakly acid and neutral media. This occurs as a consequence of the change in the OR potential of the Fe^{3+}/Fe^{2+} couple and the stabilisation of a particular oxidation state of iron at higher pH. If one-electron transfers from the complex catalyst to the substrate are preferred in the system, then the fundamental process mechanism is as a rule similar to that operating in the $Fe^{2+} - H_2O_2 - S$ system (Scheme 11, fragment *I*) with the sole difference that the catalyst is a Fe^{2+} ion bound in a complex. If two-electron transfers are preferred, then the mechanism as a rule changes (fragments *II* and *III* in Scheme 11). Consequently, in order to increase the effectiveness of the ferroperoxide systems, it is necessary to choose a suitable ligand and to establish conditions under which cyclic or radical-chain H_2O_2 disproportionation and substrate oxidation processes take place. If the reducing 'strength' of the substrate (or the substrate radical) is low, effective reductants (of the type of ascorbic and dihydroxyfumaric acids, etc.), capable of regenerating the active form of the catalyst (Fe^{2+}), must be introduced into the system.

The substrates S which do not form complexes are oxidised in the reaction volume by the $^{\bullet}OH$ radicals (sequences *D* or *C* in Scheme 11), while those which possess a reducing capacity (S_1) are oxidised in sequences *D* (or *C*), *E*, and *B* (Scheme 11) and also by Fe^{3+} ions (or complexes).

The substrates S_1 which form complexes with Fe^{2+} alter the OR potential of the catalyst, which may increase the catalytic activity of the latter and the fundamental mechanisms of the disproportionation of H_2O_2 and the oxidation of substrate may remain virtually unaltered under these conditions (fragment *IV* in Scheme 11) or may undergo some changes (fragment *II*). Depending on the mechanism operating, such substrates may be oxidised via an inner-sphere route (via the transfer of one or two electrons) and also in the reaction volume by the $^{\bullet}OH$ or $O_2^{\bullet-}$ radical species generated. If S_L forms complexes only with Fe^{3+}, the process mechanism includes sequence *A* instead of sequence *B* (Scheme 11).

All the ferroperoxide systems can be divided into two groups in terms of the H_2O_2 and substrate oxidation mechanisms: a radical-ion mechanism (cyclic or radical-chain) mechanism operates in the first group and is described by fragments *I*, *II*, and *IV*, while an ion-molecule mechanism operates in the second group (fragment *III* in Scheme 11).

3. Oxidation of organic substrates by the Fe^{3+} (LFe^{3+}) – H_2O_2 system

As observed already in an early investigation,[74,75] the Fe^{3+} aquo-ions also catalyse the decomposition of H_2O_2. The disproportionation of the Fe^{3+} ions proceeds via a radical-chain mechanism,[1,3,16,85,154,155] which includes stages involving the generation of $^{\cdot}OH$ free radicals. Since the formation of radicals actually ensures the high reactivity of the Fenton reagent in the oxidation reactions of organic substrates, one may expect that the substrates will be oxidised effectively also in the Ruff system, i.e. this system may be used for hydroxylation. Indeed, it has been shown[154] that acetone, *tert*-butyl alcohol, methanol, acetic acid, and other substrates are oxidised by the Ruff system.

The data concerning the influence of the type of substrate radical on the mechanism of the decomposition of H_2O_2 and on the oxidation of the substrate in the $Fe^{3+} - H_2O_2 - S_x$ system (and hence also on the composition of the oxidation products) [3] agree almost fully with those which have been obtained in the study of the oxidising activity of the Fenton reagent. The principal postulates and conclusions concerning the oxidation of S in the $Fe^{2+} - H_2O_2$ system are therefore applicable also to the oxidation of organic substrates by the Ruff system.

The mechanism of the oxidation of S by Fe^{3+} ions, as well as certain coordination compounds of trivalent iron, in the course of the catalytic disproportionation of H_2O_2, has been considered from similar standpoints.[70,85,89,142,156–162]

The reactions involving the oxidation of organic dyes by the Ruff system (and also by the Fenton reagent) are used widely in the kinetic methods for the determination of microamounts of iron ions in weakly acid aqueous media.[3,163–168]

The set of consecutive stages occurring in each specific case in the oxidation of substrates in the $Fe^{3+} - H_2O_2$ systems depends on the type of substrate, the properties of the substrate radical formed, and the experimental conditions (primarily on the concentrations of the reactants and on the occurrence of the process under aerobic or anaerobic conditions). All the factors noted above affect the process mechanism in the given system, as in the $Fe^{2+} - H_2O_2$ system. In planning the experiment and in considering the mechanism of the oxidation of substrates by the Ruff system, one may be guided by the generalised Scheme 11, which has been developed for the Fenton reagent and ferroperoxide systems.

III. Intermediates of the type of ferryl ions and complexes in the catalysis of oxidation processes

The fundamental mechanisms of the activation of oxygen, the catalytic decomposition of hydrogen peroxide, and the oxidation by the latter of organic substrates in the presence of iron ions or coordination compounds of iron were examined above. The role of the intermediate reactive species formed on reduction of O_2 or decomposition of H_2O_2 — the superoxide ($HO_2^{\cdot}$) and especially hydroxyl ($^{\cdot}OH$) radicals — was fairly widely dealt with in this connection.

Since the beginning of the 1930s, the nature and role of the reactive species formed in the interaction of iron ions or complexes with hydrogen peroxide has been the subject of numerous publications and discussions. Since the investigations of Haber and Weiss,[169,170] the view that the initial activation of H_2O_2 by Fe^{2+} ions is accompanied by the formation of the $^{\cdot}OH$ radical has been quite firmly established.

$$Fe^{2+}(aq) + H_2O_2 \longrightarrow Fe^{3+}(aq) + OH^- + {}^{\cdot}OH \qquad (1)$$

This was confirmed by the experimental observation of the acceleration of the polymerisation of various monomers when H_2O_2 and Fe^{2+} ions are introduced into the reaction medium, by the analysis of the products of the hydroxylation of numerous organic compounds by the Fenton system, and by comparing the rate constants for the elementary stages in the interaction of various substrates with hydroxyl radicals (generated in the radiolysis of water), and also by the results of the study of the catalytic decomposition of H_2O_2 by the Fe^{2+} aquo-ions.[3]

However, the question arises whether reaction (1) is elementary. If it is not, then what are the reactive species which precede the appearance of the $^{\cdot}OH$ radical and what are their properties? Many investigators postulate that the generation of Fe^{3+} ions and the hydroxyl radicals $^{\cdot}OH$ by the $Fe^{2+}(aq.) - H_2O_2$ system does not constitute unambiguous proof that reaction (1) is elementary and that these species are merely the detectable products of a complex process.

Since the study of Bray and Gorin[171] up to the present time, there has existed also another point of view, according to which the hydrogen peroxide decomposition process in the $Fe^{2+}(aq.) - H_2O_2$ system proceeds with formation of the ferryl

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{IV}{=}O^{2+} + H_2O \qquad (2)$$

ion $(Fe^{IV} = O)^{2+}$:

$$L_nFe^{2+} + H_2O_2 \longrightarrow (L_nFe^{IV}{=}O)^{2+} + H_2O\,. \qquad (3)$$

At a higher pH, a complex is formed:

The occurrence of stage (2) requires the simultaneous transfer of two electrons from the catalyst to H_2O_2. Although direct experimental evidence for the formation of the ferryl ion FeO^{2+} in the given system has not been obtained, nevertheless this idea has been supported by many investigators,[2,116,172–177] who used it to account for the mechanism of the activity of the Fenton reagent. Subsequently the possibility of the formation of the ferryl species as a constituent of complexes at pH 7 and not in an acid medium, where only the $Fe^{2+}(aq.) - H_2O_2$ system may exist, was also considered.[178] Be it as it may, one cannot rule out the possibility of the formation of the ferryl ion in ferroperoxide systems. It may be that the interaction of Fe^{2+} with H_2O_2 results in the initial formation of an intermediate complex, where electron transfers lead to the generation of the ferryl ion, giving

$$Fe^{2+} + H_2O_2 \underset{-H^+}{\rightleftharpoons} Fe^{2+}(HO_2^-) \xrightarrow{H^+} \qquad (4)$$

$$\longrightarrow FeO^{2+} + H_2O \longrightarrow Fe^{3+} + HO^- + {}^{\cdot}OH$$

rise to the $^{\cdot}OH$ radicals as a result of the reaction with water.

If the contribution of the inner-sphere electron transfer in the intermediate complex, leading to the formation of FeO^{2+}, is large and the ferryl ion interacts rapidly with a water molecule, then only the $^{\cdot}OH$ radicals and Fe^{3+} ions are detected in the system. This explains the impossibility of the experimental detection of the FeO^{2+} species in the Fenton system. This problem has been analysed in detail in the monograph of Sychev and Isak.[3]

In more complex systems (metal complexes, enzymes and their models which incorporate iron at the active centre of the enzyme, as well as hydrogen peroxide and dioxygen), there is an increase in the likelihood of the generation of the ferryl species bound in a complex as a consequence of the greater probability of the transition of iron to the Fe(IV) oxidation state and the stabilisation of the latter by the surrounding ligands (L). The number of examples of this kind has been increasing recently.

There is experimental proof that at a low pH the $^{\cdot}OH$ radicals are generated by reaction (1) in the Fenton system, whereas at a high pH, where the iron ion is bound in a complex, there is an increase in the probability of the appearance, instead of the $^{\cdot}OH$ radical, of the less reactive ferryl complex species $L_nFe^{IV}{=}O^{2+}$ via reaction (3). This species acts more specifically as an oxidant.

The mechanisms of reactions (1) and (3) apparently include the formation of the intermediate Fe^{II} and Fe^{III} peroxo-complexes.[178] However, it is not entirely clear which oxidising species are formed in the course of these reactions. The proof of the formation at different pH of oxidising species differing from one another is provided by the characteristic features of the product distribution in the reactions of a series of substrates. In acid media, the distribution is close to that attained when the $^{\bullet}OH$ radicals, generated by radiolysis, are employed whereas in neutral and alkaline media it is more stereospecific. In other words, in the latter case the oxidant is not the $^{\bullet}OH$ radical but another species, tentatively ferryl iron.[29,179-183] Different experimental methods have been used in experiments of this kind:[184,185] pulse radiolysis, the stopped flow method, the generation of iron(IV) compounds as a result of the oxidation of iron(III) salts or complexes by $^{\bullet}OH$ free radicals, and the reduction of the ferrate ion (FeO_4^{2-}) to the perferryl ion (FeO_4^{3-}) by the hydrated electron or the $CO_2^{\bullet-}$ radical. Ferryl (Fe^{IV}) and perferryl (Fe^{V}) forms of iron have different spectroscopic characteristics. On the other hand, in terms of their chemical behaviour they are very similar and this is why perferryl can sometimes be used as a model for the investigation of the interaction of ferryl with organic substrates. Thus iron in the +4 oxidation state has been detected in the presence of inorganic ligands (OH^-, $P_2O_7^{4-}$, and HCO_3^-/CO_3^{2-}) or their mixtures.[185]

$$^{\bullet}OH + Fe(OH)_4^- \longrightarrow Fe^{IV} + H_2O \quad (k = 10^8 \text{ litre mol}^{-1} \text{ s}^{-1})$$

$$^{\bullet}OH + HCO_3^-/CO_3^{2-} \longrightarrow H_2O/OH^- + CO_3^{\bullet-} \quad (k = 4 \times 10^8 \text{ litre mol}^{-1} \text{ s}^{-1})$$

$$CO_3^{\bullet-} + L_nFe^{III} \longrightarrow L_nFe^{IV} + CO_3^{2-} \quad (k = 2.4 \times 10^8 \text{ litre mol}^{-1} \text{ s}^{-1})$$

$$^{\bullet}OH + [Fe^{III}OH(P_2O_7)_2]^{6-} \longrightarrow [Fe^{IV}(OH)(P_2O_7)_2]^{5-} + OH^- \quad (k = 5 \times 10^7 \text{ litre mol}^{-1} \text{ s}^{-1})$$

Although the different iron(IV) complexes have very similar spectroscopic characteristics ($\lambda_{max} \approx 430$ nm, $\varepsilon = 900 \pm 100$ litre $mol^{-1} s^{-1}$), the kinetics of their reactions depend on the pH and the nature of the ligand (the half-reaction time $\tau_{1/2}$ varies from 0.1 to 1.0 s).[184-186] The iron(V) compounds are relatively stable in alkaline solutions ($\tau_{1/2} \approx 170$ ms) and their UV spectra have a shoulder between 260 and 300 nm [$\varepsilon = (4 - 5) \times 10^3$ litre $mol^{-1} s^{-1}$].[185] The iron(V) complexes are much more reactive than the iron(VI) complexes: the ratio of the rate constants for the oxidation of formate is

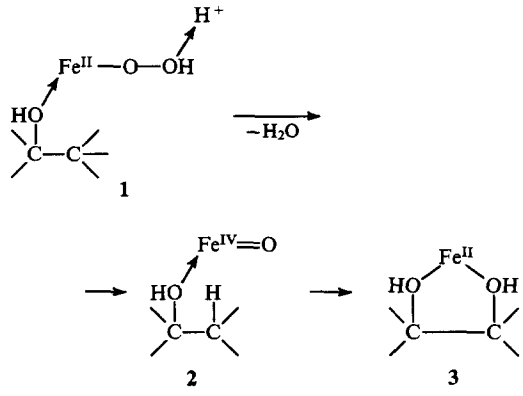
$$\frac{k_{Fe^V + HCOO^-}}{k_{Fe^{VI} + HCOO^-}} = 10^5 .$$

Such or an even greater increase in reactivity is observed on passing from iron(V) to iron(IV) complexes.

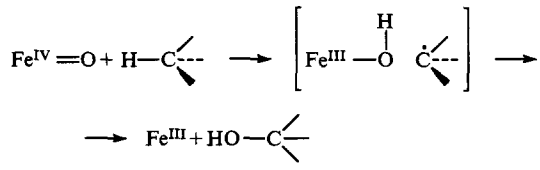
In systems of the Fenton type under the conditions involving the formation of superoxidised iron states, the latter may exhibit a greater specificity (stereospecificity) in oxidation and hydroxylation reactions.[186] Such specificity is especially important when the reactions proceed in biological systems.

One of the first fairly convincing experimental pieces of evidence for the generation of the ferryl ion in oxidation-reduction catalytic reactions has been obtained by Groves.[187] In the oxidation of cyclohexanol by hydrogen peroxide in the presence of iron(II) salts and perchloric acid in acetonitrile, in addition to cyclohexanone, the products included cyclohexanediols, 72% of which comprised *cis*-cyclohexane-1,3-diol. Such regioselectivity was explained by the appearance of an iron(IV) intermediate capable of subsequently transferring an oxygen atom. This view has been confirmed by the existence of a whole series of salts and other compounds in which the oxidation state of iron is +4.

The above regioselectivity might have been the result of the formation of an iron(II) complex **1** with the OH group of cyclohexanol and the peroxide ion. The reaction is accompanied by the heterolysis of the peroxide, which leads to the formation of complex **2**, and the insertion of oxygen in the substrate (complex **3**).



The transfer of oxygen from the ferryl intermediate to the carbon atom of cyclohexanol, accompanied by the formation of the corresponding diol, most probably proceeds in accordance with the mechanism



Somewhat later, the iron in the 'ultrahigh' oxidation state was detected in the reaction of hydrogen peroxide with the water-soluble iron(III)-porphyrin.[188] The compound formed, in which the iron atom is in the same oxidation state, is characterised by an appreciable lifetime in aqueous solution.[184] The reduction potential of the ferryl/ferriporphyrin couple is ~ 0.9 V, which is lower by 1.3 V than for the $^{\bullet}OH/H_2O$ couple at pH 7.[178] The maximum (FeO^{2+} – chelate)/(Fe^{3+} – chelate) potential is approximately 2 V, i.e. the ferryl complex is a weaker and more selective oxidant than the $^{\bullet}OH$ radical.

Yet another piece of experimental evidence for the possibility of the formation of a ferryl complex is provided by the results obtained in the study of the interaction of the coordination compound Fe^{II}EDTA with H_2O_2 and the way the system is acted upon by various alcohols, aminoacids, and acids. The reaction of Fe^{II}EDTA with H_2O_2 may involve the formation of either the $^{\bullet}OH$ radical or the ferryl complex of EDTA, the latter being more probable. Indeed, it has been shown that this process can be described by the following equations:[189]

$$Fe^{II}EDTA + H_2O_2 \xrightarrow{k_1} I_1 \xrightarrow{Fe^{II}EDTA} Fe^{III}EDTA$$

$$I_1 + H_2O_2 \xrightarrow{k_2} I_2 \xrightarrow{Fe^{II}EDTA} Fe^{III}EDTA$$

I_1 and I_2 = intermediates

where $k_1 = 1.75 \times 10^4$ and $k_2 = 3.2 \times 10^3$ litre $mol^{-1} s^{-1}$. It has been suggested that the intermediate I_1 is most probably the ferryl-EDTA complex and not the hydroxyl radical, while the intermediate I_2, capable of reacting with ferricytochrome *c*, is the $^{\bullet}OH$ radical. The difference between I_1 and I_2 is manifested by their different reactivities towards *tert*-butyl alcohol and ethanol ($^{\bullet}OH$ radical-fixing agents). The intermediate I_1 is not fixed by *tert*-butyl alcohol, whereas the intermediate I_2 is fixed. I_1 is much less reactive towards the benzoate ion, *tert*-butyl alcohol, the acetate ion, arginine, and serine than the $^{\bullet}OH$ radical, but it is fixed by compounds with easily oxidisable functional groups such

as ethanol and isopropyl alcohol. All this indicates that the intermediate I_1 does not effect reactions characteristic of the hydroxyl radical and as an oxidant has a reactivity closer to that of the metal ion, i.e. it resembles the complex (FeO^{2+})EDTA.[189]

Although the formation of the 'OH radical in the Fe^{2+}–EDTA – H_2O_2 systems has been confirmed by various methods (the spin trapping method,[190] the hydroxylation of aromatic compounds,[191] and comparison of the rate constants for the interaction of certain substances with the above radicals and the 'OH radicals obtained by radiolysis),[192] nevertheless there exists the view, based on the dehydration of cytochrome *c* in the given system, according to which the reactive species is more likely to be the ferryl complex and not the 'OH radical. The formation of the ferryl complex may precede the formation of 'OH radicals. Indeed, two oxidising species are generated in the reactions of haemoglobin with H_2O_2, one of which hydroxylates aromatic compounds (the 'OH radical), while the other cannot effect this reaction.[193] It has been suggested that this second species is the ferryl complex. Thus there are two possibilities for the formation of reactive species in vivo.[194–201] The predominance of one or other possibility depends on the biological target to which the iron ions bind.[193]

The generation of the ferryl group on protonation of plant peroxidases has been confirmed with the aid of resonance Raman spectroscopy. A hydrogen bond, in which the oxygen atom bound to the ferryl ion of the peroxidase participates, arises in this process.[202–204] The formation of the ferryl group has been confirmed also by the study of the interaction of peroxidases and catalases with peroxides.[205] Two intermediates are formed (green and red compounds), the first of which is formally $Fe^{V}O^{3+}$, or more precisely a $[P^{\cdot+}Fe^{IV}O]^{3+}$ haem (one electron is transferred to iron by the porphyrin ligand), while the other is an Fe^{IV} haem. Indeed, bands characteristic of the vibrations of the $Fe^{IV}=O$ groups have been noted in the resonance Raman spectra of the second haem intermediate. The frequencies of these vibrations are extremely sensitive to the effect of the environment. Peroxidase exhibits an enzyme activity only when the $Fe^{IV}=O$ group binds the hydrogen of a remote aminoacid group.

The interaction of ferrimyoglobin with H_2O_2 has also been examined as a possible model of the activity of catalase. It was postulated that the structure of the intermediate includes the ferryl ion (FeO^{3+}).[206]

The presence of the ferryl group in model systems simulating the peroxide oxidation of lipids has been demonstrated experimentally.[207] Whereas it had been suggested previously that the 'OH radical is the initiator of the peroxide oxidation (peroxidation) of lipids, later this role began to be attributed to an ionic complex of adenosine diphosphate ($ADP.Fe^{2+}.O_2$). Initiation by the 'OH radical is more likely in the absence of appreciable amounts of iron chelates. Otherwise (for example, in biological systems) the peroxidation of lipids apparently proceeds without the involvement of the hydroxyl radical. Two additional electrons convert the initial complex into the ferryl complex. This reaction resembles reaction (2).[187] It has been postulated that the ferryl ions are formed preferentially in the reaction of the

$$ADP\cdot Fe^{2+}\cdot O_2 \xrightarrow{2H^+,\,2\bar{e}} ADP\cdot(FeO_2)^{2+} + H_2O$$

adenosine diphosphate complex of iron(II) with hydrogen peroxide. The principal evidence for the absence of the hydroxyl radicals from the $ADP\cdot Fe^{2+}\cdot O_2$ system is the fact that, after the addition of a strong acceptor (mannitol), the rate of peroxidation of lipids remains almost unchanged. Thus the oxidation is promoted by the ferryl ions forming part of the ADP complex and not by the 'OH radicals.

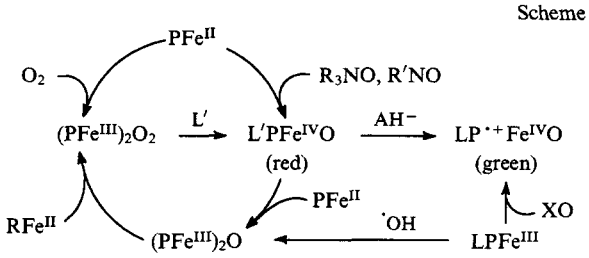
The involvement in the process of 'OH radicals or ferryl complexes depends to some extent on the hydrogen peroxide concentration in the system, which has been observed in the reaction involving the membrane peroxidation of lipids.[208] At low H_2O_2 concentrations and in the presence of haemoproteins (myoglobin, haemoglobin), lipids are oxidised mainly by ferryl species, whereas at high concentrations they are oxidised by hydroxyl radicals.

The epoxidation of alkenes and the hydroxylation of alkanes by various oxidants in the presence of iron-porphyrin complexes can proceed via different mechanisms.[5,209] The mechanism of the epoxidation of alkenes by iodosobenzene, hydrogen peroxide, and hydroperoxides (the catalysts are various porphyrin complexes of iron) includes the formation of the $P^{\cdot+}Fe^{IV}=O$ oxoporphyrin π-radical-cation as the oxidant. This species has not been isolated, but its existence has been confirmed by the presence in the resonance Raman spectrum of an intense band at 852 cm^{-1} (~ 15 K), which appears during the irradiation by a laser of the oxygenated iron complex of *meso*-tetraphenylporphyrin $Fe(TPP)O_2$.[210] This species may be formed in the presence

$$Fe(TPP)Cl + XO \longrightarrow Fe^{IV}O(TPP^{\cdot})Cl + X.$$

of an oxidant (XO) in accordance with the mechanism
The length of the $Fe=O$ bond is ~ 1.60 – 1.66 Å.[211] Examination of the molecular orbitals in the $FeO(P)H_2O$ complex (P = porphyrin) shows that the ferryl group has the electronic configuration $\sigma^2\pi^4\pi^{*2}$, i.e. it contains the $Fe=O$ double bond.[212] The paths leading to the formation of such species at temperatures below −50 °C have been examined in fair detail. Depending on the source of oxygen, the nature of the axial ligand (L′ or L), the way in which these species are obtained, the solvent, and the temperature, the oxo-transfers occur with formation of different intermediates.[213]

Scheme 12

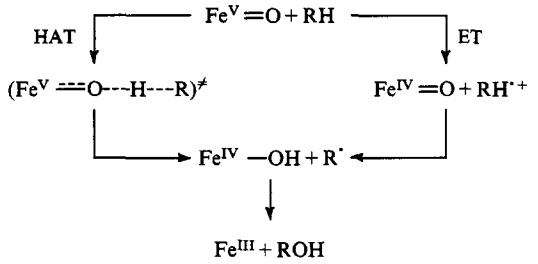


Here PFe^{II} is the porphyrin complex of iron(II), $L'PFe^{IV}O$ is the complex with the additional ligand L′ = methylimidazole or pyridine), $LP^{\cdot+}Fe^{IV}O$ is a similar complex with $L = ClO_4^-$, $LPFe^{III}$ is the iron(III) complex, $(PFe^{III})_2O$ is the dinuclear oxoiron(III) complex, $(PFe^{III})_2O_2$ is the μ-peroxo-dimer, AH^- is the electron acceptor, and XO is the oxidant (R_3NO or R′NO). The $Fe^{IV}O$ species cannot be detected in aqueous solutions or isolated in the form of the corresponding porphyrin complex. It can be more easily detected in a nonaqueous medium. The different routes to its formation are presented in Scheme 12.

When alkanes are hydroxylated by dioxygen in the presence of the same catalyst, the oxoiron(IV)-porphyrin participates in the process. The mechanism of the hydroxylation by iodosobenzene is radical in character. When this reaction proceeds with participation of hydrogen peroxide, the oxidising species is the 'OH radical, whereas in the case where hydroperoxides participate in the reaction, two oxidation mechanisms are possible: with formation of RO' (free-radical reactions) and with generation of high-valence oxoferryl species.

The hydroxylation of the substrate RH by an oxygen donor (iodosobenzene, peroxy-acids, etc.) in the presence of iron(III)-porphyrin has been discussed.[214] Two possible mechanisms were postulated: with hydrogen atom transfer (HAT) and with electron transfer (ET) from RH to the perferryloxygen atom ($Fe^{IV}=O$) formed in the system.

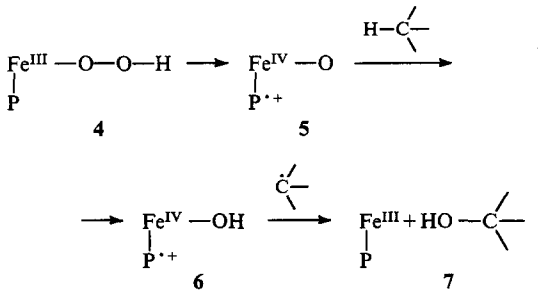
Scheme 13



The electron transfer path predominates when the hydroxylation substrates are electron-rich substances. An oxoferryl compound and a substrate radical-cation are formed in this case. The latter is deprotonated and affords the same pair of substances as in the transfer of a hydrogen atom. The interaction of this pair leads to the formation of a hydroxylated substrate. If the process is carried out in solvents with a low polarity and with the participation of substrates with an oxidation potential below 1.2–1.4 V, the HAT mechanism is preferred. In more polar solvents and with the participation of a substrate with an oxidation potential of 1.2–1.8 V, the ET mechanism predominates.

The formation of the oxoiron(IV)-porphyrin radical-cation is postulated in the hypothetical model of the generation of the active catalyst in hydroxylation reactions effected by cytochrome P-450.[215,216] The mechanism of this process provides for the heterolytic dissociation of the O–O bond in the hydroperoxoiron complex **4** with formation of the iron-porphyrin **5**, which has undergone one-electron oxidation and is an active oxidant. On reaction with the substrate, this complex accepts a hydrogen atom and gives rise to the hydroxoiron(IV) complex **6**. The radical centre of the substrate then recombines with the OH group of the hydroxoiron(IV) complex, which leads to the formation of the hydroxylated substrate and the initial ferri-form **7** of cytochrome P-450. The mechanism of this process can be represented in the following form:[217]

Scheme 14

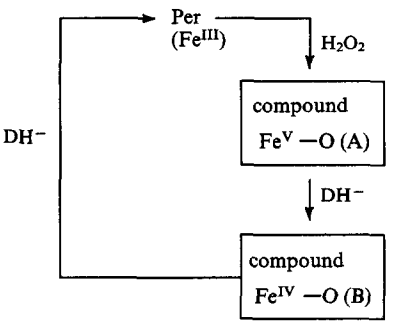


The interaction of various peroxidases (Per) with hydrogen peroxide results in the formation of outer- and inner-sphere intermediates and then of the compound PerO of the ferryl type ($Fe^V - O$ or more precisely $P^{\cdot+}Fe^{IV}O$):[218]

$$Per + H_2O_2 \rightleftharpoons (PerH_2O_2) \rightleftharpoons PerH_2O_2 \longrightarrow PerO + H_2O.$$

The formation of the Fe–O bond and other rearrangements do not require that a high energy barrier be overcome (the activation energy for this process is approximately 14.7 kJ mol^{-1}). The rates of formation of compounds of the type Fe^VO are similar for different haemoproteins. The addition of an oxygen atom to the Fe^{III} atom of the native enzyme converts the latter formally into the Fe^V state but, in the presence of a suitable reductant (DH^-) or of an additional electron, the source of which may be some kind of haemoprotein, the final product becomes a compound of the type $Fe^{IV}O$, which can be in its turn reduced to the Fe^{III} state of the initial peroxidase.

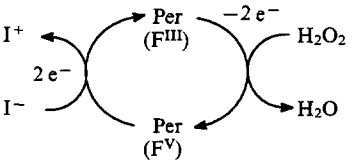
Scheme 15



This reaction cycle is characteristic, in particular, of horse peroxidase (the data on the magnetic susceptibilities of compounds A and B have been interpreted as referring to the Fe^V and Fe^{IV} states respectively). In the case of other peroxidases (chloroperoxidase, cytochrome *c* peroxidase), approximately the same reactions with some deviations have been observed.

The reactions of a type Fe^VO compound can be demonstrated in relation to the interaction of the native horse peroxidase with the iodide ion.

Scheme 16



The same two-electron mechanisms of the interaction of the enzyme with hydrogen peroxide and of compound A with the iodide ion is characteristic also of chloroperoxidase. When nitrous acid (or the nitrite anion) participates in the usual enzymic cycle, compound A undergoes one-electron reduction to compound B and the latter is reduced to the initial peroxidase.

The reactions of a type $Fe^{IV}O$ compound have been investigated in particular detail in relation to horse peroxidase. Compounds A and B may compete with one another for the reductant. At a low pH, this competition is won by compound B, whilst at pH 9 it is won by compound A. Under such conditions, the yield of compound B may be made quantitative and the conversion of $Fe^{IV}O$ into PFe^{III} may be observed spectrophotometrically at the wavelength $\lambda = 425$ nm. In the general case, the interaction of various peroxidases with hydrogen peroxide affords compounds A and B in a similar way, although these processes also differ somewhat from one another.

The details of the oxidation of iron(III) porphyrinate by hydrogen peroxide or by organic peroxides in the catalytic cycle involving peroxidases and catalases were refined in subsequent studies. Thus it has been demonstrated by electronic and Mössbauer spectroscopy and also by EPR spectroscopy that compound A is the oxoiron(IV)-porphyrin π-radical-cation,[219] i.e.

$$P^{\cdot+}F^{III} + H_2O_2 \longrightarrow P^{\cdot+}Fe^{IV}{=}O,$$

whereas compound B is formed as a result of the one-electron reduction of compound A:

$$P^{\cdot+}Fe^{IV}{=}O + DH^- \longrightarrow PFe^{IV}{=}O + {}^{\cdot}DH.$$

The formation of compound A in the cytochrome P-450 cycle has also been postulated.

The better understanding of the mechanisms of the interaction of H_2O_2 or of the hydroperoxides ROOH with peroxidases, catalases, and cytochrome P-450 considered here is assisted by the study of model systems of the type $PFe^{III} - X - H_2O_2(ROOH)$. Evidence has been obtained[220]

that the peroxide (hydroperoxide) O–O bond is dissociated homolytically in the $(Ph_4P)Fe^{III}Cl - H_2O_2(ROOH)$ systems (Ph_4P = 5,10,15,20-tetraphenylporphyrinate) in methanol. This results in the formation of highly oxidised forms of iron porphyrinate of the oxoferryl type.

$$(Ph_4P)Fe^{III}(Cl) + ROOH \longrightarrow [(Ph_4P)Fe^{IV}O(Cl)RO^{\cdot}] \longrightarrow \begin{cases} [(Ph_4P^{\cdot+})Fe^{IV}O(Cl)] + RO^- \\ [(Ph_4P)Fe^{IV}O(Cl)] + RO^{\cdot} \end{cases}$$

It is much more difficult to investigate the catalytic decomposition of H_2O_2 in model systems of the type $PFe^{III}X - H_2O_2$ and to demonstrate the formation in this process of oxoferryl complexes in aqueous solutions, because in this instance it is necessary to create conditions preventing the appearance of the inactive dinuclear iron(III) porphyrinates and the stabilisation of oxoferryl species. The use of the $(TDSP)Fe^{III}(H_2O) - H_2O_2 - ABTS - H_2O$ model systems (30 °C), where $(TDSP)Fe^{III}(H_2O)$ = 5,10,15,20-tetra(2,6-dimethyl-3-sulfophenyl)porphyrinatoiron(III) hydrate and ABTS = 2,2′-azinodi(3-ethylbenzothiazoline-6-sulfonate), a trapping agent for the highly oxidised form of iron, made it possible to avoid the formation of dinuclear complexes and to stabilise the oxoiron(IV) porphyrinate species.[188] Depending on the pH (in the range 1–12), iron(III) complexes of different composition are formed initially: $(TDSP)Fe^{III}(H_2O)(H_2O_2)$ at a low pH, $(TDSP)Fe^{III}(OH^-)(H_2O_2)$ at an intermediate pH, and $(TDSP)Fe^{III}(OH^-)(HO_2^-)$ at a high pH. The homolytic or heterolytic dissociation of the peroxide O–O bond in the intermediate leads to the formation of $(TDSP)Fe^{IV}O$ and $^{\cdot}OH$ and of $(TDSP^{\cdot+})Fe^{IV}O$ and H_2O respectively.

Thus very numerous pieces of experimental evidence have been obtained in recent years for the generation of ferryl ions, their complexes, and enzyme compounds of types A and B, which are strong and at the same time specific oxidants for organic substrates (in hydroxylation, epoxidation, etc. reactions), competing with $^{\cdot}OH$ radicals. The $(Fe^{IV}=O)^{2+}$ species and $^{\cdot}OH$ radicals are highly reactive: the former can be converted into the latter under the conditions of the catalytic oxidation of any kind of substrate, for example in the $Fe^{2+}(aq.) - H_2O_2 - S$, $L_nFe^{2+} - H_2O_2 - S$, and enzyme $-Fe^{2+} - O_2(H_2O_2) - S$ systems. Hence it follows that the experimental identification of the ferryl species is in general fairly difficult and the question of the generation of such 'ultra-oxidised' iron states in the specific systems investigated is not yet clear. Even in the case where the formation of such species has been demonstrated by some kind of experimental method (with varying degrees of reliability), the information obtained is factual in character and does not account for the differences between the catalytic activities (for example in the decomposition of hydrogen peroxide) of different transition metal ions and of the different effects on the latter by the ligands and also for the appearance of different intermediate species (peroxo-complexes, free radicals) in the initiation steps.

Hence arises the need for the theoretical estimation of the possibility of the generation of ferryl species in the step involving the initiation of the decomposition of H_2O_2, starting with the simplest Fenton system $Fe^{2+}(aq.)-H_2O_2$ (working in weakly acid media) and ending with more complex $L_nFe^{2+} - H_2O_2$ systems.

It has been suggested that the initiation stage in the decomposition of hydrogen peroxide in the Fenton system is elementary.[1] According to an alternative view, the generation of the $^{\cdot}OH$ radical and the Fe^{3+} ion is not unambiguous evidence that this stage is elementary. It may be that the two-electron transfer from the catalyst to the substrate results in the initial formation of the ferryl ion.[171]

$$[(H_2O)_5Fe^{II}(H_2O)]^{2+} + H_2O_2 \xrightarrow[-H_2O,\ -H^+]{} [(H_2O)_5Fe^{IV}O]^{2+} \xrightarrow{H_2O} [(H_2O)_5Fe^{III}(OH^-)]^{2+} + {}^{\cdot}OH$$

It was later suggested[177] that a peroxo-complex is generated intially and a complex with a ferryl ion is formed from it as a consequence of intramolecular electronic transitions. The latter complex is then converted into an iron(III) complex and $^{\cdot}OH$.

$$[(H_2O)_5Fe^{II}(H_2O)]^{2+} + H_2O_2 \xrightarrow{-H_2O} [(H_2O)_5Fe^{II}(H_2O_2)]^{2+} \xrightarrow{-H^+} [(H_2O)_4(OH^-)Fe^{IV}O]^{+} \xrightarrow{H_2O} [(H_2O)_4(OH^-)_2Fe^{III}]^{+} + {}^{\cdot}OH$$

However, as already stated above, there is no convincing experimental evidence in the literature for the proposed mechanisms of the initiation of the decomposition of H_2O_2. On the contrary, according to the data of Koppenol and Liebman,[178] $^{\cdot}OH$ radicals are formed in this system in acid media and the possibility of the appearance of ferryl complexes increases only in neutral and alkaline media (where the iron ions are bound in complexes). Nevertheless, the idea that a ferryl species is formed in ferroperoxide systems has been discussed in numerous investigations.[3]

For a theoretical consideration of the possibility of the initial formation of ferryl species in the Fenton system, quantum-chemical calculations of the electronic structure of $Fe(H_2O)_6^{n-}$ and of a series of hypothetical complex compounds, postulated[171,177] as intermediates, have been performed. Calculations have also been carried out for all the peroxide species (H_2O_2, HO_2^-, $HO_2^{\cdot}$, and $^{\cdot}OH$) by the LCAO-MO SCF method in terms of the Mulliken–Wolfsberg–Helmholtz (MWH) approximation.[221] Self-consistent atomic charges and orbital populations as well as the electronic energy levels and the coefficients of the LCAO of the corresponding MO were found from these calculations (Fig. 1). Furthermore, the electron transfer from the MO of the complex to the MO of the peroxide species has been assessed quantitatively and the amounts of charge transferred (δq) have been found.

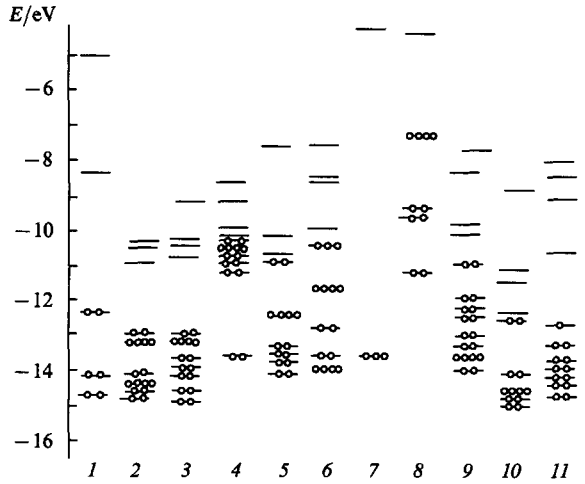


Figure 1. Energy level diagram for the molecular orbitals of the active regions of the molecules: (*1*) H_2O_2; (*2*) $[Fe^{II}(H_2O)_6]^{2+}$; (*3*) $[Fe^{II}(H_2O)_5.(H_2O_2)]^{2+}$; (*4*) $[Fe^{II}(OH^-)(H_2O)_4(H_2O_2)]^{+}$; (*5*) $[Fe^{IV}O(H_2O)_4(OH^-)]^{+}$; (*6*) $[Fe^{III}(OH)_2(H_2O)_4]^{+}$; (*7*) $^{\cdot}OH$; (*8*) HO_2^-; (*9*) $[Fe^{II}(H_2O)_5(HO_2^-)]^{+}$; (*10*) $[Fe^{IV}O(H_2O)_5]^{2+}$; (*11*) $[Fe^{III}(OH^-)(H_2O)_5]^{2+}$.

Analysis of the energy levels of the complexes indicates a low probability of the formation of the peroxo-complex $[Fe^{II}(H_2O)_5(H_2O_2)]^{2+}$ (energy level set *3*) and the impossibility of the occurrence of intramolecular transformations in which $[Fe^{II}(OH^-)(H_2O)_4(H_2O_2)]^+$ (*4*) and $[Fe^{IV}O(H_2O)_4(OH^-)]^+$ (*5*) are generated, because the levels of the highest occupied molecular orbitals (HOMO) and the lowest unoccupied orbitals (LUMO) of these species are much higher than the corresponding levels of both $[Fe(H_2O)_6]^{2+}$ (*2*) and $[Fe^{II}(H_2O)_5(H_2O_2)]^{2+}$ (*3*). Thus the formation of the ferryl ion in a very acid medium is impossible, in agreement with the experimental data.

However, as the pH increases, the intermediate peroxo-complex $[Fe^{II}(H_2O)_5(HO_2^-)]^+$ may be formed, which is indicated by analysis of the nature of the HOMO and LUMO levels of the species $[Fe(H_2O)_6]^{2+}$ (*2*) and HO_2^- (*8*) and of the hypothetical complex $[Fe^{II}(H_2O)_5(HO_2^-)]^+$ (*9*) and also by calculation of the charge transfer from the aquoiron(II) complex to H_2O_2 and from HO_2^- to the aquo-complex ($\delta q = -0.05$ e and 0.76 e respectively). Comparison of the energy levels of the MO of the peroxo-complex $[Fe^{II}(H_2O)_5(HO_2^-)]^+$ (*9*), on the one hand, and the MO of the complexes $[Fe^{IV}O(H_2O)_5]^{2+}$ (*10*) and $[Fe^{III}(OH^-)(H_2O)_5]^{2+}$ (*11*), on the other, indicates the possibility of a multistage course for the process.

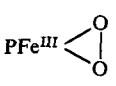
$$[Fe^{II}(H_2O)_6]^{2+} + H_2O_2 \xrightarrow[-H^+]{} [Fe^{II}(H_2O)_5(HO_2^-)]^+ \xrightarrow{H^+}$$

$$\longrightarrow [Fe^{IV}O(H_2O)_5]^{2+} \xrightarrow{H_2O} [Fe^{III}(H_2O)_5(HO^-)]^{2+} + {}^{\cdot}OH$$

Thus, quantum-chemical calculations have confirmed the possibility of the formation of the peroxo-complex $[Fe^{II}(H_2O)_5(HO_2^-)]^+$ and the ferryl ion $[Fe^{IV}O(H_2O)_5]^{2+}$ as intermediates. If the reactions considered are rapid, then it is in fact impossible to detect these species at the present level of experimental technique and only $[Fe^{III}(H_2O)_5(OH^-)]^{2+}$ and the radical ${}^{\cdot}OH$ can be detected in the system. This indicates the limits of the existing experimental possibilities and confirms the importance of the quantum-chemical calculations.

IV. Porphyrin and other iron complexes in the catalysis of epoxidation and hydroxylation reactions

Numerous studies (see, for example, Refs 222–229, etc.) have been devoted to the mechanisms of the oxidation of alkenes, alkanes, and other organic substrates by dioxygen under the influence of various monooxygenases (cytochrome P-450 and others) and these problems will not be specially considered here. It is sufficient to note that the prosthetic group in monooxygenases is the iron(III) complex of the porphyrin (P), which in the course of the interaction with O_2 is converted into the highly reactive ferryl species $P^{\cdot+}Fe^{IV}=O$ or $PFe^{IV}=O$ (compounds A and B), which selectively epoxidise or hydroxylate alkenes or alkanes. When these reactions take place only with participation of iron complexes of porphyrin, which may be regarded as the closest structural model of monooxygenases, similar oxoferryl species are also formed. The mechanisms of the epoxidation and hydroxylation by these model compounds have their characteristic features, determined by the nature of the oxidant transferring oxygen to the iron atom of the porphyrin complex, the characteristics of the catalyst and the solvent, and the temperatures.[230–232] Thus the introduction of individual substituents into the porphyrin can prevent the transition of the monomeric peroxoiron(II) complex of the porphyrin[233–236]



into the μ-oxodimer $(PFe^{III})_2O$.[237] Under conditions where the peroxoiron(III) complex of tetramesitylporphyrin (TMP) was acylated by acetic anhydride (Ac_2O) at low temperatures (−45 °C), the product was $TMP^{\cdot+}Fe^{IV}=O$.[238,239] The same reactive species was generated in a series of other model systems[239,240] and in the interaction of peroxidase with H_2O_2.[241] The formation of a similar species from the acylated iron complex (TMPFeOOAc) is the rate-determining stage of the entire process.[242] On this basis, the catalytic model system[242]

$$T_{piv}PPFeBr - Zn(Hg) - MV^{2+} - Ac_2O - O_2 ,$$

was developed. Here $T_{piv}PP$ = tetra(α,α,α,α-*o*-pivaloylaminophenyl)porphyrin, whose complex with iron is not converted into the μ-oxodimer,[243] while the dioxygen complex $T_{piv}PPFe(O_2)$ is stable at room temperature,[244,245] Zn(Hg) is zinc amalgam, which plays the role of the reductant, and MV^{2+} is methylviologen, which facilitates electron transfer from the reductant to $T_{piv}PPFe(O_2)$. The oxidation by this system of substrates (RH) such as cyclohexene, cyclohexane, and 1,2-dimethylcyclohexane was investigated.[242] The reactions occurring in this process are presented in Scheme 17.

Scheme 17

1. $Zn(Hg) + MV^{2+} \longrightarrow MV^{\cdot+}$
2. $Zn(Hg) + PFe^{III} \longrightarrow PFe^{II}$
3. $MV^{\cdot+} + PFe^{III} \longrightarrow PFe^{II} + MV^{2+}$
4. $PFe^{II} + O_2 \longrightarrow PFeO_2$
5. $PFeO_2 + MV^{\cdot+} \longrightarrow PFeO_2^-$
6. $PFeO_2^- + Ac_2O \longrightarrow P^{\cdot+}Fe^{IV}=O + 2\,AcO^-$
7. $P^{\cdot+}Fe^{IV}=O + RH \longrightarrow PFe^{III} + ROH$
8. $P^{\cdot+}Fe^{IV}=O + MV^{2+} \longrightarrow PFe^{III} + \text{products}$
9. $MV^{\cdot+} + O_2 \longrightarrow MV^{2+} + O_2^{\cdot-}$
10. $O_2^{\cdot-} + Ac_2O \longrightarrow AcO_2^{\cdot} + AcO^-$
11. $AcO_2^{\cdot} + RH \xrightarrow[-AcOOH]{} R^{\cdot} \xrightarrow{O_2} ROH + R'O$
12. $P^{\cdot+}Fe^{IV}=O + PFe^{III} \longrightarrow \text{products}$

The following equation can be written for the rate of formation of cyclohexanol (ROH):[246]

$$\frac{d[ROH]}{dt} = \frac{k_7[RH](k_1[MV^{2+}] + k_2[PFe^{III}])}{2\,(k_7[RH] + k_8[MV^{2+}] + k_{12}[PFe^{III}])} + \frac{k_9[O_2](k_1[MV^{2+}] - k_2[PFe^{III}])}{2\,k_3[PFe^{III}]} .$$

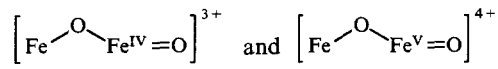
This equation agrees well with experimental data. The activity of the system may be greatly increased by immobilising the above catalyst on a solid polymeric support. The activation of O_2 in the hydrocarbon oxidation processes in the presence of metalloporphyrins can be achieved also by means of other systems.[247,248]

A wider range of iron-porphyrins in acetonitrile solutions was used in subsequent studies and the kinetics of the oxidation of cyclohexane by atmospheric oxygen (at 20 °C) in the presence of carboxylic acids (acetic and benzoic) and a reductant (zinc dust) were investigated both with and without the introduction of methylviologen.[249] The addition of methylviologen was accompanied by the accelerated absorption of O_2 and the generation of H_2O_2. On interaction with H_2O_2, the iron-porphyrins gave rise to a species of the type $P^{\cdot+}Fe^{V}=O$ or $P^{\cdot+}Fe^{IV}=O$ [250] and the oxidation mechanism resembles the 'shunted' mechanism involving the oxidation of hydrocarbons by cytochrome P-450. In the absence of methylviologen, the activation of O_2 in these systems is

apparently achieved almost in the same way as in the cytochrome P-450 system.[249]

In order to form an oxene (an oxygen atom) from O_2 and transfer it to iron, it is necessary to bind the water residue (O^{2-}) to acceptors of some kind (the most suitable acceptor is acetic anhydride). The latter interacts with O_2 and iron-porphyrin and gives rise to the complex PFe–O–O–Ac at −70 °C, which is converted into $P^{\cdot+}Fe{=}O$ at −50 °C.[251] Numerous pieces of evidence have been obtained for the involvement of precisely the $P^{\cdot+}Fe{=}O$ species (detected spectroscopically) in the interaction with alkenes and alkanes.[251–256,279] The ferryl complex with the radical-cation of a nonhaem ligand, which interacts with alkanes,[257] has recently been characterised for the first time, i.e. the study of the analogues of nonhaem monooxygenases has been initiated.

The possibility of the formation of a ferryl species, but this time as part of the composition of a dinuclear complex, has been postulated also in reactions involving the use of methane monooxygenase.[253,258,259] A general method of synthesis of complexes of this kind has been developed[260,261] and alkanes have been oxidised by hydrogen peroxide in acetonitrile with their participation. The postulated mechanism of the oxidation of alkanes includes the formation of a hydroxoperoxoiron complex, which decomposes heterolytically with formation of the ferryl species[253]

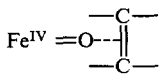


Apart from the haem and nonhaem[262–265] iron complexes, generating ferryl intermediates on treatment with oxenoids (O_2, H_2O_2, ROOH, PhIO, ClO^-, etc.), other active species may also be formed. Brief information about these has been published.[253,266]

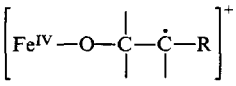
The possibility of the replacement of O_2 by other oxidants capable of transferring an oxygen atom to the metalloporphyrin and of generating the same oxoferryl species as those produced by dioxygen has been discussed in detail in a number of reviews.[5,242,267,268]

Oxidants such as iodosobenzene (PhIO), NaClO, H_2O_2, and hydroperoxides (ROOH) are usually employed in alkene epoxidation reactions catalysed by iron-porphyrin complexes. The epoxidation of alkenes in the FeTPP–PhIO catalytic system (H_2TPP = tetraphenylporphyrin) is stereospecific: only *cis*-epoxides are obtained from *cis*-alkenes. *cis*-Alkenes are much more reactive than their *trans*-isomers. The oxidant for the substrate is the oxoiron(IV)-porphyrin π-radical-cation $P^{\cdot+}Fe^{IV}{=}O$, which can react in different ways with the alkene, affording intermediates:

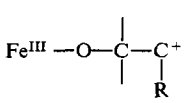
via the direct transfer of an oxygen atom,



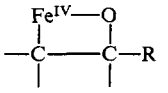
via the free-radical addition of the alkene,



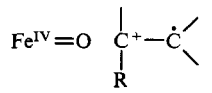
or its electrophilic addition,



via the formation of ferra(IV)oxetane,



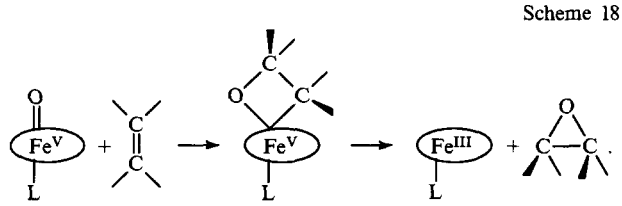
or via electron transfer with formation of an alkene radical-cation[5,269]



The decomposition of the ferra(IV)oxetane to the epoxide, electron transfer or partial charge transfer from the alkene to the oxoiron(IV)-porphyrin π-radical-cation, and other processes have been considered on the basis of kinetic data as the rate-determining stages of the reaction.[5,270]

It was postulated that the intermediate metallooxenes[271] are formed when oxygen is transferred from the highly oxidised oxoiron-porphyrins to the alkenes in the epoxidation reactions.[268,272–275] The following mechanism has been proposed for this process:[272,273]

Scheme 18



It has proved impossible to characterise the intermediate ion complex with the aid of EPR and NMR spectra.[274] The principal piece of evidence for its formation is the proportions of the reaction products. The involvement of the ferra(IV)oxetane in the epoxidation of *cis*-cyclooctene (as well as norbornene) in the presence of *meso*-[tetra(pentafluorophenyl)porphyrinato]-iron(III) chloride [$(F_{20}TPP)Fe^{III}(Cl)$] and C_6F_5IO has been reflected in the mechanism of this process developed on the basis of kinetic data.[276,277]

Scheme 19

$(F_{20}TPP)Fe^{III} + C_6F_5IO \rightleftharpoons (F_{20}TPP)Fe^{III}-OIC_6F_5$

$(F_{20}TPP)Fe^{III}-OIC_6F_5 \longrightarrow (F_{20}^{\cdot+}TPP)Fe^{IV}O + C_6F_5I$

$(F_{20}^{\cdot+}TPP)Fe^{IV}O + \text{alkene} \rightleftharpoons \text{Fe(IV)oxetane}$

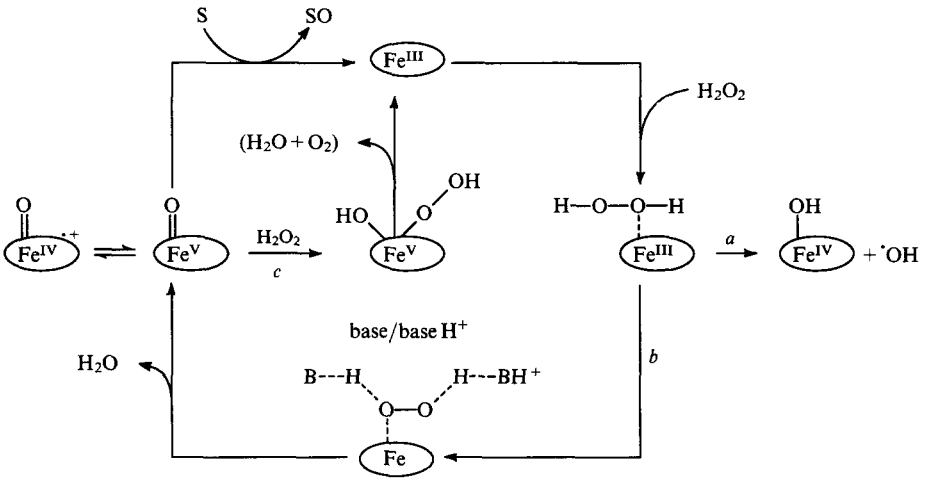
$\text{ferra(IV)oxetane} \longrightarrow (F_{20}TPP)Fe^{III} + \text{epoxide}$

The rate constants indicate that the rate of the process is determined by the stage involving the decomposition of ferra(IV)oxetane to the epoxide and the initial catalyst $(F_{20}TPP)Fe^{III}$.[277]

However, in the study of, for example, the oxidation of *trans*-cyclooctene and other alkenes in the presence of iron porphyrinates as catalysts, the idea of the formation of the ferraoxetane as an intermediate was rejected and the epoxidation was regarded as a result of electron transfer from the alkene to the highly oxidised iron intermediate.[278–281] In the case where the epoxidation substrate was ethene, a biradical intermediate was more likely to participate in the reaction than the ferraoxetane.[282] In the oxoiron-porphyrin systems, radical intermediates are formed preferentially in the reactions with alkenes. Thus one must take into account the possibility that the epoxidation reactions proceed not only via metallaoxetanes but also via other routes, especially since the evidence for the existence of metallaoxetanes is incomplete. This situation resembles somewhat that which has arisen in the study of the possibility of the existence of the oxoferryl ion. Indeed, if the ferraoxetane is highly reactive (this means that it is short lived), then it is difficult or impossible to detect it experimentally. Hence it follows that the question of the formation of metallaoxetanes in the epoxidation reaction remains controversial.[283]

The epoxidation of alkenes (S) by hydrogen peroxide in the presence of iron-porphyrin complexes may proceed via different reaction paths:[5] via a homolytic path with the generation of $^{\cdot}OH$

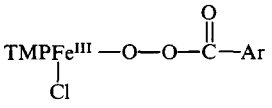
Scheme 20



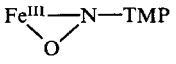
(path *a*, Scheme 20), via a heterolytic path with formation of oxoferryl species (path *b*), and via a catalase path, in which the addition of a second H_2O_2 molecule with formation of O_2 and H_2O is postulated (path *c*). Path *b* is the main one,[5,209] while path *c* is the second in importance.

The epoxidation by hydroperoxides involves their decomposition by iron(III)-porphyrins as a result of a homolytic process with formation of a complex between oxoiron(IV) and the alkoxyl radical RO·,[5,284] i.e. via a free-radical mechanism, although other paths are not ruled out.

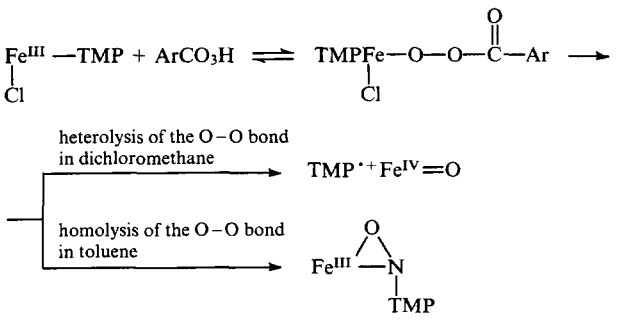
The nature of the solvent also exerts a significant effect on the nature of the intermediates formed and on the process selectivity. Thus, in the epoxidation of a 1 : 1 mixture of norbornylene and α-methylstyrene by chloroperbenzoic acid in the presence of the complex Fe^{III}TMP(Cl) [tetramesitylporphyrinatoiron(III) chloride] as the catalyst at −78 °C in dichloromethane, norbornylene is oxidised to a greater extent than α-methylstyrene (100 : 9).[285] In these reactions, the colour of the solution changed from brown to green after the addition to the system of $ArCO_3H$ as the source of oxygen, which indicates the formation of the oxoiron(IV)-porphyrin π-radical-cation ($TMP^{\cdot+}Fe^{IV}=O$) from the intermediate peracid complex of iron.



When the epoxidation is carried out in an aromatic solvent (toluene), the selectivity with respect to the alkenes changes significantly: comparable amounts of norbornylene and α-methylstyrene are oxidised. In this case, the active species in the epoxidation process is the *N*-oxide[286]



while the formation of the $TMP^{\cdot+}Fe^{IV}=O$ species is less probable.[285]

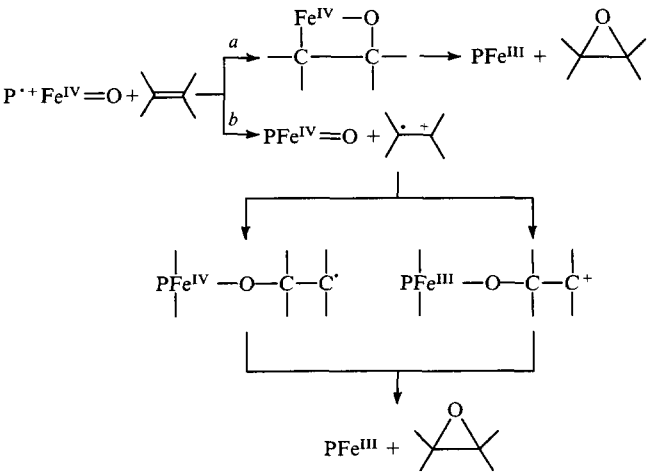


Hence the nature of the active intermediate species produced and the selectivity determined by this factor depend to a large extent on the choice of solvent.

The nature of the substituents in the porphyrin ring and of the axial ligand also influences the activity of the catalyst in the epoxidation reactions. It has been established that an increase in the number of electron-accepting substituents in the porphyrin ring and an increase in the electron-accepting capacity of the axial ligand increase the electrophilicity (oxidising power) of the intermediate oxoiron(IV)-porphyrin π-radical-cation, as a consequence of which the activity of this species increases.

The details of the formation of the type $P^{\cdot+}Fe^{IV}=O$ intermediates in living systems are not as yet entirely clear. One of the possible routes is the formation of a peroxide bridge. For example, in the interaction of the complex $[Fe^{III}(OH^-)(TMP)]^+$ with *p*-$NO_2C_6H_4CO_3H$, the intermediate Fe^{III}(TMP) peroxybenzoate is formed initially and its decomposition then affords $(TMP^{\cdot+})Fe^{IV}=O$, i.e. the same species as in the processes occurring under the influence of cytochrome P-450. It has been suggested that the mechanisms of the epoxidation of different alkenes (for example, norbornene) in the presence of iron(III)-tetraarylporphyrin and pentafluoroiodosobenzene by systems modelling cytochrome P-450 involve the formation of the $P^{\cdot+}Fe^{IV}=O$ intermediate, which interacts with alkenes at a rate close to that of a diffusion process, as a result of which it is impossible to isolate it at normal temperatures. It has been suggested in this connection[287] that electrocyclic addition (*a*) and electron transfer (*b*) mechanisms operate.

Scheme 21



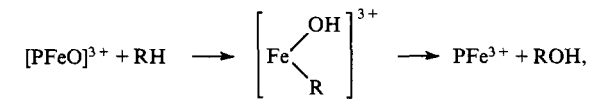
The first mechanism includes the electrolytic addition of the alkene to $Fe^{IV}=O$ with formation of a ferracyclooxetane and the second involves initial electron transfer with formation of a

radical-cation and the subsequent decomposition of the latter into either radical or cationic species. The idea of electron transfer (path *b*) agrees with all the available kinetic data and with the proportions of the reaction products. This is the most probable mechanism of the oxidation of alkenes in both model and enzyme systems.[287]

The characteristic features of processes involving the hydroxylation of alkanes as well as the epoxidation of alkenes depend on the source of oxygen, the nature of the catalyst, and other factors. Thus the oxidation of cyclohexane with the aid of PhIO and FeTTPCl [*meso*-(tetra-*o*-tolylporphyrinato)iron chloride] leads to the formation of cyclohexanol and cyclohexanone, hydroxylation proceeding via a radical mechanism.[5] It has been shown[288] that alkanes may be oxidised also in accordance with a cryptoradical mechanism via the formation of the $P^{\cdot+}Fe^{IV}=O$ active species.

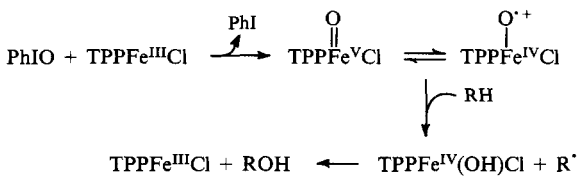
The introduction of substituents into the porphyrin alters the regioselectivity of the oxidation of alkanes.[239,289–291] The regioselectivity of these reactions should depend on steric and electronic factors, which has in fact been demonstrated in a study of the oxidation of hexane by iodosobenzene, where a tetraphenylporphyrin complex of iron (TPPFeCl) was used as the catalyst.[242] The ratio of the oxidation products (2-hexanol and 3-hexanol) was then determined mainly by steric factors, while the ratio of 1-hexanol and 3-hexanol depended on both steric and electronic characteristics of the substituents. An increase in steric hindrance in the porphyrin molecule increased the proportions of both 1-hexanol and 2-hexanol relative to 3-hexanol because of the greater accessibility of the atoms of the first two alcohols. The introduction of electron-accepting substituents into the porphyrin molecule promotes the generation of a more electrophilic oxoferryl species, which also facilitates the formation of the primary alcohol. Thus the study of the steric and electronic effects in model systems made it possible to understand better the nature of similar effects generated by proteins in the monooxygenase enzyme systems.[242,292,293]

Insertion of an oxygen atom into a C–H bond of the alkane in model systems is apparently a two-electron process, which proceeds with the intermediate formation of an alkylhydroxocomplex,[242] i.e.

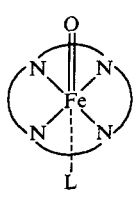


although the preliminary formation of the $[PFeOH + R^{\cdot}]^{3+}$ couple cannot be ruled out in individual instances.

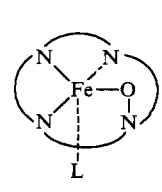
A similar mechanism of the hydroxylation of cyclohexane (RH) by iodosobenzene has been proposed on the basis of the analysis of spectroscopic and EPR data.[294]



As in many other investigations (see, for example, Refs 268 and 295–297), in this case the structure of the active catalyst (the oxoferryl species) was represented by formula **8**.

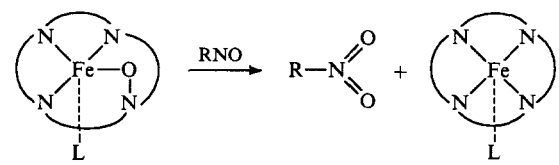


8



9

However, both experimental[298–300] and theoretical[212,301–303] points of view give rise to doubts about structure **8**. As a result, another structure (formula **9**) was proposed in which the oxygen atom was inserted in one of the iron–nitrogen bonds. This model of the oxoiron-porphyrin was used [304] to describe the oxidation of the nitroso-compounds RNO (R = Ar or Bu^t) to the nitro-compounds RNO_2. In the presence of PhIO and the very effective catalyst TPPFe(III)Cl at 0 °C and even at −78 °C (in dichloromethane), this reaction proceeds very rapidly, so that the yield of the nitro-compound reaches more than 90% after several minutes. The tentative mechanism of the formation of RNO_2 from the oxoferryl species **9** can be represented in the following way:[304]



In the presence of *meso*-[tetra(pentafluorophenyl)porphyrinato]iron (F_{20}TPP)Fe, isobutane is hydroxylated at a low temperature in Bu^{t}OH with a selectivity up to 95%. The hydroxylation can occur even at room temperature, but this requires *meso*-[tetra(pentafluorophenyl)-β-octabromoporphyrinato]iron as the catalyst. The proposed mechanism involves the reduction of the iron(III)-porphyrin complex to the iron(II) complex, the formation of an oxoiron μ-complex, and its subsequent conversion into the $Fe^{IV}=O$ form. The latter reacts with isobutane, abstracting a hydrogen atom.[5]

In the presence of hydrogen peroxide as the source of the oxygen, polyhalogenated iron-porphyrins, containing bromine, chlorine, or fluorine in the β-pyrrole positions, catalyse the hydroxylation of aromatic compounds (for example, benzene to phenol) at room temperature.[5]

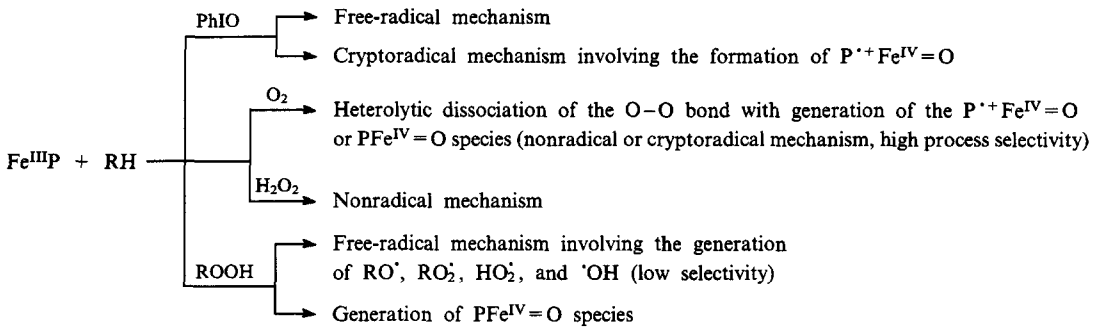
On the other hand, if the oxidants are alkyl hydroperoxides ROOH, then two paths leading to the activation of a C–H bond of the substrate are followed in the presence of iron-porphyrins: via the homolytic cleavage of the O–O peroxide bond with formation of a RO$^{\cdot}$ free radical or via the heterolytic dissociation of this bond with generation of oxoferryl species.[305] Thus the mechanisms of the hydroxylation of alkanes when different oxygen sources are employed can be represented in a general form as shown in Scheme 22.

These hydroxylation mechanisms predominate, although it has been suggested that, depending on the nature of the iron porphyrinates, the choice of the solvent, and temperatures, other mechanisms, differing in certain details, may also operate.[5]

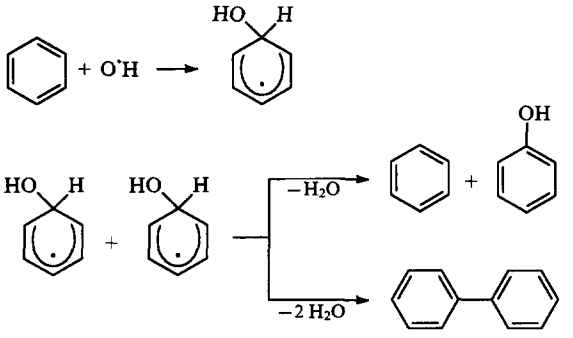
Despite the entire wide variety of the systems modelling monooxygenases and of the iron-porphyrin complexes employed in them, and also despite the dependence of the mechanisms of the oxidation of alkenes and alkanes on the surroundings of the catalyst active centre, one may say that, overall, the processes involving the epoxidation and hydroxylation of organic substrates proceed via the formation of highly reactive oxoferryl iron complexes, although one cannot fully exclude other paths.

Numerous studies have been devoted to the catalytic hydroxylation of the aromatic ring by the Fenton reagent ($Fe^{2+} + H_2O_2$).[130,306–311] Under these conditions, benzene, phenol, and their derivatives are hydroxylated in an aqueous medium via the generation of $^{\cdot}OH$ radicals, which interact with the corresponding substrates via the formation of various intermediate substrate radicals. For example, the hydroxylation of benzene involves the formation of the hydroxycyclohexadienyl radical, which, on subsequent disproportionation or dimerisation, is converted into phenol or biphenyl respectively.

Scheme 22

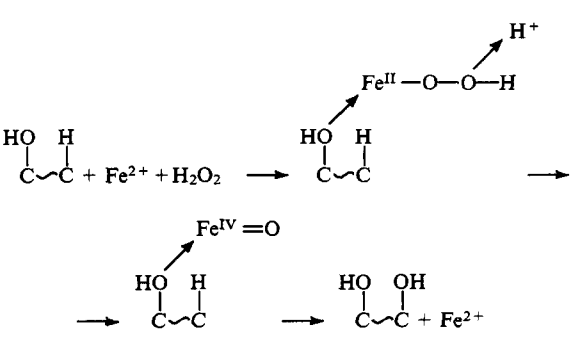


Scheme 23



The effectiveness of the hydroxylation of benzene by the Fenton reagent depends in many respects on the reactant ratios, the pH of the medium, and other factors. The selectivity of the hydroxylation of benzene and phenol derivatives is low and the reaction proceeds via a radical mechanism. It has been shown that, in the hydroxylation of the aromatic ring (especially in benzene) by the Fenton, Udenfriend [$Fe^{3+}-O_2(H_2O_2)$-EDTA-AH_2, where AH_2 = ascorbic acid], and Hamilton ($Fe^{3+}-L-H_2O_2$, where L = different ligands) systems, the highest yield of the product is observed in the last case.[130] However the selectivity and yields are nevertheless low in all the systems, although it is sometimes possible to increase them.[312]

In aqueous-aprotic or aprotic solvents, both the selectivity and the yield of the hydroxylation products increase in a number of instances and a series of physicochemical characteristics also change. It therefore becomes impossible to describe the hydroxylation reaction as a radical process involving the interaction of ·OH with substrates, and the formation of an oxoferryl species, which promotes the insertion of an oxygen atom in the C–H and C=C bonds and in the aromatic ring, is postulated in this instance. For example, in the oxidation of an alcohol by the Fenton reagent in acetonitrile, proportions of the isomers in the reaction products uncharacteristic of a radical process are observed, which can be accounted for by the fact that the active hydroxylating species is not the ·OH radical but an oxoferryl compound.[313]



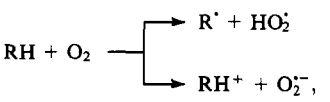
The formation of an oxoferryl intermediate in a process involving the Fenton reagent is also indicated by the extremely high NIH shifts (the migration of hydrogen isotopes on hydroxylation of labelled compounds), which are observed when an oxygen atom is inserted into the 4-deuteriochlorobenzene, 4-deuterioanisole, and 1,4-dideuterionaphthalene in nitromethane and acetonitrile (the NIH shifts are 38%, 30%, and 68% respectively). Small NIH shifts correspond to radical processes. Thus, in the hydroxylation of the first two compounds in water, the NIH shifts were 2% and 3% respectively.[314,315] The appreciable increase in the NIH shift on passing from aqueous to aprotic media shows that in the latter case the hydroxylation of aromatic compounds proceeds via the formation of oxoferryl intermediate.[315]

V. The role of iron compounds in the manifestation of toxicity by the products of the reduction of O_2 in vivo

Iron compounds as catalysts activate O_2 and H_2O_2, generating reactive species $O_2^{\cdot-}$, ·OH, and $LFeO^{2+}$) via the reduction of dioxygen and hydrogen peroxide. These species are responsible for the toxicity of the products of the reduction of O_2, participating both in the peroxide oxidation of lipids and in the decomposition (damage) of deoxyribonucleic acids (DNA) and other biological targets in vivo.[316]

Iron complexes play an important role in the peroxide oxidation of lipids, i.e. in a process where the substrates are aliphatic acids, especially polyunsaturated acids. This process exerts a significant effect on biological membranes, influences the toxicity of medicinal preparations, and contributes to carcinogenesis and other manifestations of the oxidative stress. A detailed survey of the lipid peroxidation processes may be found in many of the articles in a collected volume.[317] In the present section, attention is concentrated on the role of iron compounds in this process and on their interaction with oxygen species, especially with the superoxide radical-ion $O_2^{\cdot-}$.

The direct interaction of O_2 with organic compounds in vivo, i.e.



with formation of $O_2^{\cdot-}$ is extremely slow as a consequence of the endothermic nature of this reaction. However, in biological systems a number of reductants, for example the flavines (FH_2), may interact nonenzymically with O_2 via a radical mechanism to form the hydroperoxyl radical $HO_2^{\cdot}$.[318]



The hydroperoxyl radical is also generated in the autoxidation of cytochrome P-450[319] in the xanthine–xanthine oxidase system and in many other cases.[318]

The interaction of $O_2^{\cdot-}$ with H_2O_2 affords the radical $^{\cdot}OH$:

$$O_2^{\cdot-} + H_2O_2 \longrightarrow O_2 + OH^- + {}^{\cdot}OH.$$

However, in aqueous solution the rate constant for this reaction is close to zero and at low concentrations of the starting materials the interaction does not take place noncatalytically.

The presence in vivo of iron ions or compounds (under physiological conditions, at micromolar concentrations) makes this reaction catalytic (the Haber–Weiss reaction).

$$Fe^{3+} + O_2^{\cdot-} \longrightarrow Fe^{2+} + O_2$$
$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + {}^{\cdot}OH$$
$$O_2^{\cdot-} + H_2O_2 \xrightarrow{Fe^{III}} O_2 + OH^- + {}^{\cdot}OH$$

In aqueous solutions, $O_2^{\cdot-}$ has reducing rather than oxidising properties. However, in vivo there are many other reductants (NADPH, NADH, cysteine, etc.), which may compete with $O_2^{\cdot-}$. Hydrogen peroxide readily permeates through cell membranes, whereas $O_2^{\cdot-}$ can pass only through special channels.[320] Furthermore, a ferryl species together with a suitable iron complex, similar to the active compounds A and B of peroxidase and cytochrome P-450 as regards the oxidation state of oxoiron, may be formed via the reaction

$$LFe^{3+} + {}^{\cdot}OH \longrightarrow (LFe^{IV}{=}O)^{2+} + OH^-,$$

and also via another route.

The human organism contains on average approximately 4 g of iron, 66% of which is present in haemoglobin, ~ 10% in myoglobin, a small amount in various iron-containing enzymes and in the transport protein transferrin, while the rest is present in storage tissues (ferritin and haemosiderin) and in certain other tissues, organs, and intercellular fluids.[320]

The presence of iron in the living organism makes possible the formation of ferryl species or $^{\cdot}OH$ radicals. The latter are capable of abstracting a hydrogen atom from the lipid (LipH) and of forming a hydrocarbon radical derived from polyunsaturated aliphatic acids (Lip$^{\cdot}$), which reacts rapidly with O_2 and generates a peroxyl radical ($LipO_2^{\cdot}$). This radical interacts with the lipid molecule, forming the lipid hydroperoxide (LipOOH), which is fairly stable under physiological conditions. One of the functions of compounds of iron (and certain other transition metals) consists in catalysing the decomposition of LipOOH. In vivo, such iron complexes may be formed by phosphates, phosphate esters (ADP), and porphyrins (haemoglobin, methaemoglobin, peroxidase, cytochrome P-450, other cytochromes, and nonhaem iron-proteins) and can participate in the propagation of the membrane lipid peroxidation chain with formation of alkoxyl and alkylperoxyl radicals (LipO$^{\cdot}$ and $LipO_2^{\cdot}$ respectively), which stimulate the given chain reaction. All these reactions can be represented as follows:[320]

$$LipH + {}^{\cdot}OH \longrightarrow Lip^{\cdot} + H_2O,$$
$$Lip^{\cdot} + O_2 \longrightarrow LipO_2^{\cdot},$$
$$LipO_2^{\cdot} + LipH \longrightarrow LipOOH + Lip^{\cdot},$$
$$LipOOH + LFe^{2+} \longrightarrow LFe^{3+} + OH^- + LipO^{\cdot},$$
$$LipOOH + LFe^{3+} \longrightarrow LFe^{2+} + H^+ + LipO_2^{\cdot}.$$

It is frequently assumed that the iron complexes initiate the peroxide oxidation of lipids. In reality, however, in most cases they also induce the decomposition of the lipid hydroperoxides formed previously and the generation of oxygen radicals ($O_2^{\cdot-}$ and $^{\cdot}OH$).

$$LFe^{2+} + O_2 \rightleftharpoons LFe^{2+}O_2 \longleftrightarrow LFe^{3+}O_2^{\cdot-} \rightleftharpoons$$
$$\rightleftharpoons LFe^{3+} + O_2^{\cdot-}$$
$$2O_2^{\cdot-} + 2H^+ \longrightarrow H_2O_2 + O_2$$
$$LFe^{2+} + H_2O_2 \longrightarrow LFe^{3+} + OH^- + {}^{\cdot}OH$$

Indeed the hydroperoxides formed on peroxidation are unstable and their subsequent decomposition to iron(II, III) compounds leads to the formation of numerous products, containing aldehyde, keto-, hydroxy-, epoxy-, and carboxy-groups. The aldehyde products formed are frequently responsible for the poor taste of many food products, in particular for the incipient bitter taste of fats and oils. It has been shown that highly reactive aldehydes, such as hydroxyalkenals (for example, 4-hydroxynonenal) are formed in vivo on peroxidation of liver microsomal lipids and that, by accumulating in the NADPH–Fe systems, they inhibit the syntheses of many substances important for cells.[321]

The available kinetic data also fail to confirm the hypothesis[322] that the peroxidation of lipids is initiated by species of the type $Fe^{2+}O_2 \leftrightarrow Fe^{3+}O_2^{\cdot-}$ or $O_2^{\cdot-}$. The $O_2^{\cdot-}$ species cannot be an initiator in the absence of iron ions.[323] Indeed, it has been shown[324] that the cell toxicity of the product of the adriamycin (an antibiotic used in tumour therapy) redox cycle in vivo is associated with the enhanced formation of oxygen radicals, which initiate the peroxide oxidation of lipids only in the presence of Fe^{3+} ions.

Redox cycle:

$$\text{Adriamycin} + \tfrac{1}{2}\text{NADP} + H^+ \xrightarrow{\text{NADPH–cytochrome P-450}} \text{adriamycin semiquinone} + \tfrac{1}{2}NADP^+$$
$$\text{Adriamycin semiquinone} + O_2 \longrightarrow \text{adriamycin} + O_2^{\cdot-}$$

Stimulation:

$$Fe^{3+} + O_2^{\cdot-} \longrightarrow Fe^{2+} + O_2$$

Peroxidation of lipids:

$$LipH + O_2 + Fe^{2+} + H^+ \longrightarrow Lip^{\cdot} + H_2O_2 + Fe^{3+}$$
$$Lip^{\cdot} + O_2 \longrightarrow LipO_2^{\cdot}$$
$$LipO_2^{\cdot} + LipH \longrightarrow LipOOH + Lip^{\cdot}$$
$$Fe^{3+} + \tfrac{1}{2}NADPH + H^+ \xrightarrow{\text{NADPH–cytochrome P-450}} Fe^{2+} + NADP^+$$

Seemingly the $^{\cdot}OH$ radical should be the initiator of the peroxidation of lipids.[325] However, another point of view has been put forward nowadays, according to which the initiator of this process is tentatively identified as the ferryl species and not the $^{\cdot}OH$ radical, since the latter cannot be detected with the aid of usual trapping agents. It may be that the $^{\cdot}OH$ radical reacts with the hydrophilic lipid 'heads' and does not therefore reach the aliphatic acid side chains.[320] The formation of the ferryl species has also been postulated in the model microsomal and xanthine oxidase oxidation processes.[322]

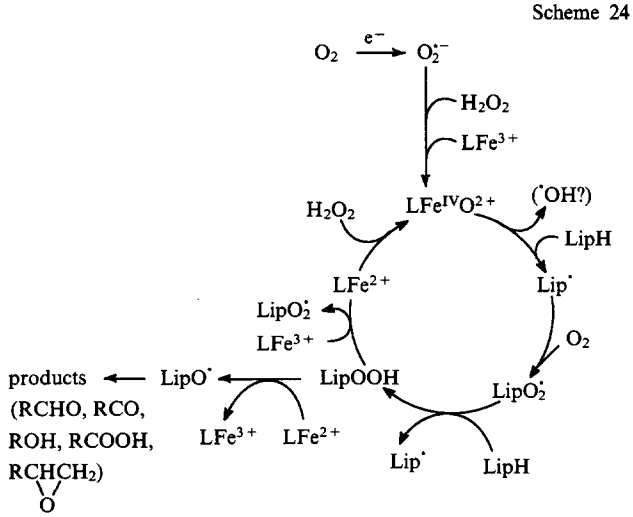
$$ADP{-}Fe^{2+}O_2 \xrightarrow[-2e^-]{2H^+} ADP{-}[FeO]^{2+} + H_2O$$

It has been assumed that this species may be the main product of the reaction of the adenosine diphosphate (ADP) complex of iron(II) with H_2O_2. This assumption was based on the fact that the addition of mannitol (which removes the $^{\cdot}OH$ radicals) to the $ADP{-}Fe^{2+} - H_2O_2 - LipH$ system did not alter the rate of peroxidation of lipids.

Similar claims concerning the formation of the ferryl species have been made in a communication[323] which dealt with the study of the model nonhaem system Fe^{2+} – diethylenetriaminepentaacetic acid – H_2O_2 – LipH. However, the idea that the oxoferryl species plays an initiating role requires further confirmation and elucidation.

Nevertheless, the peroxidation of lipids catalysed by the ferryl species $LFeO^{2+}$ (or $^{\bullet}OH$?) may be illustrated by Scheme 24.

Scheme 24



Reductants such as ascorbate, NADH, NADPH, and others, which on interaction with H_2O_2 can also generate $^{\bullet}OH$ and can play an even more important role than $O_2^{\bullet-}$, are present in the cells in fairly large amounts.[326] Furthermore, H_2O_2 may oxidise ADP – Fe^{2+} to ADP – F^{3+} (L = ADP), generating $^{\bullet}OH$, although the latter does not initiate the peroxidation of the lipid under these conditions, which is indicated by the finding that mannitol (an $^{\bullet}OH$ trapping agent) does not inhibit the reaction.[327] Thus the problem of the initiation of the peroxide oxidation of lipids is to a large extent controversial.

Together with the peroxide oxidation of lipids, there are a multiplicity of other processes, whose substrates are biological targets capable of being damaged by the products of the catalytic reduction of O_2 in the presence of iron compounds (degradation of deoxyribonucleic acid, phagocytosis, autoxidation of monosaccharides, and other reactions). In order to carry out in vivo reactions of the Haber – Weiss type, it is necessary to have not only sources of $O_2^{\bullet-}$ (discussed above), but also sufficient amounts of H_2O_2 and iron compounds.

Hydrogen peroxide is produced by bacteria of various types, it is generated in phagocytes, in spermatozoa, in mitochondria, and in many other formations. Thus H_2O_2 is produced by a series of enzymes (for example, by glycolate and urate oxidases).[320] the crystalline lens of the human eye also contains micromolar concentrations of hydrogen peroxide.[328] Its vapour is evolved even during human respiration[329] (although such vapour may be partly or fully the product of activity of dental bacteria[320]).

Iron compounds, not bound to a protein, at concentrations of several micromoles per litre, migrating between transferrin, cell cytoplasm, mitochondria, and ferritin and interacting with H_2O_2, can effect Fenton type reactions in which $^{\bullet}OH$ radicals are generated.[330] In aqueous solution, the $O_2^{\bullet-}$ species reduce iron(III) to iron(II), creating thereby conditions for the occurrence of the catalytic Haber – Weiss reaction accompanied by the formation of the $^{\bullet}OH$ radical. Under these conditions, different ligands affect differently the ability of $O_2^{\bullet-}$ to reduce iron(III). For example, the specific ligands desferrioxamine and bathophenanthroline inhibit this reaction [iron(III) is not reduced to iron(II)], while ethylenediaminetetraacetic acid, adenosine triphosphate, and picolinic acid promote it by the rapid reduction of the corresponding iron(III) complexes to iron(II) complexes.[320]

The use of specific complex forming agents, which bind iron(III) and thereby prevent its reduction, can promote the inhibition of the oxidative damage in the therapy of afflictions of the heart, the kidneys, the skin, and other tissues and can also weaken the post-traumatic degeneration of tissues in the brain and the spinal column.[193]

The $^{\bullet}OH$ radical formed in vivo by the Haber – Weiss reaction acts more disruptively and specifically than the same radical generated by radiolysis. In the former case, following its formation the radical interacts (by virtue of its high reactivity) with the nearest biological target separated from it by not more than 5 – 10 Å, while in the latter case the interaction takes place over a larger volume of the solution. On the other hand, if the $O_2^{\bullet-}$ radical-ion, with a low reactivity towards many biological molecules, is generated, then it is capable of diffusing over fairly long distances until it encounters an iron(III) complex of a biological target (for example, DNA).[193,196–198] The iron(III) in these complexes is reduced by the $O_2^{\bullet-}$ species to iron(II). By interacting with H_2O_2, the iron(II) compounds may generate $^{\bullet}OH$ in the vicinity of a biological target, which serves as the ligand for iron(III) and a substrate for $^{\bullet}OH$. These $^{\bullet}OH$ radicals, generated by a locally specific mechanism, act more effectively and selectively than the same radicals obtained directly in the cell.[331]

The phagocytotic mechanism of the action of $^{\bullet}OH$ in the cell is described similarly.[332] The biological target may be protected by introducing into the system substances such as thiourea and mannitol, which are capable of binding iron and of extracting it from the biological targets.[196,197,333]

An alternative to the formation of $^{\bullet}OH$ radicals is the generation of iron(IV) or ferryl species, which, being less reactive than $^{\bullet}OH$, exhibit also a different toxicity in relation to biological objects. Such compounds have been identified in the reactions of hydrogen peroxide with the water-soluble iron(III)-porphyrin.[188]

Protection against the toxicity of $O_2^{\bullet-}$ is known to be achievable with the aid of many iron(III) compounds, which catalyse the dismutation of $O_2^{\bullet-}$ via the action of superoxide dismutases in accordance with the 'ping-pong' mechanism.

$$Fe^{3+} + O_2^{\bullet-} \longrightarrow Fe^{2+} + O_2$$

$$\underline{Fe^{2+} + O_2^{\bullet-} + 2H^+ \longrightarrow Fe^{3+} + H_2O_2}$$

$$2O_2^{\bullet-} + 2H^+ \longrightarrow H_2O_2 + O_2$$

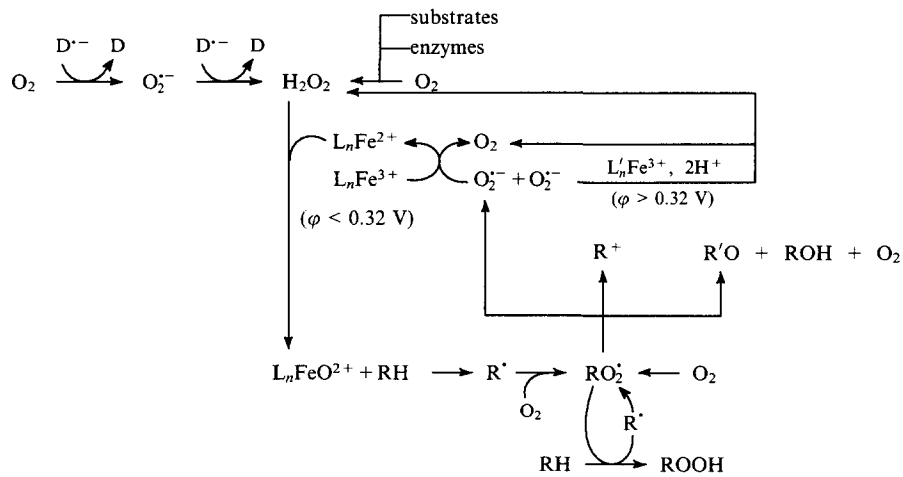
If the rate of the third stage exceeds significantly the rate of the second stage of the Haber – Weiss mechanism, then the iron compound will protect the biological system against the toxicity of $O_2^{\bullet-}$.[331]

A number of enzymes (catalase, glutathione peroxidase, cytochrome *c* peroxidase) protect the organism against oxidative damage.[334]

A thermodynamic condition for the occurrence of the Haber – Weiss reaction is a fairly low reduction potential of the iron complex ($\varphi = 0.32$ V under standard conditions).[335] For a higher potential ($\varphi = 0.32 - 0.94$ V), the iron complexes catalyse the dismutation reaction, but not the Haber – Weiss reaction. Thus, by employing different ligands, it is possible to vary the superoxide toxicity (this includes also a reduction of the toxicity). The inhibition or, conversely, the enhancement of the superoxide toxicity depend not so much on the stability of the iron(III) complexes formed with specific or nonspecific ligands as on the oxidation – reduction potential of iron, which varies under their influence. Depending on this factor, the process proceeds either via the dismutation path, whereupon the toxicity is suppressed, or via the path involving the Haber – Weiss reaction whereupon it is enhanced.

The overall mechanism of the manifestation of the oxygen toxicity has been described.[335,336] It can be supplemented slightly by taking into account the influence of specific (L') and nonspecific (L) ligands (Scheme 25).

Scheme 25



The electron donor $D^{\cdot -}$ reduces O_2 to $O_2^{\cdot -}$ and H_2O_2. By acting on L_nFe^{II}, the latter forms the ferryl species L_nFeO^{2+}, which, being an oxidant, interacts with the biological target, generating $R^{\cdot}$. On combining with O_2, the radical $R^{\cdot}$ gives rise to $RO_2^{\cdot}$, which is converted jointly with RH into the hydroperoxide ROOH and $R^{\cdot}$. Depending on the nature of the ligand (L or L') and the oxidation-reduction potentials φ, either the Haber–Weiss reaction or the dismutation reaction can take place. Lipids can also serve as the biological targets RH. Since the cell contains numerous reductants (for example, ascorbic acid), which may reduce iron(III) directly to iron(II) at a higher rate than that achieved by the superoxide radical-ion $O_2^{\cdot -}$, the decisive role of the latter in the manifestation of oxygen toxicity becomes doubtful, although it is not excluded.[187,337]

Oxygen toxicity is manifested in the autoxidation of monosaccharides (for example, glyceraldehyde). The monosaccharide enediols formed are oxidised catalytically by iron compounds, generating ketoaldehydes, $O_2^{\cdot -}$, H_2O_2, and $^{\cdot}OH$.[338] The oxidation of monosaccharides may be accompanied by the glycolysis of the proteins and a colour change (to brown). It promotes the appearance of hyperglycaemia (diabetes), i.e. the joint oxidation of tissues, which is frequently accompanied by secondary processes — atherosclerosis, kidney failure, cataracts, and pathological conditions in the eye retina. The autoxidation of monosaccharides may promote the appearance of diabetic complications. The concentration of monosaccharides increases greatly in hyperglycaemia, i.e. the content of hydrogen peroxide and other reactive species ($O_2^{\cdot -}$, $^{\cdot}OH$), participating in the autoxidation of monosaccharides, also rises. For example, the above species, toxic to cells, may be generated in erythrocytes and in the crystalline lens of the eye. The catalytic oxidation of the monosaccharide enediols by iron compounds may be accompanied by oxidative stress in hyperglycaemia and the atherosclerosis associated with it.[338]

VI. Conclusion

Comparative analysis of the experimental and theoretical data on the catalytic activation of dioxygen and hydrogen peroxide and the oxidation of organic substrates by these compounds made it possible to devise general mechanisms for these processes. In considering the mechanisms of catalytic reactions, the possible role of intermediates of the type of ferryl ions and complexes was emphasised, since their identification and vigorous investigation have begun comparatively recently. We attempted to consider from a single standpoint three main mechanisms of catalytic oxidation-reduction processes: radical, radical-chain, and ion-molecule. Since porphyrin and certain other iron complexes as well as ferryl species play an extremely important role in living organisms, the epoxidation and hydroxylation reactions with participation of these species have been examined in greatest detail. Using the general mechanisms of the catalytic oxidation-reduction reactions, we discussed in detail also the role of iron compounds in the manifestation of toxicity by the products of the reduction of dioxygen in vivo.

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