2.3.3 Peroxidation Reactions

Driven by the inability to use molecular oxygen as an oxidant efficiently for the transformation of organic compounds, chemists have used it in a partially reduced form - i.e. hydrogen peroxide [1] or derivatives thereof. H$_2$O$_2$ offers some significant advantages as it is cheap and environmentally benign - the only by-product of oxidation being water. However, it is relatively stable and requires to be converted into a more active form in order to become an effective oxidant. This is generally accomplished either with organic or inorganic 'promoters' to furnish alkyl, peroxycarboxylic or hypervalent transition metal complexes. Owing to these drawbacks, the number of industrial-scale oxidation processes using H$_2$O$_2$ as the oxidant is very limited [2]. On the other hand, biocatalytic activation of H$_2$O$_2$ by peroxidases allow a number of synthetically useful and often highly enantioselective peroxidation reactions, which offer a valuable alternative to traditional chemical methodology.

Peroxidases [EC 1.11.1.7] are a heterogeneous group of redox enzymes found ubiquitously in various sources [3], such as plants [4], microorganisms [5] and animals. They are often named after their sources (e.g. horseradish peroxidase, lacto- and myeloperoxidase) or akin to their substrates (e.g. cytochrome c-, chloro- and lignin). Although the biological rôle of these enzymes is quite diverse by ranging from (i) the scavenging of H$_2$O$_2$, (ii) free radical oligomerization and of electron-rich aromatics to (iii) the oxidation and halogenation of organic substrates, they have in common that they accept hydrogen peroxide or a derivative thereof (such as alkyl hydroperoxides) as oxidant. In line with these observations, the mechanism of action may be quite different and can involve (glutathione peroxidase) [6], vanadium (bromoperoxidase) [7, 8], manganese (manganese peroxidase) [9] and flavin in the active site (flavoperoxidase) [10]. The largest group of peroxidases studied so far are heme-enzymes with ferric protoporphyrin IX (protoheme) as the prosthetic group. Their catalytic cycle bears some similarities to that of heme-dependent mono-oxygenases (Section 2.3.2, Scheme 2.151), but owing to the diverse pathways it can catalyze, it is more complex (Scheme 2.178). The mechanism of heme-dependent peroxidase catalysis has been largely deduced from horseradish peroxidase [11-121314]. Its most important features are described as follows:

In its native state, the iron-III species is coordinated equatorially by a heme unit and axially by the sulfur atom of a cystein residue and is therefore very similar to cytochrome P 450. The first step in the reaction involves oxidation
of the Fe$^{+3}$ to form an iron-oxo derivative called. The latter contains a Fe$^{+4}$=O structure and a $\pi$-radical and is formally two oxidation equivalents above the Fe$^{+3}$-state [15]. In a peroxidase, this oxidation is achieved in a single step at the expense of H$_2$O$_2$ (path 1). In the mono-oxygenase pathway, the Fe$^{3+}$-species is oxidized by O$_2$, which requires two additional electrons (from a nicotinamide cofactor) for the net redox balance. Compound I represents the central hypervalent oxidizing species, which can react along several pathways. Path 2: Abstraction of a single electron from an electron-rich substrate such as an enol or phenol (forming a substrate-radical) yields an Fe$^{+4}$=O species denoted as Compound II (path 2a). Since the latter is still one oxidation equivalent above the Fe$^{+3}$-ground state, this process can occur a second time (forming another substrate-radical, path 2b) to finally reform the enzyme in its native state. Alternatively, incorporation of an O-atom onto a substrate (going in hand with a two-electron transfer) can occur in a single step (path 3) [16]. In the absence of any substrate, Compound I can reform the native enzyme via disproportionation of H$_2$O$_2$, denoted as 'catalase-activity' (path 4).

**Scheme 2.178.** Catalytic cycles of heme-dependent peroxidases

![Scheme 2.178. Catalytic cycles of heme-dependent peroxidases](image-url)
Due to the fact that - in contrast to mono-oxygenases - no cofactor is involved in none of the peroxidase-cycles peroxidases are highly attractive for preparative biotransformations. A number of synthetically useful reactions can be achieved (Scheme 2.179) [17-1819].

Scheme 2.179. Synthetically useful peroxidase-reactions

Oxidative dehydrogenation (path 2)

\[
2 \text{SubH} + \text{H}_2\text{O}_2 \rightarrow 2 \text{Sub} \cdot + \text{H}_2\text{O} \rightarrow \text{Sub-Sub}
\]

Oxidative halogenation (path 3, Sub = \text{Hal}^\text{-})

\[
\text{Sub} + \text{H}_2\text{O}_2 + \text{Hal}^- + \text{H}^+ \rightarrow \text{Sub-Hal} + 2 \text{H}_2\text{O}
\]

Oxygen transfer (path 3, Sub = organic compound)

\[
\text{Sub} + \text{H}_2\text{O}_2 \rightarrow \text{SubO} + \text{H}_2\text{O}
\]

**Oxidative dehydrogenation**

This type of reaction is mainly restricted to heme-peroxidases and it involves one-electron transfer processes with radical- and as intermediates. As a consequence, substrates are usually electron-rich (hetero)aromatics, which upon one-electron oxidation lead to resonance-stabilized radicals. The latter form inter- or intramolecular coupling products, such as dimers or oligomers. This reaction is commonly denoted as the 'classical' peroxidase activity, since it was the first type of peroxidase-reactions discovered. Examples of such reactions are shown in Scheme 2.180. Oxidation of phenols (e.g. guaiacol, resorcin) and anilines (e.g. aniline, \text{o-}) leads to the formation of oligomers and polymers under mild conditions [20-2122]. In certain cases, dimers (e.g. aldoximes [23], biaryls [24]) have been obtained.

**Oxidative halogenation**

A class of peroxidases are specialized in the (per)oxidation of halides (Cl\(^-\), Br\(^-\), I\(^-\) but not F\(^-\)) thus creating reactive halogenating species (such as hypohalite), which in turn form halo-organic compounds [25, 26]. These reactions are described in Section 2.7.1.
**Scheme 2.180.** Peroxidase-catalyzed oxidative dehydrogenation of aromatics

 Oxygen-transfer

From a synthetic viewpoint, selective oxygen-transfer is the most interesting peroxidation reaction. The transformations are comparable to those catalyzed by mono-oxygenases with one significant advantage - they are independent on redox-cofactors, such as NAD(P)H.

Among the various types of reactions - C-H bond oxidation, epoxidation of alkenes and heteroatom oxidation - only the most useful transformations are described below.

2. To date, the largest industrial-scale process is the oxidation of propene to propene oxide using tert-Bu-OOH.
6. Flohe L (1979) CIBA Foundation Symposium 65: 95
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15. Compound I is comparable to the Fe⁴⁺⁵ oxo-species in the mono-oxygenase cycle (see Scheme 1.251).
16. Path 3 represents a two-electron transfer process.