

**Chemical Stability
of Pharmaceuticals**
A Handbook for Pharmacists

Second Edition

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To the memory of Lloyd R

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CHAPTER 5

Oxidation and Photolysis

Oxidative and photochemical reactions are, for the most part, one-electron reactions as opposed to reactions discussed in Chapter 4, which are two-electron reactions. For the hydrolytic reactions in Chapter 4, a free pair of electrons on a heteroatom in one molecule, a nucleophilic center, attacked an electrophilic center on a second molecule, whereas oxidative and photochemical reactions proceed through free radical or free-radical-like reaction pathways.

Most drugs exist in a reduced form, so the presence of 20% oxygen in the atmosphere creates obvious potential stability problems for these molecules. That is, many molecules tend to be converted to a more oxidized state. Kinetically, however, there is a sufficient energy barrier to many such reactions (the energy of activation) that not all molecules are subject to measurable rates of spontaneous oxidation or autoxidation. The radiation from the sun and artificial light, particularly visible and ultraviolet light, is also ubiquitous, so that molecules capable of rearranging upon absorption of radiation energy must be protected.

Our overall mechanistic understanding of oxidative and photochemical reactions is poor. The reason for this will be understandable as this chapter proceeds. Simply stated, many oxidative and photochemical reactions involve very complex reaction pathways with multiple intermediates so that even though the stoichiometry of a reaction might be given by Eq. (5.1) the kinetic law is not as simple as Eq. (5.2).



$$\frac{d[\text{ROOH}]}{dt} = k[\text{RH}][\text{O}_2]$$

Also, unlike two-electron reactions which are often limited to acid/base or nucleophilic catalysis, trace quantities of environmental agents can readily catalyze one-electron reactions. The trace contamination of metal ions can catalyze oxidative reactions by many orders of magnitude in the presence of a photosensitizing agent. A molecule that in the absence of the photosensitizer is not photolabile to undergo an appreciable reaction.

In this chapter we introduce, from a kinetic point of view, the kinetics and other factors that govern oxidative and photochemical reactions and how these reactions can be prevented or inhibited.

A. OXIDATION

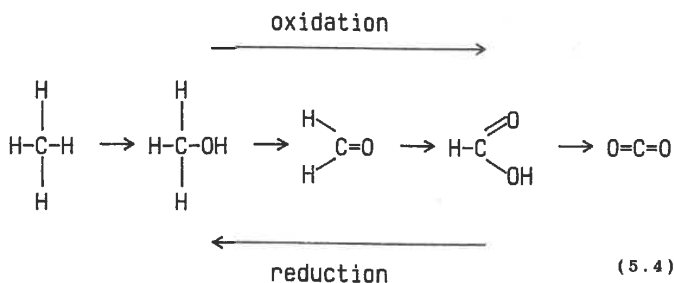
1. Nature of Oxidation

When one considers oxidation, it is important to realize that this reaction is a complete process. One partner is reduction. One cannot have oxidation without the other. Oxidation/reduction (redox) involves the transfer of one or more oxygen atoms, the transfer of electrons, or the transfer of electron pairs. The most familiar, inorganic redox system can be represented by Eq. (5.3), where e^- represents an electron.

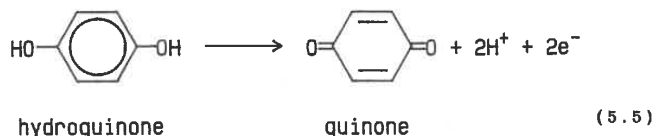


number of electrons. Thus redox reactions involve electron-transfer processes, and this aspect should be considered if the basic process is to be understood.

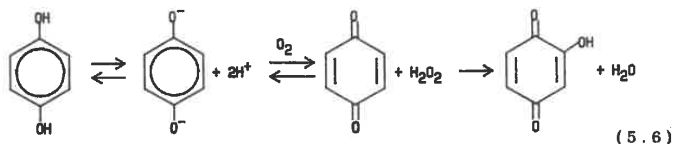
In the case of organic compounds a common measure of the oxidation state of carbon, the oxidation number, is determined by the number of bonds from carbon to more electronegative atoms. For example, the state of oxidation of carbon in organic compounds increases as shown in Eq. (5.4). Earlier, the mechanism of this process was suggested by the stoichiometry



Also the simple redox system illustrated by Eq. (5.3) is made more complex by the medium in which the reaction occurs. For example, the oxidation of hydroquinone (1,4-dihydroxybenzene) to its quinone (*p*-benzoquinone) is often illustrated in the textbooks by Eq. (5.5).



Yet in aqueous solution, free electrons, e^- , do not exist and the state of ionization of the hydroquinone is affected by the solution pH. Therefore in aqueous solution the oxidation of hydroquinones is more accurately described by Eq. (5.6).



As will be discussed later, the oxidation of hydroquinone and other phenols is even more complex than shown by Eq. (5.6) in that the product of the immediate oxidation, the quinone, can catalyze the oxidation

further. This process is called product catalysis.

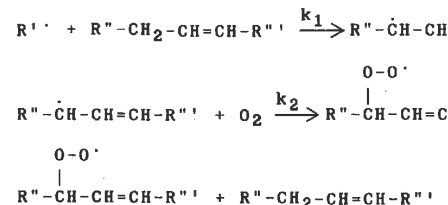
2. Kinetics of Oxidation

Oxidations that take place spontaneously under conditions are often called "autoxidation." Many of these are free-radical reactions and the catalysts are chemical species that produce free radicals. Oxygen, in its ground state, has two unpaired electrons with the electronic configuration



Oxygen, therefore, would "like" to accept two electrons to complete its outer electron shell to produce O_2^{2-} . To do so, oxygen must accept two electrons from a donor molecule(s) and in so doing generate other free-radical molecules.

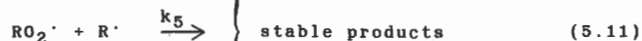
In most autoxidation reactions, the initiation step is often involved, the initiation of the reaction does not involve molecular oxygen itself in its ground state but rather involves reactive oxygen species that initiate oxidation reactions. Let us consider the kinetic behavior of olefin autoxidation by Eqs. (5.7)-(5.9)



The reaction given by Eq. (5.7) represents the initiation reaction. Generally the s

oxygen but some other peroxy radical present in the solution, trace quantities of metal ions such as ferrous or cupric ions, or radicals formed in the solution from the absorption of light (visible or ultraviolet).

The reactions given by Eqs. (5.8) and (5.9) represent *chain propagation* reactions, i.e., one radical produces one radical plus a hydroperoxide molecule. Radical species in solution, apart from reacting with oxygen or another unreacted molecule to produce another free radical, can also react with each other to produce stable or metastable products. This step is called a *chain termination* step and three examples are given in Eqs. (5.10)-(5.12).



Considering this reaction mechanism, and simplifying Eqs. (5.7)-(5.9) to Eqs. (5.13)-(5.15),



assuming normal levels of oxygen, applying a steady-state assumption to the radical species $RO_2 \cdot$ and $R \cdot$, letting $k_2[R \cdot][O_2] = k_3[RO_2 \cdot][RH]$, and $k_4 = k_5 = k_6 = k_t$, it can be shown that the rate of hydroperoxide formation is given by Eq. (5.16) where r_i is the initiation rate.

$$\frac{d[ROOH]}{dt} = \left(\frac{r_i}{k_t}\right)^{\frac{1}{2}} k_3[RH] \frac{k_2[O_2]}{k_3[RH] + k_2[O_2]} \quad (5.16)$$

It is obvious from this expression that the rate of hydroperoxide formation is proportional to the square root of the initiation rate, r_i . Also, if oxygen

concentration is very high, k_2 Eq. (5.16) collapses to Eq. (5.17):

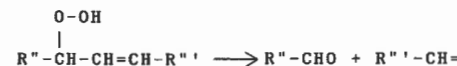
$$\frac{d[ROOH]}{dt} = \left(\frac{r_i}{k_t}\right)^{\frac{1}{2}} k_3[RH]$$

The reaction will apparently be first order in the reacting material, RH. On the other hand, if $k_2[O_2]$, then Eq. (5.18) is realized.

$$\frac{d[ROOH]}{dt} = \left(\frac{r_i}{k_t}\right)^{\frac{1}{2}} k_2[O_2]$$

Under these conditions the reaction is "zero order" with respect to RH, that is, it will not appear in Eq. (5.18), and the reaction is first order in $[O_2]$. If the term r_i actually represents the rate of formation of O_2 , the order of the reaction with respect to O_2 could be as high as 1.5.

The mechanism defined by Eqs. (5.13)-(5.15) shows that the species ROOH is stable and does not react to form other products. In the case of a hydroperoxide, it can break down to produce nonvolatile products as well as multiple radicals.



The rancidity of unsaturated colorants in oil-based paints is the result of this reaction which breaks olefinic bonds to produce aldehydes and multiple radicals. Eq. (5.19), one hydroperoxide molecule produces multiple radicals. If this reaction is favored, we have a chain propagation reaction. If branching reactions will be observed, the oxidation kinetics are even more complex than those defined by Eqs. (5.13)-(5.15).

Qualitatively, the kinetics of oxidation reactions follow the pattern illustrated in Fig. 5.1. A characteristic of many such reactions is a time or lag phase corresponding to the formation of radicals via the initiation step.

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