Chemical Stabilit
of Pharmaceutica
A Handbook for Pharm

Second Edition

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To the memory of Lloyd K

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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).

$$RH + O_2 \longrightarrow ROOH \tag{5.1}$$

$$\frac{d[ROOH]}{dt} = k[RH][O_2]$$

Also, unlike two-electron reactions w[...] often limited to acid/base or nucleo[...] trace quantities of environmental age[...] ly catalyze one-electron reactions[...] trace contamination of metal ions ca[...] tive reactions by many orders of ma[...] presence of a photosensitizing agent [...] cule that in the absence of the photo[...] is not photolabile to undergo an app[...] cal reaction.

In this chapter we introduce, fr[...] point, the kinetics and other factors[...] tive and photochemical reactions a[...] these reactions can be prevent[...] inhibited.

A. OXIDATION

1. Nature of Oxidation

When one considers oxidation, it is i[...] ize that this reaction is a comple[...] partner is reduction. One cannot ha[...] other. Oxidation/reduction (redox) [...] the transfer of one or more oxygen [...] or the transfer of electrons. The [...] familiar, inorganic redox system can [...] Eq. (5.3), where e^- represents an ele[...]

$$reduced\ form \rightleftharpoons oxidized + ne[...]$$

number of electrons. Thus redox rea[...] tron-transfer processes, and this as[...] sidered if the basic process is to be [...]

In the case of organic compounds a[...] oxidation state of carbon, the oxida[...] termined by the number of bonds from [...] For example, the state of oxidation o[...] pounds increases as shown in Eq. ([...] earlier, the mechanism of this proces[...] ple as suggested by the stoichiometry[...]

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$$\xrightarrow{\text{oxidation}}$$

$$H-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-H \longrightarrow H-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-OH \longrightarrow \underset{H}{\overset{H}{>}}C=O \longrightarrow H-C\underset{OH}{\overset{O}{<}} \longrightarrow O=C=O$$

$$\xleftarrow{\text{reduction}}$$

(5.4)
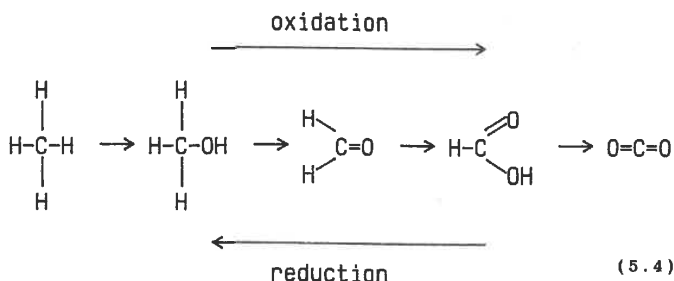
Also the simple redox system illustrated by Eq. (5.3) is made more complex by the medium in which the reaction occurs. For example, the oxidation of hydroquinone (1,4-dihydroxybenzene) to its quinone (p-benzoquinone) is often illustrated in the textbooks by Eq. (5.5).

$$HO-\langle\bigcirc\rangle-OH \longrightarrow O=\langle\bigcirc\rangle=O + 2H^+ + 2e^-$$

hydroquinone   quinone

(5.5)
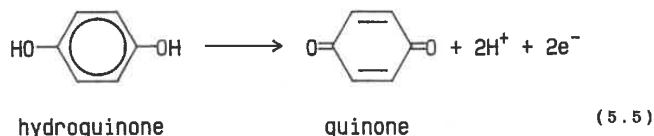
Yet in aqueous solution, free electrons, e^-, do not exist and the state of ionization of the hydroquinone is affected by the solution pH. Therefore in aqueous solution the oxidation of hydroquinones is more accurately described by Eq. (5.6).

$$\langle\bigcirc\rangle \rightleftharpoons \langle\bigcirc\rangle + 2H^+ \underset{O_2}{\rightleftharpoons} \langle\bigcirc\rangle + H_2O_2 \longrightarrow \langle\bigcirc\rangle + H_2O$$

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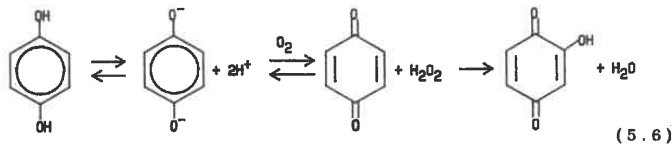
As will be discussed later, the oxidation of hydroquinone and other phenols is even more complex than shown by Eq. (5.6) in that the product of the immediate oxidation, the quinone, can catalyze the oxidation
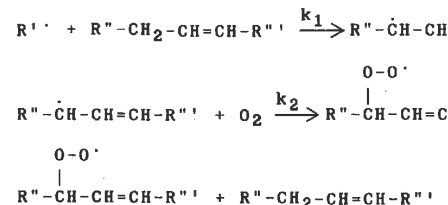
further. This process is called product catalysis.

2. Kinetics of Oxidation

Oxidations that take place sponta[neously under natural] conditions are often called "autoxi[dations." A major]ity of these are free-radical reac[tions.] [Free radi]cals are chemical species that p[ossess an unpaired] electron. Oxygen, in its ground st[ate, is a diradical] with the electronic configuration

$$\cdot\ddot{O}:\ddot{O}\cdot$$

Oxygen, therefore, would "like" [to complete its outer] electron shell to produce O_2^{2-}, t[he peroxide ion.] To do so, oxygen must accept two [electrons from] donor molecule(s) and in so doin[g would] generate other free-radical molecul[es.]
In most autoxidation reactions, [although oxygen] is often involved, the initiation o[f the chain re]action does not involve molecula[r] oxygen itself in its ground state d[oes not ini]tiate oxidation reactions. Let us [consider the gener]al kinetic behavior of olefin aut[oxidation as given] by Eqs. (5.7)-(5.9)

$$R'\cdot + R''-CH_2-CH=CH-R''' \xrightarrow{k_1} R''-\overset{\cdot}{C}H-CH[...]$$

$$R''-\overset{\cdot}{C}H-CH=CH-R''' + O_2 \xrightarrow{k_2} R''-\overset{\overset{O-O\cdot}{|}}{C}H-CH=C[...]$$

$$R''-\overset{\overset{O-O\cdot}{|}}{C}H-CH=CH-R''' + R''-CH_2-CH=CH-R''' [...]$$

The reaction given by Eq. (5.7) rep[resents the initia]*tion* 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).

$$RO_2{}^{\cdot} + RO_2{}^{\cdot} \xrightarrow{k_4} \quad \left.\begin{array}{l}\\ \\ \\ \\ \end{array}\right\} \text{stable products} \qquad (5.10)$$

$$RO_2{}^{\cdot} + R^{\cdot} \xrightarrow{k_5} \qquad (5.11)$$

$$R^{\cdot} + R^{\cdot} \xrightarrow{k_6} \qquad (5.12)$$

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

$$\text{initiator} \xrightarrow{k_1} R^{\cdot} \qquad (5.13)$$

$$R^{\cdot} + O_2 \xrightarrow{k_2} RO_2{}^{\cdot} \qquad (5.14)$$

$$RO_2{}^{\cdot} + RH \xrightarrow{k_3} ROOH + R^{\cdot} \qquad (5.15)$$

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.

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

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...
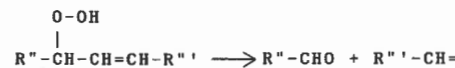Eq. (5.16) collapses to Eq. (5.17):

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

The reaction will apparently be fir... ing material, RH. On the other h... $k_2[O_2]$, 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 reactio... zero order" with respect to RH, that... appear in Eq. (5.18), and the react... order in $[O_2]$. If the term r_i actua... O_2, the order of the reaction with... O_2 could be as high as 1.5.

The mechanism defined by Eqs. (5... that the species ROOH is stable and... tion products are stable. In the ca... hydroperoxide can break down to pr... nonvolatile products as well as mult...

$$\begin{array}{c} O-OH \\ | \\ R''-CH-CH=CH-R''' \longrightarrow R''-CHO + R'''-CH= \end{array}$$

The rancidity of unsaturated cool... based paints is the result of thi... olefinic bonds to produce aldehydes... hols as well as multiple radicals.... Eq. (5.19), one hydroperoxide mol... radicals. If this reaction is favo... we have a chain propagation rea... branching reactions will be obser... does occur, the oxidation kinetics a... even more complex than those defin... tion, propagation, and termination s...

Qualitatively, the kinetics of ox... cal reactions follow the pattern il... 5.1. A characteristic of many such... time or lag phase corresponding to t... of radicals via the initiation step.

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