

**Chemical Stability
of Pharmaceuticals**

A Handbook for Pharmacists

Second Edition

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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).



$$\frac{d[\text{ROOH}]}{dt} = k[\text{RH}][\text{O}_2] \quad (5.2)$$

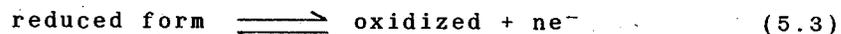
Also, unlike two-electron reactions where catalysis is often limited to acid/base or nucleophilic catalysis, trace quantities of environmental agents can powerfully catalyze one-electron reactions. For example, trace contamination of metal ions can catalyze oxidative reactions by many orders of magnitude, and the presence of a photosensitizing agent can cause a molecule that in the absence of the photosensitizing agent is not photolabile to undergo an apparent photochemical reaction.

In this chapter we introduce, from a basic viewpoint, the kinetics and other factors affecting oxidative and photochemical reactions and describe how these reactions can be prevented or at least inhibited.

A. OXIDATION

1. Nature of Oxidation

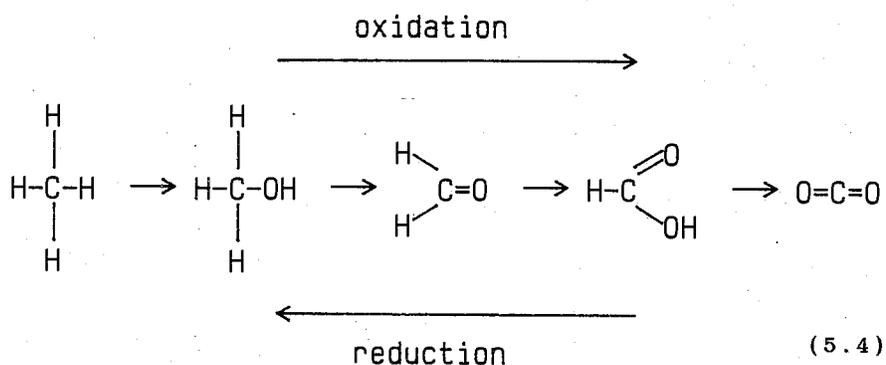
When one considers oxidation, it is important to realize that this reaction is a complementary one; its partner is reduction. One cannot happen without the other. Oxidation/reduction (redox) reactions involve the transfer of one or more oxygen or hydrogen atoms or the transfer of electrons. The classical, and familiar, inorganic redox system can be described by Eq. (5.3), where e^- represents an electron and n the



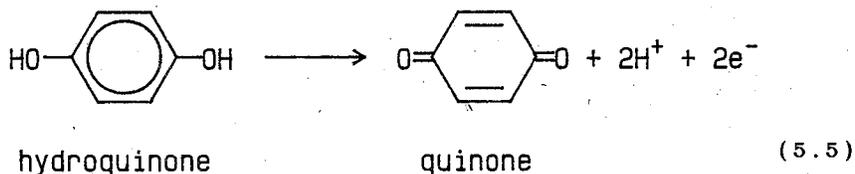
number of electrons. Thus redox reactions are electron-transfer processes, and this aspect must be considered if the basic process is to be understood.

In the case of organic compounds and especially the oxidation state of carbon, the oxidation state is determined by the number of bonds from carbon to oxygen. For example, the state of oxidation of one-carbon compounds increases as shown in Eq. (5.4). As stated earlier, the mechanism of this process is not as simple as suggested by the stoichiometry of the reaction.

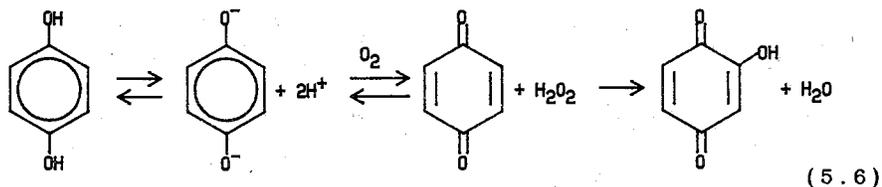
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Also the simple redox system illustrated by Eq. (5.3) is made more complex by the medium in which the reaction occurs. For example, the oxidation of hydroquinone (1,4-dihydroxybenzene) to its quinone (*p*-benzoquinone) is often illustrated in the textbooks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

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