

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

Second Edition

Kenneth A. Connors
School of Pharmacy, The University of

Gordon L. Amidon
College of Pharmacy, The University of

Valentino J. Stella
School of Pharmacy, The University of

A Wiley-Interscience Publication

JOHN WILEY & SONS

New York • Chichester • Brisbane • Toronto

To the memory of Lloyd R

Copyright © 1986 by John Wiley & Sons, Inc.

All rights reserved. Published simultaneously in Canada.

Reproduction or translation of any part of this work beyond that permitted by Section 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, Inc.

Library of Congress Cataloging in Publication Data:

Connors, Kenneth A. (Kenneth Antonio), 1932-
Chemical stability of pharmaceuticals.

"A Wiley-Interscience publication."

Includes bibliographies and index.

1. Drug stability. I. Amidon, Gordon L. II. Stella, Valentino J., 1946- . III. Title. [DNLM: 1. Drug Stability—handbooks. 2. Kinetics—handbooks. QV 735 C752c]

RS424.C66 1986 615'.18 85-31455

ISBN 0-471-87955-X

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

v

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, first, the kinetics and other factors that govern oxidative and photochemical reactions and second, how these reactions can be prevented or inhibited.

A. OXIDATION

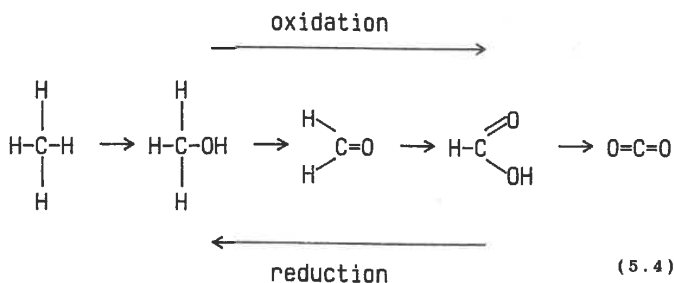
1. Nature of Oxidation

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.

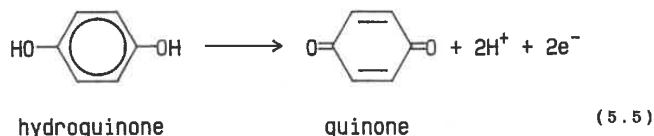


number of electrons. Thus redox reactions involve electron-transfer processes, and this aspect must be considered if the basic process is to be understood.

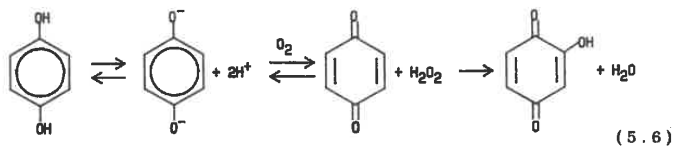
In the case of organic compounds a common measure of the oxidation state of carbon, the oxidation number, is determined by the number of bonds from carbon to more electronegative atoms. For example, the state of oxidation of carbon in organic compounds increases as shown in Eq. (5.4). Earlier, the mechanism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

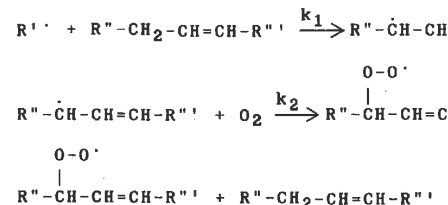
2. Kinetics of Oxidation

Oxidations that take place spontaneously under conditions are often called "autoxidation." Many of these are free-radical reactions and are catalyzed by chemical species that can donate an electron. Oxygen, in its ground state, has the electronic configuration



Oxygen, therefore, would "like" to accept an electron 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.

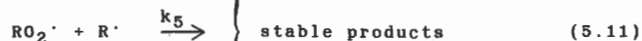
In most autoxidation reactions, molecular oxygen is often involved, the initiation of the reaction does not involve molecular oxygen itself in its ground state but rather reactive oxygen species that initiate oxidation reactions. Let us consider the kinetic behavior of olefin autoxidation by Eqs. (5.7)-(5.9)



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):

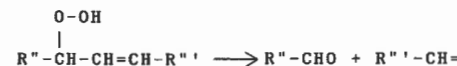
$$\frac{d[ROOH]}{dt} = \left(\frac{r_i}{k_t} \right)^{\frac{1}{2}} k_3 [RH]$$

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 is proportional to $[O_2]$, 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 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 can produce 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), propagation, and termination steps.

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.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.