

**Chemical Stability  
of Pharmaceuticals**

---

A Handbook for Pharmacists

**Second Edition**

**Kenneth A. Connors**

School of Pharmacy, The University of Wisconsin

**Gordon L. Amidon**

College of Pharmacy, The University of Michigan

**Valentino J. Stella**

School of Pharmacy, The University of Kansas

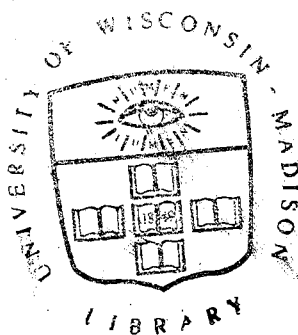
A Wiley-Interscience Publication

**JOHN WILEY & SONS**

New York • Chichester • Brisbane • Toronto • Singapore

Noven Ex. 1015

Page 1 of 35



455.00

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

## 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).



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

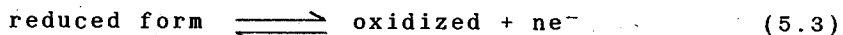
Also, unlike two-electron reactions where catalysis is often limited to acid/base or nucleophilic catalysis, trace quantities of environmental agents can powerfully catalyze one-electron reactions. For example, trace contamination of metal ions can catalyze oxidative reactions by many orders of magnitude, 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

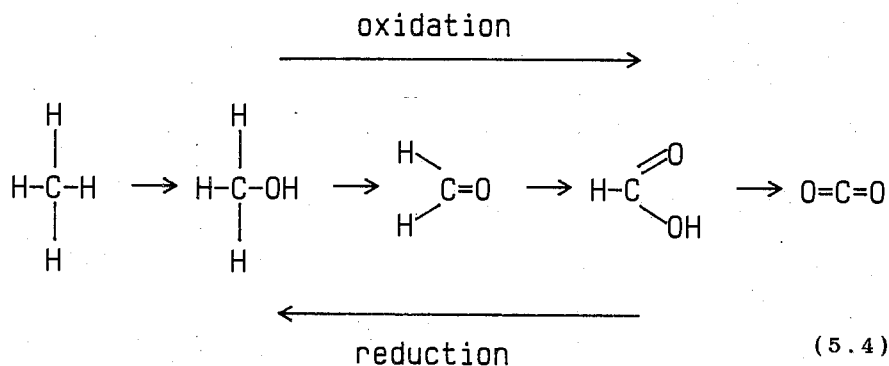
When one considers oxidation, it is important to realize that this reaction is a complementary one; its partner is reduction. One cannot happen without the other. Oxidation/reduction (redox) reactions involve the transfer of one or more oxygen or hydrogen atoms or the transfer of electrons. The classical,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



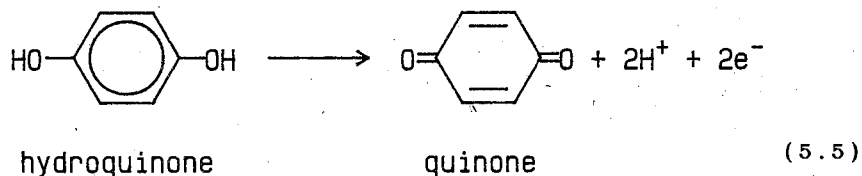
number of electrons. Thus redox reactions are electron-transfer processes, and this aspect must be considered if the basic process is to be understood.

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.

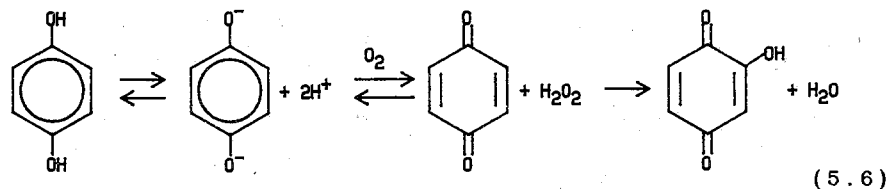
## 84 Oxidation and Photolysis



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,  $\text{e}^-$ , 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

# 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.