

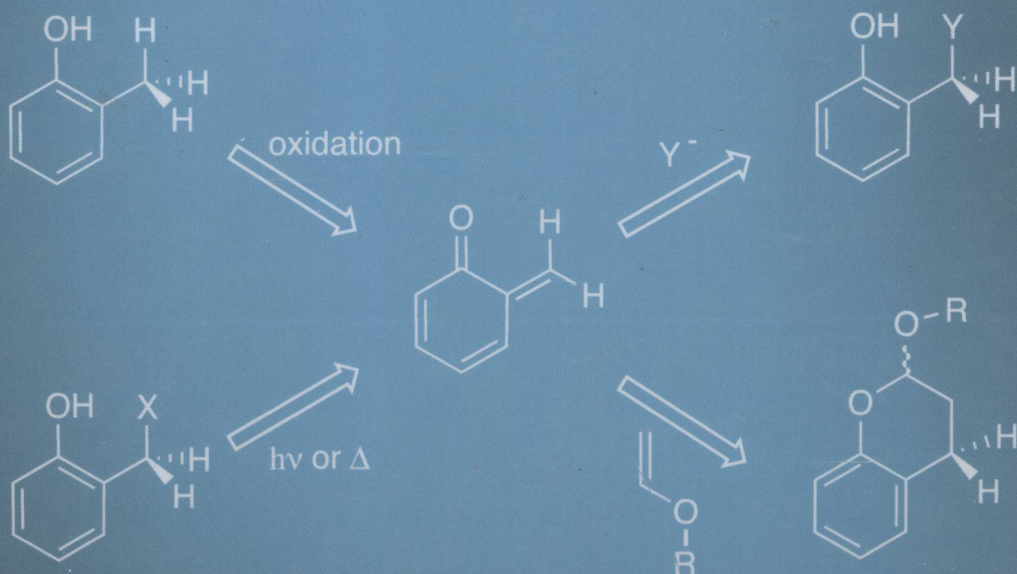
WILEY SERIES ON REACTIVE
INTERMEDIATES IN CHEMISTRY
AND BIOLOGY

VOLUME ONE

Steven E. Rokita, Series Editor

QUINONE METHIDES

Steven E. Rokita, Editor



0621.25
Q7

QUINONE METHIDES

Edited by

STEVEN E. ROKITA

 **WILEY**

A John Wiley & Sons, Inc., Publication



E2010000844



Copyright © 2009 by John Wiley & Sons, Inc. All rights reserved

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at <http://www.wiley.com/go/permission>.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of the contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data:

Quinone Methides / [edited by] S.E. Rokita.

p. cm. — (Wiley series on reactive intermediates in chemistry and biology ; v. 1)

Includes index.

ISBN 978-0-470-19224-5 (cloth)

1. Intermediates (Chemistry) I. Rokita, Steven Edward.

QD476.R416 2009

547'.2—dc22

2008038605

Printed in the United States of America
10 9 8 7 6 5 4 3 2 1

QUINONE METHIDES

Wiley Series of Reactive Intermediates in Chemistry and Biology

Steven E. Rokita, Series Editor

Quinone Methides

Edited by Steven E. Rokita

PREFACE TO SERIES

Most stable compounds and functional groups have benefited from numerous monographs and series devoted to their unique chemistry, and most biological materials and processes have received similar attention. Chemical and biological mechanisms have also been the subject of individual reviews and compilations. When reactive intermediates are given center stage, presentations often focus on the details and approaches of one discipline despite their common prominence in the primary literature of physical, theoretical, organic, inorganic, and biological disciplines. The *Wiley Series on Reactive Intermediates in Chemistry and Biology* is designed to supply a complementary perspective from current publications by focusing each volume on a specific reactive intermediate and endowing it with the broadest possible context and outlook. Individual volumes may serve to supplement an advanced course, sustain a special topics course, and provide a ready resource for the research community. Readers should feel equally reassured by reviews in their speciality, inspired by helpful updates in allied areas and intrigued by topics not yet familiar.

This series revels in the diversity of its perspectives and expertise. Where some books draw strength from their focused details, this series draws strength from the breadth of its presentations. The goal is to illustrate the widest possible range of literature that covers the subject of each volume. When appropriate, topics may span theoretical approaches for predicting reactivity, physical methods of analysis, strategies for generating intermediates, utility for chemical synthesis, applications in biochemistry and medicine, impact on the environmental, occurrence in biology, and more. Experimental systems used to explore these topics may be equally broad and range from simple models to complex arrays and mixtures such as those found in the final frontiers of cells, organisms, earth, and space.

Advances in chemistry and biology gain from a mutual synergy. As new methods are developed for one field, they are often rapidly adapted for application in the other. Biological transformations and pathways often inspire analogous development of new procedures in chemical synthesis, and likewise, chemical characterization and identification of transient intermediates often provide the foundation for understanding the biosynthesis and reactivity of many new biological materials. While individual chapters may draw from a single expertise, the range of contributions contained within each volume should collectively offer readers with a multidisciplinary analysis and exposure to the full range of activities in the field. As this series grows, individualized compilations may also be created through electronic access to highlight a particular approach or application across many volumes that together cover a variety of different reactive intermediates.

Interest in starting this series came easily, but the creation of each volume of this series required vision, hard work, enthusiasm, and persistence. I thank all of the contributors and editors who graciously accepted and will accept the challenge.

University of Maryland

STEVEN E. ROKITA

INTRODUCTION

The term “quinone methide” first appeared in literature in 1942 to describe the quinone analogue in which one of the carbonyl oxygens is replaced by a methylene group. Reactivity associated with such a species is typically greater than that of the parent quinone but more moderate than that of the corresponding quinodimethane in which both carbonyl oxygens are replaced by methylene groups. The single methylene substitution is still quite sufficient to create a highly transient intermediate or at least the perception of one, and this perception likely discouraged its initial study. Investigations were at first limited to polymerization and photochemistry. These topics have continued to develop and gain greater sophistication as the subtleties of quinone methides have been revealed. Despite approximately 1400 literature contributions and many reviews on quinone methides as of 2008, the current book is the first devoted to this fascinating and useful intermediate.

Most laboratories did not begin to recognize the widespread occurrence and potential applications of quinone methides until 20 years after its first report. Now, with an ever-increasing appreciation of the structural dependence of quinone methide reactivity, its use has become more frequent and diverse as illustrated by the topics covered in this volume. Their role in lignin formation was recognized as early as 1960. Soon after, the first stable quinone methide was discovered in the natural products taxodione and taxodone and offered a stark contrast to the expectation of its fleeting existence. Although the quinone methide derived from the food preservative 2,6-di-*tert*-butyl-4-methylphenol was first characterized in 1963, its discovery as a product of oxidative metabolism was published 20 years later. Just prior to this, the concept of bioreductive alkylating agents was introduced to form quinone methide intermediates for treating hypoxic tumors. Both reductive and oxidative metabolisms form quinone

methides have since become a very important topic for quinone methides in drug design as well as drug safety.

Quinone methides are associated with sclerotization, the natural tanning process that stabilizes insect cuticle, as well as reactions of vitamin K and tocopherols including vitamin E. Quinone methides have also been integral to the design of many mechanism-based inactivators of enzymes, which has been adapted most recently to screen for catalytic activity within antibody libraries. Perhaps the field of organic synthesis has become the most frequent benefactor of quinone methides now that reliable methods are available for their generation and control. Of the various approaches for manipulating quinone methide reactivity, its complexation with transition metals remains the most remarkable. Finally, the reversibility of quinone methide reaction has established an excellent basis for polymer and dendrimer disassembly to the likely benefit of numerous processes in material science, biology, and medicine. My own laboratory has also been intrigued by this reversibility and in particular by its ability to extend the potential lifetime of electrophiles in biological systems.

My involvement in quinone methides arose very much by chance and was neither planned nor anticipated as typical of the serendipity associated with the pursuit of basic research. Interest has since been sustained by the intellectual challenges of this topic and the community of investigators sharing its exploration. What had once been left to the realm of physical and polymer chemists soon became the province of organic, medicinal, and theoretical chemists, biochemists, toxicologists, entomologists, biologists, and those involved in forestry and food sciences. The scientific literature is so vast that we struggle to remain current even in just the literature of our immediate disciplines, and yet innovation is often found in complementary perspectives and methodology. By assembling this collection of topics, I hope to entice readers already familiar with quinone methides to look beyond their typical focus and discover new inspiration and opportunities in allied areas. Concurrently, I hope that the range of topics and perspectives provides a comfortable entry for readers from a broad range of backgrounds and interests.

The volume has been created as a snapshot of significant activity on quinone methides and it neither attempts to cover the entire range of topics nor present comprehensive reviews on a subset of topics. A variety of excellent reviews have already been published on many of the interesting and important details. The authors of this volume embody the breadth of research involving quinone methides, and I am very much indebted to their dedication to this volume and the field in general. These authors along with many others past and present are responsible for our current understanding of quinone methides. I hope this volume will incite an even greater interest in quinone methides that in turn will merit further reviews and monographs in the future.

CONTRIBUTORS

Takuya Akiyama, Dairy Forage Research Center, USDA-Agricultural Research Service, Madison, WI, USA; and RIKEN Plant Science Center, Suehiro, Tsurumi, Yokohama, Kanagawa 230-0045, Japan

Stefan Böhmendorfer, Department of Chemistry, University of Natural Resources and Applied Life Sciences, Muthgasse 18, A-1190 Vienna, Austria

Judy L. Bolton, Department of Medicinal Chemistry and Pharmacognosy (M/C 781), College of Pharmacy, University of Illinois at Chicago, 833 S. Wood Street, Chicago, IL 60612-7231, USA

Filippo Doria, Department of Organic Chemistry, Pavia University, V. le Taramelli 10, 27100 Pavia, Italy

Rotem Erez, Department of Organic Chemistry, School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel Aviv University, Tel Aviv 69978, Israel

Mauro Freccero, Department of Organic Chemistry, Pavia University, V. le Taramelli 10, 27100 Pavia, Italy

Hoon Kim, Department of Biochemistry and Great Lakes Bioenergy Research Center, University of Wisconsin, Madison, WI, USA

Fachuang Lu, Department of Biochemistry and Great Lakes Bioenergy Research Center, University of Wisconsin, Madison, WI, USA

Matthew Lukeman, Department of Chemistry, Acadia University, Wolfville, Nova Scotia, Canada, B4P 2R6

David Milstein, Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

Stephen F. Nelsen, Department of Chemistry, University of Wisconsin, Madison, WI, USA

Liping Pettus, Department of Chemical Research and Discovery, Amgen Inc; Thousand Oaks CA 91320, USA

Thomas Pettus, Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, CA 93106, USA

Elena Poverenov, Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

John Ralph, Department of Biochemistry and Great Lakes Bioenergy Research Center, University of Wisconsin, Madison, WI, USA; Department of Biological Systems Engineering, University of Wisconsin, Madison, WI, USA; and Dairy Forage Research Center, USDA-Agricultural Research Service, Madison, WI, USA

Michèle Reboud-Ravaux, Enzymologie Moléculaire et Fonctionnelle, FRE 2852, CNRS-Université Paris 6, T43, Institut Jacques Monod, 2 place Jussieu, 75251 Paris Cedex 05, France

Steven E. Rokita, Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742, USA

Thomas Rosenau, Department of Chemistry, University of Natural Resources and Applied Life Sciences, Muthgasse 18, A-1190 Vienna, Austria

Paul F. Schatz, Dairy Forage Research Center, USDA-Agricultural Research Service, Madison, WI, USA

Doron Shabat, Department of Organic Chemistry, School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel Aviv University, Tel Aviv 69978, Israel

Edward B. Skibo, Department of Chemistry and Biochemistry, Arizona State University, Tempe, AZ 85287-1604, USA

John A. Thompson, Department of Pharmaceutical Chemistry, School of Pharmacy, University of Colorado, Denver, C238-L15, 12631 E. 17th Avenue, Aurora, CO 80045, USA

Michel Wakselman, Institut Lavoisier de Versailles, UMR 8180, CNRS-Université Versailles Saint-Quentin, 45 Avenue des Etats Unis, F-78035 Versailles, France

Qibing Zhou, Department of Chemistry, Virginia Commonwealth University, 1001 West Main Street, Richmond, VA 23284-2006, USA

CONTENTS

Preface to Series	xiii
Introduction	xv
Contributors	xvii
 1 Photochemical Generation and Characterization of Quinone Methides	 1
<i>Matthew Lukeman</i>	
1.1 Introduction	1
1.2 Quinone Methides from Benzylic Photoelimination	2
1.2.1 Photoelimination of Fluoride	2
1.2.2 Photodehydration	3
1.2.3 Photoelimination of Quaternary Ammonium Salts	10
1.2.4 Photoelimination of Alcohols and Esters	13
1.3 Quinone Methides from ESIPT to Unsaturated Systems	14
1.3.1 Quinone Methides from ESIPT to Carbonyls	14
1.3.2 Quinone Methides from ESIPT to Alkenes and Alkynes	15
1.3.3 Quinone Methides from ESIPT to Aromatic Carbon	19
1.4 Other Photochemical Routes to Quinone Methides	23
1.5 Conclusions and Outlook	25
References	25

2	Modeling Properties and Reactivity of Quinone Methides by DFT Calculations	33
	<i>Mauro Freccero and Filippo Doria</i>	
2.1	Introduction	33
2.2	QM Reactivity as Alkylating Agents	35
2.2.1	Computational Models	35
2.2.1.1	Basis Set Choice	36
2.2.1.2	Energetics of the Benzylation by <i>o</i> -QM in the Gas Phase and in Aqueous Solution	38
2.2.2	H-Bonding and Solvent Effects in the Benzylation of Purine and Pyrimidine Bases	39
2.2.2.1	Cytosine Benzylation under Kinetic Control	39
2.2.2.2	Stability/Reactivity of the QM-Cytosine Conjugates	40
2.2.2.3	Purine Bases Benzylation: Kinetic and Thermodynamic Aspects	41
2.3	Reactivity as Heterodiene	43
2.4	Tautomerizations Involving Quinones and Quinone Methides	47
2.4.1	QM Versus Quinone Stability: Substituent Effects	49
2.5	<i>o</i> -Quinone Methide Metal Complexes	50
2.5.1	Geometries and Reactivity as Function of the Metal and the Structural Features	50
2.6	Generation of <i>o</i> -QM	53
2.6.1	Generation of <i>o</i> -QM Tethered to Naphthalene Diimides by Mild Activation	53
2.6.2	Thermal Generation of <i>o</i> -QM in Oxidative Processes in the Gas Phase	54
2.7	Thermal Decomposition of <i>o</i> -QM in the Gas Phase	57
2.8	QM Generation in Lignin Formation	59
2.9	Conclusion and Perspective	61
	References	61
3	Quinone Methide Stabilization by Metal Complexation	69
	<i>Elena Poverenov and David Milstein</i>	
3.1	Introduction	69
3.2	QM-Based Pincer Complexes	70
3.2.1	Formation	70
3.2.2	Reactivity and Modifications	70
3.2.3	Os-Based, <i>p</i> -QM Complexes	72
3.3	One-Site Coordinated QM Complexes	73
3.3.1	η^2 - <i>ortho</i> -QM Complexes	73
3.3.1.1	Formation	73
3.3.1.2	Release and Reactivity of η^2 - <i>o</i> -QMs	73

3.3.2	η^2 - <i>p</i> -QM Complexes	74
3.3.2.1	Formation	74
3.3.2.2	Controlled Release and Modification of η^2 - <i>p</i> -QMs	75
3.4	η^4 -Coordinated QM Complexes	77
3.4.1	Formation of η^4 -Coordinated QM Complexes	77
3.4.2	Reactivity of η^4 -Coordinated QM Complexes	78
3.4.3	η^4 -Coordinated QM Complexes of Mn	79
3.5	Characterization of QM Complexes	80
3.5.1	IR	80
3.5.2	^1H and ^{13}C (^1H) NMR	80
3.5.3	X-Ray	81
3.6	Conclusion and Future Applications	83
	Acknowledgments	84
	References	84
4	Intermolecular Applications of <i>o</i>-Quinone Methides (<i>o</i>-QMs) Anionically Generated at Low Temperatures: Kinetic Conditions	89
	<i>Thomas Pettus and Liping Pettus</i>	
4.1	Introduction to <i>o</i> -QMs	89
4.2	Thermal Generation Conditions	90
4.3	Low-Temperature Kinetic Generation of <i>o</i> -QMs	92
4.3.1	Formation of the <i>o</i> -QMs Triggered by Fluoride Ion	92
4.3.2	Stepwise Formation of <i>o</i> -QMs	95
4.3.3	Kinetically Controlled Cycloadditions	102
4.4	Mechanistic Investigations	109
4.5	Long-Term Prospects	113
	References	115
5	Self-Immolative Dendrimers Based on Quinone Methides	119
	<i>Rotem Erez and Doron Shabat</i>	
5.1	Introduction	119
5.2	Substituent-Dependent Disassembly of Dendrimers	122
5.3	Elimination-Based AB ₃ Self-Immolative Dendritic Amplifier	126
5.4	Controlled Self-Assembly of Peptide Nanotubes	132
5.5	AB ₆ Self-Immolative Dendritic Amplifier	135
5.6	Enzymatic Activation of Second-Generation Self-Immolative Dendrimers	143
5.7	Dual Output Molecular Probe for Enzymatic Activity	151
5.8	Cleavage Signal Conduction in Self-Immolative Dendrimers	154
5.9	Future Prospects	157
	References	160

6	<i>Ortho</i>-Quinone Methides in Tocopherol Chemistry	163
	<i>Thomas Rosenau and Stefan Böhmendorfer</i>	
6.1	Introduction	163
6.2	α -Tocopherol and Its Derived <i>o</i> -QM: General Aspects	164
6.3	Chemo- and Regioselectivity in the <i>o</i> -QM Formation from Tocopherol	168
6.3.1	<i>o</i> -QM Versus “5a-Chromanolmethyl” Radicals	168
6.3.2	Regioselectivity in the Oxidation of α -Tocopherol: Up- <i>o</i> -QMs Versus Down- <i>o</i> -QMs	174
6.3.3	Detailed Formation Pathway and Stabilization of the Tocopherol-Derived <i>o</i> -QM 3 and Other <i>o</i> -QMs	177
6.4	Reactions of the “Common” Tocopherol-Derived <i>Ortho</i> -Quinone Methide 3	187
6.4.1	Self-Reaction of the <i>o</i> -QM: Spiro Dimers and Spiro Trimers	187
6.4.2	Spiro Oligomerization/Spiro Polymerization of Tocopherol Derivatives	190
6.4.3	Bromination of α -Tocopherol and Further Reactions of 5a-Bromo- α -Tocopherol and Other 5a-Substituted Tocopherols	195
6.4.4	Cyclization of para-Tocopherylquinone 7 into <i>o</i> -QM 3	198
6.4.5	Synthesis via <i>o</i> -QM 3 and Reaction Behavior of 3-(5-Tocopheryl)propionic Acid	199
6.5	Formation of Tocopherol-Derived <i>o</i> -QMs Involving Other Positions Than C-5A	200
6.5.1	5-(γ -Tocopheryl)acetic Acid	200
6.5.2	4-Oxo- α -Tocopherol	201
6.5.3	3-Oxa-Chromanols	203
6.5.4	Selected Substituent-Stabilized Tocopherols and Conjugatively Stabilized <i>Ortho</i> -Quinone Methides	207
6.6	Future Prospects	210
	Acknowledgments	211
	References	211
7	Characterizing Quinone Methides by Spectral Global Fitting and ^{13}C Labeling	217
	<i>Edward B. Skibo</i>	
7.1	Introduction	217
7.2	Studying the Transient Quinone Methide Intermediate	219
7.2.1	Using Spectral Global Fitting to Study Transient Quinone Methides	221
7.2.2	Enriched ^{13}C NMR Spectroscopy	222

7.3	New Insights into Methide Chemistry	224
7.3.1	Novel Methide Polymerization Reactions	224
7.3.2	Products of Dithionite Reductive Activation	229
7.3.3	Probing DNA Adduct Structures with ^{13}C -Labeled Methides	232
7.3.4	Design of a "Cyclopropyl Quinone Methide"	237
7.3.5	Kinetic Studies of the Mitosene Quinone Methide	243
7.3.6	Cyclopent[b]indole-Based Quinone Methides	250
7.3.7	Prekinamycin-Based Quinone Methides	253
7.4	Conclusions and Future Prospects	260
7.4.1	Quinone Methide O-Protonation	260
7.4.2	Antitumor Agent Design	261
7.4.3	Enriched ^{13}C NMR Monitoring of Methide Reactions	261
7.4.4	Future Prospects	262
	References	262
8	Natural Diterpene and Triterpene Quinone Methides: Structures, Synthesis, and Biological Potentials	269
	<i>Qibing Zhou</i>	
8.1	Introduction	269
8.2	Natural Diterpene QMs	270
8.2.1	Chemical Structures and Biological Activity of Natural Diterpene QMs	270
8.2.2	Dimers of Natural Diterpene QMs	274
8.3	Total Synthesis of Diterpene QMs	274
8.3.1	Stepwise Synthesis of Diterpene QMs	274
8.3.2	Diel–Alder Approach in the Diterpene QM Synthesis	276
8.3.3	Polyene Cyclization as a Mimic of Biosynthesis in Plants	279
8.4	Natural Triterpene QMs	280
8.4.1	Cytotoxicity of Natural Triterpene QMs Against Cancer Cell Lines	281
8.4.2	Anti-Inflammatory Effects of Natural Triterpene QMs	282
8.4.3	Other Biological Activities of Natural Triterpene QMs	285
8.4.4	Biosynthesis of Natural Triterpene QMs	285
8.5	Terpene QMs and Reactive Oxygen Species	285
8.6	Conclusion and Future Prospects	288
	References	288
9	Reversible Alkylation of DNA by Quinone Methides	297
	<i>Steven E. Rokita</i>	
9.1	Introduction	297
9.1.1	Reversible Alkylation of DNA	298
9.1.2	Initial Reports of Reversible Alkylation by Quinone Methides	301

9.2	Reversible Alkylation of Deoxynucleosides by a Simple Quinone Methide	303
9.2.1	Quinone Methide Regeneration is Required for Isomerization between Its N1 and 6-Amino Adducts of dA	304
9.2.2	Kinetic and Thermodynamic Adducts Formed by Quinone Methides	306
9.2.3	The Structure of Quinone Methides and Their Precursors Modulate the Reversibility of Reaction	308
9.3	Reversible Alkylation of DNA by Quinone Methide Bioconjugates	310
9.3.1	The Reversibility of Quinone Methide Reaction Does Not Preclude Its Use in Forming DNA Cross-Links	311
9.3.2	Repetitive Capture and Release of a Quinone Methide Extends Its Effective Lifetime	313
9.3.3	Intramolecular Capture and Release of a Quinone Methide Provides a Method for Directing Alkylation to a Chosen Sequence of DNA	317
9.4.	Conclusions and Future Prospects	320
	Acknowledgments	323
	References	323
10	Formation and Reactions of Xenobiotic Quinone Methides in Biology	329
	<i>Judy L. Bolton and John A. Thompson</i>	
10.1	Introduction	329
10.2	Formation of QMs	330
10.3	Alkylphenols	330
10.3.1	BHT and Related Alkylphenols: Historical Overview	330
10.3.2	Relationships of QM Structure to Reactivity and Toxicity	332
10.3.2.1	Effects of Alkyl Substitution	332
10.3.2.2	Hepatotoxicity	334
10.3.2.3	Lung Damage	335
10.3.3	Mechanisms of BHT Toxicity: Identification of Intracellular Targets	335
10.3.3.1	Gene Induction	335
10.3.3.2	Reactivities of QMs with Cellular Nucleophiles	336
10.3.3.3	Detection of QM-Protein Adducts Formed In Vitro	337
10.3.3.4	Glutathione S-Transferase P1 (GSTP1) Adduct	338
10.3.3.5	Protein Adducts Formed In Vivo	339
10.3.3.6	<i>ortho</i> -Alkylphenols	339
10.4	Methoxyphenols and Catechols	341
10.4.1	Methoxyphenols	341
10.4.2	Catechols	343