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VOLUME ONE

Steven E. Rokita, Series Editor

QUINONE METHIDES

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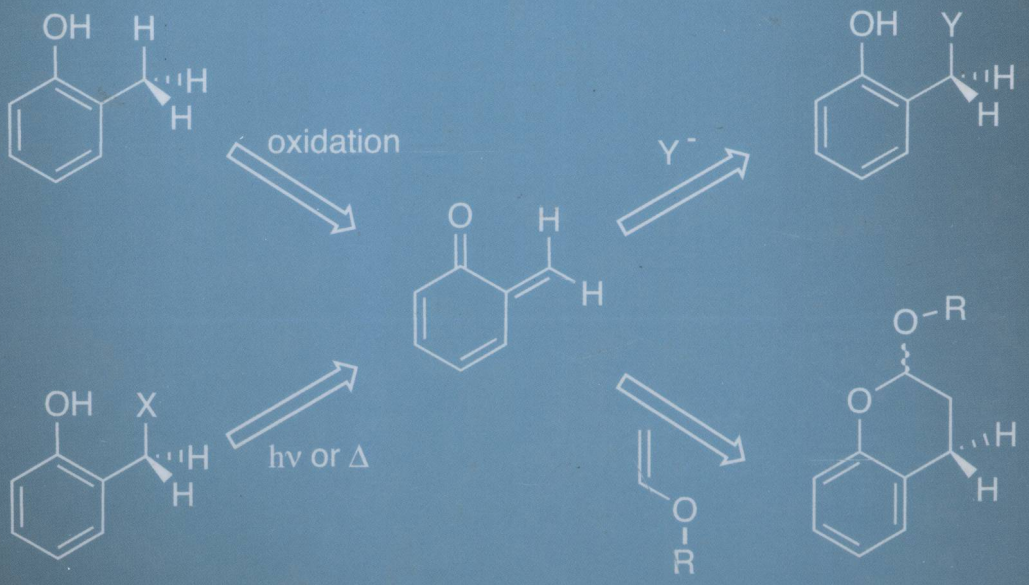

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Edited by

STEVEN E. ROKITA

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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 became 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.

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CONTENTS