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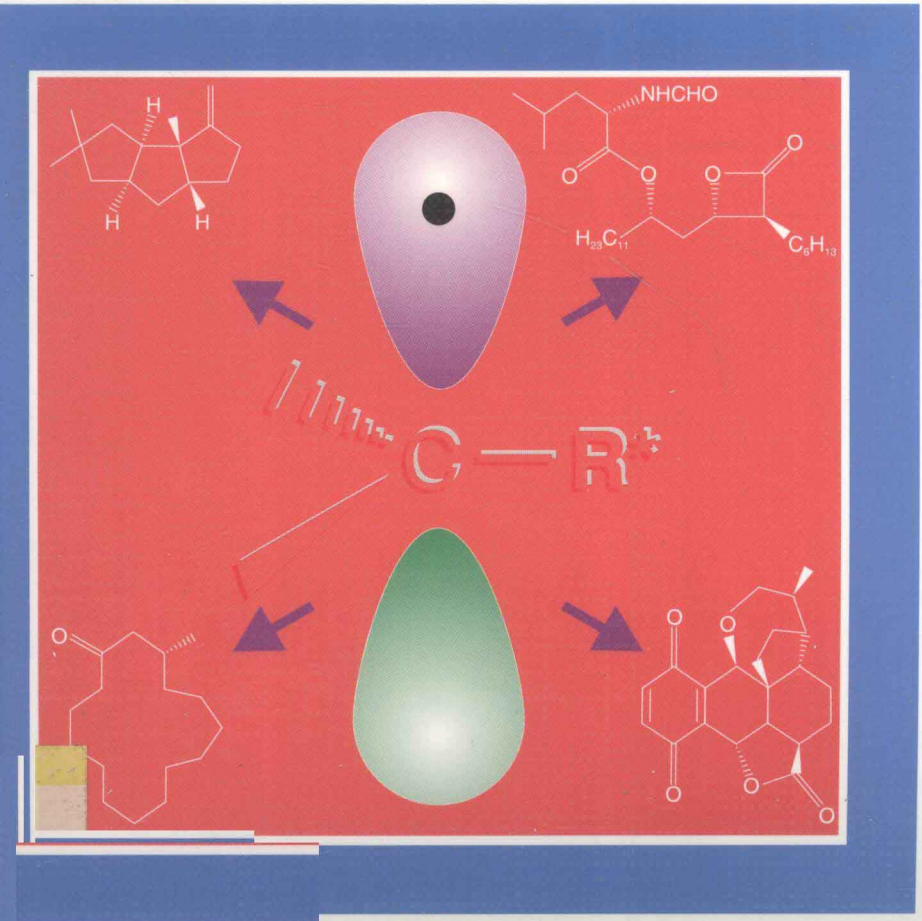
Stereochemistry of Radical Reactions

Concepts, Guidelines, and Synthetic Applications



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Concepts , Guidelines, and Synthetic Applications

With a Foreword by
Ernest L. Eliel

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Prof. D. P. Curran
Department of Chemistry
University of Pittsburgh
Pittsburgh, PA 15260
USA

Prof. N. A. Porter
Department of Chemistry
Duke University
Durham, NC 27708
USA

Prof. Dr. B. Giese
Institut für
Organische Chemie
Universität Basel
St.-Johanns-Ring 19
CH-4056 Basel
Switzerland

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Foreword

Stereochemistry, which originated in the latter part of the 19th century, has had a remarkable renaissance in the last 40 years. This is probably due to the increased importance of organic synthesis, which, in turn, relates to the rise in importance of the pharmaceutical industry.

Because of the presence of often numerous chiral centers in natural products, diastereoselectivity is crucial in their synthesis. More recently, the realization that mirror image chemical compounds often differ substantially in their pharmacological properties has stimulated the development of methods of enantioselective synthesis.

When one surveys the literature of stereochemistry through the major pertinent textbooks of the postwar period, one realizes that the focus was initially almost exclusively on ionic processes: electrophilic and nucleophilic substitution and addition reactions and their reversal. Somewhat later pericyclic reactions came into purview. However, reactions involving radical intermediates are notoriously absent from these compendia. Until some 15 years ago the common wisdom among organic chemists was that radicals lack regio- and even chemoselectivity, not to mention stereoselectivity, and that their main and arguably exclusive usefulness was in a few chain reactions including radical initiated polymerizations.

All this has changed since about 1980. It was found that radical cyclization and addition reactions can often be carried out cleanly, notably in the presence of very efficient chain transfer reagents, such as tributyltin hydride, that prevent the formation of oligomers and polymers in radical additions to olefins. Subsequently it was found that, given the appropriate environment, such reactions can proceed with high stereoselectivity. The same tenets of conformational analysis that have proved useful in constructing schemes for stereoselective ionic reactions apply to radical processes as well. This, under appropriate circumstances, includes the use of chiral auxiliaries to effect enantioselective syntheses.

The three authors of the present book have played important roles in the development of stereoselective radical reactions. All three, individually, have previously written reviews on the subject. It is fortunate for organic chemists that they have now teamed up to write the first comprehensive book on the stereochemistry of radical reactions and its applications.

Ernest L. Eliel
June 1995

Preface

The study of stereoselective radical reactions has been a microcosm of the larger field of application of radical reactions in organic synthesis—a period of neglect has been followed by swift progress and exciting developments. The purpose of this book is to review the status of the field of stereoselective radical reactions. While diastereoselective radical cyclizations and reactions of cyclic radicals have been common for some time, it had been thought until recently that levels of stereoselectivity in these reactions would be low, allowing of course for a few exceptions. Acyclic diastereocontrol has emerged only recently, but progress has been rapid. Enantioselective reactions of radicals are rare at present, but we believe that their development is now inevitable. We submit that stereoselective radical reactions are no different from other types of reactions—that they come in many flavors and at all levels of selectivity. The goals then become to learn which reactions will occur with high selectivity, and why.

In line with the title of the book, we will attempt to present the concepts that are needed to understand stereoselective radical reactions and the guidelines that are helpful to apply them. We will suggest repeatedly that stereoselective radical reactions can be understood, even predicted, by combining standard principles of conformational analysis of organic molecules with knowledge of structure and reactivity of radicals. We will illustrate these concepts and guidelines with synthetic applications that show how stereoselective radical reactions can be used to solve synthetic problems. We hope that the book will expand awareness of existing classes of stereoselective radical reactions and stimulate the development of new ones.

It is the thesis of this book that stereoselective radical reactions are both interesting and significant in their own right. The study of such reactions leads to a better understanding of the structure and reactions of organic radicals and opens new methods for the stereoselective synthesis of organic molecules. Furthermore, because there exist qualitative analogies between radical reactions and related ionic and pericyclic reactions, and because stereoselective radical reactions are often easier to understand and explain than their ionic and pericyclic counterparts, the stereoselectivity of radical reactions is of special interest across the field of asymmetric synthesis.

Therefore, the significance of stereoselective radical reactions spans the fields of stereochemistry and asymmetric synthesis.

We would like to gratefully acknowledge all the help that we received in preparing the text and figures for this book from Michele Russo, Suzanne Curran, Anne Ghosez-Giese, and Kitty Porter. We also thank our graduate students and postdoctoral coworkers, who helped in the proofreading of the book. Dennis Curran would like to thank the University of Basel for a "Reichstein Visiting Professorship" that greatly facilitated his contribution to the book. Ned Porter acknowledges receipt of an Alexander von Humboldt Senior Fellowship and the kind hospitality of Professor Dr. Christoph Rüchardt while this book was being written.

Dennis P. Curran, Ned Porter, Bernd Giese
July, 1995

Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Ad	adamantyl
Ar	aryl
Bn	benzyl
Bu	butyl
Bz	benzoyl
Cbz	carbobenzyloxy
DBU	diazabicycloundecane
DHP	dihydropyran
DME	dimethoxyethane
DTBP	di-*t*-butylperoxide
e^-	electron
Et	ethyl
Fmoc	fluorenylmethyloxy carbonate
HMPA	hexamethylphosphortriamide
Im	imidazolyl
LDA	lithium diisopropylamide
mCPBA	*m*-chloroperbenzoic acid
Me	methyl
NBS	N-bromosuccinimide
$OGlu(OAc)_4$	tetraacetylglucoside
PCC	pyridinium chlorochromate
Pr	propyl
PTOC	pyridine-2-thione carbonate
TBHP	*t*-butylhydroperoxide
Tf	trifluoromethanesulfonyl
Th	thiohydroxamate
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl
Tol	*p*-tolyl
TTMS	tris(trimethylsilyl)silicon hydride

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Chapter 1

Radical Reactions in Organic Synthesis

1.1 Introduction

As recently as a decade ago, organic radicals were regarded as interesting reactive intermediates with limited synthetic potential. As a rule, radical reactions were thought to be "messy", and the few "clean" radical reactions, like allylic and benzylic brominations with *N*-bromosuccinimide (NBS), were viewed as the exceptions that proved the rule. This view of radicals probably arose because of the notion that highly reactive intermediates could not be selective. The concept of selectivity pervades organic synthesis, and with good reason—selectivity is the key to high yields.

The logic that reactive intermediates such as radicals cannot participate in selective reactions with controlled, predictable outcomes is faulty. Research on the structures and reactions of organic radicals conducted largely by physical organic chemists in the 60s and 70s[1] laid the foundation for the synthetic explosion that followed in the 80s and is still ongoing.[2] Synthetic chemists gradually came to realize that it is only relative rates that are important for selectivity; the simple fact that radicals often react with high absolute rates is actually desirable, not undesirable. They began to realize the difference between radical/radical reactions, which often occur at the diffusion-controlled limit and are hence unselective, and radical/molecule reactions, which occur with a huge range of rate constants. They learned that the rates of radical/radical reactions are easily minimized by choosing reaction conditions in which radical concentrations are low, and that the rates of radical/molecule reactions—that is, the selectivities—can be adjusted by the experimenter over a wide range by choice of reaction partners, concentrations, temperature, and other variables.

Radical-molecule reactions are now recognized to frequently be both chemo- and regioselective. It is ironic that radical reactions, once thought to be capricious and unpredictable, have a higher level of predictability in

complex settings than most other types of reactions. This predictability is due to the large body of knowledge of radical rate constants[3] and substituent effects in simple systems, and to the fact that these effects in simple systems can often be translated to complex systems in a straightforward fashion.

The idea that radical reactions cannot be highly stereoselective has been the last perceived selectivity barrier to fall. Indeed, this selectivity barrier is more than just perceived. Consider that a reaction providing a 95/5 ratio of diastereomers at room temperature requires an energy difference in the two diastereomeric transition states of 1.7 kcal/mol. If one views this energy difference as a percentage of the activation barrier, then transformations like Diels–Alder reactions, which typically have activation barriers of 25–35 kcal/mol, should be much easier to render stereoselective than radical reactions, which typically have activation barriers of 5–15 kcal/mol. On the other hand, consider that there are many very rapid organic reactions with low activation barriers (enolate alkylations, aldol reactions) that are routinely used in both diastereoselective and enantioselective synthesis. It has been our premise for some time that radicals are normal organic species subject to the same types of steric, electronic, and stereoelectronic interactions as all other organic molecules, and that these interactions can be both understood and used in a predictable fashion to control stereochemistry. This premise underlies the entire book.

The purpose of this book is to review the status of the field of stereoselective radical reactions. While diastereoselective radical cyclizations and reactions of cyclic radicals have been common for some time, it had been thought until recently that levels of stereoselectivity in these reactions would be low, allowing of course for a few exceptions. Acyclic diastereocontrol has emerged only recently, but progress has been rapid. Enantioselective reactions of radicals are rare at present, but we believe that their development is now inevitable. We submit that stereoselective radical reactions are no different from other types of reactions—that they come in many flavors and at all levels of selectivity. The goals then become to learn which reactions will occur with high selectivity, and why.

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molecules[4] with knowledge of structure and reactivity of radicals. We will illustrate these concepts and guidelines with synthetic applications that show how stereoselective radical reactions can be used to solve synthetic problems. We hope that the book will expand awareness of existing classes of stereoselective radical reactions and stimulate the development of new ones.

1.2 Principles of Radical Reactions

To understand stereoselectivity in radical reactions, it is first necessary to have a general understanding of the principles of radical reactions and how these principles impact on synthetic planning. There are a number of excellent books and reviews that treat this topic in depth.[5–8] The goal of this section is to briefly recap some of the most important features of radical reactions in synthesis. Readers with significant experience in radical chemistry may wish to skip this section, while those with little experience may wish to augment it with additional information in the more comprehensive treatments.

1.2.1 General Considerations

Most of the radicals used in synthesis are transient, and they react with each other and with any other radicals present in the medium at the diffusion-controlled limit. For this reason, reaction conditions are usually chosen so that radical/radical reactions are avoided. Radical/molecule reactions are often conducted in chains, but methods based on oxidation and reduction are also important.

Radicals are now valued synthetic intermediates[9] because they can be used for transformations that are often difficult to accomplish by other means and because these transformations typically occur under very mild conditions where both selectivity and tolerance of functional groups are high. The kinds of protection schemes that are often essential for synthetic sequences of ionic reactions are rarely required for radical reactions; carbonyl substituents and heteroatom-hydrogen bonds (OH, NH) do not usually pose problems in radical reactions. However, protecting groups may still be required for other steps in a synthetic sequence, and nearly all popular classes of protecting groups are tolerated in radical reactions. The kinds of

β-elimination reactions and 1,2-shifts that pervade anionic (organometallic) and cationic chemistry are rare in radical chemistry, and their occurrence is readily predicted.

1.2.2 Medium and Temperature Effects

Since most radical reactions show small solvent effects, the choice of solvent is dictated not by the solvent effect on selectivity, but by other concerns. Though the rates of radical/molecule reactions are limited in principle by competing radical/radical reactions, the concentrations of radicals are so low that it is often the rates of radical/solvent reactions that limit the types of radical/molecule reactions that can be conducted. The choice of solvent is therefore dictated by the expected velocity of the desired reaction. With the exception of solvents like benzene (which reacts by radical addition), most solvents react with radicals by hydrogen atom transfer. For the slowest possible radical/molecule reactions, solvents like benzene, *tert*-butylbenzene, and *tert*-butyl alcohol are preferred. Because of its strong O–H bonds, water is also an excellent solvent for radical reactions if the reactants are soluble. This also means that dry solvents are not required. DMSO, acetonitrile, and methylene chloride are also useful. As the rates of the reactions to be conducted go up, the list of useful solvents expands to include almost all the popular organic solvents including alkanes, alcohols, ethers, and halocarbons. Supercritical CO_2 shows promise as an environmentally benign solvent for radical reactions.[10]

Temperature effects are of crucial concern for stereoselective reactions. Like many other transformations, radical reactions often provide increasing levels of stereoselectivity at lower temperatures, although the amount of improvement varies from reaction to reaction. Whether or not a given chain will propagate at low temperatures depends upon the rate of the slowest reaction in the chain. Cooling reduces the rates of all reactions, and chain propagation steps that were efficient at 80°C may no longer be fast enough at room temperature or –80°C. In short, the faster the steps that are involved in the chain, the lower the temperature at which the chain will still propagate. Chains will always get shorter at lower temperatures, so compensation by increased initiation is often required. There are now a number of chemical[11] and sonochemical[12] initiation methods that can be used to conduct chain reactions at low temperatures. Non-chain radical reactions can be conducted