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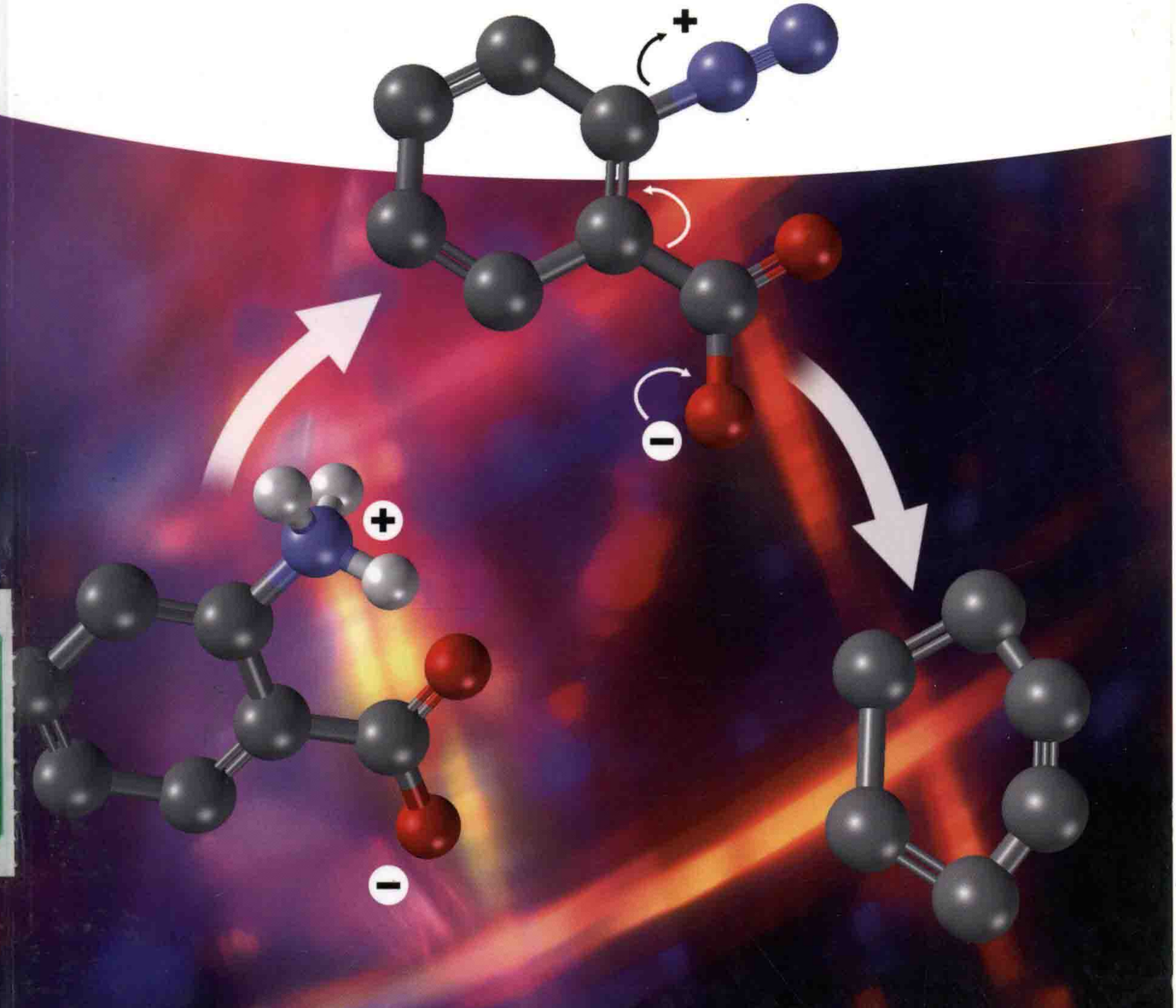
Reactive Intermediates in Organic Chemistry

Structure, Mechanism, and Reactions



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Preface

Organic chemistry has always been, and continues to be, the branch of chemistry that best connects structure with properties, which attracts particular attention because of its immense importance to life and society. Organic synthesis is a creative science involving the construction and cleavage of bonds, the strategies for which represent the central theme in organic synthesis. More than any other branch of organic chemistry, synthesis has improved our understanding of the structure, dynamics, and transition of molecules. Most synthetic problems have more than one solution, and the trick is to judge which of these is likely to have the best chance of success. Even the most experienced chemists develop routes that work well on paper but fail miserably in the laboratory. However, there are some guidelines and principles that are helpful in designing a suitable route for a particular synthesis. Whether one seeks to understand nature or to create the new materials and medicines of the future, a key starting point is thus to understand structure and mechanism of a particular reaction. For synthetic chemists it is very important to understand in detail what is going on when the molecules in the starting materials react with each other and create the molecules characteristic of the product. Knowledge about mechanisms makes it possible to develop better and less expensive methods to prepare products of technical importance.

Writing a textbook of any level is always a challenging mission. This book has been designed in view of the growing importance of intermediates in the synthesis of natural and/or non-natural molecules. The ideas of functionality and stereochemistry have their origins in the second half of the nineteenth century, and the concepts of bonding and reaction mechanism undoubtedly belong to the twentieth century. The goal of this text is to incorporate basic conceptual tools and recent advances in the area of organic synthesis and particularly in the field of reactive intermediates, which are the key steps of any transformation. A systematic understanding of the mechanisms of organic reactions is necessary as without it organic chemistry is chaos, and impossible to learn.

Theory, mechanism, synthesis, structure, and stereochemistry are discussed throughout the book in a qualitative to semiquantitative fashion. During the writing of this book I have always tried to anticipate the questions of a student and to challenge them to think about the subject, motivating them to understand and to realize why, rather than just memorizing material. Chemists present chemistry in terms of structural diagrams and for this reason all reactions have been drawn using curly arrows; the handwriting of chemistry. Curved arrows and chemical reactions introduce students to the notational systems employed in all of the mechanistic discussions in the text. Such a course is frequently offered as a course material in organic chemistry at the undergraduate and beginning graduate level. I guess one will enjoy many fruitful hours of insight in the course of studying this book and I welcome your constructive comments on its content and approach. In attempting to accomplish these objectives, my approach is substantially different from currently available titles.

I have tried to put equal weight to the three basic fundamental aspects of the study of reactive intermediates, that is, reactions, mechanisms, and stereochemistry. The organization is based on these concepts, so that students can understand the large number of organic reactions based on relatively few principles. Accordingly, this book is divided into seven chapters. The first gives a brief introduction dealing with some basic, very frequently used terms, concepts of steric and electronic effects, and sites of chemical reactivity. The student is also told why such information will be important in the study of a particular reaction mechanism. Chapters 2–6 cover specific reactive intermediates in detail regarding their structure, geometry, generation, stability, and reactions. Chapter 7 gives a brief survey of the miscellaneous intermediates. End-of-chapter summaries review the major concepts of the chapter in a concise narrative format to help readers to understand the key points. The problems at the end of each chapter represent the application of concepts, rather than a review of material explicitly presented in the text. They are designed so that students can test themselves on the material just covered before they go on to the next section. I hope the level of difficulty will present a considerable challenge to students. These problems allow students to practice and test their mastery of core principles within each chapter. A concerted effort was made to make none of the problems so difficult that the student loses confidence.

I would greatly appreciate comments and suggestions from users that will improve the text or correct errors. I can only conclude by expressing my wish that others will enjoy using this text as much as I have enjoyed writing it. In particular, I want to thank the many wonderful and talented students I have had over the years, who taught me how to be a teacher and researcher. I also want to thank the dedicated people at Wiley-VCH, Germany, Dr. Anne Brennführer (Commissioning Editor), Lesley Belfit (Project Editor), and Claudia Nussbeck (Editorial Assistant), for their truly superior editorial ability and for keeping me happy and on track.

Finally, I am grateful to my wife Meera and my son Keshav whose contributions to the project are beyond measure, and so I thank them for their understanding, love, encouragement, and assistance during the lengthy process of writing this book.

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Introduction

Chemistry is an old science that influences every aspect of life on earth (from toothpaste to life-saving medicines) because just about everything that we can touch and feel is made of chemicals, which is why it is known as the *mother science* or *central science*. The chemical cornucopia (a hollow basket filled with various kinds of festive materials) is truly impressive. While chemistry is, indeed, an old subject (~1000 BC), modern chemistry (Antoine-Laurent de Lavoisier (1743–1794), the "Father of modern chemistry") is ~230 years old, while organic synthesis is only about 150 years old. The essential feature of this central science is synthesis. The chemist who designs and completes an original and aesthetically pleasing synthesis is like the composer, artist, or poet, who with great individuality fashions new forms of beauty from the interplay of mind and spirit.

Chemistry occupies a unique middle position between physics and mathematics on the one side and biology, ecology, sociology, and economics on the other. It is said that chemistry is reducible into physics and finally mathematics. On the one hand, it deals with biology and provides explanations for how molecules determine the processes of life. On the other hand, it mingles with physics as well as mathematics, and finds explanations for chemical phenomena in the fundamental processes and particles of the universe:

> "The greatest scientific advance of the last 50 years is the way biology is becoming a molecular science (chemistry) . . . ."

Chemistry is playing a vital role in every area of our increasingly technological society that links the familiar with the fundamental.

Like all sciences, chemistry has a unique place in our pattern of understanding of the universe. It is the science of molecules, but organic chemistry is something more, that is, a tentative attempt to understand the chemistry of life. The task of the organic chemist is to make tools (molecules), that is, the art and science of constructing the molecules of nature available for various uses. Essentially all chemical reactions that take place in living systems, including in our own bodies, are organic reactions because the molecules of life – proteins, enzymes, vitamins, lipids, carbohydrates, and nucleic acids – all are organic compounds. All

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things originating from living things are organic but anything containing carbon is also organic. The food we eat, the wood to make our homes, the clothing we wear (whether natural cotton or polyester), gasoline, rubber, plastics, medicines, pesticides, herbicides, all are made from organic compounds. We can thank organic chemistry for making our life easier in the modern age, and furthermore a responsibility lies on the shoulders of synthetic organic chemists to make life even better.

Chemistry is a vibrant subject filled with light, colors, fragrance, flavors, action, and excitement; a subject that begs to be taught by the points of inquiry method. When you picked up this book, your muscles were performing chemical reactions on sugars to give you the energy you required. As you go through this book, your eyes are using an organic compound (11-*cis*-retinal) to switch visible light into nerve impulses. Gaps between your brain cells are being bridged by simple organic molecules (neurotransmitter amines) so that nerve impulses can be passed around your brain. Organic chemistry often studies life by making new molecules that give information not available from the molecules actually present in living things. Whether one seeks to understand nature or to create the new materials and medicines of the future, a key starting point is thus to understand structure and mechanism. Organic chemistry has always been, and continues to be, the branch of chemistry that best connects structure with properties.

To understand organic chemistry one must be familiar with two languages. One is the structure and representation of molecules. The second is the description of the reaction mechanism in terms of curly arrows. The first is static and the second dynamic. Synthesis is considered difficult because you need to have a grasp of lots of reactions. Well, if you have an understanding of simple basic organic chemistry plus a few special "tools" you can do a surprising amount and enjoy the challenge. A detailed understanding of reactive intermediates is at the heart of chemical transformations, and thus of modern synthetic chemistry. The term reactive further implies a certain degree of instability of the species. Reactive intermediates are typically isolable only under special conditions, and most of the information regarding the structure and properties of reactive intermediates comes from indirect experimental evidence. Reaction mechanisms are a fundamental and most important part of organic chemistry, telling us about the interaction between electron-deficient and electron-rich species. The functional group is the site of reactivity in a molecule. By looking at the structure of the functional group, it is possible to predict the kind of reactions it will undergo.

A chemical reaction at the molecular level is an event in which two molecules collide in such a way as to break one or more of their bonds and make one or more new bonds, and hence new molecules. The sequence and timing of the bond-breaking and bond-making processes will be important to our understandings of the reactions. To find out how molecules react with each other and how to predict their reactions we need to know the *reaction mechanism*. Organic chemistry encompasses a very large number of compounds (many millions). To recognize these actors (compounds), we turn to the roles they are inclined to play in the scientific drama staged by the multitude of chemical reactions that define organic chemistry. We begin by defining some basic terms that will be used very frequently as this subject is elaborated:

Chemical reaction: A chemical reaction is a process that leads to the transformation of one set of chemical substances into another. Classically, chemical reactions encompass changes that strictly involve the motion of electrons in the forming and breaking of chemical bonds between atoms, and can often be described by a chemical equation. A transformation results in the change of composition, constitution, and/or configuration of a compound (referred to as the *reactant* or *substrate*) by making or breaking of carbon–carbon (C–C), carbon–hydrogen (C–H), and/or carbon–heteroatom (C–X) bond(s). Chemical reactions are described with chemical equations, which graphically present the starting materials, end products, and sometimes intermediate products and reaction conditions.

Reactant or substrate: The starting material undergoing change in a chemical reaction. Other compounds may also be involved, and common reactive partners (reagents) may be identified. The reactant is often (but not always) the larger and more complex molecule in the reacting system. Most (or all) of the reactant molecule is normally incorporated as part of the product molecule.

Reagent: A common partner of the reactant in many chemical reactions. It may be organic or inorganic, small or large, or gas, liquid, or solid. The portion of a reagent that ends up being incorporated in the product may range from all to very little or none.

Product(s): In a chemical reaction, substances (elements and/or compounds) called *reactants* are changed into other substances (compounds and/or elements) called *products*, the final form taken by the major reactant(s) of a reaction. Product(s) are formed during chemical reactions as reagents are consumed. Products have lower energy than the reagents and are produced during the reaction according to the second law of thermodynamics.

Reaction conditions: Reaction conditions summarize the experimental details relating to how transformations are carried out in laboratory settings; the optimum environmental conditions are needed, such as temperature, pressure, time, catalysts, and solvent under which a reaction progresses smoothly.

Catalysts: Catalysts are substances that accelerate the rate (velocity) of a chemical reaction without themselves being consumed or appearing as part of the reaction product. Catalysts do not change equilibria positions. A catalyst may participate in multiple chemical transformations. Catalysts that speed up the reaction are called *positive catalysts.* Substances that slow a catalyst's effect in a chemical reaction are called *inhibitors.* Substances that increase the activity of catalysts are called *promoters,* and substances that deactivate catalysts are called *catalytic poisons.* Catalytic reactions have a lower rate-limiting free energy of activation than the corresponding uncatalyzed reaction, resulting in higher reaction rate at the same temperature.

Electrophile: An electron-deficient atom, ion, or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile. In general, electrophiles (literally *electron-lover*) are positively charged or neutral species that participate in a chemical reaction by accepting an electron pair in order to bond to a nucleophile. Because electrophiles accept electrons, they are Lewis acids.

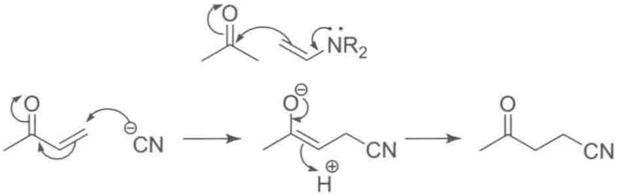
Nucleophile: An atom, ion, or molecule that has an electron pair that may be donated in bonding to an electrophile or Lewis acid; all nucleophiles are Lewis bases. **Nucleophilicity**, sometimes referred to as *nucleophile strength*, refers to a substance's nucleophilic character and is often used to compare the affinity of atoms.

The terms *nucleophile* and *electrophile* were introduced by Christopher Kelk Ingold in 1929, replacing the terms *cationoid* and *anionoid* proposed earlier by A.J. Lapworth in 1925.

1.1
Reaction Mechanism and Reaction Arrows

Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course. This is best accomplished by perceiving the reaction pathway or mechanism of a reaction. A detailed description of the changes in structure and bonding that take place during a reaction and the sequence of such events are called the *reaction mechanism*. Here, you will meet mechanisms, the dynamic language used by chemists to talk about reactions. A reaction mechanism should include a representation of plausible electron reorganization as well as the identification of any intermediate species that may be formed as the reaction progresses. Since chemical reactions involve the breaking and making of bonds, a consideration of the movement of bonding (and nonbonding) valence shell electrons is essential to this understanding. It is now common practice to show the movement of electrons with curved arrows, and a sequence of equations depicting the consequences of such electron shifts is termed a *mechanism*. In general, two kinds of curved arrows are used in drawing mechanisms. A curly arrow represents the actual movement of a pair of electrons from a filled orbital into an empty orbital, in either an intermolecular or intramolecular fashion. The tail of the arrow shows the source of the electron pair (highest occupied molecular orbital, HOMO) such as a lone pair or a pi (π) bond or a sigma (σ) bond. The head of the arrow indicates the ultimate destination of the electron-pair, which will either be an electronegative atom that can support a negative charge (a leaving group) or an empty orbital (LUMO, lowest unoccupied molecular orbital) when a new bond will be formed or an antibonding orbital (π^* or σ^*) when that bond will break.

A full head on the arrow indicates the movement or shift of an electron pair:



A partial head (fishhook) on the arrow indicates the shift of a single electron:

Chemists also use *other arrow symbols* for other purposes, and it is essential to use them correctly. These arrows include the reaction arrow: ⟶; the equilibrium arrow: ⇌; and the resonance arrow: ⟷.

Charge is conserved in each step of a reaction. If we start with neutral molecules and make a cation, we must make an anion too. Charge cannot be created or destroyed. If our starting materials have an overall charge plus (+) or minus (−) then the same charge must appear in the products.

It is a prerequisite for any mechanistic investigation that the reactants, all products, and the stoichiometry of the reaction are known. Many cases can be found in the literature where false mechanistic conclusions were drawn because this principle was neglected. Side products, even if very minor, can give useful hints concerning the mechanism as they are often derived from a common intermediate in a parallel reaction. Long-lived intermediates can be distinguished from products by analyzing the reaction mixture not only at the end but also as a function of the reaction time. Reactions where intermediates can be isolated in a normal workup are rather rare. More often, intermediates might be observable by spectroscopic techniques. The existence of short-lived intermediates or of intermediates occurring after the rate-determining step (RDS) can still be demonstrated by trapping reactions or by special techniques such as matrix isolation.

1.2
Properties and Characteristics of a Reaction

In an effort to understand how and why reactions of functional groups take place in the way they do, chemists try to discover just how different molecules and ions interact with each other as they come together. To this end, it is important to consider the various properties and characteristics of a reaction that may be observed and/or measured as the reaction proceeds. The most common and useful of these are covered below.

1.2.1
Reactants and Reagents

Variations in the structure of the reactant and reagent may have a marked influence on the course of a reaction.

1.2.2
Product Selectivity

1) **Regioselectivity:** Regioselectivity is the preference of one direction of chemical bond making or breaking over all other possible directions. It is often the case that addition and elimination reactions may proceed to more than one product. If one possible product out of two or more is formed preferentially, the reaction is said to be regioselective.
2) **Stereoselectivity:** Stereoselectivity is the property of a chemical reaction in which a single reactant forms an unequal mixture of stereoisomers during the non-stereospecific creation of a new stereocenter or during the non-stereospecific transformation of a preexisting one. The selectivity arises from differences in steric effects and electronic effects in the mechanistic pathways leading to the different products. Stereoselectivity can vary in degree but it can never be total since the activation energy difference between the two pathways is finite. If the reaction products are such that stereoisomers may be formed, a reaction that yields one stereoisomer preferentially is said to be stereoselective.
   An **enantioselective** reaction is one in which one enantiomer is formed in preference to the other, in a reaction that creates an optically active product from an achiral starting material, using either a chiral catalyst, an enzyme, or a chiral reagent. The degree of relative selectivity is measured by the enantiomeric excess (ee).
   A **diastereoselective** reaction is one in which one diastereomer is formed in preference to another (or in which a subset of all possible diastereomers dominates the product mixture), establishing a preferred relative stereochemistry. In this case, either two or more chiral centers are formed at once such that one relative stereochemistry is favored or a preexisting chiral center (which need not be optically pure) biases the stereochemical outcome during the creation of another. The degree of relative selectivity is measured by the diastereomeric excess (de).
   Stereoconvergence can be considered an opposite of stereoselectivity, when the reaction of two different stereoisomers yields a single product stereoisomer.
3) **Stereospecificity:** In chemistry, stereospecificity is the property of a reaction mechanism that leads to different stereoisomeric reaction products from different stereoisomeric reactants, or which operates on only one (or a subset) of the stereoisomers. This term is applied to cases in which stereoisomeric

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