Reinhard Bruckner

Advanced Organic Chemistry

Reaction Mechanisms

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Foreword

We are at the start of a revolution in molecular science that will more profoundly change our lives, our culture, indeed, our world than did the Industrial Revolution a century ago. From the human genome project, the largest natural product characterization effort ever, to the search for the molecular signatures of life on other planets, this molecular revolution is creating an ever-expanding view of ourselves and our universe. At the core of this revolution is chemistry, the quintessential molecular science within which is organic chemistry, a discipline that will surely be the source of many of the major advances in chemistry, biology, medicine, materials science, and environmental science in the 21st century.

In his text on organic chemistry, the translation of which has been impressively led by Professors Harmata and Glaser, Professor Bruckner has masterfully addressed the core concepts of the discipline, providing a rich tapestry of information and insight. The student of contemporary organic chemistry will be well-served by the depth and quality of this treatment. The underlying philosophy of this text is that much of chemistry can be understood in terms of structure, which in turn influences reactivity, ultimately defining the higher order activities of synthesis. Whether one seeks to understand nature or to create the new materials and medicines of the future, a key starting point is thus understanding structure and mechanism.

Professor Bruckner addresses the interrelationship of structure and mechanism with the rich insight of one schooled at the interface of physical organic chemistry and synthesis. His treatment is impressively rigorous, integrated, and broad. He achieves breadth through the careful selection of representative and fundamental reactive intermediates and reactions. Rigor and integration derive from his disciplined adherence to structure, orbital theory, and mechanism. The result is a powerfully coherent treatment that enables the student to address the rich subject matter at hand and importantly by analogy the far-ranging aspects of the field that lie beyond the scope of the book. Extending from his treatment of radicals, nucleophiles, carbenium ions, and organometallic agents to concerted reactions and redox chemistry, Bruckner provides an analysis that effectively merges theory and mechanism with examples and applications. His selection of examples is superb and is further enhanced by the contemporary references to the literature. The text provides clarity that is essential for facilitating the educational process.

This is a wonderfully rich treatment of organic chemistry that will be a great value to students at any level. Education should enable and empower. This text does both, providing the student with the insights and tools needed to address the tremendous challenges and opportunities in the field. Congratulations to Professors Bruckner, Harmata, and Glaser for providing such a rich and clear path for those embarking on an understanding of the richly rewarding field of organic chemistry.

Paul A. Wender
Stanford University

Preface to the English Edition

Writing a textbook at any level is always a challenge. In organic chemistry, exciting new discoveries are being made at an ever-increasing pace. However, students of the subject still arrive in the classroom knowing only what they have been taught, often less. The challenge is to present appropriate review material, present venerable, classic chemistry while dealing with the latest results, and, most importantly, provoke thought and discussion. At the time this book was written, there was a need for an advanced text that incorporated these aspects of our science.

The German version of the text was designed for second- and third-year chemistry majors: 60–70% of the contents of this book address students before the "Diplomchemiker-Vorexamen," while the remaining 30–40% address them thereafter. The German book is typically used one year after a standard introductory textbook such as that by Vollhardt and Schore, Streitweiser and Heathcock, or McMurry. Accordingly, in the United States this text can be used in a class for advanced undergraduates or beginning graduate students. Curricula of other English-speaking countries should allow the use of this text with optimum benefit at a similar point of progress. A good understanding of the fundamentals of organic and physical chemistry will suffice as a foundation for using this textbook to advantage.

The approach taken in this book conveys the message that the underlying theory of organic chemistry pervades the entire science. It is not necessary at this level to restrict the learning of reactions and mechanisms to any particular order. MO theory and formalisms such as electron pushing with arrows are powerful tools that can be applied not only to the classic chemistry that led to their development but also to the most recently developed reactions and methods, even those that use transition metals.

Theory, mechanism, synthesis, structure, and stereochemistry are discussed throughout the book in a qualitative to semiquantitative fashion. Fundamental principles such as the Hammond postulate that can be applied in the most varied contexts are reinforced throughout the book. Equations such as the Erying equation or the rate laws of all kinds of reactions are introduced with the view that they have context and meaning and are not merely formulas into which numbers are plugged.

The present text, to the best of our knowledge, does not duplicate the approach of any other treatment at a comparable level. We are convinced that this book, which has already filled a niche in the educational systems of German- and the French-speaking countries (a French translation appeared in 1999), will do the same in the textbook market of English-speaking countries now that an English edition has become available.

We hope that you enjoy many fruitful hours of insight in the course of studying this book, and we welcome your constructive comments on its content and approach.

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Preface to the German Edition

To really understand organic chemistry requires three passes. First, one must familiarize oneself with the physical and chemical properties of organic chemical compounds. Then one needs to understand their reactivities and their options for reactions. Finally, one must develop the ability to design syntheses. A typical schedule of courses for chemistry students clearly incorporates these three components. Introductory courses focus on compounds, a course on reaction mechanisms follows, and a course on advanced organic chemistry provides more specialized knowledge and an introduction to retrosynthesis.

Experience shows that the *second* pass, the presentation of the material organized according to reaction mechanisms, is of central significance to students of organic chemistry. This systematic presentation reassures students not only that they can master the subject but also that they might enjoy studying organic chemistry.

I taught the reaction mechanisms course at the University of Göttingen in the winter semester of 1994, and by the end of the semester the students had acquired a competence in organic chemistry that was gratifying to all concerned. Later, I taught the same course again—I still liked its outline—and I began to wonder whether I should write a textbook based on this course. A text *of this kind* was not then available, so I presented the idea to Björn Gondesen, the editor of *Spektrum*. Björn Gondesen enthusiastically welcomed the book proposal and asked me to write the "little booklet" as soon as possible. I gave up my private life and wrote for just about two years. I am grateful to my wife that we are still married; thank you, Jutta!

To this day, it remains unclear whether Björn Gondesen used the term "little booklet" in earnest or merely to indicate that he expected *one* book rather than a series of volumes. In any case, I am grateful to him for having endured patiently the mutations of the "little booklet" first to a "book" and then to a "mature textbook." In fact, the editor demonstrated an indestructible enthusiasm, and he remained supportive when I presented him repeatedly with increases in the manuscript of yet another 50 pages. The reader has Björn Gondesen to thank for the two-color production of this book. All "curved arrows" that indicate electron shifts are shown in red so that the student can easily grasp the reaction. Definitions and important statements also are graphically highlighted.

In comparison to the preceding generation, students of today study chemistry with a big handicap: an explosive growth of knowledge in all the sciences has been accompanied in particular by the need for students of organic chemistry to learn a greater number of reactions than was required previously. The omission of older knowledge is possible only if that knowledge has become less relevant and, for this reason, the following reactions were omitted: Darzens glycidic ester synthesis, Cope elimination, S_Ni reaction, iodoform reaction, Reimer–Tiemann reaction, Stobble condensation, Perkin synthesis, benzoin condensation, Favorskii rearrangement, benzil–benzilic acid rearrangement, Hofmann and Lossen degradation, Meerwein–Ponndorf reduction, and Cannizarro reaction. A few other reactions were omitted because they did not fit into the current presentation (nitrile and alkyne chemistry, cyanohydrin formation, reductive amination, Mannich reaction, enol and enamine reactions).

This book is a highly modern text. All the mechanisms described concern reactions that are used today. The mechanisms are not just *l'art pour l'art*. Rather, they present a conceptual tool to facilitate the learning of reactions that one needs to know in any case. Among the modern reactions included in the present text are the following: Barton–McCombie reaction, Mitsunobu reaction, Mukaiyama redox condensations, asymmetric hydroboration, halolactonizations, Sharpless epoxidation, Julia–Lythgoe and Peterson olefination, *ortho*-lithiation, *in situ* activation of carboxylic acids, preparations and reactions of Gilman, Normant, and Knochel cuprates, alkylation of chiral enolates (with the methods by Evans, Helmchen, and Enders), diastereoselective aldol additions (Heathcock method, Zimmerman–Traxler model), Claisen–Ireland rearrangements, transition metal–mediated C,C-coupling reactions, Swern and Dess-Martin oxidations, reductive lithiations, enantioselective carbonyl reductions (Noyori, Brown, and Corey–Itsuno methods), and asymmetrical olefin hydrogenations.

The presentations of many reactions integrate discussions of stereochemical aspects. Syntheses of mixtures of stereoisomers of the target molecule no longer are viewed as valuable—indeed such mixtures are considered to be worthless—and the control of the stereoselectivity of organic chemical reactions is of paramount significance. Hence, suitable examples were chosen to present aspects of modern stereochemistry, and these include the following: control of stereoselectivity by the substrate, the reagent, or an ancilliary reagent; double stereodifferentiation; induced and simple diastereoselectivity; Cram, Cram chelate, and Felkin–Anh selectivity; asymmetric synthesis; kinetic resolution; and mutual kinetic resolution.

B

Indicates relevance for undergraduate students

A

Indicates relevance for graduate students

You might ask how then, for heaven's sake, is one to remember all of this extensive material? Well, the present text contains only about 70% of the knowledge that I would expect from a *really well-trained* undergraduate student; the remaining 30% presents material for graduate students. To ensure the best orientation of the reader, the sections that are most relevant for optimal undergraduate studies are marked in the margin with a B on a gray background, and sections relevant primarily to graduate students are marked with an A on a red background. I have worked most diligently to show the reactions in reaction diagrams that include every intermediate—and in which the flow of the valence electrons is highlighted in color—and, whenever necessary, to further discuss the reactions in the text. It has been my aim to describe all reactions so well, that in hindsight—because the course of every reaction will seem so plausible—the readers feel that they might even have *predicted* their outcome. I tried especially hard to realize this aim in the presentation of the chemistry of carbonyl compounds. These mechanisms are presented in four chapters (Chapters 7–11), while other authors usually cover all these reactions in one chapter. I hope this pedagogical approach will render organic chemistry more comprehensible to the reader.

Finally, it is my pleasure to thank—in addition to my untiring editor—everybody who contributed to the preparation of this book. I thank my wife, Jutta, for typing "version 1.0" of most of the chapters, a task that was difficult because she is not a chemist and that at times became downright "hair raising" because of the inadequacy of my dictation. I thank my co-workers Matthias Eckhardt (University of Göttingen, Dr. Eckhardt by now) and Kathrin Brüschke (chemistry student at the University of Leipzig) for their careful reviews of the much later "version .10" of the chapters. Their comments and corrections resulted in "version .11" of the manuscript, which was then edited professionally by Dr. Barbara Elvers (Oslo). In particular, Dr. Elvers polished the language of sections that had remained unclear, and I am very grateful for her editing. Dr. Wolfgang Zettelmeier (Laaber-Waldetzenberg) prepared the drawings for the resulting "version .12," demonstrating great sensitivity to my aesthetic wishes. The typsesetting was accomplished essentially error-free by Konrad Triltsch (Würzburg), and my final review of the galley pages led to the publication of "version .13" in book form. The production department was turned upside-down by all the "last minute" changes—thank you very much, Mrs. Notacker! Readers who note any errors, awkward formulations, or inconsistencies are heartily encouraged to contact me. One of these days, there will be a "version .14."

It is my hope that your reading of this text will be enjoyable and useful, and that it might convince many of you to specialize in organic chemistry.

Reinhard Brückner
Göttingen, August 8, 1996

Acknowledgments

My part in this endeavor is over. Now, it is entirely up to the staff at Harcourt/Academic Press to take charge of the final countdown that will launch *Advanced Organic Chemistry: Reaction Mechanisms* onto the English-speaking market. After three years of intense trans-Atlantic cooperation, it is my sincere desire to thank those individuals in the United States who made this enterprise possible. I am extremely obliged to Professor Michael Harmata from the University of Missouri at Columbia for the great determination he exhibited at *all* phases of the project. It was he who doggedly did the legwork at the 1997 ACS meeting in San Francisco, that is, cruised from one science publisher's stand to the next, dropped complimentary copies of the German edition on various desks, and talked fervently to the responsibles. David Phanco from Academic Press was immediately intrigued and quickly set up an agreement with the German publisher. David Phanco was farsighted enough to include Mike Harmata on board as a "language polisher" (of the translation) before he passed on the torch to Jeremy Hayhurst in what then was to become Harcourt/Academic Press. The latter's sympathetic understanding and constant support in the year to follow were absolutely essential to the final success of the project: Mike Harmata, at that time a Humboldt Fellow at the University of Göttingen, and I needed to develop a very Prussian sense of discipline when doing our best to match the first part of the translation to the quality of the original. I am very much indebted to Professor Rainer Glaser, who reinforced the Missouri team and, being bilingual, finished the second half of the translation skillfully and with amazing speed. He also contributed very valuably to improving the galley proofs, as did Joanna Dinsmore, Production Manager at Harcourt/Academic Press. It is she who deserves a great deal of gratitude for her diligence in countless hours of proofreading, and for her patience with an author who even at the page proof stage felt that it was never too late to make all sorts of small amendments for the future reader's sake. It is my sincere hope, Ms. Dinsmore, that in the end you, too, feel that this immense effort was worth the trials and tribulations that accompanied it.

Reinhard Bruckner
Freiburg, April 25, 2001

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