REACTIVITY IN ORGANIC CHEMISTRY

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Reactivity in Organic Chemistry

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Preface to the English Edition

It is gratifying to see "*Reaktivität in der organischen Chemie, I, Produkte, Geschwindigkeiten,* and *II, Übergangszustände*, translated into the language in which most of the important contributions to the field appear (and which is also the language of many of my friends in the profession).

The translation also gave me a welcome opportunity to make corrections and revisions and to introduce a considerable amount of new material including work published in 1980.

Upon completion of the undertaking I express my gratitude foremost to Dr. Ludmila Birladeanu, of the Department of Chemistry, Harvard University, for her fine work in translating my German and otherwise helping in the preparation and publication of the book.

I am also deeply indebted to Prof. W. von E. Doering for his enthusiastic support of the English version, and I thank A. H. W. van den Berg for several new drawings.

GERHARD W. KLUMPP

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Preface

This book is based on lectures I gave at Free University Amsterdam. Assuming knowledge of material commonly treated in textbooks of organic chemistry, I aim to give an overview of essential aspects of present-day organic chemistry. No attempt has been made to be comprehensive or to adhere to historical order.

The central theme, *reactivity*, is illustrated by examples taken from the areas of synthetically important reactions and properties and behavior of reactive intermediates and covers such practical questions as "Which products are to be expected from certain starting materials?" and "What is the reaction time needed for a given substrate?"

The treatment is three-layered: an introductory description of the multiple reactivity of organic compounds is followed by a discussion of the effects of reaction conditions (thermodynamic control, various kinetic systems) on the ratios of products formed. Relationships (mostly quantitative) between structure of substrate and reaction rates are then described. Finally, to get an insight into systems whose reactivity is amenable to qualitative treatment only (and which represent the majority of situations commonly encountered in the laboratory), properties of transition states and models for their understanding are presented.

The didactic strategy used is that of repetition at various stages: nucleophilic reactions, reactions of carbonyl compounds and olefins, cycloadditions, Cope and Claisen rearrangements, aromatic substitutions, and formation and reactions of reactive intermediates are leitmotives recurring throughout the text and are treated at all three levels.

A main concern is to present material that because of the rapid development of organic chemistry is not treated in available textbooks. The novice experimenter starting out alone is offered a vast array of data taken from practice. Along with the fact that such a text does not exist in German it is hoped that these two elements will make *Reactivity in Organic Chemistry, I, Products, Rates,* and *II, Transition States* a useful and stimulating source not only for advanced students but also for colleagues and industrial chemists.

Having reached the end of the road, it is a pleasure to express my gratitude to all who contributed directly or indirectly to the accomplishment of the task: to my family, to my students, co-workers and colleagues for help, stimulation, and criticism, to Mrs. P. M. M. Zwebe-Böeseken for typing the initial draft of the manuscript [in German] and preparing many drawings, and to Georg Thieme Verlag and its staff, in particular Dr. G. Zartner, for unrestricted support in setting up the final form of the German edition.

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Reactivity in Organic Chemistry

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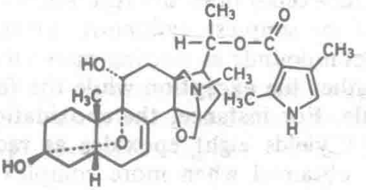
RATES

TRANSITION STATES

Introduction

“Populate the earth and subdue it” (Genesis 1:26). Results of modern organic chemistry seem to indicate that in this field the biblical command has been fulfilled. An arsenal of instrumental and theoretical methods makes it possible to isolate and determine the structure of the most complicated natural products on vanishingly small amounts of material, to perform their total syntheses, and to solve other synthetic problems that have intrigued chemists for decades. One of the many examples is the structure proof by B. Witkop et al.[1] of the extremely toxic cardiotoxin *batrachotoxin* (1) (used as arrow poison), available as one of the four components of a mixture isolated from 5000 Colombian frogs in the amount of only 110 mg.



1, Batrachotoxin

3 Cyclobutadiene

Up to now the ultimate triumph in organic synthesis may be the synthesis of *vitamin* B_{12} (2) by the joint efforts of R. B. Woodward and A. Eschenmoser and their collaborators.[2] One should also mention the recent synthesis and characterization of *cyclobutadiene* (3) in several laboratories, a problem that first emerged in 1900.[3], /4/* It is not surprising, therefore, to encounter statements such as “[it is] the modern chemist’s attitude that he can very probably make anything he wants.”[5]

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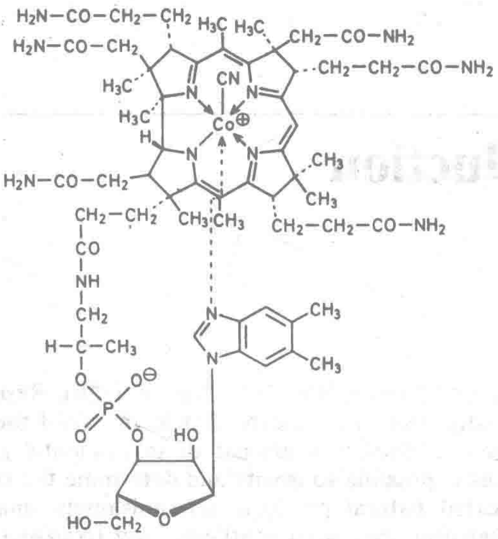
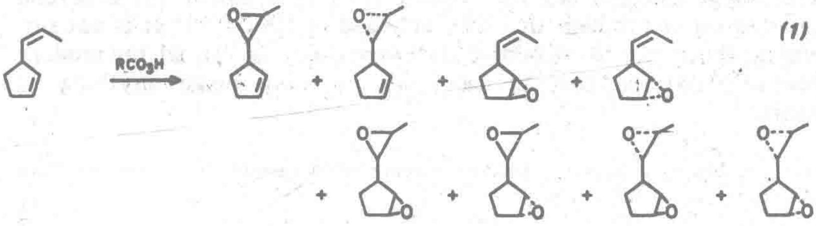
*The symbol / / indicates references containing comments along with literature sources.



2 , Vitamin B_{12}

However, even someone who has spent only a short time in an organic research laboratory knows that the conquest is far from total and that battles must be fought almost daily. Only in relatively few cases (e.g., the epoxidation of cyclohexene) does the reaction result in a single product. But if instead of the simplest, symmetric substances one wishes to use polyfunctional compounds as starting materials, the formation of a single product is rather the exception while the formation of several products is the rule. For instance, the epoxidation of 3-(*cis*-1-propenyl)-cyclopentene (*1*) yields eight epoxides as racemic mixtures. Even worse results are obtained when more complex substrates and highly reactive reagents are used. In the extreme only undesired products may be formed. In such instances, rules that teach what changes should occur in a molecule and in what part of it do not give a clear-cut answer. Only *experiment* can provide a solution, as well as hints for more successful approaches.



(1)

The more complex and unusual the substrate, the greater the danger of occurrence of unexpected or undesired reactions. In multistep syntheses, where the amount of available material diminishes with every step and thus becomes more precious [e.g., see (*2*)], satisfactory total yields can be obtained without too much loss of material and time only if one takes into consideration all possible reactions and their rates and chooses appropriate reaction conditions accordingly.

$$A \xrightarrow{80\%} B \xrightarrow{60\%} C \xrightarrow{90\%} D \xrightarrow{40\%} E \quad 17\% \text{ total} \tag{2}$$

Before success was achieved in the synthesis of vitamin B_{12} (2), the interplay of theoretical considerations and experiment required 11 years of work by 99 people.

In kinetic and mechanistic studies the formation of several products is often desirable, since the elucidation of their structure and relative concentrations may give valuable information with respect to the *reaction mechanism* and the *properties of potential intermediates.*

The concern about products is thus the most elementary and compelling aspect in any chemical reaction. In planning new reactions the following three questions must be asked:

1 Which primary *products* are possible under a given set of conditions?

2 What are the *relative amounts* of the possible products, and are they *stable* under the reaction conditions?

3 How can one *influence* the outcome in 1 and 2? In the following the attempt is made to:
  - *(a)* Correlate *reactivity* and *composition* of reaction mixtures.
  - *(b)* Review the quantitative empirical and semiempirical *structure-reactivity* relationships and their application.
  - *(c)* Present the methods of the *transition state theory* and evaluate the possibilities of influencing product composition and reactivities.

Examples used as illustrations of general principles should familiarize the reader with topics such as "*(synthetically) important classes of compounds and their transformations*" and "*(important) properties of reactive intermediates.*" Various aspects of a given topic often appear in a different context. It is assumed that the reader is familiar with the fundamental aspects of the transition state theory, reaction mechanisms, and conformational analysis.

PRODUCTS