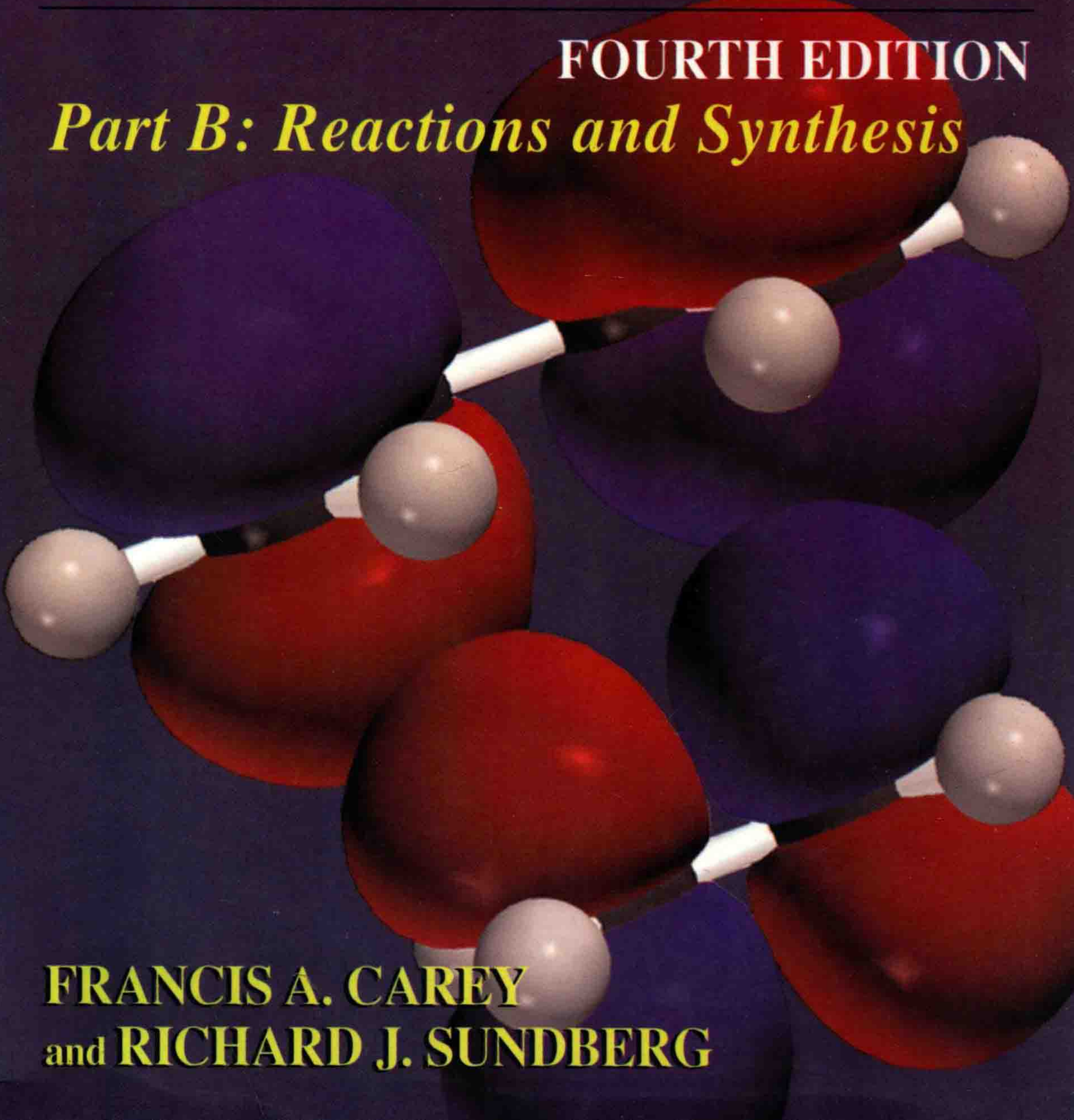
ADVANCED ORGANIC CHEMISTRY

FOURTH EDITION

Part B: Reactions and Synthesis



FRANCIS A. CAREY
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Part B: Reactions and Synthesis

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The front cover shows the key orbital interactions in the Diels-Alder reaction. The highest-occupied molecular orbital (HOMO) of 1,3-butadiene and the lowest-unoccupied molecular orbital (LUMO) of ethylene overlap in phase with one another allowing the reaction to occur in a single step.

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Part B: Reactions and Synthesis

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PART A: Structure and Mechanisms
PART B: Reactions and Synthesis

Preface to the Fourth Edition

Part B emphasizes the most important reactions used in organic synthesis. The material is organized by reaction type. Chapters 1 and 2 discuss the alkylation, conjugate addition and carbonyl addition/condensation reactions of enolates and other carbon nucleophiles. Chapter 3 covers the use of nucleophilic substitution, both at saturated carbon and at carbonyl groups, in functional group of interconversions. Chapter 4 discusses electrophilic additions to alkenes and alkynes, including hydroboration. Chapter 5 discusses reduction reactions, emphasizing alkene and carbonyl-group reductions. Concerted reactions, especially Diels–Alder and other cycloadditions and sigmatropic rearrangements, are considered in Chapter 6. Chapters 7, 8, and 9 cover organometallic reagents and intermediates in synthesis. The main-group elements lithium and magnesium as well as zinc are covered in Chapter 7. Chapter 8 deals with the transition metals, especially copper, palladium, and nickel. Chapter 9 discusses synthetic reactions involving boranes, silanes, and stannanes. Synthetic reactions which involve highly reactive intermediates—carbocations, carbenes, and radicals—are discussed in Chapter 10. Aromatic substitution by both electrophilic and nucleophilic reagents is the topic of Chapter 11. Chapter 12 discusses the most important synthetic procedures for oxidizing organic compounds. In each of these chapters, the most widely used reactions are illustrated by a number of specific examples of typical procedures. Chapter 13 introduces the concept of synthetic planning, including the use of protective groups and synthetic equivalents. Multistep syntheses are illustrated with several syntheses of juvabione, longifolene, Prelog–Djerassi lactone, Taxol, and epothilone. The chapter concludes with a discussion of solid-phase synthesis and its application in the synthesis of polypeptides and oligonucleotides, as well as to combinatorial synthesis.

The control of reactivity to achieve specific syntheses is one of the overarching goals of organic chemistry. In the decade since the publication of the third edition, major advances have been made in the development of efficient new methods, particularly catalytic processes, and in means for control of reaction stereochemistry. For example, the scope and efficiency of palladium- catalyzed cross coupling have been greatly improved by optimization of catalysts by ligand modification. Among the developments in stereocontrol are catalysts for enantioselective reduction of ketones, improved methods for control of the stereoselectivity of Diels–Alder reactions, and improved catalysts for enantioselective hydroxylation and epoxidation of alkenes.

This volume assumes a level of familiarity with structural and mechanistic concepts comparable to that in the companion volume, *Part A, Structure and Mechanisms*. Together, the two volumes are intended to provide the advanced undergraduate or beginning graduate student in chemistry a sufficient foundation to comprehend and use the research literature in organic chemistry.

Advanced Organic Chemistry

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EDITION

Part B: Reactions and Synthesis

Contents of Part B

1

Alkylation of Nucleophilic Carbon Intermediates

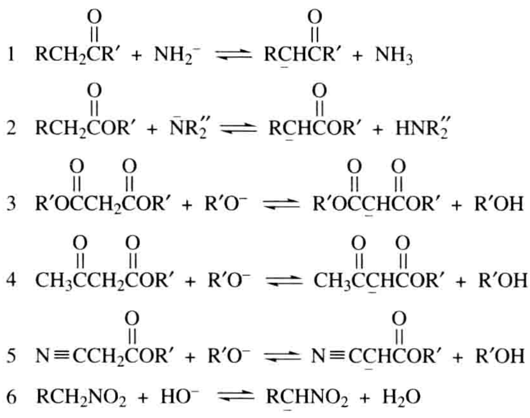
Introduction

Carbon–carbon bond formation is the basis for the construction of the molecular framework of organic molecules by synthesis. One of the fundamental processes for carbon–carbon bond formation is a reaction between a nucleophilic carbon and an electrophilic one. The focus in this chapter is on *enolate ions*, *imine anions*, and *enamines*, which are the most useful kinds of carbon nucleophiles, and on their reactions with *alkylating agents*. Mechanistically, these are usually S_N2 reactions in which the carbon nucleophile displaces a halide or other leaving group. Successful carbon–carbon bond formation requires that the S_N2 alkylation be the dominant reaction. The crucial factors which must be considered include (1) the conditions for generation of the carbon nucleophile; (2) the effect of the reaction conditions on the structure and reactivity of the nucleophile; (3) the regio- and stereoselectivity of the alkylation reaction; and (4) the role of solvents, counterions, and other components of the reaction media that can influence the rate of competing reactions.

1.1. Generation of Carbanions by Deprotonation

A very important means of generating carbon nucleophiles involves removal of a proton from a carbon by a Brønsted base. The anions produced are *carbanions*. Both the rate of deprotonation and the stability of the resulting carbanion are enhanced by the presence of substituent groups that can stabilize negative charge. A carbonyl group bonded directly to the anionic carbon can delocalize the negative charge by resonance, and carbonyl compounds are especially important in carbanion chemistry. The anions formed by deprotonation of the carbon *alpha* to a carbonyl group bear most of their negative charge on oxygen and are referred to as *enolates*. Several typical examples of proton-abstraction equilibria are listed in Scheme 1.1. Electron delocalization in the corresponding carbanions is represented by the resonance structures presented in Scheme 1.2.

Scheme 1.1. Generation of Carbon Nucleophiles by Deprotonation



1 $\mathrm{RCH_2\overset{O}{\overset{\|}{C}}R' + NH_2^- \rightleftharpoons R\underline{C}H\overset{O}{\overset{\|}{C}}R' + NH_3}$

2 $\mathrm{RCH_2\overset{O}{\overset{\|}{C}}OR' + \bar{N}R''_2 \rightleftharpoons R\underline{C}H\overset{O}{\overset{\|}{C}}OR' + HNR''_2}$

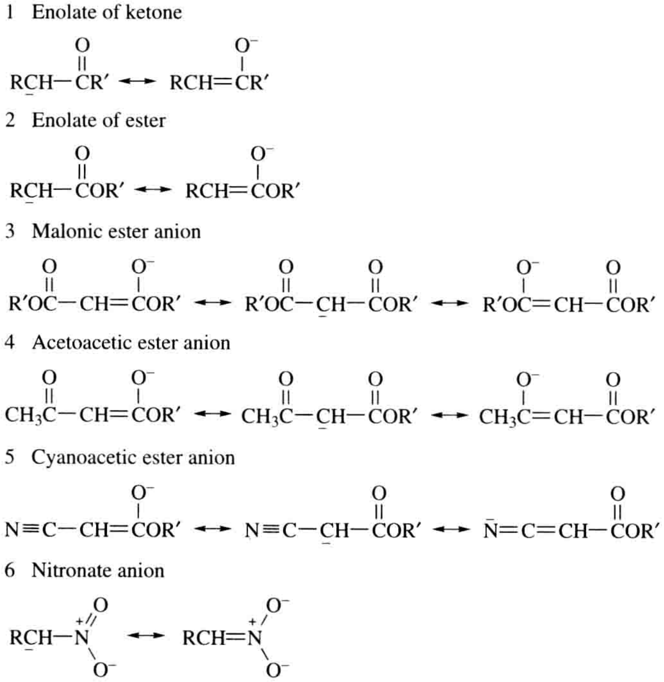
3 $\mathrm{R'O\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OR' + R'O^- \rightleftharpoons R'O\overset{O}{\overset{\|}{C}}\underline{C}H\overset{O}{\overset{\|}{C}}OR' + R'OH}$

4 $\mathrm{CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OR' + R'O^- \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}\underline{C}H\overset{O}{\overset{\|}{C}}OR' + R'OH}$

5 $\mathrm{N{\equiv}CCH_2\overset{O}{\overset{\|}{C}}OR' + R'O^- \rightleftharpoons N{\equiv}C\underline{C}H\overset{O}{\overset{\|}{C}}OR' + R'OH}$

6 $\mathrm{RCH_2NO_2 + HO^- \rightleftharpoons R\underline{C}HNO_2 + H_2O}$

Scheme 1.2. Resonance in Some Carbanions



1 Enolate of ketone

$\mathrm{R\underline{C}H{-}\overset{O}{\overset{\|}{C}}R' \longleftrightarrow RCH{=}\overset{O^-}{\overset{|}{C}}R'}$

2 Enolate of ester

$\mathrm{R\underline{C}H{-}\overset{O}{\overset{\|}{C}}OR' \longleftrightarrow RCH{=}\overset{O^-}{\overset{|}{C}}OR'}$

3 Malonic ester anion

$\mathrm{R'O\overset{O}{\overset{\|}{C}}{-}CH{=}\overset{O^-}{\overset{|}{C}}OR' \longleftrightarrow R'O\overset{O}{\overset{\|}{C}}{-}\underline{C}H{-}\overset{O}{\overset{\|}{C}}OR' \longleftrightarrow R'O\overset{O^-}{\overset{|}{C}}{=}CH{-}\overset{O}{\overset{\|}{C}}OR'}$

4 Acetoacetic ester anion

$\mathrm{CH_3\overset{O}{\overset{\|}{C}}{-}CH{=}\overset{O^-}{\overset{|}{C}}OR' \longleftrightarrow CH_3\overset{O}{\overset{\|}{C}}{-}\underline{C}H{-}\overset{O}{\overset{\|}{C}}OR' \longleftrightarrow CH_3\overset{O^-}{\overset{|}{C}}{=}CH{-}\overset{O}{\overset{\|}{C}}OR'}$

5 Cyanoacetic ester anion

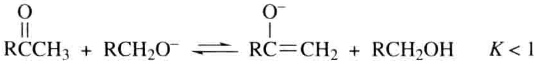
$\mathrm{N{\equiv}C{-}CH{=}\overset{O^-}{\overset{|}{C}}OR' \longleftrightarrow N{\equiv}C{-}\underline{C}H{-}\overset{O}{\overset{\|}{C}}OR' \longleftrightarrow \bar{N}{=}C{=}CH{-}\overset{O}{\overset{\|}{C}}OR'}$

6 Nitronate anion

$\mathrm{R\underline{C}H{-}\overset{+}{N}(=O)(O^-) \longleftrightarrow RCH{=}\overset{+}{N}(O^-)(O^-)}$

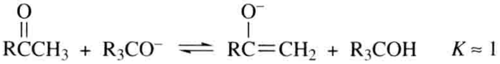
The efficient generation of a significant equilibrium concentration of a carbanion requires choice of a proper Brønsted base. The equilibrium will favor carbanion formation only when the acidity of the carbon acid is greater than that of the conjugate acid corresponding to the base used for deprotonation. Acidity is quantitatively expressed as pK_a, which is equal to $-\log K_a$ and applies, by definition, to dilute *aqueous* solution. Because most important carbon acids are quite weak acids ($pK_a > 15$), accurate measurement of their acidity in aqueous solutions is impossible, and acidities are determined in organic solvents and referenced to the pK_a in an approximate way. The data produced are not true pK_a's, and their approximate nature is indicated by referring to them as simply pK values. Table 1.1 presents a list of pK data for some typical carbon acids. The table also includes examples of the bases which are often used for deprotonation. The strongest acids appear at the top of the table, and the strongest bases at the bottom. A favorable equilibrium between a carbon acid and its carbanion will be established if the base which is used appears below the acid in the table. Also included in the table are pK values determined in dimethyl sulfoxide (pK_{DMSO}). The range of acidities that can be directly measured in dimethyl sulfoxide (DMSO) is much greater than in aqueous media, thereby allowing direct comparisons between compounds to be made more confidently. The pK values in DMSO are normally greater than in water because water stabilizes anions more effectively, by hydrogen bonding, than does DMSO. Stated another way, many anions are more strongly basic in DMSO than in water. At the present time, the pK_{DMSO} scale includes the widest variety of structural types of synthetic interest.[1] From the pK values collected in Table 1.1, an ordering of some important substituents with respect to their ability to stabilize carbanions can be established. The order suggested is $\mathrm{NO_2 > COR > CN \sim CO_2R > SO_2R > SOR > Ph \sim SR > H > R}$.

By comparing the approximate pK values of the conjugate acids of the bases with those of the carbon acid of interest, it is possible to estimate the position of the acid–base equilibrium for a given reactant–base combination. If we consider the case of a simple alkyl ketone in a protic solvent, for example, it can be seen that hydroxide ion and primary alkoxide ions will convert only a small fraction of such a ketone to its anion.



$$\mathrm{R\overset{O}{\overset{\|}{C}}CH_3 + RCH_2O^- \rightleftharpoons R\overset{O^-}{\overset{|}{C}}{=}CH_2 + RCH_2OH} \qquad K < 1$$

The slightly more basic tertiary alkoxides are comparable to the enolates in basicity, and a somewhat more favorable equilibrium will be established with such bases:



$$\mathrm{R\overset{O}{\overset{\|}{C}}CH_3 + R_3CO^- \rightleftharpoons R\overset{O^-}{\overset{|}{C}}{=}CH_2 + R_3COH} \qquad K \approx 1$$

To obtain complete conversion of ketones to enolates, it is necessary to use aprotic solvents so that solvent deprotonation does not compete with enolate formation. Stronger bases, such as amide anion ($^-\mathrm{NH_2}$), the conjugate base of DMSO (sometimes referred to as the "dimsyl" anion),[2] and triphenylmethyl anion, are capable of effecting essentially complete conversion of a ketone to its enolate. Lithium diisopropylamide (LDA), which is generated by addition of *n*-butyllithium to diisopropylamine, is widely used as a strong

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1. F. G. Bordwell, *Acc. Chem. Res.* **21:**456 (1988).
2. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **87:**1345 (1965).