REACTION MECHANISMS IN ORGANIC ANALYTICAL CHEMISTRY

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To my grandfather

ANTONIO GIOIA

PREFACE

Conventional discussions of organic analysis are organized by analytical method or technique (absorption spectroscopy, polarography, partition chromatography, mass spectrometry, etc.) or by functional group (amines, esters, olefins, and so on); much attention has also been given to classical areas of analytical interest, such as acid-base reactions, metal-ligand coordination equilibria, and solubility phenomena. This book expresses a different point of view by looking at organic analytical reactions on the basis of reaction type and mechanism. Such a shift of viewpoint sometimes allows connections to be made between ideas or observations that were formerly thought to be unrelated (if indeed they were thought of at all in the same context). In this manner it may stimulate analytical research. Moreover, this way of looking at organic analysis seems more effective, and more enjoyable, in teaching and learning the subject.

In this book I have organized and discussed analytical reactions within the framework that was developed for organic chemistry through the 1920's to 1950's, and that during the 1960's was applied to the study and systematization of bioorganic reactions. Students of analytical chemistry probably are not, as a class, well prepared for a thorough exposure to organic reaction mechanisms. This book is also, therefore, an introduction to many of the methods and concepts of physical organic chemistry. One of its contributions may be to direct the reading of the analytical chemist toward those subjects that he will find helpful in his analytical studies. I hope that no serious student of analytical chemistry will be satisfied to limit his pursuit of mechanistic studies to this book, but will follow my leads to other sources. This is a major purpose in providing a selection of literature citations. One advantage in reading elsewhere is that different points of view may be available, or even different ways of expressing the same idea, which may illuminate a difficult concept. Another advantage is the detail of experimental support and mechanistic interpretation that

is present in the original literature but that had to be abbreviated or omitted in a review of this scope.

Despite the ultimate goal of relating the mechanistic viewpoint to analytical reactions, I have tried not to be too narrowly limited by present analytical practice. Restriction of the mechanistic treatment to reactions of present analytical interest might have resulted in a spotty coverage of some topics and would not have served to stimulate analytical development by revealing possible gaps and weaknesses in the traditional emphasis. Nevertheless, my selection of topics is related ultimately to analytical reactions, and in this way I may have provided a means for the analytical student who wishes to learn more organic chemistry to focus on those areas and authors that are most apt to be of professional interest to him.

I have omitted discussions of many important reaction types, among them free radical reactions, oxidation/reductions, photochemical reactions, rearrangements, and molecular complex formation. The treatment of the topics included is systematic, but does not pretend to be complete. This is especially so with the sections titled Analytical Reactions, which summarize, within each reaction class, the reactions that have been applied in analysis. The reader may find it amusing and instructive to make additions or reassignments. Since few analytical methods have been described in mechanistic terms by their developers, it is not easy to conduct a literature survey in these terms. Many interesting analytical reactions have probably been overlooked.

Few analytical methods have been developed or improved primarily by the use of systematic studies guided by mechanistic principles. For small-scale efforts involving the adaptation of known methods to specific problems the traditional trial-and-error adjustment of conditions, aided by experience and chemical intuition, is probably superior to a serious mechanistic study. But it is precisely in developing a reliable insight into the nature of the controlling variables that the mechanistic approach taken by this book should be analytically useful.

I wish to acknowledge with thanks my indebtedness to J. S. Fritz and G. S. Hammond, whose book on organic analysis, published in 1957 while I was a graduate student, influenced my approach to analytical chemistry; to my teachers Takeru Higuchi and Myron L. Bender; to my secretary Billie Hubacher; and to my colleagues Pasupati Mukerjee and Joseph R. Robinson.

Kenneth A. Connors

Madison, Wisconsin
May 1972

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Chapter 1. INTRODUCTION

1.1 The Nature of Organic Analytical Methods

The term organic analytical chemistry obviously includes a greater part of chemistry than can be bound in one book. Some selection is necessary in treating the theoretical foundations of the subject. The distinguishing feature of the organic analytical methods in this book is the occurrence of a chemical reaction. In a broad sense, therefore, this book describes the principles of functional group analysis, this phrase being interpreted more freely than is conventional. Functional group analysis is based upon the characteristic chemical behavior of an atom or group of atoms (the functional group) in a molecule.

Functional group methods consist of two parts: (1) the chemical reaction or reactions that the sample compound is made to undergo; (2) the final measurement (the "finish"), which is usually quantitative. Sometimes these reaction and measurement components are merged together, as in a simple acidimetric titration of an amine; more frequently they are discrete, as when an ester is converted to the ferric complex of the corresponding hydroxamic acid (the reaction portion), whose concentration is then determined spectrophotometrically (the finish). Usually these methods are designed to give quantitative information (amount or purity) about a sample of known identity, but sometimes the same steps are utilized in qualitative analysis, as in classical derivatization procedures, spot tests, or derivatization prior to mass spectrometry.

It is assumed that the reader is familiar with the common organic analytical methods [1]. Detailed expositions are available in monographs [2] and review volumes [3]. These analytical methods can be discussed by considering the generalized reaction

$$\text{sample} + \text{reagent} \rightleftharpoons \text{product A} + \text{product B} \qquad (1.1)$$

Two general phenomena control the extent of this reaction. One of these is the equilibrium configuration of the system; for our purposes this is best described by the meth-

ods of thermodynamics. Chapter 2 considers some important concepts of chemical equilibria. The second controlling feature is the rate of reaction; this is treated in Chap. 3.

Table 1.I Analytically Useful Examples of Reaction (1.1)

Sample	+	Reagent	$\rightleftharpoons$	Product A	+	Product B
R-OH		$(R'CO)_2O$		$R'COOR$		$R'COOH$
R-CHO		$NH_3OH^+Cl^-$		$R-\overset{N-OH}{\overset{\|}{C}}-H$		$H_3O^+Cl^-$
RCOOR′		OH^-		$R-COO^-$		R′-OH
Ar-OH		$Ar-N{=}N^+Cl^-$		Ar-N=N-Ar-OH		HCl
$2RNH_3Cl$		$Hg(OAc)_2$ [a]		$HgCl_2$		$2RNH_3OAc$
R-OH		CH_3MgI		CH_4		R-OMgI
R-O-R		2HI		2R-I		H_2O
R-CH=CH-R		Br_2		RCHBrCHBrR		--
R-SH		$AgNO_3$		R-SAg		HNO_3

[a] Ac represents the acetyl group, CH_3CO, so OAc is acetoxy and OAc^- is acetate.

Table 1.I lists a few reactions that have been developed into analytical methods. Now consider how Eq. (1.1) might be utilized. An excess of reagent may be added to the sample. After the reaction is "complete," the actual quantitative finish is made, in this case by one of three routes: (1) the unreacted reagent can be determined, and this quantity subtracted from the total reagent added; this gives the amount of sample; (2) the amount of product A can be determined; (3) the amount of product B can be determined. The determination of excess reagent, of A or of B, may itself require further reactions. The selection of the final analytical route will be determined by features specific to the analysis. Many examples appear in later chapters.

Many analytical methods employ titrimetric or spectrophotometric finishes. The calculations required for a titrimetric determination are readily grasped with the aid of titration diagrams. As an example consider the determination of an ester by saponification (alkaline hydrolysis).

$$R\text{-}COOR' + OH^- \rightarrow R\text{-}COO^- + R'\text{-}OH \qquad (1.2)$$

It would appear that it is only necessary to add excess standard alkali, heat the solution until the ester is completely hydrolyzed, and back-titrate with standard acid. The difference between equivalents of alkali added and equivalents of acid consumed in the back-titration is equal to the equivalents of ester in the sample. This procedure is adequate for many samples. It can be refined, however, by including a blank determination. The procedure just outlined assumes that alkali is consumed only by the ester. This may not be a valid assumption, especially if the alkali concentration is rather low or if the reaction time is long, for alkali could be consumed by the glass surface and by carbon dioxide absorbed from the atmosphere. These types of error are minimized by performing a blank analysis. Figure 1.1 shows a titration diagram for the sample and blank determinations. The lengths of the lines are proportional to milliequivalents of reactants.

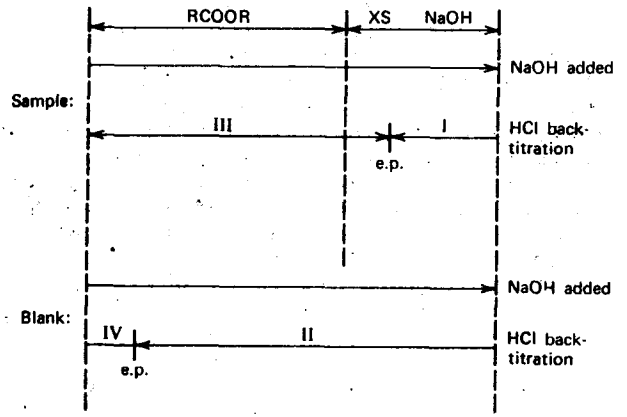

Fig. 1.1. Titration diagram for the saponification of an ester. The lengths of the lines are proportional to milliequivalents of reactants (from Ref. [1], p. 454).

If no alkali were consumed by extraneous materials, then milliequivalents of ester would equal III. This, however, is not so. Instead we find, by inspection of the diagram,

$$\text{milliequivalents of ester} = \text{III} - \text{IV}$$

which accounts for the consumption of alkali by substances other than the ester [4]. In order to calculate III and

IV, the volumes and normalities of both the alkali and the acid are required.

An alternate, and simpler, calculation is available. Figure 1.1 shows that

$$\text{milliequivalents of ester} = \text{II} - \text{I}$$

The quantities II and I can be calculated from a knowledge of the volumes and of the normality of the acid used in the back-titrations; the normality of the alkali is unnecessary as long as the same volume of the same alkali solution is used in the sample and in the blank determinations. (In effect, the blank determination is a standardization of the alkali under the conditions of the assay.) The approach illustrated by this example is widely used. Another titration diagram is shown in Figure 13.7.

Spectrophotometric finishes nearly always utilize the "working curve" technique, in which several samples of an authentic specimen, graded in amount or concentration, are subjected to the same reaction conditions as the test sample. Usually a blank determination is also carried out, with the sample compound being omitted but all other conditions being duplicated. The absorbances of the known solutions, relative to the reagent blank, are plotted against sample size or concentration to give a smooth, usually straight, line (the working curve, or standard curve), from which the unknown result can be obtained by interpolation. Calculation of the original sample content or purity then requires the appropriate dilution factors.

This method possesses the weakness that it cannot readily reveal systematic errors or deviations from the anticipated stoichiometry, because the known and unknown samples are treated alike, as far as is possible. Thus if the reaction takes place to the extent of only 95% of the theoretical, this discrepancy will occur for both the standard and the test samples, and so it will be compensated for. Often the working curve method is abbreviated by using a single standard sample instead of a series bracketing the unknown concentration; then deviations from Beer's law or from quantitative reaction cannot be detected, although the analysis may be successful if the concentrations of standard and unknown are similar. Although the inability of the standard curve method to detect nonquantitative reaction has been counted a weakness here [5], this same feature can be a strength in that adequate analyses can be conducted using systems that do not undergo quantitative reaction. In fact, the literature contains examples of such assays in which less than 20% of the sample is reacted; as long as the reaction conditions are suplicated for standard and unknown, reproduci-

ble results can be obtained (though with less than the theoretical sensitivity). Unfortunately, when a reaction is incomplete in an analytical system, the controlling variables are seldom well understood, and so duplication of the essential conditions may not be achieved. Poor reproducibility or even failure of the analysis may result. For this reason a worthy goal in the development of spectrophotometric finishes is reliance on previously established spectral properties of a product; in effect an authentic specimen of the product serves as the primary standard for the sample determination. This method allows study of the completeness of the functional group reaction. Alternatively, a full understanding of the reasons for incomplete reaction may give the analyst the necessary control over reaction conditions to establish confidence in the method.

These discussions of titrimetric and spectrophotometric finishes can be generalized to include most other techniques. Many kinds of end-point detection are applicable in titrimetry, but the basic relationships are all the same. Spectrophotometry is simply one example of a technique that is based upon a relationship between a solution property and solute concentration; in absorption spectroscopy this relationship is Beer's law. Analogous functions describe other useful techniques of measurement, such as fluorimetry, polarimetry, and gas chromatographic detection.

1.2 Plan of the Book

Descriptions of organic analytical methods have traditionally been organized around the function groups [2]--hydroxy, amino, carbonyl, carboxyl, and so on. This is a practical approach, because it starts with what the analyst already knows about his sample. Another way to arrange a treatment of organic analysis is by methods--absorption spectroscopy, acid-base titration, etc. [1,6]. Fritz and Hammond [7] showed how a consideration of the fundamental chemistry, in particular of relative rates and equilibria, might lead to the development of improved methods. Schenk has extended their treatment to several functional group determinations [8]. The present book is a further and more systematic essay into the theory of organic analytical methods. The organization is based on type of reaction.

The broadest classification of reactions is into the categories of heterolytic and homolytic reactions. In homolytic (free radical) reactions, bond cleavage occurs with one electron remaining with each atom, as in

$$R{:}X \xrightarrow{\text{homolytic}} R\cdot + \cdot X \qquad (1.3)$$

Free radical reactions are not discussed except as they appear incidentally to other processes. Heterolytic reactions occur with both electrons remaining with one of the atoms.

$$R{:}X \xrightarrow{\text{heterolytic}} R^+ + :X^- \qquad (1.4)$$

Heterolytic reactions are sometimes called ionic reactions.

A further classification is into these four categories:

1. Substitutions (displacements)
2. Additions
3. Eliminations
4. Rearrangements

Usually at least two reactants are present, and it is convenient to refer to one of these as the substrate and the other as the reagent. The distinction is arbitrary and conventional (see Sec. 4.2), and leads to a further classification in terms of reagent type. Reagents are nucleophiles (nucleus lovers) if they have an unshared electron pair and seek electron-deficient sites. Nucleophiles are either bases (in the Brønsted sense) or reducing agents; in a very general interpretation these classes are practically synonymous, for all such reagents function by donating electrons [9]. Electrophiles, which may be acids (including Lewis acids) or oxidizing agents, seek sites of high electron density.

Reactions are classified by specifying the class and the reagent type; thus a nucleophilic substitution (S_N) is a substitution reaction by a nucleophilic reagent, as in

$$I^- + C_2H_5\text{-}Br \longrightarrow C_2H_5\text{-}I + Br^- \qquad (1.5)$$

In this reaction iodide is the nucleophile. Since the substrate is aliphatic, the reaction is called an aliphatic nucleophilic substitution. An aromatic electrophilic substitution (S_E) is exemplified by Eq. (1.6), the nitronium ion being the electrophile.

Addition (Ad) reactions of multiple bonds also take place with electrophiles and nucleophiles; evidently if a reagent that is an electrophile adds to a double bond, the unsaturated bond must be functioning as a nucleophile. Eq. (1.7) is an Ad_E reaction.