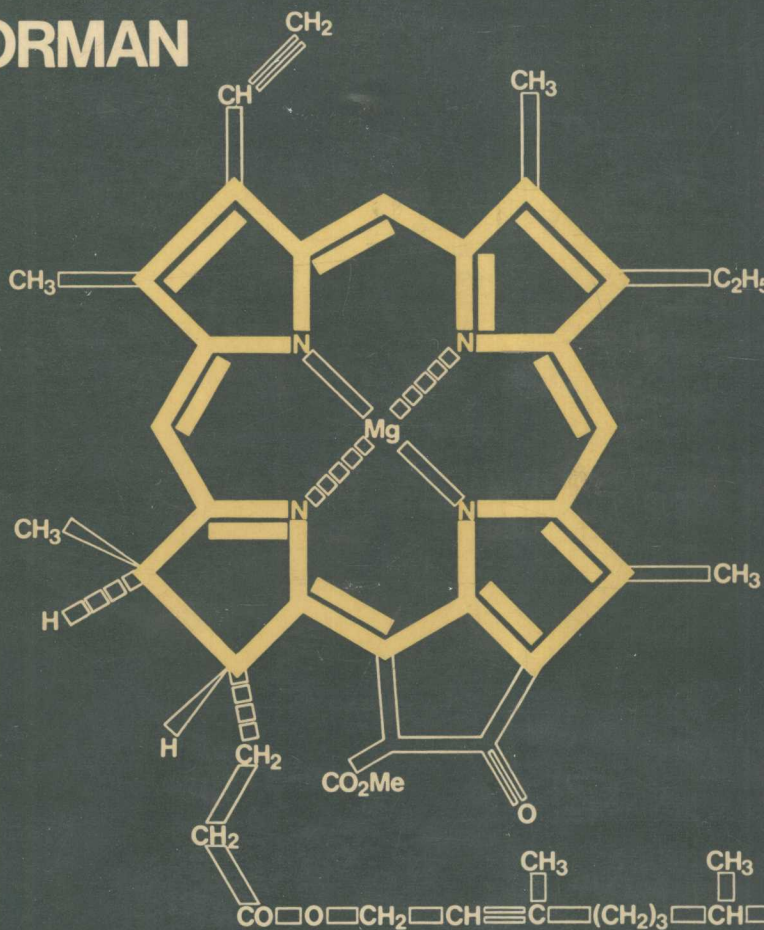


Principles of Organic Synthesis

Second Edition

R. O. C. NORMAN



Principles of Organic Synthesis

R. O. C. NORMAN F.R.S.

Professor of Chemistry, University of York

SECOND EDITION



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Preface to the First Edition

The last thirty years have witnessed a profound increase in our understanding of the ways in which organic compounds react together—their mechanisms of reaction. This has, on the one hand, become a large, discrete branch of organic chemistry; but it has also, on the other, had a considerable impact on our approach to devising methods for the synthesis of organic compounds. To the student, reaction mechanism can have a two-fold appeal: it is, in its own right, an intellectually stimulating subject in its rationalization and unification of complex processes; and it also provides a relatively simple superstructure on which the vast array of the facts of organic chemistry can be hung. In a paradoxical way, the amount to be usefully *learned* in a subject to which an array of facts is being added daily remains, as our *understanding* grows, almost unchanged.

The purpose of this book is to show how an understanding of these mechanistic principles can usefully be applied in thinking about and planning the construction of organic compounds. It is designed for those who have had a brief introduction to organic chemistry; an elementary knowledge of the nomenclature and structures of organic compounds is assumed. The text is divided into two parts. In the first five Chapters, mechanism is set in its wider context of the basic principles and concepts underlying chemical reactions: chemical thermodynamics, structural theory, theories of rates of reaction, mechanism itself, and stereochemistry. In the remaining fourteen Chapters, these principles and concepts are applied to the problems involved in putting together particular types of bonds, groupings, and compounds. The account is not intended to be exhaustive; for example, the vast body of evidence on which mechanisms are based has been omitted, nor are experimental details included. The object has been to convey a broad understanding rather than to produce a reference text.

I should like to acknowledge the help I have received from many of my former colleagues at the Dyson Perrins Laboratory, Oxford, my present colleagues in the University of York, and in particular Professor A. W. Johnson, F.R.S., who read the whole of the manuscript and made many helpful suggestions, and two of my former pupils, Messrs. A. J. Hart-Davis and J. C. MacDougall, who helped with the preparation of several Chapters.

R. O. C. NORMAN

Preface to the Second Edition

The ten years that have passed since this book was first published have served to emphasize the value to the organic chemist of approaching problems in synthesis with the aid of a thorough understanding of reaction mechanism. This is apparent in the design both of new synthetic methods and of the multi-stage synthesis of complex target molecules.

In this new edition, then, the basic Chapters which comprise Part I remain essentially unchanged while the Chapters, in Part II, which develop these basic ideas and show their operation in practice, have been brought up to date. In particular, there have been important advances in our understanding of the course of pericyclic reactions—concerted processes which occur within a cyclic array of the participating atomic centres—and this has led to the complete re-drafting of Chapter 9; valuable new methods which make use of reagents containing phosphorus, sulphur, or boron have been introduced (Chapter 15); and the use of photochemical methods in synthesis has advanced to the stage where a separate Chapter is justified. In addition, numerous new reagents have been included, especially in the Chapters on oxidation and reduction. Finally, the chance has been taken to transfer to S.I. units.

I am indebted to my colleagues Dr B. C. Gilbert and Dr J. M. Vernon for their advice in producing this edition, and especially to my colleague Dr Peter Hanson for his help in the preparation of the new material.

R. O. C. NORMAN

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Part I

Introduction to Part I

The five Chapters which comprise Part I are concerned with the principles which govern organic reactions.

The first Chapter examines the implications of the laws of thermodynamics. Reactions can "go"—that is, have equilibrium constants greater than unity—only if the products have a lower free-energy content than the reactants. The free energy of a species is related to its enthalpy, which is determined essentially by the strengths of the bonds it contains, and to its entropy, which is a measure of its degree of disorder; a low free energy corresponds to a system's having strong bonding forces and a high degree of disorder. From thermodynamic considerations there follows, for example, an understanding of why it is possible to reduce acetylene to ethylene at room temperature whereas ethylene is successfully dehydrogenated to give acetylene at a temperature of about 1,000°C.

The second Chapter considers the current theories of bonding in organic molecules and relates these to the strengths of the bonds in typical chemical groupings. Thus, the different chemical properties of benzene and ethylene are then seen to be related to the very considerable stabilization energy of the benzene ring. Other properties of organic compounds which are of importance in synthesis, such as the acidities of C—H bonds in various environments, also follow from structural theory.

That there should be a negative free-energy change is in practice a necessary but not a sufficient condition for a reaction to occur, for the *rate* at which it takes place may be negligible. Thermodynamic considerations alone indicate that hydrocarbons should not coexist with air, for the free-energy change involved in their oxidation to carbon dioxide and water is significantly negative; in practice, however, their rates of combustion at ordinary temperatures are negligible. The third Chapter sets out the theories of reaction kinetics and the effects of temperature on rate, and then introduces correlations of the rates of specific types of reaction with structure.

The planning of syntheses is helped considerably by an understanding of the mechanisms by which reactions occur. It must be emphasized that mechanisms are *theories* and not *facts* of the subject; they have been deduced from experimental observations and in some instances they transpire to be incorrect or at least in need of refinement; one should say, rather, 'the mechanism is thought to be,' than 'the mechanism is.' Nonetheless, the current mechanistic theories, which are surveyed in the fourth Chapter, not only provide an intellectually

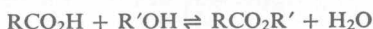
satisfying and unifying picture of the complexity of reactions, but also enable predictions to be made, with increasing assurance as the degree of rationalization of the subject increases, of the effects which structural modifications will have on the course of a reaction.

Stereochemistry—the study of the spatial relationships of atoms and bonds—would in the past have been a natural adjunct of the study of molecular structure. It is now as important to considerations of chemical dynamics as to those of chemical statics, and follows naturally, in the last Chapter, the study of kinetics and mechanism. Indeed, it is closely intertwined with mechanism; many naturally occurring compounds have a complex and highly specific stereochemistry, and it has only been through an understanding of the stereoelectronic principles of reactions that their syntheses have been successfully planned and executed.

1. Chemical Thermodynamics

1.1 Equilibrium

All chemical reactions are in principle reversible: reactants and products eventually reach *equilibrium*. In some cases, such as the esterification of an acid by an alcohol,



the equilibrium situation is quite closely balanced between reactants and products, whereas in other cases the equilibrium constant is either very high or very low, so that the reaction goes essentially to completion in one direction or the other (given the appropriate conditions). From the point of view of devising an organic synthesis it is necessary to know whether the position of equilibrium will favour the desired product. The factors which determine the equilibrium constant of a reaction and its variation with changes in conditions follow from two of the most firmly established natural laws: the First and Second Laws of Thermodynamics.

1.2 The First Law

The First Law of Thermodynamics is commonly expressed as the Law of Conservation of Energy: energy can be neither created nor destroyed. Consider a system into which an amount of heat q is introduced. The absorption of this heat may bring about both an increase in the energy of the system (manifested, for example, by a rise in the temperature) and also the performance of work, w , by the system (as, for example, the pushing back of a piston by a heated gas*). Then it follows from the First Law that, for a change from state A to state B ,

$$q = \Delta E + w$$

where ΔE is the change in energy of the system. It is convenient to define a function E as the *internal energy* of the system; ΔE is then equal to $E_B - E_A$, where E_A and E_B are the energies of the initial and final states.

If the process is carried out at constant volume, no mechanical work is done by the system and $q = \Delta E$. On the other hand, if the process is carried out at

*There are other forms of work, such as electrical work, but we shall not be concerned with these.

constant pressure the work done is $P\Delta V$, where ΔV is the change in volume of the system. Then

$$\begin{aligned} q &= \Delta E + P\Delta V \\ &= E_B - E_A + PV_B - PV_A \\ &= (E_B + PV_B) - (E_A + PV_A) \end{aligned}$$

Since E , P , and V are functions of the state of the system, $(E + PV)$ is also such a function. This property is termed the *heat content* or *enthalpy*, H , and proves to be important in chemical systems where we are usually concerned with changes taking place at constant (*e.g.*, atmospheric) pressure.

1.3 The Second Law

If a box-full of red balls and a box-full of blue balls are poured into a container and shaken up, we shall expect to find when the balls are poured back into the two boxes that each box contains approximately equal numbers of red and blue balls. On the other hand, if we start with boxes containing mixtures of the balls we shall not expect to find, after the mixing process, that all the red balls end in one box and the blue balls in the other. Again, if a poker is made red-hot at one end, the heat gradually diffuses along the poker until eventually its temperature is uniform along its whole length. We do not, however, observe the reverse of this process: a poker at ambient temperature never becomes hotter at one end and colder at the other, even though this would not necessarily contravene the First Law.

Observations of this type led to the enunciation of the Second Law of Thermodynamics, the classical form of which is that 'heat does not flow spontaneously from a colder to a hotter body.' The relevance of this Law to the example of the poker is obvious, but its applicability to the problem of mixing balls of different colours is not immediately apparent. It becomes so, however, when it is realized that the Second Law is concerned with *probabilities*: it is extremely *improbable* that a mixture of red and blue balls will, by a shuffling process, end in the ordered condition of separate groups of red balls and blue balls. Given only six red and six blue balls, it is 200 times as probable that the first six balls poured from the mixing container into one box will consist of three red and three blue than that they will be all red or all blue. Moreover, the ratio of the number of ways in which a system can be arranged in a 'random' manner to those corresponding to a particular 'ordered' arrangement increases rapidly with the number of species contained in the system, so that in the case of chemical molecules, which in any particular system under observation are numbered in many powers of ten, the likelihood of an 'ordered' system emerging spontaneously from a 'disordered' one is negligible. We should not expect that the random collisions between the molecules in the poker would result in all the

faster moving (*i.e.*, hotter) molecules accumulating at one end of the poker and all the slower moving (*i.e.*, colder) molecules at the other, but, given this ordered situation (by heating the poker at one end), we should expect the faster and slower moving molecules to attain a random arrangement, as a result of molecular movements and collisions, corresponding to a uniform temperature along the poker.

There is thus a tendency for ordered systems to become disordered. It is convenient to have a measure of the *degree of disorder* of a system, and this is defined as its *entropy*, S , where $S = k \ln W$, W being the number of ways in which the system may be arranged and k being Boltzmann's constant. In the two *irreversible* processes described above (the mixing of differently coloured balls and the achievement of uniform temperature in the poker) there is an increase in the entropy of the system, and an alternative formulation of the Second Law of Thermodynamics is that 'the entropy of an isolated system tends to increase.'

1.4 Free Energy

We assumed, in considering the mixing of red and blue balls, that no forces were operative. Suppose now that the red balls exert strong attractive forces on balls of their own kind and repulsive forces on blue balls. There will then be a tendency for the red balls to stay together so as to decrease the potential energy of the system, and this will oppose the tendency for the entropy of the system to increase. It transpires, from thermodynamical arguments, that the resulting compromise of these opposed trends is determined, for a system at constant pressure and temperature, by the value of the function $(H - TS)$: this tends to decrease, and the compromise situation (*i.e.*, equilibrium) corresponds to its minimum value. It is convenient to define a new function, G , the *Gibbs free energy*, as $G = H - TS$. A process will occur spontaneously if, as a result, G decreases. It will continue until G reaches a minimum, and this point corresponds to the equilibrium situation; forward and reverse reactions continue, but at equal rates; that is, the equilibrium is a dynamic one. Consider a reaction occurring at temperature T in the gas phase. Since

$$G = H - TS = E + PV - TS,$$

$$dG = dE + PdV + VdP - TdS$$

For an equilibrium situation it can be shown that $TdS = dq$, and since (from 1.2) $dq = dE + PdV$

$$dG = VdP$$

Since, for 1 mole of a perfect gas at a constant temperature, $PV = RT$, *i.e.*,