

The Chemistry of Free Radicals

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Preface

This book aims at giving a broad, comprehensive coverage of the fundamentals of the organic chemistry of free radicals in solution, at a level suitable for the advanced undergraduate reading for an honours degree in chemistry. At the same time, an attempt is made to bring the reader to the forefront of active investigation in a few areas in this vast and exciting field by inclusion of some material of current interest. Care is taken, however, not to overwhelm the student with too much factual information but for those interested in further details relevant references are given.

As is the current trend in organic chemistry texts the book is dominated by a mechanistic approach, and will bridge the gap between standard undergraduate textbooks on organic chemistry and the specialized treatises on free radicals. By placing emphasis on modern theory and its application to the understanding and prediction of the properties and reactions of radicals it is hoped to provide a rational framework for the whole encyclopedia of available factual data. A substantial amount of such data chosen to illustrate the basic principles enunciated are drawn from the authors' own work and an apology is made to those workers in this field whose equally important contributions the authors have not found possible to accommodate in a volume of this size.

The text opens with an introduction dealing with the historical background to the field of radical chemistry, this being followed by a brief description of electron spin resonance and nuclear magnetic resonance spectroscopy. Portrayal in some detail is then given (Chapter 3) of the characteristics of radicals reactions and the concepts underlying the theory of such reactions, including bond dissociation energies, the transition state, the Hammett equation, kinetic isotope effects, kinetics and, briefly, orbital symmetry. Once understanding of these has been achieved, it is hoped the student will find factual data falling into their logical places. After conformation, methods of radical production and relevant aspects of photochemistry have been described, a comprehensive treatment is given of the factors governing radical reactions (Chapter 9). The remaining chapters (10-17) are devoted to a survey of typical radical reactions, with a relatively detailed

coverage of addition reactions (Chapter 12), which have extensive application in preparative organic chemistry. The vast field of polymerization, however, has been accorded only cursory treatment.

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R.L.H., S.H.G., S.H.O.

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1

Introduction The 'New' Organic Chemistry

In the history of Chemistry, free radicals are a relative newcomer. The first authentic free radical was prepared only at the beginning of this century, and as to the part radicals play in chemical reactions recognition did not come until more than thirty years later. Being entities bearing unpaired electrons radicals are, as would be expected, extremely reactive and in general capable of transient existence only. Thus it is no wonder that, although there had been no lack of interest to make radicals and isolate them, no attempts were successful until 1900 when Moses Gomberg generated for the first time his famous triphenylmethyl radical, and produced experimental evidence to substantiate his claim. Some twenty-eight years elapsed before the simple methyl and ethyl radicals were prepared. These were shown to exist for only a fraction of a second.

But the discovery of radicals as chemical entities was one thing, and the recognition of their rôle in chemical reactions was another. After Gomberg's discovery, and subsequent successful attempts by others to synthesize new radicals, mainly those related to triphenylmethyl, free radicals were for many years merely a chemical novelty, and their participation as reacting entities in chemical reactions was not recognized until after 1937, following the publication of a series of papers by M. S. Kharasch and by P. J. Flory in the United States, and a significant review by D. H. Hey and W. A. Waters in England. This recognition in fact marked the stage at which the organic chemist's interest in radicals was shifted from the static to the dynamic aspects, and his eyes opened to the vast realm of a new branch of Organic Chemistry which he aptly christened the 'New' Organic Chemistry.

The 'New' Organic Chemistry was therefore 'new' not so much in the sense that radical reactions had not been encountered before, but rather that the recognition of such reactions as involving free radicals was a new concept. In fact, from the very early days of organic chemistry, a number of radical reactions had already been encountered, though not appreciated as such. For instance, the pyrolytic process, a technique much in fashion in the old days, produces radicals. This was at one time a standard method for the degradation of chemical compounds, and almost all natural products had

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at one time or another suffered this brutal treatment at the hands of the early chemists. Other reactions involving radicals had been encountered for a long time, notably that large group of reactions initiated by sunlight, oxidative processes, electrolytic reactions, the 'drying' of paints and varnishes, and so on. A number of these, in fact, were better known to the chemist as a source of nuisance rather than as chemical processes of any theoretical or practical interest. Among these the deterioration of chemicals by autoxidation perhaps deserves special mention, as it has impact on the organic chemist not only in the research laboratory but also in industry. A bottle of aniline, if no special precautions are taken to protect it from light and air, soon turns brown, then green and black, while a specimen of benzaldehyde soon forms a crust of benzoic acid. Chloroform, if not stabilized by addition of ethanol, is soon oxidized to the poisonous phosgene. Diethyl ether, an indispensable solvent, forms a highly explosive peroxide which has been the cause of many laboratory explosions.

However, although an occasional explosion in the laboratory might be a nuisance to the chemist, what irked him more must have been the apparently wayward and unpredictable manner in which a number of well studied and supposedly well understood chemical reactions took place. These reactions, free radical in nature but not so known to the chemist earlier, completely baffled him when it came to fitting them into the prevailing theory. It will be recalled that, for a long time past, the popular impression of organic chemistry, among practitioners of other branches of scientific disciplines, had been that it was very much of an empirical science comprising a host of facts without theoretical foundation, and that to be successful in organic chemistry all one needed was a colossal memory and immunity towards evil smells and smokes. This picture had begun to change since the early part of the present century, with the evolution of a general theory of organic reactions, the Electronic Theory of Organic Chemistry, to which are attached as pioneers the great names of A. Lapworth, Sir Robert Robinson, and Sir Christopher Ingold. Already in the late 1920's the electronic theory had reached an advanced state of development and was increasingly able to correlate, to a satisfactory degree, much of the information amassed by generations of chemists in the past. The organic chemist was justifiably proud of this achievement, and perhaps a little complacent in being able to explain, in terms of his theory, a good many observations on chemical behaviour and in cases even to predict the course of events in chemical reactions. There were, however, to be unaccommodating exceptions to the established rules. These 'black sheep' among chemical reactions, if we may call them such, seemed to violate all the rules and were none other than what we now know as free radical reactions. As the great majority of reactions known to the earlier organic chemists were of the ionic type, the development of the

electronic theory had been based on observations of these reactions. It is no wonder then that the theory, in its state of development at that time, was not adequate to deal with reactions in which a very different reacting species took part.

The classical example among these so-called 'abnormal' reactions, which is of both theoretical and historical interest, is the addition of hydrogen bromide to olefins. When hydrogen bromide adds to an unsymmetrical olefin two modes of addition are possible, and the course taken is prescribed by a rule known as Markownikov's rule which had been enunciated many decades ago. Unfortunately, as time went on a disturbingly large number of exceptions were found to this rule, and what was worse, to what extent the rule was obeyed, or whether it was obeyed at all, appeared to vary from experiment to experiment and from experimenter to experimenter. Obviously there was something very wrong with the rule, and this confusing state of affairs led Kharasch and his co-workers at the University of Chicago to undertake an extensive investigation lasting a number of years. After running over 500 experiments on one single reaction, namely, the addition of hydrogen bromide to allyl bromide, Kharasch made his first breakthrough in discovering what is known as the 'peroxide effect', which accounted for the 'anti-Markownikov' addition of hydrogen bromide, and a little later put forward a mechanism for the reaction which is now generally accepted. The gist of his proposal is this: Markownikov's rule is not obeyed when the reaction takes a non-ionic course, and this easily happens if free radicals have inadvertently been introduced into the reaction system through impure reactants, or in some cases even by contact with air. This 'abnormal' course can, in fact, be made the main reaction by the deliberate introduction of free radicals into the reaction system, e.g. by the addition of a peroxide. There is therefore nothing so abnormal about it after all.

This recognition of free radicals as participants in chemical reactions had far reaching consequences in organic chemistry. For one thing, it uncovered a virgin field for investigation, and the search for new reactions involving radicals was soon on. For another, and this is perhaps of greater fundamental importance, it opened up a new vista in chemical theory. Radicals, after all, arise from one of the two fundamental ways in which the covalent bond can be ruptured and so, whereas hitherto the chemist only concerned himself with ionic reagents when he studied the behaviour of chemical compounds, his study would now be only half complete if he did not examine the effect of free radicals as well.

This interdependence of theoretical development and experimental findings has been encountered time and again before. One might recall, for example, how in the late 19th century aromatic chemistry, although brought into prominence by the coal tar industry, really owed its continued proliferation

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and its orderly growth to the development of the theory of aromatic substitution. In the same way, with the chemistry of free radicals, the large majority of achievements and the most significant ones came only after, and as a result of, the laying of the theoretical foundation, and this may be considered to have been done in about 1937. Since that time the 'New' Organic Chemistry has gone from strength to strength and, although like aromatic chemistry it also owed much by way of stimulus to an industry (in this case the petroleum industry), it was the sound theory soon to emerge which correlated experimental findings and showed the way for further exploration.

By now we can survey the achievements of the past quarter of a century with some measure of satisfaction. Among these achievements, the most prominent, made during the 1940's, are no doubt the great advances in the chemistry of petroleum, the constituents of which are what organic chemists classify as the paraffin hydrocarbons. To the 19th century chemists these hydrocarbons appeared to be so devoid of chemical activity that they were named 'paraffins' or being interpreted, 'of little affinity'. These earlier practitioners, of course, used only ionic reagents (acids, bases and so on) on these compounds. Quite contrary to the name given them, these hydrocarbons in fact react with great avidity if they are attacked by free radical reagents, and undergo self sustaining reactions of a chain nature which is particularly characteristic of radical reactions in general. Thus paraffin chemistry, of which the sum total of our knowledge forty years ago could be written in a chapter, has now accumulated such a wealth of information that it practically forms a new chemistry by itself. Most of the reactions found to take place with this group of chemical compounds are applicable to organic compounds in general, and the study of the mechanism of these reactions has brought about a new perspective in the theory of organic reactions.

To give a few examples of these radical reactions, and especially those which have useful applications in everyday life, one must mention the study of the chemical process known as combustion, say of petrol or other fuels, and the consequent development of 'antiknocks' and other additives to aid the process of combustion and hence make better fuels. From a study of the process known as autoxidation we have come to understand how fats and oils, and certain other foodstuffs, deteriorate and have developed 'antioxidants' or 'inhibitors' which retard these chemical changes and can be used as food preservatives. Incidentally, this same type of reaction is responsible for the decomposition of the chemical reagents mentioned earlier, namely, aniline, benzaldehyde, and ether and indeed, for the 'ageing' or deteriorating of unprocessed natural rubber, all of which substances can be stabilized to varying degrees by the addition of small quantities of inhibitors. While autoxidation is often a nuisance and special measures have to be taken

to check it, it has been put to good use in several instances. For example the aerial oxidation of cumene (isopropylbenzene), which is carried out on an industrial scale, produces the antiseptic phenol and acetone. The drying of paints and varnishes is also a process involving free radicals, and research in this field has led to new materials designed to suit specific requirements. Again, by means of the so-called 'cracking' process, i.e., pyrolysis under controlled conditions, the relatively useless larger hydrocarbon molecules present in petroleum are broken into smaller molecules suitable for use as motor fuels. In this way we manage to double the yield of fuels obtainable from crude petroleum. Conversely, the process of polymerization, by which small molecules are built up into giant ones according to specifications, gives us 'tailored' molecules of desired sizes and shapes to serve a variety of purposes.

Mention must also be made of that prominent group of radical reactions, taking place in the vapour or liquid phase, initiated by irradiation with sunlight, ultraviolet, or gamma rays, all of which bring about the breaking of covalent bonds to generate radicals. Photochemistry, in particular, has become one of the most rapidly developing areas of research. Recent photochemical studies have thrown much light on the nature and reactions of chemical bonds.

This resumé of radical reactions would not be complete without a brief reference to the rôle of radicals in reactions taking place in biological systems. This was the subject of a good deal of speculation for a long time but the study of which had not gained much headway until recently, especially since the development of the electron spin resonance technique some years ago. The importance of the problem is evident from the list of biological processes in which free radicals have been shown to be active participants by this new technique. These include enzymatic oxidation and reduction, photosynthesis, chemiluminescence, damage to living cells by irradiation and initiation of malignant growth. Furthermore, the technique of spin labelling, e.g., by the use of stable nitroxide radicals, promises to give greater insight into cellular structure and function.

Finally, mention must be made of the part which modern instrumentation has played in the unravelling of the intricacies in radical reaction mechanisms. Such powerful tools as gas chromatography, mass spectrometry, nuclear magnetic and electron spin resonance have made possible detailed and refined analysis undreamt of twenty years ago. New avenues of research have thereby continually been opened up, and the flood of new knowledge emerging continues unabated.

2

Detection of Radicals

Except for the naturally occurring free radicals (e.g., O_2 or NO) and those considerably stabilized by resonance, radicals are in general very reactive entities and capable of transient existence only. Nevertheless a number of methods have been devised for their detection and identification. These encompass chemical means of trapping and isolation, as well as direct detection by spectroscopic methods.

2.1 Chemical methods

Radical intermediates in chemical reactions are usually of such high reactivity as to preclude their isolation or even detection by physical methods. Their transient existence may nevertheless be ascertained by trapping them with reagents for which they have high affinity and with which they combine to give stable products which can then be isolated and identified. The involvement of a carbene intermediate can, for example, be inferred if in the presence of an olefin, added as a trapping agent, cyclopropanes are produced. Similarly, the addition of toluene to a radical reaction will allow intermediate radicals to abstract α -hydrogen atoms to generate relatively stable benzyl radicals, which will persist in the reaction system until they dimerize to yield bibenzyl, a readily identifiable product. If no such trapping product is found the involvement of an intermediate radical would appear less likely but nevertheless cannot be ruled out.

Quite frequently the nature of the products from a chemical reaction offers a clue as to whether the reaction involves radicals or not. Homolytic reactions generally give rise to a variety of products arising from abstraction, addition, dimerization, fragmentation and other processes, and through a careful analysis of the products the radicals involved can often be identified.

The homolytic nature of a reaction may also be inferred from evidence of catalysis or inhibition. If the addition of radical producing substances (e.g., peroxides) or the application of ultraviolet light, which gives rise to radicals through homolytic bond cleavage, greatly accelerates the reaction it is likely that a free radical mechanism is in operation. Conversely, the addition of

inhibitors which reduce the concentration of reacting radicals will slow down or inhibit the reaction. Such inhibitors are usually substances containing active hydrogen atoms (e.g., phenols and aromatic amines) and these render the chain-propagating radicals unreactive through hydrogen donation to form inhibitor radicals which are too stable to react further or else take up some new reaction pathway. In either case the inhibitor slows down or even stops the original radical reaction. Sometimes the trapping of transient intermediates by scavengers gives stable radicals which can easily be detected by electron spin resonance techniques.

Stable paramagnetic species, e.g., oxygen and nitric oxide, can also inhibit radical reactions by reacting with the chain-propagating species. Oxygen is well-known for its unpredictable effect on radical reactions: small quantities of oxygen may initiate a reaction whereas large quantities may completely inhibit it. In many cases it is directly responsible for the induction period of a reaction (see also autoxidation, Section 10.4).

2.2 Electron spin resonance

The electron spin resonance (e.s.r.)¹ method for the detection and study of radicals has in recent years achieved great prominence and will be described in some detail here.

(A) Theory

The electron has spin and an associated magnetic moment and can be considered as a small magnet. In the presence of an external magnetic field it will align itself parallel or anti-parallel (in opposition) to the field according to quantum restrictions. Thus the energy level of the electron in an external magnetic field is split into two possible values, the difference being given by ΔE (see Fig. 2.1). A resonance condition may be achieved if electromagnetic radiation of the correct energy is applied and excitation from the lower energy state to the upper one will give rise to an absorption spectrum. The equations for the resonance condition are given below

$$\Delta E = g \left(\frac{ehH}{4\pi mc} \right) = g\beta H$$

$$\Delta E = h\nu = g\beta H$$

where g is a constant of approximately 2, e the electronic charge, h Planck's constant, m the mass of the electron, c the velocity of light, H the applied magnetic field, β the Bohr magneton and ν the frequency of the applied electromagnetic radiation. Attention should here be drawn to the similarity

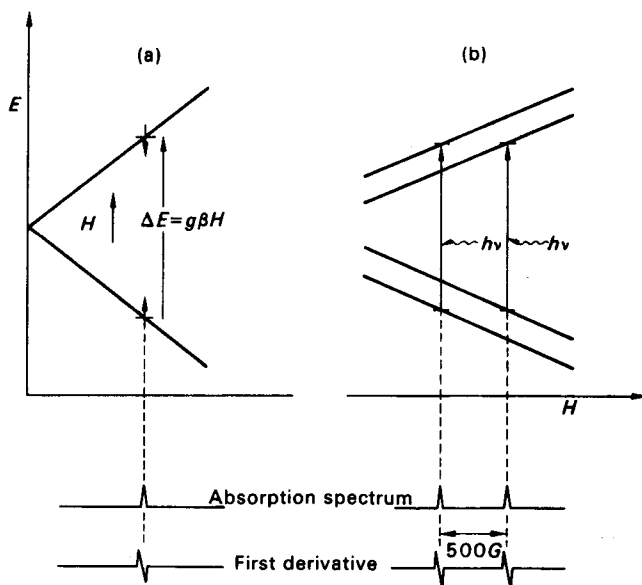


Fig. 2.1 (a) Diagram showing the transition and spectra of a free electron in a magnetic field; (b) diagram showing transitions and spectra of hydrogen atom.

of the theory of electron spin resonance (sometimes referred to as electron paramagnetic resonance (e.p.r.)) to that of nuclear magnetic resonance. Under practical conditions ν is fixed at about 9000 MHz while H is varied and resonance occurs at about 3200 gauss; ΔE is approximately 1 cal mole⁻¹. There is a very slight excess in population of the lower energy state over that of the upper one in accordance with the Boltzmann distribution so that an absorption spectrum can be obtained. Fig. 2.1 shows diagrammatically the energy levels and spectra of a free electron and of a hydrogen atom. For the hydrogen atom the electron interacts not only with the external magnetic field but also with the nucleus which has a spin of $\frac{1}{2}$. This interaction leads to a splitting of the energy levels as shown; the coupling constant of 500 gauss is obtained from the e.s.r. spectrum and this measures the extent of the electron-nuclear interaction.

In an organic radical the number of absorption lines in the e.s.r. spectrum (i.e., hyperfine structure) can be many as the unpaired electron can usually interact with a large number of protons of the radical. The spectrum of the methyl radical, with four hyperfine lines resulting from electron interaction with three equivalent protons, is shown in Fig. 2.2(a), from which the similarity of the splitting pattern of the e.s.r. spectrum and that of nuclear magnetic resonance should be noted. The splitting in the methyl radical

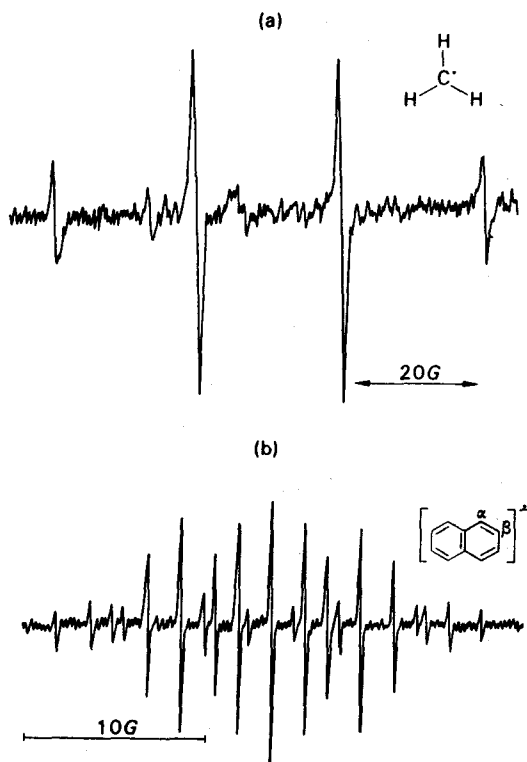


Fig. 2.2 (a) Spectrum of methyl radical in aqueous solution (R. O. C. NORMAN and B. C. GILBERT, *Adv. Phys. Org. Chem.*, 1967, 5, 57); (b) Naphthalene radical anion (A. R. FORRESTER, J. M. HAY, and R. T. THOMSON, *Organic Chemistry of Stable Free Radicals*, Academic Press, 1968, p. 93; K. MARKAU and W. MAIER, *Z. Naturf.*, 1961, 16a, 636.)

spectrum is smaller than that of the hydrogen atom because in the former the protons are much further away from the unpaired electron resulting in less interaction. A more complicated spectrum, that of the naphthalene radical anion, is shown in Fig. 2.2(b). Here there are four α - and four β -protons which would give $(4 + 1) \times (4 + 1)$ or 25 lines, all of which have been observed experimentally. Hyperfine splittings for this radical have been observed to be 4.95 gauss and 1.87 gauss, arising from coupling to the α - and the β -protons respectively.

The experimental observables for a radical are the g value, hyperfine structure and line shape. The unpaired electron is distributed over the atoms