Interpretation of Mass Spectra of Organic Compounds

H. Budzikiewicz
C. Djerassi
D. H. Williams

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Herbert Budzikiewicz
Research Associate
Stanford University

Carl Djerassi
Professor of Chemistry
Stanford University

Dudley H. Williams
Research Associate
Stanford University

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PREFACE

Mass spectrometry is a powerful tool with ramifications in many areas of physics and chemistry. In chemistry, steady progress has been made over the past twenty years in the use of mass spectrometry, and it has become a routine method for dealing with many analytical problems, isotope determinations, free radical studies and the examination of ionization phenomena. Potentially the most widely used and probably also the most important application – the structure elucidation of organic molecules – has, until recently, been neglected by most organic chemists other than those active in the petroleum field. The usual excuse, inadequate instrumentation, is not valid in this instance, and there is no reason why this field should not have developed well over ten years ago.

The use of mass spectrometry in organic chemistry is, however, becoming increasingly widespread and mass spectrometers are now being installed in many laboratories. Three years ago one had to search far and wide in the organic chemical literature to find examples of its use in structural problems. Three years hence it will be difficult to open a journal dealing with organic chemistry without encountering multiple applications of mass spectrometry. No physical tool in organic chemistry – not even infrared spectrometry – is so easily appreciated by the average organic chemist, and once used, none is so difficult to do without.

Many books have appeared during the past three years dealing with certain chemical applications of mass spectrometry, and the obvious questions may be asked: "Why another one, and why now?" The presently available monographs[1-7] all cover various facets of mass spectrometry, ranging from instrumentation, sample handling, free radicals and ionization potentials, to analytical and other chemical applications; and they cover them well. No purpose will be served in repeating that material in still another volume. However, the direction of much of the current research on the application of mass spectrometry in structural organic chemistry has led the authors to believe that the needs of at least two important groups of organic chemists are not fully served by the books now available.

First, the organic chemist working with a given class of organic compounds which are often polyfunctional in nature wishes to know how mass spectrometry can help him and where he can find the relevant guideposts. Second, the chemist conducting research on the mass spectral fragmentation behavior of organic substances, with the eventual aim of establishing some correlation with chemical structure, would like to have access to the generalizations that have already been made about the fragmentation of such compounds. Such problems are not easily or completely answered by the texts presently available.[1-7]

Progress in this area of mass spectrometry is so rapid that books quickly become outdated. Much of the material covered in this work has been published very recently or is yet unpublished, so it could not be included in other texts. Also, none of the recent books,[2-6] except for a long chapter in Beynon's classic opus,[1] is organized to deal exclusively with chemical structure or, even more importantly, with the presence of functional groups which trigger or control the over-all fragmentation process of the organic molecule. The existence of excellent chapters by Biemann[3] on the mass spectrometry of amino acids and peptides, by Grubb and Meyerson[5] on alkyl benzenes, and by Ryhage and Stenhagen[5] on esters, only emphasizes the need for such an arrangement for most of the other common organic chemical types. This is the gap that this book aims to fill. Its usefulness as a text was demonstrated when the manuscript was employed as lecture notes in a graduate course on organic chemical applications of mass spectrometry taught by one of the authors at Stanford University during the 1963 autumn quarter.

A third and perhaps most intriguing point remains: why does an organic substance fragment in a given way? This area of mass spectrometry — the elucidation of possible fragmentation mechanisms by isotope labeling — is now beginning to blossom. It is especially to the credit of McLafferty and subsequent investigators that common physical-organic concepts are being employed for the rationalization of fragmentation mechanisms. This approach can be of enormous help, but it possesses the inherent danger of breeding excessive confidence. It is very important to differentiate between mechanisms which have been substantiated by isotope labeling and by the recognition of metastable ions from those which simply seem plausible to the organic chemist unaccustomed to think in terms of high energy processes initiated by 70 eV. Nevertheless, we believe that, at this early stage, a plausible though perhaps unsubstantiated mechanistic path is preferable to the proverbial wiggly line which lacks any rationale. Hydrogen transfers, originally thought, from hydrocarbon studies, to be the curse of mass spectrometry, are actually frequently the signposts and guides to specific fragmentation mechanisms, and much attention is paid to them throughout this volume.

This book is best read, at least by the uninitiated organic chemist, in conjunction with Beynon's[1] or Biemann's[3] texts, which offer an excellent over-all introduction to mass spectrometry, or with certain selected chapters from some of the other recent monographs.[2,4-6*] We have organized our material so that it may best help in the prediction or interpretation of the principal mass spectral fragmentation processes on the basis of the functional groups present in a given organic substance. We do not discuss aliphatic hydrocarbons because (1) they are well covered in other books; (2) they are not of general interest to the structural organic chemist; (3) while of historical significance, they represent a group of organic substances whose fragmentation behavior is least suited to wide generalizations.

In this volume, we commence with the simplest and most widely distributed functional groups in organic chemistry, such as the carbonyl, hydroxyl and amino functions, and demonstrate that a great deal is already known about the fragmentation processes initiated by them upon electron impact. In chapter 5 this point is illustrated with the tropane alkaloids, where three such functionalities are attached to a small alicyclic framework, and where the principal bond ruptures are easily interpreted on the basis of the generalizations made in chapters 1 to 4 with the isolated functional groups. Other classes of relatively simple organic molecules are discussed in the remaining chapters of this book. A subsequent volume will deal with the present status of mass spectrometry in more complicated, polycyclic organic compounds, chiefly of natural origin.

In summary, we direct this book to the organic chemist — student or practitioner — who would like to get more information about how mass spectrometry can help him in his own research problems. In particular, we hope this book will assist the organic chemist in the rational interpretation of mass spectra and enable him to extract the maximum amount of information from the fragmentation pattern of a given substance. The vast majority of organic chemists will not be measuring their own mass spectra, so no attempt has been made to discuss instrumentation or other practical matters which are covered well in other books.[1-6] We have tried as much as possible to avoid overlap with other mass spectrometry texts and to cover material not readily available elsewhere.

*From a pedagogic standpoint, it is interesting to note that mass spectrometry may readily be incorporated into the traditional "qualitative organic analysis" course of American universities; see R.M. Silverstein and G.C. Bassler, Spectrometric Identification of Organic Compounds, John Wiley and Sons, New York, 1963.

We greatly appreciate the cooperation of the publisher in making possible the appearance of this volume in less than three months after receipt of the manuscript. Much of the book could not have been written without the diligent and productive research work during the past two years by a number of predoctoral and postdoctoral collaborators at Stanford University. Their names will be found in the various literature citations throughout the book. Mrs. Patricia Williams assisted greatly with much of the typing, and we express our special gratitude to Mr. Angus M. Babcock for drawing the figures. A few mass spectra were reproduced by permission of Professor E. Stenhagen (Figs. 1-8 and 2-7), Dr. J.H. Beynon (Figs. 5-5, 9-27 and 9-28) and Dr. William F. Kuhn (Figs. 5-7 and 5-8), to whom we are indebted for this favor.

Stanford University
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Herbert Budzikiewicz
Carl Djerassi
Dudley H. Williams

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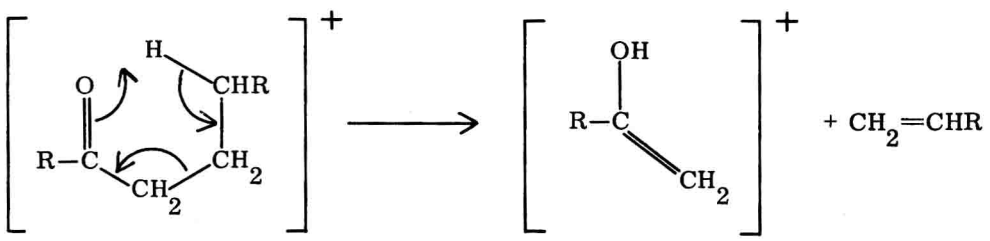
NOTE TO THE READER

At this time, when mass spectrometry is on the verge of entering the everyday thinking of many organic chemists, it seems pedagogically desirable to attempt as precise a definition as possible of the different bond fissions and transfer reactions, so as to remove the aura of mysticism which has surrounded some of the past mass spectral interpretations. At times it is difficult and even impossible to localize the positive charge in a given molecule, and it will be found that in such instances rational interpretation of the fragmentation process by standard organic-chemical concepts is the least satisfactory. This is actually the case with many hydrocarbons, where neither the location of the charge nor the existence of particularly vulnerable carbon-carbon bonds can be clearly defined. Fortunately, the reverse situation is usually encountered in the more common structural organic chemical problems which deal with substances possessing heteroatoms as well as linkages that are especially prone to undergo homolytic fission.

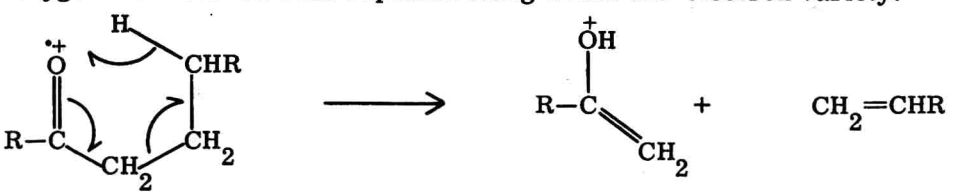
Standard organic chemical concepts, such as the energetic preference of tertiary over secondary and primary carbonium ions or radicals, the importance of allylic or benzylic activation, etc., are so readily applicable to the interpretation of mass spectrometric fragmentation processes that a certain sloppiness in symbolism has crept into most of the recent literature. For instance, carbonyl-containing compounds with a hydrogen atom in the γ-position frequently undergo, upon electron bombardment, fragmentation with migration of this γ-hydrogen to afford the enol II and an olefin (III). This process is usually indicated by arrows, as in I.



I II III

However, according to standard organic chemical practice, such arrows denote two-electron shifts. Representation I, therefore, implies the shift of a proton, which very probably does not bear any resemblance to reality. This becomes especially clear if one recalls that the very first process in mass spectrometry is the removal of a single electron to provide a molecular ion, which then undergoes further bond fissions. In general, the tendency has been not to localize such a charge, but rather to indicate it by encompassing the structural formula in brackets (see I). For the organic chemist trying to rationalize the fragmentation of a given molecule, this is unfortunate, because the location of the charged center is responsible for the course and direction of the subsequent bond ruptures. There is considerable evidence that, in substances possessing a heteroatom, it is one of the non-bonding electrons of that heteroatom which is first removed. Wherever possible, therefore, it is desirable to depict a given fragmentation process with the positive charge fixed at a specific locus, although various fragmentations may be triggered by molecular ions obtained by removal of an electron from different positions. (Relevant examples are cited in chapter 8.) If the fragmentation of the carbonyl compound I is visualized as proceeding through the molecular ion IV, then it becomes immediately obvious that, in this instance, migration of a hydrogen atom with one electron is much more likely than migration of a proton. This does not mean that ionic shifts may not operate in mass spectrometric fragmentation processes, but it illustrates the importance of differentiating clearly between homolytic and heterolytic cleavages. We are proposing, therefore, the following simple convention, which is employed throughout this book as well as in our subsequent research publications.

The usual arrow (see I) denotes a two-electron shift, while a fishhook (see IV) implies that the departing atom carries with it only one of the bonding electrons.* The fragmentation of carbonyl-containing compounds with migration of the γ-hydrogen is then depicted as in IV, the positive charge being localized on the oxygen atom and all bond ruptures being of the one-electron variety.



IV II III

* J.S. Shannon, Tetrahedron Letters, 801 (1963) has also been very careful to draw this distinction and he employed an arrow with a heavy head (⟶) for two-electron shifts and with a light one (⟶) for one-electron movements. We feel that such a convention is much more prone to result in errors of printing or interpretation, and therefore we prefer the "arrow" and "fishhook" symbolism used in this book.

Throughout this book we refer to "α-cleavage" as fission of a bond adjacent to a functionalized carbon atom; the definition of β-, γ-, ..., etc. cleavage then follows automatically. The process V → II + III would then be referred to as "β-cleavage with migration of the γ-hydrogen atom to the carbonyl oxygen."

At this point an explanation of the representation of ionized double bonds may be useful. If such ionization occurs through the removal of a π-electron, an ion radical (V) will be obtained. These ion radicals are depicted as in VI (see, for instance, ion j in section 8-2), a representation which is particularly useful when conjugated ionized dienes (see ion k in section 8-2) are invoked.

$$R-\dot{C}H-\overset{+}{C}H-R \qquad\qquad [R-CH=CH-R]^{+}$$

(V) (VI)

Metastable ions are of considerable mechanistic significance, and frequent mention is made of them throughout this volume. They are produced when an ion (a) decomposes in the accelerating region of the mass spectrometer to another ion (b) and an uncharged fragment. When this process occurs, a broad, low-intensity peak of mass below that of b is observed. This is referred to as a "metastable peak" and can be related to the parent (a) and daughter (b) ions by the simple relationship: metastable ion = b^2/a. The difference in mass between ions a and b must correspond to the uncharged species produced in such a one-step fragmentation. The recognition of a metastable ion is, therefore, very convincing evidence for the occurrence of such a process, although it does not exclude the operation of alternate paths to ion b. For further discussion, the reader is referred to Beynon's book (ref. 1 in Preface), especially to pp. 251-262 and appendix 2, where convenient nomograms are given for the calculation of ions a and b from a given metastable ion.

In this book all mass spectra are plotted in terms of relative abundance, with the most intense peak ("base peak") being taken as 100%. In a few mass spectra, it was necessary to reduce the base peak by a given factor, since otherwise the remaining peaks would have been hardly noticeable. The convention employed here is to indicate the multiplication factor necessary to restore such a peak to its real value (e.g., "x 10" in Fig. 3-3).

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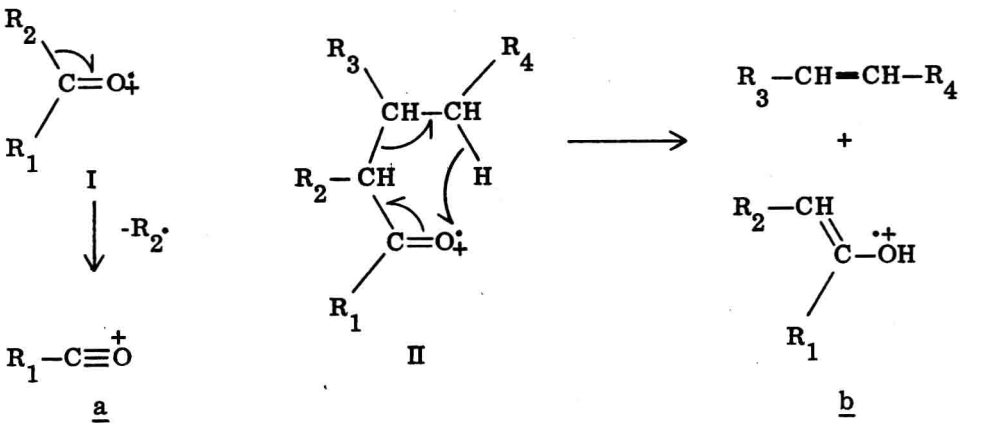
1

ALIPHATIC AND MONOCYCLIC CARBONYL COMPOUNDS

1-1. IONIZATION POTENTIALS OF THE CARBONYL GROUP

The process of removing one electron from an organic molecule upon bombardment with electrons of suitable energy gives rise to a molecular ion (M^+). This molecular ion is of fundamental importance to the organic chemist in enabling him to ascertain the molecular weight of his compound. In addition an understanding of this ionization process frequently enables one to rationalize subsequent fragmentation processes in terms of a given structure. In the case of carbonyl compounds, it has been concluded that the most facile ionization process corresponds to the removal of one of the lone pair electrons of the oxygen atom.[1] Actually, carbonyl compounds show three ionization potentials within a small energy range (e.g., acetone at 9.8, 10.6 and 11.5 eV). It is considered that the first of these (9.8 eV) corresponds to the energy necessary to remove one of the lone pair electrons of the oxygen atom, that 10.6 eV is the energy needed for the removal of a π-electron in the C=O bond, and 11.5 eV is the energy needed for the removal of a σ-electron in the C=O bond. The species resulting from the lowest energy ionization of a carbonyl compound can be represented by I . In practice, it turns out that the energy required to produce the optimum fragmentation pattern for organic chemical structural work corresponds to about 70 eV. Consequently, the number of diverse types of primary ions in a large molecule will be very great, resulting in many different fragments. However, in the case of a carbonyl compound, the predominating ion will be I , and it is this ion which will largely direct the subsequent fragmentation processes. It can be seen that a favorable fragmentation of the ion I will result from cleavage of the bond between the carbonyl group and an α-carbon atom (α-cleavage), the charge remaining with the oxygen-containing fragment a , which is stabilized by formation of the triple bond.

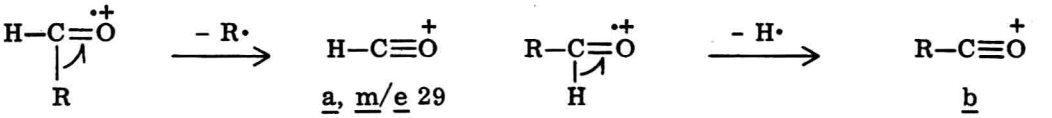


Alternatively, the ion II can fragment by cleavage of the bond between the α- and β-carbon atoms (β-cleavage) when a concerted migration of a γ-hydrogen to oxygen is possible, resulting in formation of an olefin molecule and a charged enol (b). It will be seen from the many spectra of carbonyl compounds that will be discussed in this book, that α-and β-cleavages are indeed the most important fragmentations of this class of organic compounds.

1-2. ALIPHATIC COMPOUNDS

A. Aldehydes

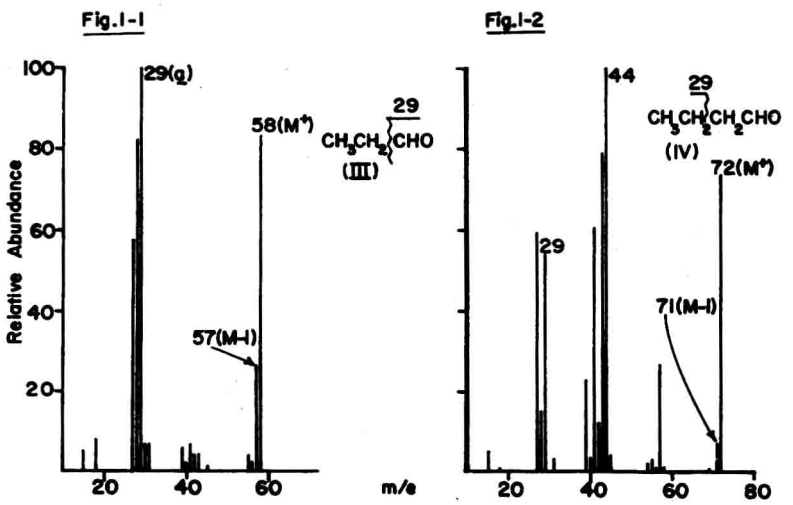
(i) α-cleavage. The absence of any carbon-carbon bonds in the formaldehyde molecule makes it a rather special case. Nevertheless, the energetics of the process $H_2C{=}\overset{+}{O}{\cdot} \rightarrow H{-}C{\equiv}\overset{+}{O} + H\cdot$ (α-cleavage) have been studied in some detail,[1] and the results are consistent with stabilization of the resulting formyl ion through triple bond formation, to the extent of 1.4 eV. It is not surprising, therefore, that m/e 29 ($H{-}C{\equiv}\overset{+}{O}$) is the base peak in the spectrum of formaldehyde.[2] Acetaldehyde is the first member of the series where two types of α-cleavage are theoretically possible, viz. cleavage of a carbon-carbon bond with formation of a formyl ion (a) and a methyl radical (R = CH_3), or cleavage of a carbon-hydrogen bond with formation of an acetyl ion (b, R = CH_3) and a hydrogen radical.



As might be expected, the former process predominates, the base peak of the acetaldehyde spectrum again being at m/e 29; loss of a hydrogen radical

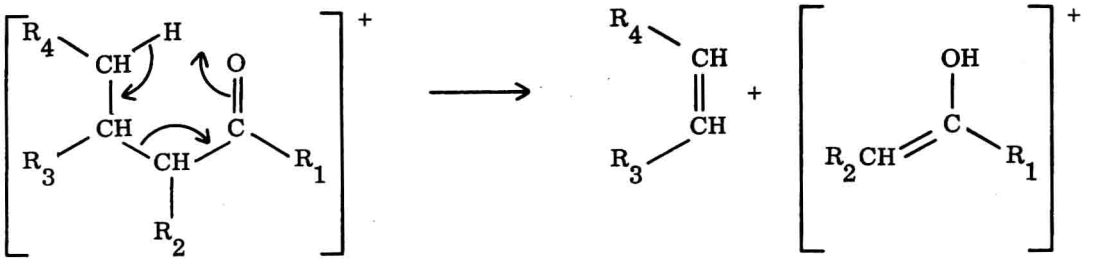
gives an M-1 peak having 42% of the intensity of the base peak. Gilpin and McLafferty[2] have obtained a large number of saturated aliphatic aldehyde spectra, which indicate that α-cleavage with formation of the formyl ion (a, m/e 29) is responsible for the base peak of the spectrum in three cases (H_2CO, CH_3CHO, CH_3CH_2CHO). While theoretically in the case of propanal, it is possible that the m/e 29 fragment is due to $C_2H_5^+$, the spectrum of ^{18}O-labeled propanal, prepared by exchange with $H_2{}^{18}O$, indicates that the m/e 29 peak is caused by the aldehyde group. Mass 29 for the straight chain aldehydes of higher molecular weight fluctuates around 40% of the highest peak. However, in ^{18}O-labeled n-butanal, it is primarily due to $C_2H_5^+$ and in the higher aldehydes it is totally due to this alkyl ion.

(ii) β-cleavage. As one passes from the spectrum of propionaldehyde (III) (Fig. 1-1) to the next higher homolog, butyraldehyde (IV) (Fig. 1-2), another more dramatic change can be seen. The base peak of the butyraldehyde spectrum is at m/e 44, which must be a rearrangement peak, since it occurs at an even mass number.*



This sudden change arises because in n-butyraldehyde and higher aldehydes a γ-hydrogen is available for transfer to the carbonyl oxygen, with concomitant β-fission via a six-membered cyclic transition state (V).[4]

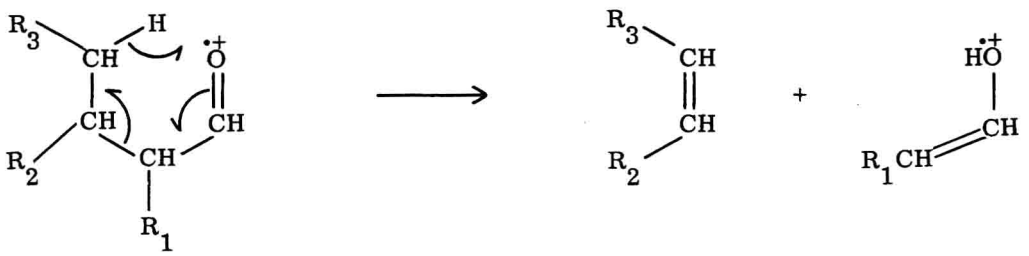
*Carbon-, hydrogen-, (and oxygen-)containing fragments arising from cleavage of one bond without hydrogen transfer will always appear at odd mass numbers.



V c

The result is elimination of a neutral olefin and formation of an m/e 44 enol ion (c, R_1=R_2=H). While this rearrangement can be conveniently written[3] as a concerted electron shift of electron pairs, it is probably more exactly represented as a homolytic process which is initiated by ionization of the carbonyl function (see II in section 1-1). This β-cleavage with hydrogen rearrangement to the oxygen-containing fragment to give m/e 44 is a very prominent feature of straight-chain aldehyde spectra when a chain of three or more carbon atoms is attached to the carbonyl group; e.g., m/e 44 is the base peak in the spectra of such aldehydes having four to seven carbon atoms. A completely analogous process operates in ketones (V, R_1 = alkyl) (see section 1-2B) and in fatty acid esters (V, R=OCH_3) (see section 1-2C). In the case of cyclic ketones (see section 1-3) and esters,[5] the transfer of a γ-hydrogen has been substantiated by deuterium labeling.

If we now turn our attention to branched aldehydes, it soon becomes apparent that examination of the fragments resulting from β-cleavage can give information as to the nature of the branching. Thus in α-methyl substituted aldehydes (VI, R_1=CH_3), the rearrangement peak now occurs not at m/e 44, but at m/e 58 (d, R_1=CH_3).

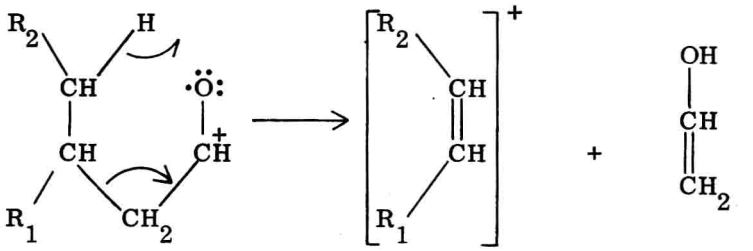


VI d

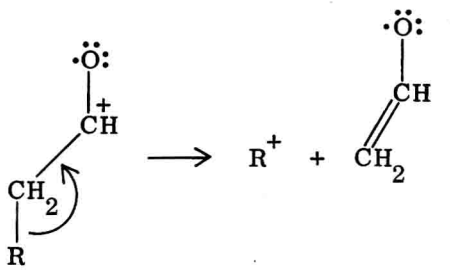
Similarly, a rearrangement peak at m/e 72 is indicative of α-ethyl substitution. It can readily be seen that in α-ethyl and larger α-substituents, either alkyl chain can be the source of the rearranged hydrogen, but in the compounds studied, the β-cleavage occurs with almost exclusive loss of the larger alkyl fragment.[2] In cases where branching occurs beyond the α-carbon atom, the position of the peak arising from β-cleavage with rearrangement is unchanged, e.g., at m/e 44 in the

spectrum of 3-methylbutanal (VI, R_1=R_3=H, R_2=Me). It is interesting to note that the major fragmentation of heptafluorobutanal ($CF_3CF_2CF_2CHO$), in contrast to n-butanal, is α to the aldehyde group giving rise to m/e 29.[6] There is no β-cleavage with transfer of a γ-fluorine atom, probably due to the fact that this would involve unfavorable bond formation between the electronegative fluorine and oxygen.

A third, important feature of aldehyde spectra in the absence of α-branching is the loss of 44 mass units. Aldehydes labeled with ^{18}O show that the fragments resulting from this loss are olefin ions of the general formula C_nH_{2n} (VII). This constitutes again β-cleavage with hydrogen transfer, except that the charge now remains with the alkyl fragment. Finally, a third type of β-cleavage should be mentioned, that which occurs without hydrogen transfer (M-43) and where the charge remains with an alkyl fragment of the general formula C_nH_{2n+1} (VIII). These last two processes can both be rationalized in terms of fragmentation of the molecular ion obtained by removal of a π-electron from the carbonyl group (section 1-1).



VII, M-44



VIII, M-43

The three possible types of β-cleavage which have been discussed above are well illustrated in the spectrum (Fig. 1-3) of n-hexanal[2] (IX), in which they give rise to m/e 44, 56 and 57 ions.