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Fragmentation Mechanisms in Mass Spectrometry

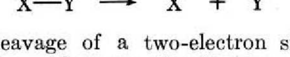
Many students have difficulty understanding and rationalizing the fragmentation mechanisms as commonly depicted in the literature and textbooks dealing with mass spectrometry; at least part of this difficulty is related to the imprecise nature of the conventions used and the resulting difficulties in electronic book-keeping. In this paper, we wish to illustrate a precise mechanistic notation which we have found useful in teaching fragmentation processes.

During the process of ionization of a molecule in a mass spectrometer, an electron is lost and a molecular ion which is both radical and cation is formed. The radical cation is commonly shown as, for example, I indicating that the species formed has a positive charge and an unpaired electron; no attempt is made in this designation to locate the charge or radical. Such notations for the radical cations are not useful in teaching the fragmentation mechanisms that occur. The fragmentations as depicted in the literature can be confusing to students who attempt to follow the bond-breaking process that occurs. Consider for example the fragmentation of radical cation I as is commonly illustrated. The percipient student may question this representation, pointing out that although a bond has been ionized, all bonds in the molecule are formally depicted as covalent, two-electron, sigma bonds. Furthermore, the arrow indicating the fragmentation process may represent either a one-electron shift or a two-electron shift.

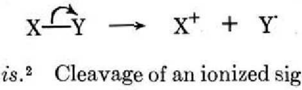
Because of these conceptual problems, we suggest that in teaching mass spectrometry the following conventions be adopted[1]

1. that in expanded formulae used to illustrate fragmentation processes, a two-electron sigma bond be represented by a line between two atoms, i.e., A—B
2. that an ionized bond, which contains *one* electron, be represented by the symbol $+\cdot$, i.e., $A\cdot{+}B$ *or* $A{+}\cdot B$
3. that a one-electron shift be indicated by a single-headed arrow and a two-electron shift be indicated by a double-headed arrow
4. that fragmentation types be defined as

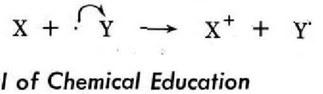
Homolysis. Cleavage of a two-electron sigma bond, one electron staying with each fragment, i.e.



Heterolysis. Cleavage of a two-electron sigma bond, both electrons staying with one or other fragment, i.e.



Hemi-Heterolysis.[2] Cleavage of an ionized sigma bond, i.e.

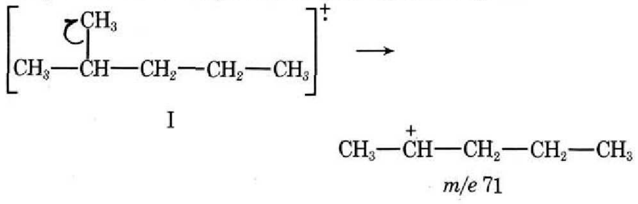


The conceptual utility of the above conventions will be illustrated by some fragmentation processes commonly encountered.

Alkanes

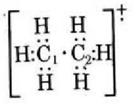
Ionization of the ethane molecule may result in loss of an electron from the C-C bond. One electron is left in the bonding sigma molecular orbital in II. Localizing this electron on C(1) at the moment of fragmentation results in seven electrons around C(1) and six electrons around C(2). C(1) can therefore be thought of as a *radical* and C(2) as a *cation*.

We therefore suggest that the ethane radical cation, which is encountered in the chemical literature as III, would be more precisely illustrated as IV.[3] Fragmentation of IV, affording methyl cation and methyl radical, can thus be explained by *hemi-heterolysis.*

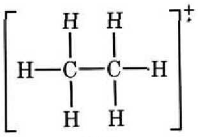


I

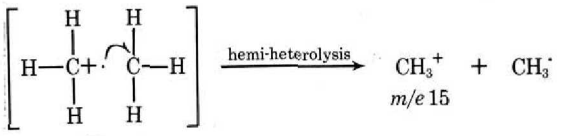
m/e 71



II



III



IV

m/e 15

Fragmentation of radical cation V which is formed by ionization of 2-methylpentane, can similarly be ex-

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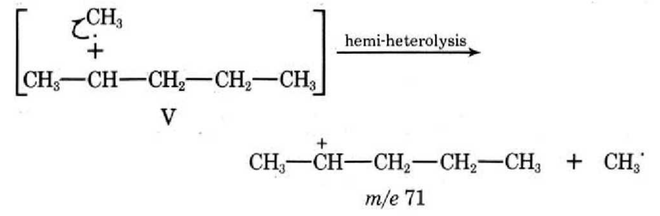
[1] This convention is based upon the widely-used notation introduced by Shannon (*Proc. Royal Austral. Chem. Inst.*, *328*, (*1964*)) and more recently employed by Djerassi et al. (H. Budzikiewicz, C. Djerassi, and D. H. Williams "Mass Spectrometry of Organic Compounds," Holden-Day Inc., San Francisco, 1967). Certain modifications are introduced with the objective of facilitating the teaching of mass spectral fragmentation processes.

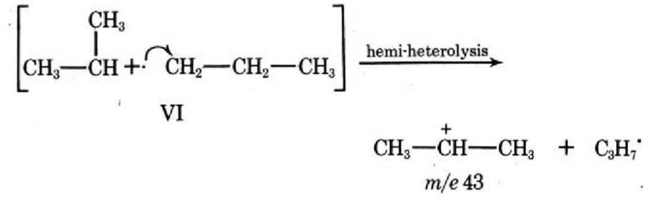
[2] This term has not, to our knowledge, been used in mass spectrometry. We consider that it is necessary to define the process of fission by which an ionized bond is cleaved, and therefore, propose "hemi-heterolysis." "Homolysis" and "heterolysis" are, of course, accepted terms in mass spectroscopy.

[3] The structure is represented as IV solely as a conceptual aid in understanding the origin of the radical cation charge and the subsequent fragmentations. The true physical state probably involves the co-existence of several ionized species.



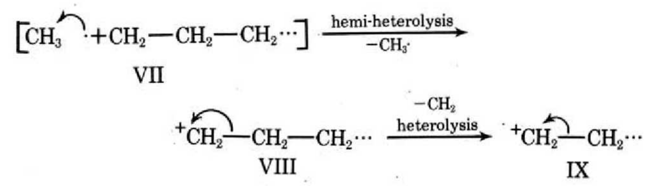
V

m/e 71



VI

m/e 43



VII

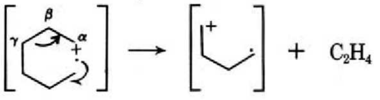
VIII

IX

plained by invoking hemi-heterolysis of the ionized bond. Note that at the very high electron voltage used in mass spectrometry it is probable that other radical cations of 2-methylpentane are formed. For example, radical cation VI is a possible precursor of the fragment which appears at m/e 43.

Unlike 2-methylpentane, long-chain hydrocarbons do not have a point of chain branching at which preferential cleavage would occur. Consequently, they tend to lose the terminal alkyl group by hemi-heterolytic cleavage, with subsequent losses of neutral methylene units by heterolytic cleavage, e.g., VII → VIII → IX etc.

A common fragmentation process of cyclic alkanes involves extrusion of a neutral olefinic moiety. This fragmentation may be described mechanistically as hemi-heterolysis of an ionized molecule X with concomitant heterolysis of the sigma bond which is β,γ to the site of ionization. Note that the resultant charged fragment XI is a radical cation.



X

XI

Alkenes

Radical cations formed by removal of a pi-electron from an olefin are often depicted in the literature as, for example, XII. Again, conceptual difficulties operate when the student uses this convention to explain fragmentations.

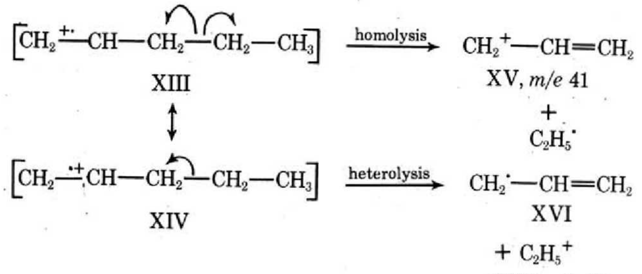
However, fragmentations of some olefins have been adequately described in the literature by considering the radical cation site to be localized. For example, 1-pentene is best represented to the student as XIII or XIV. (The origin of the radical cation charge is readily understood by considering all the valence electrons, and localizing the single pi-electron on one of the carbon atoms). We wish to emphasize the utility of this convention, and will demonstrate that the principle fragmentations of olefins are consequently easily taught.

Allylic Cleavage

Allylic cleavage can be considered as homolytic, or heterolytic fragmentation of the allylic bond. Thus, by invoking homolytic cleavage of the allylic bond in XIII, a resonance stabilized allylic cation XV, and a neutral fragment, are formed. Heterolytic cleavage of the allylic bond in the alternative radical cation XIV affords an allylic radical XVI and an alkyl cation XVII.

$$[CH_2{=}CH{-}CH_2{-}CH_2{-}CH_3]^{+\cdot}$$

XII



XIII

XV, m/e 41

XIV

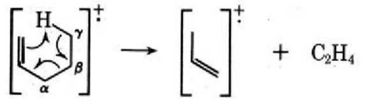
XVI

XVII m/e 29

McLafferty Rearrangement

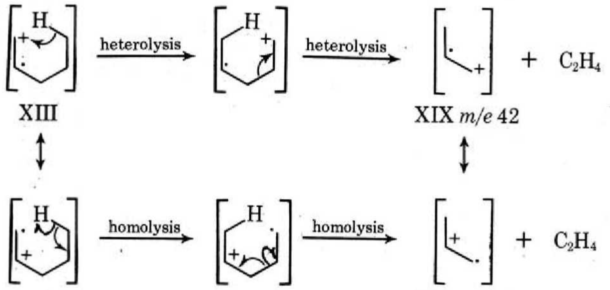
The McLafferty Rearrangement is usually illustrated in the literature as shown for XVII. Allylic cleavage of XVII accompanied by hydrogen transfer, results in formation of neutral ethylene and ionized propylene XVIII. The faults implicit in this mode of representation are again operative.

The McLafferty Rearrangement of 1-pentene can be more clearly understood by using the suggested conventions. Thus, the radical cation XIII may be shown to undergo two consecutive heterolytic cleavages,[4] leading to propene radical cation XIX and neutral ethylene. Alternatively, radical cation XIV may undergo two homolytic cleavages, affording XX, a resonance form of XIX.



XVII

XVIII m/e 42



XIII

XIX m/e 42

XIV

XX m/e 42

Note that those fragmentations which result in radical cation charge residing in the C(β)-C(γ) moiety can be rationalized by postulating heterolysis of C(γ)-H followed by homolysis of C(α)-C(β).

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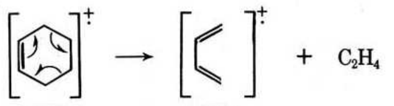
[4] Two consecutive steps have been invoked for clarity. Those who prefer to present the rearrangement as a synchronous process can concert the two cleavage steps and eliminate the intermediate radical cation.

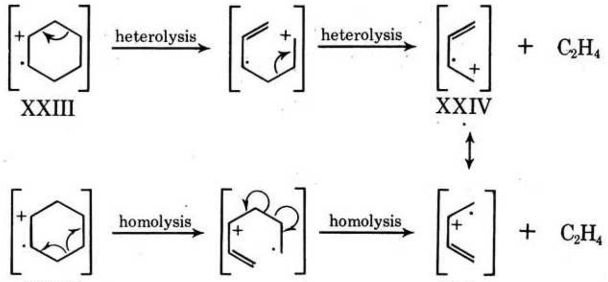
Retro-Diels Alder Reaction

Cyclic six-membered olefins often undergo fragmentation similar to the Retro-Diels Alder process. Cyclohexene radical cation, often imprecisely depicted as XXI, affords butadiene radical cation, which may be shown as XXII, and neutral ethylene.

This process is more clearly illustrated either as two consecutive heterolytic cleavages[4] from radical cation XXIII or as two consecutive homolytic cleavages. In each case, a radical cation corresponding to ionized butadiene, XXIV and XXV, and neutral ethylene, are formed.



XXI XXII



XXIII XXIV XXIII XXV

Those Retro-Diels Alder processes which afford neutral butadiene and an ethylenic radical cation can be explained in terms of heterolysis of one allylic bond, followed by homolysis of the other.

Aromatics

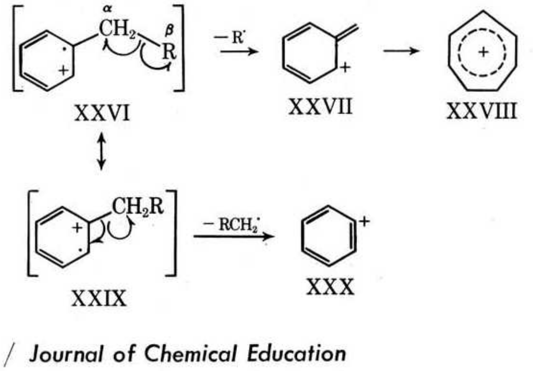
Ionization of aromatic compounds affords radical cations such as XXVI in which both the radical site and cation charge can be extensively delocalized. Subsequent fragmentations are directed by the site of ionization.

Benzylic Cleavage

As in alkenes, scission of the bond α,β- to an ionized double bond is important. Deuterium labelling studies[5] have shown that the benzylic fragmentation product XXVII rearranges by ring expansion to the stable tropylium ion XXVIII.

Vinylic Cleavage

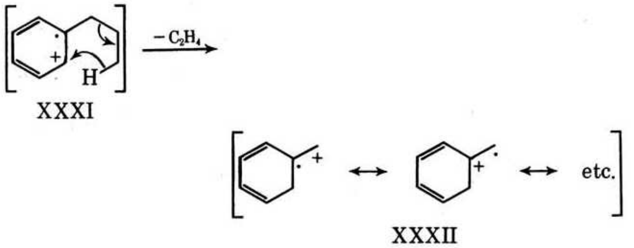
Less important than benzylic fragmentation is the cleavage of a ring-substituent bond. Resonance form XXIX may be invoked to explain the aromatic carbonium ion XXX which is formed.



XXVI XXVII XXVIII XXIX XXX

McLafferty Rearrangement

An ionized double bond in the aromatic ring can promote McLafferty rearrangement, provided a γ-H is available. Thus, fragmentation of propyl benzene XXXI is depicted as a *concerted* (or *synchronous*) process.



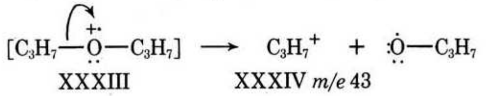
XXXI XXXII

Alcohols, Ethers, Amines, and Halides

The title compounds all contain an easily-ionized lone pair of electrons on a heteroatom. Consequently the radical cation site is localized on the heteroatom, and will be shown to direct the fragmentation processes. Alcohols, ethers, amines, and halides undergo similar fragmentation processes.

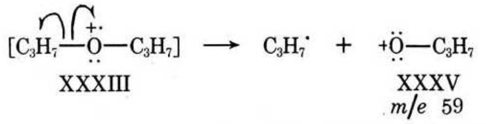
Carbon-Heteroatom Cleavage

The mass spectrum of di-*n*-propyl ether XXXIII contains fragment ions at *m/e* 43 (50% relative abundance) and *m/e* 59 (2%). *m/e* 43 is formed by heterolysis of the C-O bond (XXXIII → XXXIV). *m/e* 59 corresponds to homolysis of the C-O bond (XXXIII → XXXV). The relative abundances of these ionic fragments indicate that the former process is favored. Carbon-heteroatom cleavage is less important in alcohols than in the other title compounds.



$$[C_3H_7—\overset{+\cdot}{\ddot{O}}—C_3H_7] \longrightarrow C_3H_7^+ + :\ddot{O}—C_3H_7$$

XXXIII XXXIV *m/e* 43

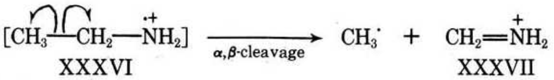


$$[C_3H_7—\overset{+\cdot}{\ddot{O}}—C_3H_7] \longrightarrow C_3H_7^\cdot + {}^+\ddot{O}—C_3H_7$$

XXXIII XXXV *m/e* 59

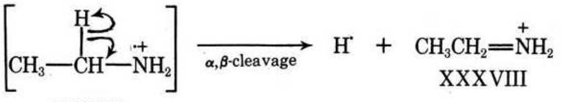
α,β-Fission

Cleavage of the bond α,β- to the heteroatom is the most significant fragmentation process in this group of compounds. For example, ethylamine XXXVI affords the immonium ion fragments XXXVII and XXXVIII by α,β-cleavage.



$$[CH_3—CH_2—\overset{\cdot+}{N}H_2] \xrightarrow[\alpha,\beta\text{-cleavage}]{} CH_3^\cdot + CH_2=\overset{+}{N}H_2$$

XXXVI XXXVII



$$\left[CH_3—\overset{H}{\overset{|}{C}H}—\overset{\cdot+}{N}H_2\right] \xrightarrow[\alpha,\beta\text{-cleavage}]{} H^\cdot + CH_3CH_2=\overset{+}{N}H_2$$

XXXVI XXXVIII

Elimination Processes

A characteristic fragmentation process of the group

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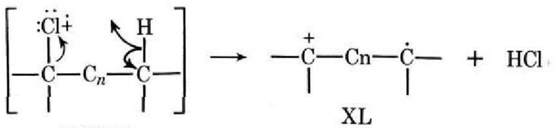
[5] H. M. Grubb and S. Meyerson *in* "Mass Spectrometry of Organic Ions" (*Editor:* F. W. McLafferty), Academic Press, New York, **1963**, pp. 516–9 and references therein.

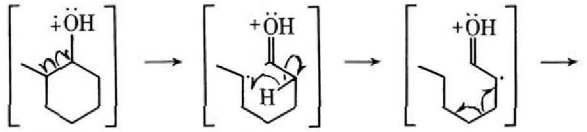


XXXIX XL

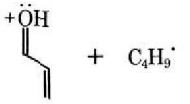
involves elimination of a neutral molecule (e.g., H_2O or HBr). This process may be envisaged (XXXIX → XL) as a concerted extrusion involving heterolysis of the C-heteroatom bond with simultaneous homolytic H-transfer through a cyclic transition state (n = 0, 1, 2). The elimination product is a radical cation.

Complex Fission in Cyclic Systems

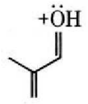
α,β-fission in a cyclic system XLI affords a ring-opened radical cation XLII which undergoes H-transfer and bond cleavage as shown, to give the oxonium ion XLIV. The alternative α,β-fission process can be shown to give oxonium ion XLV.



XLI XLII XLIII



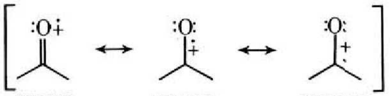
XLIV



XLV

Ketones and Aldehydes

Fragmentations of aldehydes and ketones have been adequately explained by assuming localization of radical cation charge in the carbonyl group. Under the high energy conditions of mass spectroscopy, radical cation XLVI, which is formed by removal of a lone-pair electron, has resonance forms XLVII and XLVIII.

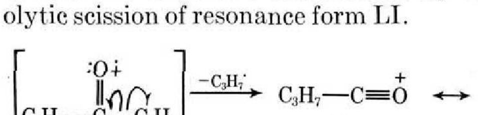


XLIX XLVII XLVIII

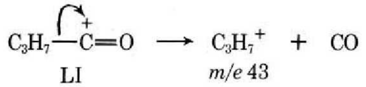
The consequent fragmentation processes can be depicted logically as follows.

α-Cleavage

Fragmentation of the carbonyl-C(α) bond (α-cleavage) is the predominant process in the mass spectra of ketones and aldehydes. Homolysis of radical cation XLIX affords oxonium ion L. Subsequent loss of neutral CO from L is rationalized by invoking heterolytic scission of resonance form LI.

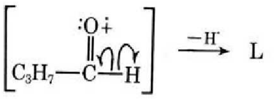


XLIX L



LI *m/e* 43

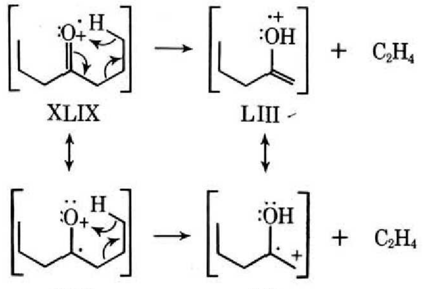
The characteristic fragment at M-1 (M is molecular weight) in the spectra of aldehydes is due to α-cleavage of the aldehyde proton (LII → L).



LII

McLafferty Rearrangement

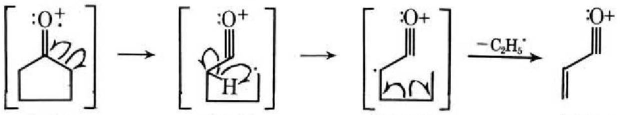
When a γ-H is available, the ubiquitous McLafferty rearrangement occurs. Ionized di-n-propyl ketone XLIX affords radical cation LIII and neutral ethylene by a concerted electrocyclic rearrangement. In an alternative representation (LIV → LV), resonance structures of XLIX and LIII are invoked.



XLIX LIII LIV LV

Complex Fission in Cyclic Systems

Cyclopentanone and cyclohexanone radical cations fragment by a sequence of homolytic fissions (LVI → LVIX), yielding a resonance-stabilized oxonium ion LVIX. Note that this process parallels those of cyclic alcohols, ethers, and halides.



LVI LVII LVIII LVIX

Esters, Acids, and Amides

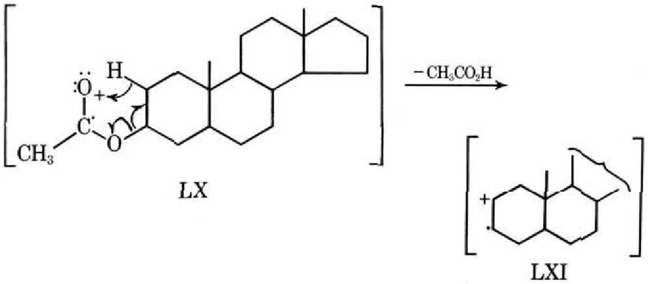
Fragmentation processes parallel those of ketones, i.e., α-fission processes and McLafferty rearrangements are conspicuous.

Functional Group Derivatives

Mass spectrometric examination of derivatives of functional groups has become increasingly important in structure elucidation. The fragmentation processes of these derivatives can be explained logically according to the principles laid out in the earlier sections.

Alcohol Derivatives

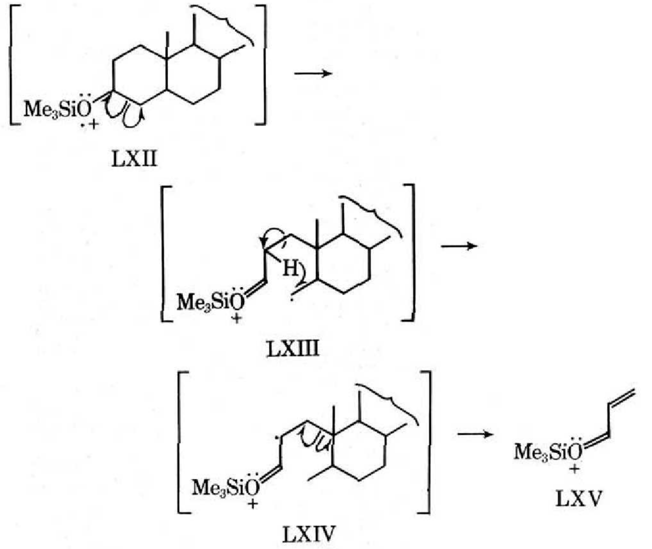
Although acetates may be the most common alcohol derivatives, they are seldom diagnostically useful in mass spectrometry. Acetate radical cations undergo facile extrusion of acetic acid (LX → LXI).



LX LXI

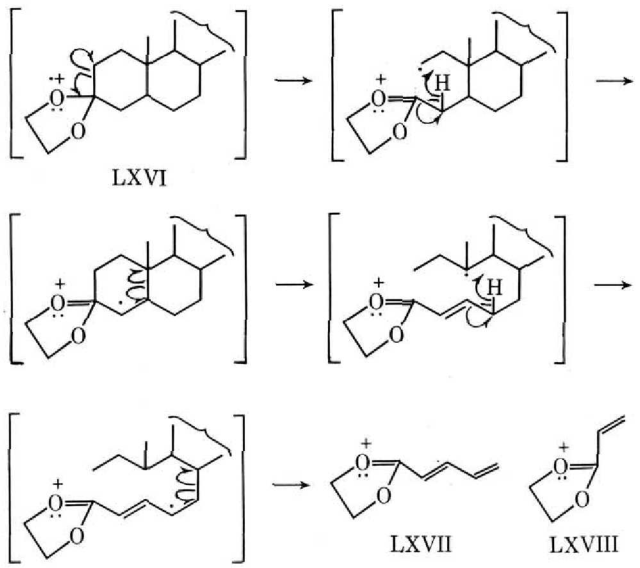
Consequently the molecular ion may be weak. The radical cation LXI undergoes subsequent Retro-Diels Alder fragmentation.

In contrast, trimethylsilyl ether derivatives of alcohols afford significant molecular ions. In addition, *they undergo predictable α,β-cleavage and complex* rearrangement processes, e.g., (LXII → LXV) and give intense fragment ions.



Ketone Derivatives

The mass spectrum of a ketone may afford some structural data. However, by forming a derivative such as an ethylene ketal (or thioketal) complementary data may be obtained, affording additional information about the functional group environment. The most spectacular example involves the ethylene ketal of androstan-3-one.[6] The radical cation LXVI fragments by a logical sequence of homolyses and H-transfers resulting in a highly-abundant resonance stabilized fragment LXVII. The alternative α,β-fission of LXVI can be shown to yield the stable fragment ion LXVIII by a similar pathway.



Summary

The commonly encountered radical cation representation, in which the charge is not localized, may confuse students. The alternative teaching conventions suggested in this paper have a distinct advantage in that electronic "book-keeping" is possible, and mechanisms can be illustrated as natural extensions of previously-encountered cation and radical mechanisms.

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[6] Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer Chem. Soc.*, **86**, 3722 (1964). G. V. Mutzenbecher, Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *Steroids*, **2**, 475 (1963).