THE MASS SPECTROMETER IN ORGANIC CHEMISTRY

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1. Theory and Design

Consider a positive particle of charge e and mass m formed in a uniform positive electric field of total potential drop V within which it is accelerated in accordance with eqn. (1) where v is the velocity appropriate to the

$$eV = \tfrac{1}{2}mv^2 \tag{1}$$

charged mass. Such a particle in motion will suffer a radiationless change of direction on passing through a magnetic field of flux density B in accordance with eqn. (2) where the symbols have their usual significance,

$$mv/R = BeV \tag{2}$$

and R is the radius of gyration of the particle of mass m. Eliminating v between the two equations one obtains the mass-spectrometer eqn. (3).

$$m/e = \frac{R^2B^2}{2V} \tag{3}$$

From these equations it follows that the trajectories of ions of different mass differ, and thereby an initial group of ions of different mass may be resolved into beams which are homogeneous in their mass-to-charge ratio (m/e). From an examination of these beams the number of each ion species present can be determined.

Whilst this particular aspect of the subject will not be developed here to any great extent, it should be noted that as the ions are formed with different velocities if the mass-to-charge ratio differs, it is not necessary to introduce a magnetic deflexion sector in order to effect mass separation. Provided the ions under consideration are produced at the same instant and are then allowed to travel along a field-free region, the drift-tube, in which they can be timed over a fixed distance, the masses of the ions can be determined.

Let t_1 and t_2 be the measured times of two singly charged ions of mass m_1 and m_2 over the same distance; then

$$t_1/t_2 = (m_1/m_2)^{\frac{1}{2}} \tag{4}$$

whence if one is known the other can be calculated.

If the consideration of instrumentation is restricted to magnetic deflexion instruments, two designs must be discussed.

Instruments in which the positive ions formed are extracted by some

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kind of electrostatic lens and then pass into the magnetic sector are single-focusing mass spectrometers. These were developed to meet circumstances in which the relative abundance of the charged species, ions, were as important as the measurement of mass. Large instruments of this design have been reported in which the ion-accelerating voltage can be varied from 40—100 kV; the magnetic flux density from 500—1600 gauss, and which have a radius of gyration of about 109 in.[1] The resolution of the ions from this instrument is about 1 part in 9000 at the base of the ion. Scanning may be effected either by varying the ion-repelling voltage or the magnetic-flux, *e.g.*, electrostatic or magnetic scanning; the former must be used in the precise determination of mass.

Recent developments in the design of mass spectrometers have been with the aim of extending their range, versatility, and precision. This has been achieved by introducing a second, electrostatic sector to remove some of the aberrations discussed subsequently. The ions formed, usually as a result of inelastic collisions of the material under examination with energetic electrons commonly of 50—70 eV, are first introduced into an electrostatic selector (after extraction from the ion-source) and brought to a focus at a slit. The slit is of such design that the correctly aligned ions pass through whereas ions which have more or less velocity than is appropriate to their mass are obstructed. The ions which penetrate enter the magnetic sector where they are resolved into ion-beams, each one homogeneous with respect to the mass-to-charge ratio. It is worthwhile pointing out that dispersion of the ions occurs in the magnetic sector only and becomes greater as the radius of gyration of the ions increases. This in turn requires higher ion-accelerating voltages and more powerful magnets. Commercial double-focusing instruments normally operate with ion-accelerating voltages of around 8 kV and magnets capable of fields of 25,000 œrsteds. The effective resolution of the double-focusing instrument having these characteristics is much greater than the commercially available single-focusing mass spectrometer which operates at 2—4 kV and with magnetic fields of up to 12,000 œrsteds. Two main variants of the double-focusing instrument are available, although other designs exist. These are known as Nier–Johnson or Mattauch–Herzog instruments following the names of their designers. Whilst the designs differ simply in the arrangement of the electrostatic and magnetic sectors, the effect upon their properties and the ancillary devices needed is considerable, and these effects arise mainly from the nature of the image plane.

In the Nier–Johnson geometry (Figure 1) the image plane, that is the surface upon which each of the several ion-beams resolved in the magnet comes to a focus, is a conic surface which is paraboloidal in two mutually perpendicular directions. Accordingly one must either devise a detector which will operate over this rather complicated surface, or more practicably

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[1] "Advances in Mass Spectrometry", ed. J. D. Waldron, Pergamon Press, London, 1959, p. 1 *et seq.*

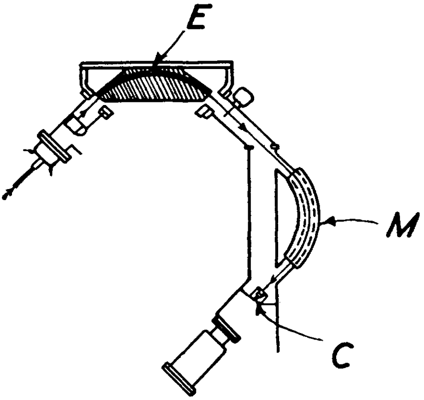

FIG. 1.
E Electrostatic selector.
M Magnetic sector.
C Collector.

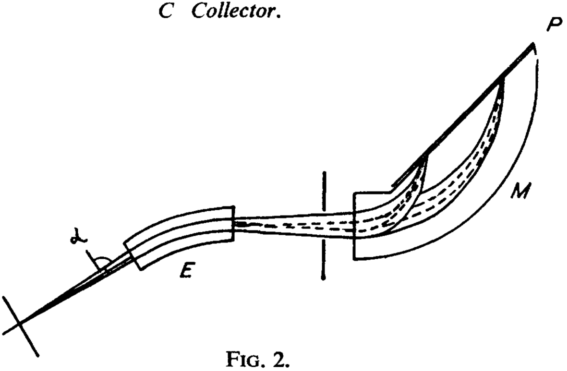

FIG. 2.
E Electrostatic selector.
M Magnetic sector.
P Photographic plate.
α Angular divergence.

measure all the ion beams at one point. The latter technique is the one adopted. The resolved ion beams are brought to a focus at a slit (the exit slit) behind which is situated the detector. In order to present the different ion beams at the slit one must scan either by varying the ion-accelerating voltage or the field of the magnet: in either case the ions are recorded successively. The quantity of each of the ions present is usually recorded by a suitable electronic device.

In the Mattauch–Herzog geometry (Figure 2) the resolved ion-beams come to a focus on a plane. The detector in this instance can be a photographic plate which will record all the ion-beams simultaneously. Each design has its own particular advantages and may be more useful in given circumstances. Thus, the Nier–Johnson design is much easier to focus and by reason of the detection method the relative abundances of the ions are easily and accurately obtained. The Mattauch–Herzog design is not as easy to focus, nor are the relative abundances of the ions readily obtained from a photographic plate. On the other hand as all the ions are recorded simultaneously one may generate them by spark-sources and field-emission devices, although with these the ion concentration may fluctuate markedly in the course of one experiment.

The main purpose of double-focusing instruments, however, is to increase the resolution of the mass spectrometer by the elimination of aberrations.

2. Aberrations and Resolving Power

The two aberrations with which mass-spectrometer design is mostly concerned are the divergence of the ion from the rectilinear path of the main axis (α) and variations in the velocity (β).

Consider an ion of mass m which travels along the optical axis with a velocity v, whilst there is a second ion of the same mass but a velocity $v(1 + \beta)$ and an angular divergence α such that $\alpha, \beta \ll 1$. The second of these ions will meet the image plane at a distance x from the optical axis, where x may be expressed as a power series in α and β; the sum of the divergence and velocity aberrations

$$x(\alpha,\beta) = C_1\alpha + C_2\beta + C_{1,1}\alpha^2 + C_{1,2}\alpha\beta + C_{2,2}\beta^2 + \ldots.$$

The coefficients C_1, C_2, etc., are functions of the instrumental parameter and are dimensionless. By correct choice of the parameters in the designs of the double-focusing mass spectrometers discussed, it is possible to make $C_1 = C_2 = 0$, the full first-order double-focusing condition, as well as one of the remaining coefficients; which one depends upon the geometry of the instrument. It is these corrections which allow spark-sources to be employed (at least in one design) and permit the determination of precise masses.

Mention has been made of the resolving power, or resolution, of a mass spectrometer without offering a formal definition. Resolution is defined somewhat differently by the different manufacturers, but it is useful to adopt the convention used in Great Britain. Two adjacent ion-beams of equal height are said to be resolved if the two ions overlap not more than 10% of the beam height. Of course this is not meant to imply that ions which are not resolved according to the definition are of no use in the organic applications of a mass spectrometer; often it is sufficient that the tops of the two peaks only should be distinct.

In double-focusing mass spectrometers and their applications it is necessary to consider not only the resolution of the mass spectrometer, but also its range. Thus with one double-focusing mass spectrometer, which is available commercially, the mass-range of the instrument using an ion-accelerating-voltage of 8 kV is approximately 1000. The resolution in this range is 5 parts in 10^5. If the ion-accelerating voltage is lowered to

2 kV, the mass-range is extended to about 32,000 but the resolution may now be 2 or 3 units at the upper end of the range; and it is of a superior performance in this regard.

3. Other Methods

Whilst in the majority of investigations into the mass-spectra of organic compounds, the ions have been produced by electron-bombardment and resolved in magnetic-deflexion instruments, there exist other techniques of a growing importance. The time-of-flight method (p. 527) has been developed into a versatile instrument which has a considerable range of applications in chemistry, and several commercial instruments are available for organic studies.[2a]

The field-emission type of source has been applied to double-focusing instruments with considerable success and much investigation of organic compounds has been made.[2b] The characteristic of such spectra seems to be in their simplicity. The spectrum consists mainly of the parent molecular ion and an occasional fragment ion which in the case of hydrocarbons corresponds to the $(P - 29)^+$ ion. The simplicity of the spectrum is against its use in the determination of the structure of the molecular ion. On the other hand this method will yield such an ion when it is absent from spectra obtained by electron bombardment. Ion–molecule collision processes do not receive any consideration here; for a discussion of these see ref. 3.

4. The Origins of Spectra

The generally accepted origin of a mass-spectrum is as follows:

$$e + XYZ \rightarrow X\overset{+}{Y}Z + 2e \tag{5}$$

$$X\overset{+}{Y}Z \rightarrow \overset{+}{X}Y + Z\cdot,\ \text{or}\ \overset{+}{Y}Z + X\cdot,\ \text{or}\ \overset{+}{X} + YZ,\ \text{etc.} \tag{6}$$

The totality of all the ions formed by impact upon the original material (XYZ) comprises the spectrum which is also known as the cracking-pattern or fragmentation pattern. This pattern will contain all possible combinations of ions as shown above, but it will also include ions of the form $X\overset{+}{Z}$ which can only arise by a rearrangement process since in the original material the two constituents of this ion were separately attached to Y, but not to each other. The occurrence of such arrangements is one of the problems which complicate exceedingly the simple interpretation of ionisation and fragmentation processes and is, moreover, a serious obstacle

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[2] "Mass Spectrometry", A NATO Advanced Study Institute, ed. R. I. Reed, Academic Press, London, 1965, (*a*) pp. 1, 37, and 61, (*b*) p. 93, (*c*) 143, (*d*) 153, and (*e*) 401.

[3] "Mass Spectrometry of Organic Ions", ed. F. W. McLafferty, Academic Press, New York, 1963, pp. 1, 65.

to the determination of the constitution of the original compound from the mass-spectrum.

When one considers the energies employed to achieve ionisation (usually 50 to 70 eV) it is clear that they are vastly in excess of the minimum energy required. The energy relationships concerned in the above eqns. 5 and 6 can be illustrated by a Born–Haber cycle

$$\begin{tikzcd}
\overset{+}{\mathrm{XYZ}} \arrow[r] & \overset{+}{\mathrm{XY}} + \mathrm{Z}\cdot + \Sigma \\
\mathrm{XYZ} \arrow[u, "-\mathrm{e}"] \arrow[r] \arrow[ur] & \mathrm{XY}\cdot + \mathrm{Z}\cdot \arrow[u, "-\mathrm{e}"']
\end{tikzcd}$$

where the letters have their usual significance, and Σ represents an excess of energy. The minimum energy is therefore the sum of the ionisation potential (I.P.) of the radical XY·, the bond-dissociation energy D(XY–Z), and Σ. The last term comprises the excess of energy which may be imparted in the ionisation process and that of the kinetic shift. However, further consideration will not be given here.[3]

In general the ionisation potential rarely exceeds 10 eV and the bond-dissociation 5 eV so that, as Σ is commonly much smaller, the incident electron beam has more than a three-fold excess of the energy needed; one must consider the possibility of the formation of both doubly and triply ionised molecules.

There is much evidence for the formation of multiply charged ions[2c,4] although these are usually neglected in the formal development of theories of the origin of mass-spectra. The practical reason for so doing is that apart from small changes in detail, the cracking-pattern of most compounds so far investigated show little difference whether they are obtained with an incident electron-beam energy of about 20 or 100 eV. Theory indicates that multiply-charged ions should fly apart with considerable velocity and would possess an energy and velocity much in excess of that required by the eqns. (1, 2, and 3) already developed. Such ions are discriminated against markedly in both single- and double-focusing mass-spectrometers. Accordingly they do not make a notable contribution to the mass-spectrum. Nonetheless most authorities agree that multiply charged ions are present and that they possibly account for 10% of all the ions formed.

A third source of ions has been little discussed, if not entirely neglected, in the consideration of the mass-spectra of organic compounds; there is the possibility of ion-formation by pre-ionisation or pre-dissociation.[4] It is

[4] R. L. Platzman, *Vortex*, 1962, **23**, 372.

conceivable that the interaction of an electron and a molecule may not lead directly to the formation of an ion, direct ionisation, but to a neutral excited molecule:

$$XYZ + e \rightarrow XYZ^* + e \tag{7}$$

The energy imparted to the molecule is postulated to be greater than, or at least as great as, the ionisation potential so that the excited molecule may subsequently undergo conversion as follows:

$$XYZ^* \rightarrow \overset{+}{XYZ} + e \tag{8}$$

$$XYZ^* \rightarrow X\cdot + YZ, \text{ or } XY\cdot + Z\cdot \textit{ etc.} \tag{9}$$

$$XYZ^* \rightarrow \overset{+}{XY} + Z\cdot + e \tag{10}$$

Many other possibilities clearly exist; but reference should be made elsewhere.[4] The other type of reaction

$$XYZ^* \rightarrow XY + Z^-$$

has not been considered as the evidence suggests it is unimportant.[4]

The principal difference between this indirect ionisation, and the direct, is thought to be one of time-scale only[5] although this consideration may be important in an understanding of mass-spectra. Of more immediate concern is the extent to which indirect ion formation may compete with direct ionisation. Relatively little study has been made of this problem, but from the available evidence one arrives at the startling conclusion that the two processes may be equally important[4] which, *inter alia,* points to the danger of constructing detailed mechanisms when the primary ionisation processes are still inadequately understood.

In summary, therefore, there are three methods of ion production: (i) the direct ionisation process, (ii) the dissociation of multiply charged ions, and (iii) the indirect production of ions.

5. Metastable Ions

In the analysis of organic structures from their cracking-patterns, it is conceivable that the recognition of metastable ions may assume an even more prominent place than they do at present although this is by no means insignificant. A customary mass spectrum comprises an array of ions derived from the original compound. These ions are of varying abundance and while one can now determine their exact mass and chemical constitution, it is not always possible to determine the relationship between them. The recognition of a metastable ion remedies this defect since the m/e value of such an ion depends explicitly upon the parent and daughter ions:

$$m^* = m_2^2/m_1 \tag{11}$$

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[5] A. J. C. Nicholson, *J. Chem. Phys.,* 1963, **39,** 954.

where m^* is the mass of the metastable ion and m_1 and m_2 are the masses of the parent and daughter ions, respectively.[6] Clearly as $m_1 - m_2 = n$ one can determine the mass and composition of the neutral fragment that is lost as an entity.

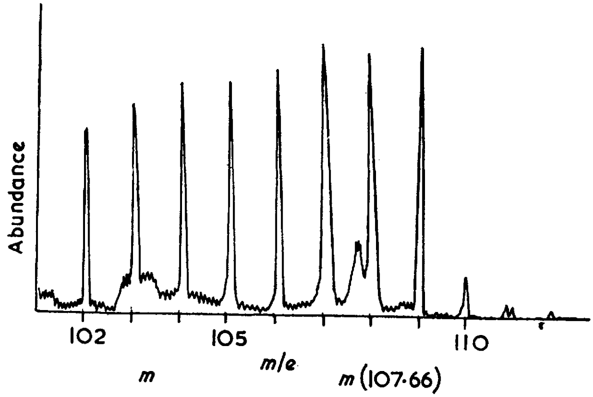

FIG. 3.
m Metastable ion.

Metastable ions are easily recognised by the characteristic shape (Figure 3) of their mass-spectra and by the fact that their mass-to-charge ratio is seldom an integer. Moreover, their properties are rather dependent upon the geometry of the instrument used. While a detailed discussion would lead us too far afield, two arguments in favour of sector-type instruments may be mentioned.

The peak due to the metastable ion is

(i) uniform and symmetrical in shape, and

(ii) they appear at the correct nominal mass, as required by the formula (11) at least to within 0·1 mass unit. Such properties are considered to be associated with ion dissociations which occur in a field-free space, as is possessed by sector instruments. Those of the Dempster type which have no field-free region give rise to metastable ions although of lower abundance; for further differences the original communications should be consulted.[6]

This relationship will not be valid if dissociation is accompanied by a release of internal energy.[2d] By using straightforward Newtonian dynamics the appropriate formula having a regard for the conservation of both energy and momentum is

$$\frac{T}{V}=\frac{1}{4}\cdot\frac{m_2}{m_1-m_2}\cdot h^2 \qquad (12)$$

where T is the energy of the process in electron volts, V is the potential

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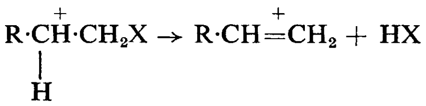
[6] F. H. Field and J. L. Franklin, "Electron Impact Phenomena and the Properties of Gaseous Ions", Academic Press, New York, 1957.

drop in the electric field, m_1 and m_2 have their usual significance, and h, the relative half-width of the ion, is equal to $\delta m^*/m^*$ where $m^* = m_2^2/m_1.(1 + h)$.

The drawback in analysing metastable ions that are produced in magnetic deflexion instruments is that there is little indication as to which ion is the parent and which is the daughter. It is of interest, therefore, to mention the nature of the metastable spectra obtained in a Bendix Time-of-flight instrument. Since the ions travel a rectilinear path after leaving the source it is apparent that, provided the parent and daughter ions and the neutral fragment continue to travel with their original velocity, they will arrive at the collector simultaneously. And provided the neutral particle has an energy in excess of a few volts it, too, will record on the detector. Thus for a dissociation not too far removed from the collector, for the conservation of momentum is not always strictly obeyed, an ion will record twice over and therefore appear more abundant than would have been the case had it remained intact. The three species can be separated by introducing into the flight path of the particles, and near to the collector, a retarding potential. Provided this potential is initially small, the neutral particle will be unaffected, the parent molecular ion negligibly retarded, and the daughter significantly so; for the latter ion has a smaller mass. The nature of the daughter ion can thus be determined. By use of a larger retarding potential the parent molecular ion may be "stepped out" and recognised, and in this way the whole nature of the metastable ion determined.[7]

6. Rearrangement

As has been mentioned (p. 531) one of the difficulties in the analysis of spectra arises from the presence of ions which are the end products of rearrangement processes. This interesting but difficult field has been the object of extensive and detailed study with the aim of finding unifying theorems which are broadly applicable and has been mainly successful in many classes of compound.[8] Such systems are well documented and one example will suffice; the common observation that in many species fission of the β-bond with a concomitant hydrogen migration occurs, *e.g.*, where



$$\mathrm{R{\cdot}\underset{\displaystyle H}{\overset{+}{C}}H{\cdot}CH_2X \rightarrow R{\cdot}CH\overset{+}{=}CH_2 + HX} \qquad (13)$$

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[7] R. E. Ferguson, K. E. McCulloh, and H. M. Rosenstock, *J. Chem. Phys.*, 1965, **42**, 100.

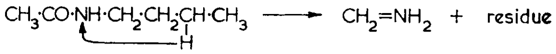
[8] (*a*) J. H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry", Elsevier, Amsterdam; (*b*) F. W. McLafferty, "Determination of Organic Structures by Physical Methods", ed. F. C. Nachod and W. D. Phillips, Academic Press, New York, 1962; (*c*) R. I. Reed, "Ion Production by Electron Impact", Academic Press, London, 1962; (*d*) F. W. McLafferty, "Mass Spectrometry of Organic Ions", ed. F. W. McLafferty, Academic Press, New York, 1963.

X = $\cdot CHO$, $\cdot CN$, $\cdot CONH_2$, $\cdot CO_2CH_2$, etc. It is perhaps worth pointing out that no compelling evidence exists that the derived ion is an alkene as indicated, and not a cyclic structure. One necessary but probably not sufficient requirement for the occurrence of a rearrangement seems to be formation of an ion which is thermodynamically very stable. The presence of the ion $m/e = 31$ ($C\overset{+}{H}_2O$) in the mass spectrum of an alcohol does not necessarily require it to be a primary alcohol (eqn. 14) as, owing to its

$$R^+CH_2OH \rightarrow \overset{+}{C}H_3O + R\cdot \qquad (14)$$

stability, it may arise through a wide variety of rearrangements.[8] Other required conditions for such rearrangements are known, including the dissociation energy of the relevant bonds and the stability of the neutral fragments.

A comprehensive classification has been reported where a distinction is drawn between general and specific rearrangements.[8b,8c] By general rearrangements are to be understood fragmentation whereby in addition to the detachment of part of the ion, *e.g.*, X in eqn. (13), a hydrogen atom is transferred in this case to yield HX which does not come from any particular methylene group in the system. Such general rearrangements are encountered in the fragmentation of the hydrindones and 5α-androstan-3-one.[9] Specific rearrangements, as their name implies, require that the migrating hydrogen should derive exclusively or substantially from one carbon atom in the structure. For example the mass-spectrum of *N*-butylacetamide shows a specific hydrogen migration in the formation of the ion $CH_2\overset{+}{=}NH_2$ (eqn. 15). The same ion, incidentally, is the base peak of all



$$CH_3\cdot CO\cdot NH\cdot CH_2\cdot CH_2\cdot \underset{H}{CH}\cdot CH_3 \longrightarrow CH_2{=}NH_2 + \text{residue} \qquad (15)$$

primary amines. Of course, both specific and non-specific rearrangements may occur in the decomposition of a given molecular ion as for instance in the fragmentation of αβ-unsaturated 3-ketosteroids. This is an observation which will well repay further study and significant contributions have already been made; in particular it has been observed that for specific rearrangements the geometry of the system is important. As a result of these experiments it was concluded that for a specific migration of a hydrogen atom the critical distance is such that $d < 1{\cdot}8$ Å, at least in the ketosteroids investigated. This spatial requirement has interesting repercussions in the general nature of the mechanistic process involved. There is a growing body of evidence to suggest that even the simpler ions which arise by electron-impact upon hydrocarbons do not have the structures often intuitively assigned, and associated theoretical considerations sup-

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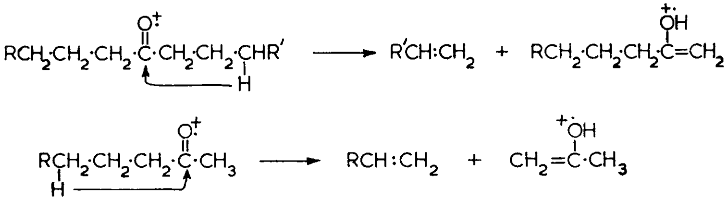
[9] C. Djerassi *et al.*, *J. Amer. Chem. Soc.*, 1963, **85**, 941, 1528, 2470; 1964, **86**, 2825, 2837; 1965, **87**, 580, 817.

port a general migration of hydrogen atoms.[6] The presence of a specific rearrangement might therefore indicate the operation of a further ionisation process, other than the direct one. Sufficient evidence is lacking to decide this point which, presumably, must await the demonstration of isotope effects. Again, an interesting problem is raised by compounds which may undergo two hydrogen rearrangements. In the decomposition sequence shown in Scheme 1, reaction (16) is followed by (17) or the sequence may be reversed. This particular reaction has been much studied both from the intrinsic interest attached to the cracking-pattern and also for its rearrangement processes. It is suspected that the first rearrangement (whichever occurs) is specific; the second is general.* Since the second step refers to the further fragmentation of an ion whereas the first may be an indirect process, it is of crucial importance that a rigorous demonstration be given; so far this is not available.

SCHEME 1



Whilst much attention has been given to rearrangements in the fragmentation processes, so far surprisingly little has been given to the possibility of rearrangement in the parent molecular ion. Some studies have been made by isotopic substitutions in an arbitrary selection of molecules and radicals, but systematic investigations are only now beginning.[10] Much of the work already done has been by substitution of deuterium for hydrogen, and while valuable in revealing unsuspected processes it is perhaps not the most advantageous replacement to effect. In common with many facets of mass-spectrometry, little is known about any selection rules which may operate in the formation of fragment ions, or even the effects upon the cracking-pattern of local energy changes in the molecular ion. However, it seems that the comparatively large changes in bonding energy which result from the replacement of hydrogen by deuterium may have a more drastic effect upon the fragmentation-pattern than the replacement of carbon-12 by carbon-13 or nitrogen-14 by nitrogen-15. Unfortunately the latter substitutions while more desirable are

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[10] L. Friedman and A. P. Wolf, *J. Amer. Chem. Soc.*, 1958, **80**, 2424; R. I. Reed, "Application of Mass Spectrometry to Organic Chemistry", Academic Press, London, 1966, p. 120.

* *Note added in proof:* A start has been made upon this problem which seems more complicated than is here supposed (Djerassi, *et al.*, *J. Amer. Chem. Soc.*, 1965, **87**, 5747, 5752; *Tetrahedron*, 1966, **22**, 1391).

usually more difficult to effect. Of the few studies reported it seems that camphene does not rearrange to any great extent upon electron-impact and that the $C_7H_7^+$ ion obtained from toluene or the isomeric xylenes rearranges to the cycloheptatrienyl ion.

In benzene the thermochemical evidence requires that the molecule opens upon impact[11] and the cracking-pattern certainly seems to favour the open-chain, at least for the correlation of structure with cracking-pattern.

TABLE

m/e	Benzene % Abundance	Probable Structure
39	13·5	$H_2C{:}C{:}\overset{+}{C}H$
50	16·8	$HC{:}\overset{+}{C}{\cdot}C{:}CH$
51	20·1	$H_2C{:}CH{\cdot}C{:}\overset{+}{C}$
52	18·9	$H_2C{:}CH{\cdot}\overset{+}{C}{:}CH$
63	2·92	
73	1·42	
74	4·70	
76	6·22	
77	13·8	$H_2C{:}CH{\cdot}CH{:}CH{\cdot}\overset{+}{C}{:}C$
78	100·0	$H_2C{:}CH{\cdot}CH{:}CH{\cdot}\overset{+}{C}{:}CH$
79	6·51	

Further studies of this kind are clearly desirable in order to determine the structure of the parent ion, for it cannot be urged too strongly that those problems which deal with the primary processes in the formation of the mass spectrum must be understood before a detailed, systematic, analysis can be undertaken with a reasonable hope of success.

7. Temperature Effects

The other source of variation in mass-spectra undoubtedly arises from temperature effects. Much of this factor has been discovered by painstaking experiments and the general problems are fairly well understood, although still largely ignored.[2,8a] The obvious temperature effect is to bring about changes in the material examined. Alcohols may dehydrate in the inlet system to yield olefins and the spectrum obtained will be of the olefin rather than the original compound. Two methods of prevention are

[11] J. Momigny, L. Brakier, and L. D'Or, *Bull. Classe Sci., Acad. roy. Belg.*, 1962, **48**. 1002.

available: (i) conduct the experiment at a lower temperature when dehydration may not occur, and (ii) modify the compound chemically to protect the thermally sensitive group; in this case by forming a methyl ether.

Temperature changes in the sample being analysed also have an effect upon the cracking-pattern. When the temperature is raised the abundance of all the ions in the spectrum diminishes, the diminution of the parent ion being more marked than that of the fragment ions; the relative distribution of the various fragment ions may also change.

In addition to these controlled changes in sample temperature, such changes may occur in the heated tungsten (or rhenium) ribbon which is the electron source. Temperature changes of the order of 20° may occur in a filament within a few hours, and as in certain circumstances a temperature change of 5° is sufficient to modify a mass spectrum profoundly, temperature control of the filament and the source region generally is of the utmost importance.

8. Structure Determination

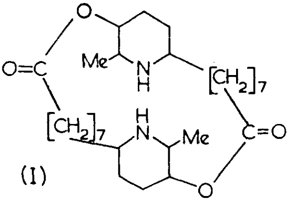
With all the difficulties and pitfalls so far noted the possibility of making much use of a mass spectrometer in the examination of organic materials must seem remote. This is not so and widespread application of the method has been made.[8,12] One method of obvious importance is to provide facilities where all known spectra could be stored and to which an unknown spectrum could be sent for identification. Having regard to the peculiarities of the different instruments available such a centre could with advantage produce the spectra also. For novel compounds other methods are available in which the mass spectrometer is combined, fashionably, with nuclear magnetic resonance equipment or with infrared instruments. However, one of the greatest advantages of the mass-spectrometric technique still remains its high sensitivity. Even with electron-bombardment as the means of ion-production an analysis may be conducted upon about 0·1 μg, and with such methods less than 1 in 1×10^5 collisions is effective. With such small amounts it is useful to consider the methods of analysis using a mass spectrometer only; beginning with the reminder that at present a mass spectrometer is blind to the niceties of the stereochemistry about a single carbon atom; a consequence of the fact that all incident ionising radiations yet employed in the production of mass spectra are plane-polarised.

The most popular method of structure analysis, although in terms of the previous discussion more correctly the determination of the structure of the molecular ion, is the correlation study.[8] With the recent extensive investigations of organic structures by mass-spectrometric methods, several variants of the simple comparison method have been developed and these

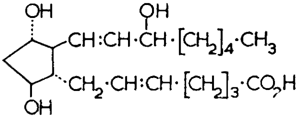
[12] M. Spiteller-Friedman and G. Spiteller, *Monatsh.*, 1964, **95**, 1234.

can be summarised in the following ways: (i) the direct use of a mass spectrum, (ii) the positioning of a functional group within the molecule by mass-spectrometric analysis, (iii) the comparison of the mass spectra of closely related compounds, (iv) chemical modification of the material before mass-spectroscopic examination, and (v) the use of mass spectrometry in combination with the evidence from nuclear magnetic resonance.

An example in which a mass spectrum provides a simple, decisive conclusion is the redetermination of the structure of carpaine.[12] Chemical evidence had previously provided a plausible structure; it was shown by the mass-spectrometric method to have twice the molecular weight previously suggested. This, together with the detailed structure shown by the fragmentation-pattern supports the formula (I).



(I)



(II) PGF$_{2\alpha}$

The positioning of a functional group (in this case a double-bond) by a correlation study has been investigated for an extensive series of diterpenes. Two types of reaction have been recognised. The fragmentation of the molecular ions of the $\Delta^{8(20)}$ unsaturated compounds occurs by fission of the allylic carbon–carbon bonds at C(6)–C(7) and C(9)–C(10). For the decomposition of the ions of Δ^7 compounds the occurrence of a retro-Diels–Alder reaction is preferred.[13] A similar explanation has been advanced for the formation of the major ions in a series of chromones.[13]

Advantage was taken of the close similarity between the mass spectrum of a derivative of a known prostaglandin and that of the same derivative of an unknown smooth muscle stimulant from menstrual fluid.[14] The trimethyl ether methyl esters of the two compounds were compared. The two spectra resemble each other closely, the main difference being that the molecule from the menstrual fluid possesses two hydrogen atoms less than the reference compound and that the parent molecular ion was more abundant in the former. This suggests a more stable molecular structure which, taken together with the detailed consideration of the cracking-pattern, supports the suggested structure (II).

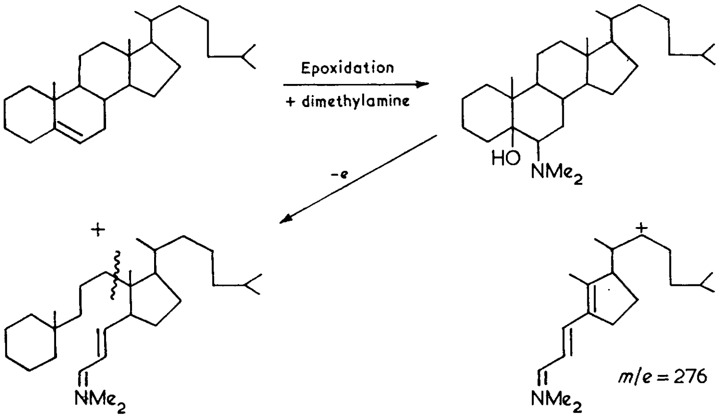
The practice of modifying the original material by chemical means has been elegantly applied in a series of papers which are mainly concerned with steroids or like structures. The function (again a double bond) is

[13] C. Enzell and R. Ryhage, *Arkiv Kemi*, 1965, **23**, 367; M. M. Badawi, T. A. Bryce, M. B. E. Fayez, and R. I. Reed, *Chem. and Ind.*, 1966, 498.

[14] E. Clayton, H. C. Hill, and R. I. Reed, "Advances in Mass Spectrometry", vol. III, ed. W. Mead, 1966, Institute of Petroleum, London, p. 669.

altered to provide a system which fragments readily upon electron impact. An interesting and instructive example is the following: the double bond is converted into the epoxide which is made to react with dimethylamine to yield the dimethylamino-alcohol. Theoretically, such compounds can cleave in one of two ways, but only that between the hydroxyl and dimethylamino-systems has ever been observed. This enables the position of the double bond to be determined as is shown for Δ^5-cholestene in Scheme 2.

SCHEME 2



Many other substitutions have been reported.[15]

A simple example which combines the information yielded by mass-spectrometric examination with that which can be obtained from nuclear magnetic resonance is the determination of the structures of lochnericine and lochnerinine.[16] This is possibly the most fashionable combination of physical methods and has been widely applied by many workers.

The mass-spectrometric method has been brilliantly exploited in many fields of organic chemistry both to provide a *rationale* for the decomposition of known molecules and to throw some light upon the nature of unknowns.[17] Some assumptions of the method are less well founded, in particular charge localisation. The accumulated evidence suggests that the orbital from which the electron is removed in forming the parent molecular

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[15] H. Audier, M. Fetizon, W. Vetter, *et al.*, *Bull. soc. chim. France*, 1963, 1324, 1971, 2827; 1964, 415.

[16] B. K. Moza, J. Trojanek, A. K. Bose, K. G. Das, and P. Funke, *Lloydia*, 1964, **27**, 416.

[17] K. Biemann, "Mass Spectrometry", McGraw-Hill, New York, 1962; H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass-Spectra of Organic Compounds", Holden-Day Inc., San Francisco, 1964; "Structure Elucidation of Natural Products by Mass Spectrometry", vol. 1, Alkaloids; vol. 2, Steroids, Triterpenoids, Sugars, and Miscellaneous Classes, Holden-Day Inc., San Francisco, 1964.

ion is delocalised; *i.e.*, it extends over the whole molecule. This being so one can argue intuitively that if the loss of electron density from any given centre is so slight the properties associated with the neutral molecule can "show through".

Accordingly, if one is dealing with a large molecule, or in certain circumstances a hydrocarbon of moderate size, one may expect the behaviour of the parent molecular ion to parallel that of the neutral species in high-temperature reactions, and there is some evidence for this. On the other hand as the molecules become smaller, although not to the lower limits, the effect of removing an electron even from a delocalised orbit may modify the behaviour of the molecular ion. This leads to the experimentally verifiable conclusion that the cracking-patterns of large molecules are often more readily interpreted than those from molecules of moderate size. Because the orbitals even of an alkane ion may be considered as delocalised, the concept of assigning particular fragments in the spectrum to certain features in the molecule is neither uniformly successful, nor always a failure. The validity of the arguments depends upon the particular problem and its success or otherwise is often only appreciated in hindsight.

While it is true that the abundance of an ion depends upon temperature, it is not true of the mass which is temperature-independent. The introduction of double-focusing mass spectrometers has directed attention to constructing a mass spectrum based upon the composition of all the fragment ions rather than upon some deduced structures and known abundances: the production of atom "maps" is now important in this form of analysis.[18] Having the probable constitution of the ions is of great assistance in determining the likely relation between the various fragment ions, but the sequence of such fragmentations from the initial molecular ion is essential information in reconstructing the molecule. This is assisted by the presence of metastable ions which confirms the relationships and by the fact that, under certain conditions, the mass of the metastable ion may be obtained with sufficient precision to indicate the composition of the elided fragment. Nevertheless, it seems regrettable that the abundances of the ions so patiently obtained should then be largely ignored.

9. Other Instrumental Methods

A particularly promising procedure has been devised whereby it is possible to relate the ions formed to the electrons detached in their formation.[19] It is of interest in its present form (in spite of the rather low resolution of which it is capable) because it can be considered free from most of the discriminatory properties already discussed; it is potentially of considerable importance in that more elaborate versions may provide a direct

[18] K. Biemann, P. Bommer, A. L. Burlingame, and W. J. McMurray, *Tetrahedron Letters*, 1963, 1969.

[19] K. E. McCulloh, T. E. Sharp, and H. M. Rosenstock, *J. Phys. Chem.*, 1965, **42**, 3501.

experimental demonstration of the fragmentation sequence which occurs to produce the cracking-pattern.

The other development is a systematic study of negative-ion spectra formed by an electron-attachment reaction; these are rather little studied, largely because of the lack of sensitivity of organic compounds to such additions; and owing to instrumental difficulties. Accordingly this pursuit is confined to one or two laboratories which have reported interesting, even striking results.

Low-energy electrons seem necessary to obtain a successful attachment reaction to yield the negative molecular ion. Accordingly little extra energy is imparted to this ion which is consistent with the, limited, observation that with such ions extensive fragmentation does not occur. Some systematic investigations have been made and the behaviour of 3β-acetoxychol-5-ene can be considered as typical.[20] The spectrum comprises ions at m/e = 367, 385, 427, 428, and 429. Of these m/e = 427 corresponds to the molecular ion less one hydrogen, the commonly occurring process, with isotope contributions at 428 and 429. Loss of acetic acid from the parent molecular ion yields m/e = 367 which is assumed to stand in the same relation to cholesta-3,5-diene as m/e 427 to the original acetoxy-compound. In addition the ion m/e 385 is considered as arising from cholesterol which was present as an impurity.

It is clear that the negative-ion spectrum is much simpler than one obtained in positive-ion production. Nevertheless difficulties may occur also in negative-ion formation, the commonest being the attachment to the compound of atoms or groups which may in themselves form stable anions; oxygen or hydroxyl groups are often found as such addenda.

One further advantage of negative-ion spectra should be mentioned. The formation of these ions does not seem to be associated with the hydrogen migrations so characteristic of positive ions.[3]

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[20] M. von Ardenne, K. Steinfelder, R. Tümmler, and K. Schreiber, *Experientia*, 1963, **19**, 178.