

DIRECTED FRAGMENTATION IN MASS SPECTROMETRY BY INTRODUCTION OF FUNCTIONAL  
GROUPS : A NEW CHAPTER IN AN OLD STORY

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**Abstract** - The fragmentation mechanisms of the ethylene ketals of variously substituted cycloalkanones have been reinvestigated by deuterium labelling and at low electron energies. The data suggest a reaction involving hydrogen migration and recyclisation of the ring-cleaved molecular ion.

INTRODUCTION

The silylation of primary alcohols (Ref. 1) is one of the earliest examples of the introduction of a functional group in order to facilitate the interpretation of a mass spectrum. The analysis of a mixture is made much easier and the determination of the molecular weights unambiguous. The mass spectra of alkaloids are usually simple and they consist of a few peaks only. Since 1962 this observation made us look systematically for functional groups which were easy to introduce and which would have the same directing effect on the fragmentation as the nitrogen containing groups. The ethylene ketal group soon appeared to be one of the most promising in this field (Ref. 2). Thus, while the mass spectrum of a 3-ketosteroid exhibits a large number of peaks which are difficult to interpret, that of the corresponding ethylene ketal is much simpler (Fig. 1). The mechanism established by Djerassi (Ref. 3, Fig. 2) elucidates the fragmentation of steroids (Ref. 3 and 4) and aliphatic or alicyclic compounds (Ref. 5). Even the position of an acetylenic bond in a chain can be determined (Ref. 6).

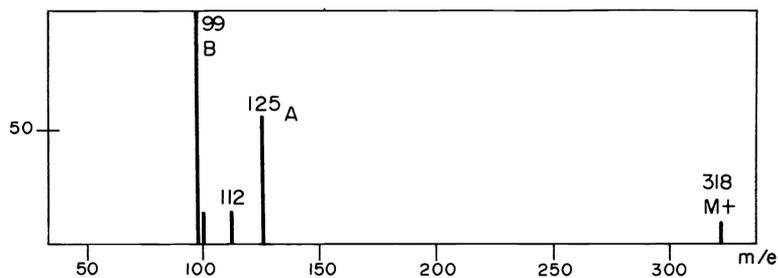


Fig. 1

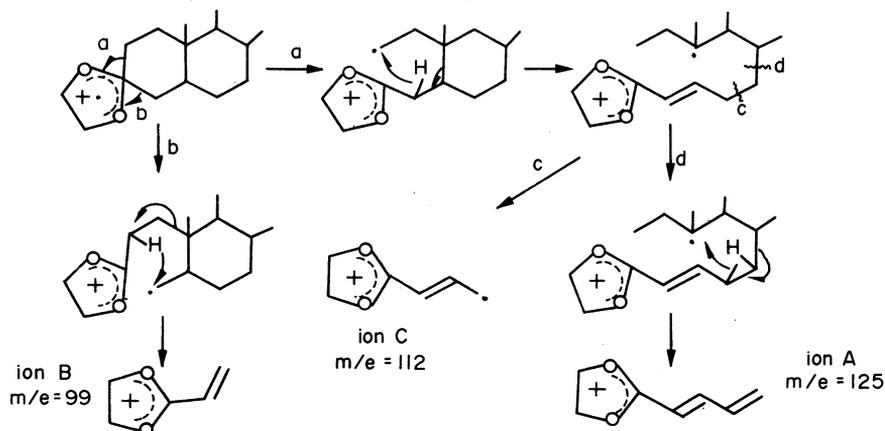
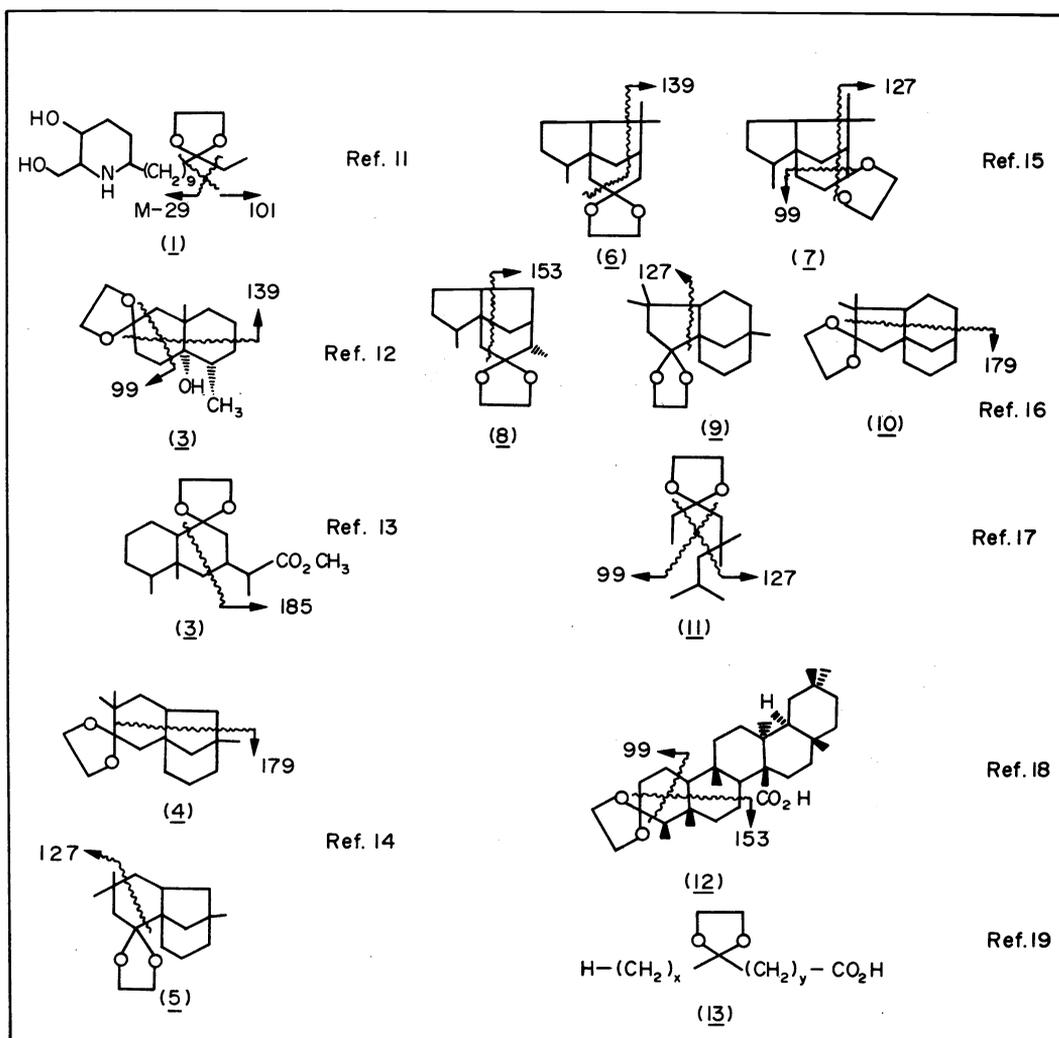


Fig. 2

The formation of the ion  $m/e = 112$  is much more complex than anticipated (Ref. 7). The use of derivatives has expanded with the growth of coupled GC-MS and it has also been extended to olefins (Ref. 8), polyols (Ref. 9) and primary alcohols (Ref. 10). However, if silyl derivatives have an indisputable superiority in the analytical field, it seems that the ethylene ketals are more appropriate for structure determinations as is shown by the examples in Table I.

TABLE I



In spite of these results some minor peaks still remain unexplained. Of course, the obscure points would have been ignored if it had not been observed that at low voltage the intensity of certain peaks increased tremendously and that the general appearance of the spectrum was often considerably modified. A re-investigation of the mechanism thus became necessary.

## REACTION PATHWAY

Numerous experimental data, some of which will be presented later are in favour of a non-concerted mechanism for the fragmentation of ethylene ketals. In particular, the scrambling of hydrogens in positions 2 and 6 to the functional group implies the existence of several intermediates. The molecular ion rearranges (Ref. 20) by forming radical ions identical to those produced by the direct bond cleavage. A detailed study of the reaction pathway shows that depending on the compounds studied and the nature and position of the substituents, these primary intermediates have quite different fates.

Cyclohexanone ethylene ketal (14)

Fig. 3 represents the successive steps in the fragmentation of ethylene ketal of cyclohexanone.

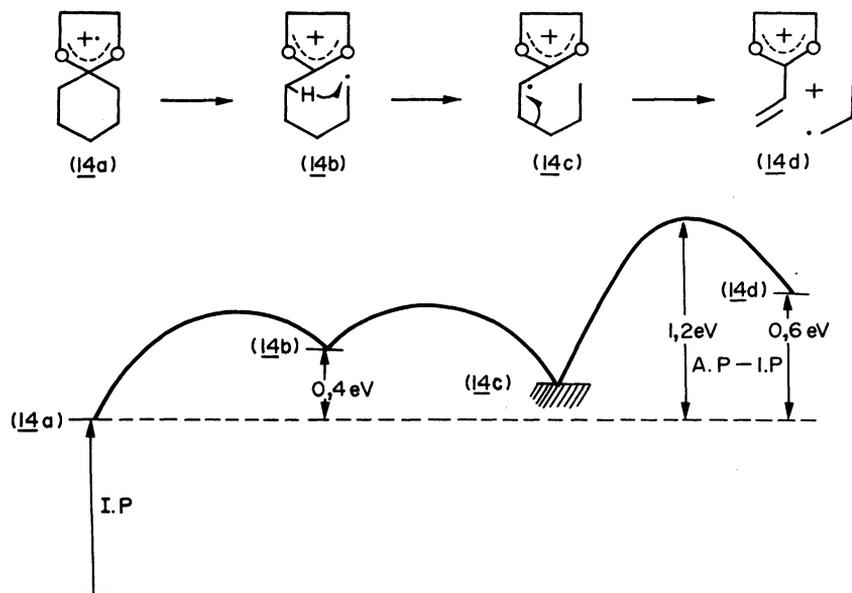


Fig. 3

The energy necessary for the first cleavage and the  $\Delta H_f$  of the first open ion (14b) were determined by measuring the difference between the A.P. and I.P. for the ions  $m/e = 101$  and  $m/e = 115$ , arising from the ethylene ketal of 3-hexanone. The observed difference of 0.40 eV gives a value for the  $\Delta H_f$  (14b) of 5.86 eV (Note a). The isomerisation of (14b) leads to a more stable ion (14c). The minimal energy drop is 0.13 eV. This corresponds to the change from a primary to a secondary radical where the electron is delocalised. The energy of the final state (6.90 eV) has been calculated. It is the sum of the  $\Delta H_f$  of the ion (14d) ( $m/e = 99$ ) and the  $\Delta H_f$  of the propyl radical (Ref. 21). The  $\Delta H_f$  of the  $m/e = 99$  ion was determined by measuring the A.P. of the M-1 ion (15b) of the ethylene ketal of acrolein (15) (Fig. 4)

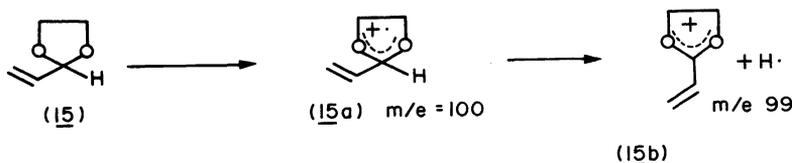


Fig. 4

The relatively large difference between A.P. (14d) and I.P. (14a) is indicative of the existence of a strong kinetic shift (0.6 eV), the origin of which is associated with the formation of the ion  $m/e = 113$  by a mechanism that will be explained later. The A.P. of this ion is lower than that of (14d)  $m/e = 99$  (Ref. 22).

Note a. This value could be accurately determined by photoelectron spectroscopy and by a calculation of the kinetic shift (Ref. 22).

### Influence of substituents

Substituents can modify the relative positions of these energy levels. Thus an OH-group or a gem-dimethyl at position 4 leads to a final state with lower energy than of the intermediate open ions on account of the stability of the radical formed. In the case of ethylene ketal of 2,2'-dimethylcyclohexanone the first step requires very little energy. A tertiary radical is actually formed from the first cleavage (Fig. 5).

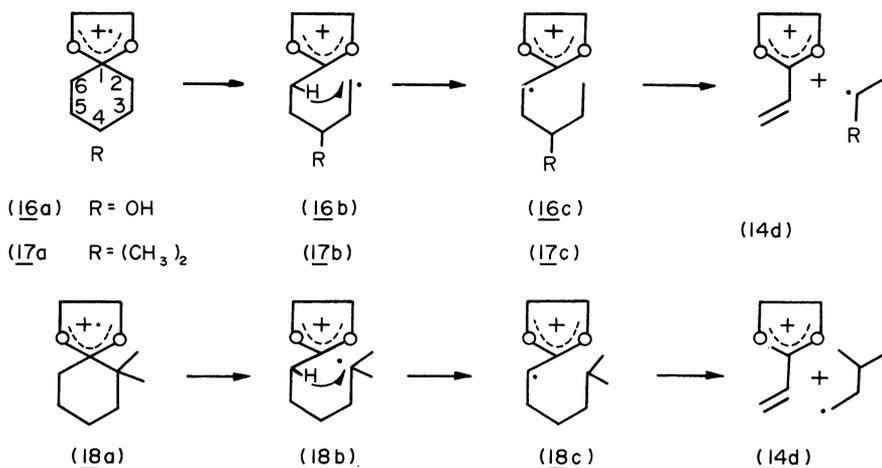


Fig. 5

The observed results may be explained on the basis of the proximity of the energy levels and their relative positions.

### REARRANGEMENT OF MEDIUM RINGS

The spectrum of cyclohexanone ethylene ketal exhibits not only the expected peak at  $m/e = 99$  (ion A) but also a peak at  $m/e = 113$  (ion B). The relative ratio of their abundances (denoted hereafter as (99)/(113)) is observed to decrease as the voltage is lowered. The formation of ion B is probably due to the fragmentation of a rearranged ion (Ref. 23). The peak  $m/e = 113$  is shifted respectively to  $m/e = 127$  and  $m/e = 130$  in the spectrum of derivatives (19a) and (20a) which have a CH<sub>3</sub> and CD<sub>3</sub> in position 4 (Fig. 6). These data confirm the existence of a new rearrangement (Ref. 24) which is different from the classical mechanism and seems to be very widespread. To our knowledge this rearrangement has been mentioned only by Seibl (Ref. 25) in the case of cyclohexanone, but involves both ring contraction and enlargement. It accounts for the intriguing difference in the spectra of medium-ring and large ring ketones and ketals at high and low voltage (Ref. 27).

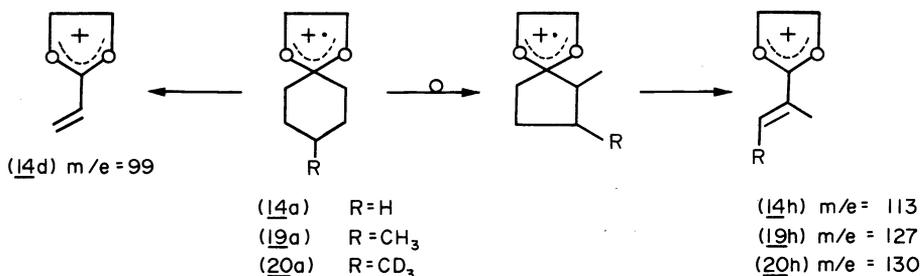


Fig. 6

## Mechanism of the rearrangement

The mechanism of this new rearrangement was studied with deuterated and  $^{13}\text{C}$ -labelled compounds. Fragmentation of the ethylene ketal of cyclohexanone (14a) starts with  $\text{C}_1\text{-C}_2$  cleavage  $\alpha$  to the heteroatom. Transfer of a  $\text{C}_3$ -hydrogen and homolysis of the  $\text{C}_4\text{-C}_5$  bond results in (14d),  $m/e$  99 (classical mechanism,<sup>6</sup> see above).

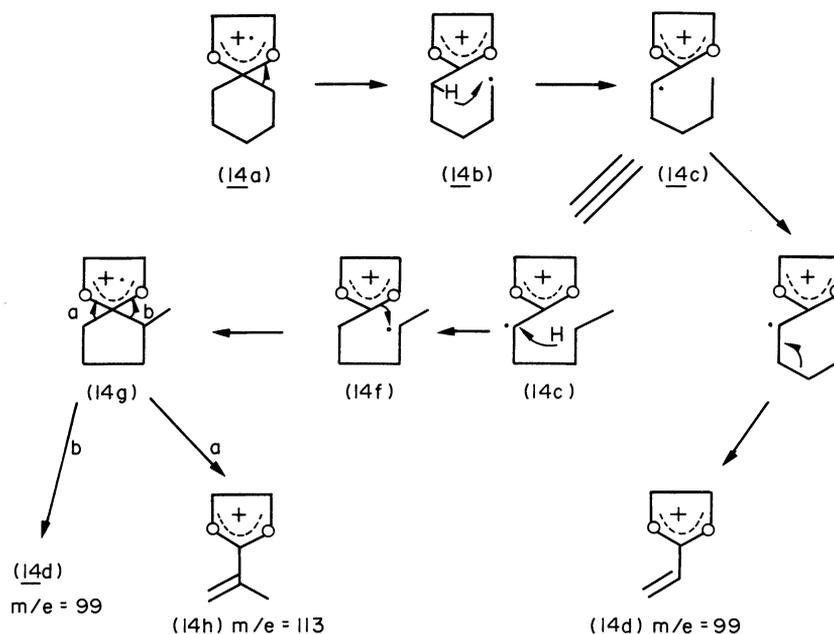


Fig. 7

The new rearrangement competes at low electron energies. A hydrogen from  $\text{C}_3$  is transferred to  $\text{C}_6$  giving (14f) which recycles to a rearranged molecular ion (14g). Cleavage by the classical mechanism forms ion A (14d)  $m/e$  99 and ion B (14h),  $m/e$  113. The spectrum of the tetradeuterated (21a) confirms the first H-transfer (Fig. 8). Besides the peak at  $m/e$  100 (classical mechanism), peaks at  $m/e$  99 and 116 are found, whose intensities increase at low electron voltage. The second hydrogen transfer is derived from the spectrum of the compound deuterated at  $\text{C}_3$  (Fig. 9). At 70 eV the only observed peaks are found at  $m/e$  99 and  $m/e$  101 (ions (22b) and (22c)) while at 10 eV new in tense peaks at  $m/e$  100 (ion (22d)) and  $m/e$  113 (ion (22e)) are observed. The reverse rearrangement has also been observed. The spectrum of the 2-methyl- $\text{d}_3$ -cyclopentanone dioxolane (23a) exhibits a peak at  $m/e$  100 with its decreasing intensity at low voltage. This peak is explained by the proposed rearrangement (Fig. 10).

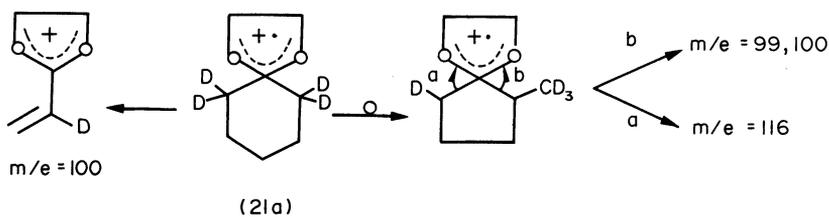


Fig. 8

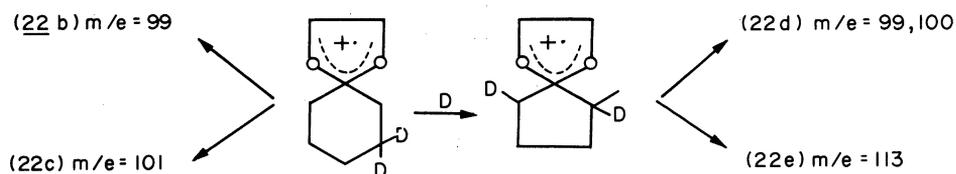


Fig. 9

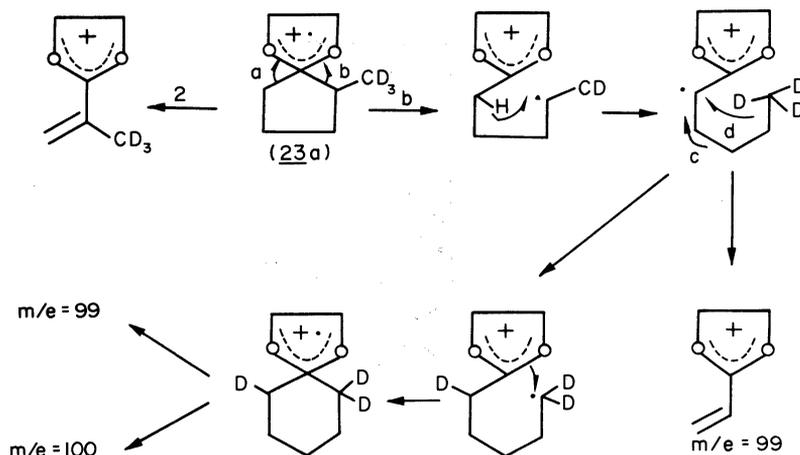


Fig. 10

#### Successive rearrangements and hydrogen transfers

The spectrum of the ethylene ketal of 2-methyl- $d_3$ -cyclopentanone (23a) exhibits peaks at  $m/e = 114$  and  $m/e = 115$  in addition to the expected peak  $m/e = 116$ . The same peaks are observed in the spectrum of ethylene ketal of tetradeuterated cyclohexanone (21a). The corresponding ions are formed by successive rearrangements and by specific exchanges of hydrogen (or deuterium) atoms and not by a purely random scrambling or by competing mechanisms. The absence of hydrogen exchanges in compounds (24) and (25) excludes the hypothesis of a random scrambling and confirms that these exchanges are linked to the existence of the described open forms. The decreasing intensities of the  $m/e = 116$ , 115 and 114 peaks confirm the successive character of isomerisations and exclude any thermodynamic equilibrium between various isomers of the molecular ion prior to fragmentation (Fig. 11).



The spectrum of 2-methylcyclopentanone ethylene ketal, labelled with carbon 13, confirms this hypothesis and enables to specify the respective amounts of each of the rearranged forms. At high voltage the spectrum shows only peaks at  $m/e = 99$  and  $m/e = 114$ , whereas peaks  $m/e = 100$  and  $m/e = 113$  appear at low voltage (Fig. 12). The determination of the quantity of each cyclised form calculated from the intensity of various peaks proves the importance of the rearranged forms at low voltage.

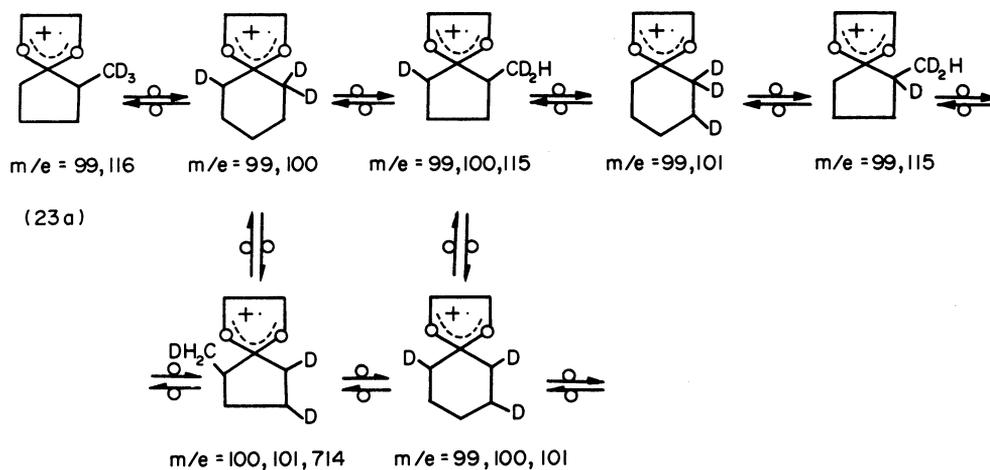


Fig. 11

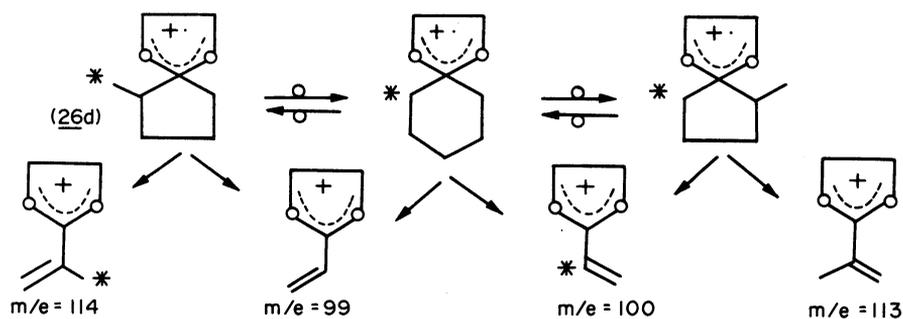


Fig. 12

## REARRANGEMENT AND REACTION PATHWAY

The previous data indicate that there is competition between the rearrangement and the direct fragmentation (see the effect of the decreasing voltage) and that this competition takes place on one of the intermediate open ions. Experimental studies also indicate that the proportions of the rearranged forms become smaller with the increasing stability of the final state of the direct fragmentation. Thus the more stable the radical formed, the greater is the amount of the initial non-rearranged form (Table 2).

TABLE 2  
% Initial non-rearranged form.

45%	63%	OH >95%
40%	60%	90%

The effect of stability applies also to the ion formed. The extent of hydrogen exchange is quite significant in the compound (27) (ratio (100)/(99)) but becomes less important in the compound (28) (ratio (128)/(127)). This seems to suggest that the competition again takes place in the open form (Fig. 13).

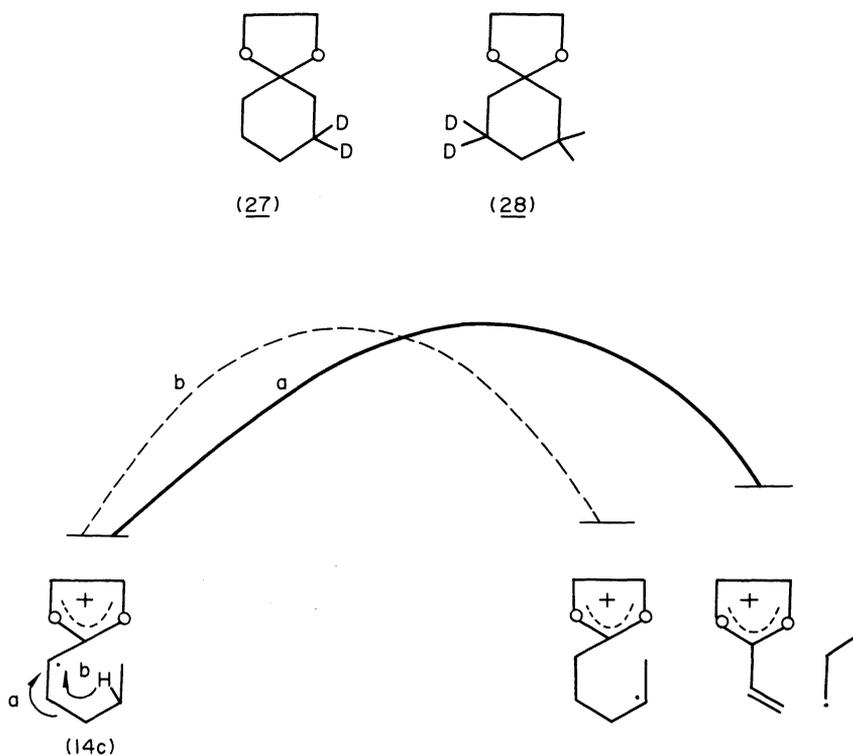


Fig. 13

In the case of cyclohexanone ethylene ketal the two transition states directing the rearrangement are energetically very close. Since the frequency factor of the simple cleavage is greater than that of the hydrogen transfer, the rearrangement is favoured at low voltage. If the energy level of the final state is lowered, for example by introduction of a hydroxyl group in position 4, then the direct fragmentation is preferred and the rearrangement is practically non-existent (Table 2).

#### SOME APPLICATIONS

The spectrum of the ethylene ketal of methyl jasmonate (29a) is a very good example of this rearrangement (Ref. 24) (Fig. 14 and 15).

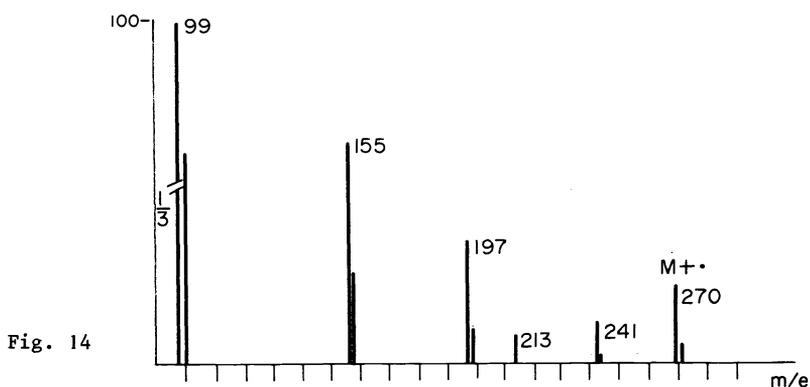
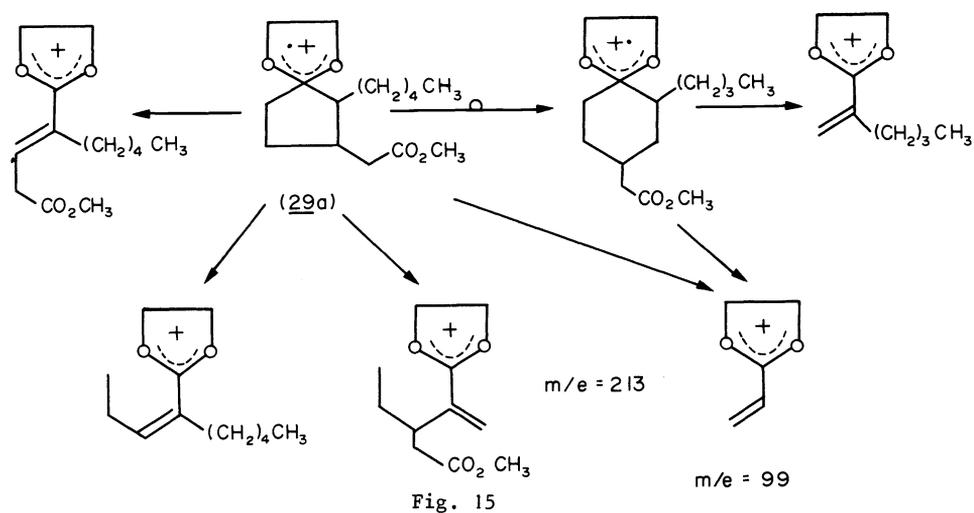


Fig. 14



Some weak but unambiguous peaks which are observed in the spectra of steroid ketals (Figs. 16a and 16b) can be explained on the basis of ring contraction .

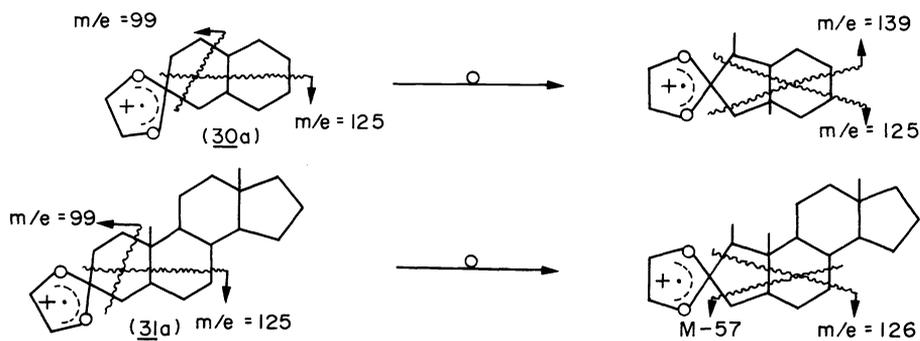


Fig. 16 a

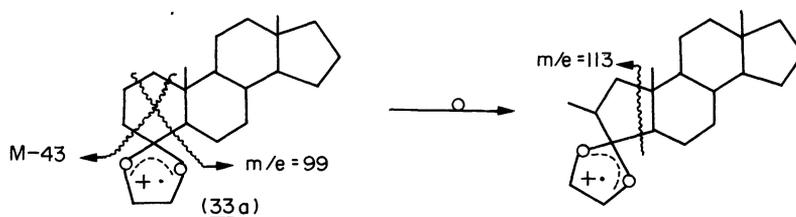
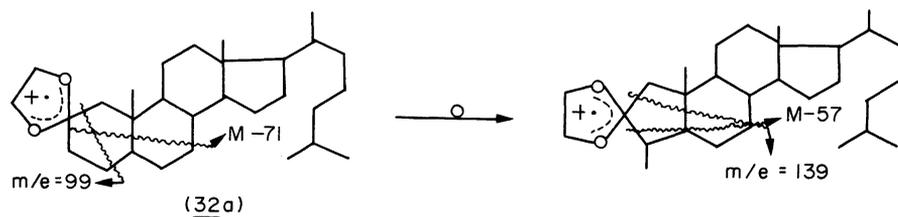


Fig. 16 b

Although it may be comparatively weak the rearrangement with ring expansion may also be observed (Fig. 17)

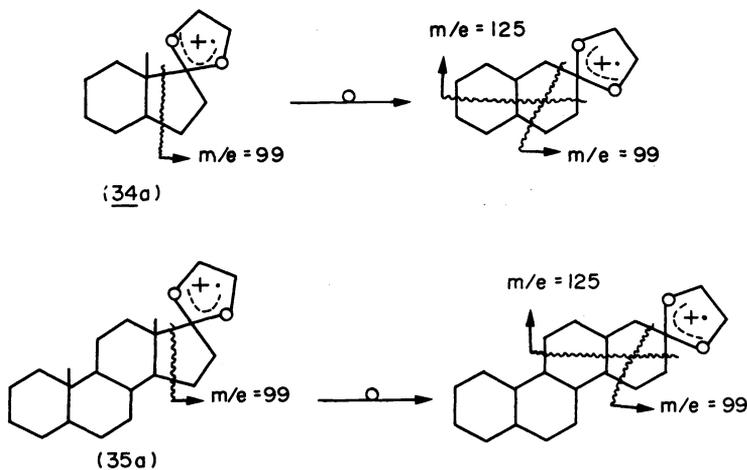


Fig. 17

The rearrangement may generally be observed in ketones, alcohols, ethers and cyclic amines . An example is illustrated in Fig. 18 .

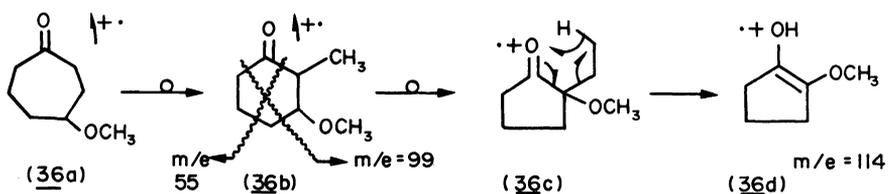


Fig. 18

REARRANGEMENT OF MEDIUM AND LARGE RINGS

The rearrangement described above is general and does not depend on the nature of the functional group or on the size of the ring . Thus the ketals of  $\alpha$ -alkyl cyclopentanones form not only 6-membered but also 7-membered rings . For example, if  $R = CD_3$  the peak at  $m/e = 116$  is observed (Fig. 19) .

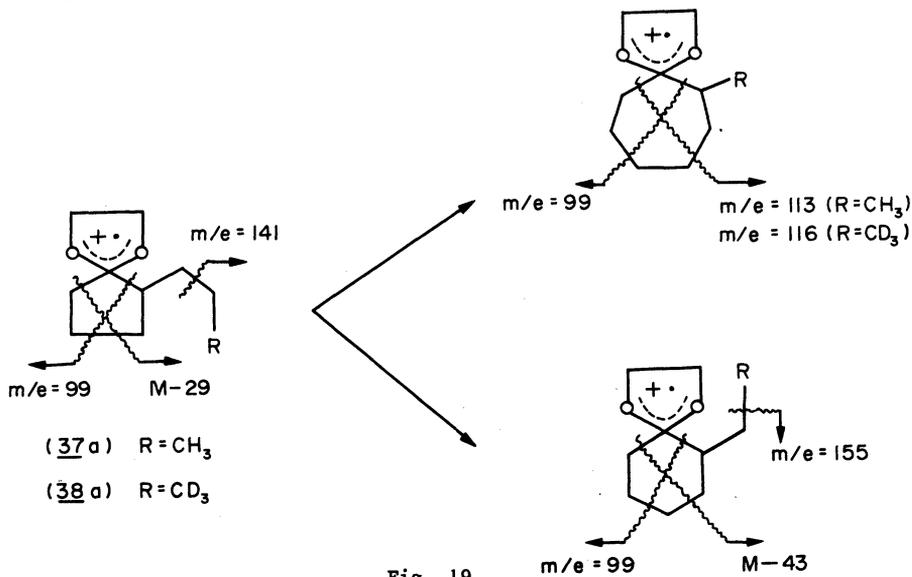


Fig. 19

A dioxolane derived from a large ring ketone undergoes the inverse rearrangement with ring contraction. A detailed study carried out on 7-membered and 8-membered rings suggests that this process is identical to that already studied. However, an important factor which directs the rearrangement is the stability of the ring and priority is given to the formation of the 6-membered ring (Fig. 20).

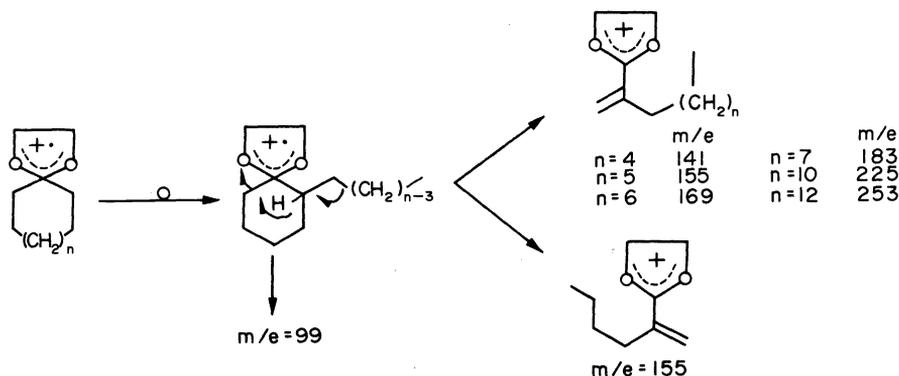


Fig. 20

This may explain why the low voltage spectrum of cycloundecanone exhibits two strong peaks at  $m/e = 155$  and  $m/e = 169$  (Fig. 21).

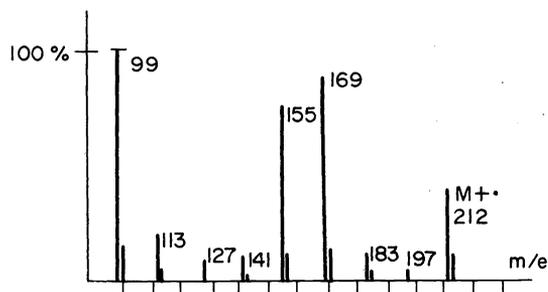


Fig. 21 . Spectrum of ethylene ketal of cycloundecanone (at 10 eV)

#### Application to the cyclanones

Although the high voltage spectrum of cyclanones is very complex, the low voltage spectrum is simpler (Fig. 22).

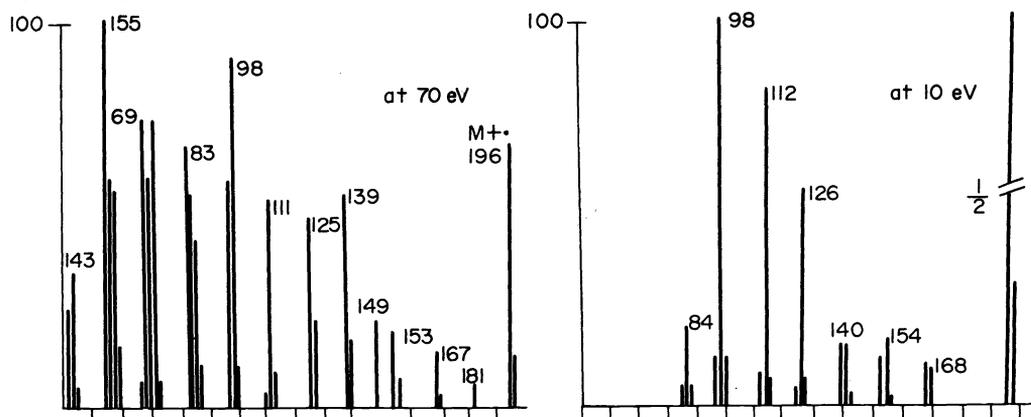


Fig. 22 Spectrum of 2-methylcyclododecanone

A mechanism similar to the one which was established for the ethylene ketals allows for the explanation of the observed peaks. This mechanism has been confirmed by deuteration. The example of cyclooctanone illustrates this type of fragmentation (Fig. 23).

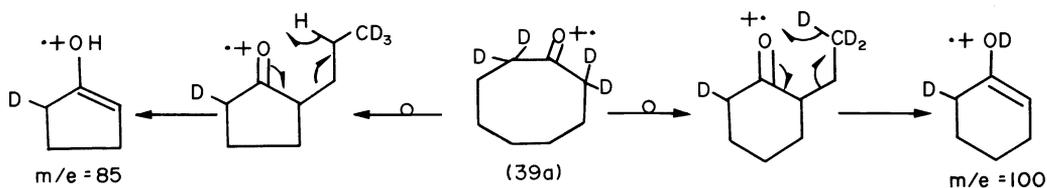


Fig. 23

Although formal evidence is not yet available the rearrangement can explain the fragmentation of 1-methyl-2-decalone without contradicting published results (Ref. 28) (Fig. 24).

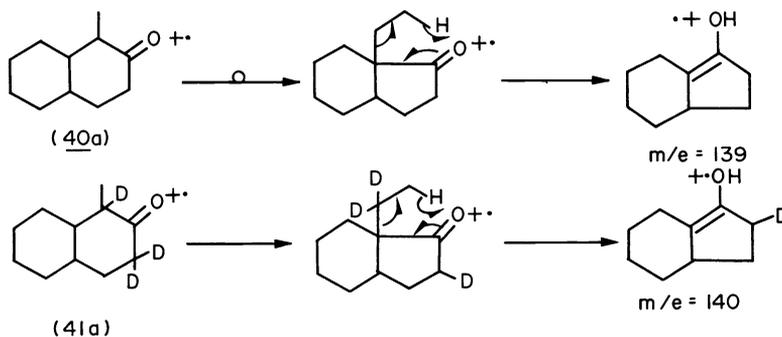
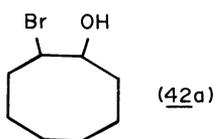


Fig. 24

The reaction of *cis*-bromohydrin (42a) with silver carbonate deposited on Celite gives a



mixture which contains an ethylenic alcohol A in addition to the expected carbonyl derivatives. Under the same condition *trans*-bromohydrin yields an isomeric ethylenic alcohol B (Note b). The localisation of deuterium and hence the determination of the structure of alcohols A and B is possible by mass spectrometry. Once again the spectrum is much simplified at low voltage. The ring contraction results essentially in the ion-radical of 2-ethylcyclohexanone (Fig. 25).

Note b. The reduction of these alcohols with deuterium in the presence of Wilkinson's catalyst, followed by oxidation, gives the deuteriated cyclo-octanones (melting point,  $^{13}\text{C}$  N.M.R., Ref. 29).

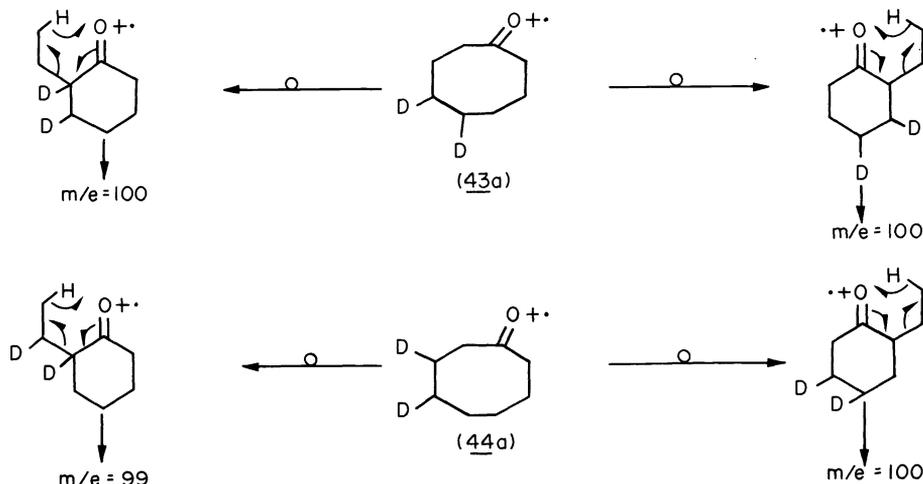


Fig. 25

The most intense peak can be explained by a McLafferty fragmentation which forms ions  $m/e = 100$  from the structure (43a) and the peaks  $m/e = 99$  and  $m/e = 100$  of equal intensity from the structure (44a).

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