Intramolecular Hydrogen Transfer in Mass Spectra. II. The McLafferty Rearrangement and Related Reactions

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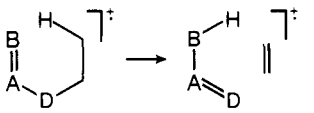
I. Introduction

Part I of this review[1] covered the important intramolecular hydrogen rearrangements undergone by aliphatic hydrocarbons and aromatic compounds on electron impact. This second part will thus focus on one single type of hydrogen rearrangement which has become known as the McLafferty rearrangement. The literature has been covered through 1972 for this review.

We define the McLafferty rearrangement as the transfer of a *gamma* hydrogen to a double-bonded atom through a six-membered transition state, with *beta* bond cleavage (eq 1). We recognize that, on the one hand,



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others have applied the name to a wider class of reactions, and on the other there is objection to the introduction of name reactions into the literature of mass spectrometry. It seems to us that the nomenclature is so widely used that it cannot be ignored, and that, properly defined, it is convenient enough that it need not be resisted. It should be pointed out, however, that, like the Friedel–Crafts reaction which was first reported by Wurtz, the reaction was not first observed by McLafferty. The earliest reference to a rearrangement fitting the definition is found in 1952 in a study of rearrangements in aliphatic acids.[2] The analogy to the photochemical behavior of ketones was noted in 1954.[3] McLafferty first recognized the importance of cyclic transition states in general in his early study of decompositions[4] and described the mechanism of the process in more detail later.[5] By this time other observations of the reaction had been published.[6] The cyclic transition state was postulated independently by Manning.[7]

This type of rearrangement has been carefully reviewed by Meyerson and McCollum,[8] and more recently a concise review has also appeared.[9] Many examples of the McLafferty rearrangement are cited in a review of the mass spectrometry of carbonyl compounds,[10] as well as in one of the other works cited.[9] This review will therefore only summarize information that is readily available in these sources and will discuss in detail developments of general importance since they were written.

II. Mechanistic Aspects of the Rearrangement of Carbonyl Compounds

A. Structure of the Products

The McLafferty rearrangement in carbonyl compounds may be represented by eq 2. The evidence leading to this formulation of the reaction has been ably summarized,[8] and it will be sufficient here to mention the main arguments adduced in its favor.

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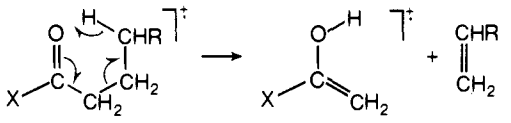

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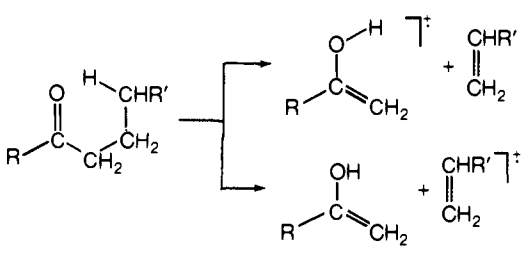
The evidence for retention of the original $XCOCH_2$ group as one entity in the ionized product is supplied from studies of labeled molecules[11] and from molecules with α-branching, where the α branch is retained in the ionized product. The migration of a hydrogen atom from the γ carbon atom in a specific fashion is supported by studies of various deuterated ketones[12-21] and esters[20-23] studed at 70 eV. In further support of the specificity of rearrangement in ketones and esters, the rearrangement is absent or of low intensity in both ketones[24] and esters[25] which do not contain any γ-hydrogen atoms. Aliphatic aldehydes also undergo specific γ-hydrogen transfer in the formation of the ionized enolic product.[26-28]

It was perhaps fortunate that the early studies of the specificity of rearrangement were carried out at 70 eV, since more recent work has shown that scrambling of the hydrogen atoms in alkyl chains occurs at low ionizing voltages or in ions of long lifetime decomposing in field-free regions.[29] Similar scrambling could account for the lower specificity of γ-hydrogen transfer observed in non-carbonyl McLafferty rearrangements (section III), but it is difficult to distinguish between reactions occurring through transition states of different ring sizes and specific hydrogen transfer occurring after partial hydrogen scrambling.

It has been previously noted[9] that the observed specificity for migration of the γ hydrogen is in accord with steric requirements for overlap with the highly directional orbital of the unpaired electron on oxygen. This requirement leads to some conclusions about the stereochemistry of the reaction which will be discussed in section II.D.

Evidence for the enolic structure of the product ion has been adduced from ionization potential measurements.[8] These showed that the product ion of the rearrangement of methyl stearate had an ionization potential of around 9.1 eV, compared with 10.5 eV for the ionization potential of methyl acetate and 8.6 eV calculated for the enol form. In a combination of photoionization studies and thermochemical calculations it was shown that the ion $C_3H_6O^+$ derived from 2-pentanone did not have the same heat of formation as the molecular ions of acetone, 1,2-propene oxide, allyl alcohol, or methyl vinyl ether, suggesting that it must have the structure of the one remaining isomer, *i*.e., the enol form of acetone.[30] In a critical review of this and other work, Bentley and Johnstone conclude that "it is still possible that the product of the McLafferty rearrangement of 2-pentanone does not have an analog that exists as a ground-state molecule, but in terms of ionized ground-state structures, the enol represents probably the best form."[31]

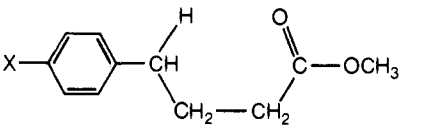
It may be noted in passing that the low ionization potential of the enolic product ion is responsible both for the importance of the reaction and for the fact that charge normally resides on this fragment (eq 3).



(3)

(4)

The alternative process in which charge resides on the olefin fragment (eq 4) has been called the "reverse McLafferty rearrangement,"[32] but this name is somewhat misleading and either "complementary McLafferty rearrangement"[33] or "McLafferty rearrangement with charged olefinic product" is to be preferred. The authors of this review favor the latter term as being free from ambiguity. In any event, this process is favored when the olefinic portion has a lower ionization potential than the enolic portion.[8] An example of this effect may be seen from a study of variously substituted methyl γ-phenylbutyrates (1),[34] which rearranged to give predominantly the enolic ion when the substituent X was CN, but gave largely the olefinic ion when the substituent X was OCH_3, capable of stabilizing the olefinic ion and thus lowering its ionization potential.



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Other evidence for the enolic structure of the product ion of the normal McLafferty rearrangement comes from studies of the reactions of this ion. These will be discussed also in section II.F, but it may be mentioned that the decompositions of the product ions from menthone (**2a**) and the isomeric 2-isopropyl-3-methylcyclohexanone (**2b**) are in complete accord with their formulations as enol ions (Scheme I).[9] Similarly, the fragmentation of the

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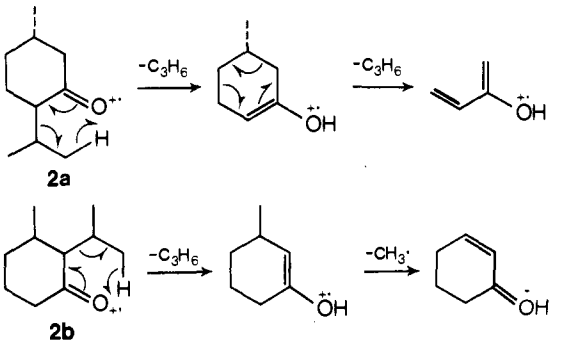
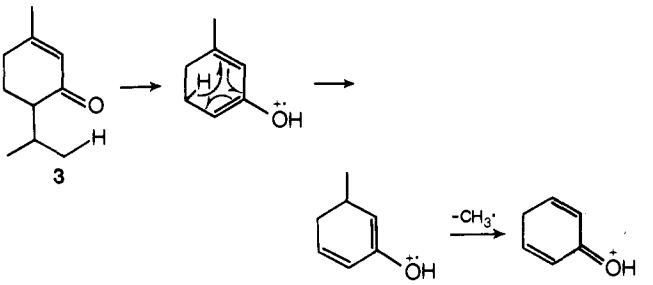


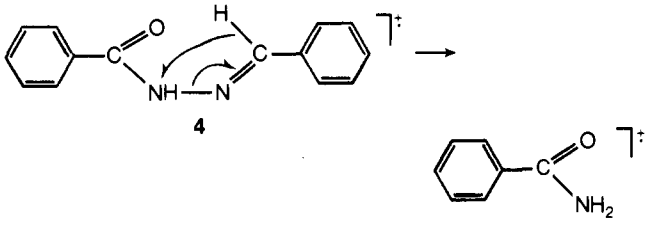
product ion from piperitone (**3**) is in accord with an enolic formulation.[35]



Further support of the enol formulation has come from elegant studies of the ion–molecule reactivity of the normal McLafferty product ion from 2-hexanone by ion cyclotron resonance (icr) spectroscopy.[36] In this study it was shown that the McLafferty product ion had the same reactivity in seven different ion–molecule reactions as an enol ion generated from 1-methylcyclobutanol, and differed from the keto ion of acetone in these same systems. Even this result is not absolutely conclusive,[28] but

the weight of evidence is strongly in favor of the traditional formulation of the reaction as a δ-hydrogen transfer to form an olefin and an ionized enol. Further evidence for the enolic structure of the product comes from study of decompositions of the product ion (section II.F).

It should be noted carefully that this conclusion applies with full force only to the rearrangements of alkyl-substituted ketones and esters and cannot be generalized to all "McLafferty rearrangements." As a specific example of the dangers inherent in such generalizations, it has been shown[37] that the acyl hydrazone **4** rearranges to give the amide ion (*i.e.*, a keto ion) rather than the isomeric enol, showing in this admittedly specialized case that rearrangement does not always give the enol form of the product ion.



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B. Concertedness of the Reaction

In principle the McLafferty rearrangement could proceed either in a concerted manner, with simultaneous hydrogen transfer and β cleavage, or in a stepwise fashion with initial hydrogen transfer being followed by β cleavage. There is now a convincing body of evidence to indicate that the reaction, in fact, occurs *via* a stepwise pathway. Thus a study of the metastable peaks due to loss of ethylene from $CH_3CH_2CH_2COOD$ showed the expected peak for loss of C_2H_4 and also a substantial peak for loss of C_2H_3D, which can be explained by the stepwise process of Scheme II.[38,39] In the more rapid fragmentations occurring in the source, however, loss of C_2H_3D was not observed, indicating that under these conditions the β cleavage must be occurring faster than rotation of the $-C(OH)OD^+$ group and back-transfer of a hydrogen atom of the δ-carbon atom.[39]

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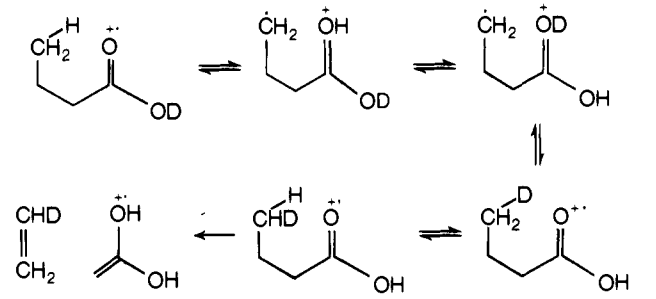
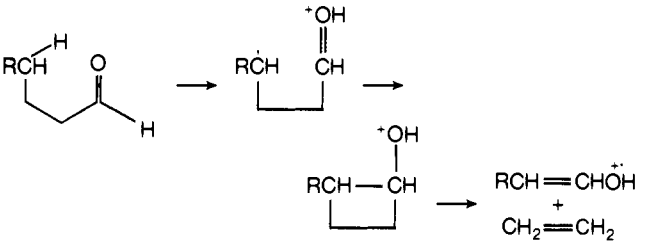


A stepwise pathway is also suggested by the observation that the loss of C_2H_4 from the molecular ion of aliphatic aldehydes involves largely the loss of the δ- and β-methylenes.[26-28] In analogy with the photochemical pathway (see section V.E) the mechanism of Scheme III was suggested, involving an initial stepwise δ-hydrogen transfer, followed by cyclobutanol formation and loss of ethylene.[26,28] In support of this proposal is the fact that the postulated cyclobutanol intermediate has a similar fragmentation pattern to the aldehyde.

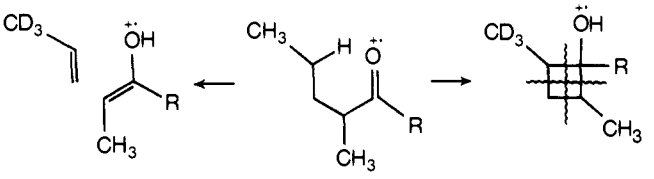
The formation of such cyclobutanol intermediates appears to be a sensitive function of the structure of the carbonyl compound, and their formation in α-branched

SCHEME III

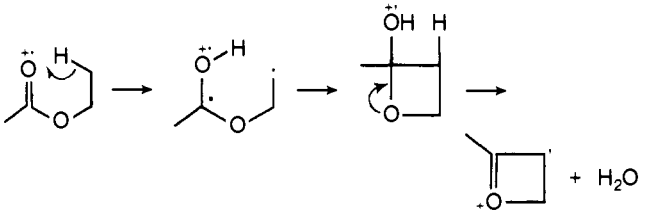


aldehydes and ketones was excluded by a neat experiment with a labeled α-methyl aldehyde and ketone[40] (Scheme IV). The symmetrical cyclobutanol intermediate, if formed, would fragment to yield *both* $(M - C_3H_3D_3)^+$ and $(M - C_3H_6)^+$ ions. In the event, only the former ion was observed, excluding the cyclobutanol intermediate in this case. A similar study of butyraldehyde-*4,4,4-d*$_3$ indicated that no cyclobutanol formation occurred in this case either. On the other hand, the intermediacy of a cyclobutanol intermediate has been invoked to explain the loss of water from ethyl acetate (Scheme V).[41] A similar four-membered ring can account for the loss of formaldehyde from 1-butyl esters and acetaldehyde from 2-butyl esters,[8] although not without modification, for the seemingly similar loss of formaldehyde from neopentyl esters.[41a]

SCHEME IV

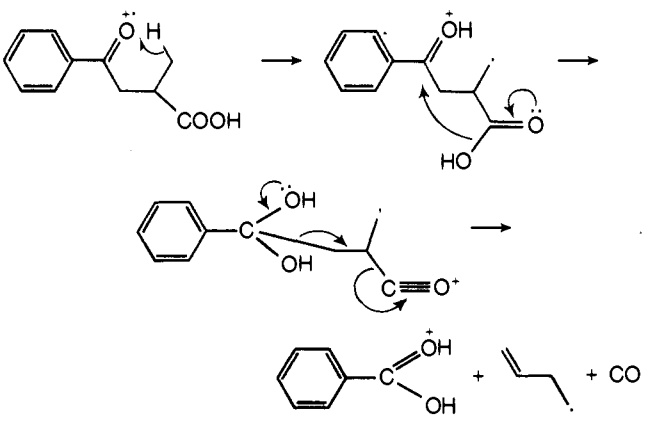


SCHEME V



Acceptance of a stepwise mechanism for hydrogen transfer makes it possible to rationalize several other mass spectrometric fragmentations. The rearrangement of β-aroyl-α-methylpropionic acids to give an ion $[Ar\text{-}COOH_2]^+$ has been proposed to proceed by the stepwise pathway of Scheme VI,[42] while the ϵ cleavage of Δ^2-en-

SCHEME VI



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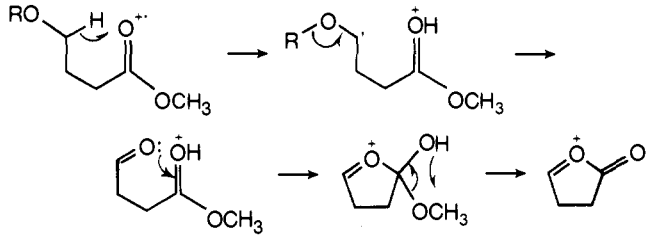


ones and -enoates[43] and of 4-alkoxy butyrates[44] may also be explained by an initial stepwise transfer of a γ hydrogen to the carbonyl group (Scheme VII).

Theoretical studies of the problem of concertedness in the McLafferty rearrangement will be discussed in section II.G.

C. Structural Factors Affecting the Rearrangement

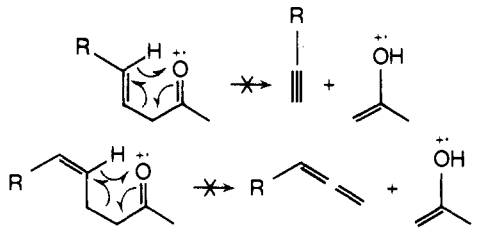
In the next three sections we will discuss in turn some of the structural, steric, and electronic factors that influence the McLafferty rearrangement. Such a division is of course quite arbitrary since the three factors are closely interrelated, but some division was necessary to clarify the mass of work that has been done on this subject.

1. Product Stability

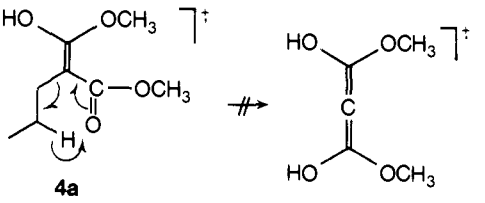
The stability of the product ion and molecule from the rearrangement will naturally have considerable effects on the nature of the rearrangement, particularly if the transition state resembles the products rather than the reactants. These effects are primarily twofold: the suppression of rearrangement when a highly strained olefin would result, and the operation of a McLafferty rearrangement with charged olefinic product when the latter is particularly stable.

An example of the suppression of the rearrangement is the observation that rearrangement was not observed in many unsaturated carbonyl compounds which would require the elimination of an acetylene or an allene (Scheme VIII)[9,45-48] (although *m/e* 94 does appear in

SCHEME VIII



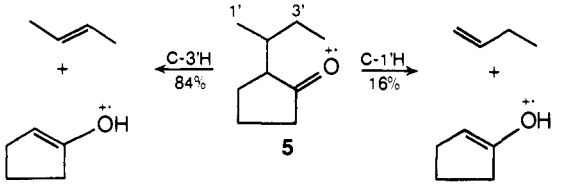
the spectrum of vinyl phenyl ether[4]). However, in these cases it is difficult to separate the effects of product stability from the effect of the strong bond between the γ hydrogen and a vinylic carbon, and it is entirely possible that the failure of the reaction to go is caused largely by the latter factor.[48a] The failure of certain fluoro ketones to rearrange has been attributed to a strengthening of the C–H(γ) bond (section II.D), and it has been shown that the formation of allenic products *per se* is no bar to rearrangement (section III.A). On the other hand, the enolic ion **4a** fails to undergo rearrangement as indicated,[48b] so the formation of an allenic product is clearly sufficient to tip the balance against rearrangement in some cases. Normal rearrangement was not observed in various bridgehead acetone derivatives where the olefin product



4a

would be appreciably strained.[49] Interestingly enough, ions at (M − 58)$\cdot^+$, corresponding to the McLafferty rearrangement with a charged olefinic product, were observed in the spectra of these compounds. In view of the lack of data on the ionization potentials of strained olefins, it is not possible to state with certainty whether these ions have the olefin structure or some other structure, or indeed whether they are formed by this route.

Since terminal olefins are less stable than their nonterminal isomers, it might be expected that their formation would be less likely. Unfortunately, it has not proved possible to distinguish this effect from other possible effects such as the energetically more favored removal of hydrogen from a secondary as compared to a primary site and conformational factors in the reactant ion. In the case of 2-sec-butylcyclopentanone (**5**), for example, all these factors favored predominant (84%) hydrogen transfer from the 3′ position.[50,51]



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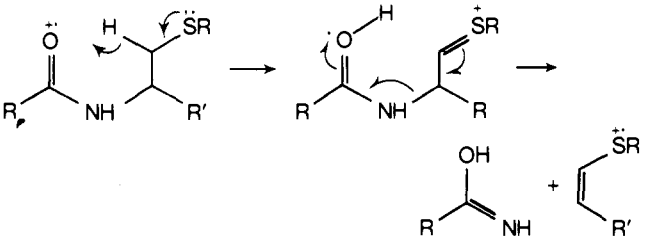
If the ionization potential of the olefin fragment is below that of the enol, the McLafferty rearrangement with charge retention on the olefin predominates, as discussed in section II.A. An example of this reaction is found in the fragmentation of some derivatives of cystine and lanthionine, where the sulfur atom stabilizes the ionized olefin (Scheme IX).[32] Similarly, the rearrangement

SCHEME IX

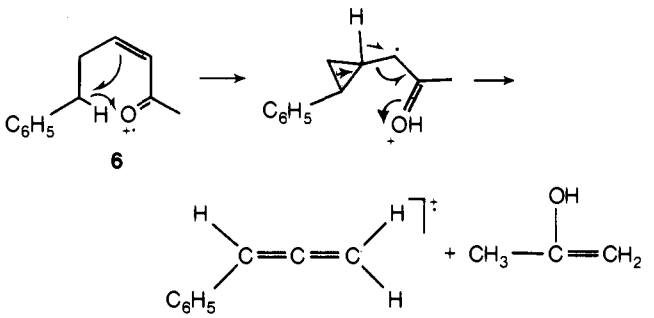


of several unsaturated carbonyl compounds was shown to yield the ionized olefin product in cases where the double bond was initially in the δ,ϵ position or could migrate to that position preceding rearrangement.[33,52] In the case of 6-phenylhex-3-en-2-one (6) an interesting ion at (M − 58)$^+$ was suggested on the basis of labeling evidence to arise by the pathway of Scheme X.[52] This pathway illustrates both the stepwise nature of the McLafferty rearrangement and also the influence of a phenyl group in directing the fragmentation into a normally unavailable pathway. For additional examples, see Meyerson and Leitch[52a] and references cited therein.

The McLafferty rearrangement with charged olefinic product is a significant reaction in aliphatic aldehydes. In this case, however, it has been shown by deuterium labeling studies that the reaction is not a specific one.[26,28] In hexanal, for example, the ion at *m/e* 56 was shown to arise by transfer of *both* γ and δ hydrogens to the car-

bonyl group, although specific hydrogen transfer after partial hydrogen randomization along the alkyl chain is an alternative possibility.[26]

SCHEME X



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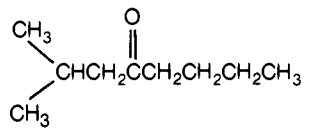
2. *Molecular Size*

As the size of the molecule under investigation is increased, the contribution of the McLafferty rearrangement to the total ionization of the molecule would be expected to decrease, since the opportunities for alternate fragmentations would be correspondingly greater. This effect is illustrated by the spectra of a series of esters, where the per cent of the total ion current carried by the rearrangement ion decreased as the chain length increased.[53]

3. *Nature of the Hydrogen Atom Abstracted*

In molecules where there is a choice between a secondary and a primary hydrogen atom, abstraction of the secondary hydrogen is preferred. Thus in isobutyl *n*-butyl ketone (**7**), abstraction of the secondary hydrogen is pre-



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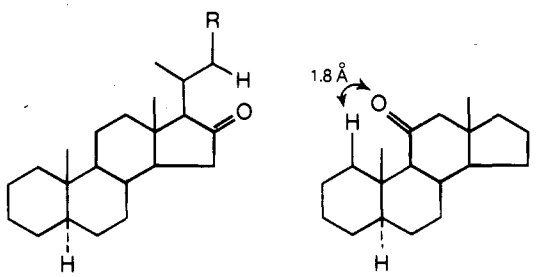
ferred by a factor of about 10:1 over primary hydrogen abstraction.[51] Unfortunately, however, any effect due to differing conformational preferences of the two alkyl chains is difficult to predict. A similar preference for abstraction of a secondary hydrogen atom was noted in the spectrum of 2-sec-butylcyclopentanone (**5**), but in this case both the conformational factor and the differing olefins produced made calculation of the magnitude of the effect impossible.[50] In another substituted cyclopentanone, this time in the steroid series, a similar effect was observed.[54]

Using the definition of an isotope effect for rearrangement reactions as "atoms of deuterium per atom of hydrogen transferred for the (hypothetical) case in which equal numbers of deuterium and hydrogen atoms are available for transfer," the isotope effect for McLafferty rearrangement in methyl butyrate was found to be 0.88,[23] and 0.92 in methyl pentanoate.[21] In aliphatic ketones the effect was close to 1.00, but in 2-propylcyclohexanone it was 0.87.[21] These isotope effects are not changed significantly at low ionizing voltages (a nominal 10 eV).

D. Steric Factors Affecting the Rearrangement

The importance of the interatomic distance between the carbonyl oxygen atom and the γ-hydrogen atom was explored in a definitive series of papers by Djerassi and his coworkers.[55-58] These workers, using examples from the steroid field, found that McLafferty rearrangement did not occur unless the interatomic distance was less than 1.8 Å.[57] Distances greater than this between the two key atoms prevent the rearrangement. Thus rearrangement occurred in 16-keto steroids (**8**),[54] where the γ-hydrogen atom can approach the oxygen to within 1.5 Å, but not in 11-keto (**9**)[55,56] or 15-keto (**10**)[57] steroids, where the in-



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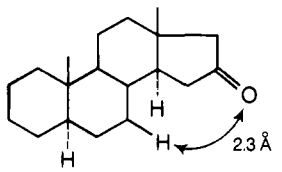

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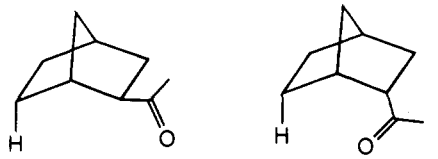
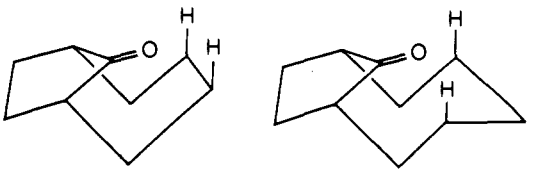
teratomic distance ranges between 1.8 and 2.3 Å. Putative examples where the interatomic distance exceeds the maximum value can be explained by an alternative mechanism.[58,59] In support of these results, the exo isomer of 2-acetylnorbornane (**11**) does not rearrange, while the endo isomer (**12**) does; the relevant distances are 2.2 and 1.6 Å.[60]



11 12

A second stereochemical factor which affects rearrangement is the angle τ between the plane of the carbonyl group and the γ hydrogen. In acyclic molecules this angle can be close to zero, but in certain rigid molecules it can approach 90°. If overlap of the highly directional orbital of the unpaired electron on oxygen is essential for reaction, as has been suggested,[9] then it would be predicted that reaction should not occur for molecules in which τ was constrained to be appreciably greater than zero. In a theoretical study of the McLafferty rearrangement,[61] it was calculated that the activation energy of the rearrangement was increased by about 76 kcal/mol for $\tau = 45°$.

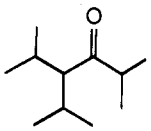
This prediction has been tested experimentally by studies of the bicyclic ketones **13** and **14**.[62] Both these ketones have a carbonyl to γ hydrogen internuclear distance of 1.6 Å, as measured from Dreiding models, but the value of τ is about 80° in **13** and only 50° in **14**. It was found that *only* **14** underwent McLafferty rearrangement, thus confirming the importance of τ as a factor in



13 14

the rearrangement. The fact that **14** was observed to undergo rearrangement in spite of its relatively large τ value is probably due in part to the fact that measurements obtained on the molecule may not reflect in detail the situation obtaining in an excited molecular ion. The observation that even as small a cyclic ketone as cyclononanone undergoes McLafferty rearrangement[63,64] also supports the observation that rearrangement can occur, albeit with reduced ion abundance, when τ is appreciably greater than zero.

A third steric factor influencing rearrangement is that of nonbonded interactions in the molecular ion undergoing fragmentation. A study of the influence of hindered rotation on the rearrangement of 2-*sec*-butylcyclopentanone[49] has already been referred to; unfortunately, it did not prove possible to separate conformational effects from other factors influencing the reaction. Nonbonded interactions have been proposed as the reason for the low (2% of base peak) intensity of the McLafferty rearrangement ion in the highly branched ketone **15**.[65] We



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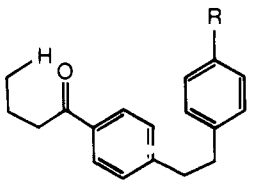
have not found any other clear-cut examples of the effect of nonbonded interactions on the McLafferty rearrangement, and it is suggested that this area could use further study.

E. Electronic Factors Affecting the Rearrangement

1. Substituent Effects

The question of the nature of activation of the carbonyl group for the reaction has been studied chiefly from the viewpoint of the effect of various substituents on the reaction. Thus the fact that the reaction is suppressed in the diphenylethane **16**, R = NH_2, which would be expected to have the greatest electron deficiency on the amino group, while occurring normally in **16**, R = NO_2, has



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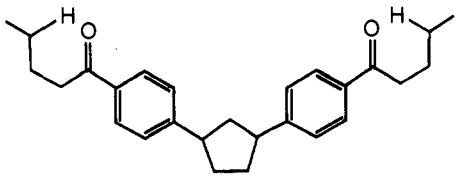
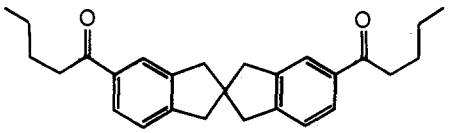


17

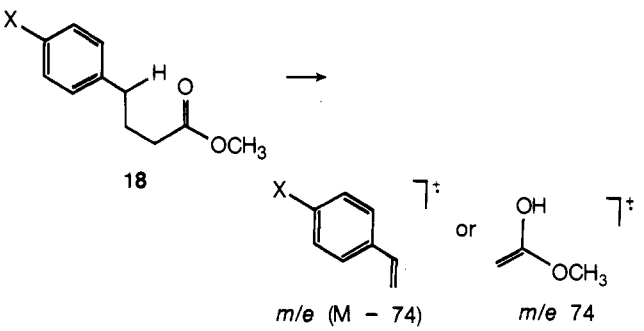
been proposed as evidence that the reaction requires a charge localization on the carbonyl group.[66] Transmission of effects through space has been proposed as the means of localizing excitation in the chromophore with the lower ionization potential.[66a] However, McLafferty rearrangement is observed in two cases where the charge cannot be localized on the carbonyl group. In the first of these, McLafferty rearrangement with charged olefinic product was observed in some ω-phenyl carbonyl compounds at ionizing voltages below the ionization potential of the carbonyl group.[67] In the second study, two consecutive rearrangements were observed in diacylated diphenylcyclopentanes (**17**)[8a] and in the diketone **17a**.[68b]



17a

If it is assumed that a partial charge or radical site is necessary for fragmentation, then both these examples appear to need the transmission of electronic effects through "nominally" saturated carbon chains. An alternative explanation is simply that these molecules fragment in the way that they do because they are able to achieve enough vibrational energy in the correct degrees of freedom for rearrangement to occur.

Substituent-effect studies have been carried out on β-bromoethyl benzoate,[69] methyl phenylbutyrates (**18**),[70,71]

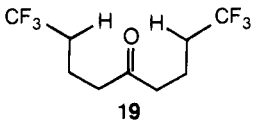


18

m/e (M − 74) *m/e* 74

butyrophenone,[72,73] and *p*-phenylbutyrophenone.[74] In the first case, powerful electron-donating substituents inhibit the McLafferty rearrangement (or else enhance the expulsion of bromine relative to it). In the second case the factors influencing the observed substituent effect are analyzed in some detail in terms of the quasi-equilibrium theory,[75] and it is concluded that substituent effects *per se* are unreliable indicators of the nature of the transition state in a complex reaction such as the McLafferty rearrangement. It was, however, noted that there was only a small substituent effect on the appearance potentials of the $(M - 74)^+$ or *m/e* 74 ions, and this result tends to indicate that there is little or no requirement for charge stabilization at the γ position in the transition state (*i.e.*, this appears to preclude proton or hydride ion transfer).[71] The substituent effects observed in the variously substituted butyrophenones have been discussed briefly,[74] and it was concluded that the qualitative arguments of charge localization do not sufficiently explain the observed data. Here again, the quasi-equilibrium theory probably offers a more satisfying explanation of the observed data.

Substituent effects have also been observed in a few other systems. Thus the trifluoromethyl ketone **19** under-

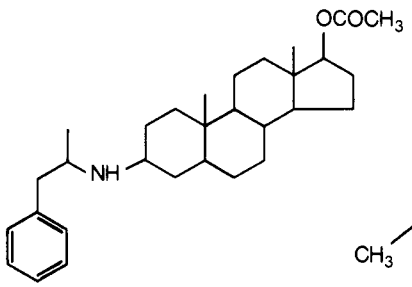


19

went rearrangement to a much smaller extent than the corresponding dialkyl ketone.[76] It is not clear whether this effect is due to the known strengthening of a C–H bond adjacent to a trifluoromethyl group or to some polar effect in the transition state. In view of the stepwise nature of the reaction and the probability that it proceeds *via* a "radical abstraction" pathway,[71] the former explanation seems the most likely.

2. Suppression of the McLafferty Rearrangement

Suppression of the McLafferty rearrangement has already been noted in the discussion of the diphenylethane **16**.[66] In general, rearrangement is suppressed or drastically reduced in importance when a molecule contains a site of lower ionization potential than that of the carbonyl group, thus providing a "sink" into which most of the charge deficiency can flow. Thus rearrangement is suppressed in various steroid amino esters **20**,[77] in esters of type **21**,[78] and in amino ketones of types **22**[79] and **23**.[80]



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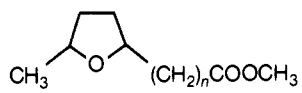

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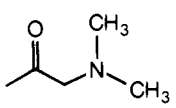

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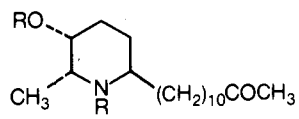
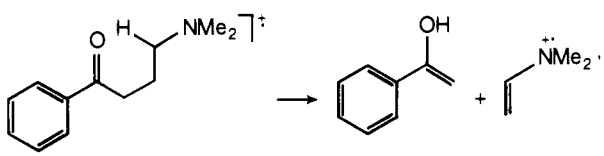


23

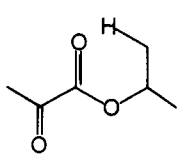
ω-Amino esters also show similar suppression of rearrangement.[81] However, if the amino group is suitably located with respect to the carbonyl group, McLafferty rearrangement with charged olefin product occurs, as exemplified by the fragmentation of the ketone **24**.[82] The fact that this reaction is not suppressed while the other reactions of amino ketones are is probably due to a combination of two factors. In the first place, the charge in **24** is undoubtedly largely localized on the nitrogen atom,



24

and the pertinent carbon–hydrogen bond is consequently weakened, facilitating the reaction. Secondly, the stability of the charged ionic product undoubtedly provides additional driving force for the rearrangement (section II.C).

The McLafferty rearrangement is also suppressed in isopropyl pyruvate (**25**)[83] and α-hydroxy ketones (**26**).[84]



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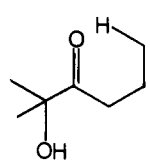
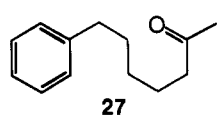


26

3. Other Factors Affecting McLafferty Rearrangement

Since so many functional groups can enter into McLafferty reactions, it would be interesting to compare competitions of different functional groups for hydrogen transfer. Relatively few studies of this type have appeared, including those of the course of a second rearrangement of product ions (section II.F), but it has been shown that there is a slight preference for hydrogen transfer to the ketone carbonyl as compared to the phenyl ring in phenyl ketones like **27**.[85] A study of the rearrangement of an ω-



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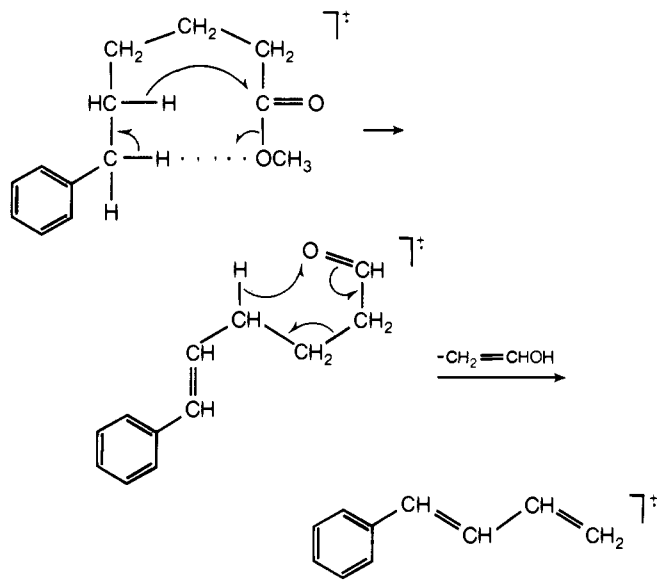
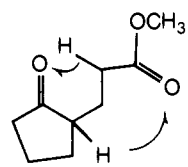
phenylalkylmethyl ester in which the carbonyl group was six carbon atoms from the ring phenyl carbon atom showed that the reaction took the unexpected course indicated in Scheme XI,[48a] but an analysis of peaks due to

SCHEME XI

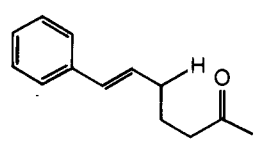


the rearranged ions formed by hydrogen migration to the phenyl ring and to the ester carbonyl suggested that there was a slight preference for migration to the latter group. On the othe hand, in the case of the keto ester **28**, there is a preference for hydrogen transfer to the ke-



28

tone carbonyl as compared with the ester carbonyl.[85] Rearrangement to the double bond is completely suppressed in **29**, the only rearrangement ion observed being that of the McLafferty rearrangement to the carbonyl group with charge retention on the olefinic product.[51] On the other hand, rearrangement of **30** occurs both by the



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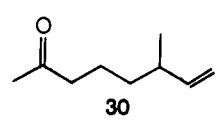
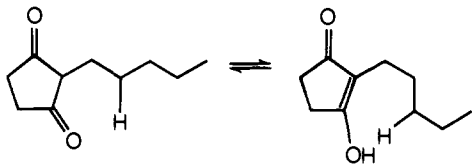


30

carbonyl and olefinic McLafferty pathways: the latter is postulated to occur after initial migration of the double bond to an internal position.[33] This difference may be explained by the observation that the itinerant hydrogen in **29** is allylically activated, while no such activation (presumably) is involved in **30**. In spite of this rationalization, it is clear that competition between functional groups in the McLafferty rearrangement is a sensitive function of the structure of the compound involved, and careful studies are required to ensure that all possible extraneous factors have been eliminated from the system studied.

The effect of both source and inlet temperature on the McLafferty rearrangement has been studied by various

authors. Changing the temperature of the inlet system has been claimed to affect the fraction of certain β-diketones present in the keto form.[86] This conclusion has been criticized by Cooks and his coworkers, who found pronounced effects of source temperature on the spectrum of acetylacetone but little or no effects of the inlet temperature.[86a] The conclusion that mass spectra are sensitive to source temperature but insensitive to inlet temperature—provided, of course, that no thermal reactions occur in the inlet system—was reached independently by Meyerson and his coworkers.[86b] In another study, however, a temperature effect was not noted: the diketone **31** showed ions resulting from both the normal

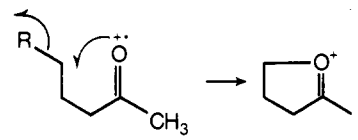


31

McLafferty reaction and rearrangement to the enol double bond.[87] A more general examination studies the effect of temperature on the McLafferty rearrangement and competing cleavage and loss of methyl in simple ketones.[88] In general, it was found that the abundance of all the fragment ions studied, including the McLafferty product ion, increased relative to the molecular ion abundance as the temperature increased. These results were used to estimate the activation energies, frequency factors, and effective number of oscillators for the various reactions studied.

As previously mentioned (section II.A), the McLafferty reaction is a very favorable one, and in many cases the rearrangement ion forms the base peak in the low voltage spectra of carbonyl compounds. An example is the rearrangement ion from methyl *n*-butyl ketone, which is far more abundant than all the other ions in the spectrum at 10 eV.[89] However, in more complex molecules alternate fragmentation processes become more important than the McLafferty rearrangement at low voltage. These processes are almost invariably also rearrangement processes of low activation energy, and are thus just those which would be predicted to predominate at low internal energy. Thus in hexanal the reactions leading to loss of water, loss of ethylene, and loss of C_2H_4O from the molecular ion all give more intense peaks at 12 eV than does the McLafferty rearrangement ion, although this ion gives rise to the base peak at 70 eV.[26] Even in aliphatic ketones, other processes compete effectively with the McLafferty rearrangement at low voltage. Thus in 2-octanone, the McLafferty ion, while still giving rise to the base peak in the spectrum, only carries 18.4% of the ion current (Σ_{40}) at 10 eV, as compared with 30% at 70 eV.[90] Other processes which become important at low voltage include McLafferty rearrangement with double hydrogen transfer (section IV.A), formation of a rearrangement ion containing an additional methylene group (section IV.C), and the loss of a propyl radical. This latter reaction, which at first sight violates the rule that simple bond cleavage reactions are less significant at low internal energies, was clarified by studies of methyl loss from 2-hexanone, which indicated that the C-6 methyl rather than the C-1 methyl was lost, presumably by the mechanism of eq 5 (R = CH_3).[91] This loss is, of course, analogous to the loss of propyl from 2-octanone (R = C_3H_7).

Finally, a series of studies has appeared which is predicated on the intervention of different electronic states for the rearrangement and for simple cleavages: the former



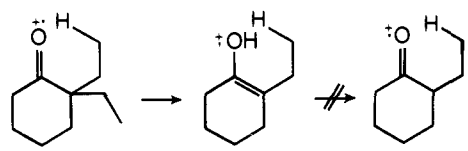
(5)

corresponds to a removal of an n electron, the latter to that of a σ electron.[92,93]

F. Reactions of the Enolic Product Ion

1. Reketonization

Several of the arguments used to support the enolic structure of the McLafferty rearrangement product ion can be used in support of the hypothesis that reketonization does not occur to any substantial extent prior to fast reactions occurring in the mass spectrometer ion source. Thus the different fragmentations undergone by the rearrangement ions from the isomeric cyclohexanones **2a** and **2b** (Scheme I) would not be possible if the ions reketonized in the ion chamber. Similarly, the failure of the rearrangement ion from 2,2-diethylcyclohexanone (**32**, eq 6) to undergo a second McLafferty rearrangement (see also below) indicates that reketonization is not a factor in

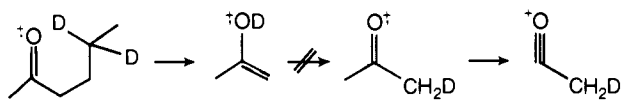


(6)

32

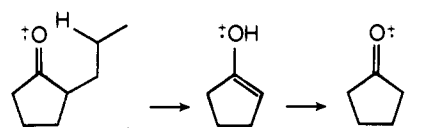
this case,[94] while the absence of $C_2H_2DO^+$ in the mass spectrum of $CH_3COCH_2CH_2CD_2CH_3$ may be taken as evidence that the enolic ion does not revert to the keto form prior to loss of CH_3 in normal fragmentations (Scheme XII).[94] The McLafferty rearrangement ions of

SCHEME XII



several esters and a ketone were observed to decompose further in a fashion different from the keto forms of the products introduced as separate compounds.[95] Reketonization does not occur either under normal conditions in the ion cyclotron resonance (icr) spectrometer, since keto and enol ions could be distinguished by their different ion–molecule reactions.[36]

In spite of this evidence that reketonization does not occur in ions decomposing within about 10^{-6} sec of their formation, evidence has recently accumulated that reketonization does occur in ions with longer lifetimes. Reketonization of the enol ion from 2-*n*-propylcyclopentanone (eq 7) was observed in an icr spectrometer operated so



(7)

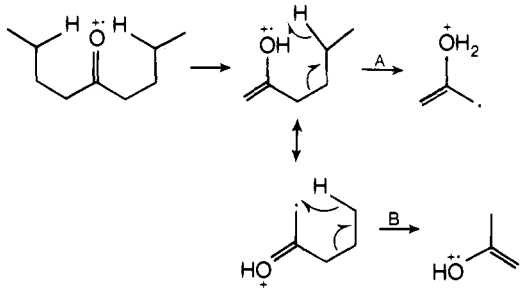
as to increase ion residence times to the range 10^{-3}–10^{-1} sec; the enol form initially produced converted to the keto form (as shown by its ion–molecule reactions) as the residence time increased.[96] Similarly, reketonization of the enolic ion from 2-ethylcyclopentanone may be inferred from the observation that both cyclopentanone and the $C_5H_8O^+$ ion from 2-ethylcyclopentanone show identical behavior in both unimolecular and collision-induced decompositions observed by ion kinetic energy

spectrometry (ikes).[97] Here again, the longer lifetime of ions sampled by ikes ensures that ions studied by this technique have had adequate opportunity to rearrange. Interestingly, such reketonization was not shown by the enol ion from 2-hexanone, indicating that the reaction is a sensitive function of ion structure. Reketonization has been inferred to take place, however, prior to the fragmentations of enolic ions occurring in the field-free regions of the mass spectrometer. Thus both enolic $C_3H_6O^+$ ions and $C_4H_8O^+$ ions were shown to isomerize to the keto form prior to fragmentation to give the CH_3CO^+ and $C_2H_5CO^+$ ions.[98,99] The mechanism of isomerization of $C_2H_5C(OH)CH_2^+$ to $CH_3CH_2COCH_3^+$ is deduced to involve two 1,4-hydrogen shift rearrangements, while isomerization of $CH_3CHC(OH)CH_3^+$ to the keto form involves a 1,2- followed by a 1,4-hydrogen shift.[99] In the enolic ion produced from butyrophenone, however, the additional hydrogen atom lost with the methylene group as a methyl radical comes from the phenyl ring and not from the enolic oxygen atom.[100]

2. *Further Rearrangement of the Enolic Product Ion*

The enolic product ion of the McLafferty rearrangement can undergo a second rearrangement with hydrogen migration and β cleavage (Scheme XIII) provided that a suitable alkyl chain is available.[100a]

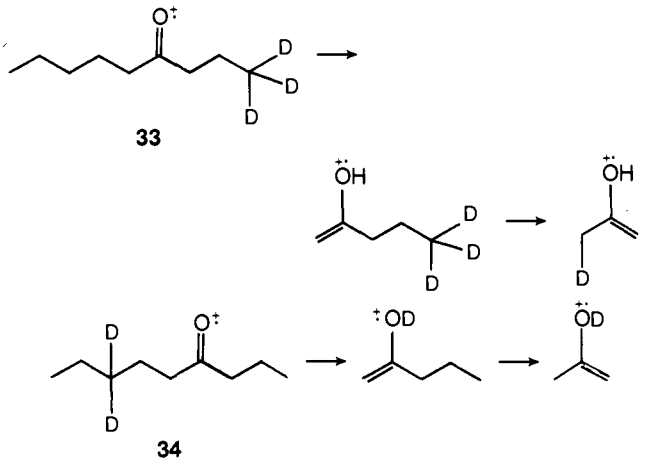
SCHEME XIII



Studies with deuterium-labeled ketones showed that the second rearrangement, like the first, is site specific; only γ hydrogens are transferred to the product ion.[19] As has already been mentioned, reketonization of the enol ion does not occur prior to the second rearrangement, as shown by the failure of 2,2-diethylcyclohexanone to undergo the second rearrangement (eq 6).[94] Similarly, the second rearrangement is absent in dimethyl dipropylmalonate; somewhat surprisingly, in view of the results cited earlier for the β-diketone **31**, the enol ion from the dipropylmalonate also fails to undergo a McLafferty rearrangement involving the enolic double bond.[48b]

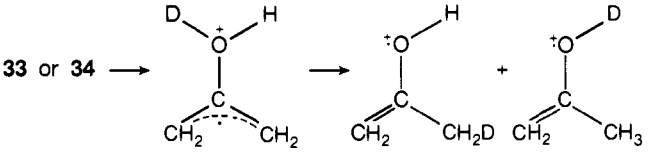
The question of the structure of the product ion of the second rearrangement has been actively investigated in the last few years. At least two pathways are in principle possible for the rearrangement (Scheme XIII). In pathway A, rearrangement of the hydrogen takes place to the oxygen atom to give an oxonium ion as the product, while in pathway B rearrangement takes place to carbon, forming another ionized enol as the product. Pathways involving reketonization of the enol ion are, of course, excluded by the work already discussed and by the high specificity of the γ-hydrogen atom transfer in the fragmentation of the methyl enol ether of γ-d_2-2-hexanone.[94] The former pathway was supported by theoretical considerations[61] and by metastable ion studies,[101] but ion cyclotron resonance studies have failed to find any difference in reactivity between the single rearrangement product from a methyl ketone and the second rearrangement product from a corresponding longer chain ketone.[36,102,103] Particularly telling was a study of the labeled species **33** and **34** (Scheme XIV).[102,103] Because

SCHEME XIV



of the preference for transfer of a secondary hydrogen over a primary one, these compounds rearranged predominantly as shown, and the product ions could be distinguished by icr. This work also excluded the intervention of the oxonium ion as an intermediate which rearranged to the enol ions, since in this case the enol ions from **33** and **34** should have the same composition (Scheme XV), a situation which was found not to be the case. These results thus all support pathway B of Scheme XIII for this reaction.

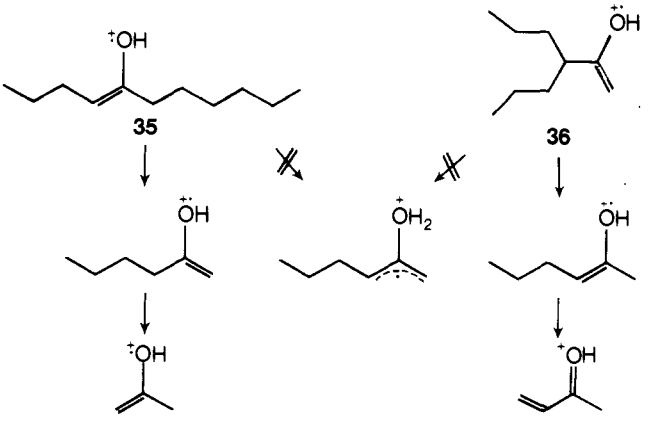
SCHEME XV



Later studies in unimolecular reactivity confirm these results;[98] the initial argument based on metastable peak intensities failed to take internal energy differences into account.[104]

Supporting evidence that the second McLafferty rearrangement also proceeds *via* pathway B in the high-energy, short-lived ions decomposing in the ion source and therefore observed in the conventional mass spectrum comes from a recent study of the fragmentation of the ions **35** and **36** (generated from cyclobutanol precursors) (Scheme XVI).[105] Rather than fragmenting through a common oxonium ion intermediate, these ions rearranged

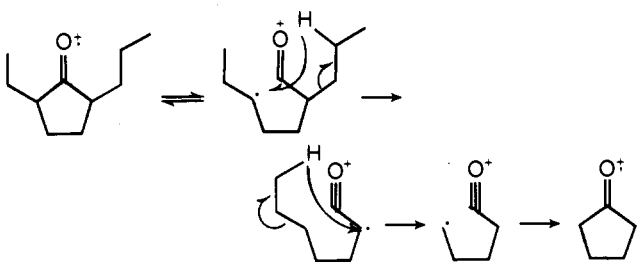
SCHEME XVI



by pathway B to their own unique enolic ion, which then underwent a further characteristic decomposition.

It should be noted finally that not all reactions which appear to be McLafferty rearrangements of an initially rearranged ion necessarily proceed by the same pathway. A case in point comes from a recent study in our laboratories which showed that 2-ethyl-5-*n*-propylcyclopentanone undergoes rearrangement in the ion cyclotron resonance spectrometer to give normal and second rearrangement ions which appear *not* to be enolic at short residence times. At long residence times the second rearrangement product appears to be ketonic, however; the mechanism of Scheme XVII is one possible rationalization of these observations. This study points out once again the very subtle structural factors which affect ion decomposition pathways, and serves as a warning against making sweeping generalizations about mass spectrometric mechanisms on the basis on one example of a reaction type.[106]

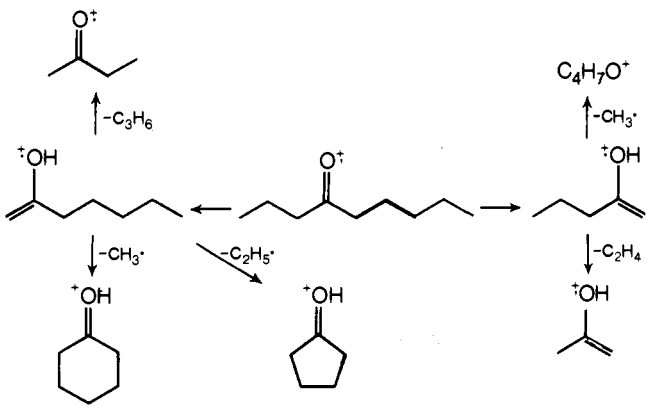
SCHEME XVII



3. *Other Decompositions of the Enolic Ion*

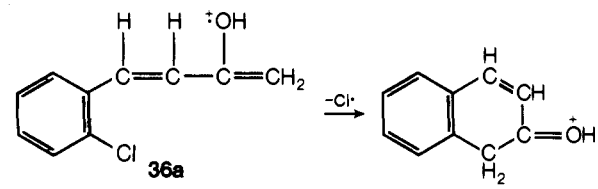
Decompositions of the enolic ions formed by the single McLafferty rearrangement have been studied both by metastable ion studies[98,99] and by ion kinetic energy (ike) studies.[107] The ions $C_3H_6O\cdot^+$ and $C_4H_8O\cdot^+$ formed from 2-alkanones and 3-alkanones decompose by loss of a methyl ($C_3H_6O\cdot^+$)[98,107] or methyl and ethyl ($C_4H_8O\cdot^+$)[99] radical to give acylium ion products. The hydrogen migrations implicit in these fragmentations have been investigated.[98,99] Nonan-4-one yields two enol ions which undergo a variety of fragmentations, which are shown in outline in Scheme XVIII.[109] The original

SCHEME XVIII



paper should be consulted for details of these transformations of the enolic ions, but it should be noted that the ions shown on the left side of the scheme are less abundant than those on the right side. The energy release involved in loss of a methyl radical from the rearrangement of the $C_8H_8O^+$ ion of alkyl phenyl ketones and from acetophenone has been studied, and it was shown that much less energy was released in the latter case.[108] This result was interpreted as evidence in favor of the enolic formulation of the rearrangement ion. Finally, the ($M - C_2H_4)\cdot^+$ rearrangement ion from ethyl benzoate has been studied by ikes.[110] It was shown by a double-labeling study using $C_6H_5(C^{18}O)OC_2D_5$ that after loss of C_2D_4, the remaining D atom and two ortho H atoms have exchanged before loss of OH. The two oxygen atoms are not totally equivalent, however; it is more likely that D is attached to ^{18}O and o-H is attached to ^{16}O. Thus the loss of ethylene from this ester is indeed a reaction with a six-membered transition state, not a four-membered one.

Loss of chlorine from the McLafferty product ion **36a** is attributed to the displacement reaction shown.[111]



36a

G. Theoretical Treatments of the Rearrangement

Several theoretical studies of the McLafferty rearrangement have been carried out. One study using Mulliken nonempirical molecular orbital theory found the stepwise process to be favored over the concerted mechanism, and found that the reaction had a substantially higher activation energy for nonplanar transition states.[61] This study also discussed the relative probability of hydrogen transfer as a proton, a hydrogen atom, or a hydride ion, and concluded that a forced choice between proton and hydrogen atom transfer may be simplistic. Hydride ion transfer was ruled out on the basis of calculated net charges found in the transition on empirical grounds in another study.[112] Finally, the question of the second McLafferty rearrangement was discussed, the conclusion being reached that the most likely product is the symmetrical oxonium ion (path A, Scheme XIII).

A second treatment utilized perturbation molecular orbital theory and found the concerted mechanism to be a favorable process.[113] The differences between these theoretical approaches point up the weaknesses in our understanding of the reactive states of gaseous organic ions. A theoretical study has also appeared which is concerned with carbon–carbon bond rupture probabilities only.[114]

H. Summary

It is convenient at this point to summarize the basic facts which are known with some certainty to apply to the McLafferty rearrangements of ketones and esters. It should again be emphasized that these same facts do not necessarily apply to "McLafferty" rearrangements in other systems, nor necessarily even to McLafferty rearrangements in all the possible carbonyl systems.

1. The rearrangement involves the specific removal of the γ hydrogen to the carbonyl oxygen atom (II.A).

2. Cleavage of the α,β carbon–carbon bond yields an ionized enol and an olefin (II.A).

3. The reaction is a stepwise reaction (II.B).

4. Formation of stable product ions provides substantial driving force for the reaction. If the olefin product is particularly stable, the McLafferty reaction with charge retention on the olefin product is favored (II.C.1).

5. Secondary hydrogen atoms are abstracted more readily than primary (II.C.3).

6. Hydrogen atoms are transferred more readily than deuterium atoms, although the effect is small (II.C.3).

7. There is a maximum interatomic H(γ)–O distance of 1.8 Å for reaction (II.D).

8. There is a maximum angle of about 50° between the transferred hydrogen and the plane of the carbonyl group (II.D).

9. Hydrogen transfer probably occurs as a hydrogen atom (II.E.1).

10. Rearrangement may be suppressed if there is a noninteracting site of low ionization potential in the molecule (II.E.2).

11. In general, the carbonyl group competes effectively with other functional groups in competitive situations (II.E.3).

12. The enolic ion does not reketonize under normal conditions but may reketonize under long-lifetime conditions (II.F.1).

13. The second rearrangement of a rearranged ion gives as its product ion an enolic species rather than an oxonium ion (II.E.2).

14. The enolic ion decomposes principally by loss of an alkyl fragment, preceded by hydrogen rearrangement (II.F.3).

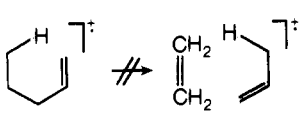
III. McLafferty Rearrangement in Noncarbonyl Systems

In this section mechanistic details of the McLafferty rearrangements of various systems will be discussed. It is not the purpose of this section to catalog all the different types of rearrangement which can be classified as "McLafferty" rearrangement: examples of many of these will, however, be found in section VII of this review. McLafferty rearrangements in various even-electron systems are discussed in section IV.A.

A. Unsaturated Systems

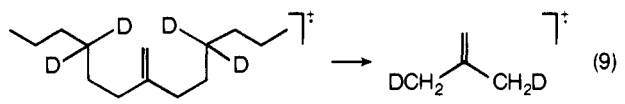
McLafferty rearrangements occur widely in both olefins and aralkyl compounds. Reactions considered to be McLafferty rearrangements in aromatic compounds with side chains have been discussed in Part I of this review, section II.D,[1] and will not be discussed further here; a recent discussion of this subject has also appeared elsewhere.[115]

Hydrogen migrations in alkenes have been discussed in two recent publications,[116,117] as well as in the first part of this review, section I.B.[1] It is clear from these studies that more or less extensive hydrogen scrambling, depending on the alkene structure, precedes fragmentation by the McLafferty rearrangement. Thus in 1-pentene, elimination of ethylene is *not* well represented by eq 8;



(8)

instead, a series of 1,2-shifts of hydrogen preceding ethylene elimination was proposed on the basis of deuterium labeling evidence.[118] In contrast to this simple alkene, the more highly substituted alkenes rearrange with little preceding hydrogen randomization.[116,117] Thus 1,1-di(*n*-hexyl-3,3-d_2)ethylene (**37**) is claimed to rearrange specifically by a consecutive McLafferty rearrangement to yield an ion $C_4H_6D_2^+$ which is responsible for the base peak in the spectrum (eq 9). This conclusion is challenged, however, in the latter paper cited,[117] and it is shown that some hydrogen randomization does precede rearrangement even under mild ionization conditions. The loss of

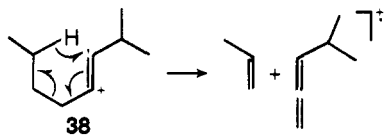


(9)

37

propylene from 2,4-dimethyl-1-pentene is also claimed to be specific.[118a] Extensive hydrogen rearrangement has also been observed preceding the fragmentation of several 1-phenylheptenes,[119] and hence the mass spectra of such compounds are not very effective at distinguishing between double bond isomers.

Alkynes also show some hydrogen randomization prior to decomposition, but not as extensively as the alkenes. Deuterium labeling may thus be used to follow reaction pathways, and two recent papers report on the fragmentation of such compounds.[120,121] McLafferty rearrangement is of only modest importance in linear alkynes, but it becomes a major fragmentation pathway in some branched-chain alkynes, for example, 2-methyloct-3-yne (**38**).[121]



(10)

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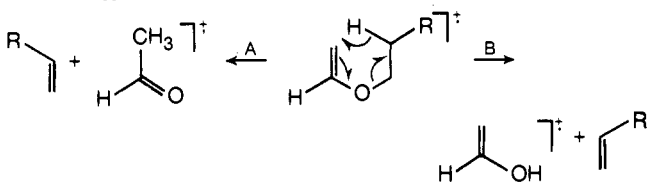
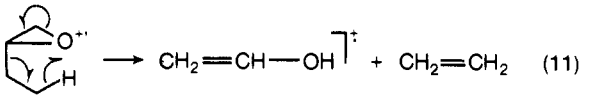
B. Alcohols and Ethers

Alcohols and ethers as a class do not exhibit McLafferty rearrangement in the molecular ion unless some other functionality (such as a double bond, ketone, ester, etc.) is present in the molecule to provide a terminus for the migration of hydrogen. As an example of this latter situation, the hydrogen of the hydroxy group is transferred to the double bond through a six-membered ring in various substituted 1-buten-4-ols.[122] In alkyl vinyl ethers, an important ion of mass 44 was originally postulated to arise *via* a McLafferty rearrangement (Scheme XIX, path A).[123] However, it was later suggested on the basis of appearance potentials that this ion should be ionized vinyl alcohol (Scheme XIX, path B),[8] Recent deuterium labeling studies have shown that the product ion is indeed best represented as ionized vinyl alcohol, resulting from nonspecific hydrogen transfer to the ether oxygen atom.[124] α,β-Unsaturated secondary alcohols have been proposed to undergo isomerization to ketones followed by normal McLafferty rearrangement of the product ketone.[125,126]

SCHEME XIX



Aliphatic epoxides exhibit two distinct rearrangements in their fragmentation: an "inside" rearrangement (eq 11) and an "outside" rearrangement (eq 12).[127] To the extent that three-membered rings may approximate the reactivity of double bonds, these rearrangements may be ac-



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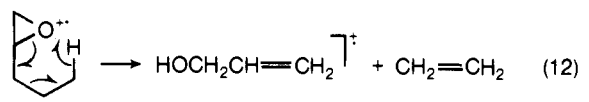


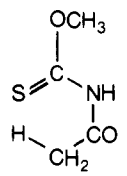
(12)

counted for in the broad sense as McLafferty rearrangements. Similar rearrangements are observed in the spectra of alkylaziridines (section III.D).

C. Sulfur-Containing Systems

Sulfur compounds can undergo the McLafferty rearrangement either by having sulfur serve as the terminus for hydrogen transfer (analogously to the carbonyl group), by providing an S=O group in the molecule, or by generation of other sites of unsaturation in the molecule during unimolecular decomposition.

In the case of compounds containing the thiocarbonyl group, McLafferty rearrangements have been reported *inter alia* for O-alkyl thioesters,[128] methoxythiocarbonyl amides (**39**),[129] alkylphenylthioureas (**40**),[130] and *S*-(alkoxythiocarbonyl)thiohydroxylamines (**41**).[131]



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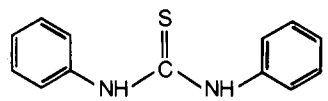

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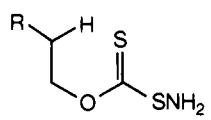
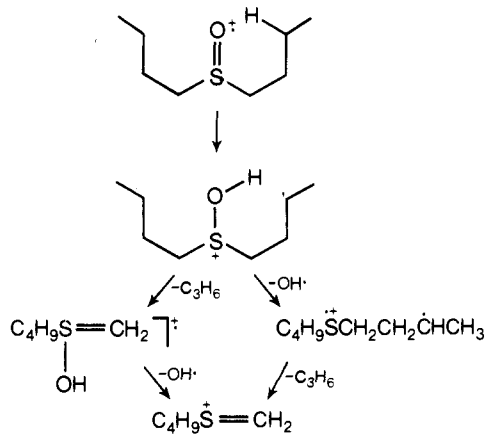


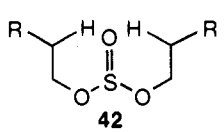
41

McLafferty rearrangements have been postulated to account for some of the observed ions in the spectra of various compounds with an S=O bond. Thus in the spectra of aliphatic sulfoxides the loss of a hydroxyl radical is an important fragmentation pathway.[132] This loss has been studied by deuterium labeling in di-*n*-butyl sulfoxide, and the pathways of Scheme XX have been proposed to

SCHEME XX



account for it and other fragmentations.[133] It should be noted, however, that deuterium transfer was only approximately 50% specific for the γ position. A McLafferty rearrangement has also been proposed to occur in the spectra of various alkyl sulfites (**42**)[134] and alkyl sulfonates.[135]



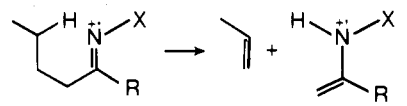
42

The case where sulfur generates another site of unsaturation will be discussed below in section IV.A.

D. Nitrogen-Containing Systems

The great variety of nitrogen-containing compounds that has been studied precludes any sort of comprehensive discussion of their rearrangements in the space available. However, the most important and interesting compounds of nitrogen for our purposes are nitrogen analogs of the carbonyl group, and these will be discussed briefly, followed by some examples of more exotic systems.

In principle, suitably substituted nitrogen-containing carbonyl derivatives such as hydrazones, oximes, semicarbazones, and similar compounds would be expected to undergo McLafferty rearrangement in an analogous manner to carbonyl-containing compounds (eq 13). This

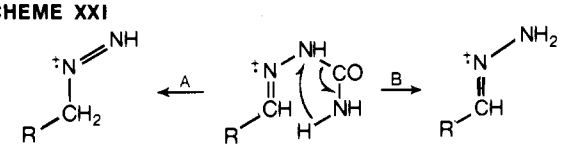


(13)

expectation is amply fulfilled. Thus both aliphatic aldoximes and ketoximes show intense ions due to the McLafferty rearrangement; in the case of suitably substituted ketoximes the consecutive McLafferty rearrangement was prominent.[136,137] Interestingly, although the rearrangement of ketoximes is site specific, like the corresponding rearrangement in ketones, it does not show the same sensitivity to the nature of the hydrogen abstracted as does the carbonyl analog.[137] In view of the likely stepwise nature of the fragmentation, this may indicate that the second step is the "slow step" of the fragmentation in this case. Another difference between the rearrangements of ketones and ketoximes is the enhanced contribution of the latter rearrangements to the total ion current, probably reflecting the absence of the important α-cleavage decomposition in these compounds. It may also be noted that a small portion (around 7%) of the rearrangement ions is not due to McLafferty rearrangement but rather to methyl migration.[137]

Aliphatic semicarbazones also show abundant ions due to McLafferty rearrangement. In the case of *n*-valeraldehyde semicarbazone, the McLafferty rearrangement ion forms the base peak in the spectrum,[138] while for the di-*n*-butylsemicarbazone the ions for both double and single McLafferty rearrangement are prominent.[138] In this case, the type of hydrogens abstracted does play a role in the rearrangement, secondary hydrogens being abstracted in preference to primary ones.[138] A second rearrangement of semicarbazones involves the loss of HCNO from the molecular ion. This loss has been suggested to occur through a six-centered "McLafferty" rearrangement (Scheme XXI, path A)[138] and also through a four-centered rearrangement (Scheme XXI, path B).[139] The absence of some expected fragments of the product of rearrangement by pathway A supports the formulation of the rearrangement as that of pathway B.[139]

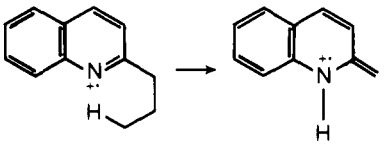
SCHEME XXI



The McLafferty rearrangement is also significant in the spectra of hydrazones,[140] methoxycarbonylhydrazones,[141] azomethines,[142] and nitrophenylhydrazones.[140,143-145]

McLafferty rearrangement is relatively unimportant in nitriles, presumably because of the bond angle problem associated with the linear disposition of bonds about car-

bon.[146,147] In several compounds with a C=N group as part of a ring system (*i.e.*, heterocyclic compounds), however, rearrangement may occur readily. As an example, the McLafferty rearrangement ion in 2-*n*-propylquinoline (eq 14) gives rise to the base peak in the spectrum

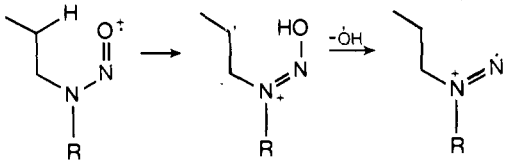


(14)

of this compound.[148] Deuterium labeling confirmed the specificity of this rearrangement for γ hydrogen.[148] An analogous rearrangement also occurs in isoquinolines,[148] and the isotope effect for deuterium as against hydrogen rearrangement has been studied in this system.[20,23] The value observed (0.70) denotes a significantly larger effect than is observed either for carbonyl compounds (0.80–1.00) or for butylbenzene (0.88). The difference may reflect a different charge distribution in the ion of the isoquinoline, or different hybridization at hydrogen as opposed to carbon or oxygen.

Other analogous rearrangements have been observed *inter alia* in the spectra of alkyl pyridines,[149] pyrazines,[149] purines,[150] and oxazoles.[151]

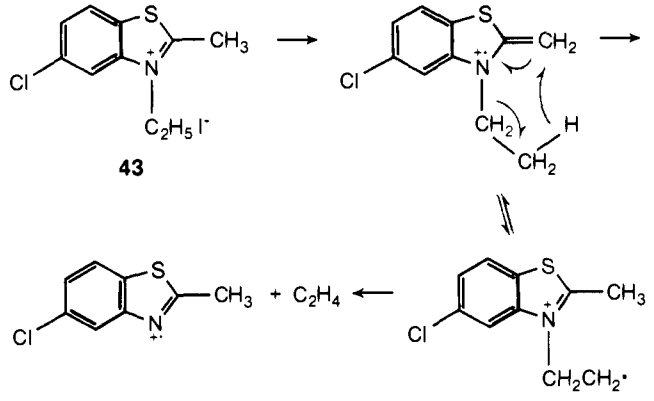
Aziridines show both "outside" and "inside" McLafferty rearrangements exactly analogously to epoxides.[152] The loss of OH from dialkyl-*N*-nitrosoamines has been rationalized in terms of an initial γ-hydrogen transfer analogous to the first step of the McLafferty rearrangement (eq 15).[153,154] This reaction is similar in some respects to the loss of OH from sulfoxides.[133]



(15)

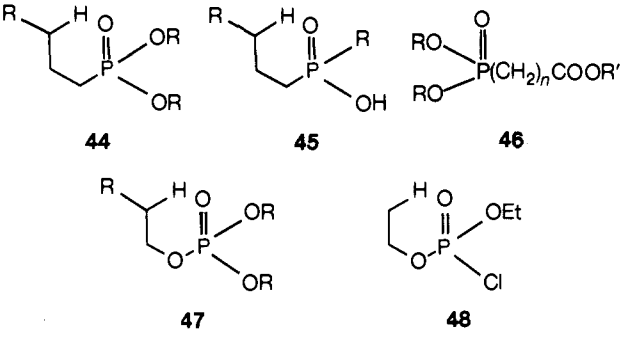
Finally, mention should be made of the rearrangement of the benzothiazolium salt **43**, which was proposed to occur by a stepwise process (Scheme XXII) on the basis of the observed hydrogen randomization preceding ethylene loss.[155]

SCHEME XXII



E. Other Systems

Various compounds containing the P=O group undergo McLafferty rearrangement if they have suitably substituted alkyl chains. Thus dialkyl alkylphosphonates (**44**),[156,157] dialkylphosphinic acids and esters (**45**),[158] carboalkoxyphosphonates (**46**),[159] and possibly alkyl phosphates (**47**)[160] and phosphorochloridates (**48**)[161] have been found to undergo the reaction.



44 **45** **46**

47 **48**

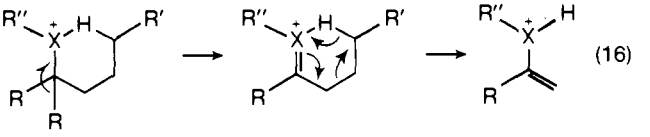
McLafferty rearrangements have also been proposed to occur in a variety of organometallic systems, which are included in Tables II–XI.

The preceding discussion may have given the false impression that the occurrence of the McLafferty rearrangement has been definitely established in each of the systems cited. This is definitely not the case. In actual fact, relatively few of the many examples discussed in the preceding sections have been studied by isotopic labeling or by any other technique such as measurement of ion energies. This situation presents both a warning and a challenge: a warning that we should not take too literally any and every claim for a new rearrangement to be a "McLafferty rearrangement" until such claim has been substantiated with reasonable evidence, and a challenge to researchers in mass spectrometry to reinvestigate these systems to determine whether they do, in fact, undergo the McLafferty rearrangement.

IV. Reactions Related to the McLafferty Rearrangement

A. McLafferty Rearrangement in Even-Electron Systems

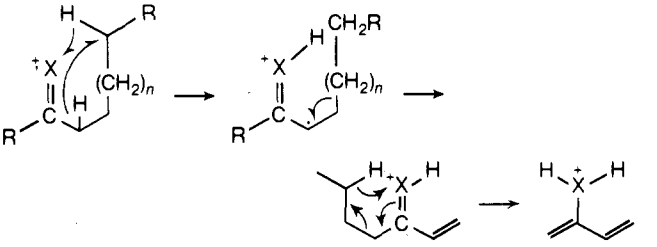
A reaction formally analogous to the McLafferty rearrangement is observed in the fragmentation of even-electron ions generated (usually by alkyl loss) from suitable precursors. Such a rearrangement is observed in immon-



(16)

ium ions generated from amines,[162] amino ketones and esters,[163,164] ethers,[162] and thioethers.[165] A similar even-electron ion has been postulated to rearrange to give a protonated ketene ion in the spectrum of various δ-lactones,[166] while the even-electron ions produced by β,γ cleavage of certain carbonyl compounds and their nitrogen analogs (Scheme XXIII) also decompose by a

SCHEME XXIII



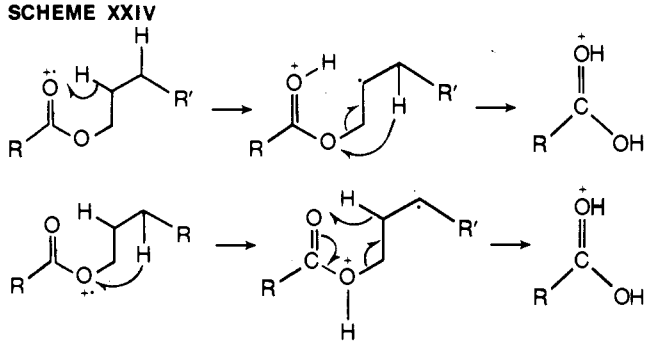
McLafferty rearrangement.[167,168] An analogous even-electron ion from dialkylmalonic acids also rearranges by a similar pathway.[168]

In spite of the formal analogy to the McLafferty rearrangement, studies with deuterium-labeled compounds have shown that rearrangement is not specific for γ-hydrogen atoms in the case of the protonated Schiff bases and onium ion species illustrated in eq 16 (X = NH or O[162] or X = S[164]). Rearrangement is specific, however, in the case of the rearrangements outlined in Scheme XXIII,[167,168] so apparently the nature of the rearrangement depends significantly on the particular even-electron substrate. It should be noted that the fact that an ion has an even number of electrons does not require that they all be paired in the entire population of ions.

B. McLafferty Rearrangement with Double Hydrogen Transfer

Formation of a rearrangement ion containing one H atom more than the normal McLafferty product[168a] is a reaction which is typical of esters.[169] Labeling studies on *sec*-butyl acetate,[170] ethyl and isopropyl acetate,[171] ethyl propionate and ethyl butyrate,[172] various *n*-alkyl acetates,[173-174] and *n*-butyl propionate[175] indicate that the reaction is not as site specific as the McLafferty rearrangement proper. Some hydrogen scrambling may precede the formation of rearrangement ions in some cases,[172] but in general it appears that one hydrogen atom is abstracted more or less specifically from the γ position, while the second hydrogen is abstracted randomly from the available positions; other interpretations are also possible, however, and there is no agreement on the "correct" mechanism for this process. The mechanisms[174,175] of Scheme XXIV have been suggested as possibilities. It is noteworthy that deuterium isotope effects appear to be significant for this reaction.[176]

SCHEME XXIV

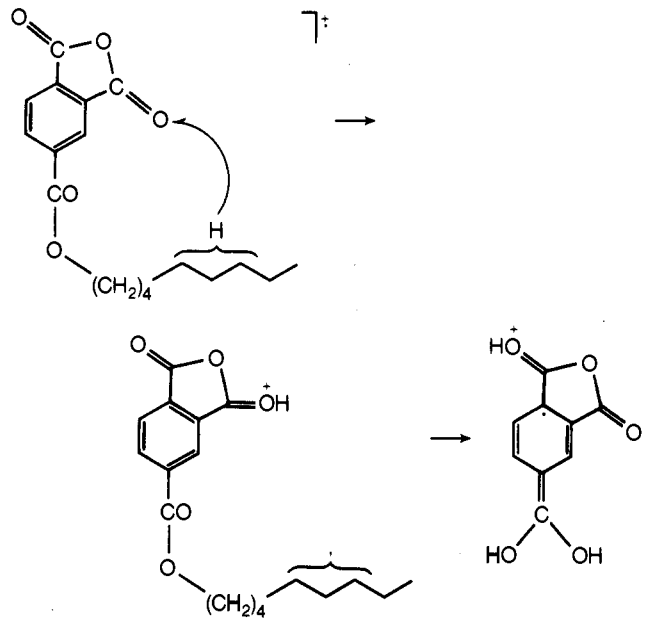


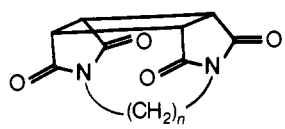
The McLafferty rearrangement with double hydrogen transfer is also observed in the spectra of alkyl ketones; it is particularly significant in the low-voltage, low-temperature spectra of these compounds although it is observable at 70 eV also.[90,177] In long-chain alkyl ketones one of the hydrogen atoms is transferred nonspecifically from a carbon atom a great distance down the chain, while the other is transferred specifically from the γ position.[177] In smaller ketones, such as 2-octanone, however, hydrogen transfer appears to come largely from the γ and δ carbons.[90]

Transfer of two hydrogens in a presumably similar pattern has been observed in the spectra of *N*-alkylmaleimides,[178] diaziridinones,[179] nitrophenylhydrazones,[180,140] methoxycarbonylhydrazones,[141] *N*-alkyluracils,[181,182] dialkyl phosphinates,[158] carboalkoxyphosphonates,[159] and phosphorochloridate esters.[161]

An unusual triple hydrogen migration is observed in esters of trimellitic anhydride,[183] and the course of this reaction has recently been studied by deuterium labeling.[184] Unfortunately, the occurrence of nonspecific pathways for the double hydrogen rearrangement of esters precluded any simple analysis of the data, but it was inferred that in the case of the nonyl ester hydrogen originated primarily from the 5, 6, **7**, and 8 positions of the ester alkyl chain (Scheme XXV). Triple hydrogen migrations were also observed in the corresponding phthalimides[184] and in diazatetracyclotetraones (**49**).[179]

SCHEME XXV



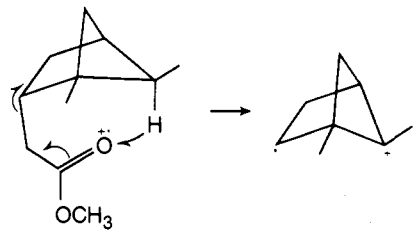


49

C. Analogous Rearrangements with Larger Transition States

Since the McLafferty rearrangement is not a concerted process, there is no absolute requirement for a six-membered transition state. Undoubtedly the major driving force for the reaction as it normally proceeds is the formation of two stable products, but when the normal process becomes unavailable for any structural or stereochemical reason, it may be replaced by an alternative process that is probably only slightly less favorable energetically. It may also happen that a competing process is strongly favored for some reason and thus is preferred over normal rearrangement, even though the latter is not particularly unfavorable.

As examples of cases where normal rearrangement is unfavorable we may cite the nitriles,[185-188] where transfer of a hydrogen atom in a seven-membered transition state has been proposed. Since the geometry of the cyano group would preclude a normal six-membered transition state, this result is readily understandable. An analogous process is postulated for cyanamides.[189] Several carbonyl compounds also have been implicated in fragmentations involving rearrangements *via* seven-membered transition states. Thus an irradiation product of carvone camphor fragments by the pathway of eq 17;[190] normal rearrangement is obviously precluded in this compound. A similar situation where normal rearrangement is impossible occurs in the amide **50**; here again, what is apparently a rearrangement *via* a seven-membered transition state probably occurs to give the normal enolic McLafferty product ion.[191]



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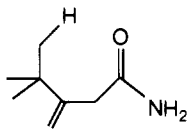
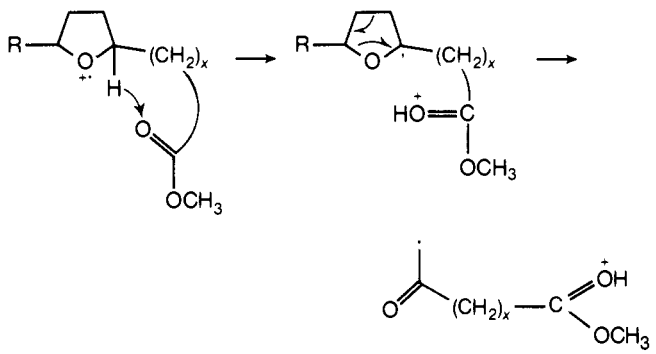


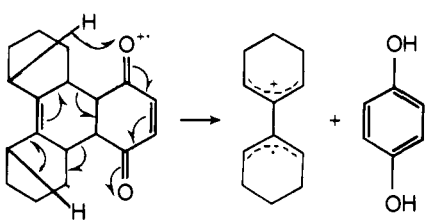
50

In other situations, rearrangement *via* a large transition state takes precedence over normal McLafferty rearrangement because of some structural preference for the larger transition state. Such is the case, for example, in the rearrangement of some α-substituted tetrahydrofuran esters, where abstraction of a remote hydrogen yields a stabilized radical (Scheme XXVI).[78] Similar factors ap-

SCHEME XXVI

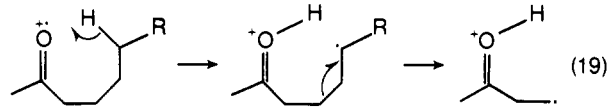


pear to be at work in the rearrangements of the Diels–Alder adducts of the type indicated in eq 18. Migration of the allylic hydrogens indicated (shown to occur by deuterium labeling) takes preference over migration of the available γ hydrogens, presumably because the former are allylically activated.[192,193] For additional examples, see Meyerson and Leitch[52a] and the references cited therein.



(18)

Larger transition states than six-membered are a common feature of reactions involving reciprocal hydrogen transfer. Thus the β,γ cleavage of aliphatic ketones is proposed to proceed by a reciprocal hydrogen transfer (Scheme XXIII) involving a seven-membered hydrogen transfer to oxygen.[90,167] Similar reciprocal hydrogen transfers have been postulated in the fragmentation of certain steroidal ketones[54] and simple ketones.[194] Another rearrangement of aliphatic ketones, observed only at low voltages, is that leading to rearrangement ions containing an additional methylene group.[195] A seven-membered transition state has been suggested here also (eq 19), but hydrogen scrambling at low voltage precluded any attempt to determine the exact origin of the migrant hydrogen.[90]



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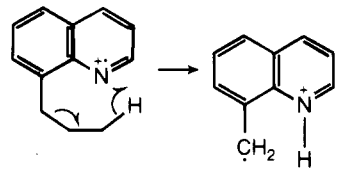
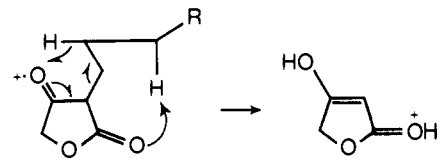
Other reactions which have been proposed to proceed through a seven-membered transition state include the fragmentation of 8-*n*-propylquinoline (eq 20),[148] various



(20)

aliphatic acids,[185,187] methyl 2-hexenoate,[196] lactones of the bakkenolide series,[197] certain naturally occurring 2-oxoquinolines,[198,199] and an isoxazole.[200] In the case of methyl 2-hexenoate, however, an alternate formulation of the rearrangement involving only six-membered rings is possible.[43] A McLafferty rearrangement involving simultaneous transfer of two hydrogens *via* a bicyclic transition state has been proposed to account for certain ions in the spectra of some tetronic acid derivatives (eq 21).[201]

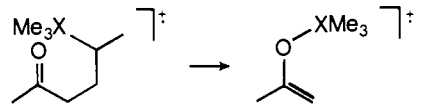


(21)

The possible intervention of eight-membered transition states has been proposed in connection with the fragmentation of an ϵ-phenyl-α,β-unsaturated ketone,[52] while terpenoid esters of the juvenile hormone class show rearrangements which must involve large transition states.[202]

D. Rearrangements of Groups Other Than Hydrogen

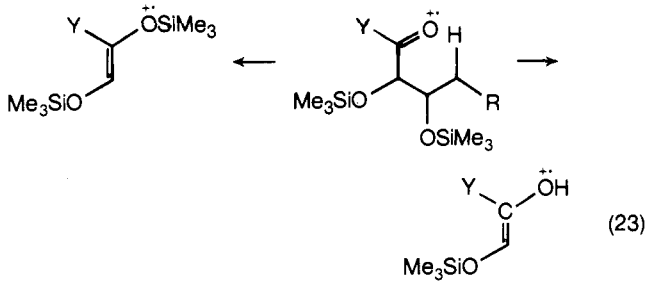
In addition to hydrogen atoms, a limited number of other groups can undergo migration to a carbonyl group or its equivalent on electron impact. The failure of a methyl group to migrate has already been noted (section II.A),[24] but a phenyl migration from carbon to nitrogen has been observed.[203] Both the trimethylsilyl[204] and trimethylstannyl[205] groups migrate from carbon to carbonyl oxygen atoms (eq 22). This reaction may not obey all the



(22)

"rules" of the McLafferty rearrangement, however, since recent work in our laboratory has shown that the trimethylsilyl group will also rearrange to a carbonyl group *via* an eight-membered transition state.[206] Rearrangement of trimethylsilyl groups bonded initially to oxygen has been noted frequently;[207-209] in general, the silyl group will rearrange to a suitable site (usually a carbonyl group or other oxygen-containing functional group) over a wide range of different cyclic intermediate sizes. In a recent example, the competition between rearrangement of a silyl group and the normal McLafferty rearrangement was studied.[210] In all the reactions studied the hydrogen rearrangement produced ions of lower abundance than the competing trimethylsilyl rearrangement (eq 23). The rearrangement of a trimethylsilyl group to a carbon–carbon double bond has also been observed.[211]

Transfer of OR through a six-membered transition state is postulated to occur in the thioglycollic acids and esters.[212]



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V. Analogous Reactions in Other Excited Species

The discussion up to this point has been concerned only with the rearrangement of gaseous positive ions generated by electron impact in the source of a mass spectrometer. There are, however, other methods of generating excited species which will undergo reactions analogous to the McLafferty rearrangement, and these will be discussed in this section. The first four subsections deal with ionic species other than the singly charged positive ions generated on electron impact, while the last three subsections are concerned with excited species other than ions.

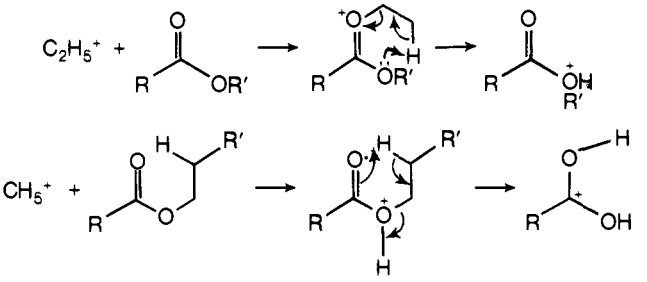
A. Field Ionization

Because rearrangement reactions have a lower frequency factor than simple bond cleavages, the latter reaction is favored in those ions decomposing in the source in field ionization mass spectrometry, because of the shorter lifetimes of such ions (*ca.* 10^{-9}–10^{-12} sec, as compared with *ca.* 10^{-6} sec for electron impact). It is not surprising, therefore, that the McLafferty rearrangement is of only low intensity in field ionization mass spectra, and indeed the first searches for it were unsuccessful.[213] Later studies uncovered small peaks due to the rearrangement. The metastable peak for this was more readily detected than the fragment ion itself.[214,215] An explanation that has been advanced for the observation of fragment ion peaks is that the rearrangements occur in the condensed phase on the surface of the anode.[216,217] However, a recent study of temperature effects on the field ionization mass spectrum of menthone shows that the main McLafferty rearrangement reaction is faster than the comparable direct bond cleavages.[218] A similar effect is noted in the formation of rearrangement ions from some aliphatic acid esters; in some cases the rearrangement ion yielded the base peak in the spectrum.[219] Similarly, sequence-characteristic rearrangement peaks in the field ionization spectra of some benzyloxycarbonyl and *tert*-butyloxycarbonyl derivatives of simple peptides retain their importance relative to simple cleavage peaks, as compared with electron impact spectra.[220] McLafferty rearrangement peaks are also observed in ions of long lifetime produced by field ionization of hexanal, and the point is made that these ions decompose in essentially similar ways to those generated by electron impact.[221] Clearly the situation in field ionization spectrometry is not treated in its entirety by the simple time-scale argument outlined at the beginning of this section.

B. Chemical Ionization

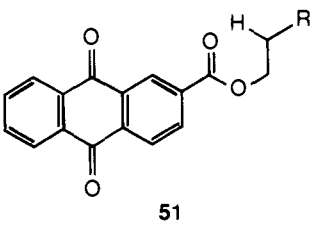
The ions generated from carbonyl compounds in chemical ionization are generally either protonated or alkylated on the carbonyl group or, in the case of esters, possibly on the ether oxygen also.[222,223] The ions thus formed may fragment by pathways analogous to the McLafferty rearrangement (Scheme XXVII). Little work appears to have been done on the rearrangements of aliphatic ketones or aldehydes under chemical ionization conditions, but if the mechanisms of Scheme XXVII are correct, it would be predicted that rearrangement would not occur in simple carbonyl compounds.

SCHEME XXVII



C. Negative Ionization

Negative-ion mass spectra have been reported for only a few carbonyl compounds, and no McLafferty-type rearrangement has as yet been observed in these compounds. In one compound where such a rearrangement could conceivably have taken place (**51**), no rearrangement was reported.[224]



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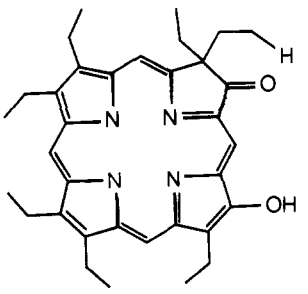
D. Doubly Charged Molecules

Again there is a dearth of information regarding possible McLafferty rearrangements in doubly charged ions. However, those cases which have been studied indicate that the McLafferty rearrangement occurs readily in such ions. Thus McLafferty rearrangement occurs with high relative intensity in the doubly charged ion of the porphine **52**,[225] and also in the doubly charged ion **53** generated from a parent trimethysilyl ether.[226] On the other hand, the high energy content of doubly charged ions apparently precludes the operation of the McLafferty rearrangement in doubly charged parent ions related to **53**; thus in contrast to the behavior of the singly charged ions, only the fragment ion **53** undergoes such rearrangement.[226]



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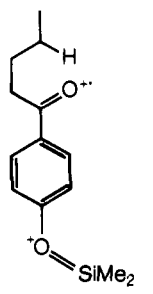

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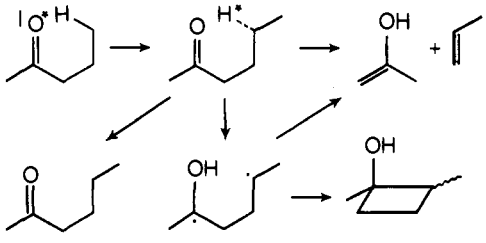
E. Photochemical Analogies to the McLafferty Rearrangement

It is not the purpose of this review to examine in detail the chemistry of the Norrish type II rearrangement, which

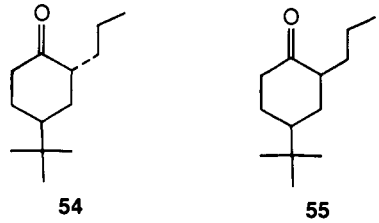
is frequently cited as the analogous reaction in solution chemistry to the McLafferty rearrangement in the mass spectrometer. Early comparisons of the parallels between the Norrish type II rearrangement and the McLafferty rearrangement have been reviewed,[8] and the type II reaction itself has recently been concisely reviewed.[226a] Theoretical comparisons have been made with Mulliken nonempirical molecular orbital theory between the rearrangement in the ion and that in the neutral species,[61] while particular comparisons have been drawn for phenyl alkyl ketones.[227]

In general, considering the extremely different reaction conditions, the two reactions are surprisingly similar. Thus in the type II rearrangement a γ-hydrogen atom is transferred to the carbonyl group to give an enolic product molecule. The reaction is stepwise, and cyclobutanol formation can occur.[226] Indeed, it was the formation of cyclobutanol products in the type II reaction that suggested a similar pathway for fragmentation of aliphatic aldehydes.[26-28] The reactions of Scheme XXVIII have been proposed for type II rearrangements of singlet 2-hexanone.[226a] In other parallels with the McLafferty rearrangement, the type II rearrangement is prohibited when the hydrogen to be transferred is vinylic,[228] and isotope effects in photochemistry and mass spectral rearrangements have been compared.[229,230]

SCHEME XXVIII



A striking parallel between photochemical and mass spectrometric reactions is the *failure* of isopropyl pyruvate to undergo either the McLafferty or type II rearrangements; instead, cleavage of the CO–CO bond determines the products.[83] On the other hand, there are several cases on record where the photochemical and mass spectrometric reactions do not parallel each other. Thus, for example, the excess energy present in the gaseous ion allows the McLafferty rearrangement to proceed equally well in **54** as in **55**, although the type II cleavage



54 **55**

differs in the two examples,[231-233] while certain macrocyclic ketones undergo McLafferty rearrangement but do not form type II cleavage products.[64] Similarly, a comparison of the mass spectral[82] and photochemical[234] behavior of some amino ketones concludes that correlations of mass spectral and photochemical behavior are limited because electronic excitation is more localized in the lowest excited states of molecules than charge is in electron-impact produced molecular ions. A further example of this is found in a study of some aryl ketones, such as 2-butyrylanthracene, which undergo McLafferty rearrangement although they do not undergo type II rearrangement to any detectable extent.[235]

TABLE I. Relative Efficiencies of β Cleavage with Hydrogen Transfer in Photolytic, Radiolytic, and Electron Impact Reactions

Compound	Quantum yield	G values	[*m/e* 58]/[*m/e* 43] × 100
$CH_3COCH_2CH_3$	0.00	0.0	0.2
$CH_3COCH(CH_3)_2$	0.00	0.0	0.1
$CH_3COCH_2CH_2CH_3$	0.27	0.15	7
$CH_3COCH_2CH_2CH_2CH_3$	0.40	0.29	42
$CH_3COCH_2CH(CH_3)_2$	0.35		32
$CH_3COCH_2CH_2CH_2CH_2CH_3$	0.40	0.16	50
$CH_3COCH_2C(CH_3)_3$	0.23		22

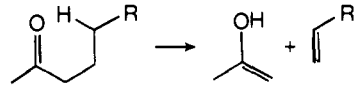
Thus although the type II rearrangement closely parallels the McLafferty rearrangement in many respects, yet there still remain enough differences to warrant caution in extrapolation from one situation to the other.

Finally, mention may be made of the fact that alkylquinolines undergo a "type II" elimination analogous to their mass spectral fragmentation previously discussed (eq 14, section III.D).[236]

F. Radiolytic Analogies to the McLafferty Rearrangement

Chemistry initiated by high-energy radiation, *e.g.*, γ-rays possessing million electron volts of energy, often bears a resemblance to the high-energy chemistry initiated by the lower energy processes initiated by irradiation with visible or near-ultraviolet light, and therefore to mass spectral reactions analogous to photochemical reaction. The general possibility of excitation according to the same pathways as those in photochemistry seems clear if one recalls that only a small fraction of the total energy of the γ-ray is transferred to each molecule with which it interacts.

Radiolysis of alkyl ketones having available γ hydrogens leads to products which correspond closely with those observed in the mass spectrometer.[237] This parallelism extends also to phenyl alkyl ketones[237] and is particularly striking when a series of related ketones is compared for the rearrangement of eq 24 (Table I).[238]

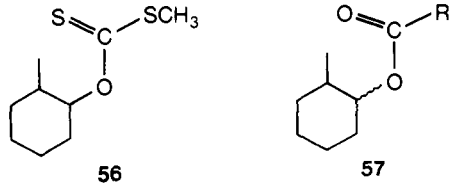


(24)

On the other hand, high voltage electron irradiation of several phenyl alkyl ketones did not give any evidence for rearrangement with β cleavage, although unfortunately the product acetophenone molecule could have decomposed further and no attempt was made to analyze for the presence of the appropriate alkene products.[239]

G. Thermolytic Analogies to the McLafferty Rearrangement

A limited amount of work has been done on thermolytic analogies of the McLafferty rearrangement. The best studied parallel is for the reactions of the *S*-methyl xanthates (**56**), which give the Chugaev reaction on thermolysis by a cis elimination pathway, and similarly show a



56 **57**

TABLE II. McLafferty Rearrangements in Carboxylic Acids

	Ref
Aliphatic acids in general	2, 38, 185, 187, 254
Butyric acid	255
Butyric and pentanoic acids	37, 39
Pentanoic acid	185, 187
Long-chain aliphatic acids	256
Deuterated aliphatic acids	257
6-Substituted alkanoic acids	258
β-Aroyl-α-methylpropionic acids	259
α-Amino acids	249
Olefinic acids in general	260
β,γ-Unsaturated carboxylic acids	261
Alkylidenemalonic acids	262
Di- and tricarboxylic acids (CI)	263
1-Viridifloric acid	264
Tetronic acid derivatives	265
Pulvic acid derivatives	266
Petroleum steroid carboxylic acids	267
Bitter constituents of *Simaroubaceae*	268
Homoadamantane derivatives	269

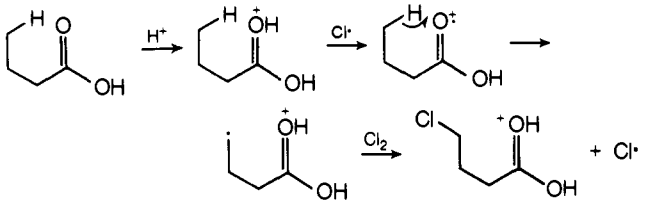
TABLE III. McLafferty Rearrangements in Aldehydes

Aliphatic aldehydes	26, 27, 40, 270
Aliphatic aldehydes (fims)	217
Hexanal, heptanal, nonanal	28
Heptanal	271
Bisulfite complexes	270
Substituted cinnamic aldehydes	272
Aromatic aldehydes	67

preference for cis elimination in the mass spectrometer.[240] The mass spectral rearrangement of the corresponding cyclohexyl esters (**57**) also paralleled their thermal rearrangement to some extent, although detailed differences were observed and are discussed in the reference cited.

An interesting solution chemistry analogy to the McLafferty rearrangement has been uncovered in the selective chlorination of carboxylic acids in 90% H_2SO_4.[241] The pathway of Scheme XXIX was proposed to account for this observation; it should be noted, however, that chlorination on longer chain acids than butyric acid was less specific, giving substantial chlorination on the ω carbon as well as on C-4.

SCHEME XXIX



VI. McLafferty Rearrangement as a Tool for Structure Elucidation

In all the preceding discussion, the emphasis has been on the mechanism of the McLafferty rearrangement in one form or another. It should never be overlooked, however, that the rearrangement serves as one of the most useful fragmentation mechanisms for purposes of structure elucidation by mass spectrometry. Of course, in any real life structural problem, the McLafferty rearrangement is only one of several fragmentation pathways that will be used in deducing a structure from a mass spectrum. Nevertheless, it is particularly useful for several reasons.

TABLE IV. McLafferty Rearrangements in Amides

Acyclic Amides	
Butyramide	255
Secondary and tertiary amides	273
N,*N*-Dimethylamides	274
N-Alkyltrifluoroacetamides	275
N-Dodecyldodecanamide	276
3,7-Diacetyl-3,7-diazadodecane	277
Acylpyrrolidines	278, 279
Acylhydrazines	280
α-Substituted *N*-methylbenzylamides	281
Lidocaine and metabolites	282
1-Carbamoylpyrazolines	283
C_{11} monocyclic petroleum acid derivative	284
Phytosphingosine ceramides	285
Lactams	286, 287
Azasteroid derivatives	288
3,9-Dimethyl-3,9-diazabicyclo-[4.2.1]nonan-4-one	289
α-Lactam fragment	290
Bisaziridinones	291
Diaziridinones	179
Diketopiperazines	292
2-Oxoquinolines	199, 200, 293
N-Alkyluracils	181, 182
Barbiturates	294, 295
Oxoquinazolines	296
Isoxalinones	297
Sydnones	298
Pteridin-4(3*H*)-ones	299
Acetylated peptides	300
Cyclodepsipeptides	301, 302
Imides	303–306
N-Alkylmaleimides	178
Peptide derivatives	307
Phenylalanine peptides	248
Benzyloxycarbonyl and *tert*-butyloxy-carbonyl derivatives	308
Acetylated peptides	300
Phthaloylamino acids	309
Alkaloid derivatives	
Colchicine alkaloids	310
Crotonosine alkaloids	311

In the first place, being a rearrangement reaction, it gives odd-electron product ions in most cases (see, however, section IV.A for some exceptions to this rule). The odd-electron ions are frequently distinguishable from their even-electron congeners even in low-resolution mass spectra, and this fact makes the rearrangement easy to pick out. Secondly, the large amount of work that has been done on the rearrangement (as evidenced by the length of this review!) ensures that the chemist has a firm foundation on which to base his interpretation. Thirdly, it is a fragmentation pathway that will always operate provided that the structural features of the molecule are consonant with the structural and stereochemical requirements outlined in this review. Thus the *absence* of rearrangement is also good evidence that an appropriate molecular structure does not exist in the compound under investigation. Finally, the wide variety of structural types that undergo rearrangement, coupled with the common occurrence of such key functional groups as ketones and esters in natural products, makes the rearrangement well-nigh ubiquitous.

A telling example of the predictive utility of the McLafferty rearrangement comes from recent work on the application of artificial intelligence for chemical inference—in this case, the interpretation of low-resolution mass spectra of ketones.[241a] The McLafferty rearrangement plays a key role in the attempt to interpret the mass spectra of

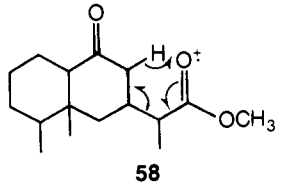
TABLE V. McLafferty Rearrangements in Esters

Simple aliphatic esters in general	23, 40, 85, 96 167, 169, 312, 313
Fims	214, 217, 219
Acetates[a]	
Ethyl acetate	171
Isopropyl acetate	171, 314
n-Butyl acetate	173, 174, 315
sec-Butyl acetate	170
C_5 to C_7 acetates	174, 316, 317
Cycloalkyl acetates	318
Bicyclo[2.2.1]heptyl acetates	319
Steroid enol acetates of Δ^4-3-ketones	320
Saccharide acetates and related compounds	321–323
Methyl esters	
Methyl butyrate	20, 21, 23, 75, 324
Methyl valerate and caproate	324
Methyl esters of fatty acids	22, 53, 278, 325–334
Methyl esters of branched long-chain acids	335–341
Methyl esters of olefinic long-chain acids	197, 327, 342
Methyl long-chain hydroxy esters	343, 344
Methyl α-hydroxy and α-methoxy long-chain esters	345, 346
Methyl 11-aminoundecanoate	347
Methyl long-chain amino esters	348
Methyl esters of trimethylsilyloxy long-chain acids	349
Dimethyl esters of long-chain diacids	350
Methyl esters of polymethoxy long-chain acids	351
Perdeuterio methyl esters	176
Other typical esters	
Ethyl propionate and butyrate	172
Isopropyl propionate and butyrate	172
Phenethyl esters and ethyl esters	352
Butyl hexanoates	353
α,β-Unsaturated esters	43
Unsaturated esters, general	260, 354
Aromatic esters	69, 110, 354
Aralkyl esters	34, 70, 71
Acetylenic esters	355
6-Substituted alkanoates	258
Typical difunctional and polyfunctional esters	
Amino esters	77, 81, 163, 164, 356
3-Chloroalkanoates	43
Enamine esters	357
β-Keto esters	358–362
γ-Keto esters	363
Keto esters and ethyleneketal esters	364
Diesters	365–368
Triesters of trimellitic acid	184
Triglycerides	369, 370
Glyceryl lactate trimethylsilyl ethers	371
Carbonates	372
S-Methyl xanthates	240
Carbamates	373–375
Angolide	301
Mitomycin antibiotics	376
Lactones	
γ-Lactone	377
δ-Lactones	166
Triterpene lactones	378
Bakkenolides	197
Lomatin and derivatives	379
Diterpene lactones	380
Cyclic esters of aliphatic α-hydroxy acids	381
Carpaine lactones	382
Nobiline, dendrobine, and synthetic intermediates	383
Pyrones	384
Others	
Cyclic keto ethers rearranging to esters	385, 386
Dehydro dimer of methyl stearate and *tert*-butyl peroxide	387
Methyl esters of bicyclic terpenes	388
Pimaricin	389
Dimethyl pinifolate	390
Fluoro alcohol esters	391
α-Dihydrohippeastrine	392
Phthalimidophenyl esters of petroleum acids	393
Chlorine d_6 trimethyl ester	394
Esters from dehydration of triterpenoids	395
Carnitine derivatives	396
Methyl phaseate	397
Sphingosine esters	398
Erinin, corymine, isocorymine	399
Methyl operculinate	400
Norcassamine	401
Butenolide derivatives	402
Alditol trifluoroacetates	403
Monocrotalin	404
Methyl dihydropalustraminate	405
Derivatives of 1,2,4-triazine	406

[a] Loss of acetic acid from acetate esters forms part of a separate planned section on the loss of HX, and references will be given in more detail there.

ketones by computer. Another approach to computer-assisted interpretation has been discussed, in which it was reported that a computer can be instructed to trace the McLafferty rearrangement and to identify structural groups on both sides of the functional group.[242] The use of the McLafferty rearrangement in structure elucidation has also been discussed in a recent book on the interpretation of mass spectra.[243]

A specific example of the utility of the rearrangement, both for what it showed to be present and for what it showed *not* to be present, comes from the structure elucidation of fluorensic acid.[244] Observation of the rearrangement depicted in **58** (arrows) indicated the presence of the ester side chain, but the absence of the rearrangement shown in **59** (arrows) contraindicated the presence of a carbonyl group in the 6 position (or 8 position). Other evidence showed that this group should be located in the 9 position, as in **58**.



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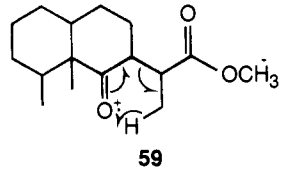

59

Further examples of the use of the McLafferty rearrangement in structural elucidation may be gleaned by studying Tables II–XI. At this stage, mention may be made of its usefulness in structural work on juvenile hormone,[245] in the sequencing of peptides,[246–251] and in

TABLE VI. McLafferty Rearrangements in Ketones

	Ref
Aliphatic ketones, general	6, 12–16, 18–21, 26, 36, 40, 61, 88–90, 92, 93, 96, 98, 99, 101, 104, 107, 112, 167, 177, 407–411
Pentanone	3, 30, 412
2-Hexanone	95
3-Methyl-2-pentanone	412
Isobutyl *n*-butyl ketone	51
Trifluoromethyl butyl ketone	76
Long-chain aliphatic ketones	253
Sterically crowded aliphatic ketones	65
Bisulfite complexes	270
"Protonated ketone" fragments	168
Charge exchange spectra	413
Fims	217
Icr	36, 102, 103
Ikes	107, 109
Computer interpretation	241, 317, 414
Rearranged α,β-unsaturated secondary alcohols	125, 126
Aromatic ketones	
Phenyl alkyl ketones	85, 227, 235
Butyrophenone	72–74, 100, 415
Valerophenone	416
Fims	216, 417
Ikes	108
Substituted butyrophenones (neuroleptic drugs)	418
Butyrylphenyl nitrophenyl ethers	419
Acyldiphenylethanes	66
Acyldiphenylcyclopentanes	68
De-*N*-morphinan derivatives	420
Monascorubrin	421
Totarolone	422
cis-Norlobelanine	423
Butyrylfilicinic acid	424
Alicyclic ketones	20, 21
Cyclobutanones	425
Cyclopentanones	50, 54, 97, 426
Cyclohexanones	94, 385, 386, 411, 426
Menthone and related compounds	427, 428
Piperitone	35
Cycloheptanones	386
Cyclononanones	63, 64
Catenane derivatives	429
α-Arylidene cyclic ketones	430
Camphor and derivatives	431
Hydrindan derivatives	432, 433
Decalin derivatives	
α-Decalones	434
β-Decalones	435
Terpene ketones	436–438
Pseudoguaianolides	439
Bornane derivatives	440
Acetylnorbornanes	60
Bicyclooctene and other bridgehead derivatives	49
Benzocycloalkenones	441
Spiroalkanones	442
Fims	443, 444
Steroidal ketones	
General	445, 446
3-Keto steroids	447
4-Keto steroids	448
6-Keto steroids	449
11-Keto steroids	56, 450–453
12-Keto steroids	58
15-Keto steroids	57, 454
16-Keto steroids	55, 426, 455
17-Keto steroids	456, 457
20-Keto steroids	59, 230, 458, 459
Hydroxypregnanediones	460
Viridomycin acid C	461
Other natural products	
Anodendrosides	462
Carotenoids	463, 464
Cassaine	401
Cresol dehydrogenation products	465
Cucurbitacins	466
1,3-Dehydroserratinine	467
Diterpene glucosides	468
Elephantopin and related compounds	469
Gedunin and related compounds	470
C-Glucosyl derivatives	471
Hops bitter acid principles	472
Ichthyothereol	473
Meliacins	474
Polyphenol derivatives	475
Pseudoindoxyl alkaloids	476
Pseudopelletierine	477
Triterpenoids	438, 478
Vobasine	479
Zearalenone metabolites	480
Diketones	
General	481, 482
β-Diketones	86, 483, 484
2,4-Pentanedione	485
Long-chain diketones	486
2,11-Dodecanedione	487
Cyclic diketones	
β-Diketones	87, 488, 489
Dimedone and derivatives	490, 491
Cyclopentanediones and -triones	87, 492
Cyclohexanediones	488
Quinones	
Lapachols	493
Naphthoquinones	494
Piloquinone	495
Diels–Alder adducts of quinones	496
Unsaturated ketones	33, 260
α,β-Unsaturated ketones	43, 51, 497
With hydrogen γ to a triple bond	47
Aryl enones	498
Styryl ketones	499
Dienones	500, 501
Cims	502
Other bifunctional ketones	
Amino ketones	79, 80, 82, 163, 503
Epoxy ketones	504
Keto ethers	386
Keto acids	505
β-Keto sulfoxides	506
α-Stannyl ketones	507

various alkaloids.[252] The rearrangement is so useful diagnostically that alkenes are sometimes converted to carbonyl compounds in order to elucidate their structure by mass spectrometry.[253]

In summary, therefore, the McLafferty rearrangement is a widely used and valuable tool for the structure elucidation of many different classes of both synthetic and naturally occurring organic compounds.

TABLE VII. McLafferty Rearrangements to Carbon

Olefins and Other Compounds with Rearrangement to Aliphatic Carbon	
Simple Carbon Compounds	
Acetylenes	120, 121
Carotenoids	463, 464
1-Hexylcyclohexene-1	508
Monoterpenes	509
Polysubstituted olefins	508
Simple olefins	116–119
Bornane derivatives	440
Pseudoguaianolides	439
1-Adamantyl derivatives	510
$\Delta^{24(28)}$-Steroids	511
Triterpenoids	512, 513
Other Compounds	
Acetylenic alcohols	514
Alcohols	167
Amino sugars	515
Athanasia furan sesquiterpenes	516
Bufadienolides	517
1-Buten-4-ols	122
Cashew nutshell oil products	518
Chellanthatrol	519
Cholestenones	520
β-Diketone enol ethers	483
Diterpene lactones	380
Enamine esters	352
Enediols	521
α,β-Enones	51
Erigeron cumulene	522
3-Fluoro-5-androstenes	523
Kauranols	524
Limaspermin	525
Lomatin and derivatives	379
Meliacins	474
7-Methoxycoumarin derivatives	526
Phyllantidine	527
Pleiomutin	528
6-Propyl-2,3-dihydropyran-2,4-dione	529
γ-Pyrans	530
Pyrimidine dimer hydroxy adduct	531
Refractine and pleiocarpine alkaloids	532
Rimocidin aglycone derivatives	533
Triterpene lactones	378
Vinyl ethers	94
Vinyl carbinols	534
Widdrol	535
Phenyl Compounds and Others with Rearrangement to Aromatic Carbon	
Benzene Derivatives	
Aromatic alcohols	20, 21, 536–539
Benzyl alkyl ethers	20, 21
Carboalkoxypyrones	384
2,5-Dihydroxy-3-ethyl-1,4-naphthoquinone	494
2,3-Diphenylbutanes	540
Dryopteris phloroglucinol derivatives	541
N-Methyl-*O*-arylcarbamates	373
Mucronin-B	542
1-Pentyl triphenylmethyl ether	543
Phenyl butyl ether	544
2-Phenylethanol and derivatives	536–538
3-Phenylpropanol	539
o-Tolyl methanesulfonate	545
Nitrogen Aromatics	
Alkylaminopyrimidines	546
Alkylamino-1,3,5-triazines	547
Alkylpyridines and *N*-oxides	548
N-Alkylpyrroles	549
Piericidin A	550
Simazine	551
Tomatillidine	552
Vitamin B_1 models	553
Sulfur Aromatics	
2-(3-Methylbutyryl)thiophenes	554

TABLE VIII. McLafferty Rearrangements in Nitrogen Compounds

Nitrogen Derivatives of Ketones	
Hydrazones	37, 140, 141, 144
Nitrophenylhydrazones	140, 143–145, 180, 555
O-Methyl oximes	556
Oximes	136, 137, 167, 557
Schiff bases	142
Semicarbazones	138, 139, 167, 558
Alkaloids	
Acryophilline	559
Carpaine derivatives	382
Colchicine alkaloids	310
Crotonosine alkaloids	311
α-Dihydrohippeastrine	392
Indole alkaloids	560
Ipecacuanha alkaloids	561
Leurosine	562
Methyl dihydropalustraminate	405
cis-Norlobelanine	423
Oxindole alkaloids	563
Pleiocarpine derivatives	564
Pseudoindoxyl alkaloids	476
Pseudopelletierine	477
Quinine alkaloids	565
Quinolizidine alkaloids	566
Refractine–pleiocarpine class	532, 564
Rhoeadine alkaloids	567
Salamander alkaloids	568
Sarpagine	569
Schizozygin methine	570
Sparteine derivatives	571
Spermidine derivatives	572
Steroidal alkaloids	573, 574
Telea alkaloids	293
Tomatillidene	552, 575
Tropane derivatives	576
Uleine and derivatives	577
Vobasine alkaloids	578
Amino acids and derivatives	
Acetylated peptides	300
Amino esters	164, 579–581, 348
Asparagine and derivatives	582
Benzyloxycarbonyl and *tert*-butyloxycarbonyl peptides	308
Cyclic peptides	583
Cyclodepsipeptides	301, 302
Diketopiperazines	292
Phthaloylamino acids	309

TABLE VIII (Continued)

Peptides	246–251, 584
Sporidesmolides	585
Typical Nitrogen Heterocycles	
Aziridines	152
Barbiturates	294, 295, 586
Benzimidazoles	587, 588
Benzothiazolium salts	155
Benzotriazinones	589
Bisaziridinones	291
Diaziridinones	179
Hexahydrotetrazenes	590
Hydantoins	591
Imidazolines	592
Indazolones	593
Indolizines	594
Isoxazoles	201, 595, 596
Isoxazolinones	297
Morphinans	597
Oxazole S	151
Oxazolidinediones	591
Oxadiazoles	598
Oxoquinazolines	296, 599
Oxoquinolines	199, 200, 293
Oxoquinolizidines	600
Phenothiazines	601, 602
Piperidines	603
Porphyrins	225, 604, 605
Pteridines	606
Pteridin-4(3*H*)-ones	299
Purines	150
Pyrazines	149, 607
Pyrazolines	283
Pyridines	149, 548, 608
Pyridine *N*-oxides	548, 608, 609
Pyridoxin derivatives	610
Pyrimidines	531, 546, 553, 611
Pyrimidones	612
Pyrroles, *N*-substituted	549
Pyrrolidines	279, 613
Quinolines	20, 23, 148, 614–616
Riboflavin derivatives	617
Simazine	551
Sydnones	298
Thiazoline	618
Thiazolone derivatives	619
Thiazolo[3,2-*a*]pyridine oxides	620, 621
1,2,4-Triazines	406
1,3,5-Triazines	547, 622
Triazoles	240
Uracils	181, 182, 623
Other Compounds	
Amines	162, 163
Amino ketones and esters	79–81
3-Azabicyclo[3.3.1]nonan-9-ol	624
6-Azabicyclo[3.2.1]octane derivatives	625
Azasteroids	288
2-Dimethylamino-*N*,*N*′-dimethylacetamide	626
Etioluciferamine	627
Haloperidol and related neuroleptics	628
Nitrosoalkanes	629
Nitrosamines	153, 154
α-Trifluoroacetamino carbonium ions	630

TABLE IX. McLafferty Rearrangements in Sulfur Compounds

Typical Sulfur Functional Groups	
Dithiocarbonate esters	631
Dithiocarboxylate esters	632, 633
Dithiophthalimides	634
Isothiocyanates	635
β-Keto sulfoxides	506
Malathion	551
Methoxythiocarbonylamides	129
Sulfides	124, 165, 623
Sulfites	134
Sulfones	133, 636–638
Sulfonates	135, 545
Sulfonyl carbamates	639
Sulfoxides	132, 133
Thioacyl hydrazones	129
Thiocarbamoyl derivatives	283
Thioesters	20, 21, 128, 632, 633
Thioglycollates	207
Thiohydroxylamines	131
Thioureas	130, 640
Xanthate esters	240
Typical Sulfur Heterocycles	
Benzisothiazole *S*-dioxides	641
Benzothiazolium salts	155
Phenothiazenes	596, 597
Thiazolines	618
Thiazolones	619
Thiazolo[3,2-*a*]pyridine oxides	620, 621
Thiophenes	554, 642, 643

TABLE X. McLafferty Rearrangements in Phosphorus Compounds

Dialkylphosphinate esters	158
Carboalkoxyphosphonate esters	159
Malathion	551
Phosphate esters	160
Phosphochloridate esters	161
Phosphonate esters	156
β-Alkoxyethoxyphosphonate esters	157
Phosphoramidate esters	644
2-Arylaziridin-2-ylphosphonate esters	645

TABLE XI. McLafferty Rearrangements in Metal-Containing Compounds

π-Cyclohexadieneiron compounds	646
Metal complexes of 2-*n*-butyl-8-hydroxyquinolines	616
Beryllium β-diketonates	647
π-Alkyl benzoate–chromium compounds	648
Organotin complexes	507
Metal acetylacetonates	649, 650
Aluminum isopropoxide polymers	651

VII. Further Examples of the McLafferty Rearrangement

There are many further examples of the McLafferty rearrangement cited, and, in some cases, studied in the literature. We have gathered these into tables arranged according to the functional groups involved in accepting the hydrogen atom (see Tables II–XI). For several classes of compounds it was inconvenient to tabulate

data this way, and so general tables were prepared of nitrogen-, sulfur-, phosphorus-, and metal-containing compounds undergoing McLafferty rearrangements. Where appropriate, these are cross-listed with the tables according to functional group.

It is important to note that not all references from the text have been incorporated into the tables. Persons desiring a more nearly complete survey of examples for a functional group should consult both the earlier portion of this review and the tables.

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