Studies in Mass Spectrometry. XXX.[1] Substituent Effects in Mass Spectrometry. Comparison of Charge Localization and Quasi-Equilibrium Theories

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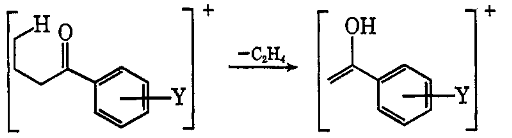
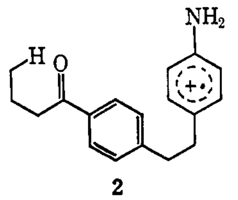
Contribution from the University Chemical Laboratory, Cambridge, United Kingdom. *Received February 6, 1968*

Abstract: It has been established that there is a general trend for the ratio $[M^+ - OMe]/[M^+]$ to decrease sharply in the mass spectra of some γ-substituted methyl butyrates as the ionization potential of the γ substituent is decreased. It is argued that in the general case of evaluating substituent effects upon the reaction $M^+ \rightarrow A^+$, the measured ratio $[A^+]/[M^+]$ is potentially dependent upon (i) a substituent effect upon the energy of activation required for reaction, (ii) a substituent effect upon the fraction (n/N) of activated complexes resulting in reactions, and (iii) a substituent effect upon the fraction of ions with insufficient energy to undergo the reaction in question. Data in the literature which are most conveniently interpreted in terms of charge localization do not appear to be inconsistent with an equilibrium hypothesis.

Important attempts have recently been made to illustrate quantitative correlations between the rate of a given fragmentation reaction of a molecular ion and the nature of an influencing substituent.[2-4] Correlations of this type require a quantitative relationship between the rate of fragmentation and the relative concentrations of the parent and fragment ions reaching the collector. The approach has been used by Wachs and McLafferty[5,6] to study the McLafferty rearrangement in some substituted butyrophenones (**1** → a). They conclude that the McLafferty rearrangement (i) is enhanced by an increased positive charge at the reaction site (the ratio $[M^+ - C_2H_4]/[M^+]$ is much greater when Y is an electron-withdrawing substituent than when it is an electron-donating substituent),[5] and (ii) is much slower (in terms of $[M^+ - C_2H_4]/[M^+]$ ratios) when a structural change in Y "has removed the site of charge localization to a position isolated from the ketone moiety" (see, for example, **2**).[6]



1, M^+ a, $M^+-C_2H_4$



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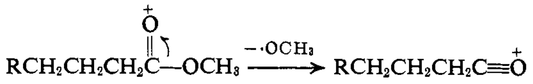
To investigate the above-mentioned concept of "charge localization,"[7] it is necessary to choose a series of compounds which undergo a facile fragmentation at one site in the molecule, while the substituent is changed to another (remote) site. γ-Substituted methyl butyrates (**3**) were chosen because (i) loss of a methoxyl radical (see b) is a common factor in the spectra of methyl esters and (ii) the intervention of three methylene groups between the substituent and carbomethoxyl groups should be sufficient in most cases to eliminate substituent effects on the stability of b.



$$RCH_2CH_2CH_2\overset{\overset{+}{O}}{\overset{\|}{C}}-OCH_3 \xrightarrow{-\cdot OCH_3} RCH_2CH_2CH_2C\equiv\overset{+}{O}$$

3 b

The steady-state treatment applied to the $M^+ - 31$ ion at low electron voltage (14 eV, at which voltage no decomposition products of the $M^+ - 31$ ion appear in the mass spectrum) gives the following relationship[4]

$$Z = \frac{[M^+ - 31]}{[M^+]} = \frac{k_A}{\sum k_{inst}}$$

where k_A is the unimolecular rate constant for the loss of methoxyl from M^+ and k_{inst} has the usual meaning. Hence, if the assumptions that (i) relative abundances at the detector reflect relative abundances in the ion chamber and that (ii) instrument constants are the same for all $M^+ - 31$ ions are valid, then Z is in proportion to the rate constants for loss of methoxyl from all the γ-substituted methyl butyrates (**4–12**).[4] The experimental values of Z are given in Table I for the compounds $RCH_2CH_2CH_2COOCH_3$, and the ionization potentials of the compounds are also tabulated. Ionization potentials were determined by use of the semilogarithmic plot method and the estimated accuracy is ±0.3 eV, with the exception of methyl γ-p-methoxyphenylbutyrate (**11**) in which case the estimated accuracy is ±0.5 eV. For our purposes, the ordering of the ionization potentials is more important than their absolute magnitude. In order to enable valid kinetic comparisons to be made, the spectra were run under identical conditions of source and heated inlet temperature, electron beam energy, and accelerator potential.

The results show that, in general, the "rate" of loss of methoxyl decreases markedly with decreasing ioniza-

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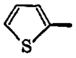
[1] Part XXIX: R. G. Cooks, I. Howe, S. W. Tam, and D. H. Williams, *J. Am. Chem. Soc.*, 90, 4064 (1968).
[2] M. M. Bursey and F. W. McLafferty, *ibid.*, 88, 529 (1966).
[3] M. M. Bursey and F. W. McLafferty, *ibid.*, 88, 4484 (1966).
[4] M. M. Bursey and F. W. McLafferty, *ibid.*, 89, 1 (1967).
[5] F. W. McLafferty and T. Wachs, *ibid.*, 89, 5043 (1967).
[6] T. Wachs and F. W. McLafferty, *ibid.*, 89, 5044 (1967).
[7] See, for example, (a) F. W. McLafferty in "Determination of Organic Structures by Physical Methods," F. C. Nachod and W. D. Phillips, Ed., Academic Press Inc., New York, N. Y., 1962; (b) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964.

Table I. Variation of [$M^+ - 31$]/[M^+] at 14 eV for the Compounds $RCH_2CH_2CH_2CO_2Me$ with Ionization Potential

Compd	R	$Z =$ [$M^+ - 31$]/ [M^+]	IP, eV	AP ($M^+ - 31$), eV
4	Cl	223	10.29	11.28
5	H	16.9	10.48	11.10
6	Br	7.15	9.85	11.15
7	CH_3CO	4.00	9.73	11.05
8	p-$NO_2C_6H_4$	0.804	8.88	11.05
9	C_6H_5	0.295	8.57	11.11
10		0.232	8.43	11.05
11	p-$MeOC_6H_4$	0.099	7.8	11.10
12	CH_3O_2C	∞	. . .	11.05

tion potential associated with the functional groups R. In terms of the charge localization approach these results would be explained in terms of (i) random (or almost random) removal of an electron from the lower lying molecular orbitals by 14-eV electrons, followed by (ii) rapid localization of the charge in the lowest lying molecular orbital.[6,8] "Rapid" in this context implies electronic reorganization at a rate which is fast compared with rates of fragmentation. Thus, in the case of methyl γ-phenylbutyrate (**9**), for example, it is argued that the charge would be localized in the phenyl ring prior to fragmentation and not on the carbonyl group (see **3** → b).

However, the above arguments do not embody all of the assumptions of the quasi-equilibrium theory (QET),[9,10] and since the compatibility (or lack of compatibility) of the QET and charge localization concepts do not appear to have been considered in detail in the literature, we think it worthwhile to discuss them here. In the QET, it is assumed that the energy of the excited molecular ion is rapidly and uniformly distributed among *all* accessible quantum states subject to energy and angular momentum restrictions. The radiationless transitions between accessible quantum states occur *via* crossing of potential surfaces, and the rate of randomization of energy is assumed to be fast compared with fragmentation rates. The validity of this latter assumption has been questioned[11-13] for small molecular ions just above the ionization potential, but in molecular ions such as those discussed in this paper it is felt that the density of electronic states is sufficiently high to permit rapid crossings of potential surfaces.

Since the transitions are assumed to be very rapid and radiationless, according to the QET all accessible quantum states corresponding to a given total internal energy ($E_{\text{int}} = E_{\text{el}} + E_{\text{vib}} + E_{\text{rot}}$) of a certain ion will be occupied with equal probability, except where degeneracy permits a proportionately higher occupancy. In the absence of collisions E_{int} is constant, E_{vib} and E_{rot} are not interconvertible (angular momentum restriction), and hence $E_{\text{el}} + E_{\text{vib}}$ is constant. Lower electronic states are not energetically more favorable. However, for lower electronic states, the number of vibrational quanta is larger. In the case of a set of similar harmonic oscillators, for n quanta and s oscillators the number of states is $(n + s - 1)!/n!(s - 1)!$ (*i.e.*, for a given internal energy, lower electronic states have more vibrational quanta and hence a greater degeneracy). In summary, in terms of the QET all accessible electronic states are in rapid reversible equilibrium, but for a given internal energy there will be marked tendency for low-lying electronic states to be more highly populated.

The model provided by the QET may be used to interpret the results presented in this paper in terms of absolute rate theory. It is postulated that a certain fraction of quantum states correspond to so-called activated complexes;[9,10] these complexes lead to fragmentation. In this discussion we are concerned with those activated complexes which lead to loss of a methoxyl radical from the molecular ion (*i.e.*, those activated complexes perhaps corresponding to the electronic state represented by **3**, and possessing sufficient vibrational energy to fragment). Equilibration between the electronic state represented by **3** and electronic states corresponding, for example, to removal of an electron from the γ substituent could, in principle, occur (i) *via* electron transfer through the hydrocarbon chain if one is considering ions of E_{int} in excess of the ionization potential of the hydrocarbon portion and/or (ii) *via* direct interaction of the γ substituent and ester group through space in the conformationally mobile butyrates. Although it is convenient to describe the electronic state from which methoxyl loss should be a relatively fast process, the treatment is not, in general, reliant on such a description. In the present case, the appearance potentials of the $M^+ - OCH_3$ ions from the compounds **4–12** are all higher than the ionization potential of methyl butyrate (see Table I). Therefore, it is established that methoxyl radicals are not eliminated until the energy supplied from the electron beam is sufficient to generate vibrationally excited forms of the electronic state corresponding to **3**.[14]

As a temporary expedient, we shall consider only those ions with a single internal energy (E_{int}) sufficient to excite activated complexes leading to loss of a methoxyl radical. The equilibrium postulate permits the assumption that the fraction of ions which are activated complexes leading to loss of methoxyl is *at all times* equal to the fraction of quantum states which represent the corresponding activated complex states.[10]

The rate of reaction (ρ) for loss of methoxyl for the given E_{int} can be equated to the concentration of activated complexes multiplied by the rate of rupture of the relevant C–O bond

$$\rho = k_x[X]$$

where [X] is the concentration of activated complexes and k_x is the unimolecular rate constant for rupture of the C–O bond. Moreover, if n,N are the number of

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(8) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, pp 10–14.

(9) H. M. Rosenstock, M. B. Wallenstein, A. L. Wahrhaftig, and H. Eyring, *Proc. Natl. Acad. Sci., U. S.*, 38, 667 (1952).

(10) H. M. Rosenstock and M. Krauss in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter 1.

(11) W. A. Chupka, *J. Chem. Phys.*, 30, 191 (1959).

(12) B. Steiner, C. F. Giese, and M. G. Inghram, *ibid.*, **34**, 189 (1961).

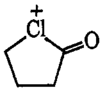
(13) W. A. Chupka and M. Kaminsky, *ibid.*, **35**, 1991 (1961).

(14) Attention is however drawn to the observation that fragmentation can occur in the vicinity of the carbonyl group of some ω-phenyl-substituted carbonyl compounds using electron beam energies insufficient to ionize the carbonyl group [J. L. Occolowitz, *Australian J. Chem.*, 20, 2387 (1967)]. For example, methyl γ-phenylbutyrate fragments *via* loss of methanol below the ionization potential of methyl butyrate. Presumably, vibrationally excited forms of methyl γ-phenylbutyrate ionized on the phenyl group are involved in this reaction.

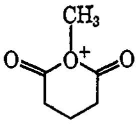
quantum states which correspond, respectively, to the activated complex and total molecular ions possessing E_{int}, then

$$[X] = (n/N)[M^+]$$
$$\rho = k_x(n/N)[M^+]$$
$$k_A = k_x(n/N)$$

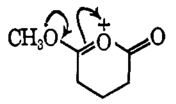
where k_A is the rate constant for the formation of $M^+ - 31$ ions from the molecular ions $[M^+]$ possessing the given E_{int}. In the general case k_x can be assumed sensibly constant for different remote γ substituents.[15] A change in the rate constant k_A could therefore be explained in terms of the change in the fraction (n/N) of activated complexes leading to methoxyl expulsion in the molecular ion. Since it has been argued previously that low-lying electronic states possessing a relatively large amount of vibrational energy will have a higher degeneracy, it can be seen that N should increase relative to n on lowering the ionization potential of a remote γ substituent in the substituted methyl butyrates, and in this way the treatment would account qualitatively for the data recorded in Table I. In only two of the compounds is the rate of loss of methoxyl not in accord with the treatment; when R = CH_3O_2C or Cl, the reaction is much "faster" than anticipated (Table I). In these cases, there are good reasons to believe that k_x will be greatly increased because of the nature of R. Thus chlorine may participate to some extent in the expulsion of a methoxyl radical to give the cyclic ion c,[17] while analogous cyclic species (d or d′) can be generated when R = CH_3O_2C.



c



d



d′

The discussion has so far neglected the presence of an energy distribution among the various molecular ions. Obviously the parameters taken from the mass spectrum represent mean k values, averaged over a whole range of specific k values. Thus the $[M^+ - 31]/[M^+]$ ratios may not only be a function of n/N (now summing the various n/N ratios for all possible values of E_{int} which can result in loss of a methoxyl radical) and k_x, but also of the possibly different energy distributions present in the molecular ions of compounds **4**–**12**.

It is important to remember that the ions in the ion source are noninteracting and hence that the original energy distribution is not subject to change and so determines completely which ions can and cannot dissociate. The consideration that 14-eV electrons may produce positive ions by transferring any amount of energy between the limits of the ionization potential and 14 eV, immediately illustrates that the energy distributions must be different for each compound. Indeed, if the amount of energy which is transferred from the electron beam is less than the appearance potential of the M − 31 ion, but as high or higher than the ionization potential of the compound in question, then ions will be produced which cannot equilibrate with the activated complexes leading to loss of a methoxyl radical. The fraction of such ions with insufficient energy to decompose by loss of a methoxyl radical should increase with decreasing ionization potential and will contribute to a change in the measured $[M^+ - 31]/[M^+]$ ratio with changing ionization potential of the γ substituent. To measure crudely the fraction of such ions, we have derived an internal energy distribution from the consideration of three factors. The probability of producing an ion of given energy (E) will be dependent upon (i) the cross-section effect,[18] (ii) the Franck–Condon factor for the transition,[19] and (iii) number and degeneracy of quantum states corresponding to that internal energy.[19] We have assumed that the cross section effect is proportional to the energy excess $E_{\text{el}} - E$ where E_{el} is the electron beam energy. We have further assumed that the combined effect of factors ii and iii causes an increase in transition probability and that this probability increases linearly with $E - IP$. This latter assumption is of course greatly oversimplified but does provide a useful working model for 14-eV electrons. The rate of increase in transition probability due to factor iii alone will be very large with increasing $E - IP$. The nature of factor ii is very much in doubt for electron impact upon large polyatomic molecules, and it may initially be difficult to see how it could compensate for the very rapid rise in transition probability due to factor iii. However, it has recently been established that such compensation does occur in the photoionization of some aromatic molecules.[20] While it is appreciated that differing energy distributions result from photon and electron impact, the overall similarity of spectra obtained at low electron beam energies or by using 21.21-eV photons, in conjunction with the experimental energy distributions for photon impact, encourage us in the belief that the simple model is useful.

Therefore, if f(E)dE is the fraction of ions having an internal energy between the limits E and $E + dE$, then

$$f(E)dE = A(E_{\text{el}} - E)(E - IP)dE$$

where A is a constant. The constant A can be evaluated by normalizing the integrated area under the f(E) *vs.* E curve to unity, *i.e.*

$$\int_{IP}^{E_{\text{el}}} f(E)dE = \int_{IP}^{E_{\text{el}}} A(E_{\text{el}} - E)(E - IP)dE = 1$$

Integration of this expression gives

$$A = \frac{6}{(E_{\text{el}} - IP)^3}$$

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(15) One could anticipate an apparent significant increase in k_x with increasing size of the γ substituent. In the one available study,[16] it has been shown that the abundance of primary product ions *vs.* that of the molecular ions generally increases with an increase in the number of degrees of freedom. However, this factor is obviously unimportant relative to other effects in the present case since, for example, the $[M^+ - 31]/[M^+]$ ratio for **9** is greater than for **11**. An opposite effect would be predicted if the degree of freedom factor were dominant.

(16) F. W. McLafferty and W. T. Pike, *J. Am. Chem. Soc.*, **89**, 5951 (1967).

(17) Chlorine has previously been postulated to act as a bridging atom in the formation of five-membered cyclic ions [see F. W. McLafferty, *Anal. Chem.*, **34**, 2 (1962)].

(18) S. Geltman, *Phys. Rev.*, **102**, 171 (1956).

(19) See, for example, M. Krauss and V. H. Dibeler in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, p 121.

(20) A. D. Baker, D. P. May, and D. W. Turner, *J. Chem. Soc., B*, 22 (1968).

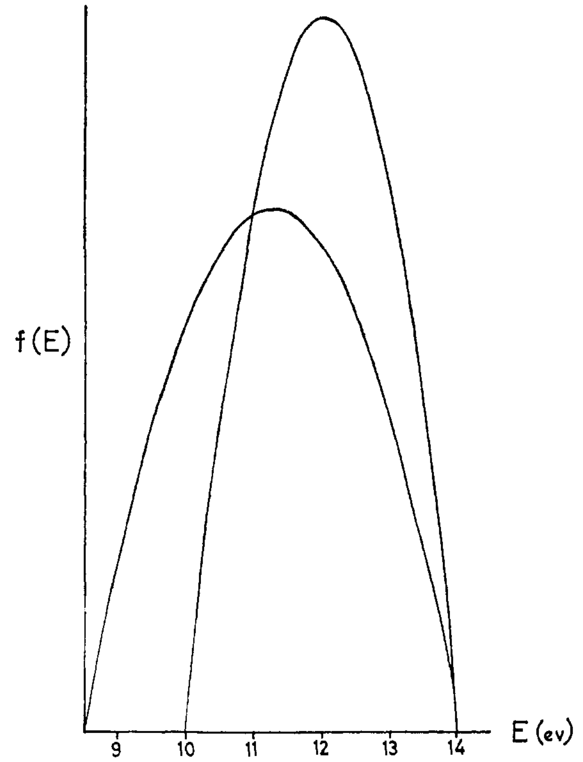
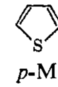


Figure 1. Comparison of calculated energy distributions in the 14-eV spectra of compounds with ionization potentials of 8.5 and 10.0 eV.

When the fraction of ions possessing a given internal energy is plotted against that internal energy, a parabolic-shaped energy distribution curve is obtained (Figure 1). Energy distributions corresponding to 14-eV spectra of compounds with arbitrarily chosen ionization potentials of 8.5 and 10.0 eV are compared in Figure 1. The areas under the curves have been normalized using the above expression for *A*. It is clear from the comparison made in Figure 1, that since the appearance potentials of the $M^+ - 31$ ions from **4–12** are similar, the fraction of ions which do not possess sufficient internal energy to possibly dissociate by loss of a methoxyl radical will increase on lowering the ionization potential of the compound. The percentage of total ion current carried by the various molecular ions of **4–12** is given in Table II, and compared with the calculated percentage of ions with insufficient energy to possibly dissociate by loss of methoxyl.

Table II. Fraction of Total Ion Current ($\% \Sigma_{30}$) Carried by Molecular Ions in Relation to Calculated Fractions (%) of Ions with Insufficient Energy to Lose Methoxyl

Compd	R	M^+ ($\% \Sigma_{30}$)	Ions,[a] %
4	Cl	0.2	13
5	H	1.5	8
6	Br	4	19
7	CH_3CO	3	23
8	*p*-$NO_2C_6H_4$	6	35
9	C_6H_5	22	43
10		33	46
11	*p*-$MeOC_6H_4$	43	55
12	CH_3O_2C	0	. . .

[a] With insufficient energy to lose methoxyl.

The data accumulated in Table II emphasize the possibility that the abundance of the molecular ion will be affected by a change in the fraction of ions with insufficient energy to undergo the reaction in question (although the latter ions will, of course, be able to undergo other, more facile reactions to some extent). Clearly, if the substituent effect on $[A^+]/[M^+]$ in part reflects a change in the fraction of ions with insufficient energy to undergo the reaction in question, the substituent effect on $[A^+]/[M^+]$ may not in all cases be securely interpreted to support a certain mechanism for that reaction.[21]

In summary, it may be stated that the relative abundances of ions A^+ and M^+, measured in a mass spectrometer for the electron impact induced reaction $M^+ \rightarrow A^+$, will potentially be a function of all the following variables (on varying the nature of a substituent group). (1) There may be a tendency for $[A^+]/[M^+]$ to increase as the number of degrees of freedom in the substituent is increased.[16] (2) There may be a substituent effect on the actual rate (k_x) of the reaction under consideration (*i.e.*, the substituent may change the energy of activation for the reaction). (3) There will be a substituent effect upon the fraction (n/N) of activated complexes leading to the reaction under consideration. (4) The introduction of a substituent of low ionization potential can make accessible quantum states which are unable to equilibrate with the activated complexes leading to the reaction under consideration.

In the present work, where $[M^+ - 31]/[M^+]$ ratios are much lower than for methyl butyrate (see compounds **8–11**, Table I), it is believed that effects 1 and 2 are relatively small and that the decreases in $[M^+ - 31]/[M^+]$ are largely associated with effects 3 and 4.[22]

The treatment has important consequences for the significance of ρ values obtained from substituent effects on reaction rates (*i.e.*, values obtained from log Z/Z_0 *vs.* σ plots).[2–5,23] In general, the effect of introducing an electron-donating substituent into an aromatic ring is to lower the ionization potential. Hence, effect 4 will tend to make ρ values more positive for a reaction $M^+ \rightarrow A^+$. Even ignoring effect 4, if the new quantum states which are introduced by lowering the ionization potential are ones from which the reaction under study either does not occur, or is slower, then the measured daughter ion to parent ion ratio will decrease due to a decrease in n/N, even in the absence of a substituent effect on k_x. The problem is that substituents, in addition to possibly modifying reaction rates from the various electronic states, will also alter the relative populations and numbers of electronic states.

The above conclusions are based on the initial assumptions of the QET. If one admits also the possibility of competing radiative transitions prior to fragmentation, then this could have the effect of increasing the population of ions with insufficient energy to pos-

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[21] A referee has pointed out that a change in the value of the exponent of $E - IP$, would not change the nature of the conclusion drawn from Figure 1, since the pair of curves while different from those drawn would still have the same relative relation to each other.

[22] In addition to the four effects enumerated above, we have recently been able to show that the ratio $[A^+]/[M^+]$, measured for the reaction $M^+ \rightarrow A^+$ at the collector, may not accurately reflect the relative concentrations of A^+ and M^+ in the source; the error is a function of the reaction rate [I. Howe and D. H. Williams, *Chem. Commun.*, 220 (1968)]. The error is greatest when the transition under consideration gives an abundant metastable peak, but will be negligible in the present context.

[23] P. Brown and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 2711 (1967).

sibly lose methoxyl for a substituent of low ionization potential in the present work. However, we are not in a position to evaluate this possibility at present. It is noteworthy that in terms of the tenets of the QET, the concept of charge localization[7] has proved a useful expedient (with even predictive power) due to a combination of the following reasons. (a) The larger majority of accessible electronic states are in rapid reversible equilibrium, but lower lying electronic states are more highly populated due to the large number of associated vibrational states. (b) For a given internal energy, the lower lying electronic states have more vibrational energy and on these grounds (as well as in terms of population) decomposition from them is more probable given comparable activation energies for decomposition in comparison with higher electronic states—see (c). (c) The electronic state corresponding to an electron missing from the highest occupied molecular orbital can lead to fragmentation *via* processes of low activation energy in those cases where the charge localization concept has been most successful (*e.g.*, ketals[24] and dimethylamino compounds[25]).

However, it is important to remember that the equilibrium hypothesis would appear to be capable of explaining existing data, and therefore the charge is not necessarily localized in the classical sense, except perhaps in a small fraction of ions of relatively low internal energy.[26]

Experimental Section

All spectra were determined using an AEI MS9 mass spectrometer operating at a source temperature of 170°, a heated inlet temperature of $\sim$150°, electron beam energy of 14 eV, and an accelerator potential of 8 kV. All samples were introduced *via* the heated inlet system.

The esters were either commercially available or preparable from the corresponding commercially available acids with diazomethane. Purity was checked by melting point or vapor phase chromatography and, where impure, the compounds were purified by recrystallization and vapor phase chromatography, respectively.

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[24] (a) H. Audier, M. Fetizon, J.-C. Gramain, J. Schalbar, and B. Waegel, *Bull. Soc. Chim. France*, 1880 (1964); (b) J. T. B. Marshall and D. H. Williams, *Tetrahedron*, 23, 321 (1967); (c) Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, 86, 3722 (1964).

[25] H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol II, Holden-Day, Inc., San Francisco, Calif., 1964, Chapters 17 and 18.

[26] NOTE ADDED IN PROOF. Since this paper was submitted, other relevant papers dealing with "charge localization" and substituent effects have been published (or are in press) see A. Mandelbaum and K. Biemann, *J. Am. Chem. Soc.*, 90, 2975 (1968); R. G. Cooks, R. S. Ward, I. Howe, and D. H. Williams, *Chem. Commun.*, in press; F. W. McLafferty, *ibid.*, in press. We wish to thank Professor McLafferty for sending to us a copy of his manuscript *prior to* publication.

Mass Spectrometry in Structural and Stereochemical Problems. CLXI.[1] Elucidation of the Course of the Characteristic Ring D Fragmentation of Steroids[2]

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Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received May 9, 1968*

Abstract: The electron impact induced fragmentation of ring D in steroids, which involves loss of carbon atoms 15, 16, and 17 together with their substituents, is of considerable mechanistic as well as structural significance. It appears to be the most general fragmentation of steroids and lends itself to a convenient determination of the length of the C-17 side chain. These fissions of the 13–17 and 14–15 bonds occur with and without the apparent transfer of a hydrogen atom, and several mechanistic proposals have been made during the past 10 years about the nature of these processes. Extensive deuterium labeling of virtually all carbon atoms in 5α-cholestane or 5α-pregnane has shown that all of the earlier proposals were partly or totally incorrect. It has now been found that the cleavage of the 13–17 and 14–15 bonds is not a simple reaction but rather involves the reciprocal transfer of hydrogens from C-16 and C-18, apparently to make possible the expulsion of an olefin rather than of a cyclopropane. The single hydrogen transfer accompanying the alternative ring D fragmentation has been shown to originate largely from C-14, and a rationalization for such a (generally unfavorable) fission of two bonds connected to one carbon atom is offered. The availability of the various deuterated analogs, whose syntheses are described in this paper, has also made possible mechanistic assignments to many of the other fragment ions.

The potential application of mass spectrometry to the structure elucation of steroids was noted over 10 years ago,[5] and shortly thereafter it was recognized that one of the most general fragmentations of sterols and related C-17-substituted steroids is the loss of 42 mass units together with the C-17 side chain. It is interesting to note that the variety of proposals offered as rationalizations for this characteristic fragmentation encompass in chronology as well as in terms of conceptual approach virtually the entire history of organic mass spectrometry. In the case of steroid hydrocarbons such as 5α-cholestane (X) and 5α-pregnane

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[1] For paper CLX, see T. Muraski and C. Djerassi, *J. Org. Chem.*, 33, 2962 (1968).

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[3] Taken in part from the Ph.D. thesis (1965) of L. T.

[4] Postdoctoral fellow (1966–1967) and recipient of a Fulbright Travel Grant from the U. S. Educational Commission in the United Kingdom.

[5] P. de Mayo and R. I. Reed, *Chem. Ind.* (London), 1481 (1956).