Mass Spectrometry in Structural and Stereochemical Problems. CXLIV.[1] Unusual Fragmentations in the Low-Voltage Spectra of Aliphatic Ketones[2]

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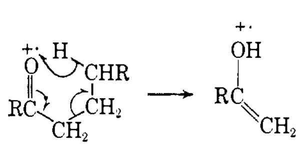
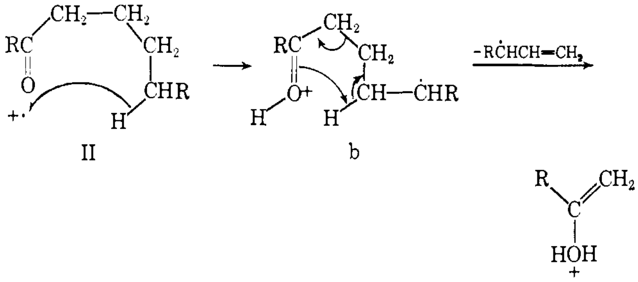
Abstract: An examination of the mass spectra of isotopically labeled aliphatic ketones at low voltage (10 ev) has shown that deuterium scrambling occurs among carbon atoms of the aliphatic chains. The site specificity of the "protonated McLafferty rearrangement" ion has been determined and an interesting reciprocal hydrogen-transfer process has been shown to operate in the genesis of the peak at *m/e* 71 in the spectrum of 2-octanone. An ion corresponding to the McLafferty rearrangement plus 14 mass units has been found to be an important fragmentation of aliphatic ketones at low voltage.

Much information has been obtained regarding the mass spectrometric fragmentation of aliphatic ketones[4a] and in particular their propensity of undergoing the McLafferty rearrangement (I → a).[5]



I a

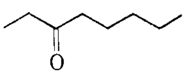
In addition to the McLafferty rearrangement (I → a), a correspoinding double hydrogen-transfer process[4b] has been observed in the mass spectra of aliphatic acids[6] and ketones.[7] Although a postulate has appeared in the literature[7] regarding the site specificity (II → b → c) of this double hydrogen-transfer process, no deuterium labeling studies have been performed to resolve this interesting problem.



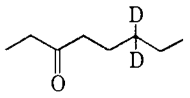
II b c

During our studies of the mass spectra of a series of diverse aliphatic ketones at low electron voltages (10–12 ev)[8] we observed the increased importance of the "protonated McLafferty rearrangement ions" relative to their abundance at 70 ev (*cf.* Figures 1–6a). Selected positions of the hexyl chain of 2-octanone were specifically labeled with deuterium in an attempt to identify the sites of hydrogen abstraction in this energetically highly favorable process.

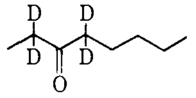
Before proceeding to a discussion of this rearrangement process, mention must be made of an interesting phenomenon noted in the low-voltage (10–12 ev) spectra of aliphatic ketones specifically labeled with deuterium. Evidence has been obtained for randomization along the carbon atoms of the alkyl chains of deuterium initially introduced site specifically. A discussion of the low-voltage mass spectra of 3-octanone (III) (Figure 1a) and its deuterated analogs IV, V, and VI (Figures 2, 3, and 4) will serve as examples of this randomization process which was also observed in isobutyl *n*-butyl-3,3-d_2 ketone and deuterated analogs of 2-octanone.



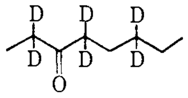
III



IV



V



VI

The low-voltage (10 ev) spectra (Figures 1a–4) of 3-octanone and its deuterated analogs IV, V, and VI in the range *m/e* 99–104 are particularly revealing. Thus, 3-octanone (III) at 10 ev (Figure 1a) has a base peak at *m/e* 99 corresponding to loss of an ethyl radical by the usual α-cleavage to the acylium ion. In the deuterated analogs V and VI, the low-voltage spectra (Figures 3 and 4) display prominent peaks at *m/e* 102 and 103 and at *m/e* 104 and 105, respectively, in addition to the anticipated peaks at *m/e* 101 and 103, due in each instance to M − CH_3CD_2. The peaks at higher mass must arise in each case from a depletion of the deuterium content of the la-

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[1] Part CXLIII: W. Carpenter, A. M. Duffield, and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 6164 (1967).

[2] Financial assistance (Grant No. AM 04257) from the National Institutes of Health of the U. S. Public Health Service is gratefully acknowledged. The purchase of the Atlas CH4 mass spectrometer was made possible by National Aeronautics and Space Administration Grant NsG 81-60.

[3] Recipient of a Senior Postdoctoral Fellowship while on leave from the U. S. Naval Ordnance Test Station, China Lake, Calif.

[4] (a) For a detailed and up-to-date coverage see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, Chapters 3 and 4. (b) As shown in Chapter 4, such double hydrogen transfers are also common in the spectra of certain esters. Steroid lactones apparently behave in a similar fashion: S. Meyerson, *et al.*, *Can. J. Chem.*, **44**, 279, 1866 (1966).

[5] F. W. McLafferty, *Anal. Chem.*, 31, 82 (1959). For an extensive review, see Sections 3-7 in ref 4.

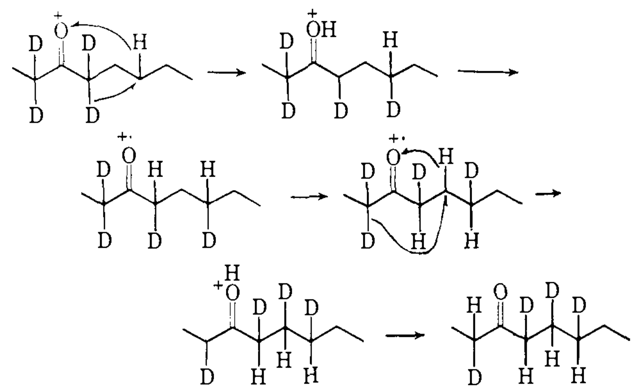
[6] N. C. Rol, *Rec. Trav. Chim.*, **84**, 413 (1965).

[7] G. Spiteller, "Massenspektrometrische Strukturanalyse organischer Verbindungen," Verlag Chemie, Weinheim, 1966, p 127.

[8] W. Carpenter, A. M. Duffield, and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 6167 (1967).

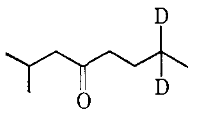
beled ethyl chain. The mass spectrum (Figure 2) of dideuterated 3-octanone IV shows that the ethyl chain is lost by α cleavage (M − 29), while an additional peak is seen one mass unit lower, which can arise only from deuterium exchange with the ethyl chain. This deuterium exchange at low voltage between carbon atoms of alkyl chains can be explained by the rationalization presented in Scheme I.

Scheme I



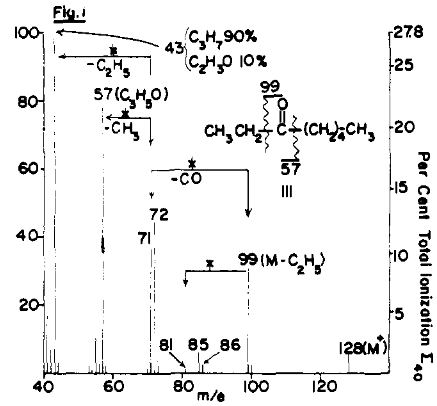
The alternative α-cleavage fragmentation (loss of the n-pentyl chain) in 3-octanone (III) is minimal at 10 ev,[8] and the degree of deuterium scrambling is impossible to define using this peak: the lower the energy of the incident electron beam, the greater the degree of scrambling. The 9-ev spectrum of the hexadeuterated analog VI of 3-octanone in the region m/e 100–105 bears a strong resemblance to that predicted on a statistical basis[9] for random hydrogen–deuterium exchange between the six methylene groups.

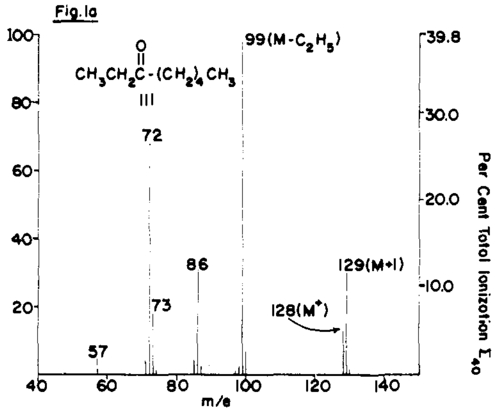
Although equilibration of deuterium between carbon atoms of aliphatic ketones is particularly manifest at low voltage, some small amount of exchange evidently also occurs at 70 ev. For example, the 70-ev mass spectrum (Figure 5) of isobutyl n-butyl-3,3-d_2 ketone (VII) contains a small peak at m/e 86 which is slightly greater than the isotope peak of m/e 85 plus the calculated amount of the d_1 species from m/e 87, and this slight discrepancy may arise from exchange of deuterium between the n- and isobutyl groups of VII followed by α cleavage of the equilibrated compound. Small peaks whose origin can be explained in an analogous fashion were found adjacent to the "M − 29 peak group" in the 70-ev mass spectra of the deuterated analogs IV, V, and VI of 3-octanone.

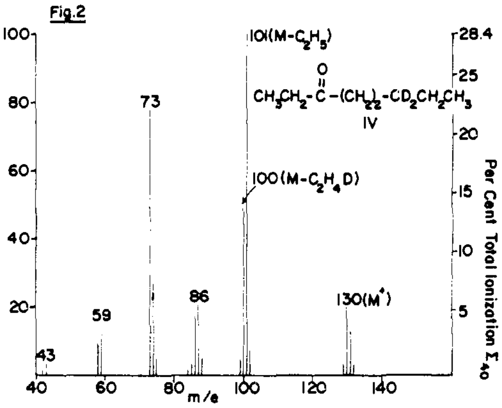


VII

"MacLafferty Plus One" Rearrangement. The 70-ev mass spectrum (Figure 6) of 2-octanone (VIII) contains a peak at m/e 59 which corresponds to a "protonated rearrangement" species. At low voltage (10 ev; Figure 6a) this fragmentation mode is markedly enhanced. In order to determine the points of origin of the transferred hydrogen atoms, we have prepared 2-octanone specifically labeled with deuterium at C-5,







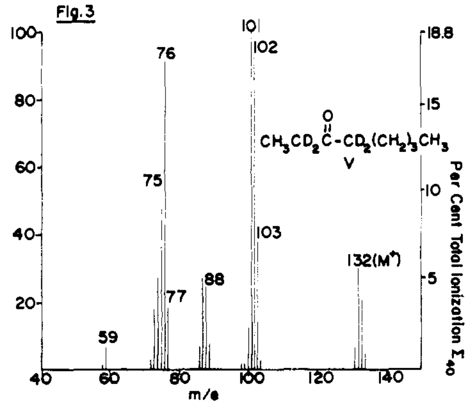


Figure 1. Mass spectrum of 3-octanone at 70 ev.
Figure 1a. Mass spectrum of 3-octanone at 10 ev.
Figure 2. Mass spectrum of 3-octanone-6,6-d_2 at 10 ev.
Figure 3. Mass spectrum of 3-octanone-2,2,4,4-d_4 at 10 ev.

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(9) Based on the formula

$$P = \{100n!/[(n-x)!x!]\}p^x q^{n-x}$$

where P = percentage of the α-cleavage product containing x deuterium atoms; p = ratio of the number of exchangeable sites of the n-pentyl chain to the total number of exchangeable sites (11:16); $q = 1 - p(^5/_{16})$.

Fig.4

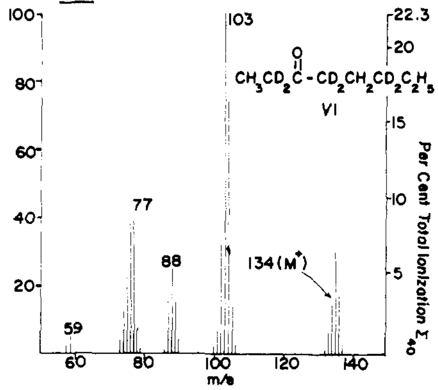


Fig.5

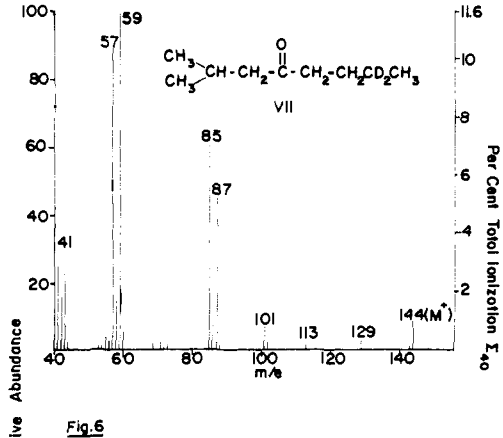


Fig.6

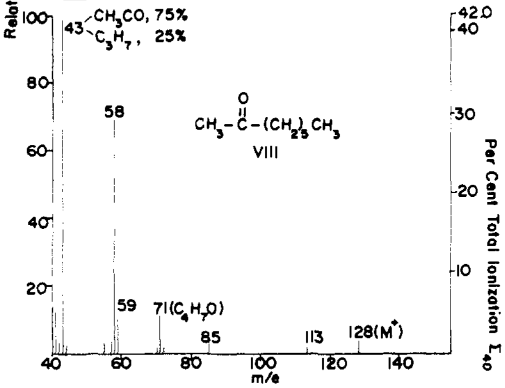


Fig.6a

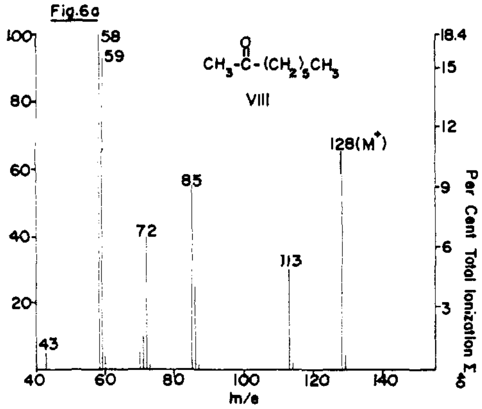


Figure 4. Mass spectrum of 3-octanone-2,2,4,4,6,6-d_6 at 10 ev.

Figure 5. Mass spectrum of isobutyl *n*-butyl-3,3-d_2 ketone at 70 ev.

Figure 6. Mass spectrum of 2-octanone at 70 ev.

Figure 6a. Mass spectrum of 2-octanone at 10 ev.

C-6, C-7, and C-8, as well as the 1,1,1,3,3-d_5 analog. The low-voltage (10 ev) spectra of these derivatives show unmistakable signs of partial randomization of deuterium as seen from the presence of M − CH_3 and M − CH_2D ions. In view of this exchange the percentage transfer of deuterium in the labeled 2-octanones at 10 ev (Table I) will be expected to be erroneous to an unknown degree. For this reason we have calculated the percentage transfer of deuterium at 70, 15, 12, and 10 ev, and it is apparent that the results for 70- and 15-ev electrons agree within experimental error and that only at lower electron voltages are the anticipated discrepancies observed. Although no evidence of randomization of deuterium was witnessed at either 70 or 15 ev, the equilibration may have occurred to a small extent and hence the values quoted for these energies are considered reliable to only ±5% since, in addition, the peak in question (*m/e* 59) is only of relatively low abundance at higher electron energies.

Table I. Mass Distribution of Ion c in Deuterated Analogs of 3-Octanone

VIII	Isotopic purity	% relative abundance at 70 ev	15 ev	12 ev	10 ev
5,5-d_2	98% d_2	59 (31)	59 (33)	59 (33)	59 (53)
	2% d_1	60 (69)	60 (67)	60 (67)	60 (47)
6,6-d_2	90% d_2	59 (33)	59 (38)	59 (40)	59 (47)
	10% d_1	60 (67)	60 (62)	60 (60)	60 (50)
					61 (3)
7,7-d_2	96% d_2	59 (62)	59 (62)	59 (45)	59 (50)
	2% d_1	60 (38)	60 (38)	60 (45)	60 (44)
	2% d_0				61 (6)
8,8,8-d_3	97% d_3	59 (85)	59 (85)	59 (90)	59 (93)
	3% d_0	60 (15)	60 (15)	60 (10)	60 (7)
1,1,1,3,3-d_5	88% d_5	64 (100)	64 (100)	64 (100)	63 (10)
	10% d_4				64 (90)
	2% d_3				

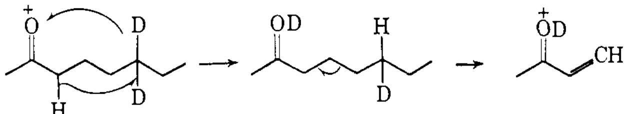
The values in Table I for the percentage of hydrogen transfer at 70 ev from the *n*-hexyl chain of 2-octanone (VIII) show that the so-called "McLafferty plus one rearrangement" is not just a normal site-specific McLafferty transfer[7] (C-5 of 2-octanone) followed by abstraction of a second hydrogen atom. Indeed, this double hydrogen-transfer process must be a unique mechanism in which transfer of hydrogen through six- and seven-membered ring intermediates are clearly the ones of preference, while an additional contribution arises through an eight-membered intermediate (Table I). The utilization of six-, seven-, and eight-membered transition states, in preference to all other ring sizes, has been shown to operate in a double hydrogen rearrangement process of aliphatic ethers.[1]

m/e **71 Peak of 2-Octanone.** The peak at *m/e* 71 in the 70-ev spectrum (Figure 6) of 2-octanone is oxygen containing to the extent of 95% as shown by high-resolution mass measurements. Ordinarily, such a peak would not have excited undue interest since it nominally corresponds to simple cleavage of the C-4, C-5 carbon–carbon bond. However, a displacement in part to *m/e* 72 was observed in some of the deuterated analogs (Table II) of 2-octanone. Hence, a reciprocal hydrogen-transfer process must be operative in a portion (~75%, Table II) of the genesis of this ion.

Table II. Mass Distribution at 70 ev of Ion e, *m/e* 71, in Deuterated Analogs of 2-Octanone

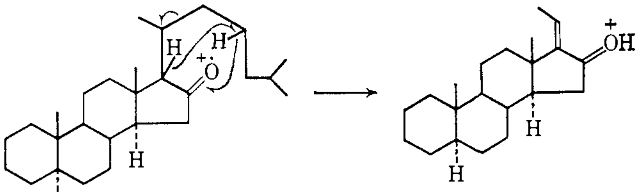
VIII	Isotopic purity	% relative abundance at 70 ev
5,5-d_2	98% d_2	71 (95)
	2% d_1	72 (5)
6,6-d_2	90% d_2	71 (60)
	10% d_1	72 (40)
7,7-d_2	96% d_2	71 (70)
	2% d_1	72 (30)
	2% d_0	
8,8,8-d_3	97% d_3	71 (100)
	3% d_0	
1,1,1,3,3-d_5	88% d_5	74 (22)
	10% d_4	75 (60)
	2% d_3	76 (18)

A mechanistic rationalization invoking a reciprocal hydrogen-transfer process for the formation of part (40%) of the ion yield at mass 71 is depicted by VIIIa → d → e. This mechanism received support from the 70-ev spectrum of 2-octanone-1,1,1,3,3-d_2 in which the peak at *m/e* 71 in the unlabeled compound is located to the extent of 60% at *m/e* 75.



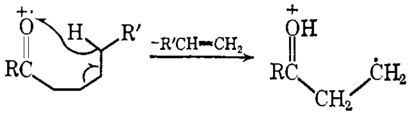
VIIIa d e, *m/e* 72

The genesis of ion e is very similar to a reciprocal hydrogen-transfer process shown to be operative in the genesis of the important *m/e* 301 peak in the mass spectrum of cholestan-16-one (IX).[10]



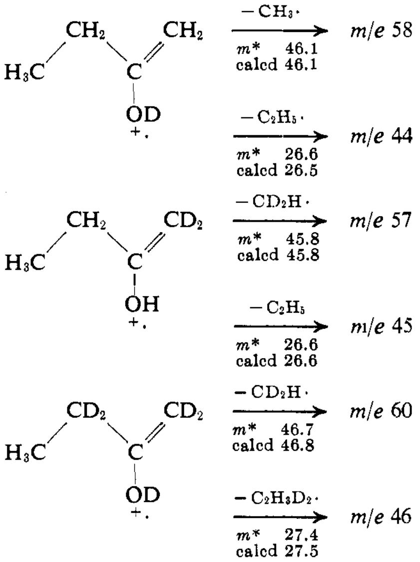
IX *m/e* 301

"McLafferty Plus 14" Ions. The mass spectra of aliphatic ketones determined with low energy electrons (10 ev) often exhibit prominent ions corresponding to the McLafferty rearrangement plus 14 mass units, and a metastable ion in the 70- and 12-ev spectra of 3-octanone indicated that this fragment arose directly from the molecular ion. A similar phenomenon has been observed in the 70-ev spectra of aliphatic acids.[6] As we observed these peaks in reasonable yields only while working at low voltage, under conditions shown to produce deuterium scrambling, we were frustrated in our attempt to determine the site specificity of this process from label transfer in the deuterated analogs. In any event, the process appears to be of the following type.

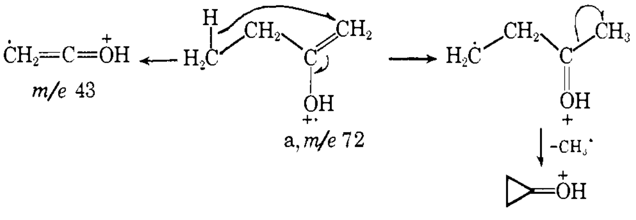


In connection with our studies of the low-energy spectra of aliphatic ketones we have made a detailed investigation of the metastable peaks present in the 70-ev spectra of these compounds and have demonstrated the occurrence of some interesting, although relatively minor, fragmentation processes. For example, the McLafferty rearrangement ion a (R = C_2H_5; *m/e* 72) derived from 3-octanone eliminates both a methyl and an ethyl radical, generating peaks (Figure 1) at *m/e* 57 and 43. The occurrence of metastable ions pertaining to the loss of methyl and ethyl radicals from the McLafferty rearrangement ion of deuterated analogs of 3-octanone are summarized in Scheme II.

Scheme II



Based on the results presented in Scheme II, a consistent rationalization for the loss of a methyl and an ethyl radical from the McLafferty rearrangement product of 3-octanone (a, R = C_2H_5) can be written as follows.



Another interesting decomposition, supported in all cases by the appropriate metastable ion, is the loss of water from the α-cleavage product (RCO^+) provided R ⩾ n-C_5. The driving force for this complex rearrangement (transfer of at least four hydrogen atoms being involved) evidently is the formation of water and a stable carbonium ion, and one possible rationalization is presented for the loss of water from one α-cleavage product (*m/e* 99) of 3-octanone (see equation below).

In summary, it may be seen that the generalizations about the mass spectral behavior of aliphatic ketones (one of the most widely studied groups of organic compounds in mass spectrometry)[4] from 70-ev spectra frequently do not apply to low-voltage spectra. This is true of the ubiquitous α fission[8] as well as of the hydrogen rearrangements outlined above. Fortunately, hydrogen randomizations occur principally at

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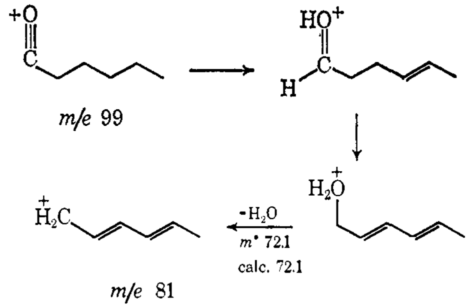
(10) C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 269 (1964).



low voltages,[11] since otherwise their occurrence would preclude the use of the powerful deuterium labeling technique for mechanistic purposes. It is important to be cognizant of this limitation in order to avoid gross misinterpretations based on low-voltage spectra of deuterated ketones. Work on the nature of the ionized species undergoing such hydrogen rearrangements is clearly indicated, and a potentially fruitful approach may consist of detailed photoionization studies.

Experimental Section[12]

Deuterated Ketones. Isobutyl *n*-butyl-3,3-d_2 ketone has been described previously.[14] All 2-octanones labeled in the hexyl chain beyond the α-carbon atom were prepared from the corresponding labeled hexyl bromides which were first converted to the Grignard reagents and then treated with an excess of acetaldehyde to form the labeled 2-octanols. These were converted to the ketones by Jones' oxidation.[15] Final purification was performed by preparative gas chromatography. The procedure for γ-labeled 3-octanones was identical with the above except that the Grignard reagent of phenyl-3,3-d_2 bromide[16] was treated with propionaldehyde.

α Deuteration of Ketones. The α deuteration of 3-octanone was performed by a double exchange in methanol-O-*d*, using a trace of potassium hydroxide as catalyst. 3-Octanone-2,2,4,4,5,5-d_6 was prepared from 3-octanone-5,5-d_2 by double exchange in acidic deuterium oxide.[17] α-Deuterated 2-nonanone and 3-octanone were prepared by a single passage through an acidic deuteration gas chromatographic column.[18]

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(11) Instances of hydrogen–deuterium exchange prior to fragmentation at higher electron energies have been discussed by F. W. McLafferty, *Anal. Chem.*, 31, 82 (1959), and for certain esters by E. Stenhagen, *Chimia*, 20, 349 (1966), while W. A. Bryce and E. W. C. Clarke, "Advances in Mass Spectrometry," J. D. Waldron, Ed., Pergamon Press, London, 1959, p 392, have observed an increase in hydrogen–deuterium exchange in 1-butene-4-d_3 on reducing the electron energy of the incident electrons.

(12) All low-resolution mass spectra were determined with an Atlas CH4 mass spectrometer, using the TO-4 ion source (temperature 200°) and a gas cartridge. All low-voltage spectra correspond to nominal electron volt values and were recorded with zero potential on the draw-out plates of the gas cartridge. Metastable peaks were observed with the aid of a logarithmic transfer recorder.[13] Some of the low voltage spectra were repeated on the MS-9 and CEC-103C mass spectrometer, and in these instances the spectra were similar to those determined on the Atlas CH4 instrument except that no $M + 1$ or $M + 2$ ions were observed.

(13) R. T. Aplin, H. Budzikiewicz, H. S. Horn, and J. Lederberg, *Anal. Chem.*, 37, 776 (1965).

(14) H. Budzikiewicz, C. Fenselau, and C. Djerassi, *Tetrahedron*, 22, 1391 (1966).

(15) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(16) S. Sample and C. Djerassi, *J. Am. Chem. Soc.*, **88**, 1937 (1966).

(17) J. Seibl and T Gäumann, *Helv. Chim. Acta*, **46**, 2857 (1963).

(18) W. J. Richter, M. Senn, and A. L. Burlingame, *Tetrahedron Letters*, 1235 (1965).