Mass Spectrometry in Structural and Stereochemical Problems. CLXXXVIII.[1] The Electron Impact Induced Behavior of Branched Ketones and Esters, with Special Emphasis on Hydrogen Rearrangements[2]

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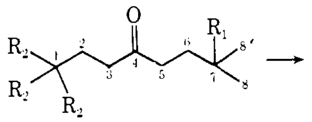
Abstract: Striking differences in the specificity of hydrogen transfers between straight chain and certain branched ketones and esters have been uncovered. Thus, the mass spectra of deuterated analogs of 7-methyl-4-octanone (I) and several other γ- and δ-branched carbonyl compounds exhibit strong evidence that partial hydrogen–deuterium randomization is occurring, even at ordinary ionizing voltages. The extent of randomization appears to be independent of ionizing voltage in the 70–15-eV range. The mass spectrum of the parent compound (I) exhibits an important peak at *m/e* 81, corresponding to the loss of water from the α-cleavage ion. Similar peaks were observed in the mass spectra of numerous homologous ketones, demonstrating the diagnostic utility of this hitherto largely ignored fragmentation. The origins of the hydrogen atoms eliminated in this unusual process were studied, and a plausible mechanism, supported by ion cyclotron resonance studies, was suggested.

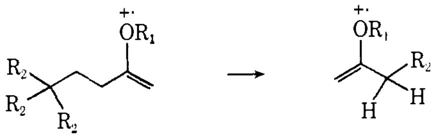
The electron impact induced behavior of aliphatic ketones has been subjected to intense scrutiny since the early days of mass spectrometry.[4] It is remarkable, however, that this scrutiny has largely been confined to straight-chain ketones, presumably because it was assummed that the mass spectra of branched-chain ketones would not differ markedly from those of their straight-chain analogs. However, a cursory examination of the mass spectra of 7-methyl-4-octanone (I) and several deuterated analogs (prepared in connection with other work) revealed two striking and unexpected observations: (1) extensive hydrogen–deuterium randomization was occurring *at ordinary ionizing voltages.* This observation contrasts with those previously reported for straight-chain ketones, which undergo extensive hydrogen–deuterium randomization only at very low (10–12 eV) ionizing voltages.[5,6] (2) An intense peak, corresponding to the elimination of water from the α-cleavage ion, was observed. This peak is virtually absent in the mass spectra of analogous straight-chain ketones.

In order to define better the mechanisms and generalities of these processes, the mass spectra of a large number of branched-chain carbonyl compounds were examined.

Discussion of the Mass Spectral Results. Comparison of the mass spectra of 7-methyl-4-octanone (I, Figure 1) and its 7-d_1 analog (II, Figure 2) demonstrates clearly that partial randomization is occurring even at 70 eV. For example, the stereospecificity of the single and double McLafferty rearrangements is well established; transfer occurs almost exclusively from the γ position.[7] Thus, in the absence of hydrogen–deuterium randomization, the product ion of the single McLafferty rearrangement of II should shift quantitatively from *m/e* 86 (a) to *m/e* 87 (a′). In fact, a significant peak remains at *m/e* 86 ($C_5H_{10}O$ by high resolution mass spectroscopy), demonstrating that the C-7 deuterium atom has partially rearranged to positions 8,8′, and/or 6. If the C-7 deuterium atom were statistically distributed throughout the molecule, the expected ratio of the intensity of *m/e* 86 to *m/e* 87 is 0.80; in fact, a ratio of 0.55 is observed at 70 eV.



I, $R_1 = R_2 = H$
II, $R_1 = D$; $R_2 = H$
III, $R_1 = H$; $R_2 = D$



a, $R_1 = R_2 = H$; *m/e* 86
a′, $R_1 = D$; $R_2 = H$; *m/e* 87
a″, $R_1 = H$; $R_2 = D$; *m/e* 89

b, $R_1 = R_2 = H$; *m/e* 58
b′, $R_1 = D$; $R_2 = H$; *m/e* 59
b″, $R_1 = H$; $R_2 = D$; *m/e* 59

That the peak due to the double McLafferty rearrangement of II does not shift completely from *m/e* 58 (b) to *m/e* 59 (b′) is indicative of transfer of the C-7 deuterium atom to positions 8,8′, 6,2, and/or 1 before fragmentation. The experimentally observed ratio of the intensity of *m/e* 58 to *m/e* 59 is 0.35. Thus, the C-7 deuterium atom undergoes extensive randomization before the McLafferty rearrangements occur.

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(1) For paper CLXXXVII, see J. R. Trudell, S. D. Sample, and C. Djerassi, *Org. Mass Spectrom.*, in press.

(2) Financial assistance by the National Institutes of Health (Grants No. AM-12758 and AM-04257) is gratefully acknowledged.

(3) National Institutes of Health Predoctoral Fellow, 1968–present.

(4) For a comprehensive review of the mass spectral behavior of ketones, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, Chapter 3.

(5) W. Carpenter, A. M. Duffield, and C. Djerassi, *J. Amer. Chem. Soc.*, 90, 160 (1968).

(6) A. N. H. Yeo, R. G. Cooks, and D. H. Williams, *Chem. Commun.*, 1269 (1968); A. N. H. Yeo and D. H. Williams, *J. Amer. Chem. Soc.*, 91, 3582 (1969).

(7) S. Meyerson and J. D. McCollum, *Advan. Anal. Chem. Instr.*, 2, 184 (1963); H. Budzikiewicz, C. Feneslau, and C. Djerassi, *Tetrahedron*, 22, 1391 (1966).

Table I. Intensities of Peaks Corresponding to Hydrogen–Deuterium Randomization, Expressed as a Percentage of the Peak Corresponding to Normal Fragmentation

Compound	eV	Single McLafferty, %	Double McLafferty, %	α Fission, %	
				$M^+ - Pr^a$	$M^+ - R^a$
7-Methyl-4-octanone-1,1,1-d_3 (III) (97% d_3)	70	10	0	0	14
	15	9	0	0	14
7-Methyl-4-octanone-3,3,5,5-d_4	70	4	0	4	0
(92% d_4)	15	4	0	8	0
7-Methyl-4-octanone-6,6-d_2 (V)	70	11	18	0	0
(98% d_2)	15	10	13	0	0
7-Methyl-4-octanone-7-d_1 (II)	70	35	55	22	15
(97% d_1)	15	35	65	22	15
7-Methyl-4-octanone-8,8,8,8′,8′,8′-d_6 (IV)	70	16	25	0	0
(98% d_6)	15	16	25	0	0
8-Methyl-4-nonanone-3,3,5,5-d_4	70	0	10	28	0
(98% d_4)	15	7	10	28	0
8-Methyl-4-nonanone-6,6-d_2	70	5	4	8	10
(98% d_2)	15	3	4	8	10
8-Methyl-4-nonanone-7,7-d_2	70	20	4	8	10
(98% d_2)	15	20	4	8	10
8-Methyl-4-nonanone-8-d_1 (XIV)	70	15	15	30	4
(99% d_1)	15	15	15	30	4
8-Methyl-4-nonanone-9,9,9,9′,9′,9′-d_6 (XIII)	70	20	30	20	5
(98% d_6)	15	20	30	20	4
4-Nonanone-1,1,1-d_3 (VI)	70	0	0	0	5
(98% d_3)	15	0	0	0	5
4-Nonanone-7,7-d_2 (VII)	70	10	2	7	7
(97% d_2)	15	10	2	7	7

[a] α cleavage peaks designated on basis of ketone structure RC(=O)Pr.

The single and double McLafferty rearrangement peaks of several other deuterated analogs of 7-methyl-4-octanone show evidence of partial hydrogen–deuterium randomization. Thus, the mass spectrum of 7-methyl-4-octanone-8,8,8,8′,8′,8′-d_6 (IV) should exhibit a peak at *m/e* 86 corresponding to the McLafferty rearrangement; a peak is observed at *m/e* 87 (87/86 = 0.25 at 70 eV). Similarly, the peak associated with the double McLafferty rearrangement (b) appears partially at *m/e* 58 and partially at *m/e* 59 (59/58 = 0.16 at 70 eV). The mass spectra of 7-methyl-4-octanone-6,6-d_2 (V) and -1,1,1-d_3 (III) exhibit comparable evidence of randomization (see Table I).

The McLafferty rearrangements are not the only fragmentation processes which indicate the occurrence of hydrogen–deuterium randomization in branched ketones. For example, α cleavage of II should generate peaks at *m/e* 100 and *m/e* 71; in fact, significant oxygen-containing peaks appear at *m/e* 99 and *m/e* 72 (see Figure 2). This observation can best be explained by postulating intramolecular hydrogen transfer between the two alkyl chains before fragmentation. A similar explanation is required for the existence of an *m/e* 73 peak in addition to the expected *m/e* 74 α-fission peak in the mass spectrum of III.

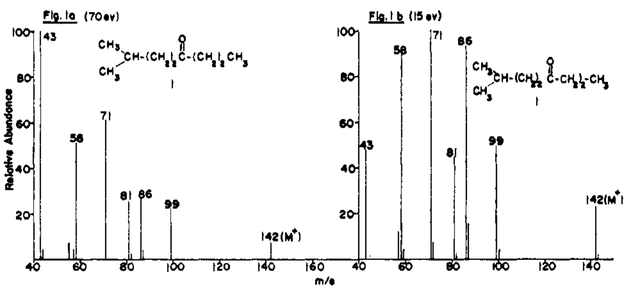


Figure 1. Mass spectrum of 7-methyl-4-octanone (I) determined at (a) 70 eV, and (b) 15 eV.

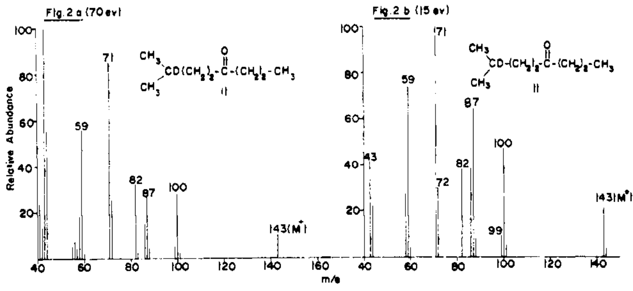
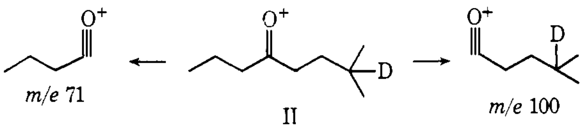
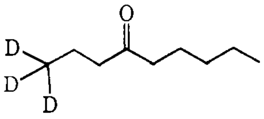


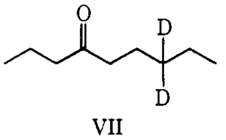
Figure 2. Mass spectrum of 7-methyl-4-octanone-7-d_1 (II) determined at (a) 70 eV, and (b) 15 eV.

For purposes of comparison, 4-nonanone-1,1,1-d_3 (VI) and -7,7-d_2 (VII) were prepared, and their mass spectra examined; as anticipated, randomization was markedly less complete (see Table I).





VI



VII

To determine the generality of the effect of a γ-methyl substituent, the mass spectra of several other γ-d_1 derivatives were examined. The McLafferty rearrangement of 5-methyl-2-hexanone-5-d_1 (VIII) should pro-

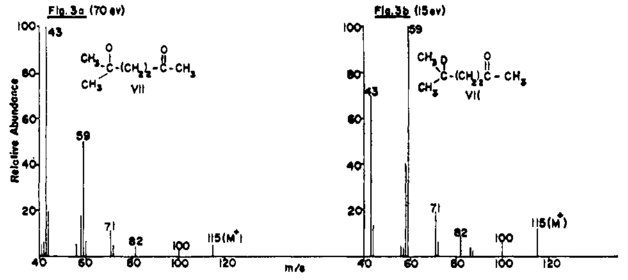


Figure 3. Mass spectrum of 5-methyl-2-hexanone-5-d_1 (VIII) demined at (a) 70 eV, and (b) 15 eV.

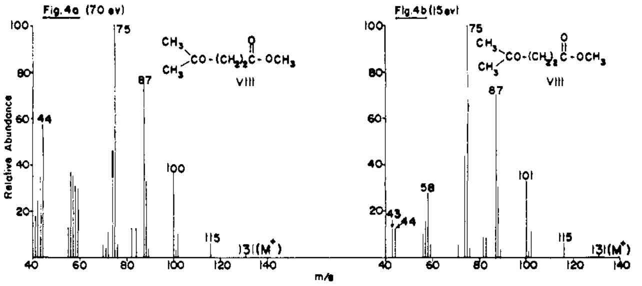
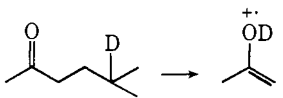
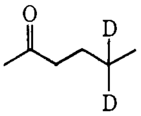


Figure 4. Mass spectrum of methyl 4-methylpentanoate-4-d_1 (IX) determined at (a) 70 eV, and (b) 15 eV.

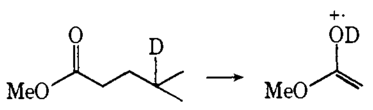
duce the ion b′ (*m/e* 59) if no hydrogen–deuterium exchange intervenes; in fact, significant amounts of ions of mass 58 (C_3H_6O by high resolution) are produced (see Figure 3). Similarly, the McLafferty rearrangement ion of methyl 4-methylpentanoate-4-d_1 (IX) shifts only partially to *m/e* 75 (see Figure 4). In contrast, the McLafferty rearrangement is over 95% specific for the analogous straight-chain compounds, 2-hexanone-5,5-d_2 (X) and methyl pentanoate-4,4-d_2 (XI).[8]



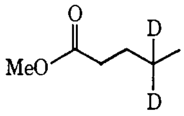
VIII b′, *m/e* 59



X

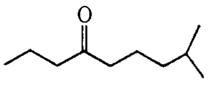


IX *m/e* 75

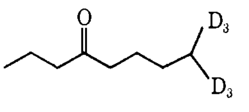


XI

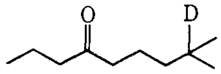
It was of interest to determine whether the effect observed was peculiar to γ-branched compounds. Consequently, a number of deuterated analogs of a δ-branched ketone, 8-methyl-4-nonanone (XII), were prepared. Evidence of extensive randomization was observed in several of these analogs. For example, 8-methyl-4-nonanone-9,9,9,9′,9′,9′-d_6 (XIII) should, in the absence of hydrogen–deuterium randomization, undergo the McLafferty rearrangement to produce a peak at *m/e* 86; in fact, a significant peak appears at *m/e* 87 (87/86 = 0.30, after correcting for the McLafferty + 1 ion[5]). Similarly, an α-cleavage peak of 8-methyl-4-nonanone-8-d_1 (XIV) should appear cleanly at *m/e* 114; a significant peak, corresponding to interchain hydrogen–deuterium randomization, appears at *m/e* 113 (113/114 = 0.30). Numerous other examples could be cited (see Table I).



XII



XIII



XIV

Despite the preparation of numerous deuterium labeled analogs of 7-methyl-4-octanone and 8-methyl-4-nonanone, the detailed pattern of hydrogen–deuterium transfers involved in randomization has not been established. Several broad conclusions can be drawn, however: (1) intrachain randomization apparently occurs (the results of earlier low ionizing voltage work could be accommodated on the basis of interchain transfer only, since only a few deuterated ketones were studied[5,6]); (2) the tertiary γ- and δ-labeled compounds show evidence of more extensive randomization than compounds labeled elsewhere. Since many of the mechanisms proposed for randomization involve radicals or radical-like transition states, it is tempting to attribute this observation to the greater stability of tertiary radicals over secondary or primary ones; (3) randomization patterns are apparently extremely sensitive to minor structural variations. The δ-branched compound undergoes much more extensive interchain transfer than the γ-branched, whose randomization appears to be largely intrachain.

Further studies are necessary to establish more definitely the characteristics of hydrogen–deuterium randomization, but it is already clear that its great facility under certain favorable structural conditions must be taken into consideration in mechanistic studies based on deuterium labeling.

The α-Cleavage–H_2O Peak. The mass spectra of straight-chain aliphatic ketones sometimes exhibit a very weak peak (less than 5% of the base peak) corresponding to the loss of H_2O from the α-cleavage ion(s), a process invariably accompanied by an intense metastable ion. Although this remarkable fragmentation, which must involve the breaking of at least five bonds, has already been observed, its small size has precluded deuterium labeling experiments.[5]

Our results demonstrate that loss of H_2O from the α-cleavage ion is dramatically enhanced if this fragment ion has a methyl substituent on the penultimate carbon, at least three carbon atoms removed from the carbonyl group. For example, in the mass spectrum of 8-methyl-4-nonanone (XII), the intensity of the α-cleavage–H_2O peak is 75% of the base peak, and five times as intense as the parent α-cleavage peak. In contrast, the corresponding peak in the mass spectrum of the analogous straight-chain ketone, 4-nonanone, is less than 1% of the base peak and is about $^1/_{100}$ the intensity of the parent α-cleavage ion. Even when the branching site is six carbon atoms removed from the carbonyl function, as in 11-methyl-4-dodecanone (XV), the α-cleavage–H_2O peak is 13% of the base peak and half as intense as the parent α-cleavage peak. In comparison, the

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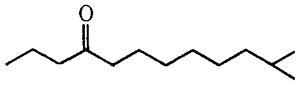
[8] Ng. Dinh-Nguyen, R. Ryhage, S. Stallberg-Stenhagen, and E. Stenhagen, *Arkiv Kemi*, 18, 393 (1961).

Table II. Variation in the Intensity of the α-Cleavage–H_2O Peak with Ketone Structure. Intensities Are Expressed as Percentages Relative to the Base Peak in Each Spectrum

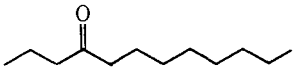
Ketone	Ion volt, eV	Mass of base peak *m/e*	Intensity of α-cleavage peak	Intensity of α-cleavage–H_2O peak	Ratio
7-Methyl-4-octanone (I)	70	43^b	22	26	1.2
	15	71^a	50	45	0.9
8-Methyl-4-nonanone (XII)	70	43^b	16	75	4.7
	15	95^d	35	100	2.9
9-Methyl-4-decanone	70	43^b	16	68	4.2
	15	86^c	26	85	3.3
10-Methyl-4-undecanone	70	71^a	11	32	2.9
	15	86^c	17	38	2.2
11-Methyl-4-dodecanone (XV)	70	43^b	26	13	0.5
	15	86^c	33	12	0.4
8-Ethyl-4-decanone (XVII)	70	43^b	25	50	2.0
	15	86^c	45	63	1.4
4-Nonanone	70	43^b	57	0.5	0.01
	15	71^a	87	0.5	0.006
4-Dodecanone (XVI)	70	71^a	57	3	0.05
	15	86^c	66	3	0.04

^{a} *m/e* 71 corresponds to the α-cleavage fragment $C_3H_7C{\equiv}O^+$. ^{b} *m/e* 43 corresponds to $C_3H_7^+$. ^{c} *m/e* 86 corresponds to the McLafferty rearrangement peak. ^{d} *m/e* 95 corresponds to the α-cleavage–H_2O fragment.

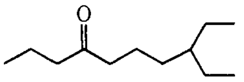
corresponding peak in the mass spectrum of an analogous straight-chain ketone, 4-dodecanone (XVI), is less than 3% of the base peak and is $^1/_{20}$ as intense as the parent α-cleavage peak. The intensities of these peaks in the mass spectra of a number of ketones are listed in Table II.



XV



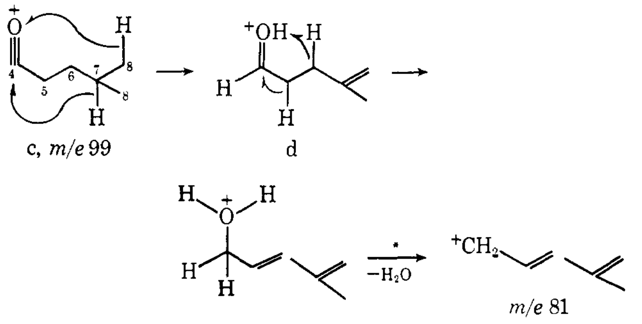
XVI



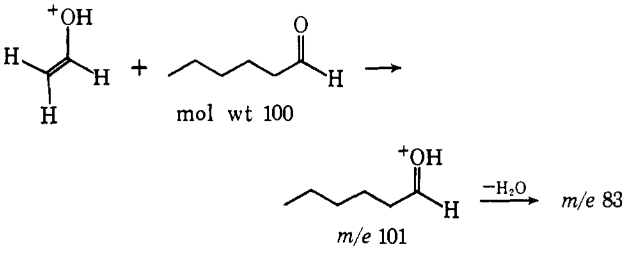
XVII

Deuterium labeling studies were initiated to determine the origins of the hydrogen atoms eliminated as H_2O. Appropriate labeled analogs of 7-methyl-4-octanone (I) were prepared. These experiments demonstrated that the α-cleavage–H_2O ion of mass 81 arises almost exclusively from the loss of the C-6 and C-8 hydrogen atoms. A possible rationalization for this process is presented in Scheme I, the driving force being initial transfer of the tertiary hydrogen to the carbonyl carbon. The resulting tertiary radical then labilizes the two adjacent positions (C-8 and C-6) leading to the observed results.

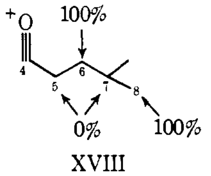
Scheme I



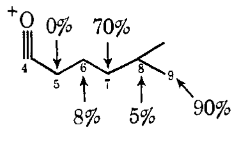
Ion cyclotron resonance experiments lend strong support to this mechanism. Ions analogous to d can be readily generated in the ion cyclotron resonance spectrometer by ion–molecule reactions. Appreciable loss of water has been observed from protonated aldehydes in the ion cyclotron resonance spectrometer.[9]



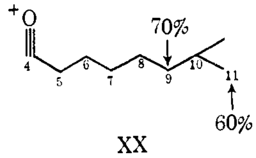
Further deuterium labeling studies were initiated to determine the origins of the hydrogen atoms eliminated from the α-cleavage ion of 8-methyl-4-nonanone (XII), a δ-branched ketone. Surprisingly, the hydrogen atoms lost originated from C-7 and C-9, predominantly.[10] Next, 10-methyl-4-undecanone-9,9-d_2, and -11,11,11, 11′,11′,11′-d_6 were prepared; in each case, elimination of HDO was the predominant process, even though loss of deuterium from the latter compound must involve a ten-membered-ring transition state. Thus, a pattern had been established; the eliminated hydrogen atoms originated principally from the carbon atom two



XVIII



XIX



XX

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[9] J. L. Beauchamp, private communication.

[10] Because of the extensive hydrogen–deuterium randomization observed in the mass spectra of labeled analogs of 8-methyl-4-nonanone, the numbers appearing in structure XIX are only approximate.

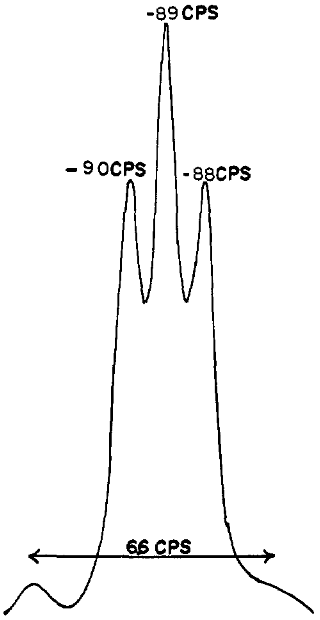


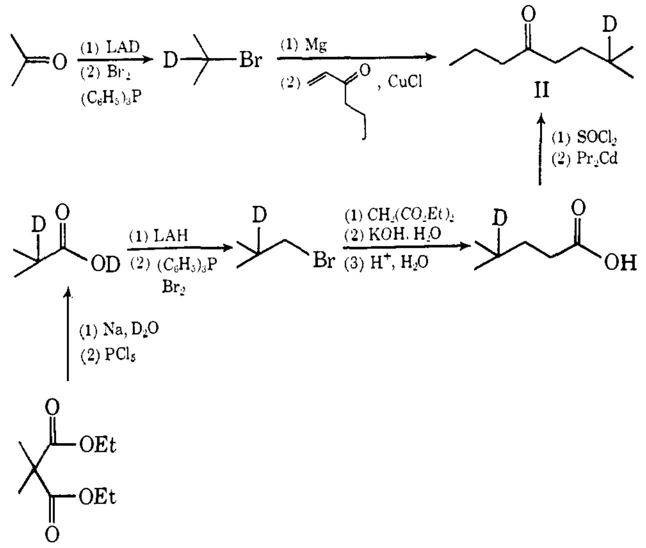
Figure 5. Enlargement of 100-MHz nmr spectrum of the isopropyl group of 7-methyl-4-octanone-7-d_1 (II).

removed from the chains end (see XVIII, XIX, and XX) and from a terminal carbon. To confirm this pattern, 9-methyl-4-decanone-8,8-d_2 and 11-methyl-4-dodecanone-10,10-d_2 were prepared; in each case, the labeled positions were predominately eliminated, as expected, thus supporting the conclusion that the triggering factor is invariably the initial migration at the tertiary hydrogen atom to the carbonyl carbon, irrespective of ring size.

Since it is well established in organic mass spectrometry that secondary and tertiary hydrogens have greater migratory aptitude than primary ones, it was surprising to observe that 8-ethyl-4-decanone (XVII) did not show enhanced loss of water relative to the corresponding methyl-branched ketone, 8-methyl-4-nonanone (XII) (see Table II). This observation is, however, consistent with the view that the fragmentation is triggered by the cleavage of the tertiary carbon–hydrogen bond.

It should be pointed out that this fragmentation may have important diagnostic applications. The ratio of the intensities of the α-cleavage–H_2O peak to the intensity of the α-cleavage peak is largest in 8-methyl-4-nonanone (4.7 at 70 eV). However, even for 11-methyl-4-dodecanone (XII), whose branching site is seven carbon atoms removed from the carbonyl group, the ratio is 0.5, roughly ten times that observed for the corresponding straight-chain compound, 4-dodecanone (XIII) (see Table II). Thus, observation of an intense α-cleavage–H_2O peak offers a means of distinguishing branched ketones from straight-chain ketones, a distinction which had previously been difficult or impossible to draw.

Synthesis of Labeled Compounds. It is extremely important that the specifically deuterated compounds utilized in these studies of hydrogen–deuterium randomization be prepared in a high state of isotopic purity. The mass spectrum (Figure 2) of 7-methyl-4-octanone-7-d_1 (II) exhibits by far the most compelling evidence of scrambling, and particular effort was devoted to establishing that compound's isotopic purity. Two independent synthetic sequences were employed.



The mass spectra of the compound prepared in different ways were indistinguishable. Perhaps even more convincing proof that II was specifically labeled was obtained from its 100-MHz nmr spectrum (Figure 5). The terminal isopropyl group appears as an intense triplet (J = 1 cps) with very weak shoulders (J = 7 cps). The ratio of the area under the triplet to the area under the shoulders corresponds to the ratio of deuterium to hydrogen in the 7 position and is obviously much too large to account for the effects described earlier.

Experimental Section[11]

7-Methyl-4-octanone-7-d_1 (II). (a) To a 500-ml three-necked round-bottomed flask fitted with a dropping funnel, magnetic stirrer, and nitrogen inlet system was placed 100 ml of dry diglyme.[12] The solution was cooled in an ice bath, and 1.15 g (0.0275 mol) of lithium aluminum deuteride was added carefully with stirring. Next, a mixture of 5.8 g (0.1 mol) of acetone in 50 ml of dry diglyme was added with cooling. After addition was complete, the mixture was heated to 100° for 2 hr. After cooling the mixture to 0°, a 10% excess of diethylene glycol monobutyl ether was added. The flask was fitted with a short-path distillation apparatus, and the product distilled (bp 70–150°). The distillate was redistilled through a vacuum jacketed Vigreux column, and 5.15 g (84%) of 2-propanol-2-d_1 (bp 82–83°) was collected.[13]

The alcohol was converted to the corresponding bromide by the procedure of Wiley, *et al.*[14] Dry 2-propanol-2-d_1 (3.05 g, 0.05 mol) was mixed with 14 g (0.053 mol) of dry triphenylphosphine in 50 ml of dry dimethylformamide under a nitrogen atmosphere. Bromine was added dropwise with cooling, until an orange color just persisted. Two distillations yielded 3.96 g (0.032 mol, 64%) of 2-bromopropane-2-d_1 (bp 70–71°).

The Grignard reagent prepared from 3.10 g (0.025 mol) of 2-bromopropane-2-d_1 and an equivalent amount of Mg was cooled to −10°. Propyl vinyl ketone (1.47 g, 0.015 mol) dissolved in 75 ml of anhydrous ethyl ether was added slowly, together with small portions of cuprous chloride. After the addition was complete (about 5 hr after it had begun), the mixture was hydrolyzed with 10% HCl and washed with 10% HCl, water, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The solvent was removed under reduced pressure, and the resulting oil was distilled to remove polymeric impurities. Vapor phase chromatog-

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(11) The mass spectral data were obtained by Mr. R. Ross on an MS-9 mass spectrometer using a heated glass inlet system with steel manifolding. All ionizing voltages mentioned are nominal values.

(12) L. F. and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 255.

(13) Z. Friedman and A. T. Jurewicz, *J. Org. Chem.*, **33**, 1254 (1968).

(14) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

raphy on a 10 ft 10% XE-60 column at 165° gave 1.40 g (40% based on labeled bromide) of 7-methyl-4-octanone-7-d_1 (II) (97% d_1).

(b) Dimethyl diethylmalonate was hydrolyzed and decarboxylated in D_2O, and the resulting acid was reduced with lithium aluminum hydride essentially according to the procedure of Duffield, *et al.*[15] The resulting 2-methyl-1-propanol-2-d_1 was converted to the corresponding bromide by the procedure of Wiley, *et al.* (described above),[14] and homologated with diethyl malonate.[16] The resulting 4-methylpentanoic acid-4-d_1 was converted to the corresponding acid chloride by treatment with an excess of thionyl chloride; after distillation, the acid chloride was added to a benzene suspension of dipropylcadmium. The resulting 7-methyl-4-octanone-7-d_1 (98% d_1) was obtained in almost quantitative yield.[17]

7-Methyl-4-octanone-8,8,8,8′,8′,8′-d_6 (IV). Reduction of perdeuterioacetone[18] with lithium aluminum hydride in dry diglyme[13] yielded 2-propanol-1,1,1,3,3,3-d_6, which was converted to the corresponding bromide by the procedure of Wiley, *et al.*[14] Cuprous chloride catalyzed addition of the corresponding Grignard reagent to propyl vinyl ketone (see above) gave the desired labeled octanone (IV) (98% d_6).

7-Methyl-4-octanone-1,1,1-d_3 (III). Perdeuterioacetic acid[18] was reduced with lithium aluminum hydride according to the procedure of Friedman and Jurewicz,[13] converted to the bromide,[14] and homologated in the usual manner.[15] The resulting butanoic acid-4,4,4-d_3 was converted to the corresponding acid chloride and added to an equivalent amount of diisopentylcadmium to give the octanone in excellent yield at high isotopic purity (97% d_3).

7-Methyl-4-octanone-6,6-d_2 (V) (97% d_2) was prepared by the lithium aluminum deuteride reduction of isobutyric acid, conversion of the resulting alcohol to the corresponding bromide which was homologated to 4-methylpentanoic acid-3,3-d_2, and treatment of the corresponding acid chloride with dipropylcadmium, all in the usual manner.

7-Methyl-4-octanone-3,3,5,5-d_4 (VI) (92% d_4) was prepared by the repeated equilibration of the parent ketone (I) with deuteriomethanol containing 10% heavy water and a catalytic amount of sodium deuterioxide. The product was recovered by removing the solvent under vacuum. The discolored liquid was further purified by vapor phase chromatography through a 10-ft Carbowax column (170°) preequilibrated with heavy water.[19]

5-Methyl-2-hexanone-5-d_1 (VIII) (98% d_1) was prepared by the cuprous chloride catalyzed addition of the Grignard reagent prepared from 2-bromopropane-2-d_1 to methyl vinyl ketone, according to the already described procedure.

Methyl 4-methylpentanoate-4-d_1 (IX) (98% d_1) was prepared analogously from 2-bromopropane-2-d_1 and methyl acrylate.

8-Methyl-4-nonanone (XII) was prepared by treating propyl vinyl ketone with an excess of triisobutylborane according to the procedure of Brown, *et al.*[20]

Dry isobutylene was added at 0° to 0.01 mol of BH_3 in tetrahydrofuran until the uptake of gas ceased (about 1 hr). The reaction mixture was stirred at room temperature for 3 hr; water (0.02 mol) was then added, followed by 0.5 g (0.005 mol) of propyl vinyl ketone. After the mixture had stirred for 5 hr at room temperature, the solvent was removed under vacuum, and the product separated from the residual boron-containing by-product by distillation. Vapor phase chromatography (10-ft Carbowax column operated at 185°) resulted in a 70% yield of 8-methyl-4-nonanone (XII).

8-Methyl-4-nonanone-8-d_1 (XIV) was prepared in a similar manner. Generation of BD_3 was accomplished by treating a tetrahydrofuran solution of sodium borodeuteride[21] with an equivalent amount of BF_3 etherate.[22] Work-up as already described gave a good yield of the desired compound, X (99% d_1).

8-Methyl-4-nonanone-9,9,9,9′,9′,9′-d_6 (XIII). Perdeuterioacetone was treated with an equivalent amount of triphenylphosphine–methylene phosphorane; the 2-methylpropene-3,3,3,3′,3′,3′-d_6 generated was collected in a Dry Ice cooled trap, and treated with an equivalent amount of BH_3. The resulting trialkylborane was converted to the desired ketone (XIII) (98% d_6) in the usual manner.

8-Methyl-4-nonanone-7,7-d_2. Reduction of isobutyric acid with lithium aluminum deuteride in diglyme[13] gave the corresponding deuterated alcohol, which was converted to 2-methyl-1-bromopropane-1,1-d_2 according to the procedure of Wiley, *et al.*[14] Diethyl malonate homologation[16] followed by lithium aluminum hydride reduction gave 4-methyl-1-pentanol-3,3-d_2, which was converted to the corresponding bromide by treatment with hydrobromic acid–sulfuric acid. Conversion of the bromide to the corresponding organocadmium reagent, and treatment with butyryl chloride according to the procedure of Cason and Prout[17] gave 8-methyl-4-nonanone-7,7-d_2 (97% d_2).

8-Methyl-4-nonanone-6,6-d_2. Reduction of isopentanoic acid with lithium aluminum deuteride in diethyl ether gave 3-methyl-1-butanol-1,1-d_2 which was converted to the bromide and homologated with diethyl malonate according to already described procedures to yield 5-methylhexanoic acid-3,3-d_2. The labeled acid was converted to the corresponding acid chloride by treatment with thionyl chloride; reaction with dipropylcadmium gave 8-methyl-4-nonanone-6,6-d_2 (98% d_2) in high yield.

8-Methyl-4-nonanone-5,5,3,3-d_4. Repeated (four times) exchange of the parent ketone in deuteriomethanol containing 10% heavy water and 5% sodium deuterioxide gave the desired product in high isotopic purity (98% d_4).

8-Methyl-4-nonanone-1,1,1-d_3 (XIII). Perdeuterioacetic acid[18] was reduced with lithium aluminum hydride according to the procedure of Friedman and Jurewicz,[13] converted to the bromide,[14] and homologated in the usual manner.[16] The resulting butanoic acid-4,4,4-d_3 was converted to the corresponding acid chloride and added to an equivalent amount of diisohexylcadmium to give the desired ketone.

9-Methyl-4-decanone, 10-methyl-4-undecanone, 11-methyl-4-dodecanone (XV), and 8-ethyl-4-decanone (XVII) were prepared by treating the appropriate alkene with BH_3, then water and propyl vinyl ketone, according to the already described procedure.[20]

9-Methyl-4-decanone-8,8-d_2 (98% d_2) was prepared by the cuprous chloride catalyzed addition of the Grignard reagent prepared from 4-methyl-1-bromopentane-2,2-d_2 (whose preparation is described above) to propyl vinyl ketone according to the already described procedure.

10-Methyl-4-undecanone-9,9-d_2 (98% d_2) was prepared in a similar manner from 5-methyl-1-bromohexane-4,4-d_2 (whose preparation is described above).

10-Methyl-4-undecanone-11,11,11,11′,11′,11′-d_6. The Grignard reagent prepared from 2-bromopropane-1,1,1,3,3,3-d_6 was added to an ether solution containing an equivalent amount of allyl bromide at such a rate that gentle refluxing occurred. After the addition was complete, the mixture was refluxed for 2 hr; work-up with 10% hydrochloric acid followed by distillation yielded a 20% ethereal solution of the coupling product, 4-methyl-1-pentene-5,5,5,5′,5′,5′-d_6.[23] Treatment with an equivalent amount of BH_3 gave the corresponding trialkylborane which, on reaction with propyl vinyl ketone followed by hydrolysis, gave the desired ketone (98% d_6) in good yield.[20]

11-Methyl-4-dodecanone-10,10-d_2. Diethyl malonate homologation of 4-methyl-1-bromopentane-3,3-d_2 (preparation already described), followed by lithium aluminum hydride reduction and conversion to the corresponding bromide, yielded 6-methyl-1-bromoheptane-5,5-d_2. Conversion to the Grignard reagent and cuprous chloride catalyzed addition to propyl vinyl ketone gave 11-methyl-4-dodecanone-10,10-d_2 (97% d_2) in very poor yield.

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