Mass Spectrometry in Structural and Stereochemical Problems. CXXXVI.[1] Primary Hydrogen Isotope Effects in the McLafferty Rearrangement[2]

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Abstract: Measurements, at 70 ev and lower ionizing energies, of the primary hydrogen isotope effect in the mass spectrometric cyclic transfer process known as the McLafferty rearrangement indicate that a broad range of isotope effect (*IE*) values from 0.5 to 1.0 is encountered among ketones, esters, and aromatic and heterocyclic substrates. An attempt has been made to rationalize the results by analogy with related processes in solution chemistry and photochemistry.

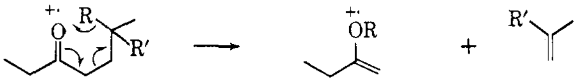
Although a number of measurements have been made on the primary and secondary isotope effects accompanying replacement of hydrogen by deuterium in the mass spectra of simple organic compounds,[3] these have been restricted to a comparison of C–H *vs.* C–D bond cleavage with loss of the H or D radical. Such processes have been adequately described in terms of the π and Γ effects which give a measure of the discrimination against deuterium loss in the partially deuterated compound (π effect) and of the enhancement of loss of a hydrogen radical in the partially deuterated compared with the undeuterated compound (Γ effect). Natalis[3] has also discussed the operation of an isotope effect in the hydrogen *vs.* deuterium migration processes in butene-4-d_3 and cyclopentane-d_1 and concluded that the migration of deuterium was electron energy dependent, the transfer of hydrogen being favored at low electron voltages.

The specificity and broad applicability of the well-documented McLafferty rearrangement[4] afforded the opportunity of studying the competition in a six-membered cyclic transfer process between hydrogen and deuterium attached to the same carbon atom. Only one such measurement[5] had been published previously of the primary isotope effect (*IE*) in the case of the γ-d_1- and γ-d_2-methyl butyrates and a reasonable value of 0.88 was obtained for both labeled compounds, the *IE* having been defined as equal to the "atoms of deuterium per atom of hydrogen transferred for the hypothetical case in which equal numbers of deuterium and hydrogen are available." This definition gives an isotope effect which is qualitatively comparable with the π effect for the C–H *vs.* C–D fission process but which shows considerably less discrimination against deuterium transfer, as may be expected for a cyclic transfer in which bond breaking and bond making occur concomitantly.

Our preliminary publication[6] showed the rather broad range of hydrogen isotope effects that may be encountered in the McLafferty rearrangement, embracing competitive transfers to doubly bonded oxygen, carbon, nitrogen, and sulfur. In the present paper we discuss these results in more detail together with the relevant experimental evidence. Many of the *IE* values recorded in our preliminary note[6] have been remeasured at low electron energies in order to suppress subsequent secondary fragmentations of the rearrangement ions.

A. Aliphatic Ketones. McLafferty Rearrangement to Carbonyl Oxygen

Previous publications[7] have left no doubt as to the site specificity of γ-hydrogen transfer in both the single and double McLafferty rearrangements exhibited by dialkyl ketones under electron impact. The *IE* calculated for 3-heptanone-6-d_1 (II), whose mass spectrum was recorded on two different mass spectrometers (A.E.I. MS-9 and Atlas CH-4) at decreasing electron voltages, is given in Table I. At 70 ev both values indicate that essentially no isotope effect is operative, *i.e.*, $IE = 1.0$.



I, R = R′ = H
II, R = H; R′ = D

a, R = H; m/e 72
b, R = D; m/e 73

Particularly noteworthy is the observation that the *IE* values increase markedly at low ionizing voltages (see Table I), contrary to expectations. A low-voltage study of the mass spectrum of unlabeled 3-heptanone (I) showed no contribution from a "protonated McLafferty" species c which does appear in the spectra of higher homologs,[8] *e.g.*, 3-octanone (III), analogous to that observed in the mass spectra of higher esters[9] and which would enhance the contribution of the m/e 73 peak (b) in the low electron voltage spectra of II. However the mass spectrum of 3-octanone-6-d_2 (IV) did exhibit more than the expected proportion of the

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[1] For paper CXXXV see B. Zeeh, G. Jones, and C. Djerassi, *Chem. Ber.*, in press.

[2] We are indebted to the National Institutes of Health (Grants No. AM-04257 and CA-07195) for financial assistance. The purchase of the Atlas CH-4 mass spectrometer was made possible by NASA Grant NsG 81-60.

[3] For a recent review see M. Corval and M. R. Viallard, *Bull. Soc. Chim. France*, 3710 (1966). Also P. Natalis, *Bull. Soc. Chim. Belges*, 73, 389 (1964).

[4] For a recent review and leading references see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, Section 3–7.

[5] D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 284 (1964).

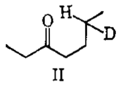
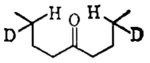
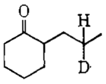
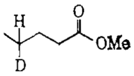
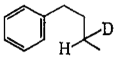
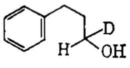
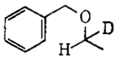
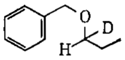
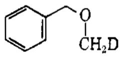
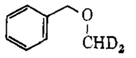
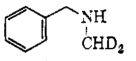
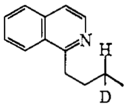
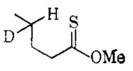
[6] J. K. MacLeod and C. Djerassi, *Tetrahedron Letters*, 2183 (1966).

[7] H. Budzikiewicz, C. Fenselau, and C. Djerassi, *Tetrahedron*, **22**, 1391 (1966), and earlier references.

[8] W. Carpenter, A. M. Duffield, and C. Djerassi, submitted for publication.

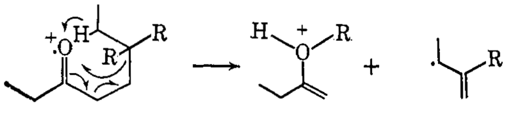
[9] C. Djerassi and C. Fenselau, *J. Am. Chem. Soc.*, **87**, 5756 (1965), and references cited therein.

Table I. Mass Spectrometric Hydrogen Isotope Effects (*IE*) in γ-Hydrogen Rearrangements

	70 ev		20 ev		15 ev^a		12 ev^a		10 ev^a		Isotopic compn,
Compd	CH-4	MS-9	CH-4	MS-9	CH-4	MS-9	CH-4	MS-9	CH-4	MS-9	%
 II	0.98^b 1.02 1.01	0.97			1.11		1.23	1.07	1.41	1.37	98, d_1 2, d_0
 VI	1.01										96, d_2 4, d_1
 XII	0.87^c	0.86	0.88		0.91			0.84		0.91	97, d_1 3, d_0
 XVII	0.92^b 0.91	0.92						0.89		0.96	98, d_1 2, d_0
 XIX	0.80^d 0.88^{d,e}										99, d_1 1, d_0
 XXII	0.83^e				0.89^e		0.88^e		0.91^e		3.7, d_2 93.5, d_1 2.8, d_0
 XXV	0.51^{b,f}	0.56^f						0.56		0.54	98, d_1 2, d_0
 XXVI	0.50^{b,f} 0.57		0.58		0.58		0.55		0.54		98, d_1 2, d_0
 XXVIII	0.42^f						0.54				93.5, d_1 6.5, d_0
 XXIX	0.39^f						0.47				80, d_2 16, d_1 4, d_0
 XXXI	0.34^f						0.48		0.46		98, d_2 2, d_1
 XXXII	0.75^b 0.79		0.81				0.78		0.76		98, d_1 2, d_0
 XXXIV	0.80^b 0.82		0.80		0.79		0.80				98, d_1 2, d_0

[a] Low electron voltage values are nominal and are not directly comparable on the two instruments. [b] Previously published value.[6] [c] Published value of 0.78 corrected.[11] [d] Recorded on a C.E.C. 21-102/103 mass spectrometer.[16] [e] Corrected for γ-hydrogen specificity (<95%). [f] Low electron voltage values more meaningful because of large tropylium ion peak (*m/e* 91) at 70 ev.

"protonated McLafferty" ion d (*m/e* 74) at low ionizing energies in comparison with the unlabeled compound III, corresponding to a loss of nondeuterated *n*-butene from the molecular ion IV. A possible explanation for

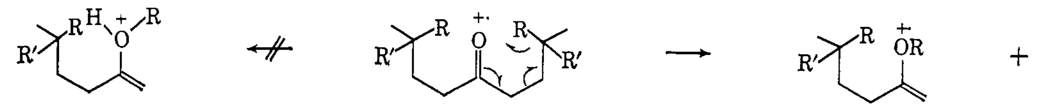


III, R = H c, R = H; *m/e* 73

IV, R = D d, R = D; *m/e* 74

this unusual fragmentation is outlined in the next paragraph. The increase in the *m/e* 73 peak (b) over that of *m/e* 72 (a) at low electron voltage in the spectrum of 3-heptanone-6-d_1 (II) is probably attributable to an analogous loss of undeuterated propene by this alternate pathway.

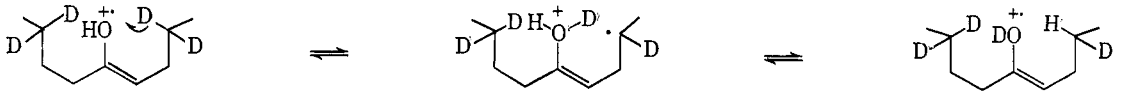
A similar situation arose in the study of the isotope effect for the single McLafferty rearrangement in 5-nonanone-2,8-d_2 (VI). Although the mass spectrum of the unlabeled compound V showed no evidence of a "protonated McLafferty" species i at *m/e* 101, the γ,γ′-d_4 derivative VII, both at 70 ev and lower electron energies, displayed a considerable enhanced peak at *m/e* 104 corresponding to the loss of 42 mass units, which was greater than the normal ^{13}C isotope contribution of the McLafferty rearrangement ion h at *m/e* 103. The possibility of ketene loss from the molecular ion



i, R = R′ = H; *m/e* 101
j, R = R′ = D; *m/e* 104

V, R = R′ = H
VI, R = H; R′ = D
VII, R = R′ = D

e, R = R′ = H; *m/e* 100
f, R = H; R′ = D; *m/e* 101
g, R = D; R′ = H; *m/e* 102
h, R = R′ = D; *m/e* 103

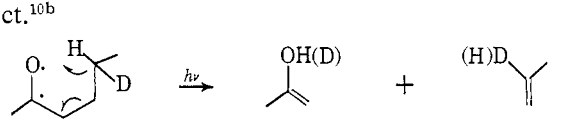


VIII

IX

which would conveniently account for this M − 42 peak in the spectrum of VII was ruled out by high-resolution measurements on the *m/e* 100 peak (e = 100% $C_6H_{12}O$) in the unlabeled ketone V. We are forced to conclude that the appearance of this anomalous ion in the labeled 3-heptanone (II), 3-octanone (IV), and 5-nonanone (VII) may be due to reciprocal hydrogen–deuterium transfers between the α and γ positions, *e.g.*, VIII → IX, taking place *via* the enolic form VIII prior to fragmentation of the molecular ion. Further studies of this anomaly are at present underway in connection with a detailed examination[8] of the low-voltage spectra of aliphatic ketones.

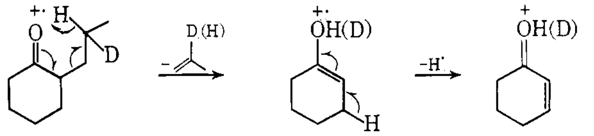
Making appropriate allowances for the contribution of this M − 42 species, the calculation of the *IE* value for the single McLafferty rearrangement in the mass spectrum of 5-nonanone-2,8-d_2 (VII) gives a result (1.01) in close agreement with that recorded for 3-heptanone-6-d_1 (II) at 70 ev (Table I). An interesting comparison may be made with the photochemical analogy of this mass spectrometric transfer process, the Norrish type II rearrangement of a γ-hydrogen or deuterium to the carbonyl oxygen atom. In 2-hexanone-5-d_1 (X), the relative ratio of propene-2-d_1 to propene (XI) resulting from irradiation of this ketone was 5.7 in the absence of a quencher and 2.7 in the presence of 5 *M* piperylene.[10a] The reciprocal of these values, 0.175 and 0.37, affords a basis for comparison with the *IE* of *ca.* 1.0 measured for the McLafferty transfer process in simple ketones (Table I) and this shows that the photochemical rearrangement under the conditions employed exerts a significantly greater hydrogen isotope effect.[10b]



X

XI

Having established the virtual absence of a hydrogen isotope effect in the single McLafferty rearrangement in dialkyl ketones, it was rather surprising that the *IE* value for the same process in 2-propyl-2′-d_1-cyclohexanone (XII) was 0.87,[11] indicating a significant discrimination against transfer of deuterium (Table I).



XII

k, *m/e* 98 (99)

l, *m/e* 97 (98)

A rationale for the lower *IE* value at 70 ev of XII as compared with II and VI may be found in the stereochemical requirements of the McLafferty rearrangement. It has been noted[12] that for this hydrogen transfer to occur the maximum interatomic O–H distance should be less than 1.8 A and it is conceivable (although atomic models do not bear this out) that the cyclohexanone ring restricts the geometry so that the H and D are farther from the $C{=}O\cdot^{+}$ than in the acyclic ketones II and VI. The slightly shorter C–D bond distance compared with that of the C–H bond could further enhance hydrogen transfer by decreasing the O–D interatomic distance in XII. However a more likely explanation is that the specificity of the cyclic process is less than quantitative for the γ-hydrogen, as the only measure of the site specificity in alicyclic ketones has been made on 2-ethyl-2′-d_3-cyclopentanone[13] which does not preclude possible transfer (of the order of 5%) from the δ- or ϵ-hydrogens in longer alkyl side chains (*e.g.*, in XII).

As mentioned in our preliminary communication,[6] the existence of differing isotope effects for closely related processes may have ramifications in other quantitative aspects of mass spectrometry which involve deuterium labeling studies. In this regard we have reexamined data on the competitive transfer of γ-hydrogens attached to primary *vs.* secondary carbon atoms in the mass spectra of γ-d_2- and γ'-d_6-*n*-butyl isobutyl ketone (XIII and XIV)[7] and γ-d_2-*sec*-butylcyclopentanone[14] (XV) and rerun these compounds at low electron energies. The results are shown in Table II, using the pertinent *IE* values of 1.0 for XIII and XIV

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(10) (a) D. R. Coulson and N. C. Yang, *J. Am. Chem. Soc.*, **88**, 4511 (1966), and previous references. (b) R. P. Borkowski and P. Ausloos, *J. Phys. Chem.*, **65**, 2257 (1961), have studied the photolysis of 2-pentanone-4,5,5-d_3 in the vapor and liquid phases and measured the effect of change in intensity, concentration, wavelength, and temperature on the ratio $C_2D_3H/C_2H_2D_2$ from the type II process $D_2C{=}CHD + CH_3COCH_3 \leftarrow CH_3COCH_2CHDCD_2H \rightarrow DHC{=}CHD + CH_3COCH_2D$. The ratio (which is the reciprocal of the defined *IE* uncorrected statistically) is found to be independent of intensity but increases with increasing wavelength and ketone concentration and decreases with increasing temperature. The H *vs.* D transfer probabilities reflected in this ratio, which varies from 0.58 on radiolysis to 2.72 for vapor-phase photolysis to 6.4 for low-temperature, liquid-phase photolysis, indicate that at high energies and low concentrations in the vapor phase the ratio $C_2D_3H/C_2H_2D_2$ approaches the statistical value of 0.5 In fact, Ausloos obtained a value of 0.5 for the mass ratio 58/59 (= CH_3COCH_3/CH_3COCH_2D) in the mass spectrometric H *vs.* D McLafferty rearrangement of 2-pentanone-4,5,5-d_3 at 13 ev, which is equivalent to an *IE* value of 1.0. This further supports our finding that there is no isotope effect in this electron impact induced process in simple ketones.

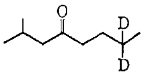
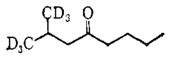
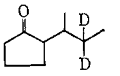
(11) The previously published[6] *IE* value of 0.78 was not corrected for the contribution of the ion l formed by loss of a hydrogen radical from the rearrangement species k.

(12) C. Djerassi, *Pure Appl. Chem.*, **9**, 159 (1964); C. Djerassi, G. von Mutzenbecher, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Am. Chem. Soc.*, **87**, 817 (1965).

(13) J. Seibl and T. Gäumann, *Z. Anal. Chem.*, **197**, 33 (1963).

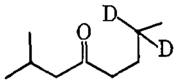
(14) H. Fritz, H. Budzikiewicz, and C. Djerassi, *Chem. Ber.*, **99**, 35 (1966).

Table II. Recalculated Values of Primary *vs.* Secondary Hydrogen Transfers in the Single McLafferty Rearrangement in γ-d_2- and γ'-d_6-*n*-Butyl Isobutyl Ketone and 2-(γ-d_2-*sec*-Butyl)cyclopentanone

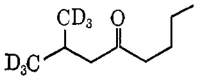
Compound	Isotopic purity, %	Transfer process	70 ev[d]		15 ev[d]	12 ev[d]
	95, d_2	Primary H	11[a]	12[c]	12[a]	11[a]
	5, d_1	Secondary D	89	88	88	89
XIII						
	86.0, d_6	Primary D	6[a]	4[c]	5[a]	3[a]
	12.5, d_5					
	1.5, d_4	Secondary H	94	96	95	97
XIV						
	86, d_2	Primary H	11[b]	10[c]	11[b]	11[b]
	12, d_1					
XV	2, d_0	Secondary D	89	90	89	89

[a] Recorded on the Atlas CH-4 mass spectrometer. [b] Recorded on the A.E.I. MS-9. [c] Recorded on the C.E.C. Model 21-103C mass spectrometer. [d] Measured values corrected for ${}^{13}C$ natural abundance, other noncontributing isobaric peaks, deuterium isotope composition, *IE* values, and statistical availability (6:2 or 3:2) of hydrogen for transfer.

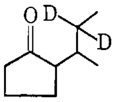
and 0.87 for XV, the latter being coincidently almost the same as that of methyl butyrate[5] (0.88) which was the *IE* value used in the earlier papers.[7,14] It is interesting to note that the recalculated primary *vs.* secondary ratios for XIII and XV are identical at 70 ev (11% *vs.* 89%) and do not change at lower electron voltages, while the ratio in the d_6-ketone (XIV) differs from the other two at 70 ev (6% *vs.* 94%), and discrimination against primary hydrogen transfer increases as the electron energy is decreased (3% *vs.* 97% at 12 ev).



XIII

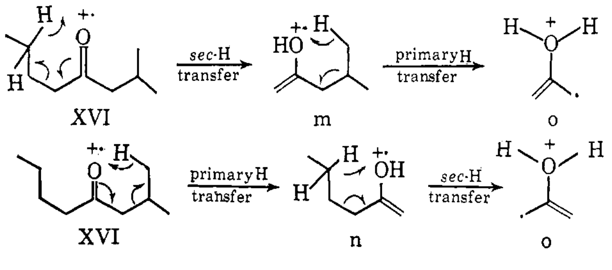


XIV



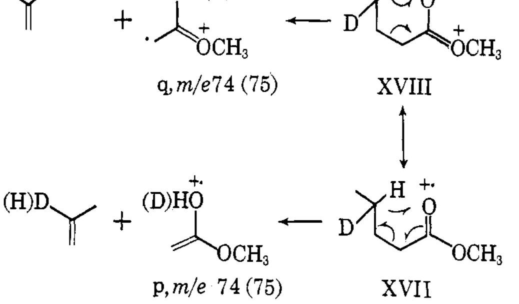
XV

However it is questionable whether the results from the two labeled *n*-butyl isobutyl ketones XIII and XIV are meaningful as the two possible rearrangement species m and n from the unlabeled ketone XVI are themselves subject to a primary *vs.* secondary hydrogen transfer discrimination in their further fragmentation to the ion o, as well as an unknown isotope effect in the case of the deuterated derivatives XIII and XIV for the double McLafferty transfer (m → o and n → o). The ion m would be expected to undergo less fragmentation to the double McLafferty species o than the ion n, the effect of both primary *vs.* secondary competitive processes being to increase the relative abundance of m over that of n.



B. Aliphatic Esters. McLafferty Rearrangement to the Carbomethoxyl Group

In order to substantiate the *IE* result of 0.88 previously obtained for γ-d_1- and γ-d_2-methyl butyrate,[5] we chose to study the hydrogen isotope effect in γ-d_1-methyl valerate (XVII) where there is a statistically equal probability of D or H transfer. Earlier workers[15] have established the specificity of γ-hydrogen transfer in the mass spectra of methyl esters while our high-resolution measurements on the *m/e* 74 and 75 rearrangement peaks in the spectrum of XVII have confirmed the composition of these peaks as C_2H_6O and C_2H_5DO corresponding to the species p.



The calculated *IE* value for γ-d_1-methyl valerate (XVII) of 0.92 at 70 ev is in good agreement with that measured previously[5] for methyl butyrate and does not show any significant variation at low electron voltages (Table I). One can speculate that the reason why this value is less than that (1.0) observed for 3-heptanone-6-d_1 (II) may be because the methoxyl group can stabilize the molecular ion XVII by electron donation to the positively charged oxygen atom as in XVIII. Rearrangement then can proceed through either contributing form to furnish ions p and q, the over-all effect being a distribution of the absorbed vibrational energy of the molecule and by analogy with established vapor-phase photolysis data[10b] would be expected to exhibit a stronger isotope effect.

C. Aromatic Compounds. McLafferty Rearrangement to the Benzene Ring

1. ***n*-Butylbenzene.** The published result,[6] calculated from the spectrum of *n*-butyl-3'-d_1-benzene,[16]

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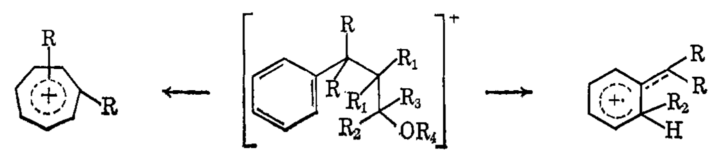
(15) N. Dinh-Nguyen, R. Ryhage, S. Ställberg-Stenhagen, and E. Stenhagen, *Arkiv Kemi*, **18**, 393 (1961).

(16) Measured by Dr. S. Meyerson on a C.E.C. 21-102/103 mass spectrometer at 70 ev. See J. D. McCollum and S. Meyerson, *J. Am. Chem. Soc.*, **81**, 4116 (1959).

Table III. The Effect of Reciprocal Hydrogen (or Deuterium) Transfers on the Tropylium Ion (v) and McLafferty Rearrangement Ion (s) at 70 ev in the Mass Spectra of Deuterated Hydrocinnamyl Alcohol[a,b]



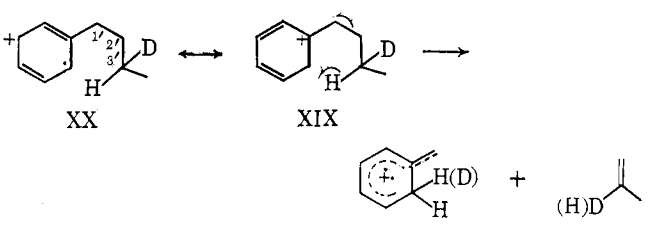
v, R = H; *m/e* 91

s, R = R_2 = H; *m/e* 92

m/e	R = R_1 = R_2 = R_3 = R_4 = H XXI	R = R_1 = R_2 = R_4 = H; R_3 = D XXII	R = R_1 = R_4 = H; R_2 = R_3 = D XXIII	R = D; R_1 = R_2 = R_3 = R_4 = H XXIV	R = R_2 = R_3 = R_4 = H; R_1 = D	R = R_1 = R_2 = R_5 = H; R_4 = D
91	100	100	100	7	100	100
92	50	39	26	17	64	48
93	. . .	22	50	99	20	9
94	. . .	. . .	. . .	42	8	. . .
Isotopic compn, %	. . .	2.8, d_0 93.5, d_1 3.7, d_2	99.5, d_2 0.5, d_1	96, d_2 4, d_1	98, d_2 2, d_1	60, d_1 40, d_0

[a] Relative abundance corrected for natural ^{13}C isotope abundance; uncorrected for deuterium isotope composition. [b] Measured on the Atlas CH-4 and A.E.I. MS-9 mass spectrometers.

indicated that an isotope effect of 0.80 was operative for the transfer of H *vs.* D to the aromatic nucleus (XIX → r).

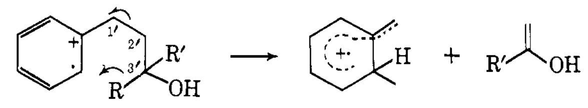


XX XIX

s, *m/e* 92 (93)

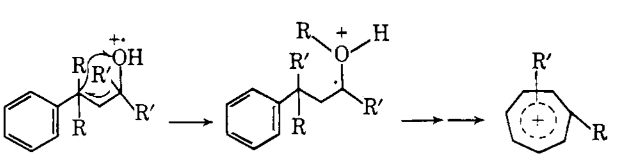
However, the specificity of the above process is only 95%, the remainder of the hydrogen rearrangement coming from the 4' position.[16] After correcting for this fact, the *IE* is increased to 0.88 (Table I), a value remarkably consistent with that observed for the esters (section B). The transfer mechanism differs from that postulated for the ketones II and VI in that the responsible molecular ion is visualized as the one with a π electron removed from the aromatic nucleus (*vs.* a nonbonded p electron from the oxygen atom in the ketones) and the resulting molecular ion XIX is stabilized by charge delocalization throughout the ring (XIX ↔ XX, etc.). By analogy with the esters (section B) the anticipated lowering of the vibrational energy of the molecule through delocalization may account for a stronger hydrogen isotope effect for XIX than in the case of the simple acyclic ketones II and VI.

2. **Hydrocinnamyl Alcohol.** Our previously published measurement[6] of the *IE* value (0.50) for the 3'-d_1 derivative XXII of this compound had assumed complete specificity of γ-hydrogen transfer based on the then available information[17] pertaining to this rearrangement. However our own later recording of the mass spectrum of hydrocinnamyl alcohol-3'-d_2 (XXIII) showed that although the rearrangement ion s at *m/e* 92 in XXI had quantitatively shifted to *m/e* 93 (t) there was still a considerable peak present at *m/e* 92 at 70 ev representing an apparent deuterium transfer specificity of only 66% (Table III). It would appear that the ion of mass 92 in the spectrum of XXIII is not the hydrogen rearrangement ion s but rather that it is a monodeuterated tropylium ion w which is produced by fission of the benzylic bond after prior partial hydrogen transfer in the molecular ion between all three side-chain positions and the hydroxyl group (*e.g.*, XXI → u → v). This conclusion was supported by the spectrum of hydrocinnamyl alcohol-1'-d_2 (XXIV) which showed that aside from the expected d_2-tropylium ion x of mass 93, there were also present contributions from the d_1 (w, *m/e* 92) and d_0 (v, *m/e* 91) species (Table III). The spectra of the 2'-d_2 and O-*d* derivatives of XXI indicated that these positions were also participating in the reciprocal exchanges analogous to that observed in the mass spectra of deuterated chromans.[18]



XXI, R = R' = H
XXII, R = H; R' = D
XXIII, R = R' = D

s, R = H; *m/e* 92
t, R = D; *m/e* 93



XXI, R = H; R' = H
XXIII, R = H; R' = D
XXIV, R = D; R' = H

u, R = R' = H

v, R = R' = H; *m/e* 91
w, R = D; R' = H; *m/e* 92
x, R = R' = D; *m/e* 93

Lowering the electron voltage substantially reduced the contribution of the tropylium ion to the mass spectrum of the hydrocinnamyl alcohols, at the same time increasing the apparent specificity of the γ-hydrogen rearrangement to a maximum of 94% at 12 ev. At this energy level the hydrogen isotope effect in XXII is 0.88 after correction for the above specificity while at

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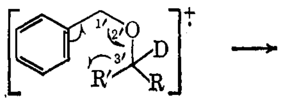
(17) J. D. McCollum and S. Meyerson, unpublished results quoted in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, p 510.

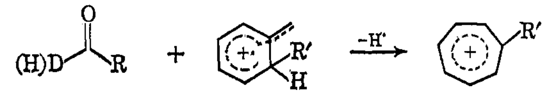
(18) S. D. Sample, Ph.D. Thesis, Stanford University, 1966.

15 ev the corrected *IE* value is 0.89 (Table I). These results are in excellent agreement with the value (0.88 cor) obtained for *n*-butylbenzene and one can conclude that the same factors are responsible for the lowered isotope effect in both cases for the cyclic transfer process (XXI → s).

3. Benzyl Alkyl Ethers. Before studying the isotope effect in this class of compound it was necessary to determine the specificity of the hydrogen transfer process which furnishes the *m/e* 92 peak, tentatively represented by the species s. In benzyl propyl ether-3′-d_2 (XXVII) the γ specificity at 70 ev was 94% increasing to >98% below 18 ev, the increase being due to the gradual disappearance of the *m/e* 91 peak (tropylium ion v), in particular that part of it which is derived from the McLafferty rearrangement ion s of mass 92 by loss of a hydrogen radical as evidenced by a metastable peak for s → v at *m/e* 90 in the 70-ev mass spectrum of the unlabeled benzyl alkyl ethers. Similarly the process t → w was eliminated at low electron voltage in the labeled derivatives (Figure 1a and b).



XXV, R = Me; R′ = H
XXVI, R = Et; R′ = H
XXVII, R = Et; R′ = D
XXVIII, R = R′ = H
XXIX, R = H R′ = D

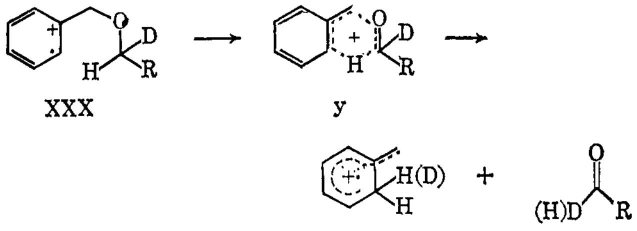


s, R′ = H; *m/e* 92 v, R = H; *m/e* 91
t, R′ = D; *m/e* 93 w, R′ = D; *m/e* 92

Table I outlines the extent of the *IE* values measured for the four compounds XXV, XXVI, XXVIII, and XXIX on two mass spectrometers (MS-9 and CH-4) over a range of electron energies. In the case of the two labeled benzyl methyl ethers XXVIII and XXIX, because the rearrangement peak at 70 ev is small compared to the *m/e* 91 tropylium ion intensity, the 12-ev *IE* values are considered to be more meaningful.

One must establish a rationale for the large discrimination against deuterium transfer for the benzyl ethers studied (0.5 and 0.6), and the most reasonable first assumption to make is that the oxygen atom in some way participates in the fragmentation process in view of the variation of these values from that of *n*-butylbenzene-3′-d_1 (XIX) (0.88). On the otherh and, the corrected *IE* value for hydrocinnamyl alcohol-3′-d_1 (XXII) at low electron voltage is also 0.88, indicating that in this instance the heteroatom does not have any influence on the H *vs.* D transfer probability even though it is adjacent to the rearrangement site as in the benzyl alkyl ethers.

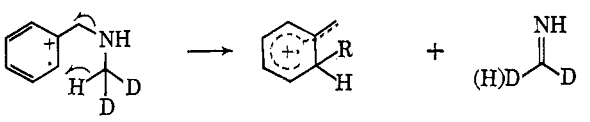
It is conceivable that this transfer process (XXX → r), unlike those in XXII and XIX, can be represented as a reverse ene reaction in an electron-deficient cyclic system similar to the electron impact induced retro-Diels–Alder fragmentation,[19] with participation of the nonbonding electrons of the oxygen atom in the proposed transition state (y). Such a situation might be expected to create a more symmetrical A···H···B transfer, which has been predicted[20] to be optimal for strong isotope effects.



XXX y

r, *m/e* 92 (93)

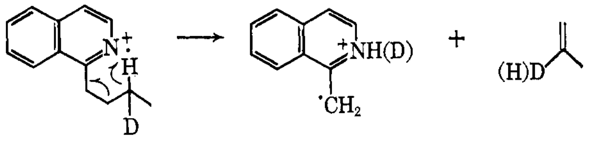
N-Methyl-d_2-benzylamine (XXXI; see Figure 2b) has a measured *IE* value of 0.48 at 12 ev (Table I) which is almost identical with that (0.47) of the corresponding dideuterated oxygen analog XXIX. A comparison of Figures 2a and b indicates that the more basic nitrogen heteroatom in XXXI also has little effect on the extent of the McLafferty rearrangement. The mass spectrum of the sulfur analog of the above series, benzyl methyl sulfide, showed an insignificant amount of γ-hydrogen rearrangement and a preponderance of α cleavage to furnish the tropylium ion v at mass 91. Consequently no *IE* measurements could be made for this compound.



XXXI s, R = H; *m/e* 92
t, R = D; *m/e* 93

D. 1-Butylisoquinoline. Rearrangement to Double Bonded Nitrogen

On electron impact, 1-butyl-3′-d_2-isoquinoline has been shown to transfer deuterium specifically (95% at 70 ev; >99% at 20 ev) with expulsion of monodeuteriopropene.[21] The hydrogen isotope effect for this mass spectrometric process in the γ-d_1 analog (XXXII → z) is 0.79 at 70 ev, 0.81 at 20 ev, decreasing to 0.76 at lower electron energy (Table I).



XXXII z, *m/e* 143 (144)

There are two factors which differentiate this rearrangement process from that of the other aromatic compounds studied (section C) and may conceivably be responsible for the stronger isotope effect in XXXII. First, the charge radical in the molecular ion may reside either partially on the nitrogen atom as in XXXII or be delocalized throughout the ring system. The second factor relates to the size differences between the bonding nitrogen (in XXXII) and carbon (in XIX) orbitals, the former having more s character which may critically affect the N–H orbital overlap in the transfer process XXXII → z and discriminate against deuterium rearrangement due to the shorter C–D bond distance.

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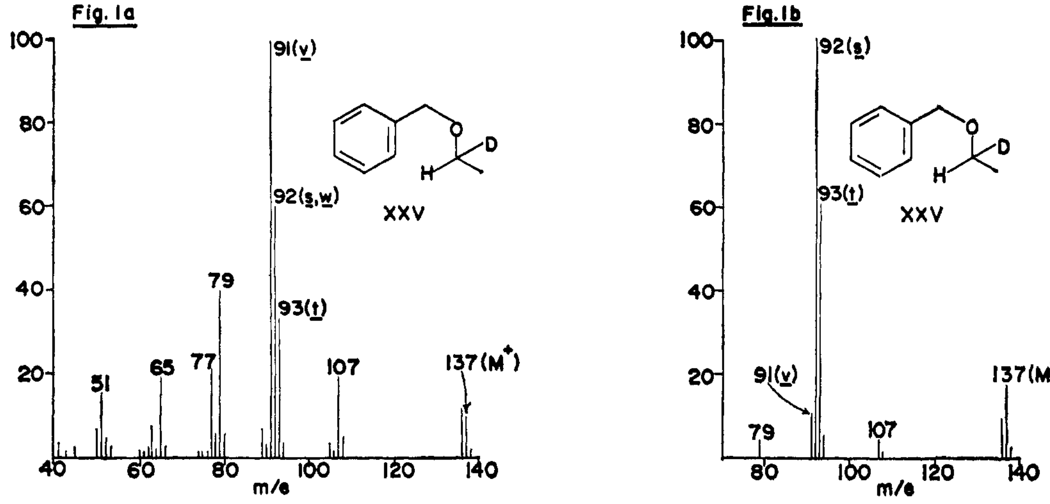
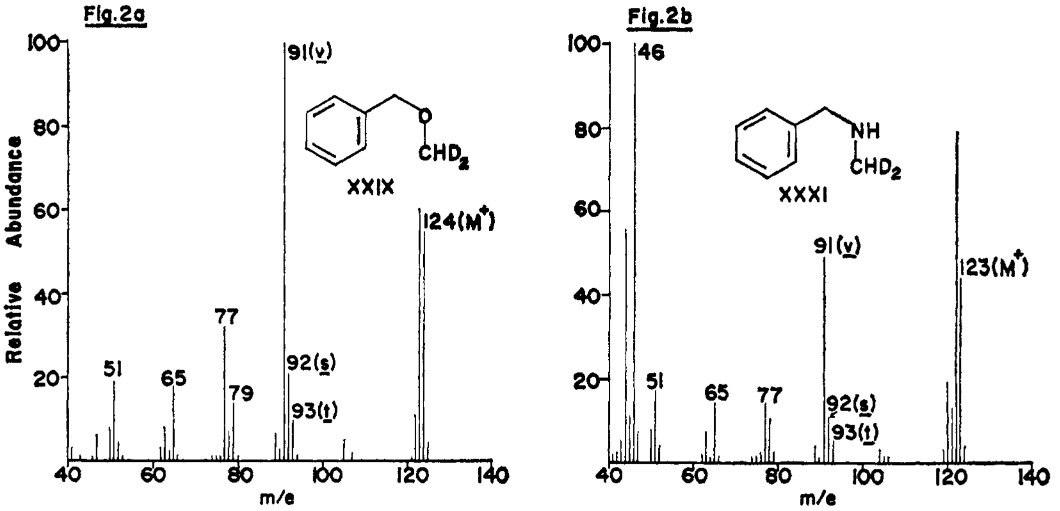
[19] H. Budzikiewicz, J. I. Brauman, and C. Djerassi, *Tetrahedron*, **21**, 1855 (1965).

[20] F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

[21] S. D. Sample, D. A. Lightner, O. Buchardt, and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967).





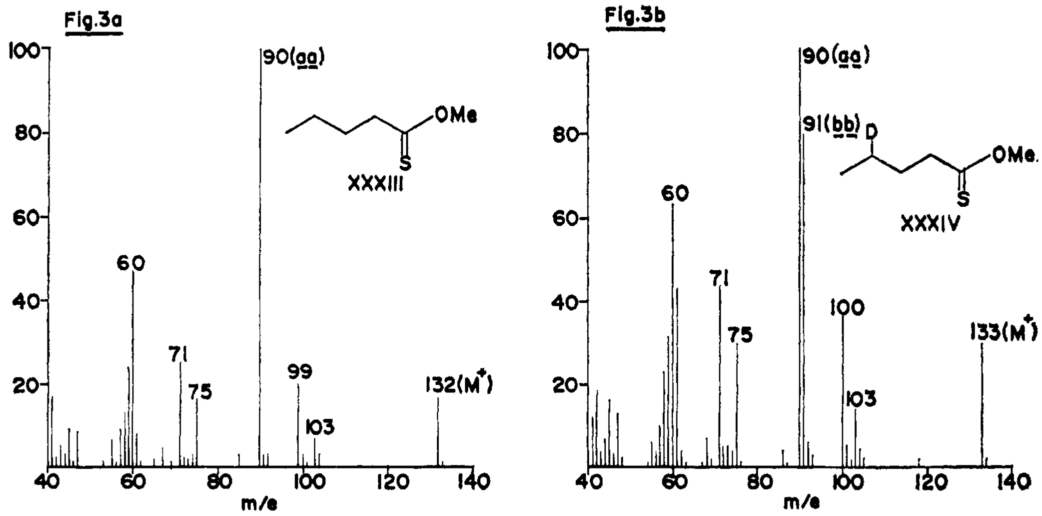
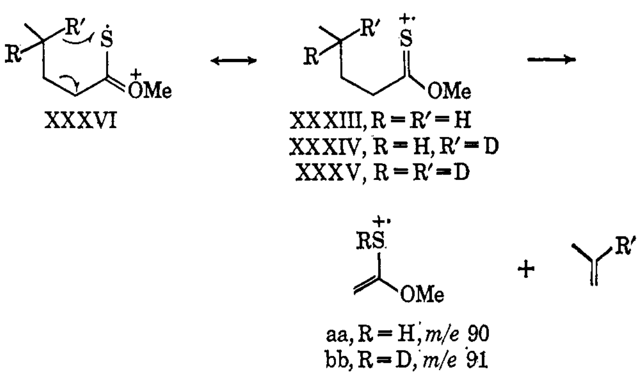


Figure 1. Mass spectrum of benzyl ethyl ether-3′-d_1 at 70 ev (a) and at 12 ev (b).
Figure 2. Mass spectra of benzyl methyl ether-3′-d_2 (a) and N-methyl-d_2-benzylamine (b) at 70 ev.
Figure 3. Mass spectra of methyl thionvalerate (a) and its γ-d_1 derivative (b) at 70 ev.

E. Thion Esters. Rearrangement to Doubly Bonded Sulfur

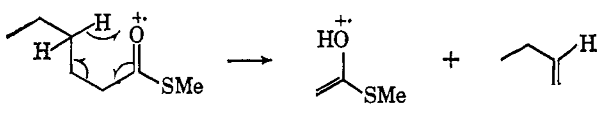
In order to complete the scope of this investigation by including rearrangement to doubly bonded sulfur, it was necessary to first find a suitable substrate which would give a site-specific six-membered electron impact induced hydrogen transfer to an electron-deficient sulfur atom. Methyl thionvalerate (XXXIII) displays a large McLafferty rearrangement peak (aa) in its mass spectrum (Figure 3a), the specificity of the process being 97% at 70 ev but decreasing to 94% at 12 ev, from measurements made on the γ-d_2 derivative XXXV. It is interesting to note that the isomeric thio esters, *e.g.*, XXXVII, show only a very weak McLafferty rearrangement ion cc (<0.5% of the total ionization).[22]



XXXVI

XXXIII, R = R′ = H
XXXIV, R = H, R′ = D
XXXV, R = R′ = D

aa, R = H, *m/e* 90
bb, R = D, *m/e* 91



XXXVII

cc

For reasons of charge distribution between the sulfur and oxygen atoms (XXIII → XXXVI) as discussed in the analogous case of methyl valerate (section B), a lower isotope effect would be expected for the γ-d_1 thion ester XXXIV than in the simple ketones (Figure 3b). That the actual *IE* value (0.80 at 70 ev with no change down to 12 ev; see Table I) is even less than that of methyl valerate-γ-d_1 (XVII) may be attributed to either the larger size or the lower electronegativity of the sulfur atom compared with the oxygen atom both of which could conceivably affect the transfer probability of a hydrogen *vs.* a deuterium atom.

The foregoing evaluation of the information collected on the isotope effect in mass spectrometric rearrangements is merely a rudimentary attempt to apply knowledge acquired from a more detailed study of primary isotope effects in solution chemistry and photochemistry to these gas-phase processes. The assumption that the kinetics in both media should resemble one another may or may not be tenable in such cases and certainly it is not always easy to reconcile one result with the next by such arguments. Virtually no information is available about the concerted or nonconcerted nature of electron impact induced hydrogen rearrangements, or whether proton, hydrogen radical, or hydride ion transfer is involved. It is possible that these primary hydrogen isotope effects coupled with other substitution techniques may shed some further light on the mechanism of these processes.

Another important variable in such *IE* measurements is the mass spectrometer and the conditions under which it is operating. Although the two Nier–Johnson type sector instruments, the A.E.I. MS-9 and Atlas CH-4 spectrometers, gave comparable results, it is possible that on instruments using different ion source optics these values could differ. In this regard, the spectrum of γ-d_1-heptanone-3 (II) was recorded on the Varian M-66 cycloidal mass spectrometer and showed *IE* values of 0.89 at 70 ev, increasing to 0.95 at lower ionizing energies. The reason for the significant decrease in this value compared with that recorded on the MS-9 and Atlas instruments of *ca.* 1.0 at 70 ev could be related to the time which an ion actually spends in the source region of the mass spectrometer. As the draw-out voltages are considerably higher in the M-66 spectrometer (1000 v/in.) than in the two other instruments, the time spent by an ion in the ionizing region will be less by about a power of 10 for mass 100 ($T = 1.02d\sqrt{M/V}$) and hence the fragmentations of that ion with a lifetime within this critical range (10^{-5} to 10^{-6} sec as evidenced by the presence of metastable ions corresponding to these processes) will be most affected by such changes. Ion source temperature, repeller plate voltage, and source pressure are further factors which may influence the value of the primary isotope effect in mass spectrometry just as it is important to take into account secondary fragmentation of the rearrangement ion which may itself exert an isotope effect. To eliminate this possibility we have attempted to measure *IE* values at low electron energies, as well as the conventional 70 ev when secondary fragmentation and high energy primary fragmentation are largely suppressed.

Experimental Section[23]

Ethyl Bromide-1-d_1. Acetaldehyde (7 ml) in ice-cold water (5 ml) was added dropwise (using a Dry Ice–acetone condenser) to a solution of sodium borodeuteride (Merck Sharp and Dohme, 1.5 g) in water (10 ml) cooled to 10°. After stirring for several hours, allowing the temperature of the reaction mixture to slowly increase to ambient, the insoluble complex was decomposed by dropwise addition of 20% sulfuric acid. The aqueous solution was fractionally distilled, the fraction boiling between 77 and 85° being collected. The ethanol-1-d_1 after being dried over magnesium sulfate was used later in the preparation of 3′-d_1-benzyl ethyl ether. Mass spectrometry established the position of the deuterium atom in the vpc purified labeled alcohol as the M − 15 peak had moved quantitatively from *m/e* 31 in the unlabeled compound to *m/e* 32 in the monodeuterated derivative. The remainder of the distillate was converted to the corresponding bromide by fractionation from 48% hydrobromic acid (28 ml)–concentrated sulfuric acid (7 ml) in good yield (7 ml). The ethyl bromide-1-d_1 was dried (calcium chloride) and after purification by vpc its isotopic content was measured by mass spectrometry (98% d_1, 2% d_0).

***n*-Propyl bromide-2-d_1** was prepared from the above labeled bromide by carbonation of the Grignard reagent, reduction of the resulting γ-d_1-propionic acid with lithium aluminum hydride, and bromination with 48% hydrobromic acid–concentrated sulfuric acid[24] (4:1).

***n*-Butyl bromide-3-d_1** was synthesized by chain extension of ethyl bromide-1-d_1 using diethyl malonate, then lithium aluminum hydride reduction, followed by bromination in the usual manner.

3-Heptanone-6-d_1 (II). To the Grignard reagent from *n*-butyl bromide-3-d_1 (0.7 ml) and magnesium (150 mg) in ether was added propionaldehyde (0.5 ml) in ether. After refluxing for 1 hr, the reaction complex was worked up in the usual manner and the resultant alcohol oxidized to 3-heptanone-6-d_1 (in acetic acid solution) using the Jones reagent.[25]

5-Nonanone-2,8-d_2 (VI) was prepared by the literature method from *n*-butyl bromide-3-d_1.[7] The γ,γ′-di-*n*-butyl ketone was previously prepared in this laboratory.[7]

2-*n*-Propyl-2′-d_1-cyclohexanone (XII) was prepared by alkylation[26] of the pyrrolidine enamine of cyclohexanone with *n*-propyl

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[22] W. H. McFadden, R. M. Seifert, and J. Wasserman, *Anal. Chem.*, 37, 560 (1965).

[23] Conditions for operation of the Atlas CH-4 mass spectrometer were: inlet line temperature 150°; reservoir temperature 90°; ion source temperature 200°; ionizing current 10 μa; electron voltage nominal 10–70 ev. For the MS-9 conditions were: inlet and ion source temperature 200°; ionizing current 100 μa; electron voltage nominal 10–70 ev. All compounds labeled and unlabeled were purified by vpc, most of the unlabeled compounds being obtained commercially except where indicated.

[24] A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 2913 (1965).

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

[26] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrel, *J. Am. Chem. Soc.*, **85**, 207 (1963).

iodide-2-d_1 prepared by iodination of the labeled alcohol[27] with constant boiling hydriodic acid.

Methyl Valerate-γ-d_1 (XVII). The Grignard reagent prepared from *n*-butyl bromide-3-d_1 (0.7 ml) and magnesium (150 mg) in ether was carbonated by pouring onto Dry Ice and the reaction mixture worked up in the usual way for acidic products. After methylation with diazomethane, the deuterated methyl ester of valeric acid was purified by vpc.

Labeled benzyl alkyl ethers (XXV to XXIX) were synthesized by the reaction of benzyl chloride, sodium hydroxide, and the appropriately labeled alcohol,[28] *i.e.*, for XXV, ethanol-1-d_1; for XXVI, propyl alcohol-1-d_1 (from $NaBD_4$ reduction of propionaldehyde); for XXVII, propyl alcohol-1-d_2 (from LAD reduction of propionic acid); for XXVIII, methanol-d_1 (prepared from $NaBD_4$ reduction of paraformaldehyde); and for XXIX, methanol-d_2 (prepared by cautious reduction of formic acid with LAD). The unlabeled ethers were prepared by the same method using unlabeled methanol, ethanol, and 1-propanol.

***n*-Methylbenzylamine-3′-d_2 (XXXI).** *n*-Formylbenzylamine was synthesized by the method of Blicke and Lu[29] and converted to the required N-methylbenzylamine-3′-d_2 by reduction with LAD in the usual way.

1-*n*-Butyl-3′-d_1-isoquinoline (XXXII). The method described by Sample, *et al.*,[21] employing alkylation of lithium-metalated 1-methylisoquinoline, was used to prepare this compound from *n*-propyl bromide-2-d_1. The corresponding dideuterated derivative was made available by Dr. S. Sample.[21]

Methyl Thionvalerate-γ-d_1 (XXXIV). Methyl chlorothioformate[30] (0.3 ml) in ether solution was added slowly to a cooled (0°) ethereal solution of the Grignard reagent composed of *n*-butyl bromide-3-d_1 (0.5 ml) and magnesium (100 mg). The reaction mixture was allowed to warm up to room temperature, left stirring for a further 2 hr, then decomposed by dropwise addition of saturated sodium sulfate solution. After filtration and removal of the solvent *in vacuo*, the product was purified by preparative vpc on a silicon rubber column at 80° (retention time, 5.5 min). The unlabeled thion ester XXXIII was obtained in the same manner.

Anal. Calcd for $C_6H_{12}OS$: C, 54.5; H, 9.1; S, 24.2. Found: C, 54.66; H, 8.91; S, 24.31.

The γ-d_2 derivative XXXV was synthesized by the same route from methyl thiochloroformate and *n*-butyl bromide-γ-d_2.[31]

Acknowledgment. We wish to thank Dr. A. M. Duffield for recording some of the mass spectra on the Atlas CH-4, Mr. R. Ross for high-resolution measurements on the A.E.I. MS-9, and Varian Associates for the mass spectrum of 3-heptanone-6-d_1 measured on their M-66 instrument. We are grateful to Dr. J. I. Brauman for helpful discussions.

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(27) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1956, p 285.

(28) W. T. Olson, H. F. Hipster, C. M. Buess, I. A. Goodman, I. Hart, J. H. Lamneck, and L. C. Gibbons, *J. Am. Chem. Soc.*, **69**, 2541 (1947).

(29) I. F. Blicke and C. J. Lu, *ibid.*, **74**, 3933 (1952).

(30) M. Delépine, *Bull. Soc. Chim. France*, 904 (1911), and preceding papers.

(31) A. M. Duffield, R. Beugelmans, H. Budzikiewicz, D. A. Lightner, D. H. Williams, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 805 (1965).

Mass Spectrometry in Structural and Stereochemical Problems. CXXXVII.[1] Examples of Interaction of Remote Functional Groups after Electron Impact[2]

Mark M. Green[3] and Carl Djerassi

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. Received May 9, 1967

Abstract: Oxygen rearrangement on electron impact has been found to be an important fragmentation pathway in various (I–VII) cyclic ketones containing methoxyl and hydroxyl groups. This oxygen migration, which produces, for example, the *m/e* 60 ion ($C_2H_4O_2$) from the molecular ion of 4-hydroxycyclohexanone (II), occurs in six- and seven-membered rings, with the two functional groups in both a 1,3 and 1,4 relationship. Heavy substitution around the ketone group appears to enhance the rearrangement while substitution adjacent to the hydroxyl or methoxyl group acts as a depressant. Deuterium labeling of 4-methoxy- and 4-hydroxycyclohexanone (I and II) suggested the intermediacy of the molecular ion of methyl Δ^5-hexenoate (XIII) in the case of 4-methoxycyclohexanone (I) and support for this proposal was provided by the synthesis of XIII. The rearrangement has been found to be unimportant in acyclic ketones containing primary methyl ether groups.

The attraction of organic chemists to rearrangement reactions is in no small way related to the important driving forces revealed by way of these processes.[4] Even if this were not the case, one is frequently stimulated to study these reactions for the intellectual challenge they provide.[5]

These reasons are no less binding in the study of electron impact produced ion reactions. Indeed, the developing use of mass spectrometery for structure determination adds further to the need for understanding these processes.[6]

There has been no scarcity of rearrangements in mass spectrometry, but most of these have involved hydrogen migration. Although recent work has uncovered rearrangements of larger groups,[7] these are far

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(1) For paper CXXXVI see J. K. MacLeod and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 5182 (1967).

(2) Financial support from the National Institutes of Health (Grant No. AM-04257) is gratefully acknowledged. The purchase of the Atlas CH-4 mass spectrometer was made possible through NASA Grant No. NsG 81-60.

(3) National Institutes of Health Postdoctoral Fellow, 1966–1967.

(4) Ample examples are found in "Molecular Rearrangements," P. deMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963.

(5) See, for example, a recent popular book providing this stimulation: S. Ranganathan, "Fascinating Problems in Organic Reaction Mechanisms," Holden-Day, Inc., San Francisco, Calif., 1967.

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