the hydrogen flow rate was 50 cc./min. The labeled ester Ib was collected from the column after 16 min. This method gave 66% incorporation of [18]O.[4]

Mass Spectrometry in Structural and Stereochemical Problems. LXXXIV.[1] The Nature of the Cyclic Transition State in Hydrogen Rearrangements of Aliphatic Ethers[2,3]

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Contribution from the Department of Chemistry, Stanford University, Stanford, California. Received July 6, 1965

As recognized first by McLafferty,[4] the two most characteristic fragmentation processes of aliphatic ethers (i) upon electron impact are α-fission to an oxonium ion (ii) and subsequent hydrogen rearrangement to a second oxonium ion (iii) with expulsion of an olefin fragment.
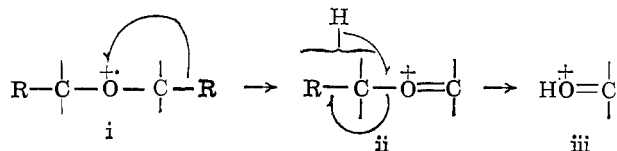
The second step (ii → iii), also noted in amines and thioethers, has generally been accepted as the prototype of a four-membered cyclic transition state in mass spectrometric rearrangement processes. By means of deuterium labeling in suitable ethers with sufficiently long side chains, it has now been demonstrated that three-, four-, five-, and six-membered cyclic transition states are feasible, with the latter three occurring to approximately the same extent. When a choice between abstraction of primary (methyl) or secondary (methylene) hydrogen is available, the latter is favored. Other features of the mass spectrometric fragmentation of aliphatic ethers are also discussed in the light of the spectra of their deuterated analogs.

The behavior of aliphatic ethers upon electron bombardment in the mass spectrometer has been studied in detail by McLafferty,[4] who was the first to call attention to the two most diagnostic processes, namely α-fission next to the oxygen atom and subsequent hydrogen transfer with ejection of an olefin molecule. The α-fission process can be illustrated conveniently in the mass spectrum (Figure 1) of an unsymmetrical ether such as ethyl *sec*-butyl ether (I),[4] and it will be noted that following the usual generalization in mass spectrometry,[4,5] the more highly substituted radical (in

this instance, ethyl) is lost preferentially to give the second most intense ion (a, m/e 73) in the spectrum (Figure 1). Alternate α-cleavage with expulsion of a methyl radical (m/e 87 in Figure 1) occurs to a much smaller extent. By labeling individually the two carbon atoms in the ethyl chain, it has now been possible to answer unambiguously the remaining question[5] concerning this α-fission, namely whether the methyl group is lost from the *sec*-butyl (b) or ethyl (b') chain or from both sites. The present results (Table I) demonstrate the exclusive origin from the more highly substituted locus (see b).
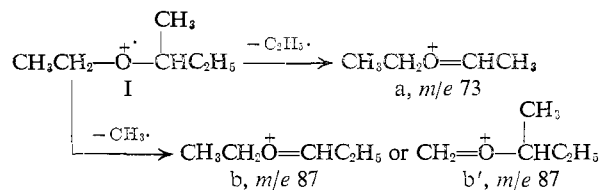
Theoretically, the m/e 73 peak could also arise by O–C cleavage with loss of the ethyl chain, but such a process would lead to an unfavored species where the heteroatom possesses only an electron sextet and the labeling results (Table I) confirm the absence of such a decomposition path. In fact when O–C fission does occur, as is particularly noted[4] in higher alkyl ethers (see also Figure 4), the charge remains predominantly with the alkyl portion (see m/e 29 and 57 in Figure 1) and an alkoxy radical is lost.

Mechanistically, by far the most intriguing reaction of ethers in the mass spectrometer is the subsequent decomposition of the α-fission products by hydrogen transfer to oxygen and olefin expulsion. McLafferty[4] noted that such a process did not occur with methyl ethers and thus required at least a β-hydrogen. Using the α-cleavage product a as progenitor, the reaction was visualized as a → c and apparently has been accepted in the literature[6-8] as the prototype of a four-membered cyclic transition state even in those com-

(1) Paper LXXXIII: J. Poisson, M. Plat, H. Budzikiewicz, L. J. Durham, and C. Djerassi, in press.

(2) Taken in part from the Ph.D. Thesis of C. F., Stanford University, 1965.

(3) Financial support (Grants No. CA-07195 and AM-04257) by the National Institutes of Health of the U. S. Public Health Service is gratefully acknowledged. The purchase of the Atlas CH-4 mass spectrometer was made possible through NASA Grant NsG 81-60. C. F. wishes to thank the Computation Center, Stanford University, for a Student Time Grant.

(4) F. W. McLafferty, *Anal. Chem.*, **29**, 1782 (1957).

(5) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, pp. 50–52.

(6) J. H. Beynon, "Mass Spectrometry and Its Application to Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1960, p. 363.

(7) F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).

(8) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 116.

Compd.	Isotopic purity[b]	M^+	M − 15	M − 29	M − 43	M − 45	M − 57
$C_2H_5OCH(CH_3)C_2H_5$ (I)	...	102	87	73	59	57	45
$CH_3CD_2OCH(CH_3)C_2H_5$ (II)	$92\% \; d_2$	104 (q)	89 (q)	75 (q)	60 (15%)	57 (q)	46 (17%)
	$8\% \; d_1$				59 (85%)		45 (83%)
$CD_3CH_2OCH(CH_3)C_2H_5$ (III)	$74\% \; d_3$	105 (q)	90 (q)	76 (q)	60 (78%)	57 (q)	46 (74%)
	$9\% \; d_2$				59 (22%)		45 (26%)
	$4\% \; d_1$						
	$13\% \; d_0{}^c$						

[a] The symbol q denotes a quantitative transfer (>95%). All numerical values are considered accurate to ±5% for peaks in excess of 20% relative abundance. Correction for isotopic contaminants and ^{13}C contributions have been made in all instances. [b] In view of the very low intensity of the molecular ion, the isotopic purity was calculated using both the M − 15 (m/e 87) and M − 29 (m/e 73) peaks. [c] The unusually large d_0 content results from the fact that some diethyl ether, present as a contaminant in 2,2,2-d_3-ethanol, is cleaved to un-labeled ethanol during the hydrogen bromide–sulfuric acid step in the preparation of ethyl bromide.

pounds where hydrogens beyond the β-carbon atom are available for transfer.

$$CH_2\!-\!CH_2\!-\!\overset{+}{O}\!=\!CHCH_3 \rightarrow H\overset{+}{O}\!=\!CHCH_3 + CH_2\!=\!CH_2$$

c, m/e 45

a, m/e 73
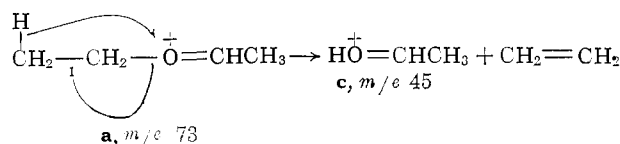
However, in our own review[5] of the mass spectrometric behavior of ethers we pointed out that "the evidence for such four-membered transition states is scant...while the type of fragmentation exemplified by a → c is also found in ethers with alkyl groups larger
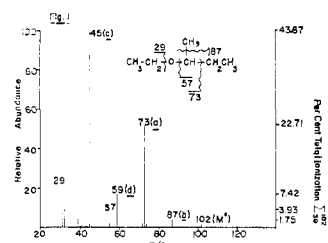

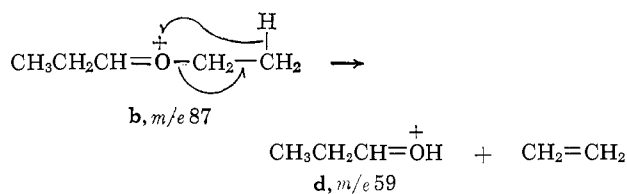Figure 1. Mass spectrum (70 e.v.) of ethyl sec-butyl ether (I).

than ethyl, no definite evidence has as yet been presented about the origin of the transferred hydrogen in such substances." Our own interest in mass spectrometric hydrogen transfer processes,[9] because of their important mechanistic bearing, prompted us to examine critically this particular reaction in aliphatic ethers. Indeed, the two labeled ethyl sec-butyl ethers II and III (see Table I) already showed that even if only two carbon atoms are available, a significant amount (17%) of hydrogen originates from the α-position, thus implying the operation of a three-membered transition state in addition to the expected four-membered one.

The same results were encountered in examining the shifts (Table I) upon deuteration of the m/e 59 peak, which corresponds[5] to the hydrogen transfer-cum-olefin elimination product d derived from the alternate α-fission product b (m/e 87), the operation of this path being substantiated by the detection of a metastable peak[10] at m/e 40.0 ($59^2/87 = 40.0$). Here again, the

(9) C. Djerassi, Pure Appl. Chem., 9, 159 (1964).
(10) All metastable peaks were determined by means of the logarithmic transfer recorder developed recently in these laboratories: R. T. Aplin, H. Budzikiewicz, H. S. Horn, and J. Lederberg, Anal. Chem., 37, 776 (1965).

results with the labeled compounds (II, III) demonstrate that a three-membered transition state is also feasible for this process.

$$CH_3CH_2CH\!=\!\overset{+}{O}\!-\!CH_2\!-\!CH_2 \longrightarrow$$

b, m/e 87

$$CH_3CH_2CH\!=\!\overset{+}{O}H \;+\; CH_2\!=\!CH_2$$

d, m/e 59

It is pertinent to note that the sum total of the hydrogen transfers in the production of species c and d equals, 91–93% as determined (Table I) from the methylene (II) and methyl (III) labeled ethers. This points to the existence of an isotope effect, which is of the same order of magnitude as that observed[11] in esters for a hydrogen transfer to oxygen.

In the light of the results encountered with ethyl sec-butyl ether (I), it was clearly of interest to extend such a deuterium labeling study to an ether with a longer side chain in order to determine whether ring sizes larger than four were also operative in the ether hydrogen-transfer process.

The first candidate selected was isopropyl n-butyl ether (IV), deuterium labeling being effected in all of the carbon atoms of the butyl chain as well as in the methyl groups of the isopropyl substituent (compounds V–IX in Table II). Its mass spectrum had not been reported in the earlier literature,[4] but on the basis of the generalizations outlined above concerning the fragmentation of ethers, it could be predicted that it would exhibit a spectrum which would lend itself particularly readily to mechanistic scrutiny of the hydrogen transfer of species e, in which four sites are available in the n-butyl chain for hydrogen migration. In ethyl n-butyl ether or n-propyl n-butyl ether, this type of ion is much less intense,[4] because of the preferred α-fission with loss of the heavier propyl radical (as compared to loss of a methyl or ethyl radical) and subsequent principal production of an ion analogous to g, in which the availability of γ- and δ-hydrogens cannot be studied. By introducing a branch in the propyl side chain, α-cleavage in that portion of the molecule is greatly increased (see also exclusive methyl loss from the sec-butyl group in ethyl sec-butyl ether (Figure 1)).

The data are self-explanatory and, aside from a consideration of the hydrogen-transfer mechanism, only

(11) D. H. Williams, H. Budzikiewicz, and C. Djerassi, J. Am. Chem. Soc., 86, 284 (1964).

Table II. Principal Mass Spectral Peaks in Isopropyl n-Butyl Ether (Figure 2) and Deuterated Analogs[a]

| Compd.	Isotopic purity[b]	M⁺	M − 15	M − 43	M − 59	M − 71	M − 73
$(CH_3)_2CHOCH_2CH_2CH_2CH_3$ (IV)	...,	116	101	73	57	45	43
$(CH_3)_2CHOCD_2CH_2CH_2CH_3$ (V)	>99% d_2	118 (q)	103 (q)	75 (q)	59 (q)	46 (15%) 45	43 (92%) 44 45
$(CH_3)_2CHOCH_2CD_2CH_2CH_3$ (VI)	95% d_2 5% d_1	118 (q)	103 (q)	73 (q)	59 (q)	46 (35%) 45	43 (83%) 44 45
$(CH_3)_2CHOCH_2CH_2CD_2CH_3$ (VII)	94% d_2 6% d_1	118 (q)	103 (q)	73 (q)	59 (q)	46 (40%) 45	43 (88%) 44 45
$(CH_3)_2CHOCH_2CH_2CH_2CD_3$ (VIII)	95% d_3 4% d_2 1% d_1	119 (q)	104 (q)	73 (q)	60 (q)	46 (2-9%) 45	43 (80%) 44 45 46
$(CD_3)_2CHOCH_2CH_2CH_2CH_3$ (IX)	99% d_6	122 (q)	104 (q)	79 (q)	57 (q)	48 (q)	49 (87%) 43

[a] See footnote a in Table I. [b] In view of the low intensity of the molecular ion, the isotopic purity was calculated using the M − 15 peak.

one peak assignment merits comment. This refers to the m/e 43 peak, which by high resolution mass measurements[12] was shown to consist to the extent of over 90%
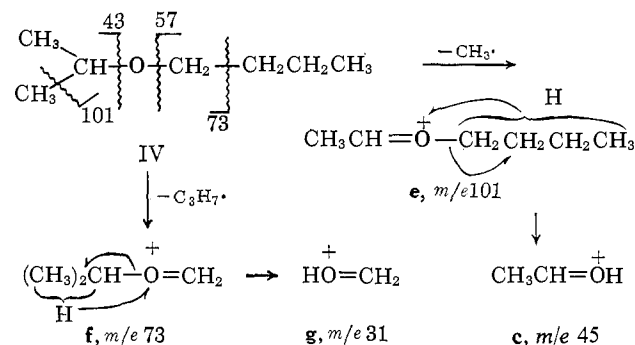
of C_3H_7 with only a small contribution from C_2H_3O. The peak shifts summarized in Table II show that while the major part of the m/e 43 peak corresponds, as expected, to the isopropyl fragment, a portion arises by further decomposition of the butyl ion (m/e 57). These two hydrocarbon fragments (m/e 43 and 57 in Figure 2) need not necessarily originate by direct O–C cleavage as indicated schematically in structure IV. At least a portion of these ions arises by heterolysis of the α-cleavage products e (m/e 101) and f (m/e 73) by expulsion of acetaldehyde and formaldehyde, respectively, as demonstrated by the detection of metastable peaks[10] at m/e 32.2 (57²/101 = 32.2) and m/e 25.3 (43²/73 = 25.3).

The most significant conclusion to be derived from the data collected in Table II pertains to the hydrogen transfer involved in the genesis of species c (m/e 45) from the α-cleavage product e (m/e 101).[13] In contrast to the
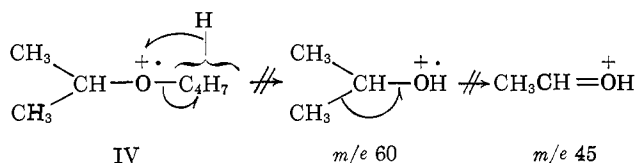
(12) Performed by Drs. R. T. Aplin and D. Becher with an A.E.I. MS-9 double-focussing mass spectrometer.

(13) This particular sequence of events is substantiated by the presence[10] of a metastable peak at m/e 20.1 (45²/101 = 20.04), while none could be observed for the reverse sequence (m/e 60 → m/e 45) nor is there a peak at m/e 60 in the mass spectrum (Figure 2).

generalizations from the literature[4,6–8] hydrogen is abstracted from all four possible sites in the butyl chain. The extent of this fragmentation process is

greatly reduced when the ionizing energy is reduced from 70 (Figure 2) to 15 e.v. (Figure 2a), but the origin of the itinerant hydrogen is not at all affected quantitatively as determined by the 15-e.v. spectra (not re-
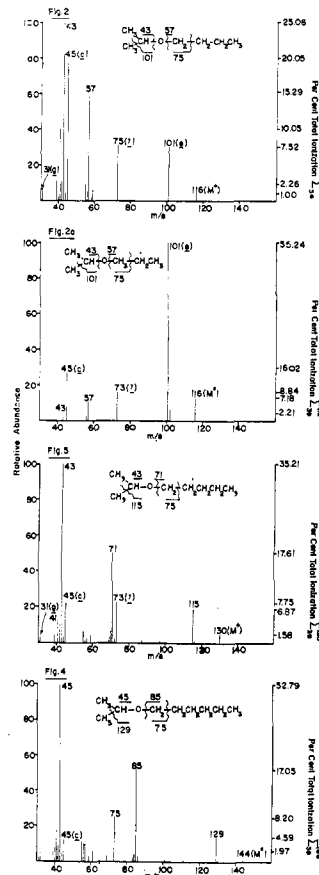
Figure 2. Mass spectrum (70 e.v.) of isopropyl n-butyl ether (IV).
Figure 2a. Mass spectrum (15 e.v.) of isopropyl n-butyl ether (IV).
Figure 3. Mass spectrum (70 e.v.) of isopropyl n-pentyl ether (X).
Figure 4. Mass spectrum (70 e.v.) of isopropyl n-hexyl ether.

Table III. Principal Mass Spectral Peaks in Isopropyl n-Pentyl Ether (Figure 3) and Deuterated Analogs[a]

Compd.	Isotopic purity[b]	M − 15	M − 57	M − 59	M − 85	M − 87
$(CH_3)_2CHOCH_2CH_2CH_2CH_2CH_3$ (X)	...	117	73	71	45	43
$(CH_3)_2CHOCD_2CH_2CH_2CH_2CH_3$ (XI)	97% d_2 3% d_1	117 (q)	75 (q)	73 (q)	46 (10%) 45	43 (62%) 44 45
$(CH_3)_2CHOCH_2CD_2CH_2CH_2CH_3$ (XII)	97% d_2 3% d_1	117 (q)	73 (q)	73 (q)	46 (26%) 45	43 (62%) 44 45
$(CH_3)_2CHOCH_2CH_2CD_2CH_2CH_3$ (XIII)	97% d_2 3% d_1	117 (q)	73 (q)	73 (q)	46 (25%) 45	43 (62%) 44 45
$(CH_3)_2CHOCH_2CH_2CH_2CD_2CH_3$ (XIV)	96% d_2 4% d_1	117 (q)	73 (q)	73 (q)	46 (29%) 45	43 (62%) 44 45
$(CH_3)_2CHOCH_2CH_2CH_2CH_2CD_3$ (XV)	86% d_3 7% d_2 7% d_1	118 (q)	73 (q)	74 (q)	46 (1-10%) 45	43 (62%) 44 45 46

[a] See footnote a in Table I. [b] Calculated by using both the molecular ion and M − 15 peaks.

produced) of the deuterated analogs V–VIII. Particularly noteworthy is the apparent preference for a four- and five-membered transition state at the expense of a six-membered one, which is known[9] to be favored in certain other mass spectral hydrogen-transfer reactions. It seemed to us that one possible explanation for the reduced operation of a six-membered transition state would be that, in a butyl ether, this would require abstraction of hydrogen from a primary rather than a secondary site, a factor which in at least two instances partially[14] or completely[15] prevented an otherwise specific hydrogen transfer.

Consequently, isopropyl n-pentyl ether (X) as well as the five analogs XI–XV labeled with deuterium in the pentyl chain were synthesized and their mass spectra were determined (Figure 3 and Table III). The formulation of the principal peaks, illustrated schematically in structure X, follows from the peak shifts caused by deuterium introduction (Table III) and is completely analogous to the previously discussed lower homolog IV, except for the much greater incidence of hydrocarbon species (m/e 43 and m/e 71) at the expense of the mechanistically important, but now quantitatively much less significant m/e 45 ion (c). This is demonstrated even more strikingly by the mass spectrum (Figure 4) of the next higher homolog, isopropyl n-hexyl ether, where the m/e 45 species carries only 4.6% of the total ionizing current (Σ₃₉) as compared to 7.8% for X (Figure 3), 20.0% for IV (Figure 2), and no less than 32.7% for I (Figure 1). Just as shown with isopropyl n-butyl ether (IV), here also the hydrocarbon fragments need not necessarily arise by direct O–C cleavage as indicated by the wavy lines in formula X, but can also be formed by loss of the appropriate aldehyde from the α-cleavage product. Thus a metastable peak[10] at m/e 43.9 (71²/115 = 43.8) lends support to the assumption that at least part of the C_5H_{11} ion (m/e 71) results from heterolysis of the M − 15 fragment (m/e 115) with ejection of an acetaldehyde equivalent. It should also be noted from Table III that the deuterium labeling results demonstrate that nearly 40% of the m/e 43 (C_3H_7) species is formed by further de-

(14) H. Fritz, H. Budzikiewicz, and C. Djerassi, Ber., in press.
(15) C. Djerassi and S. D. Sample, Nature, in press.

composition of the pentyl chain rather than by originating exclusively from the isopropyl part of the molecule.

X
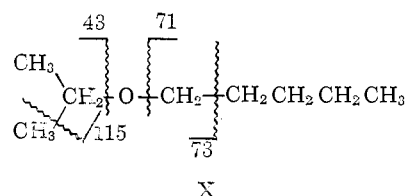
The most important conclusion derived from the data of Table III pertains again to the hydrogen transfer accompanying the m/e 45 ion formation. As summarized in Table IV, migration of a δ-hydrogen

Table IV. Origin of Hydrogen Transfer in m/e 45 Ion Production in Isopropyl n-Butyl (IV) and Isopropyl n-Pentyl (V) Ethers
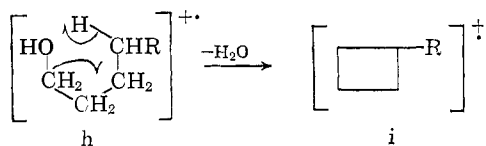
Position	% transfer	
	IV[a]	X[b]
α	15	10
β	35	26
γ	40	25
δ	2–9[c]	29
ε	...	1–10[c]
	92–99	91–100

[a] See Table II. [b] See Table III. [c] In the d_3-ethers part of the $C_3H_7^+$ ion (mass 43) appears at 46 ($C_3H_4D_3^+$) as well as at 45 ($C_3H_5D_2^+$) and, while the total of these extraneous contributions to the peaks at m/e 45 and 46 can be calculated, it is impossible to quantitatively separate the two and thus a range must be reported.
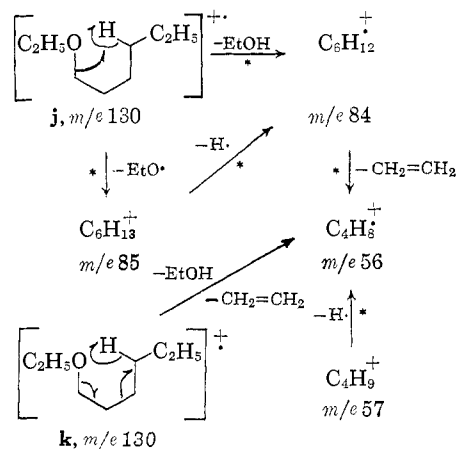
now becomes significantly greater, the difference between the values for the butyl (IV) and pentyl (X) ether clearly reflecting the preference for abstraction of a hydrogen atom from a secondary as compared to a primary site. An equally significant conclusion to be derived from Table IV is that, all other factors being equal, a four-, five-, and six-membered cyclic transition state is about equally favored, with a three-membered one being feasible but less favored. This conclusion is in striking contrast to the recently examined[16] loss of ketene from N-n-valerylpyrrolidine

labeled with deuterium in every carbon atom of the acyl group, where predominant hydrogen transfer through a four-membered cyclic transition state could be demonstrated. To our knowledge, this is the only example where a preference for a four-membered ring has been demonstrated unambiguously even when larger rings are feasible, and should be contrasted with the pronounced preference for a six-membered transition state in the dehydration of alcohols[17] (h → i).

$$\left[\begin{array}{c} \text{HO} \quad \text{H} \quad \text{CHR} \\ \text{CH}_2 \quad \text{CH}_2 \\ \text{CH}_2 \end{array}\right]^{+\cdot} \xrightarrow{-\text{H}_2\text{O}} \left[\begin{array}{c} \boxed{\quad} \text{--R} \end{array}\right]^{+}$$

h   i

An analogous reaction can be discerned in the mass spectrum (Figure 5) of ethyl n-hexyl ether (XVI), where a significant m/e 84 peak corresponds formally to the loss of ethanol. If written in the following manner (j), analogous to the dehydration[17] of h, one would assume that the δ-hydrogen atom should be implicated almost exclusively. However, as seen from the mass spectrum (Figure 6) of the δ-d_2-deuterated analog, only $ca.$ 33% of deuterium appears to be transferred from that position. In addition, there is observed[10] a metastable peak (all reactions in the following flow sheet for which a metastable peak could be detected are marked with an asterisk) for the transition m/e 85 (M − EtO) → m/e 84 (M − EtOH). Competing hydrocarbon fragmentations thus preclude any quantitative estimates of specific hydrogen transfers in the one-step elimination of ethanol from the molecular ion j. A similar complication has been ignored by the Spitellers,[18] who interpret the existence of an intense ion of mass 56 in the mass spectrum[4] of di-n-hexyl ether in terms of a concerted loss of hexyl alcohol, and ethylene and the transfer of a δ-hydrogen atom analogous to the formulation k for ethyl n-hexyl ether, whose mass spectrum (Figure 5) also exhibits a very intense m/e 56 peak. The latter is indeed shifted to the extent of at least 35% and perhaps as much as 75% to m/e 57 in the spectrum (Figure 6) of the δ-d_2-analog (the wide range is due to the fact that the move-

Figure 5. Mass spectrum (70 e.v.) of ethyl n-hexyl ether (XVI).
Figure 6. Mass spectrum (70 e.v.) of ethyl 4,4-d_2-n-hexyl ether.

ments of the m/e 55 and 57 peaks cannot be predicted with certainty), but, in addition, there were observed metastable peaks[10] corresponding to the loss of ethylene from the M − EtOH ion (m/e 84) as well as the loss of hydrogen from a butyl ion (m/e 57). Thus it is again impossible to state quantitatively[19] to what extent specific hydrogen transfer from the δ-position is implicated in the postulated[18] one-step production (see k) of the m/e 56 species.

Experimental Section[20]

Ethyl sec-Butyl Ether (*I*) *and Labeled Analogs II and III.* Sodium (2.3 g.) was dissolved in a mixture of 5 ml. of ethanol and 100 ml. of dioxane by heating, 10 ml. of sec-butyl bromide was added, and the mixture was heated under reflux for 36 hr. Water and diethyl ether were added, and after thorough washing with water, the desired ether was isolated by gas phase chromatography on a polybutylene glycol column maintained at room temperature. The labeled analogs were prepared by utilizing either 1,1-d_2-ethanol, obtained by lithium aluminum deuteride reduction of acetic acid, or 2,2,2-d_3-ethanol, derived from diethyl malonate by the procedure[21] employed earlier in the synthesis of 2,2-d_2-propanol from diethyl methylmalonate.

Isopropyl n-Butyl Ether (*IV*) *and Labeled Analogs V–IX.* Sodium (0.4 g.) was dissolved in 20 ml. of

(16) A. M. Duffield and C. Djerassi, *J. Am. Chem. Soc.*, in press. See also related observation in succinimides: A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *ibid.*, 87, 2913 (1965).

(17) See W. Benz and K. Biemann, *ibid.*, 86, 2375 (1964); S. Meyerson and L. C. Leitch, *ibid.*, 86, 2555 (1964), and references cited therein.

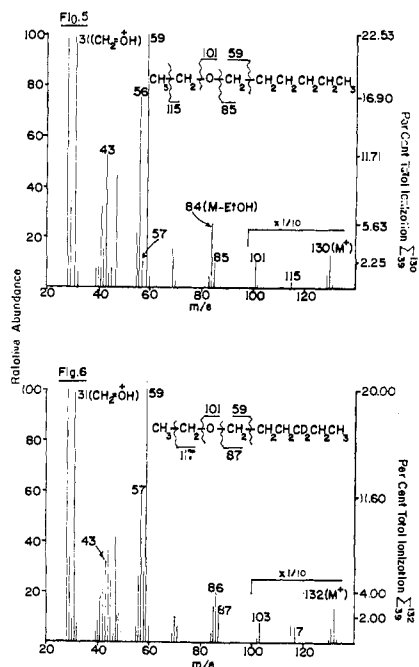(18) G. Spiteller and M. Spiteller-Friedmann, *Monatsh.*, 95, 257 (1964).

(19) It is pertinent to note that in the 15-e.v. spectrum the hydrocarbon peaks are sufficiently reduced so that a more accurate estimation (63–68%) of the δ-hydrogen transfer can be made.

(20) All mass spectra were measured with an Atlas CH-4 mass spectrometer equipped with an AN-4 ion source (temperature 60°) and a logarithmic transfer recorder.[10] Unless specified otherwise, the ionizing energy was maintained at 70 e.v. We are indebted to Drs. R. T. Aplin and H. Budzikiewicz for the measurements and for advice in the numerous calculations. All ethers were purified by gas phase chromatography using a Wilkens Aerograph instrument equipped with a polybutylene glycol column.

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

Flow sheet:

$$\left[\text{C}_2\text{H}_5\text{O} \quad \text{H} \quad \text{C}_2\text{H}_5\right]^{+\cdot} \xrightarrow[*]{-\text{EtOH}} \text{C}_6\text{H}_{12}^{+\cdot}$$

j, m/e 130 m/e 84

$* \downarrow -\text{EtO}\cdot$ $\quad \nearrow -\text{H}\cdot \quad$ $* \downarrow -\text{CH}_2=\text{CH}_2$

$\text{C}_6\text{H}_{13}^{+}$ $\text{C}_4\text{H}_8^{+\cdot}$

m/e 85 $\xrightarrow{-\text{EtOH}}$ $\quad$ m/e 56

$\quad -\text{CH}_2=\text{CH}_2 \quad$ $-\text{H}\cdot \uparrow *$

$$\left[\text{C}_2\text{H}_5\text{O} \quad \text{H} \quad \text{C}_2\text{H}_5\right]^{+\cdot}$$ $\quad$ C_4H_9^{+}

k, m/e 130 m/e 57

isopropyl alcohol, butyl bromide (2 g.) was added, and the mixture was heated under reflux for 2–5 hr. before isolating the desired ether by gas phase chromatography (column temperature 25°). The labeled butyl bromides were synthesized by the earlier described procedure.[21] d_6-Acetone (Nuclear Research Chemicals, Inc., Orlando, Fla.) was reduced with lithium aluminum hydride to the corresponding d_6-isopropyl alcohol, which was then converted to IX.

Isopropyl n-Pentyl Ether (X) and Labeled Analogs XI–XV. The same procedure was employed as described for the lower homolog IV except that *n*-pentyl bromide was substituted. The 3,3-d_2- and 4,4-d_2-pentyl bromide syntheses have already been described[21] and the 1,1-d_2-analog was obtained by lithium aluminum deuteride reduction of valeric acid followed by treatment with 48% hydrobromic acid in concentrated sulfuric acid. 2,2-d_2-Pentyl bromide was prepared from the appropriately labeled butyl bromide[21] by carbonation

of the Grignard reagent followed by lithium aluminum hydride reduction and transformation into the bromide. 5,5,5-d_3-Pentyl bromide was synthesized from 2,2,2-d_3-acetic acid (Calbiochem, Los Angeles) which was reduced with lithium aluminum hydride. The labeled ethanol was converted to 2,2,2-d_3-ethyl bromide, the Grignard reagent of which was condensed with ethylene oxide by the procedure[21] used to synthesize 4,4-d_2-pentyl bromide. 4,4,4-d_3-Butanol was treated with 48% hydrobromic acid in concentrated sulfuric acid and the resulting butyl bromide was transformed into 5,5,5-d_3-pentyl bromide as described for 2,2-d_2-pentyl bromide.
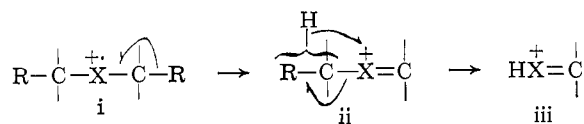
Ethyl 4,4-d_2-n-Hexyl Ether. 2,2-d_2-Butyl bromide was transformed into the Grignard reagent and the latter was treated with ethylene oxide in the manner described earlier[21] for pentyl bromide. The resulting hexyl alcohol was transformed into the bromide and then heated under reflux with sodium ethoxide in ethanol.

Mass Spectrometry in Structural and Stereochemical Problems. LXXXV.[1] The Nature of the Cyclic Transition State in Hydrogen Rearrangements of Aliphatic Amines[2,3]

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The two most significant peaks in the mass spectra of aliphatic amines ($X = NH$ or NR) are usually associated with α-cleavage (i → ii) and subsequent hydrogen rearrangement (ii → iii) with production of an immonium ion (iii, $X = NH$ or NR) and expulsion of an olefin frag-

ment. The hydrogen migration has been assumed to proceed through a four-membered cyclic transition state in amines ($X = NH$ or NR) as well as ethers ($X = O$). However, recent work[1] with deuterium-labeled ethers has demonstrated that three-, five-, and six-membered rings are also feasible, and it is for that reason that the mass spectra of deuteriated N-methyl-N-isopropyl-n-butyl-, and -n-pentylamine were examined. The results demonstrate that, just as in ethers,[1] transition states involving three-, four-, five-, and six-membered rings can operate in the hydrogen-transfer step but that the nature of the heteroatom ($X = O$ vs. $X = N$) does exert some effect

as judged by quantitative differences between ethers and amines.

Four-membered transition states in mass spectrometric rearrangement processes are not well established, especially when there exist alternate paths proceeding through larger ring intermediates, notably six-membered ones. One authenticated case[4] is the loss of propylketene from the M − 1 species **a** of N-valerylpyrrolidine (I) where the hydrogen transfer to the immonium ion **b** was established by deuterium labeling to proceed to the extent of nearly 75% through a four-membered, cyclic transition state.

One of the most plausible, four-membered transition states which has been implicated[5] for hydrogen rearrangements involves the well-known elimination of an
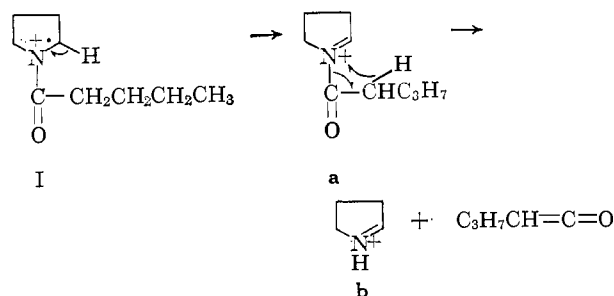
(1) Paper LXXXIV: C. Djerassi and C. Fenselau, *J. Am. Chem. Soc.*, **87**, 5747 (1965).

(2) Taken in part from the Ph.D. Thesis of C. F., Stanford University, 1965.

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(4) A. M. Duffield and C. Djerassi, *J. Am. Chem. Soc.*, in press.

(5) R. S. Gohlke and F. W. McLafferty, *Anal. Chem.*, **34**, 1281 (1962).