Mass Spectrometry in Structural and Stereochemical Problems. CCII.[1] Interaction of Remote Functional Groups in Acyclic Systems upon Electron Impact[2]

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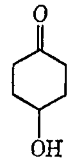
Received November 10, 1970

In a series of 4-alkoxybutyrates and related substances, the scope and limitations of the unexpected β cleavage at the ether function have been investigated. Deuterium-labeling experiments and high resolution mass measurements indicated that no rearrangements or reciprocal hydrogen transfers were involved in this process. The intensity of the β-cleavage ion became unimportant as the alkoxy group increased in size. Major fragmentation pathways were elucidated with the aid of high resolution mass measurements, metastable defocusing techniques, and deuterium-labeling studies, and indirect evidence for interaction of the remote functional groups was found.

Shortly after the applicability of mass spectrometry to organic chemistry was recognized, the fragmentation patterns of almost every class of compound were extensively investigated, notably with the aid of deuterium labeling and high resolution mass measurements.[4] Recently efforts were initiated in these laboratories[5] to develop programs for computer assisted interpretation of the mass spectra of several classes of compounds. Only acyclic, monofunctional substances have been studied thus far, and a substantial degree of success has been achieved. However, one of the ultimate goals of this program is the computer-aided analysis of the spectra of more complicated molecules. To this end it was important to determine whether two functional groups in the same molecule would give rise to fragmentations independent of one another or to unique fragmentations resulting from direct interaction of the two groups. Of the cases studied thus far,[6-13] the latter possibility seems to be more prevelant. Direct interaction of the functional groups,[6-10] migration of electron rich groups to carbonium ion centers,[11] and anchimeric assistance[12,13] were the reasons cited to explain the unusual fragmentation patterns in these instances.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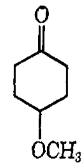
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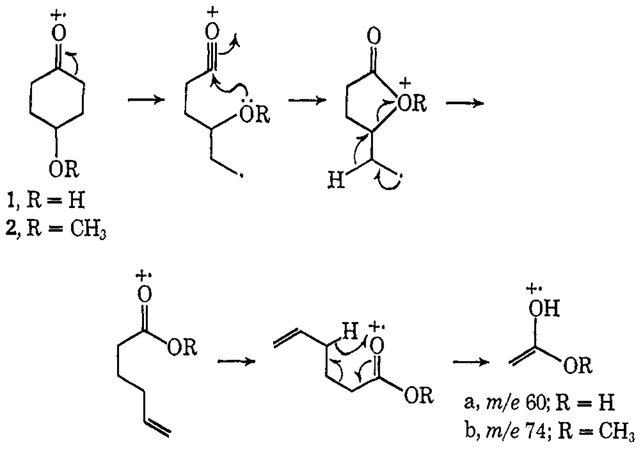
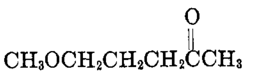
SCHEME I

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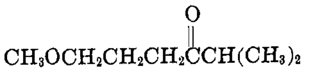
$CH_3OCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$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$CH_3OCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH(CH_3)_2$

One of the earliest examples of the interaction of remote functional groups upon electron impact was afforded from studies in our laboratories[6] of the mass spectra of 4-hydroxy- (**1**) and 4-methoxycyclohexanone (**2**). Intense ions at *m/e* 60 for **1** and *m/e* 74 for **2** were observed, and high resolution mass measurements indicated their composition to be $C_2H_4O_2$ and $C_3H_6O_2$, respectively. With the aid of deuterium-labeling studies, the mechanism in Scheme I was offered to account for the formation of these ions. In the course of that work,[6] the spectra of two acyclic analogs of these substances, 5-methoxy-2-pentanone (**3**) and 6-methoxy-2-methyl-3-hexanone (**4**), were recorded (Figure 1 and 2) to determine if evidence for interaction of the two functional groups similar to that shown in Scheme I could be found. While no such evidence was encountered in the spectrum of **3**, the operation of some functional group interaction in **4** was indicated by the fact that 10% of the intense *m/e* 59 peak (Figure 2) was shown by high-resolution mass measurements to correspond to

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(1) For paper CCI, see S. Eadon, C. Djerassi, J. H. Beynon, and R. M. Caprioli, *Org. Mass. Spectrom.*, submitted for publication.

(2) Financial support from the National Institutes of Health (Grant No. AM 04257) is gratefully acknowledged.

(3) (a) National Science Foundation Postdoctoral Fellow, 1969–1970; (b) National Institutes of Health Postdoctoral Fellow, 1967–1968; (c) Postdoctoral Fellow, 1966–1968.

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

(5) (a) J. Lederberg, G. L. Sutherland, B. G. Buchanan, E. A. Feigenbaum, A. V. Robertson, A. M. Duffield, and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 2973 (1969); (b) A. M. Duffield, A. V. Robertson, C. Djerassi, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, *ibid.*, **91**, 2977 (1969); (c) G. Schroll, A. M. Duffield, C. Djerassi, B. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, *ibid.*, **91**, 7440 (1969); (d) A. Buchs, A. M. Duffield, G. Schroll, C. Djerassi, A. B. Delfino, B. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, *ibid.*, **92**, 6871 (1970). (e) Y. M. Sheikh, A. Buchs, A. B. Delfino, G. Schroll, A. M. Duffield, C. Djerassi, B. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, *Org. Mass Spectrom.*, **4**, 493 (1970); (f) A. Buchs, A. B. Delfino, A. M. Duffield, C. Djerassi, B. G. Buchanan, E. A. Feigenbaum, and J. Lederberg, *Helv. Chim. Acta*, **53**, 1394 (1970).

(6) (a) M. M. Green and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 5190 (1967); (b) M. M. Green, D. S. Weinberg, and C. Djerassi, *ibid.*, **88**, 3883 (1966).

(7) M. Vandewalle, N. Schamp, and M. Franque, *Bull. Soc. Chim. Belg.*, **75**, 848 (1966).

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(10) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **34**, 3147 (1969), and references therein.

(11) (a) R. G. Cooks and D. H. Williams, *Chem. Commun.*, 51 (1967); (b) R. G. Cooks, J. Ronayne, and D. H. Williams, *J. Chem. Soc., C* 2601 (1967).

(12) R. H. Shapiro and K. B. Tomes, *Org. Mass Spectrom.*, **3**, 333 (1970), and references therein.

(13) (a) R. J. Highet and P. F. Highet, *Tetrahedron Lett.*, 1803 (1970); (b) R. E. Wolff and A. Caspar, *ibid.*, 1807 (1970).

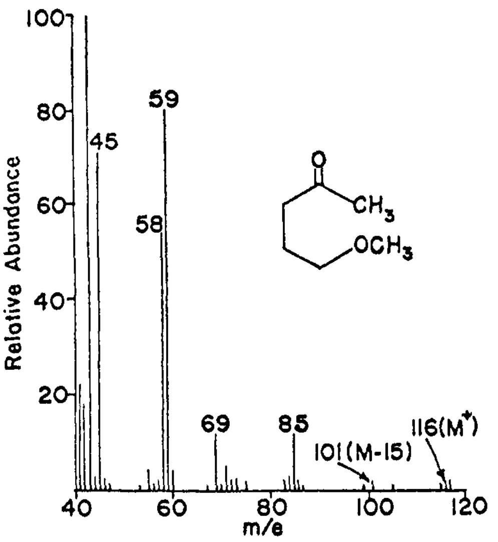
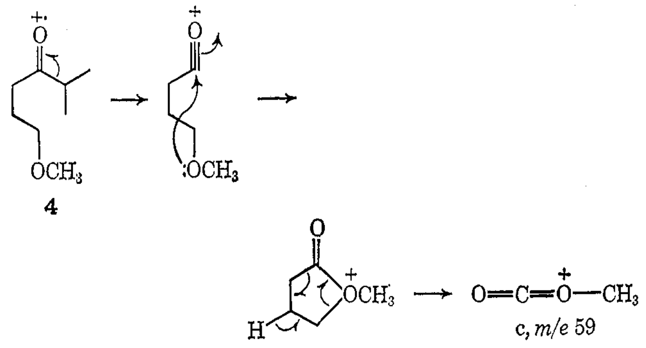
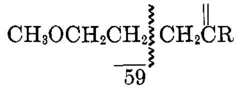


Figure 1.—Mass spectrum (70 eV) of 5-methoxy-2-hexanone (**3**).

$C_2H_3O_2$. Formation of this ion was rationalized as shown in Scheme II. A surprising feature of the spectra of these two compounds was that the intense (second largest peak at 70 eV, base peak at low electron volts) ions of mass 59 had the composition C_3H_7O (except as mentioned above for **4**), which corresponds formally to β cleavage at the ether function with charge retention on the ether moiety. Under normal circumstances, β cleavage in aliphatic ethers is not a favorable process (methyl butyl ether has only a very small peak at *m/e* 59).[14,15] Likewise β cleavage at the keto function

Scheme II





$$\underbrace{\mathrm{CH_3OCH_2CH_2}}_{59}\,\vdots\,\mathrm{CH_2}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{R}$$

with charge retention on the alkyl fragment is also an inefficient process.[16] *A priori*, it would be expected that the favored modes of cleavage in **3** and **4** would be α cleavage at the ether function and a McLafferty rearrangement[17] at the keto function; indeed, intense peaks corresponding to these cleavages were observed in Figures 1 and 2. However, the *m/e* 59 peak appears to be of equal importance in both cases. Thus it was felt that this anomalous cleavage might be due to some type of interaction of the two functional groups, and, since similar cleavages had been observed in recent studies of the fragmentation patterns of ω-amino esters[13b] and long chain aliphatic methoxy esters,[18] it was of obvious interest to study this problem in greater detail.

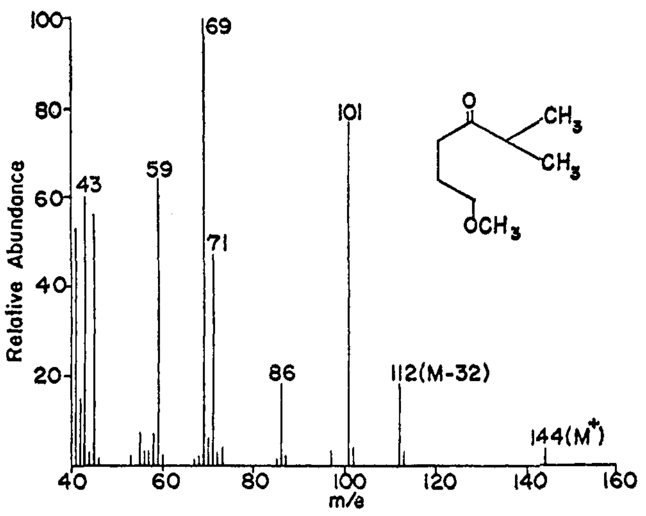


Figure 2.—Mass spectrum (70 eV) of 6-methoxy-2-methyl-3-hexanone (**4**).

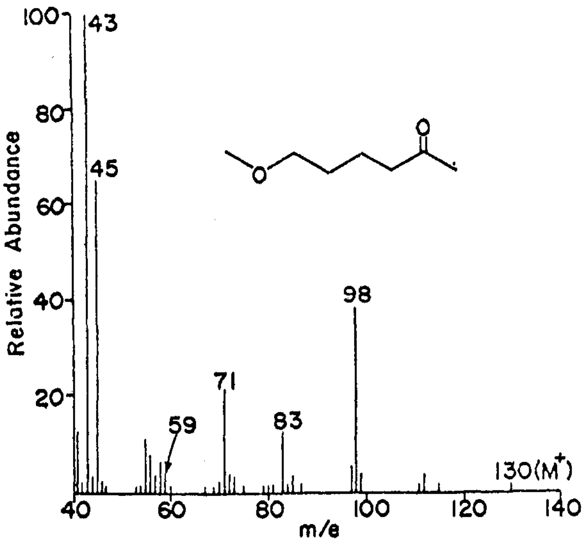
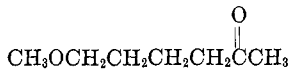


Figure 3.—Mass spectrum (70 eV) of 6-methoxy-2-hexanone (**5**).

Results and Discussion

Compounds **3** and **4** both have a keto function separated by three methylene units from a methyl ether function. As a first step in studying the process leading to the "anomalous" *m/e* 59 peak, it was decided to determine what the effect of varying the distance between these two groups would be. Accordingly, 6-methoxy-2-hexanone (**5**) was synthesized and its mass spectrum recorded[19] (Figure 3). Inspection of Figure 3 reveals



$$\mathrm{CH_3OCH_2CH_2CH_2CH_2}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{CH_3}$$

5

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[14] Reference 4, p 227.

[15] S. L. Bernasek and R. G. Cooks, *Org. Mass Spectrom.*, **3**, 127 (1970).

[16] Reference 4, p 135.

[17] F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).

[18] M. Creef, R. E. Wolff, G. H. Dramman, and J. A. McCloskey, *Org. Mass Spectrom.*, **3**, 399 (1970).

[19] Although all mass spectra were recorded at both 70 and 12 eV, only the 70-eV spectra are reproduced.

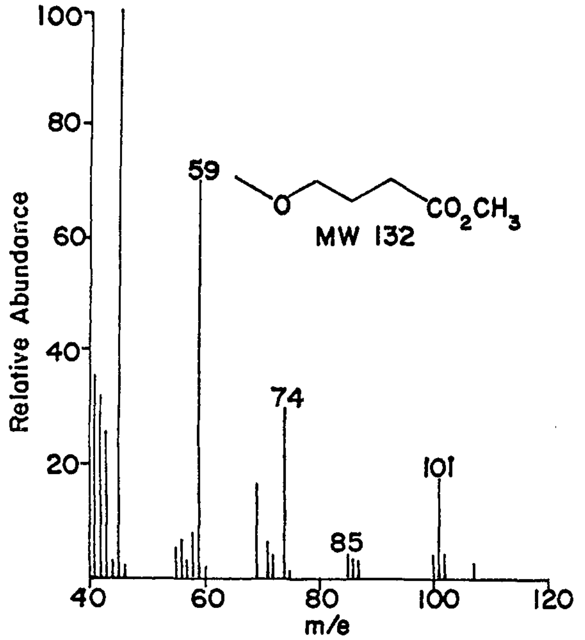


Figure 4.—Mass spectrum (70 eV) of methyl 4-methoxybutyrate (6). No molecular ion was observed in the spectrum.

only very low intensity peaks at *m/e* 59 and 73 (the ion homologous to the ion of mass 59 in the spectrum of **3**), and at low electron volts these peaks disappeared completely. The fragmentation pattern of 4-methoxy-2-butanone was not investigated for the obvious reason that β cleavage at the ether function would also be α cleavage at the keto function in this molecule, a very favorable process.[20] Thus it was concluded that a necessary condition for the formation of the *m/e* 59 ion in these substances is that the functional groups be separated by three and only three methylene units. This result is in contrast to the situation in the ω-amino esters[13b] where loss of $CH_2CO_2CH_3$ was found to be independent of the separation of the two functional groups.

Having established this condition, it appeared in order to determine if the keto function was also necessary for the formation of this ion. Specifically, would any functional group bearing a carbonyl moiety be sufficient? To this end, methyl 4-methoxybutyrate (**6**) was synthesized and its mass spectrum recorded (Figure 4). As in the spectra of **3** and **4**, the *m/e* 59 fragment in this spectrum was very intense (rel intensity 70%, Σ_{40} 17.5%, base peak at 15 eV). In this instance, α cleavage at the methoxycarbonyl function with charge retention on the methoxycarbonyl group could also give an ion of mass 59. However, high-resolution mass measurements indicated that the composition of this ion was predominately (86%) C_3H_7O; scanning in the metastable mode[21] indicated that the molecular ion was a precursor of this ion. Likewise, in the spectrum (not shown) of 4-methoxybutyric acid (**7**) an intense ion (rel intensity 60%, Σ_{40} 30.0%) of mass 59 was observed. In support of the postulate that the two functional groups could not be separated by more than three methylene units, the spectrum (not shown) of methyl 5-methoxyvalerate (**8**) had no peaks at either *m/e* 59 or 73. These results led to the conclusion that the keto function could be replaced by other groups bearing a carbonyl moiety to give the *m/e* 59 peak, and it now remained to be established whether any oxygen-containing function would suffice to produce this ion. The preparation of 4-methoxy-1-butanol (**9**) was therefore effected and its mass spectrum (Figure 5) recorded. Only very small peaks were found at *m/e* 59 at both high and low ionizing voltages; instead, a very intense peak appeared at *m/e* 58, which corresponds to the loss of the elements of water and ethylene from the parent ion (the structure of this ion will be discussed in a forthcoming communication in the context of a related problem). Apparently a carbonyl function is necessary for the formation of the *m/e* 59 peak. Thus, it was concluded that, in order to generate this anomalous ion from a methyl ether, a carbonyl function has to be located in the molecule and be separated by three methylene units from the ether function. The simplest explanation of these results is that this process is dependent upon the stability of the departing radical, $\cdot CH_2R$, with some driving force being provided by anchimeric assistance from the methoxy group to give the oxiranium ion d. When R = $COCH_3$, CO_2CH_3, or CO_2H, the radical is allylically stabilized, whereas when R = CH_2OH or alkyl there is no possibility of such stabilization.

$$\overset{59}{CH_3OCH_2CH_2}\,|\,\overset{59}{CH_2\,|\,CO_2CH_3}$$

6

$CH_3OCH_2CH_2CH_2CO_2H$
7

$CH_3OCH_2CH_2CH_2CH_2CO_2CH_3$
8

$CH_3OCH_2CH_2CH_2CH_2OH$
9

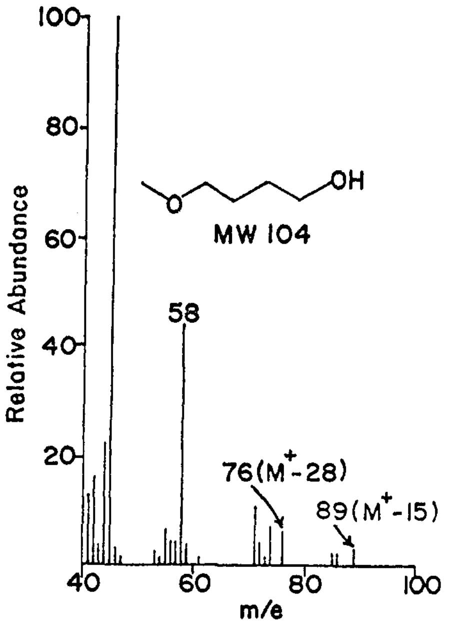
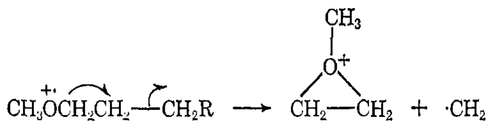


Figure 5.—Mass spectrum (70 eV) of 4-methoxy-1-butanol (7). No molecular ion was observed in the spectrum.



d, *m/e* 59

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[20] Reference 4, p 134.

[21] (a) J. H. Beynon, *Nature*, **204**, 67 (1964); (b) K. R. Jennings, "Some Newer Physical Methods in Structural Chemistry," R. Bonnett and J. G. Davies, Ed., United Trade Press, London, 1967, p 105.

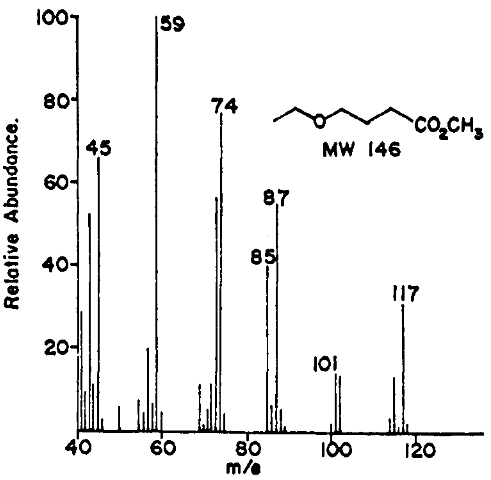


Figure 6.—Mass spectrum (70 eV) of methyl 4-ethoxybutyrate (**13**). No molecular ion was observed in the spectrum.

Essentially the same conclusions were reached in the case of the ω-amino esters.[13b]

In order to verify that no hidden rearrangements or reciprocal hydrogen transfer reactions were occurring to give ion d, several deuterated analogs of **6** were synthesized and their mass spectra recorded. Table I lists the pertinent information regarding the *m/e* 59 ion in the spectra of methyl 4-methoxy-4,4-dideuteriobutyrate (**10**), methyl 4-methoxy-2,2-dideuteriobutyrate (**11**), and methyl-d_3 4-methoxybutyrate (**12**). Accounting

$$\underset{\mathbf{10}}{CH_3OCD_2CH_2CH_2CO_2CH_3} \qquad \underset{\mathbf{11}}{CH_3OCH_2CH_2CD_2CO_2CH_3}$$

$$\underset{\mathbf{12}}{CH_3OCH_2CH_2CH_2CO_2CD_3}$$

for the fact that 14% of the *m/e* 59 ion in the spectrum of **6** had the composition $C_2H_3O_2$, then it may be seen from Table I that the position of ion d is shifted completely to *m/e* 61 in **10** but is unchanged in **11** and **12**. These results confirm that ion d includes carbon atoms 3 and 4 as well as the methyl ether group and thus lend further support to the mechanism shown above.

Table I

Partial Mass Spectral Peaks in the Spectra of Methyl 4-Methoxybutyrate and Some Deuterated Analogs[a]

m/e	$CH_3O(CH_2)_3$-CO_2CH_3	CH_3OCD_2-$(CH_2)_2CO_2CH_3$[b]	$CH_3O(CH_2)_2$-$CD_2CO_2CH_3$[c]	$CH_3O(CH_2)_3$-CO_2CD_3[d]
59	70	17	79	88
60	2	3	3	4
61		62	1	3
62		1		10

[a] At 70 eV, heated inlet. See also the Experimental Section. [b] 97% d_2, 3% d_1. [c] 19% d_0, 36% d_1, 30% d_2, 13% d_3, 2% d_4. [d] 82% d_3, 18% d_2.

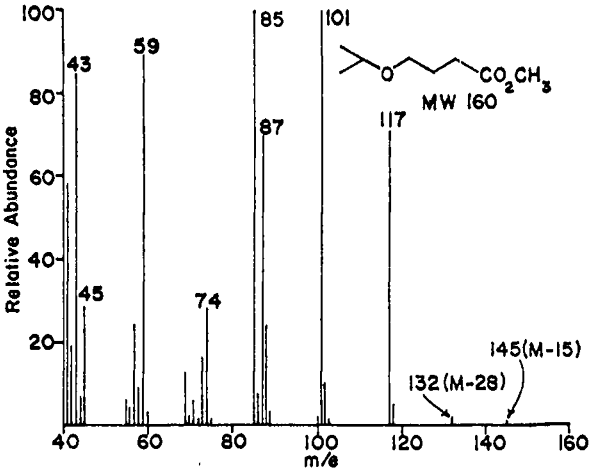


Figure 7.—Mass spectrum (70 eV) of methyl 4-isopropoxybutyrate (**14**). No molecular ion was observed in the spectrum.

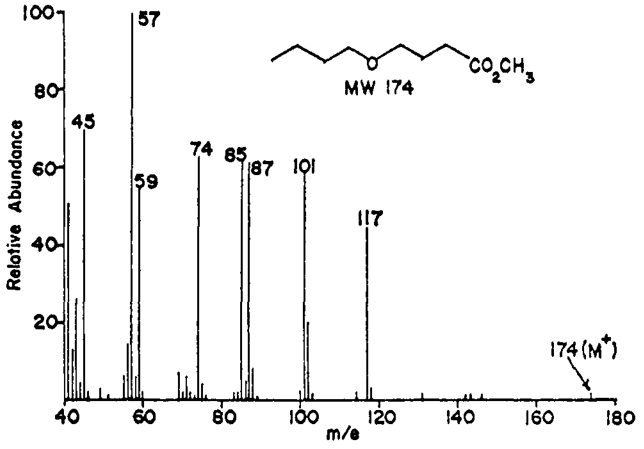
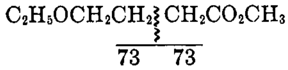


Figure 8.—Mass spectrum (70 eV) of methyl 4-*n*-butoxybutyrate (**15**).

Having now established the genesis of the "anomalous" ion of mass 59, it was decided to determine what the effect of different ether alkyl groups would be on the formation and intensity of this ion. Accordingly, compounds **13**, **14**, and **15** were synthesized and their mass spectra recorded (Figures 6, 7, and 8, respectively).

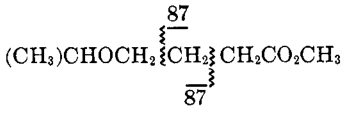
$$ROCH_2CH_2CH_2CO_2CH_3$$
13, R = C_2H_5
14, R = $CH(CH_3)_2$
15, R = *n*-C_4H_9

In the spectrum of **13**, the peak analogous to the *m/e* 59 peak in **6** should be shifted by 14 mass units to *m/e* 73 (C_4H_9O), and, as expected, an intense peak was observed at this position (rel intensity 56%, Σ_{40} 8.9%) in Figure 6. However, this ion could also result from β cleavage at the ether function with charge retention on the ester portion of the molecule. This ambiguity was

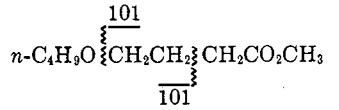


$$\underbrace{C_2H_5OCH_2CH_2}_{73}\wr\underbrace{CH_2CO_2CH_3}_{73}$$

eliminated by high-resolution mass measurements, which indicated that this ion's composition was C_4H_9O. In addition to coming from the molecular ion, scanning in the metastable mode indicated that the *m/e* 73 fragment (C_4H_9O) also arose from ions of masses 101 ($C_5H_9O_2$) and 115 ($C_6H_{11}O_2$). Fragments analogous to d in **14** and **15** should be shifted to *m/e* 87 and 101, respectively, and Figures 7 and 8 show intense peaks at these



$$(CH_3)CHOCH_2\wr\overset{87}{\overbrace{\underbrace{CH_2}_{87}}}\wr CH_2CO_2CH_3$$



$$n\text{-}C_4H_9O\wr\overset{101}{\overbrace{\underbrace{CH_2CH_2}_{101}}}\wr CH_2CO_2CH_3$$

TABLE II

PRINCIPAL MASS SPECTRAL PEAKS IN THE SPECTRA OF METHYL 4-ALKOXYBUTYRATES,[a] $RO(CH_2)_3CO_2CH_3$

		m/e values (% relative abundance)								
Compd, R =	No.	M+	M − R	M − OCH_3	M − OR	$C_4H_7O_2$	M − (R + CH_3OH)	McLafferty ion	C_3H_2O[b] + $C_2H_3O_2$	C_2H_5O
CH_3	6	132 (0)	117 (2)	101 (17)	101 (17)	87 (3)	85 (4)	74 (30)	59 (70)	45 (100)
C_2H_5	**13**	146 (0)	117 (31)	115 (13)	101 (14)	85 (55)	85 (40)	74 (77)	59 (100)	45 (64)
$CH(CH_3)_2$	**14**	160 (0)	117 (71)	129 (0)	101 (100)	87 (70)[c]	85 (100)	74 (28)	59 (89)	45 (28)
n-C_4H_9	**15**	174 (0)	117 (100)	143 (2)	101 (54)[d]	87 (62)	85 (56)	74 (87)	59 (55)	45 (70)

[a] Footnote *a*, Table I. [b] For details see Table V. [c] 3% $C_5H_{19}O$. [d] 18% $C_6H_{13}O$.

TABLE III

PRINCIPAL MASS SPECTRAL PEAKS IN THE SPECTRA OF METHYL 4-ETHOXYBUTYRATE AND SOME DEUTERATED ANALOGS[a]

			m/e values (% relative abundance)								
Compd	No.	Approx % of isotopic purity	M+	M − Et	M − OCH_3	M − EtO	$C_4H_7O_2$	*M* − (R + CH_3OH)	McLafferty ion	$C_2H_3O_2$	C_2H_5O
$EtO(CH_2)_3CO_2CH_3$	**13**		146 (0)	117 (31)	115 (13)	101 (14)	87 (55)	85 (40)	74 (77)	59 (100)	45 (63)
$EtOCD_2(CH_2)_2CO_2CH_3$	**16**	97 d_2, 3 d_1	148 (0)	119 (28)	117 (13)	103 (15)	89 (50)	86 (30)	75 (33)	59 (29) 61 (100)	45 (19) 47 (46)
$EtOCH_2(CD_2)_2CO_2CH_3$	**17**	86 d_4, 14 d_3	150 (0)	121 (42)	119 (20)	105 (24)	91 (62)	89 (53)	76 (100)	59 (97) 61 (58)	45 (71) 47 (67) 49 (0)
$EtO(CH_2)_3CO_2CD_3$	**18**	18 d_2, 83 d_3	149 (0)	120 (37)	115 (20)	104 (20)	87 (61)	85 (60)	77 (87)	59 (100) 62 (39)	45 (29) 48 (9)

[a] Footnote *a*, Table I.

positions. As in the spectrum of **13**, two different compositions are possible for each ion. In these instances, however, high-resolution mass measurements indicated that the *m/e* 87 peak corresponded predominately (97%) to $C_4H_7O_2$ and the *m/e* 101 peak largely (82%) to $C_5H_9O_2$. *These data indicate that the generation of ions analogous to d (m/e 59) is not favorable in the higher alkoxybutyrates.* It is probable that this is a result of a decrease in the ion current available for the β-cleavage ion because of the increased number of possible modes of fragmentation (note the intense peaks at *m/e* 43 in Figure 7 and *m/e* 55, 57, and 71 in Figure 8) in these substances rather than an increase in the energy requirements for the β-cleavage process.

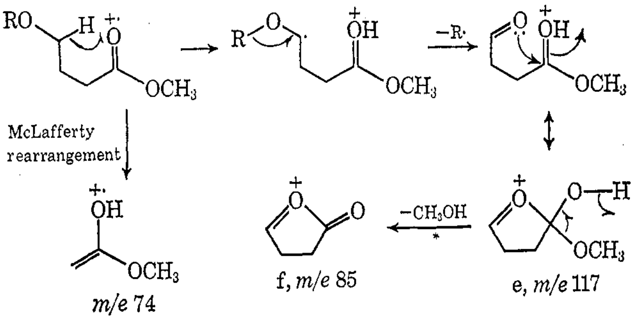
Dramatic differences between the higher mass regions are noticed when Figure 4 is compared to Figures 6–8. Not only are the intensities of the ions in this region much larger in the latter three spectra, but also ions appear there which are not present in Figure 4. The positions and intensities of some of these ions are summarized in Table II, and the reasons for these differences and probable origin of these ions are discussed below.

m/e **117 and 85 Peaks.**—Excluding that of **6**, the highest mass peak of major significance in the spectra (Figures 6–8) of the 4-alkoxybutyrates (**13**–**15**) was found at *m/e* 117. The composition of this ion was found to be $C_5H_9O_2$ in each case, which corresponds to the loss of the alkyl portion of the ether function. Intense metastable peaks were also observed in these spectra in the region *m/e* 61.6–61.8, formally representing the loss of methanol from the *m/e* 117 fragment ($85^2/117 = 61.7$). High-resolution mass measurements for each substance indicated the composition of the mass 85 ion to be $C_4H_5O_2$, and metastable mode scanning experiments[21] likewise indicated that the mass 117 fragment was the only precursor of this ion. To further elucidate the mechanistic details of these transformations, several deuterium-labeled analogs (**16**–**18**) of **13** were synthesized and their mass spectra recorded. The pertinent spectral data for these substances are summarized in Table III. It is easily seen from this table that it is the terminal ethyl group that is lost to give the *m/e* 117 ion in **13**. Likewise it can be deduced that the loss of methanol from the *m/e* 117 precursor involves the methoxycarbonyl group and the hydrogen atoms attached to the C-4 carbon atom. A mechanism consistent with these data is shown below. That the *m/e* 117 peak is not present in the spectrum of **6** is probably a reflection of the lower stability of the methyl radical in comparison to the ethyl, isopropyl, and *n*-butyl radicals. Although it is a matter of conjecture whether these ions are best represented by open chain or cyclic structures, it is probable that in view of the conceivable alternatives e and f represent the lowest energy forms. It is interesting that the first step in this process is also the first step in the McLafferty rearrangement, indicating perhaps that in these instances the McLafferty rearrangement is not concerted. However, the overall process does not seem to be competitive with this rearrangement, since the *m/e* 74 ion (McLafferty rearrangement ion) is prominent in the spectra of all of the alkoxybutyrates.

$C_2H_5OCD_2CH_2CH_2CO_2CH_3$
16

$C_2H_5OCH_2CD_2CD_2CO_2CH_3$
17

$C_2H_5OCH_2CH_2CH_2CO_2CD_3$
18



m/e **101 and 102 Peaks.**—Table II shows that in general the intensity of the fragment of mass 101 in

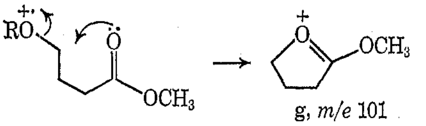
TABLE IV

PRINCIPAL MASS SPECTRAL PEAKS IN THE SPECTRA OF METHYL-d_3 4-ALKOXYBUTYRATES, $RO(CH_2)_3CO_2CD_3$[a]

			m/e values (% relative abundance)							
Compd, R =	No.	Approx % of isotopic purity	M +	M − R	M − OR	$C_4H_7O_2$	M − (R + CH_3OH)	McLafferty ion	$C_2H_3O_2$	C_2H_5O
CH_3	12	82 d_3,	135 (0)	120 (3)	101 (30)	87 (1)	85 (4)	77 (40)	59 (88)	45 (100)
		18 d_2			104 (2)				62 (10)	48 (2)
C_2H_5	18	18 d_2,	149 (0)	120 (37)	101 (0)	87 (61)	85 (60)	77 (87)	59 (100)	45 (79)
		82 d_3			104 (20)				62 (40)	48 (9)
$CH(CH_3)_2$	19	21 d_2,	163 (0)	120 (45)	101 (0)	87 (59)[b]	85 (100)	77 (60)	59 (8)	45 (28)
		79 d_3			104 (70)				62 (67)	48 (2)
n-C_4H_9	20	19 d_2,	177 (0)	120 (30)	101 (15)[c]	87 (50)	85 (58)	77 (50)	5 (2)	45 (53)
		81 d_3			104 (50)				62 (44)	48 (10)

[a] Footnote *a*, Table I. [b] 3% $C_5H_{11}O$. [c] $C_6H_{13}O$.

the spectra (Figures 4, 6–8) of **6**, **13**, **14**, and **15** increases as the size of the alkyl group increases. For **6**, this fragment can be formed by loss of a methoxy group from either the ether terminus or the methoxycarbonyl group. In general, the latter process does not appear to be very favorable (column 3, Table II). High-resolution mass measurements showed the composition of this ion to be $C_5H_9O_2$ (except for the 18% contribution of $C_4H_{13}O$ in the spectrum of **15**). If the structure of this ion is correctly represented by g, then it would be expected that the position of this peak should be shifted to *m/e* 104 in the spectra of the methyl-d_3 esters. These

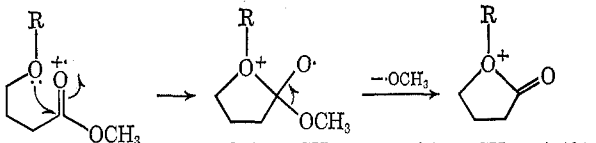


g, *m/e* 101

esters were prepared from the corresponding acids using deuterated diazomethane,[22] and their relevant spectral data are summarized in Table IV. With the exception

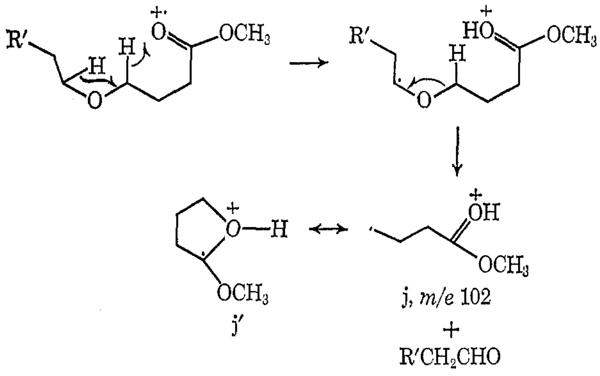
$RO(CH_2)_3CO_2CD_3$
12, R = CH_3
18, R = C_2H_5
19, R = $CH(CH_3)_2$
20, R = *n*-C_4H_9

of the spectrum of **12**, the fragment of mass 101 was shifted to *m/e* 104 (the small fragment at *m/e* 101 in the spectrum of **20** is due to the *β*-cleavage ion, $C_6H_{13}O$). The fact that the methoxy group in **12** is lost from the methoxycarbonyl group in contrast to the situation found in the other ethers (**18**–**20**) is somewhat difficult to rationalize. It was first thought that these results could be explained on the basis of radical stabilities; that is, that the methoxy radical was much less stable than the other alkoxy radicals. However, it has recently been shown[23] that there exists no difference in the stabilities of the methoxy, ethoxy, isopropoxy, and *n*-butoxy radicals. Perhaps the best explanation may be the increased steric hindrance to formation of cyclic intermediates in the larger systems. For R = CH_3, attack of the methoxy oxygen on the ester carbonyl followed by loss of a methoxy radical would give the very stable ion i. For R greater than methyl, however, the increased steric hindrance inhibits the formation of h, and the alkoxy radical is lost from the terminus to give ion g.



h, R = CH_3 i, R = CH_3; *m/e* 101

The composition of the fragment of mass 102 in the spectra of **13**, **14**, and **15** was shown by high-resolution mass measurements to be $C_5H_{10}O_2$, and the position of this peak was shifted to *m/e* 105 in the spectra (Table IV) of **18**, **19**, and **20** and to *m/e* 104 and 106 in the spectra (Table III) of **16** and **17**, respectively. Thus this fragment must contain the methoxycarbonyl group and carbon atoms 2, 3, and 4 as well as a hydrogen atom from the ether alkyl group. Formally this corresponds to an ionized methyl butyrate molecule, although there is no driving force to form this ion. A possible mechanistic pathway leading to the *m/e* 102 fragment is given below. To test the validity of this mechanism, compounds **21** and **22** were synthesized and their mass spectra recorded. In the spectrum of **21** (not shown), the characteristic peaks at *m/e* 117, 102, 101, 87, 85, 74, 59, and 45 were exhibited, in addition to a small peak of mass 129 corresponding to *β* cleavage at the ether function. According to the above formulation, it would be expected that the *m/e* 102 peak in the spectrum of **21**



j′ j, *m/e* 102

$CH_3(CH_2)_4CH_2O(CH_2)_3CO_2CH_3$ $CH_3(CH_2)_4CD_2O(CH_2)_3CO_2CH_3$
21 **22**

should be shifted to *m/e* 103 in the spectrum of **22** (not shown), and indeed, accounting for the contribution of the ^{13}C isotope of the *m/e* 101 peak, the *m/e* 102 peak was shifted completely to *m/e* 103 in the spectrum of **22**. An unexpected result encountered in the spectra of

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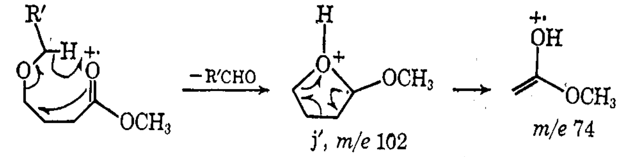
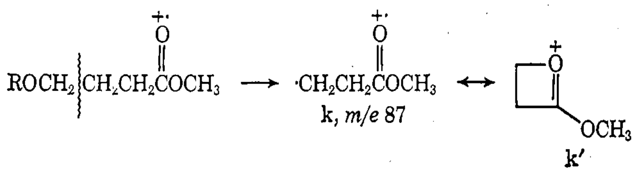
(22) (a) K. J. Van Der Merwe, P. S. Steyn, and S. H. Eggers, *Tetrahedron Lett.*, 3923 (1964); (b) D. W. Thomas and K. Biemann, *J. Amer. Chem. Soc.*, **87**, 5447 (1965).

(23) S. W. Benson and R. Shaw, *Advan Chem. Ser.*, **75**, 288 (1969).

these two substances was that the peak of mass 74 in the spectrum of **21** (McLafferty ion) was shifted about 50% to *m/e* 75 in the spectrum of **22**. This result suggests that at least in part the peaks at masses 102 and 74 were not formed as indicated above. A possible alternative formulation is shown below.



m/e **87 Peak.**—Whereas there is only a very weak peak at *m/e* 87 in the spectrum (Figure 4) of **6**, this peak is of major importance in the spectra (Figures 6–8) of the other esters. The composition of this ion was found to be $C_4H_7O_2$ (except in the spectrum of **14**, for which 3% was found to be $C_5H_{11}O$). Some probable structures for this ion and their possible modes of formation are shown below. Of these possible structures (k, k′, n), several lines of evidence indicate that n is the best representation of this ion. First, a strong metastable ion was observed at *m/e* 65.8 $(87^2/115 = 65.9)$ in the spectrum (Figure 6) of **13**. Second, for **14** and **15** scanning in the metastable mode indicated that the mass 87 ion did not originate from the corresponding molecular ions but rather from a mass 118 precursor as well as from other fragment ions (*m/e* 102 and 129 for **14** and 102 and 143 for **15**). Finally, Tables III and IV show conclusively that the *m/e* 87 fragment contains the C-4 carbon atom but not the ester methoxyl moiety. It is not clear whether n is formed from l or m, and evidence from scanning in the metastable mode indicates that it is probably formed from both. Whether from l or m, it is easy to see why this is not a very favorable process in the spectrum of **6** since the initial transfer of a hydrogen atom from the alkyl chain would not be very feasible.



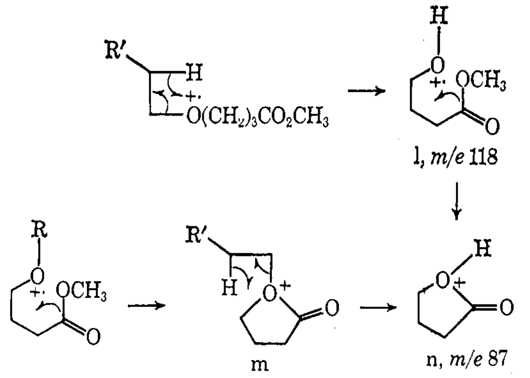


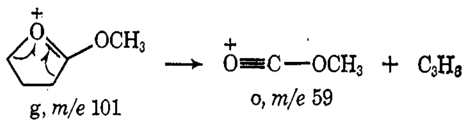
Table V

Summary of the High Resolution and Metastable Defocusing Data for the *m/e* 59 Peak in the Spectra of the Methyl 4-Alkoxybutyrates, $RO(CH_2)_3CO_2CH_3$

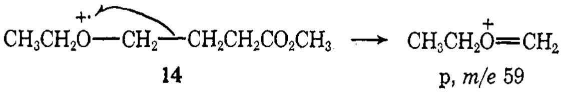
Compd, R =	No.	C_3H_7O, %	$C_2H_3O_2$, %	Probable parent ions[a]
CH_3	6	86	14	87, 101, 132
C_2H_5	13	78	22	87, 101
$CH(CH_3)_2$	14	66	34	87, 101
n-C_4H_9	15	35	65	85, 87, 101, 116

[a] As determined by the metastable defocusing technique.

m/e **59 Peak.**—The composition of this ion was found to be a mixture of C_3H_7O and $C_2H_3O_2$, and Table V lists the percentages of the two compositions for each of the alkoxybutyrates. Also listed there are the results of some metastable mode scanning experiments carried out on this ion. Because of the complexity of the data associated with this ion, few general conclusions can be drawn regarding its genesis. As mentioned earlier, the major portion of the *m/e* 59 peak in the spectrum of **6** is attributable to the β-cleavage ion d; presumably the minor component is derived by α cleavage at the carbomethoxy function to give o.



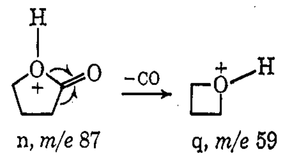
In the case of **13**, α cleavage at the ether function would give p with the composition C_3H_7O. Table III lends support to this hypothesis in that in the spectrum



$$CH_3CH_2\overset{+\cdot}{O}—CH_2—CH_2CH_2CO_2CH_3 \longrightarrow CH_3CH_2\overset{+}{O}=CH_2$$

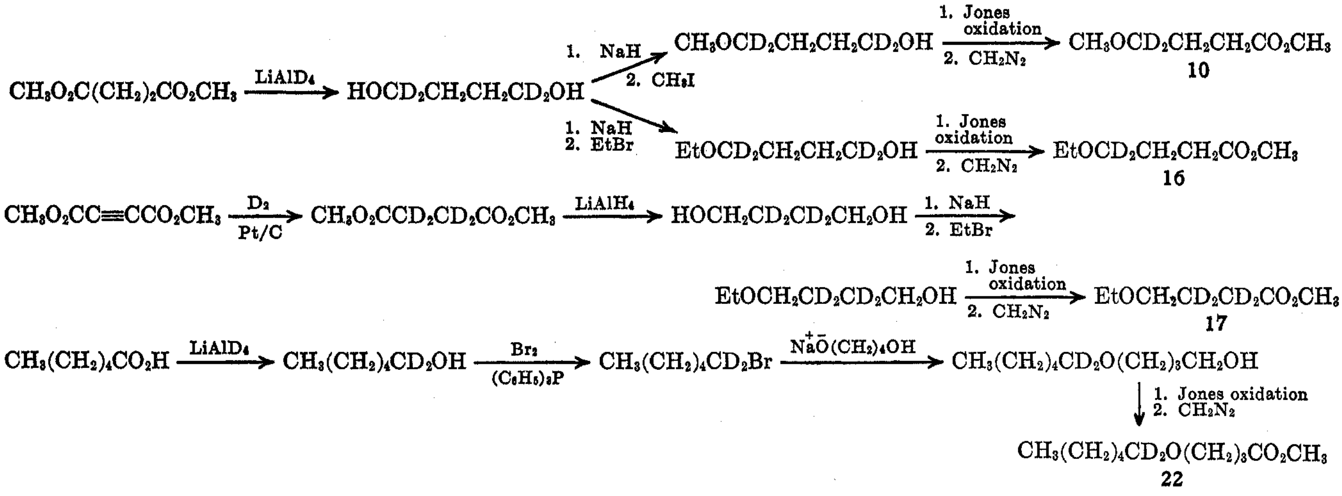
14 p, *m/e* 59

of **16** a large portion of the *m/e* 59 peak is shifted to *m/e* 61. Again it is probable that to a large extent the minor component of this ion is formed by α cleavage at the carbomethoxy function to give o. The metastable mode scanning results listed in Table V indicate that in all four esters this ion is formed to some extent from an *m/e* 87 precursor. Assuming the structure of the *m/e* 87 ion to be as postulated above (n), then *m/e* 59 can be formed by loss of carbon monoxide from n to give q.

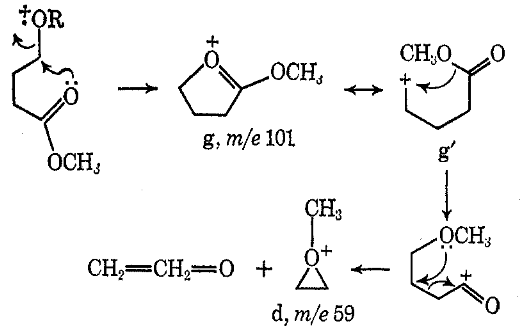


In the spectrum of **14**, the formation of the C_3H_7O portion of the mass 59 ion is more difficult to rationalize. Whereas the major portion of this ion was shown to have the composition C_3H_7O, its position was shifted almost entirely to *m/e* 62 in the spectrum (Table IV) of **19**. These results imply either that the predominant composition of this ion is $C_2H_3O_2$ or that some unusual rearrangement of the methoxy moiety to the alkyl chain is occurring. Similar puzzling results exist for **15** in that high-resolution mass measurements indicate the ratio of the abundances of the C_3H_7O to $C_2H_3O_2$ ions to be roughly 1:2, whereas the spectrum (Table IV) of **20** indicates this ratio to be on the order of 1:20. These apparent inconsistencies were clarified by high-resolution mass measurements of the *m/e* 62 fragment in the spectra of **19** and **20**. These measurements indicated that $C_3H_4D_3O$ and not $C_2D_3O_2$ was the predominant composition of this fragment (relative intensities of 65:35% in **19** and 61:39% in **20**, respectively). Thus,

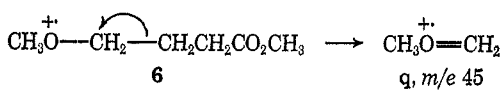
SCHEME III



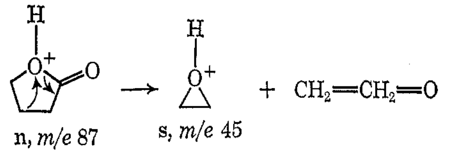
contrary to expectations, migration of the methoxy group from the carbonyl group to an sp^3 hybridized carbon atom must have occurred. Bearing in mind that the *m/e* 101 fragment was a precursor of the *m/e* 59 fragment common to all four unlabeled esters (**6**, **13**, **14**, and **15**), a possible formulation of the genesis of the *m/e* 59 fragment of composition C_3H_7O in the spectra (Figures 7 and 8) of **14** and **15** is given below. Migrations of methoxyl groups to carbonium ion centers have been shown previously[11] to be facile processes.



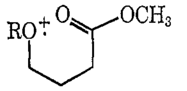
***m/e* 45 Peak.**—A substantial peak was exhibited at *m/e* 45 in the spectra of all four alkoxy esters. The only composition allowable for this ion is C_2H_5O. In the spectrum of **6** this ion is the base peak and undoubtedly results from the usual α cleavage at the ether function to give q.[24] This conclusion is supported by the findings that the position of this ion is shifted to



m/e 47 in the spectrum of **10** but is unchanged in the spectra of **11** and **12**. For **13**, **14**, and **15** there appears to be a variety of possible ways to form C_2H_5O. Indeed, the data in Tables III and IV and the results from metastable defocusing experiments indicate that such is the case. Considering, for instance, the *n*-butoxy ether **15**, ions of mass 73, 87, 101, and 132 were indicated as probable precursors for the *m/e* 45 ion. Likewise, for the ethoxy derivative **13** it was shown that the two carbon atoms in this fragment came partially from C-3, C-4, and the ethyl group. The only ion common to all four esters implicated as a possible precursor of the *m/e* 45 ion was the *m/e* 87 ion.



Summary.—One of the purposes of this work was to investigate whether the ion of mass 59 in the spectra of **3** and **4** resulted from an interaction of the two functional groups. In general, no evidence could be found linking the direct interaction of the two groups with the formation of this ion. However, indirect evidence for such interactions in the spectra of the alkoxybutyrates was deduced from an analysis of the *m/e* 117, 101, and 85 peaks. Several fragmentations were also noted which were characteristic of the individual functional groups. It is probable that the functional group interactions were facilitated by charge sharing between the two functional groups to give a coiled molecular ion.[9]



Syntheses of Labeled Compounds.—For this investigation it was necessary to synthesize several labeled 4-alkoxybutyrates with deuterium at the C-2, C-3, and C-4 positions as well as at the carbon in the alkyl chain α to the ether oxygen. The reaction pathways employed to obtain these substances are summarized in Scheme III, and the isotopic purity of the products is given in the appropriate table.

Experimental Section

The low-resolution mass spectra were obtained by Mr. R. G. Ross using an AEI MS-9 double-focusing mass spectrometer (heated inlet 150°, ion source temperature 180°). The high-resolution data were also obtained by Mr. Ross with the same instrument, and metastable transitions in the first-field-free region were observed with the aid of the metastable defocusing

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[24] The exact structure of the α-cleavage ions of aliphatic ethers has recently been studied in detail by icr spectroscopy. See J. Beauchamp and R. C. Dumbar, *J. Amer. Chem. Soc.*, **92**, 1477 (1970).

technique.[21] All substances were purified by vpc (5 ft × 0.25 in. SE-30, 5%, on Chromosorb G), prior to spectral analyses.

Infrared spectral data were recorded with a Perkin-Elmer Model 700 spectrophotometer, and the nmr spectra were secured with a Varian Model T-60 spectrometer. All nmr measurements were made in CCl_4 solutions containing 1% TMS as an internal standard. Chemical shifts are reported in parts per million downfield from the standard, and coupling constants are reported in hertz. Elemental analyses were performed by Mr. E. Meier and Mr. J. Consul of the Stanford Microanalytical Laboratory.

Methyl 4-Alkoxybutyrates.—The substances were prepared by Jones oxidation[25] of the corresponding 4-alkoxy-1-butanol to the acid and subsequent methylation of the acid with diazomethane. In a typical procedure a 1:10 solution of the appropriate 4-alkoxy-1-butanol in acetone (distilled from $KMnO_4$) was cooled to 0° and Jones reagent[26] was added dropwise with stirring until the color of the reagent persisted. The reaction mixture was then stirred at room temperature for 30 min and the chromium salts were filtered off. Acetone was removed at reduced pressure, excess saturated NaCl solution added, and the solution extracted three times with ether. The ether solution was dried ($MgSO_4$) and concentrated, and the acid was then esterified with diazomethane in the usual manner[27] without further purification. The methyl 4-alkoxybutyrates were separated from the crude reaction mixtures by distillation at reduced pressures and vpc and were identified by their ir, nmr, and mass spectra.

Methyl 4-methoxybutyrate (**6**): bp 60–62° (8 mm) [lit.[28] bp 70–71° (11 mm)]; ir (film) 1735 cm^{-1} (C=O); nmr δ 3.60 (s, 3 H, CO_2CH_3), 3.33 (t, 2 H, J = 6 Hz, CH_2O), 3.26 (s, 3 H, CH_3O), 2.32 (m, 2 H, CH_2CO_2), 1.85 (m, 2 H, CH_2CH_2O).

Methyl 4-ethoxybutyrate (**13**): bp 68° (7 mm); ir (CCl_4) 1740 cm^{-1} (C=O); nmr δ 3.63 (s, 3 H, CO_2CH_3), 3.38 (m, 4 H, CH_2O), 2.34 (t, 2 H, J = 6 Hz, CH_2CO_2), 1.82 (m, 2 H, CH_2CH_2O), 1.13 (t, 3 H, J = 6 Hz, CH_3CH_2). *Anal.* Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.47; H, 9.38.

Methyl 4-isopropoxybutyrate (**14**): bp 66–70° (5 mm); ir (CCl_4) 1740 cm^{-1} (C=O); nmr δ 3.60 (s, 3 H, CO_2CH_3), 3.37 (m, 3 H, CH_2O, CHO), 2.34 (t, J = 6 Hz, CH_2CO_2), 1.84 (m, 2 H, CH_2CH_2O), 1.07 (d, 6 H, J = 6 Hz, $(CH_3)_2CH$). *Anal.* Calcd for $C_8H_{16}O_3$: C, 60.00; H, 10.10. Found: C, 59.82, H, 9.95.

Methyl 4-*n*-butoxybutyrate (**15**): bp 73–75° (4 mm); ir (film) 1738 cm^{-1} (C=O); nmr δ 3.62 (s, 3 H, CO_2CH_3), 3.35 (t, 4 H, J = 6 Hz, CH_2OCH_2), 2.30 (t, 2 H, J = 6 Hz, CH_2CO_2), 1.89 (m, 2 H, $CH_2CH_2CO_2$), 1.41 (m, 4 H, CH_2CH_2), 0.87 (m, 3 H, CH_3CH_2). *Anal.* Calcd for $C_9H_{18}O_3$: C, 62.01; H, 10.41. Found: C, 61.78; H, 10.20.

Methyl 4-*n*-hexoxybutyrate (**21**): bp 88° (2 mm); ir (film) 1740 cm^{-1} (C=O); nmr δ 3.64 (s, 3 H, CO_2CH_3), 3.37 (m, 4 H, CH_2O), 2.30 (m, 2 H, CH_2CO_2), 1.27 (m, 10 H, CH_2CH_2), 0.87 (m, 3 H, CH_3CH_2). *Anal.* Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.42; H, 10.91.

6-Methoxy-2-hexanone (**5**).—Methylation of 5-carboxyl-2-pentanone (Aldrich Chemical Co.) with diazomethane was carried out in the usual manner to give 5-methoxycarbonyl-2-pentanone. To 4.5 g of this ester in 50 ml of benzene was added 2.1 g of ethylene glycol and a trace of *p*-toluenesulfonic acid and the mixture was heated overnight. The mixture was cooled, washed with water, dried ($MgSO_4$), and evaporated to give 5.2 g of crude ketal. To 0.8 g of $LiAlH_4$ in 25 ml of ether was added 3.8 g of this ketal and the resultant mixture was stirred for 4 hr at room temperature. Standard work-up yielded 3.4 g of the crude ethylene ketal of 6-hydroxy-2-hexanone. Treatment of 2.4 g of this material with 1.8 g of NaH (54.7% mineral oil dispersion) and 5.5 g of methyl iodide in refluxing benzene for 12 hr yielded the ethylene ketal of the crude 6-methoxy-2-hexanone. Deketalization was accomplished by heating the ketal in 90% aqueous acetic acid for 2 hr. After work-up, the crude product was purified by vpc to give **5**, ir (film) 1708 cm^{-1} (C=O), bp 72° (10 mm) [lit.[29] bp 65–67° (8 mm)].

Methyl 5-Methoxypentanoate (**8**).—To 8.0 g of 1,5-pentanediol mixed with a few milliliters of dry benzene was added slowly 3.8 g of NaH (54.7% mineral oil dispersion) and the resultant mixture was stirred at reflux for 2 hr. After cooling, 34.0 g of methyl iodide was added and refluxing continued for 12 hr. After cooling again, excess saturated NaCl solution was added, the solution was extracted with ether, and the organic extracts were dried ($MgSO_4$) and evaporated to give 4.5 g of yellow oil. Distillation of this material at 80° (7 mm) gave 2.0 g of 5-methoxy-1-pentanol. Conversion of this material to **8** was accomplished by a procedure analogous to that described above for the 4-alkoxybutyrates, bp 70° (9 mm) [lit.[28] bp 70–71° (11 mm)].

Deuterium-Labeled Esters and Alcohols.—The methyl-d_3 4-alkoxybutyrates (**12**, **18**, **19**, and **20**) were prepared from the corresponding 4-alkoxybutyric acids according to the procedure of Biemann,[22b] with the exception that phenol was used instead of phenol-*O-d*. The 4,4-dideuterio-4-alkoxybutyrates (**10** and **16**) were prepared from 1,1,4,4-tetradeuterio-1,4-butanediol in the same manner as the unlabeled esters. This tetradeuterated butanediol was obtained by slowly adding 8.7 g of methyl succinate to 3.0 g of $LiAlD_4$ in 150 ml of THF (distilled from $LiAlH_4$), refluxing for 24 hr, and working up in the usual manner. Likewise, methyl 2,2,3,3-tetradeuterio-4-methoxybutyrate (**17**) was prepared from 2,2,3,3-tetradeuterio-1,4-butanediol, and this diol was prepared by catalytic deuteration of methyl acetylenedicarboxylate using deuterium gas (3 atm) and a platinum catalyst (5% on charcoal). Methyl 4-(1′,1′-dideuterio-*n*-hexoxy)butyrate was prepared from 1,1-dideuteriohexyl bromide and 1,4-butanediol in the usual manner. The 1,1-dideuteriohexyl bromide was prepared by an $LiAlD_4$ reduction of hexanoic acid to give 1,1-dideuterio-1-hexanol, followed by bromination of this alcohol using triphenylphosphine and bromine.[30]

Registry No.—**3**, 17429-04-8; **4**, 17429-05-9; **5**, 29006-00-6; **6**, 29006-01-7; **7**, 29006-02-8; **12**, 29006-03-9; **13**, 29006-04-0; **14**, 29006-05-1; **15**, 29006-06-2; **16**, 29006-07-3; **17**, 29006-08-4; **18**, 29006-09-5; **19**, 29006-10-8; **20**, 28995-64-4; **21**, 28995-65-5.

Acknowledgment.—We wish to thank Professor J. I. Brauman for his valuable comments and Professor A. L. Weinheimer (University of Oklahoma) for the preparation of **15** during his sabbatical leave at Stanford University.

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